**Report Title :** Empagliflozin CDM validation analyses – Technical report

**Report Number :**

**Report to :** [redacted], Boehringer Ingelheim UK

**Submitted on :** 14 October 2014

**Document Version :** 5.0

**Document Status :** **Base case, one way sensitivity analyses, and PSA**

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## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| ACE | Angiotensin-converting enzyme |
| BDR | Background diabetic retinopathy |
| BI | Boehringer Ingelheim |
| BMI | Body mass index |
| Cana | Canagliflozin |
| CDM | [IMS] CORE Diabetes Model |
| Dapa | Dapagliflozin |
| ESRD | End-stage renal disease |
| Empa | Empagliflozin |
| GRP | Gross proteinuria |
| GTI | Genital tract infection |
| HbA1c | Glycohemoglobin |
| HDL-c | HDL-cholesterol |
| HF | Heart failure |
| INS | Insulin |
| LDL-c | LDL -cholesterol |
| LY | Life year |
| MA | Microalbuminuria |
| MET | Metformin |
| MI | Myocardial infarction |
| NMA | Network meta-analysis |
| OAD | Oral anti-diabetic drug |
| PDR | Proliferative diabetic retinopathy |
| PVD | Peripheral vascular disease |
| QALY | Quality-adjusted life year |
| RCT | Randomised Clinical Trial |
| SBP | Systolic blood pressure |
| SGLT-2 | Sodium-glucose cotransporter-2 |
| SD | Standard deviation |
| SU | Sulfonylurea |
| SVL | Severe vision loss |
| T2DM | Type 2 diabetes mellitus |
| UKPDS | United Kingdom Prospective Diabetes Study |
| UTI | Urinary tract infection |

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# Executive Summary

This report represents the results of the cost-effectiveness of treatment with empagliflozin versus selected comparator regimens in three populations and lines of treatment. The analysis was conducted using the IMS Core Diabetes Model v8.5+ in April 2014. The clinical inputs for the analysis were derived from a pooled analysis of clinical studies and a network meta-analysis and were provided by Boehringer Ingelheim. The objective of the report is to provide an alternative analysis to the analysis performed by Boehringer Ingelheim using BI proprietary model.

There were patient populations included in the analysis were: I) patients undergoing 2$^{nd}$ line treatment who are no longer responding adequately to metformin (MET); II) patients undergoing 3$^{rd}$-line treatment who are no longer responding adequately to metformin (MET) plus sulfonylurea (SU); III) patients undergoing 3$^{rd}$ line treatment who are no longer responding adequately to metformin TZD; and IV) patients who are no longer responding adequately to backbone insulin therapy (INS).

In the analysis both empagliflozin and comparator treatments were given on top of the respective background therapies: MET, MET+SU, MET+TZD and INS. The comparators of interest were dapagliflozin, sitagliptin and canagliflozin at different doses.

The treatment effects were obtained from a network meta-analysis (NMA) provided by Boehringer Ingelheim and included the impact of treatments on HbA1c, systolic blood pressure (SBP) and patient weight. In addition, data on the rates of hypoglycaemic events and infections (namely urinary tract infections (UTI) and genital tract infection (GTI)) were used as inputs. The time horizon for the cost-effectiveness analysis was lifetime to capture the lifetime outcomes of diabetes.

These point estimates of the costs and health outcomes are largely driven by the clinical inputs drawn from the NMA and the pooled analysis of the empagliflozin RCT, most importantly the changes of HbA1c, systolic blood pressure and body weight. The NMA results are characterised by considerable uncertainly.

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Contents

1. Background 11
2. Objectives and scope 12
3. Analysis 12
3.1. IMS CORE diabetes model overview 13
3.1.1. Model outcomes 13
3.2. Base-case analyses 13
3.2.1. Perspective 14
3.2.2. Patient population 14
3.2.3. Time horizon and discounting 15
3.2.4. Treatment pathways 15
3.2.5. Sensitivity analysis 15
4. Model Inputs 16
4.1. Baseline characteristics 16
4.2. Treatment effects 17
4.2.1. HbA1c 18
4.2.2. Systolic blood pressure (SBP) 18
4.2.3. Lipids 18
4.2.4. Body Mass Index (BMI) 18
4.2.5. Clinical inputs 18
4.3. Utilities 24
4.4. Costs 25
4.4.1. Cost of comparator drugs and consumables 25
4.4.2. Drug prices 25
4.4.3. Cost of complications 26
4.5. Other clinical inputs to the CORE model 28
4.6. Mortality 29
4.6.1. Non-specific mortality 29
5. Base-case analyses results 31
5.1. Summary of costs and outcomes 31
5.1.1. 2nd line, patients not adequately responding to MET 31
5.1.2. 3rd line, patients not adequately responding to MET+SU 34
5.1.3. 3rd line, patients not adequately responding to MET+TZD 37
5.1.4. Patients not adequately responding to INS 39
5.2. Detailed results: dual therapy regimens 42
5.2.1. Empagliflozin 10mg +MET vs. dapagliflozin 10 mg +MET 42
5.2.2. Empagliflozin 25mg +MET vs. dapagliflozin 10 mg +MET 43
5.2.3. Empagliflozin 10mg+MET vs. Sitagliptin 100mg+MET 44
5.2.4. Empagliflozin 25mg+MET vs. Sitagliptin 100mg+MET 45
5.2.5. Empagliflozin 25mg+MET vs. Canagliflozin 300mg+MET 46
5.2.6. Empagliflozin 10mg+MET vs. Canagliflozin 100mg+MET 47
5.2.7. Empagliflozin 10mg+MET vs. Canagliflozin 300mg+MET 48
5.2.8. Empagliflozin 25mg+MET vs. Canagliflozin 100mg+MET 49
5.3. Detailed results: triple therapy regimens – MET+SU 50
5.3.1. Empagliflozin 10mg vs Sitagliptin 100 mg 50
5.3.2. Empagliflozin 25mg vs Sitagliptin 100 mg 51
5.3.3. Empagliflozin 10mg vs Canagliflozin 100 mg 52

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5.3.4. Empagliflozin 25mg vs Canagliflozin 100 mg 52
5.3.5. Empagliflozin 10mg vs Canagliflozin 300 mg 54
5.3.6. Empagliflozin 25mg vs Canagliflozin 300 mg 55
5.4. Detailed results: triple therapy regimens MET TZD 56
5.4.1. Empagliflozin 10mg +MET+TZD vs Sitagliptin 100mg +MET+TZD 56
5.4.2. Empagliflozin 25mg +MET+TZD vs Sitagliptin 100mg +MET+TZD 57
5.4.3. Empagliflozin 10mg +MET+TZD vs Canagliflozin 100mg +MET+TZD 58
5.4.4. Empagliflozin 25mg +MET+TZD vs Canagliflozin 100mg +MET+TZD 59
5.4.5. Empagliflozin 10mg +MET+TZD vs Canagliflozin 300mg +MET+TZD 60
5.4.6. Empagliflozin 25mg +MET+TZD vs Canagliflozin 300mg +MET+TZD 61
5.5. Detailed results: regimens with INS 63
5.5.1. Empagliflozin 10mg +INS vs Dapagliflozin 10mg +INS 63
5.5.2. Empagliflozin 25mg +INS vs Dapagliflozin 10mg +INS 64
5.5.3. Empagliflozin 10mg +INS vs Sitagliptin 100mg +INS 65
5.5.4. Empagliflozin 25mg +INS vs Sitagliptin 100mg +INS 66
5.5.5. Empagliflozin 10mg +INS vs Canagliflozin 100mg +INS 67
5.5.6. Empagliflozin 25mg +INS vs Canagliflozin 100mg +INS 68
5.5.7. Empagliflozin 10mg +INS vs Canagliflozin 300mg +INS 69
5.5.8. Empagliflozin 25mg +INS vs Canagliflozin 300mg +INS 70
5.6. Incidence of complications of diabetes 72
5.6.1. 2nd line, patients who are no longer responding adequately to MET 72
5.6.2. 3rd line, patients who are no longer responding adequately to MET+SU 84
5.6.3. 3rd line, patients who are no longer responding adequately to MET+TZD 96
5.6.4. Patients not responding adequately to INS 104
6. Sensitivity analyses (OWSA) 117
6.1. QWSA – 1: Convergence of BMI in the long run 117
6.2. Population I (OWSA – BMI convergence) 118
6.3. Population II (OWSA – BMI convergence) 121
6.4. Population III (OWSA – BMI convergence) 124
6.5. Population IV (OWSA – BMI convergence) 126
6.6. OWSA - 2: Setting SBP change to 0 for Sitagliptin 130
6.7. Population III 130
6.8. Population IV 131
7. Probabilistic sensitivity analysis (PSA) 132
7.1. PSA in Population I 134
7.1.1. Empagliflozin 10mg vs Dapagliflozin 10mg (Population I) 134
7.1.2. Empagliflozin 25mg vs Dapagliflozin 10mg(Population I) 134
7.1.3. Empagliflozin 10mg vs Sitagliptin 100mg (Population I) 136
7.1.4. Empagliflozin 25mg vs Sitagliptin 100mg (Population I) 137
7.2. PSA in Population II 138
7.2.1. Empagliflozin 10mg vs Sitagliptin 100mg (Population II) 138
7.2.2. Empagliflozin 25mg vs Sitagliptin 100mg (Population II) 139
7.2.3. Empagliflozin 10mg vs Canagliflozin 100mg (Population II) 140

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7.2.4. Empagliflozin 25mg vs Canagliflozin 100mg (Population II) 141
7.2.5. Empagliflozin 10mg vs Canagliflozin 300mg (Population II) 142
7.2.6. Empagliflozin 25mg vs Canagliflozin 300mg (Population II) 143
7.3. PSA in Population III 144
7.3.1. Empagliflozin 10mg vs Sitagliptin 100mg (Population III) 144
7.3.2. Empagliflozin 25mg vs Sitagliptin 100mg (Population III) 145
7.3.3. Empagliflozin 10mg vs Canagliflozin 100mg (Population III) 146
7.3.4. Empagliflozin 25mg vs Canagliflozin 100mg (Population III) 147
7.3.5. Empagliflozin 10mg vs Canagliflozin 300mg (Population III) 148
7.3.6. Empagliflozin 25mg vs Canagliflozin 300mg (Population III) 149
7.4. PSA in Population IV 150
7.4.1. Empagliflozin 10mg vs Dapagliflozin 10mg 150
7.4.2. Empagliflozin 25mg vs Dapagliflozin 10mg 151
7.4.3. Empagliflozin 10mg vs Sitagliptin 100mg 152
7.4.4. Empagliflozin 25mg vs Sitagliptin 100mg 153
8. References 154

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# List of tables

Table 1: Base case analyses - Populations I-IV 14
Table 2 Baseline characteristics of the cohorts 16
Table 3: Patients who are no longer responding adequately to MET 19
Table 4: Patients who are no longer responding adequately to MET+SU 20
Table 5 Patients who are no longer responding adequately to MET+TZD 21
Table 6 Patients who are no longer responding adequately to any insulin therapy (INS) 22
Table 7 Health state and treatment related utilities 24
Table 8 Cost of complications 26
Table 9 Other clinical inputs to the CORE model (management of T2DM patients) 28
Table 10 Life tables 29
Table 11 Base case results, 2nd line 31
Table 12 Base case results, 3rd line (MET+SU) 34
Table 13 Base case results, 3rd line (MET+TZD) 37
Table 14 Base case results, patients not responding to backbone insulin 39
Table 15 Empagliflozin 10mg +MET vs. dapagliflozin 10 mg +MET 42
Table 16: Cost breakdown (Empa 10mg+MET vs. dapa 10mg+MET) 42
Table 17 Empagliflozin 25mg +MET vs dapagliflozin 10 mg +MET 43
Table 18: Cost breakdown (Empa 25mg+MET vs. dapa 10mg+MET) 43
Table 19 Empagliflozin 10mg+MET vs. Sitagliptin 100mg+MET 44
Table 20 Cost breakdown (Empagliflozin 10mg+MET vs. Sitagliptin 100mg+MET) 44
Table 21 Empagliflozin 25mg+MET vs. Sitagliptin 100mg+MET 45
Table 22 Cost breakdown (Empagliflozin 25mg+MET vs. Sitagliptin 100mg+MET) 45
Table 23 Empagliflozin 25mg+MET vs. Canagliflozin 300mg +MET 46
Table 24 Cost breakdown (Empagliflozin 25mg+MET vs. Canagliflozin 300mg +MET) 46
Table 25 Empagliflozin 10mg+MET vs. Canagliflozin 100mg +MET 47
Table 26 Cost breakdown (Empagliflozin 10mg+MET vs. Canagliflozin 100mg +MET) 47
Table 27 Empagliflozin 10mg+MET vs. Canagliflozin 300mg +MET 48
Table 28 Cost breakdown (Empagliflozin 10mg+MET vs. Canagliflozin 300mg +MET) 48
Table 29 Empagliflozin 25mg+MET vs. Canagliflozin 100mg +MET 49
Table 30 Cost breakdown (Empagliflozin 25mg+MET vs. Canagliflozin 100mg +MET) 49
Table 31: Base case: Empagliflozin 10mg vs Sitagliptin 100 mg 50
Table 32: Cost breakdown: Empagliflozin 10mg vs Sitagliptin 100 mg 50
Table 33 Base case: Empagliflozin 25mg vs Sitagliptin 100 mg 51
Table 34 Cost breakdown: Empagliflozin 25mg vs Sitagliptin 100 mg 51
Table 35: Base case: Empagliflozin 10mg vs Canagliflozin 100 mg 52

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Table 36: Cost-breakdown : Empagliflozin 10mg vs Canagliflozin 100 mg 52
Table 37 Base case: Empagliflozin 25mg vs Canagliflozin 100 mg 53
Table 38 Cost breakdown: Empagliflozin 25mg vs Canagliflozin 100 mg 53
Table 39 Base case: Empagliflozin 10mg vs Canagliflozin 300 mg 54
Table 40 Cost breakdown: Empagliflozin 10mg vs Canagliflozin 300 mg 54
Table 41 Base case Empagliflozin 25mg vs Canagliflozin 300 mg 55
Table 42 Cost breakdown Empagliflozin 25mg vs Canagliflozin 300 mg 55
Table 43 Base case: Empagliflozin 10mg +MET+TZD vs Sitagliptin 100mg +MET+TZD 56
Table 44 Cost breakdown: Empagliflozin 10mg vs Sitagliptin 100mg (MET+TZD) 56
Table 45 Base case: Empagliflozin 25mg +MET+TZD vs Sitagliptin 100mg +MET+TZD 57
Table 46 Cost breakdown: Empagliflozin 25mg +MET+TZD vs Sitagliptin 100mg +MET+TZD 57
Table 47 Base case: Empagliflozin 10mg +MET+TZD vs Canagliflozin 100mg +MET+TZD 58
Table 48 Cost breakdown: Empagliflozin 10mg +MET+TZD vs Canagliflozin 100mg +MET+TZD 58
Table 49 Base case: Empagliflozin 25mg +MET+TZD vs Canagliflozin 100mg +MET+TZD 59
Table 50 Cost breakdown: Empagliflozin 25mg +MET+TZD vs Canagliflozin 100mg +MET+TZD 59
Table 51 Base case: Empagliflozin 10mg +MET+TZD vs Canagliflozin 300mg +MET+TZD 60
Table 52 Cost breakdown: Empagliflozin 10mg +MET+TZD vs Canagliflozin 300mg +MET+TZD 60
Table 53 Base case: Empagliflozin 25mg +MET+TZD vs Canagliflozin 300mg +MET+TZD 61
Table 54 Cost breakdown: Empagliflozin 25mg +MET+TZD vs Canagliflozin 300mg +MET+TZD 61
Table 55 Base case: Empagliflozin 10mg +INS vs Dapagliflozin 10mg +INS 63
Table 56 Cost breakdown: Empagliflozin 10mg +INS vs Dapagliflozin 10mg +INS 63
Table 57 Base case: Empagliflozin 25mg +INS vs Dapagliflozin 10mg +INS 64
Table 58 Cost breakdown: Empagliflozin 25mg +INS vs Dapagliflozin 10mg +INS 64
Table 59 Base case: Empagliflozin 10mg +INS vs Sitagliptin 100mg +INS 65
Table 60 Cost breakdown: Empagliflozin 10mg +INS vs Sitagliptin 100mg +INS 65
Table 61 Base case: Empagliflozin 25mg +INS vs Sitagliptin 100mg +INS 66
Table 62 Cost breakdown: Empagliflozin 25mg +INS vs Sitagliptin 100mg +INS 66
Table 63 Base case: Empagliflozin 10mg +INS vs Canagliflozin 100mg +INS 67
Table 64 Cost breakdown: Empagliflozin 10mg +INS vs Canagliflozin 100mg +INS 67

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Table 65 Base case: Empagliflozin 25mg +INS vs Canagliflozin 100mg +INS 68
Table 66 Cost breakdown: Empagliflozin 25mg +INS vs Canagliflozin 100mg +INS 68
Table 67 Base case: Empagliflozin 10mg +INS vs Canagliflozin 300mg +INS 69
Table 68 Cost breakdown: Empagliflozin 10mg +INS vs Canagliflozin 300mg +INS 69
Table 69 Base case: Empagliflozin 25mg +INS vs Canagliflozin 300mg +INS 70
Table 70 Cost breakdown: Empagliflozin 25mg +INS vs Canagliflozin 300mg +INS 70
Table 71 Complications: Empagliflozin 10mg Dapagliflozin 10mg (+MET) 72
Table 72 Complications: Empagliflozin 25mg Dapagliflozin 10mg (+MET) 73
Table 73 Complications: Empagliflozin 10mg Sitagliptin 100mg (+MET) 75
Table 74 Complications: Empagliflozin 25mg Sitagliptin 100mg (+MET) 76
Table 75 Complications: Empagliflozin 25mg Canagliflozin 300 (+MET) 78
Table 76 Complications: Empagliflozin 10mg Canagliflozin 100 (+MET) 80
Table 77 Complications: Empagliflozin 10mg Canagliflozin 300 (+MET) 81
Table 78 Complications: Empagliflozin 25mg Canagliflozin 100 (+MET) 83
Table 79 Complications: Empagliflozin 10mg Sitagliptin 100mg (MET+SU) 84
Table 80 Complications: Empagliflozin 25mg Sitagliptin 100mg (MET+SU) 86
Table 81 Complications: Empagliflozin 10mg Canagliflozin 100mg (MET+SU) 88
Table 82 Complications: Empagliflozin 25mg Canagliflozin 100mg (MET+SU) 90
Table 83 Complications: Empagliflozin 10mg Canagliflozin 300mg (MET+SU) 92
Table 84 Complications: Empagliflozin 25mg Canagliflozin 300mg (MET+SU) 94
Table 85 Complications: Empagliflozin 10mg Sitagliptin 100mg (MET+TZD) 96
Table 86 Complications: Empagliflozin 25mg Sitagliptin 100mg (MET+TZD) 97
Table 87 Complications: Empagliflozin 10mg Canagliflozin 100mg (MET+TZD) 99
Table 88 Complications: Empagliflozin 25mg Canagliflozin 100mg (MET+TZD) 100
Table 89 Complications: Empagliflozin 10mg Canagliflozin 300mg (MET+TZD) 101
Table 90 Complications: Empagliflozin 25mg Canagliflozin 300mg (MET+TZD) 103
Table 91 Complications: Empagliflozin 10mg Dapagliflozin 10mg (INS) 104
Table 92 Complications: Empagliflozin 25mg Dapagliflozin 10mg (INS) 106
Table 93 Complications: Empagliflozin 10mg Sitagliptin 100mg (INS) 107
Table 94 Complications: Empagliflozin 25mg Sitagliptin 100mg (INS) 109
Table 95 Complications: Empagliflozin 10mg Canagliflozin 100mg (INS) 110
Table 96 Complications: Empagliflozin 25mg Canagliflozin 100mg (INS) 112

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Table 97 Complications: Empagliflozin 10mg Canagliflozin 300mg (INS) 113
Table 98 Complications: Empagliflozin 25mg Canagliflozin 300mg (INS) 115
Table 99 Impact of the BMI convergence assumptions on costs and outcomes (Tx added to MET) 118
Table 100 Impact of the BMI convergence assumptions on cost-effectiveness (Tx added to MET) 120
Table 101 Impact of the BMI convergence assumptions on costs and outcomes (Tx added to MET+SU) 121
Table 102 Impact of the BMI convergence assumptions on cost-effectiveness (Tx added to MET+SU) 122
Table 103 Impact of the BMI convergence assumptions on costs and outcomes (Tx added to MET+TZD) 124
Table 104 Impact of the BMI convergence assumptions on incremental cost-effectiveness (Tx added to MET+TZD) 125
Table 105 Impact of the BMI convergence assumptions on costs and outcomes (Tx added to INS) 126
Table 106 Impact of the BMI convergence assumptions on costs effectiveness (Tx added to INS) 128
Table 107: No SBP effect (=0) in the sitagliptin arm vs empagliflozin 10mg 130
Table 108: No SBP effect (=0) in sitagliptin vs empagliflozin 25mg 130
Table 109: No SBP effect (=0) in sitagliptin vs empagliflozin 10mg 131
Table 110: No SBP effect (=0) in sitagliptin vs empagliflozin 10m 131

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# List of figures

Figure 1 Cost effectiveness plane: patients not adequately responding to MET 33

Figure 2 Cost effectiveness plane:, patients not adequately responding to MET+SU 36

Figure 3 Cost effectiveness plane: patients not adequately responding to MET+TZD 38

Figure 4 Cost effectiveness plane: patients not adequately responding to INS 41

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# 1. Background

Type 2 diabetes mellitus (T2DM) is a progressive long-term medical condition associated with elevated blood glucose levels (1). The prevalence of diabetes in the UK is increasing as is the prevalence of obesity, decreased physical activity, but also increased longevity after diagnosis due to better cardiovascular risk protection (1). In the UK the estimated prevalence of diagnosed or undiagnosed diabetes is around 5% (2) with 85% (3)-90% (4) of the adult diabetes patients having type 2 diabetes. The annual financial burden of diabetes on the NHS is estimated to represent 7-12% of the annual NHS budget[1].

Patients with T2DM are often initially treated with oral antidiabetic agents (OADs). In the later stages of T2DM impaired insulin secretion becomes a contributing factor to the elevation of blood glucose, necessitating the use of exogenous insulin.

Empagliflozin is a sodium-glucose cotransporter-2 (SGLT-2) inhibitor that blocks the reabsorption of glucose in the kidneys and promotes excretion of excess glucose in the urine. It is developed for use in patients with type 2 diabetes.

[1] National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update). London: Royal College of Physicians, 2008.

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# 2. Objectives and scope

BI has asked IMS to perform comparative analysis using IMS CORE Diabetes Model to repeat the cost-effectiveness analyses performed in the BI model for NICE. This report provides the detail the analytical approach, data inputs and results for all analyses conducted to validate the BI submission for NICE. The scope of the analysis covers four population and a number of treatment and comparator pairs for each of the populations as outlined below:

**Patients who are no longer responding adequately to metformin (MET)**

- Empagliflozin 10mg (+MET) vs. Dapagliflozin 10mg (+MET)
- Empagliflozin 25mg (+MET) vs. Dapagliflozin 10mg (+MET)
- Empagliflozin 10mg (+MET) vs. Sitagliptin 100mg (+MET)
- Empagliflozin 25mg (+MET) vs. Sitagliptin 100mg (+MET)
- Empagliflozin 10mg (+MET) vs. Canagliflozin 100mg (+MET)
- Empagliflozin 25mg (+MET) vs. Canagliflozin 100mg (+MET)
- Empagliflozin 10mg (+MET) vs. Canagliflozin 300mg (+MET)
- Empagliflozin 25mg (+MET) vs. Canagliflozin 300mg (+MET)

**Patients who are no longer responding adequately to MET plus Sulfonylurea (SU)**

- Empagliflozin 10mg (+MET+SU) vs. Sitagliptin 100mg (+MET+SU)
- Empagliflozin 25mg (+MET+SU) vs. Sitagliptin 100mg (+MET+SU)
- Empagliflozin 10mg (+MET+SU) vs. Canagliflozin 100mg (+MET+SU)
- Empagliflozin 25mg (+MET+SU) vs. Canagliflozin 100mg (+MET+SU)
- Empagliflozin 10mg (+MET+SU) vs. Canagliflozin 300mg (+MET+SU)
- Empagliflozin 25mg (+MET+SU) vs. Canagliflozin 300mg (+MET+SU)

**Patients who are no longer responding adequately to any thiazolidinedione (TZD)**

- Empagliflozin 10mg (+MET+TZD) vs. Sitagliptin 100mg (+MET+TZD)
- Empagliflozin 25mg (+MET+TZD) vs. Sitagliptin 100mg (+MET+TZD)
- Empagliflozin 10mg (+MET+TZD) vs. Canagliflozin 100mg (+MET+TZD)
- Empagliflozin 25mg (+MET+TZD) vs. Canagliflozin 300mg (+MET+TZD)

Patients who are no longer responding adequately to any insulin therapy (INS)

- Empagliflozin 10mg (+INS) vs. Dapagliflozin 10mg (+INS)
- Empagliflozin 25mg (+INS) vs. Dapagliflozin 10mg (+INS)
- Empagliflozin 10mg (+INS) vs. Sitagliptin 100mg (+INS)
- Empagliflozin 25mg (+INS) vs. Sitagliptin 100mg (+INS)
- Empagliflozin 10mg (+INS) vs. Canagliflozin 100mg (+INS)
- Empagliflozin 25mg (+INS) vs. Canagliflozin 100mg (+INS)
- Empagliflozin 10mg (+INS) vs. Canagliflozin 300mg (+INS)
- Empagliflozin 25mg (+INS) vs. Canagliflozin 300mg (+INS)

# 3. Analysis

The analysis was conducted using IMS Core Diabetes model (CDM) v8.5+ (Release (February 17th, 2014). The key inputs for the analysis have been discussed and agreed with Boehringer Ingelheim to maximise the alignment between the analytical settings the analysis presented in this report and the analysis conducted earlier in 2014.

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## 3.1. IMS CORE diabetes model overview

The IMS CORE Diabetes Model (CDM) is a fully documented and comprehensively validated computer simulation model that projects long-term health economic outcomes for both type 1 and type 2 diabetes patients. It takes into account baseline cohort characteristics and history of complications, current and future diabetes management patterns and concomitant medications, screening strategies and changes in physiological parameters over time.

The model is based on a series of sub-models that simulate important diabetes-related complications, including cardiovascular disease, eye disease, hypoglycaemia, nephropathy, neuropathy, foot ulcer, amputation, stroke, ketoacidosis, lactic acidosis and mortality. Each sub-model is a Markov-based model that performs Monte Carlo simulations and can incorporate time, state, time-in state, and diabetes type-dependent probabilities, derived from published sources. Cycle length of the model is one year as statistics on data such as disease prevalence, which can be used to calculate transition probabilities, are often provided as annual values.

Diabetes management strategies can be compared in different patient populations in a variety of clinical settings, allowing the identification of efficient diabetes management strategies. Clinical and economic outcomes (means and standard deviations) are calculated within the model using a non-parametric bootstrapping approach. This process simulates the lifetime progression of diabetes in cohorts of 1,000 hypothetical patients and repeats the process 1,000 times in all analyses presented in this report.

The CORE model simulations for T2DM have been validated for second order validation using the key publications used to construct the CORE model and for third order validation using epidemiological papers not used in the construction of the CORE model (5).

The IMS CDM supports two treatment algorithms, i.e. treatment trees and treatment lines. In this analysis, the treatment lines approach was used. For each of the treatments included in the analysis, it was assumed that patients start on a treatment of interest and after patient's level of HbA1c exceeds the 7.5% threshold, they switch to a rescue therapy of which the patient remains for the rest of the simulation. In the base case analyses the rescue therapy would be insulin-based; all rescue therapies have identical treatment effect.

### *3.1.1. Model outcomes*

Model outputs were reported in full for the base case analyses:

- Per patient costs over time horizon
- Per patient life year (LY)
- Per patient quality-adjusted life year (QALYs)
- Incremental costs per life year gained and per QALY gained
- Breakdown of direct costs
- Effect on HbA1c and body mass index (BMI)
- Time free of diabetes complications
- Cumulative incidence of diabetes complications

## 3.2. Base-case analyses

Analyses settings for the base-case comparisons are outlined below.

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The analyses comprised empagliflozin (10mg and 25mg) against other within-class expected direct comparators of empagliflozin, i.e. canagliflozin (100mg and 300mg) and dapagliflozin 10mg as follows: (add full scope of analyses for populations I to IV)

**Table 1: Base case analyses - Populations I-IV**

| Population I: Patients who are no longer responding adequately to metformin (MET) |
|---|
| • Empagliflozin 10mg (+MET) vs. Dapagliflozin 10mg (+MET)<br>• Empagliflozin 25mg (+MET) vs. Dapagliflozin 10mg (+MET)<br>• Empagliflozin 10mg (+MET) vs. Sitagliptin 100mg (+MET)<br>• Empagliflozin 25mg (+MET) vs. Sitagliptin 100mg (+MET)<br>• Empagliflozin 10mg (+MET) vs. Canagliflozin 100mg (+MET)<br>• Empagliflozin 25mg (+MET) vs. Canagliflozin 100mg (+MET)<br>• Empagliflozin 10mg (+MET) vs. Canagliflozin 300mg (+MET)<br>• Empagliflozin 25mg (+MET) vs. Canagliflozin 300mg (+MET) |
| Population II: Patients who are no longer responding adequately to MET plus Sulfonylurea (SU) |
| • Empagliflozin 10mg (+MET+SU) vs. Sitagliptin 100mg (+MET+SU)<br>• Empagliflozin 25mg (+MET+SU) vs. Sitagliptin 100mg (+MET+SU)<br>• Empagliflozin 10mg (+MET+SU) vs. Canagliflozin 100mg (+MET+SU)<br>• Empagliflozin 25mg (+MET+SU) vs. Canagliflozin 100mg (+MET+SU)<br>• Empagliflozin 10mg (+MET+SU) vs. Canagliflozin 300mg (+MET+SU)<br>• Empagliflozin 25mg (+MET+SU) vs. Canagliflozin 300mg (+MET+SU) |
| Population III: Patients who are no longer responding adequately to any thiazolidinedione (TZD) |
| • Empagliflozin 10mg (+MET+TZD) vs. Sitagliptin 100mg (+MET+TZD)<br>• Empagliflozin 25mg (+MET+TZD) vs. Sitagliptin 100mg (+MET+TZD)<br>• Empagliflozin 10mg (+MET+TZD) vs. Canagliflozin 100mg (+MET+TZD)<br>• Empagliflozin 25mg (+MET+TZD) vs. Canagliflozin 300mg (+MET+TZD) |
| Population IV: Patients who are no longer responding adequately to any insulin therapy (INS) |
| • Empagliflozin 10mg (+INS) vs. Dapagliflozin 10mg (+INS)<br>• Empagliflozin 25mg (+INS) vs. Dapagliflozin 10mg (+INS)<br>• Empagliflozin 10mg (+INS) vs. Sitagliptin 100mg (+INS)<br>• Empagliflozin 25mg (+INS) vs. Sitagliptin 100mg (+INS)<br>• Empagliflozin 10mg (+INS) vs. Canagliflozin 100mg (+INS)<br>• Empagliflozin 25mg (+INS) vs. Canagliflozin 100mg (+INS)<br>• Empagliflozin 10mg (+INS) vs. Canagliflozin 300mg (+INS)<br>• Empagliflozin 25mg (+INS) vs. Canagliflozin 300mg (+INS) |

### *3.2.1. Perspective*

The analyses were conducted from the UK NHS healthcare payer perspective capturing direct medical costs only (pharmacy costs plus complication and management costs).

### *3.2.2. Patient population*

The patient population comprised adults with T2D. The analysis was conducted for a closed cohort of patients. A closed cohort simulation involved the definition of a cohort with certain

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baseline characteristics which was simulated until the defined time horizon was reached, or until all patients in the cohort have died. No additional patients were included in the simulation at the start of each year of the simulation. To reflect the differences in terms of patient characteristics, separate cohorts for dual and triple therapy regimens were assumed.

### *3.2.3. Time horizon and discounting*

A lifetime time horizon was adopted to reflect all important differences in costs or outcomes between the technologies being compared in accordance with NICE recommendations (6). Annual discount rates of 3.5% were applied for both costs and outcomes.

### *3.2.4. Treatment pathways*

A treatment line algorithm was chosen for all comparisons in which a simulated patient progressed from one treatment to the full uptake of insulin after HbA1c has reached the threshold of 7.5%.

### *3.2.5. Sensitivity analysis*

A series of one-way sensitivity analyses were conducted to assess the robustness of model outputs to plausible changes in key model parameters. Two sets of sensitivity analyses were performed:

In treatment comparator pairs where there was no efficacy data for comparator treatment equivalent efficacy was assumed in base case. In sensitivity analysis such treatment effects were set to 0. BMI convergence was assumed (a detailed description to BMI convergence is provided in the *Sensitivity Analysis* section of the report).

Probabilistic sensitivity analyses (PSA) have been conducted for treatment and comparator pairs

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# 4. Model Inputs

## 4.1. Baseline characteristics

Cohorts, defined in terms of age, gender, baseline risk factors and pre-existing complications, were designed for dual and triple therapy based regimens separately. The baseline cohort characteristics used by BI were incorporated to the CDM where possible[2].

In the dual therapy regimen analyses, patients were on average approximately 56 years of age with an HbA1c of 7.5%, reported a mean duration of diabetes of 5 years and had a mean BMI of 27.5 kg/m$^2$. Patients' characteristics in the triple therapy cohort were similar to those in the dual therapy cohort: the mean value of HbA1c was assumed equal (7.5%); the mean age was similar (56 and 58 respectively), and the duration of diabetes was assumed to be the same (5 years). The 3rd line cohort contained a larger proportion of Asian population. Baseline levels of SBP were similar between the cohorts, and the levels of lipids were assumed equivalent. The prevalence/history of diabetes complications at start was assumed equal in both cohorts.

The baseline patient characteristics used in the analyses for both dual and triple therapy are presented in Table 2. Dual therapy cohort was used for comparisons based on metformin background and triple therapy cohort was used for comparisons based on background of metformin plus sulfonylurea, metformin plus insulin.

**Table 2 Baseline characteristics of the cohorts**

| Parameter | Mean (SD) | | Source |
|---|---|---|---|
| | Dual therapy cohort | Triple therapy and higher cohort | |
| HbA1c (%) | 7.5 | 7.50 (1.53) | Provided by BI |
| Age (years) | 55.9 (0.26) | 58.0 (0.00) | Provided by BI |
| Duration of diabetes (years) | 5.00 | 5.00 | Provided by BI |
| Male (proportion) | 0.549 | 0.610 | Provided by BI |
| Ethnicity (proportion)[1] | | | |
| Caucasian | 0.973 | 0.82 | Provided by BI |
| African-descent | 0.012 | 0.08 | Provided by BI |
| Hispanic | 0.00 | 0.00 | Assumed |
| Native American | 0.00 | 0.00 | Assumed |
| Asian/Pacific Islander and other | 0.015 | 0.10 | Provided by BI |
| Systolic blood pressure (mmHg) | 135.00 (20.00) | 140.00(10.20) | Provided by BI |
| Baseline total cholesterol (mg/dL) | 192.80 (44.70) | 192.80(44.70) | (7) |
| Baseline HDL-C (mg/dL) | 38.20 (0.00) | 43.82 (0.00) | Calculated based on data provided by BI for the ratio of total cholesterol and HDL |

[2] The characteristics of the cohorts are the same as those used in the CDM analysis conducted for Boehringer Ingelheim earlier in 2014

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| Parameter | Mean (SD) | | Source |
|---|---|---|---|
| | Dual therapy cohort | Triple therapy and higher cohort | |
| Baseline LDL-C (mg/dL) | 110.00(36.70) | 110.00 (36.70) | (7) |
| Baseline triglycerides (mg/dL) | 147.00 | 147.00 | (7) |
| Body mass index (kg/m$^2$) | 27.50 (5.20) | 30.42(3.06) | Provided by BI |
| Proportion smoker | 0.31 | 0.31 | Provided by BI |
| Cigarettes per day | 11 | 11 | (8) |
| Alcohol consumption (Oz per week) | 7.9 | 7.9 | (9) |
| **Prevalent conditions** | **Proportion** | | |
| Myocardial infarction | 0.0350 | 0.0350 | (10) |
| Angina | 0.000 | 0.000 | (11) |
| Peripheral vascular disease | 0.235 | 0.235 | Provided by BI |
| Stroke | 0.012 | 0.012 | Provided by BI |
| Congestive heart failure | 0.007 | 0.007 | Provided by BI |
| Atrial fibrillation | 0.0062 | 0.0062 | Provided by BI |
| Left ventricular hypertrophy | 0.042 | 0.042 | (12) |
| Microalbuminuria | 0.313 | 0.313 | (7) |
| Gross proteinuria | 0.077 | 0.077 | (7) |
| End-stage renal disease | 0.001 | 0.001 | Provided by BI[2] |
| Background diabetic retinopathy | 0.331 | 0.331 | (13) [3] |
| Proliferative diabetic retinopathy | 0.071 | 0.071 | (14) |
| Severe vision loss | 0.012 | 0.012 | Provided by BI [4] |
| Macular odema | 0.090 | 0.090 | (15) |
| Cataract | 0.110 | 0.110 | (15) |
| Uninfected ulcer | 0.000 | 0.000 | Assumed |
| Infected ulcer | 0.000 | 0.000 | Assumed |
| Healed ulcer | 0.146 | 0.146 | (16) |
| Amputation | 0.004 | 0.004 | Provided by BI |
| Neuropathy | 0.430 | 0.430 | (15) |

[1] The *prop. white* was adjusted so that the sum of all proportions equals 1
[2] Assumed same as percentage as those with renal failure
[3] Source reported 40.2% of the patients had any retinopathy, from those a total of 7.2% (4.1% males and 3.1% females) were excluded as they were suffering from macular oedema
[4] Assumed same as percentage of those who have experienced blindness on one eye

## 4.2. Treatment effects

Treatment effects were applied in the first year of treatment. In the subsequent years, physiological variables were modelled to change over time based on patterns of progression, and were also affected by a transition to full uptake of insulin. In the model, the treatment effects and the rates of adverse events were estimated for 52 weeks duration for patients who no longer

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respond to MET for patients who no longer respond to MET+SU; for the other two populations (patients who no longer respond to MET+TZD and patients who no longer respond to backbone insulin) treatment effects at 24 weeks were applied (in the absence of 52-week data); the rates of adverse events reported for 24 weeks were adjusted to the 52 week duration of the CDM cycle length.

### *4.2.1. HbA1c*

The CDM default progression (UKPDS-62) (a random-effects regression function based on panel data derived from the UKPDS Outcomes Model) approach was applied to predict the progression of HbA1c over time (17).

### *4.2.2. Systolic blood pressure (SBP)*

SBP was altered over time using a regression function derived from the UKPDS Outcomes Model (17). Microvascular complications, angina, heart failure, first stroke, first myocardial infarction, onset of vision loss and peripheral vascular disease onset were all influenced by the SBP.

### *4.2.3. Lipids*

The impact of treatment on the level of triglycerides, total cholesterol, HDL-c and LDL-c was not included in the analysis due to lack of data from the NMA.

### *4.2.4. Body Mass Index (BMI)*

Data on treatment effects on weight from the mixed treatment comparison was used to derive the treatment effects on BMI. The following formula was used to calculate BMI:

BMI=body weight/body height$^2$,

where body weight is measured in kilograms and height is measured in metres (m).

Average body height estimates of 1.77 m for men and 1.63 m for women were provided by BI. Based on a proportion of 54.9% of males used in the analysis, a weighted average of 1.71 m for height was derived. There was no BMI progression equations based on UKPDS or Framingham Heart Study data that have been implemented in the IMS CORE Diabetes Model. No change in BMI over time was modelled.

Clinical inputs (mean changes from baseline) used in the analyses are reported in summary in the tables below. Data were derived on the basis of a mixed treatment comparison provided by BI..

### *4.2.5. Clinical inputs*

Table 3, Table 4, Table 5 and Table 6 summarise the treatment effects and the probabilities and rates of adverse events uses as the model inputs. The green-shaded cells indicate which component in a treatment comparator pair has favourable outcome vs its comparator.

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**Table 3: Patients who are no longer responding adequately to MET**

| Comparator arm | ΔHbA1c (%-points) | ΔSBP (mmHg) | ΔBMI (kg/m$^2$) | non-severe hypo events | Severe hypo events[3] | Urinary Tract Infection[4] | Genital Tract Infection[5] |
|---|---|---|---|---|---|---|---|
| ***Empagliflozin 10mg vs. Dapagliflozin 10mg*** | | | | | | | |
| Empagliflozin 10mg | -0.58 | -2.89 | -0.60 | 5.87 | 0 | 7.67 | 0.08 |
| Dapagliflozin 10 mg | -0.47 | -3.80 | -0.76 | 2.93 | 0 | 10.08 | 0.12 |
| ***Empagliflozin 25mg vs. Dapagliflozin 10mg*** | | | | | | | |
| Empagliflozin 25mg | -0.62 | -4.49 | -0.80 | 4.31 | 0 | 7.35 | 0.10 |
| Dapagliflozin 10 | -0.47 | -3.80 | -0.76 | 2.93 | 0 | 10.08 | 0.12 |
| ***Empagliflozin 10mg vs. Sitagliptin 100mg*** | | | | | | | |
| Empagliflozin 10mg | -0.58 | -2.89 | -0.60 | 5.87 | 0 | 7.67 | 0.08 |
| Sitagliptin 100mg | -0.52 | 0.60 | +0.02 | 0.98 | 0 | 6.11 | 0.00[6] |
| ***Empagliflozin 25mg vs. Sitagliptin 100mg*** | | | | | | | |
| Empagliflozin 25mg | -0.62 | -4.49 | -0.80 | 4.31 | 0 | 7.35 | 0.10 |
| Sitagliptin 100mg | -0.52 | 0.60 | 0.02 | 0.98 | 0 | 6.11 | 0.00[7] |
| ***Empagliflozin 25mg vs. Canagliflozin 100mg*** | | | | | | | |
| Empagliflozin 25mg | -0.62 | -4.49 | -0.80 | 4.31 | 0 | 7.35 | 0.10 |
| Canagliflozin 100mg | -0.52 | -2.25 | -0.68 | 4.31 | 0 | 7.35 | 0.06 |
| ***Empagliflozin 25mg vs. Canagliflozin 300mg*** | | | | | | | |
| Empagliflozin 25mg | -0.62 | -4.49 | -0.80 | 4.31 | 0 | 7.35 | 0.10 |
| Canagliflozin 300mg | -0.65 | -3.42 | -0.80 | 4.31 | 0 | 7.35 | 0.06 |

[3] No difference in the rates of severe hypoglycemic events (SHE) assumed; all the rates of SHE were set to 0 in this population
[4] Expressed in rates, per 100 pt/year, in this and subsequent tables
[5] Expressed as probability of having GTI, in this and subsequent tables
[6] Assumed null
[7] Assumed null

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| Comparator arm | ΔHbA1c (%-points) | ΔSBP (mmHg) | ΔBMI (kg/m²) | non-severe hypo events | Severe hypo events[3] | Urinary Tract Infection[4] | Genital Tract Infection[5] |
|---|---|---|---|---|---|---|---|
| ***Empagliflozin 10mg vs. Canagliflozin 100mg*** | | | | | | | |
| Empagliflozin 10mg | -0.58 | -2.89 | 0.60 | 5.87 | 0 | 7.67 | 0.08 |
| Canagliflozin 100mg | -0.52 | -2.25 | -0.68 | 5.87 | 0 | 7.67 | 0.06 |
| ***Empagliflozin 10mg vs. Canagliflozin 300mg*** | | | | | | | |
| Empagliflozin 10mg | -0.58 | -2.89 | 0.60 | 5.87 | 0 | 7.67 | 0.08 |
| Canagliflozin 300mg | -0.65 | -3.42 | -0.80 | 5.87 | 0 | 7.67 | 0.06 |

**Note**: the numbers in the table may be rounded and the accurate numbers are entered into the model

**Table 4: Patients who are no longer responding adequately to MET+SU**

| Comparator arm | ΔHbA1c (%-points) | ΔSBP (mmHg) | ΔBMI (kg/m²) | non-severe hypo events | Severe hypo events[8] | Urinary Tract Infection | Genital Tract Infection |
|---|---|---|---|---|---|---|---|
| ***Empagliflozin 10mg vs. Sitagliptin 100mg*** | | | | | | | |
| Empagliflozin 10mg | -0.71 | -2.80 | -0.68 | 28.08 | 0 | 13.00 | 0.06 |
| Sitagliptin 100mg | -0.60 | +2.99 | 0.13 | 28.08 | 0 | 13.00 | 0.00 |
| ***Empagliflozin 25mg vs. Sitagliptin 100mg*** | | | | | | | |
| Empagliflozin 25mg | -0.69 | -2.72 | -0.70 | 23.23 | 0 | 13.00 | 0.05 |
| Sitagliptin 100mg | -0.60 | 2.99 | 0.13 | 23.23 | 0 | 13.00 | 0.00 |
| ***Empagliflozin 10mg vs. Canagliflozin 100mg*** | | | | | | | |
| Empagliflozin 10mg | -0.71 | -2.80 | -0.68 | 28.08 | 0 | 13.00 | 0.05 |
| Canagliflozin 100mg | -0.75 | -3.82 | -0.435 | 31.37 | 0 | 13.00 | 0.06 |

[8] No difference in the rates of severe hypoglycemic events (SHE) assumed; all the rates of SHE were set to 0 in this population

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| Comparator arm | ΔHbA1c (%-points) | ΔSBP (mmHg) | ΔBMI (kg/m²) | non-severe hypo events | Severe hypo events[8] | Urinary Tract Infection | Genital Tract Infection |
|---|---|---|---|---|---|---|---|
| ***Empagliflozin 25mg vs. Canagliflozin 300mg*** | | | | | | | |
| Empagliflozin 25mg | -0.69 | -2.72 | -0.70 | 23.23 | 0 | 13.00 | 0.05 |
| Canagliflozin 300mg | -0.97 | -3.00 | -0.77 | 26.17 | 0 | 13.00 | 0.06 |
| ***Empagliflozin 10mg vs. Canagliflozin 300mg*** | | | | | | | |
| Empagliflozin 10mg | -0.71 | -2.80 | -0.68 | 28.08 | 0 | 13.00 | 0.06 |
| Canagliflozin 300mg | -0.97 | -3.00 | -0.77 | 26.17 | 0 | 13.00 | 0.06 |
| ***Empagliflozin 25mg vs. Canagliflozin 100mg*** | | | | | | | |
| Empagliflozin 25mg | -0.69 | -2.72 | -0.70 | 23.23 | 0 | 13.00 | 0.05 |
| Canagliflozin 100mg | -0.75 | -3.82 | -0.435 | 31.37 | 0 | 13.00 | 0.06 |

**Table 5 Patients who are no longer responding adequately to MET+TZD**

| Comparator arm | ΔHbA1c (%-points) | ΔSBP (mmHg) | ΔBMI (kg/m²) | non-severe hypo events | Severe hypo events[9] | Urinary Tract Infection | Genital Tract Infection |
|---|---|---|---|---|---|---|---|
| ***Empagliflozin 10mg vs. Sitagliptin 100mg*** | | | | | | | |
| Empagliflozin 10mg | -0.44 | -4.24 | -0.73 | 6.50 | 0 | 2.17 | 0.18 |
| Sitagliptin 100mg | -0.70 | -4.24 | 0.07 | 6.50 | 0 | 2.17 | 0.00 |
| ***Empagliflozin 25mg vs. Sitagliptin 100mg*** | | | | | | | |
| Empagliflozin 25mg | -0.59 | -4.06 | -0.67 | 6.50 | 0 | 2.17 | 0.08 |
| Sitagliptin 100mg | -0.70 | -4.06 | 0.07 | 6.50 | 0 | 2.17 | 0.00 |

[9] No difference in the rates of severe hypoglycemic events (SHE) assumed; all the rates of SHE were set to 0 in this population

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| Comparator arm | ΔHbA1c (%-points) | ΔSBP (mmHg) | ΔBMI (kg/m²) | non-severe hypo events | Severe hypo events[9] | Urinary Tract Infection | Genital Tract Infection |
|---|---|---|---|---|---|---|---|
| ***Empagliflozin 10mg vs. Canagliflozin 100mg*** | | | | | | | |
| Empagliflozin 10mg | -0.44 | -4.24 | -0.73 | 6.50 | 0 | 2.17 | 0.18 |
| Canagliflozin 100mg | -0.63 | -4.11 | -0.87 | 6.50 | 0 | 2.17 | 0.06 |
| ***Empagliflozin 25mg vs. Canagliflozin 100mg*** | | | | | | | |
| Empagliflozin 25mg | -0.59 | -4.06 | -0.67 | 6.50 | 0 | 2.17 | 0.08 |
| Canagliflozin 100mg | -0.63 | -4.11 | -0.87 | 6.50 | 0 | 2.17 | 0.06 |
| ***Empagliflozin 10mg vs. Canagliflozin 300mg*** | | | | | | | |
| Empagliflozin 10mg | -0.44 | -4.24 | -0.73 | 6.50 | 0 | 2.17 | 0.18 |
| Canagliflozin 300mg | -0.77 | -3.54 | -1.19 | 6.50 | 0 | 2.17 | 0.06 |
| ***Empagliflozin 25mg vs. Canagliflozin 300mg*** | | | | | | | |
| Empagliflozin 25mg | -0.59 | -4.06 | -0.67 | 6.50 | 0 | 2.17 | 0.08 |
| Canagliflozin 300mg | -0.77 | -3.54 | -1.19 | 6.50 | 0 | 2.17 | 0.06 |

**Table 6 Patients who are no longer responding adequately to any insulin therapy (INS)**

| Comparator arm | ΔHbA1c (%-points) | ΔSBP (mmHg) | ΔBMI (kg/m²) | non-severe hypo events | Sever Hypo Events[10] | Urinary Tract Infection | Genital Tract Infection |
|---|---|---|---|---|---|---|---|
| ***Empagliflozin 10mg vs. Dapagliflozin 10mg*** | | | | | | | |
| Empagliflozin 10mg | -0.50 | -2.86 | -0.49 | 53.56 | 4.33 | 10.73 | 0.09 |
| Dapagliflozin 10 mg | -0.57 | -3.13 | -0.70 | 56.68 | 4.33 | 12.09 | 0.06 |

[10] No difference in the rates of severe hypoglycemic events (SHE) assumed; all the rates of SHE were set to baseline (placebo) in this population

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| Comparator arm | ΔHbA1c (%-points) | ΔSBP (mmHg) | ΔBMI (kg/m$^2$) | non-severe hypo events | Sever Hypo Events[10] | Urinary Tract Infection | Genital Tract Infection |
|---|---|---|---|---|---|---|---|
| ***Empagliflozin 25mg vs. Dapagliflozin 10mg*** | | | | | | | |
| Empagliflozin 25mg | -0.57 | -2.27 | -0.57 | 62.40 | 4.33 | 9.30 | 0.21 |
| Dapagliflozin 10 mg | -0.57 | -3.13 | -0.70 | 56.68 | 4.33 | 12.09 | 0.06 |
| ***Empagliflozin 10mg vs. Sitagliptin 100mg*** | | | | | | | |
| Empagliflozin 10mg | -0.50 | -2.86 | -0.49 | 53.56 | 4.33 | 10.73 | 0.09 |
| Sitagliptin 100mg | -0.60 | -2.86 | 0.00 | 53.56 | 4.33 | 10.73 | 0.00 |
| ***Empagliflozin 25mg vs. Sitagliptin 100mg*** | | | | | | | |
| Empagliflozin 25mg | -0.57 | -2.27 | -0.57 | 62.40 | 4.33 | 9.30 | 0.21 |
| Sitagliptin 100mg | -0.60 | -2.27 | 0.00 | 62.40 | 4.33 | 9.30 | 0.00 |
| ***Empagliflozin 25mg vs. Canagliflozin 100mg*** | | | | | | | |
| Empagliflozin 25mg | -0.57 | -2.27 | -0.57 | 62.40 | 4.33 | 9.30 | 0.21 |
| Canagliflozin 100mg | -0.64 | -2.63 | -0.63 | 76.44 | 4.33 | 9.30 | 0.06 |
| ***Empagliflozin 25mg vs. Canagliflozin 300mg*** | | | | | | | |
| Empagliflozin 25mg | -0.57 | -2.27 | -0.57 | 62.40 | 4.33 | 9.30 | 0.21 |
| Canagliflozin 300mg | -0.73 | -4.40 | -0.79 | 73.84 | 4.33 | 9.30 | 0.06 |
| ***Empagliflozin 10mg vs. Canagliflozin 100mg*** | | | | | | | |
| Empagliflozin 10mg | -0.50 | -2.86 | -0.49 | 53.56 | 4.33 | 10.73 | 0.09 |
| Canagliflozin 100mg | -0.64 | -2.63 | -0.63 | 76.44 | 4.33 | 10.73 | 0.06 |
| ***Empagliflozin 10mg vs. Canagliflozin 300mg*** | | | | | | | |
| Empagliflozin 10mg | -0.50 | -2.86 | -0.49 | 53.56 | 4.33 | 10.73 | 0.09 |
| Canagliflozin 300mg | -0.73 | -4.40 | -0.79 | 73.84 | 4.33 | 10.73 | 0.06 |

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*Changes in HDL cholesterol, LDL cholesterol and triglycerides are not included due to lack of data from the NMA.

## 4.3. Utilities

Quality-adjusted life expectancy (measured in QALYs, discounted at 3.5%) was calculated as a function of the states of diabetic complications reached during a given year of simulation, plus the effects of any event that may occur during that year. The minimum approach was used by default, whereby if a patient had a history of multiple events, the lower of the multiple health state utility values was applied. This method assumed that the most severe condition would dominate and other conditions would have a negligible impact on quality of life. Utility decrements associated with myocardial infarction (MI), stroke, amputation, major hypoglycaemia, GTI and UTI used in the BI analysis were incorporated to the CDM. The default settings of the CDM were used for the remaining utility data inputs.

**Table 7 Health state and treatment related utilities**

| Health state | Utility value (mean) | Range | Reference |
|---|---|---|---|
| Type 2 no complications | 0.8140 | [0-1] | IMS CDM Default |
| Myocardial infarction event | -0.0550 | [-1-0] | Provided by BI (18) |
| Post myocardial infarction | 0.7360 | [0-1] | (19) |
| Angina | 0.6820 | [0-1] | (19) |
| Congestive heart failure | 0.6330 | [0-1] | (19) |
| Stroke event | -0.1640 | [-1-0] | Provided by BI (18) |
| Post stroke | 0.5450 | [0-1] | (19) |
| Peripheral vascular disease | 0.5700 | [0-1] | (20) |
| Microalbuminuria | 0.8140 | [0-1] | Assumption |
| Gross proteinuria | 0.8140 | [0-1] | Assumption |
| Haemodialysis | 0.6040 | [0-1] | (21) |
| PD | 0.6120 | [0-1] | (21) |
| RT | 0.7500 | [0-1] | (20) |
| Background diabetic retinopathy | 0.7900 | [0-1] | (22) |
| Background diabetic retinopathy wrongly treated | 0.7900 | [0-1] | (22) |
| Proliferative diabetic retinopathy laser treated | 0.7900 | [0-1] | (22) |
| Proliferative diabetic retinopathy no laser | 0.7900 | [0-1] | (22) |
| ME | 0.7900 | [0-1] | (22) |
| Severe vision loss | 0.6700 | [0-1] | (23) |
| Cataract | 0.6200 | [0-1] | (24) |
| Neuropathy | 0.6300 | [0-1] | (23) |
| Heal ulcer | 0.8140 | [0-1] | Assumption |
| Active ulcer | 0.7500 | [0-1] | (25) |
| Amputation event | -0.2800 | [-1-0] | Provided by BI |
| Post amputation | 0.4020 | [0-1] | (19) |

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| Health state | Utility value (mean) | Range | Reference |
|---|---|---|---|
| Major hypo events | -0.0118 | [-1-0] | Provided by BI |
| Minor hypo events | -0.0035 | [-1-0] | Provided by BI |
| Keto event | 0.0000 | [0-1] | Not included in the analysis |
| Lactic acidosis event* | -0.0028 | [-1-0] | Provided by BI |
| Fear of hypoglycemic event | 0.0000 | [0-1] | Not included in the analysis |
| Oedema event (adv.ev.) ** | -0.0028 | [-1-0] | Provided by BI |
| Post oedema (adv.ev.) | 0.8168 | [0-1] | Assumption*** |

* Used as a placeholder for GTI; ** Used as a placeholder for UTI; *** Calculated as subtracting the UTI (oedema event) utility from the utility of the Type 2 no complications utility

## 4.4. Costs

Direct costs only were considered in the analysis.

### *4.4.1. Cost of comparator drugs and consumables*

Empagliflozin and canagliflozin are yet to receive marketing authorisation in Europe. A provisional assumption of price parity to 28 tablets of dapagliflozin 10mg was applied.

The cost of insulin was derived as a weighted average annual cost of insulin based on prescribing data and NHS list prices. This cost is referenced in the linagliptin Advanced Product Notification documents for England, Scotland, Wales and Northern Ireland.

NHS prescribing data were adapted from CSD Patient Data, Cegedim Strategic Data UK Ltd, annual data (MAT) for the 12 months to April 2010. CSD patient data were extracted from a longitudinal database which contains the primary care records of 1.3 million patients in the UK, from 150 GP practices. In line with the methods used in the NICE Clinical Guideline 66 to estimate insulin costs, only drug costs and the cost of testing strips have been included. Costs relating to devices, patient education and visits are not included in this analysis so the true cost of insulin is likely to be significantly higher; Annual needle and test strips were included in the cost of intravenous insulin, where applicable. Oral anti-diabetic drug costs did not account for those costs.

### *4.4.2. Drug prices*

The following annual drug prices were applied in the analysis.

| Backbone | Treatment | Cost per year, GBP |
|---|---|---|
| **Population I** [11] | | |
| Metformin | Empagliflozin 10 | 486.2495 |
| Metformin | Empagliflozin 25 | 486.2495 |
| Metformin | Canagliflozin 100 mg | 486.2060 |

[11] Patients who are no longer responding adequately to metformin (MET)

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| Backbone | Treatment | Cost per year, GBP |
|---|---|---|
| Metformin | Canagliflozin 300 mg | 617.5743 |
| Metformin | Dapagliflozin 10 | 486.2495 |
| Metformin | Sitagliptin 100 mg | 442.8108 |
| **Population II** [12] | | |
| Metformin | Empagliflozin 10 | 505.8512 |
| Metformin | Empagliflozin 25 | 505.8512 |
| Metformin | Canagliflozin 100 mg | 505.8078 |
| Metformin | Canagliflozin 300 mg | 637.1760 |
| Metformin | Sitagliptin 100 mg | 462.4126 |
| **Population III** [13] | | |
| Metformin | Empagliflozin 10 | 522.3832 |
| Metformin | Empagliflozin 25 | 522.3832 |
| Metformin | Canagliflozin 100 mg | 522.3397 |
| Metformin | Canagliflozin 300 mg | 653.7079 |
| Metformin | Sitagliptin 100 mg | 478.9445 |
| **Population IV** [14] | | |
| Insulin | Empagliflozin 10 | 873.5131 |
| Insulin | Empagliflozin 25 | 873.5131 |
| Insulin | Canagliflozin 100 mg | 873.4696 |
| Insulin | Canagliflozin 300 mg | 1004.8379 |
| Insulin | Sitagliptin 100 mg | 830.0745 |
| Insulin | Dapagliflozin | 873.5131 |
| **All populations** | Rescue therapies | 405.1600 |

Source: Boehringer Ingelheim, September 2014

### *4.4.3. Cost of complications*

The annual estimated cost of complications is presented in Table 8 below. These costs are applicable across all the comparisons included conducted. Unit costs were inflated to 2013.

**Table 8 Cost of complications**

| MANAGEMENT COSTS | Unit cost (£) | Reference |
|---|---|---|
| Annual statins[1] | 13.70 | (26) |
| Annual aspirin[2] | 10.45 | (26) |
| Annual ACE-I | 16.70 | (26) |
| Annual eye screening | 54.35* | (27) |
| Annual screening for MA | 9.78 | Calculated |

[12] Patients who are no longer responding adequately to MET plus Sulfonylurea (SU)
[13] Patients who are no longer responding adequately to any thiazolidinedione (TZD)
[14] Patients who are no longer responding adequately to any insulin therapy (INS)

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| MANAGEMENT COSTS | Unit cost (£) | Reference |
|---|---|---|
| Annual screening for GRP | 9.76 | Calculated |
| Annual foot screening program | 0 | Assumption |
| Stopping ACE due to SE | 0 | Assumption |
| Non-standard ulcer treatment (eg. Regranex) | 0 | Assumption |
| **DIRECT COSTS CVD COMPLICATIONS** | | |
| Myocardial infarction 1st year | 8,179.41 | Provided by BI |
| Myocardial infarction 2nd+ years | 5,773.99 | Provided by BI |
| Angina 1st year | 3,644.20 | (28) |
| Angina 2nd+ years | 1,203.51 | (28) |
| Congestive heart failure 1st year | 6,773.98 | Provided by BI |
| Congestive heart failure 2nd+ years | 6,565.65 | Provided by BI |
| Stroke 1st year | 10,932.60 | Provided by BI |
| Stroke 2nd+ years | 4,759.57 | Provided by BI |
| Stroke death within 30 days | 6,773.98 | Provided by BI |
| Peripheral vascular disease 1st year | 4,465.43 | (29) |
| Peripheral vascular disease 2nd+ years | 919.67 | (29) |
| **DIRECT COSTS RENAL COMPLICATIONS** | | |
| Haemodialysis 1st year | 25,878* | (30) |
| Haemodialysis 2+ years | 25,878* | (30) |
| Peritoneal Dialysis 1st year | 21,610* | (30) |
| Peritoneal Dialysis 2+ years | 21,610* | (30) |
| Renal transplant costs 1st year | 40,828* | (31) |
| Renal transplant 2+ years | 7,877* | (31) |
| **DIRECT COSTS ACUTE EVENTS** | | |
| Major hypoglycaemia (per event) | 90.00 | Provided by BI |
| Minor hypoglycaemia (per event) | 0.00 | Provided by BI |
| Lactic acid event | 36.00 | Provided by BI |
| Oedema onset (per event) | 36.00 | Provided by BI |
| Oedema follow-up | 0.00 | Assumption |
| **DIRECT COSTS EYE DISEASE** | | |
| Laser treatment | 149.00 | (32) |
| Cataract operation | 2,489* | (28) |
| Cost following cataract operation | 168* | (28) |
| Cost blindness - year of onset | 7,003 | Provided by BI |
| Cost blindness - following years | 4,720 | Provided by BI |
| **DIRECT COSTS NEUROP/FOOT ULCER/AMP** | | |
| Neuropathy 1st year | 361.60* | (26) |
| Neuropathy 2nd+ years | 361.60* | (26) |
| Amputation (per event) | 13,556 | (33) |

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| MANAGEMENT COSTS | Unit cost (£) | Reference |
|---|---|---|
| Amputation prosthesis (per event) | 12,785* | (28) |
| Gangrene treatment | 10,304* | (34) |
| Healed ulcer | 21.90* | (34) |
| Infected ulcer | 4,470* | (34) |
| Standard uninfected ulcer | 3,980* | (34) |
| Healed ulcer history of amputation | 0* | (34) |

ACE-I: Angiotensin-converting enzyme inhibitor; MA: Microalbuminuria; GRP: Gross proteinuria, *Costs inflated to 2012 based on PSSRU inflation rates. ** Calculated as sum of annual cost of Albustics® and one nurse (GP practice) visit procedure. † Calculated as sum of annual cost of Medi-Test® Protein 2 (BHR) and one nurse (GP practice) visit procedure. ‡ Assumed to be routine part of care. § Regranex (becaplermin) is withdrawn from use in the EU (European Medicines Agency); discontinued from the market in the UK in July 2011.

There is insufficient evidence to support the effectiveness of any type of protective dressing, or topical application, over any other for treating diabetic foot ulcers[15].

## 4.5. Other clinical inputs to the CORE model

The default setting of the IMS CORE was used in the base case analyses.

**Table 9 Other clinical inputs to the CORE model (management of T2DM patients)**

| | Mean | Units/Range | Source |
|---|---|---|---|
| Concomitant medication | | | |
| Prop 1° prevention ASP | 0.551 | [0-1] | (35) |
| Prop 2° prevention ASP | 0.939 | [0-1] | (36) |
| Prop 1° prevention Statins | 0.370 | [0-1] | (35) |
| Prop 2° prevention Statins | 0.884 | [0-1] | (36) |
| Prop 1° prevention ACE-I | 0.170 | [0-1] | (35) |
| Prop 2° prevention ACE-I | 0.770 | [0-1] | (36) |
| Screening and patient management proportions | | | |
| Prop on foot ulcer prevention program | 0.862 | [0-1] | |
| Prop screened eye disease | 0.828 | [0-1] | |
| Prop screened for renal disease | 0.938 | [0-1] | |
| Prop receiving intensive insulin after MI | 1.000 | [0-1] | Assumption |
| Prop treated with extra ulcer treatment | 0.000 | [0-1] | Assumption |
| Prop screened for depression – no complications | 0.000 | [0-1] | Assumption – not included in the analysis |
| Prop screened for depression – complications | 0.000 | [0-1] | |
| Other | | | |

[15] nice.org.uk/nicemedia/live/10934/29242/29242.pdf

| | Mean | Units/Range | Source |
|---|---|---|---|
| Reduction in incidence foot ulcer with prevention programme | 0.700 | [0-1] | |
| Improvement in ulcer healing rate with extra ulcer treatment | 1.390 | multiplier | |
| Reduction in amputation rate with foot care | 0.700 | [0-1] | |
| Sensitivity eye screening | 0.920 | [0-1] | (37) |
| Specificity eye screening | 0.960 | [0-1] | (37) |
| Sensitivity GRP screening | 0.830 | [0-1] | (38) |
| Sensitivity MA screening | 0.830 | [0-1] | (38) |
| Specificity MA screening | 0.960 | [0-1] | (38) |

## 4.6. Mortality

### *4.6.1. Non-specific mortality*

Non-specific mortality for the UK was incorporated to the CDM based on 2010-2012 data from the Office for National Statistics (39). Mortality data was distinguished by gender but not by racial characteristics. Caucasian, Asian and Afro-Caribbean patients were assumed not to have differences in terms of non-specific mortality. Data used is presented in XXXX Probabilities of death were presented by 5-year intervals.

**Table 10 Life tables**

| Year | $m_x$ (males) | $m_x$ (females) |
|---|---|---|
| 0 | 0.004757 | 0.003818 |
| 1 | 0.000341 | 0.000293 |
| 5 | 0.000110 | 0.000086 |
| 10 | 0.000089 | 0.000063 |
| 15 | 0.000159 | 0.000122 |
| 20 | 0.000491 | 0.000200 |
| 25 | 0.000561 | 0.000256 |
| 30 | 0.000742 | 0.000367 |
| 35 | 0.000951 | 0.000563 |
| 40 | 0.001507 | 0.000855 |
| 45 | 0.002185 | 0.001359 |
| 50 | 0.003083 | 0.002108 |
| 55 | 0.005025 | 0.003352 |
| 60 | 0.008107 | 0.005322 |
| 65 | 0.012247 | 0.007985 |
| 70 | 0.020975 | 0.013629 |
| 75 | 0.033839 | 0.022463 |
| 80 | 0.058744 | 0.041759 |

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* $m_x$ = Central rate of mortality, defined as the number of deaths at age x last birthday in the three year period to which the Interim Life Table relates divided by the average population at that age over the same period.

Source: Office of National Statistics, U.K.

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# 5. Base-case analyses results

## 5.1. Summary of costs and outcomes

The following set of tables and charts represents a summary of the results for all the treatment-comparator pairwise analyses conducted in the CDM within each of the four patient populations.

Each of the tables represents the mean discounted direct costs and the mean QALY per patient, their incremental values, and the incremental cost-effectiveness results (ICER or a statement on dominance). The subsequent sections of the report provide a detailed breakdown of costs by cost type as well the rates of different types of complications.

Detailed breakdown of costs and complication rates are available in the Excel format as generated by the CDM. These detailed tables should enable BI to interpret the results of the CDM analysis and compare the model outputs with the analysis undertaken previously.

### *5.1.1. 2nd line, patients not adequately responding to MET*

Table 11 below shows a summary of results for Population I (i.e. patients not adequately responding to MET). The results of cost-effectiveness analysis for each treatment-comparator pairs are also colour-coded

**Table 11 Base case results, 2nd line**

| | Cost | | | QALY | | | ICER |
|---|---|---|---|---|---|---|---|
| | Empagliflozin | Comparator | Difference | Empagliflozin | Comparator | Difference | |
| Empagliflozin 10mg vs. Dapagliflozin 10mg | 61,761 | 61,609 | 152 | 7.963 | 7.964 | -0.001 | Dominated [1] |
| Empagliflozin 25mg vs. Dapagliflozin 10mg | 61,535 | 61,609 | -74 | 7.995 | 7.964 | 0.031 | Dominant |

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| | Cost | | | QALY | | | ICER |
|---|---|---|---|---|---|---|---|
| | Empagliflozin | Comparator | Difference | Empagliflozin | Comparator | Difference | |
| Empagliflozin 10mg vs. Sitagliptin 100mg | 61,761 | 61,778 | -18 | 7.963 | 7.899 | 0.064 | Dominant |
| Empagliflozin 25mg vs. Sitagliptin 100mg | 61,535 | 61,778 | -243 | 7.995 | 7.899 | 0.096 | Dominant |
| Empagliflozin 25mg vs. Canagliflozin 300mg | 61,535 | 61,829 | -294 | 7.995 | 7.986 | 0.009 | Dominant |
| Empagliflozin 10mg vs. Canagliflozin 100mg | 61,761 | 61,719 | 42 | 7.963 | 7.955 | 0.008 | 5,250 |
| Empagliflozin 10mg vs. Canagliflozin 300mg | 61,761 | 61,912 | -151 | 7.963 | 7.99 | -0.027 | 5,593 [2] |
| Empagliflozin 25mg vs. Canagliflozin 100mg | 61,535 | 61,643 | -109 | 7.995 | 7.949 | 0.046 | Dominant |

**Notes**:
[1] In this Tx-Comp pair, Empagliflozin appears dominated, mainly because of higher costs. The incremental QALY of -.001 is represents an equivalent of 0.4 days and is probably not clinically meaningful.
[2] In this Tx-Comp pair, Empagliflozin treatment is associated with lower health outcomes and lower costs, and represents a trade-off between lower efficacy and cost saving.

Empagliflozin 25mg is associated with QALY gain in comparison with dapagliflozin 10mg, all doses of empagliflozin yield QALY gain vs sitagliptin; Empagliflozin is associated with QALY gains vs canagliflozin 100mg and 300mg, except for empagliflozin low dose (10mg vs canagliflozin high dose, 300mg)

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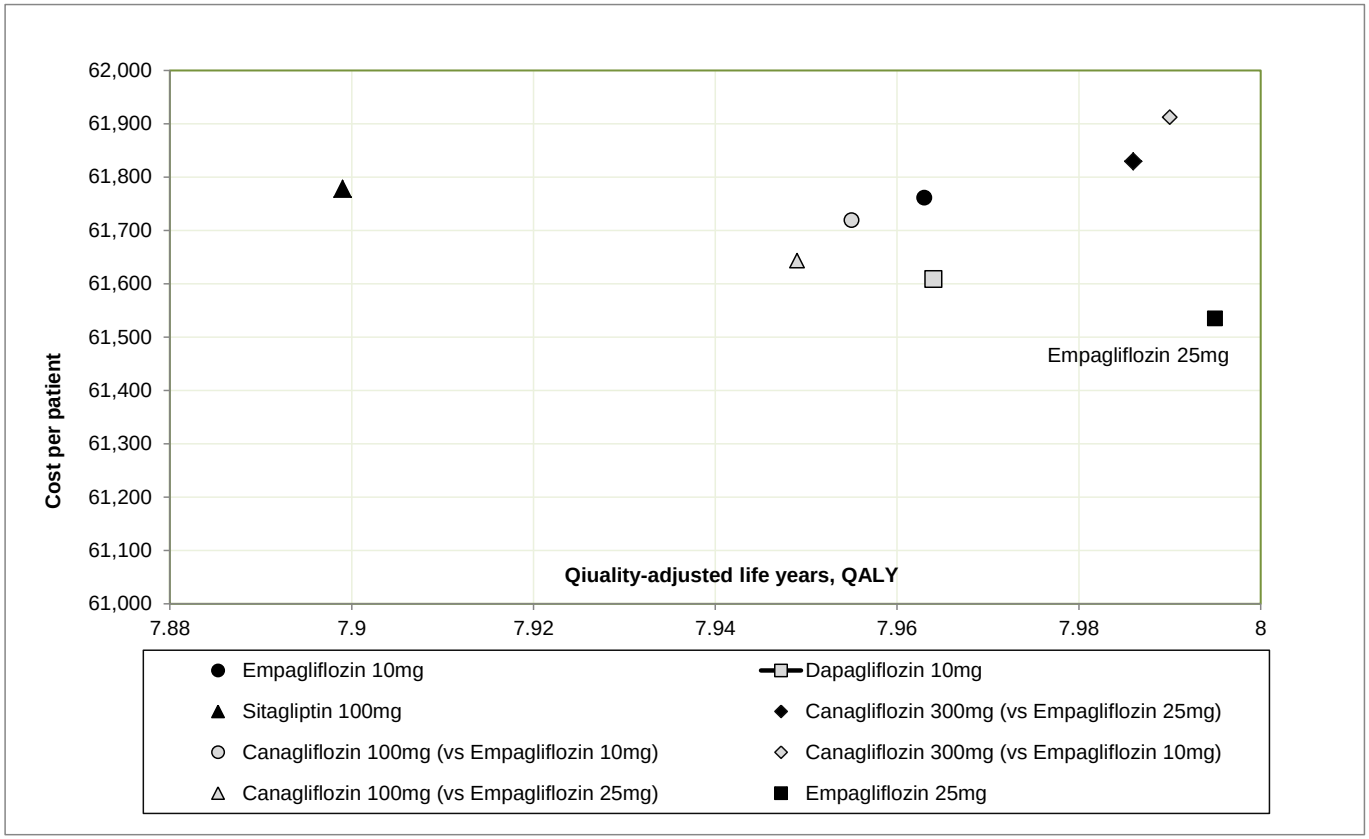
**Figure 1 Cost effectiveness plane: patients not adequately responding to MET**




The cost-effectiveness plane with point estimates for cost and QALY plotted for Population I suggests that the treatment with the lowest efficacy os sitagliptin 100mg and is dominated by the rest of the regimens. Empagliflozin 25 mg appears to be associated with the highest outcomes (QALY) within this population, however these outcomes are similar to the outcomes in Canagliflozin 300mg; the presence of the two points for Canagliflozin 300 on this diagram is explained by the pairwise comparison method (canagliflozin compared with Empagliflozin 10mg and 25 mg, where some inputs for canagliflozin were assumed to be equivalent to those in the respective dose of empagliflozin);

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### *5.1.2. 3rd line, patients not adequately responding to MET+SU*

Table 12 below shows a summary of results for Population II (i.e. patients not adequately responding to a combination treatment with MET + SU). The results of cost-effectiveness analysis for each treatment-comparator pairs are colour-coded, similar to the table for Population I.

**Table 12 Base case results, 3rd line (MET+SU)**

| | Cost | | | QALY | | | ICER |
|---|---|---|---|---|---|---|---|
| | Empagliflozin | Comparator | Difference | Empagliflozin | Comparator | Difference | |
| Empagliflozin 10mg vs. Sitagliptin 100mg | 58,778 | 59,390 | -612 | 7.571 | 7.466 | 0.105 | Dominant |
| Empagliflozin 25mg vs. Sitagliptin 100mg | 58,711 | 59,390 | -679 | 7.564 | 7.467 | 0.097 | Dominant |
| Empagliflozin 10mg vs. Canagliflozin 100mg | 58,778 | 58,794 | -16 | 7.571 | 7.569 | 0.002 | Dominant |
| Empagliflozin 25mg vs. Canagliflozin 100mg | 58,711 | 58,794 | -83 | 7.564 | 7.569 | -0.005 | 16,600 |
| Empagliflozin 10mg vs. Canagliflozin 300mg | 58,778 | 59,000 | -222 | 7.571 | 7.616 | -0.045 | 4,933 |
| Empagliflozin 25mg vs. Canagliflozin 300mg | 58,711 | 59,000 | -289 | 7.564 | 7.616 | -0.052 | 5,558 |

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In this population, empagliflozin is associated with incremental QALY of 0.105 and 0.097 vs sitagliptin 100mg for empagliflozin 10mg and 25mg respectively.
In comparison with Canagliflozin 100mg, empagliflozin 10mg is dominant, however the dominance is weak (as the difference in costs is -16GBP and QALY gain is 0.005, an equivalent of <1 day of healthy life).

In other comparisons with canagliflozin, treatment with empagliflozin (10mg and 25 mg) is associated with lower QALYs at lower costs; this puts empagliflozin in the "South-West" quadrant of the incremental cost effectiveness plane, with a trade-off between a cost saving and a reduction of outcomes.

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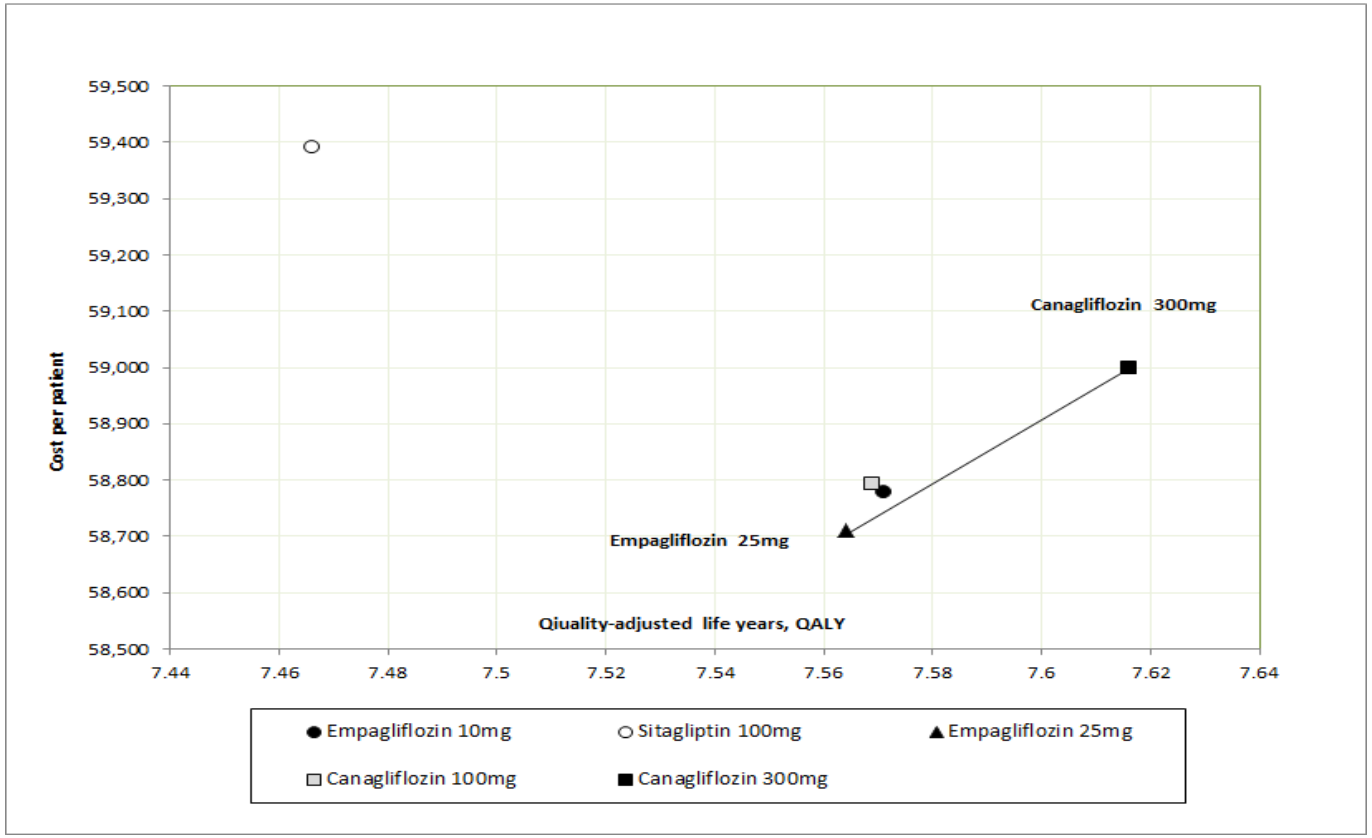
**Figure 2 Cost effectiveness plane:, patients not adequately responding to MET+SU**

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### *5.1.3. 3rd line, patients not adequately responding to MET+TZD*

**Table 13 Base case results, 3rd line (MET+TZD)**

| | Cost | | | QALY | | | ICER |
|---|---|---|---|---|---|---|---|
| | Empagliflozin | Comparator | Difference | Empagliflozin | Comparator | Difference | |
| Empagliflozin 10mg vs. Sitagliptin 100mg | 59,166 | 58,644 | 522 | 7.542 | 7.553 | -0.011 | Dominated |
| Empagliflozin 25mg vs. Sitagliptin 100mg | 58,854 | 58,644 | 210 | 7.561 | 7.553 | 0.008 | 26,250 |
| Empagliflozin 10mg vs. Canagliflozin 100mg | 59,166 | 58,751 | 415 | 7.542 | 7.579 | -0.037 | Dominated |
| Empagliflozin 25mg vs. Canagliflozin 100mg | 58,854 | 58,751 | 103 | 7.561 | 7.579 | -0.018 | Dominated |
| Empagliflozin 10mg vs. Canagliflozin 300mg | 59,166 | 59,106 | 60 | 7.542 | 7.614 | -0.072 | Dominated |
| Empagliflozin 25mg vs. Canagliflozin 300mg | 58,854 | 59,106 | -252 | 7.561 | 7.614 | -0.053 | 4,755 |

[16]

[16] The case of Empagliflozin 10 mg compared to suggest that Empagliflozin treatment is associated with lower cost but also results in lower QALY vs comparator (with the cost-effectiveness that falls into the "South-West" quadrant of the cost-effectiveness plane); In this report, such results are presented in green-shaded calls in the tables

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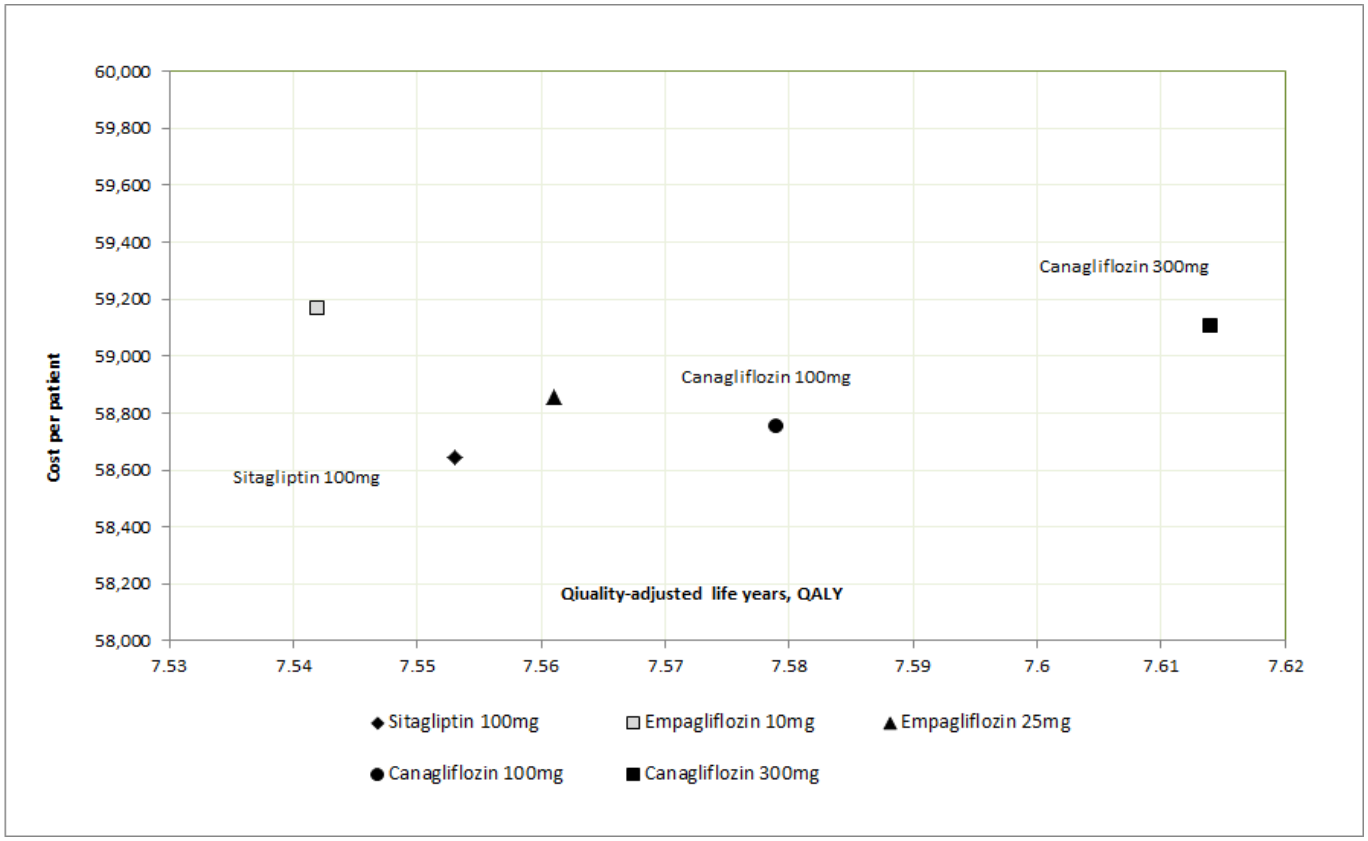
**Figure 3 Cost effectiveness plane: patients not adequately responding to MET+TZD**

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### *5.1.4. Patients not adequately responding to INS*

**Table 14 Base case results, patients not responding to backbone insulin**

| | Cost | | | QALY | | | ICER |
|---|---|---|---|---|---|---|---|
| | Empagliflozin | Comparator | Difference | Empagliflozin | Comparator | Difference | |
| Empagliflozin 10mg vs. Dapagliflozin 10mg | 60,539 | 60,360 | 179 | 7.523 | 7.545 | -0.023 | Dominated |
| Empagliflozin 25mg vs. Dapagliflozin 10mg | 60,428 | 60,360 | 68 | 7.534 | 7.545 | -0.011 | Dominated |
| Empagliflozin 10mg vs. Sitagliptin 100mg | 60,539 | 60,564 | -25 | 7.523 | 7.511 | 0.011 | Dominant |
| Empagliflozin 25mg vs. Sitagliptin 100mg | 60,428 | 60,530 | -102 | 7.534 | 7.499 | 0.036 | Dominant |
| Empagliflozin 10mg vs. Canagliflozin 100mg | 60,539 | 60,235 | 304 | 7.523 | 7.545 | -0.023 | Dominated |
| Empagliflozin 25mg vs. Canagliflozin 100mg | 60,428 | 60,333 | 95 | 7.534 | 7.551 | -0.017 | Dominated |
| Empagliflozin 10mg vs. Canagliflozin 300mg | 60,539 | 60,599 | -60 | 7.523 | 7.583 | -0.061 | 984 |

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| | **Cost** | | | **QALY** | | | **ICER** |
|---|---|---|---|---|---|---|---|
| | Empagliflozin | Comparator | Difference | Empagliflozin | Comparator | Difference | |
| Empagliflozin 25mg vs. Canagliflozin 300mg | 60,428 | 60,476 | -48 | 7.534 | 7.584 | -0.049 | 980 |

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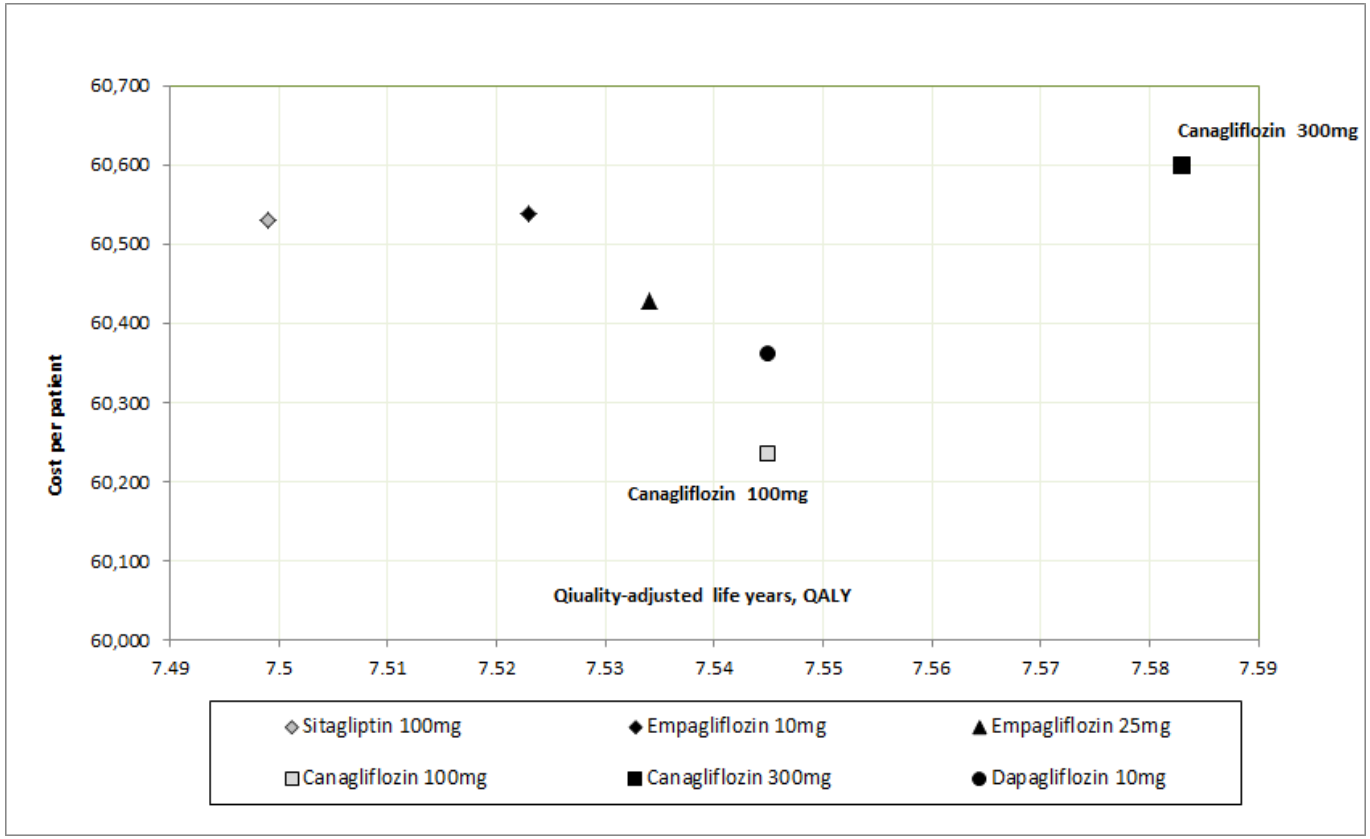
**Figure 4 Cost effectiveness plane: patients not adequately responding to INS**

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## 5.2. Detailed results: dual therapy regimens

This section is complimentary to the summary cost-effectiveness analysis above; the tables in the section provide the absolute values of the health and economics outcomes of the analysis as well as breakdown of direct costs by cost type.

### *5.2.1. Empagliflozin 10mg +MET vs. dapagliflozin 10 mg +MET*

**Table 15 Empagliflozin 10mg +MET vs. dapagliflozin 10 mg +MET**

| Model output | Empagliflozin 10mg | Dapagliflozin 10mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 13.316 | 13.308 | 0.008 |
| Undiscounted Life expectancy (years) | 19.915 | 19.897 | 0.018 |
| Quality-Adjusted Life expectancy (years) | 7.963 | 7.964 | -0.001 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 11.642 | 11.641 | 0.001 |
| Direct Costs (discounted) | **61,761** | **61,609** | **152** |

* The difference is rounded to three decimal digits

**Table 16: Cost breakdown (Empa 10mg+MET vs. dapa 10mg+MET)**

| **Direct costs** | **Empagliflozin 10mg** | **Dapagliflozin 10mg** | **Incremental** |
|---|---|---|---|
| Total Costs | **61,761** | **61,609** | **152** |
| Treatment | 5,903 | 5,889 | 14 |
| Management | 1,030 | 1,029 | 1 |
| CVD | 23,227 | 23,064 | 163 |
| Renal | 7,448 | 7,460 | -12 |
| Ulcer/Amputation/Neuropathy | 14,359 | 14,347 | 12 |
| Eye | 9,773 | 9,792 | -19 |

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| **Direct costs** | **Empagliflozin 10mg** | **Dapagliflozin 10mg** | **Incremental** |
|---|---|---|---|
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 11 | 16 | -5 |

### *5.2.2. Empagliflozin 25mg +MET vs. dapagliflozin 10 mg +MET*

**Table 17 Empagliflozin 25mg +MET vs dapagliflozin 10 mg +MET**

| Model output | Empagliflozin 25mg | Dapagliflozin 10mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 13.352 | 13.308 | 0.044 |
| Undiscounted Life expectancy (years) | 19.983 | 19.897 | 0.086 |
| Quality-Adjusted Life expectancy (years) | 7.995 | 7.964 | 0.031 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 11.698 | 11.641 | 0.057 |
| Direct Costs (discounted) | **61,535** | **61,609** | **-74** |

**Table 18: Cost breakdown (Empa 25mg+MET vs. dapa 10mg+MET)**

| Direct costs | Empagliflozin 25mg | Dapagliflozin 10mg | Incremental |
|---|---|---|---|
| Total Costs | 61,535 | 61,609 | -74 |
| Treatment | 5,920 | 5,889 | 31 |
| Management | 1,033 | 1,029 | 4 |
| CVD | 23,065 | 23,064 | 1 |
| Renal | 7,335 | 7,460 | -125 |
| Ulcer/Amputation/Neuropathy | 14,373 | 14,347 | 26 |
| Eye | 9,786 | 9,792 | -6 |

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| Direct costs | Empagliflozin 25mg | Dapagliflozin 10mg | Incremental |
|---|---|---|---|
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 14 | 16 | -2 |

**Notes**: similarly to the analysis above, there is almost no difference in the cost of treatment due to the price parity assumption. The costs/rates of complications are marginally higher in the dapa arm.

### *5.2.3. Empagliflozin 10mg+MET vs. Sitagliptin 100mg+MET*

**Table 19 Empagliflozin 10mg+MET vs. Sitagliptin 100mg+MET**

| Model output | Empagliflozin 10 mg | Sitagliptin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 13.316 | 13.247 | 0.069 |
| Undiscounted Life expectancy (years) | 19.915 | 19.769 | 0.146 |
| Quality-Adjusted Life expectancy (years) | 7.963 | 7.899 | 0.064 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 11.642 | 11.524 | 0.118 |
| Direct Costs (discounted) | 61761 | 61778 | **-18** |

**Table 20 Cost breakdown (Empagliflozin 10mg+MET vs. Sitagliptin 100mg+MET)**

| Direct costs | Empagliflozin 10mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| Total Costs | 61,761 | 61,778 | -17 |
| Treatment | 5,903 | 5,713 | 190 |
| Management | 1,030 | 1,025 | 5 |
| CVD | 23,227 | 23,452 | -225 |
| Renal | 7,448 | 7,508 | -60 |
| Ulcer/Amputation/Neuropathy | 14,359 | 14,284 | 75 |
| Eye | 9,773 | 9,789 | -16 |
| Hypoglycaemia | 0 | 0 | 0 |

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| Direct costs | Empagliflozin 10mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| GTI | 11 | 0 | 11 |

### *5.2.4. Empagliflozin 25mg+MET vs. Sitagliptin 100mg+MET*

**Table 21 Empagliflozin 25mg+MET vs. Sitagliptin 100mg+MET**

| Model output | Empagliflozin 25 mg | Sitagliptin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 13.352 | 13.247 | 0.105 |
| Undiscounted Life expectancy (years) | 19.983 | 19.769 | 0.214 |
| Quality-Adjusted Life expectancy (years) | 7.995 | 7.899 | 0.096 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 11.698 | 11.524 | 0.174 |
| Direct Costs (discounted) | 61535 | 61778 | **-243** |

**Table 22 Cost breakdown (Empagliflozin 25mg+MET vs. Sitagliptin 100mg+MET)**

| Direct costs | Empagliflozin 25mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| Total Costs | 61,761 | 61,609 | 152 |
| Treatment | 5,903 | 5,889 | 14 |
| Management | 1,030 | 1,029 | 1 |
| CVD | 23,227 | 23,064 | 163 |
| Renal | 7,448 | 7,460 | -12 |
| Ulcer/Amputation/Neuropathy | 14,359 | 14,347 | 12 |
| Eye | 9,773 | 9,792 | -19 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 11 | 16 | -5 |

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### *5.2.5. Empagliflozin 25mg+MET vs. Canagliflozin 300mg+MET*

**Table 23 Empagliflozin 25mg+MET vs. Canagliflozin 300mg +MET**

| Model output | Empagliflozin 25mg | Canagliflozin 300mg (vs Empagliflozin 25mg) | Difference |
|---|---|---|---|
| Life expectancy (years) | 13.352 | 13.337 | 0.015 |
| Undiscounted Life expectancy (years) | 19.983 | 19.954 | 0.029 |
| Quality-Adjusted Life expectancy (years) | 7.995 | 7.986 | 0.009 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 11.698 | 11.68 | 0.018 |
| Direct Costs (discounted) | 61535 | 61829 | **-294** |

**Table 24 Cost breakdown (Empagliflozin 25mg+MET vs. Canagliflozin 300mg +MET)**

| Direct costs | Empagliflozin 25mg | Canagliflozin 300mg (vs Empagliflozin 25mg) | Incremental |
|---|---|---|---|
| Total Costs | 61,535 | 61,829 | -294 |
| Treatment | 5,920 | 6,409 | -489 |
| Management | 1,033 | 1,032 | 1 |
| CVD | 23,065 | 23,029 | 36 |
| Renal | 7,335 | 7,258 | 77 |
| Ulcer/Amputation/Neuropathy | 14,373 | 14,348 | 25 |
| Eye | 9,786 | 9,735 | 51 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 14 | 8 | 6 |

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### *5.2.6. Empagliflozin 10mg+MET vs. Canagliflozin 100mg+MET*

**Table 25 Empagliflozin 10mg+MET vs. Canagliflozin 100mg +MET**

| Model output | Empagliflozin 10mg | Canagliflozin 100mg (vs Empagliflozin 10mg) | Difference |
|---|---|---|---|
| Life expectancy (years) | 13.316 | 13.298 | 0.018 |
| Undiscounted Life expectancy (years) | 19.915 | 19.879 | 0.036 |
| Quality-Adjusted Life expectancy (years) | 7.963 | 7.955 | 0.008 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 11.642 | 11.625 | 0.017 |
| Direct Costs (discounted) | 61761 | 61719 | **42** |

**Table 26 Cost breakdown (Empagliflozin 10mg+MET vs. Canagliflozin 100mg +MET)**

| Direct costs | Empagliflozin 10mg | Canagliflozin 100mg (vs Empagliflozin 10mg) | Incremental |
|---|---|---|---|
| Total Costs | 61,761 | 61,719 | 42 |
| Treatment | 5,903 | 5,889 | 14 |
| Management | 1,030 | 1,029 | 1 |
| CVD | 23,227 | 23,198 | 29 |
| Renal | 7,448 | 7,430 | 18 |
| Ulcer/Amputation/Neuropathy | 14,359 | 14,351 | 8 |
| Eye | 9,773 | 9,804 | -31 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 11 | 8 | 3 |

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### *5.2.7. Empagliflozin 10mg+MET vs. Canagliflozin 300mg+MET*

**Table 27 Empagliflozin 10mg+MET vs. Canagliflozin 300mg +MET**

| Model output | Empagliflozin 10mg | Canagliflozin 300mg (vs Empagliflozin 10mg) | Difference |
|---|---|---|---|
| Life expectancy (years) | 13.316 | 13.343 | -0.027 |
| Undiscounted Life expectancy (years) | 19.915 | 19.969 | -0.054 |
| Quality-Adjusted Life expectancy (years) | 7.963 | 7.99 | -0.027 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 11.642 | 11.69 | -0.048 |
| Direct Costs (discounted) | 61,761 | 61,912 | **-151** |

**Table 28 Cost breakdown (Empagliflozin 10mg+MET vs. Canagliflozin 300mg +MET)**

| Direct costs | Empagliflozin 10mg | Canagliflozin 300mg (vs Empagliflozin 10mg) | Incremental |
|---|---|---|---|
| Total Costs | 61,761 | 61,912 | -151 |
| Treatment | 5,903 | 6,411 | -508 |
| Management | 1,030 | 1,032 | -2 |
| CVD | 23,227 | 23,044 | 183 |
| Renal | 7,448 | 7,280 | 168 |
| Ulcer/Amputation/Neuropathy | 14,359 | 14,337 | 22 |
| Eye | 9,773 | 9,789 | -16 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 11 | 8 | 3 |

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### *5.2.8. Empagliflozin 25mg+MET vs. Canagliflozin 100mg+MET*

**Table 29 Empagliflozin 25mg+MET vs. Canagliflozin 100mg +MET**

| Model output | Empagliflozin 25mg | Canagliflozin 100mg (vs Empagliflozin 25mg) | Difference |
|---|---|---|---|
| Life expectancy (years) | 13.352 | 13.289 | 0.062 |
| Undiscounted Life expectancy (years) | 19.983 | 19.859 | 0.124 |
| Quality-Adjusted Life expectancy (years) | 7.995 | 7.949 | 0.046 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 11.698 | 11.613 | 0.085 |
| Direct Costs (discounted) | 61535 | 61643 | **-109** |

**Table 30 Cost breakdown (Empagliflozin 25mg+MET vs. Canagliflozin 100mg +MET)**

| Direct costs | Empagliflozin 25mg | Canagliflozin 100mg (vs Empagliflozin 25mg) | Incremental |
|---|---|---|---|
| Total Costs | **61,535** | **0** | 61,535 |
| Treatment | 5,903 | 5,889 | 14 |
| Management | 1,030 | 1,029 | 1 |
| CVD | 23,227 | 23,064 | 163 |
| Renal | 7,448 | 7,460 | -12 |
| Ulcer/Amputation/Neuropathy | 14,359 | 14,347 | 12 |
| Eye | 9,773 | 9,792 | -19 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 11 | 16 | -5 |

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## 5.3. Detailed results: triple therapy regimens – MET+SU

### *5.3.1. Empagliflozin 10mg vs Sitagliptin 100 mg*

**Table 31: Base case: Empagliflozin 10mg vs Sitagliptin 100 mg**

| Model output | Empagliflozin 10mg | Sitagliptin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.79 | 12.694 | 0.095 |
| Undiscounted Life expectancy (years) | 18.813 | 18.624 | 0.189 |
| Quality-Adjusted Life expectancy (years) | 7.571 | 7.466 | 0.105 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.897 | 10.716 | 0.181 |
| Direct Costs (discounted) | **58,778** | **59,390** | **-612** |

**Table 32: Cost breakdown: Empagliflozin 10mg vs Sitagliptin 100 mg**

| Direct costs | Empagliflozin 10mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **58,778** | **59,390** | **-612** |
| Treatment | 5,778 | 5,572 | 206 |
| Management | 990 | 983 | 7 |
| CVD | 22,495 | 23,139 | -644 |
| Renal | 6,816 | 7,022 | -206 |
| Ulcer/Amputation/Neuropathy | 13,545 | 13,527 | 18 |
| Eye | 9,130 | 9,131 | -1 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 8 | 0 | 8 |

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### *5.3.2. Empagliflozin 25mg vs Sitagliptin 100 mg*

**Table 33 Base case: Empagliflozin 25mg vs Sitagliptin 100 mg**

| Model output | Empagliflozin 25mg | Sitagliptin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.774 | 12.694 | 0.079 |
| Undiscounted Life expectancy (years) | 18.78 | 18.624 | 0.156 |
| Quality-Adjusted Life expectancy (years) | 7.564 | 7.467 | 0.097 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.881 | 10.717 | 0.164 |
| Direct Costs (discounted) | **58,711** | **59,390** | **-679** |

**Table 34 Cost breakdown: Empagliflozin 25mg vs Sitagliptin 100 mg**

| Direct costs | Empagliflozin 25mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **58,711** | **59,390** | **-679** |
| Treatment | 5,770 | 5,572 | 198 |
| Management | 988 | 983 | 5 |
| CVD | 22,457 | 23,139 | -682 |
| Renal | 6,802 | 7,022 | -220 |
| Ulcer/Amputation/Neuropathy | 13,523 | 13,527 | -4 |
| Eye | 9,147 | 9,131 | 16 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 7 | 0 | 7 |

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### *5.3.3. Empagliflozin 10mg vs Canagliflozin 100 mg*

**Table 35: Base case: Empagliflozin 10mg vs Canagliflozin 100 mg**

| Model output | Empagliflozin 10mg | Canagliflozin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.79 | 12.803 | -0.014 |
| Undiscounted Life expectancy (years) | 18.813 | 18.837 | -0.024 |
| Quality-Adjusted Life expectancy (years) | 7.571 | 7.569 | 0.002 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.897 | 10.895 | 0.002 |
| Direct Costs (discounted) | **58,778** | **58,794** | **-16** |

**Table 36: Cost-breakdown : Empagliflozin 10mg vs Canagliflozin 100 mg**

| Direct costs | Empagliflozin 10mg | Canagliflozin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **58,778** | **58,794** | **-16** |
| Treatment | 5,778 | 5,788 | -10 |
| Management | 990 | 991 | -1 |
| CVD | 22,495 | 22,538 | -43 |
| Renal | 6,816 | 6,775 | 41 |
| Ulcer/Amputation/Neuropathy | 13,545 | 13,534 | 11 |
| Eye | 9,130 | 9,143 | -13 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 8 | 9 | -1 |

### *5.3.4. Empagliflozin 25mg vs Canagliflozin 100 mg*

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**Table 37 Base case: Empagliflozin 25mg vs Canagliflozin 100 mg**

| Model output | Empagliflozin 25mg | Canagliflozin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.774 | 12.803 | -0.03 |
| Undiscounted Life expectancy (years) | 18.78 | 18.837 | -0.057 |
| Quality-Adjusted Life expectancy (years) | 7.564 | 7.569 | -0.005 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.881 | 10.895 | -0.014 |
| Direct Costs (discounted) | **58,711** | **58,794** | **-83** |

**Table 38 Cost breakdown: Empagliflozin 25mg vs Canagliflozin 100 mg**

| Direct costs | Empagliflozin 25mg | Canagliflozin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **58,711** | **58,794** | **-83** |
| Treatment | 5,770 | 5,788 | -18 |
| Management | 988 | 991 | -3 |
| CVD | 22,457 | 22,538 | -81 |
| Renal | 6,802 | 6,775 | 27 |
| Ulcer/Amputation/Neuropathy | 13,523 | 13,534 | -11 |
| Eye | 9,147 | 9,143 | 4 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 7 | 9 | -2 |

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### *5.3.5. Empagliflozin 10mg vs Canagliflozin 300 mg*

**Table 39 Base case: Empagliflozin 10mg vs Canagliflozin 300 mg**

| Model output | Empagliflozin 10mg | Canagliflozin 300mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.79 | 12.848 | -0.059 |
| Undiscounted Life expectancy (years) | 18.813 | 18.921 | -0.108 |
| Quality-Adjusted Life expectancy (years) | 7.571 | 7.616 | -0.045 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.897 | 10.972 | -0.075 |
| Direct Costs (discounted) | **58,778** | **59,000** | **-222** |

**Table 40 Cost breakdown: Empagliflozin 10mg vs Canagliflozin 300 mg**

| Direct costs | Empagliflozin 10mg | Canagliflozin 300mg | Incremental |
|---|---|---|---|
| Total Costs | **58,778** | **59,000** | **-222** |
| Treatment | 5,778 | 6,363 | -585 |
| Management | 990 | 994 | -4 |
| CVD | 22,495 | 22,426 | 69 |
| Renal | 6,816 | 6,605 | 211 |
| Ulcer/Amputation/Neuropathy | 13,545 | 13,516 | 29 |
| Eye | 9,130 | 9,068 | 62 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 8 | 9 | -1 |

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### *5.3.6. Empagliflozin 25mg vs Canagliflozin 300 mg*

**Table 41 Base case Empagliflozin 25mg vs Canagliflozin 300 mg**

| Model output | Empagliflozin 25mg | Canagliflozin 300mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.774 | 12.848 | -0.075 |
| Undiscounted Life expectancy (years) | 18.78 | 18.921 | -0.141 |
| Quality-Adjusted Life expectancy (years) | 7.564 | 7.616 | -0.052 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 0 | 0 | 0 |
| Direct Costs (discounted) | **58,711** | **59,000** | **-289** |

**Table 42 Cost breakdown Empagliflozin 25mg vs Canagliflozin 300 mg**

| Direct costs | Empagliflozin 25mg | Canagliflozin 300mg | Incremental |
|---|---|---|---|
| Total Costs | **58,711** | **59,000** | **-289** |
| Treatment | 5,770 | 6,363 | -593 |
| Management | 988 | 994 | -6 |
| CVD | 22,457 | 22,426 | 31 |
| Renal | 6,802 | 6,605 | 197 |
| Ulcer/Amputation/Neuropathy | 13,523 | 13,516 | 7 |
| Eye | 9,147 | 9,068 | 79 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 7 | 9 | -2 |

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## 5.4. Detailed results: triple therapy regimens MET TZD

### *5.4.1. Empagliflozin 10mg +MET+TZD vs Sitagliptin 100mg +MET+TZD*

**Table 43 Base case: Empagliflozin 10mg +MET+TZD vs Sitagliptin 100mg +MET+TZD**

| Model output | Empagliflozin 10mg | Sitagliptin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.745 | 12.796 | -0.051 |
| Undiscounted Life expectancy (years) | 18.723 | 18.822 | -0.099 |
| Quality-Adjusted Life expectancy (years) | 7.542 | 7.553 | -0.011 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.841 | 10.868 | -0.027 |
| Direct Costs (discounted) | **59,166** | **58,644** | **522** |

**Table 44 Cost breakdown: Empagliflozin 10mg vs Sitagliptin 100mg (MET+TZD)**

| Direct costs | Empagliflozin 10mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **59,166** | **58,644** | **522** |
| Treatment | 5,792 | 5,679 | 113 |
| Management | 986 | 989 | -3 |
| CVD | 22,517 | 22,548 | -31 |
| Renal | 7,017 | 6,810 | 207 |
| Ulcer/Amputation/Neuropathy | 13,623 | 13,535 | 88 |
| Eye | 9,205 | 9,080 | 125 |
| Hypoglycaemia | 0 | 0 | 0 |

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| Direct costs | Empagliflozin 10mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| GTI | 23 | 0 | 23 |

### *5.4.2. Empagliflozin 25mg +MET+TZD vs Sitagliptin 100mg +MET+TZD*

**Table 45 Base case: Empagliflozin 25mg +MET+TZD vs Sitagliptin 100mg +MET+TZD**

| Model output | Empagliflozin 25mg | Sitagliptin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.768 | 12.796 | -0.028 |
| Undiscounted Life expectancy (years) | 18.767 | 18.822 | -0.055 |
| Quality-Adjusted Life expectancy (years) | 7.561 | 7.553 | 0.008 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.873 | 10.868 | 0.005 |
| Direct Costs (discounted) | **58,854** | **58,644** | **210** |

**Table 46 Cost breakdown: Empagliflozin 25mg +MET+TZD vs Sitagliptin 100mg +MET+TZD**

| Direct costs | Empagliflozin 25mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **58,854** | **58,644** | **210** |
| Treatment | 5,820 | 5,679 | 141 |
| Management | 988 | 989 | -1 |
| CVD | 22,471 | 22,548 | -77 |
| Renal | 6,889 | 6,810 | 79 |
| Ulcer/Amputation/Neuropathy | 13,527 | 13,535 | -8 |
| Eye | 9,147 | 9,080 | 67 |

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| Direct costs | Empagliflozin 25mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 10 | 0 | 10 |

### *5.4.3. Empagliflozin 10mg +MET+TZD vs Canagliflozin 100mg +MET+TZD*

**Table 47 Base case: Empagliflozin 10mg +MET+TZD vs Canagliflozin 100mg +MET+TZD**

| Model output | Empagliflozin 10mg | Canagliflozin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.745 | 12.781 | -0.036 |
| Undiscounted Life expectancy (years) | 18.723 | 18.791 | -0.068 |
| Quality-Adjusted Life expectancy (years) | 7.542 | 7.579 | -0.037 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.841 | 10.902 | -0.061 |
| Direct Costs (discounted) | **59,166** | **58,751** | **415** |

**Table 48 Cost breakdown: Empagliflozin 10mg +MET+TZD vs Canagliflozin 100mg +MET+TZD**

| Direct costs | Empagliflozin 10mg | Canagliflozin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **59,166** | **58,751** | **415** |
| Treatment | 5,792 | 5,830 | -38 |
| Management | 986 | 989 | -3 |
| CVD | 22,517 | 22,398 | 119 |
| Renal | 7,017 | 6,819 | 198 |
| Ulcer/Amputation/Neuropathy | 13,623 | 13,558 | 65 |

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| Direct costs | Empagliflozin 10mg | Canagliflozin 100mg | Incremental |
|---|---|---|---|
| Eye | 9,205 | 9,145 | 60 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 23 | 8 | 15 |

### *5.4.4. Empagliflozin 25mg +MET+TZD vs Canagliflozin 100mg +MET+TZD*

**Table 49 Base case: Empagliflozin 25mg +MET+TZD vs Canagliflozin 100mg +MET+TZD**

| Model output | Empagliflozin 25mg | Canagliflozin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.768 | 12.781 | -0.013 |
| Undiscounted Life expectancy (years) | 18.767 | 18.791 | -0.024 |
| Quality-Adjusted Life expectancy (years) | 7.561 | 7.579 | -0.018 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.873 | 10.902 | -0.029 |
| Direct Costs (discounted) | **58,854** | **58,751** | **103** |

**Table 50 Cost breakdown: Empagliflozin 25mg +MET+TZD vs Canagliflozin 100mg +MET+TZD**

| Direct costs | Empagliflozin 25mg | Canagliflozin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **58,854** | **58,751** | **103** |
| Treatment | 5,820 | 5,830 | -10 |
| Management | 988 | 989 | -1 |
| CVD | 22,471 | 22,398 | 73 |
| Renal | 6,889 | 6,819 | 70 |

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| Direct costs | Empagliflozin 25mg | Canagliflozin 100mg | Incremental |
|---|---|---|---|
| Ulcer/Amputation/Neuropathy | 13,527 | 13,558 | -31 |
| Eye | 9,147 | 9,145 | 2 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 10 | 8 | 2 |

### *5.4.5. Empagliflozin 10mg +MET+TZD vs Canagliflozin 300mg +MET+TZD*

**Table 51 Base case: Empagliflozin 10mg +MET+TZD vs Canagliflozin 300mg +MET+TZD**

| Model output | Empagliflozin 10mg | Canagliflozin 300mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.745 | 12.811 | -0.066 |
| Undiscounted Life expectancy (years) | 18.723 | 18.849 | -0.126 |
| Quality-Adjusted Life expectancy (years) | 7.542 | 7.614 | -0.072 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.841 | 10.96 | -0.119 |
| Direct Costs (discounted) | **59,166** | **59,106** | **60** |

**Table 52 Cost breakdown: Empagliflozin 10mg +MET+TZD vs Canagliflozin 300mg +MET+TZD**

| Direct costs | Empagliflozin 10mg | Canagliflozin 300mg | Incremental |
|---|---|---|---|
| Total Costs | **59,166** | **59,106** | **60** |
| Treatment | 5,792 | 6,360 | -568 |
| Management | 986 | 991 | -5 |
| CVD | 22,517 | 22,331 | 186 |

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| Direct costs | Empagliflozin 10mg | Canagliflozin 300mg | Incremental |
|---|---|---|---|
| Renal | 7,017 | 6,727 | 290 |
| Ulcer/Amputation/Neuropathy | 13,623 | 13,539 | 84 |
| Eye | 9,205 | 9,148 | 57 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 23 | 8 | 15 |

### *5.4.6. Empagliflozin 25mg +MET+TZD vs Canagliflozin 300mg +MET+TZD*

**Table 53 Base case: Empagliflozin 25mg +MET+TZD vs Canagliflozin 300mg +MET+TZD**

| Model output | Empagliflozin 25mg | Canagliflozin 300mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.768 | 12.811 | -0.043 |
| Undiscounted Life expectancy (years) | 18.767 | 18.849 | -0.082 |
| Quality-Adjusted Life expectancy (years) | 7.561 | 7.614 | -0.053 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.873 | 10.96 | -0.087 |
| Direct Costs (discounted) | **58,854** | **59,106** | **-252** |

**Table 54 Cost breakdown: Empagliflozin 25mg +MET+TZD vs Canagliflozin 300mg +MET+TZD**

| Direct costs | Empagliflozin 25mg | Canagliflozin 300mg | Incremental |
|---|---|---|---|
| Total Costs | **58,854** | **59,106** | **-252** |
| Treatment | 5,820 | 6,360 | -540 |
| Management | 988 | 991 | -3 |

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| Direct costs | Empagliflozin 25mg | Canagliflozin 300mg | Incremental |
|---|---|---|---|
| CVD | 22,471 | 22,331 | 140 |
| Renal | 6,889 | 6,727 | 162 |
| Ulcer/Amputation/Neuropathy | 13,527 | 13,539 | -12 |
| Eye | 9,147 | 9,148 | -1 |
| Hypoglycaemia | 0 | 0 | 0 |
| GTI | 10 | 8 | 2 |

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## 5.5. Detailed results: regimens with INS

### *5.5.1. Empagliflozin 10mg +INS vs Dapagliflozin 10mg +INS*

**Table 55 Base case: Empagliflozin 10mg +INS vs Dapagliflozin 10mg +INS**

| Model output | Empagliflozin 10mg | Dapagliflozin 10mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.741 | 12.76 | -0.019 |
| Undiscounted Life expectancy (years) | 18.718 | 18.753 | -0.035 |
| Quality-Adjusted Life expectancy (years) | 7.523 | 7.545 | -0.023 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.814 | 10.851 | -0.037 |
| Direct Costs (discounted) | 60,539 | 60,360 | 179 |

**Table 56 Cost breakdown: Empagliflozin 10mg +INS vs Dapagliflozin 10mg +INS**

| Direct costs | Empagliflozin 10mg | Dapagliflozin 10mg | Incremental |
|---|---|---|---|
| Total Costs | **60,539** | **60,360** | **179** |
| Treatment | 7,046 | 7,095 | -49 |
| Management | 986 | 987 | -1 |
| CVD | 22,687 | 22,516 | 171 |
| Renal | 6,977 | 6,952 | 25 |
| Ulcer/Amputation/Neuropathy | 13,613 | 13,596 | 17 |
| Eye | 9,192 | 9,175 | 17 |

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| Direct costs | Empagliflozin 10mg | Dapagliflozin 10mg | Incremental |
|---|---|---|---|
| Hypoglycaemia | 14 | 14 | 0 |
| GTI | 12 | 8 | 4 |

### *5.5.2. Empagliflozin 25mg +INS vs Dapagliflozin 10mg +INS*

**Table 57 Base case: Empagliflozin 25mg +INS vs Dapagliflozin 10mg +INS**

| Model output | Empagliflozin 25mg | Dapagliflozin 10mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.757 | 12.76 | -0.003 |
| Undiscounted Life expectancy (years) | 18.744 | 18.753 | -0.009 |
| Quality-Adjusted Life expectancy (years) | 7.534 | 7.545 | -0.011 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.833 | 10.851 | -0.018 |
| Direct Costs (discounted) | **60,428** | **60,360** | **68** |

**Table 58 Cost breakdown: Empagliflozin 25mg +INS vs Dapagliflozin 10mg +INS**

| Direct costs | Empagliflozin 25mg | Dapagliflozin 10mg | Incremental |
|---|---|---|---|
| Total Costs | **60,428** | **60,360** | **68** |
| Treatment | 7,095 | 7,095 | 0 |
| Management | 987 | 987 | 0 |
| CVD | 22,617 | 22,516 | 101 |
| Renal | 6,917 | 6,952 | -35 |
| Ulcer/Amputation/Neuropathy | 13,570 | 13,596 | -26 |

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| Direct costs | Empagliflozin 25mg | Dapagliflozin 10mg | Incremental |
|---|---|---|---|
| Eye | 9,189 | 9,175 | 14 |
| Hypoglycaemia | 14 | 14 | 0 |
| GTI | 27 | 8 | 19 |

### *5.5.3. Empagliflozin 10mg +INS vs Sitagliptin 100mg +INS*

**Table 59 Base case: Empagliflozin 10mg +INS vs Sitagliptin 100mg +INS**

| Model output | Empagliflozin 10mg | Sitagliptin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.741 | 12.762 | -0.021 |
| Undiscounted Life expectancy (years) | 18.718 | 18.758 | -0.04 |
| Quality-Adjusted Life expectancy (years) | 7.523 | 7.511 | 0.011 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.814 | 10.802 | 0.012 |
| Direct Costs (discounted) | **60,539** | **60,564** | **-25** |

**Table 60 Cost breakdown: Empagliflozin 10mg +INS vs Sitagliptin 100mg +INS**

| Direct costs | Empagliflozin 10mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **60,539** | **60,564** | **-25** |
| Treatment | 7,046 | 6,952 | 94 |
| Management | 986 | 987 | -1 |
| CVD | 22,687 | 22,771 | -84 |
| Renal | 6,977 | 7,041 | -64 |
| Ulcer/Amputation/Neuropathy | 13,613 | 13,596 | 17 |

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| Direct costs | Empagliflozin 10mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| Eye | 9,192 | 9,188 | 4 |
| Hypoglycaemia | 14 | 14 | 0 |
| GTI | 12 | 0 | 12 |

### *5.5.4. Empagliflozin 25mg +INS vs Sitagliptin 100mg +INS*

**Table 61 Base case: Empagliflozin 25mg +INS vs Sitagliptin 100mg +INS**

| Model output | Empagliflozin 25mg | Sitagliptin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.757 | 12.743 | 0.014 |
| Undiscounted Life expectancy (years) | 18.744 | 18.713 | 0.031 |
| Quality-Adjusted Life expectancy (years) | 7.534 | 7.499 | 0.036 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.833 | 10.774 | 0.059 |
| Direct Costs (discounted) | **60,428** | **60,530** | **-102** |

**Table 62 Cost breakdown: Empagliflozin 25mg +INS vs Sitagliptin 100mg +INS**

| Direct costs | Empagliflozin 25mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **60,428** | **60,530** | **-102** |
| Treatment | 7,095 | 6,945 | 150 |
| Management | 987 | 986 | 1 |
| CVD | 22,617 | 22,803 | -186 |
| Renal | 6,917 | 6,966 | -49 |

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| Direct costs | Empagliflozin 25mg | Sitagliptin 100mg | Incremental |
|---|---|---|---|
| Ulcer/Amputation/Neuropathy | 13,570 | 13,616 | -46 |
| Eye | 9,189 | 9,187 | 2 |
| Hypoglycaemia | 14 | 14 | 0 |
| GTI | 27 | 0 | 27 |

### *5.5.5. Empagliflozin 10mg +INS vs Canagliflozin 100mg +INS*

**Table 63 Base case: Empagliflozin 10mg +INS vs Canagliflozin 100mg +INS**

| Model output | Empagliflozin 10mg | Canagliflozin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.741 | 12.77 | -0.029 |
| Undiscounted Life expectancy (years) | 18.718 | 18.77 | -0.052 |
| Quality-Adjusted Life expectancy (years) | 7.523 | 7.545 | -0.023 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.814 | 10.854 | -0.04 |
| Direct Costs (discounted) | **60,539** | **60,235** | **304** |

**Table 64 Cost breakdown: Empagliflozin 10mg +INS vs Canagliflozin 100mg +INS**

| Direct costs | Empagliflozin 10mg | Canagliflozin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **60,539** | **60,235** | **304** |
| Treatment | 7,046 | 7,133 | -87 |
| Management | 986 | 988 | -2 |
| CVD | 22,687 | 22,541 | 146 |
| Renal | 6,977 | 6,819 | 158 |

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| Direct costs | Empagliflozin 10mg | Canagliflozin 100mg | Incremental |
|---|---|---|---|
| Ulcer/Amputation/Neuropathy | 13,613 | 13,567 | 46 |
| Eye | 9,192 | 9,150 | 42 |
| Hypoglycaemia | 14 | 14 | 0 |
| GTI | 12 | 8 | 4 |

### *5.5.6. Empagliflozin 25mg +INS vs Canagliflozin 100mg +INS*

**Table 65 Base case: Empagliflozin 25mg +INS vs Canagliflozin 100mg +INS**

| Model output | Empagliflozin 25mg | Canagliflozin 100mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.757 | 12.778 | -0.021 |
| Undiscounted Life expectancy (years) | 18.744 | 18.785 | -0.041 |
| Quality-Adjusted Life expectancy (years) | 7.534 | 7.551 | -0.017 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.833 | 10.864 | -0.031 |
| Direct Costs (discounted) | **60,428** | **60,333** | **95** |

**Table 66 Cost breakdown: Empagliflozin 25mg +INS vs Canagliflozin 100mg +INS**

| Direct costs | Empagliflozin 25mg | Canagliflozin 100mg | Incremental |
|---|---|---|---|
| Total Costs | **60,428** | **60,333** | **95** |
| Treatment | 7,095 | 7,137 | -42 |
| Management | 987 | 988 | -1 |
| CVD | 22,617 | 22,587 | 30 |
| Renal | 6,917 | 6,879 | 38 |

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| Direct costs | Empagliflozin 25mg | Canagliflozin 100mg | Incremental |
|---|---|---|---|
| Ulcer/Amputation/Neuropathy | 13,570 | 13,564 | 6 |
| Eye | 9,189 | 9,143 | 46 |
| Hypoglycaemia | 14 | 14 | 0 |
| GTI | 27 | 8 | 19 |

### *5.5.7. Empagliflozin 10mg +INS vs Canagliflozin 300mg +INS*

**Table 67 Base case: Empagliflozin 10mg +INS vs Canagliflozin 300mg +INS**

| Model output | Empagliflozin 10mg | Canagliflozin 300mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.741 | 12.809 | -0.067 |
| Undiscounted Life expectancy (years) | 18.718 | 18.852 | -0.134 |
| Quality-Adjusted Life expectancy (years) | 7.523 | 7.583 | -0.061 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.814 | 10.922 | -0.108 |
| Direct Costs (discounted) | **60,539** | **60,599** | **-60** |

**Table 68 Cost breakdown: Empagliflozin 10mg +INS vs Canagliflozin 300mg +INS**

| Direct costs | Empagliflozin 10mg | Canagliflozin 300mg | Incremental |
|---|---|---|---|
| Total Costs | **60,539** | **60,599** | **-60** |
| Treatment | 7,046 | 7,679 | -633 |
| Management | 986 | 991 | -5 |
| CVD | 22,687 | 22,408 | 279 |

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| Direct costs | Empagliflozin 10mg | Canagliflozin 300mg | Incremental |
|---|---|---|---|
| Renal | 6,977 | 6,850 | 127 |
| Ulcer/Amputation/Neuropathy | 13,613 | 13,519 | 94 |
| Eye | 9,192 | 9,116 | 76 |
| Hypoglycaemia | 14 | 14 | 0 |
| GTI | 12 | 8 | 4 |

### *5.5.8. Empagliflozin 25mg +INS vs Canagliflozin 300mg +INS*

**Table 69 Base case: Empagliflozin 25mg +INS vs Canagliflozin 300mg +INS**

| Model output | Empagliflozin 25mg | Canagliflozin 300mg | Difference |
|---|---|---|---|
| Life expectancy (years) | 12.757 | 12.811 | -0.054 |
| Undiscounted Life expectancy (years) | 18.744 | 18.852 | -0.108 |
| Quality-Adjusted Life expectancy (years) | 7.534 | 7.584 | -0.049 |
| Undiscounted Quality-Adjusted Life expectancy (years) | 10.833 | 10.921 | -0.088 |
| Direct Costs (discounted) | **60,428** | **60,476** | **-48** |

**Table 70 Cost breakdown: Empagliflozin 25mg +INS vs Canagliflozin 300mg +INS**

| Direct costs | Empagliflozin 25mg | Canagliflozin 300mg | Incremental |
|---|---|---|---|
| Total Costs | **60,428** | **60,476** | **-48** |
| Treatment | 7,095 | 7,681 | -586 |
| Management | 987 | 991 | -4 |

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| Direct costs | Empagliflozin 25mg | Canagliflozin 300mg | Incremental |
|---|---|---|---|
| CVD | 22,617 | 22,344 | 273 |
| Renal | 6,917 | 6,754 | 163 |
| Ulcer/Amputation/Neuropathy | 13,570 | 13,528 | 42 |
| Eye | 9,189 | 9,125 | 64 |
| Hypoglycaemia | 14 | 14 | 0 |
| GTI | 27 | 8 | 19 |

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## 5.6. Incidence of complications of diabetes

This section is supplementary and provides a detailed breakdown of the rates of diabetes complications measured as in % of patients in the cohort. The incremental column provides %-point difference. The cells where the difference is in favour of empagliflozin are green shaded, otherwise no colour coding was applied.

The purpose of the tables in this section is to ensure the transparency of the analysis and enable Boehringer Ingelheim to compare the results with the outputs of their proprietary model and assist with the interpretation of the differences and similarities.

### *5.6.1. 2nd line, patients who are no longer responding adequately to MET*

**Table 71 Complications: Empagliflozin 10mg Dapagliflozin 10mg (+MET)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Dapagliflozin 10mg | Incr. |
| BDR | 25.287 | 25.413 | -0.126 |
| PDR | 4.329 | 4.299 | 0.03 |
| ME | 22.508 | 22.628 | -0.12 |
| SVL | 19.678 | 19.729 | -0.051 |
| Cataract | 11.544 | 11.584 | -0.04 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Dapagliflozin 10mg | Incr. |
| MA | 33.866 | 34.028 | -0.162 |
| GRP | 21.445 | 21.495 | -0.05 |
| ESRD | 9.806 | 9.781 | 0.025 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Dapagliflozin 10mg | Incr. |
| Ulcer | 42.639 | 42.643 | -0.004 |

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| | | | |
|---|---|---|---|
| Rec ulcer | 142.366 | 141.917 | 0.449 |
| Amputation ulcer | 27.564 | 27.539 | 0.025 |
| Amputation rec Ulcer | 15.362 | 15.353 | 0.009 |
| Neuropathy | 69.25 | 69.29 | -0.04 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Dapagliflozin 10mg | Incr. |
| CHF event | 14.964 | 14.856 | 0.108 |
| PVD onset | 17.437 | 17.476 | -0.039 |
| Angina | 17.043 | 17.006 | 0.037 |
| Diabetes mortality | 26.541 | 26.557 | -0.016 |
| Stroke event | 29.425 | 29.178 | 0.247 |
| Event fatality | 36.563 | 36.554 | 0.009 |
| MI event | 39.239 | 39.373 | -0.134 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Dapagliflozin 10mg | Incr. |
| UTI | 0.322 | 0.407 | -0.085 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.28 | 0.135 | 0.145 |
| GTI | 0.336 | 0.499 | -0.163 |

**Table 72 Complications: Empagliflozin 25mg Dapagliflozin 10mg (+MET)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Dapagliflozin 10mg | Incr. |
| BDR | 25.107 | 25.413 | -0.306 |
| PDR | 4.295 | 4.299 | -0.004 |

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| | | | |
|---|---|---|---|
| ME | 22.536 | 22.628 | -0.092 |
| SVL | 19.667 | 19.729 | -0.062 |
| Cataract | 11.605 | 11.584 | 0.021 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Dapagliflozin 10mg | Incr. |
| MA | 33.919 | 34.028 | -0.109 |
| GRP | 21.485 | 21.495 | -0.01 |
| ESRD | 9.786 | 9.781 | 0.005 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Dapagliflozin 10mg | Incr. |
| Ulcer | 42.549 | 42.643 | -0.094 |
| Rec ulcer | 142.634 | 141.917 | 0.717 |
| Amputation ulcer | 27.546 | 27.539 | 0.007 |
| Amputation rec Ulcer | 15.443 | 15.353 | 0.09 |
| Neuropathy | 69.086 | 69.29 | -0.204 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Dapagliflozin 10mg | Incr. |
| CHF event | 14.819 | 14.856 | -0.037 |
| PVD onset | 17.474 | 17.476 | -0.002 |
| Angina | 17.028 | 17.006 | 0.022 |
| Diabetes mortality | 26.512 | 26.557 | -0.045 |
| Stroke event | 29.342 | 29.178 | 0.164 |
| Event fatality | 36.378 | 36.554 | -0.176 |
| MI event | 38.923 | 39.373 | -0.45 |

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| CUMULATIVE ADVERSE EVENTS (in %) | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Dapagliflozin 10mg | Incr. |
| UTI | 0.313 | 0.407 | -0.094 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.189 | 0.135 | 0.054 |
| GTI | 0.43 | 0.499 | -0.069 |

**Table 73 Complications: Empagliflozin 10mg Sitagliptin 100mg (+MET)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| BDR | 25.213 | 25.456 | -0.243 |
| PDR | 4.426 | 4.485 | -0.059 |
| ME | 21.868 | 21.981 | -0.113 |
| SVL | 18.817 | 18.87 | -0.053 |
| Cataract | 10.881 | 10.887 | -0.006 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| MA | 33.249 | 33.363 | -0.114 |
| GRP | 20.794 | 20.878 | -0.084 |
| ESRD | 9.343 | 9.353 | -0.01 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| Ulcer | 40.821 | 40.803 | 0.018 |
| Rec ulcer | 132.726 | 132.656 | 0.07 |
| Amputation ulcer | 25.75 | 25.652 | 0.098 |

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| | | | |
|---|---|---|---|
| Amputation rec Ulcer | 13.622 | 13.677 | -0.055 |
| Neuropathy | 68.116 | 68.271 | -0.155 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| CHF event | 17.168 | 17.526 | -0.358 |
| PVD onset | 17.882 | 17.971 | -0.089 |
| Angina | 14.625 | 14.726 | -0.101 |
| Diabetes mortality | 24.754 | 24.695 | 0.059 |
| Stroke event | 29.156 | 29.284 | -0.128 |
| Event fatality | 34.575 | 34.386 | 0.189 |
| MI event | 34.9 | 34.431 | 0.469 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| UTI | 0.435 | 0.45 | -0.015 |
| Major hypo | 0.172 | 0.178 | -0.006 |
| Minor hypo | 2.203 | 2.283 | -0.08 |
| GTI | 0.378 | 0 | 0.378 |

**Table 74 Complications: Empagliflozin 25mg Sitagliptin 100mg (+MET)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| BDR | 25.107 | 25.31 | -0.203 |
| PDR | 4.295 | 4.335 | -0.04 |
| ME | 22.536 | 22.655 | -0.119 |

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| | | | |
|---|---|---|---|
| SVL | 19.667 | 19.708 | -0.041 |
| Cataract | 11.605 | 11.53 | 0.075 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| MA | 33.919 | 33.887 | 0.032 |
| GRP | 21.485 | 21.543 | -0.058 |
| ESRD | 9.786 | 9.786 | 0 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| Ulcer | 42.549 | 42.478 | 0.071 |
| Rec ulcer | 142.634 | 141.093 | 1.541 |
| Amputation ulcer | 27.546 | 27.233 | 0.313 |
| Amputation rec Ulcer | 15.443 | 15.247 | 0.196 |
| Neuropathy | 69.086 | 69.354 | -0.268 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| CHF event | 14.819 | 15.284 | -0.465 |
| PVD onset | 17.474 | 17.415 | 0.059 |
| Angina | 17.028 | 17.031 | -0.003 |
| Diabetes mortality | 26.512 | 26.526 | -0.014 |
| Stroke event | 29.342 | 29.649 | -0.307 |
| Event fatality | 36.378 | 36.939 | -0.561 |
| MI event | 38.923 | 39.821 | -0.898 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |

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| | | | |
|---|---|---|---|
| UTI | 0.313 | 0.251 | 0.062 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.189 | 0.046 | 0.143 |
| GTI | 0.43 | 0 | 0.43 |

**Table 75 Complications: Empagliflozin 25mg Canagliflozin 300 (+MET)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| BDR | 25.107 | 25.156 | -0.049 |
| PDR | 4.295 | 4.28 | 0.015 |
| ME | 22.536 | 22.427 | 0.109 |
| SVL | 19.667 | 19.658 | 0.009 |
| Cataract | 11.605 | 11.602 | 0.003 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| MA | 33.919 | 33.826 | 0.093 |
| GRP | 21.485 | 21.361 | 0.124 |
| ESRD | 9.786 | 9.685 | 0.101 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| Ulcer | 42.549 | 42.534 | 0.015 |
| Rec ulcer | 142.634 | 142.138 | 0.496 |
| Amputation ulcer | 27.546 | 27.564 | -0.018 |
| Amputation rec Ulcer | 15.443 | 15.433 | 0.01 |
| Neuropathy | 69.086 | 69.085 | 0.001 |

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| CUMULATIVE INCIDENCE CVD (in %) | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| CHF event | 14.819 | 14.823 | -0.004 |
| PVD onset | 17.474 | 17.426 | 0.048 |
| Angina | 17.028 | 17.047 | -0.019 |
| Diabetes mortality | 26.512 | 26.45 | 0.062 |
| Stroke event | 29.342 | 29.438 | -0.096 |
| Event fatality | 36.378 | 36.485 | -0.107 |
| MI event | 38.923 | 38.958 | -0.035 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| UTI | 0.313 | 0.314 | -0.001 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.189 | 0.191 | -0.002 |
| GTI | 0.43 | 0.268 | 0.162 |

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**Table 76 Complications: Empagliflozin 10mg Canagliflozin 100 (+MET)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| BDR | 25.287 | 25.4 | -0.113 |
| PDR | 4.329 | 4.366 | -0.037 |
| ME | 22.508 | 22.627 | -0.119 |
| SVL | 19.678 | 19.779 | -0.101 |
| Cataract | 11.544 | 11.649 | -0.105 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| MA | 33.866 | 33.978 | -0.112 |
| GRP | 21.445 | 21.522 | -0.077 |
| ESRD | 9.806 | 9.8 | 0.006 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| Ulcer | 42.639 | 42.65 | -0.011 |
| Rec ulcer | 142.366 | 142.248 | 0.118 |
| Amputation ulcer | 27.564 | 27.52 | 0.044 |
| Amputation rec Ulcer | 15.362 | 15.334 | 0.028 |
| Neuropathy | 69.25 | 69.421 | -0.171 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| CHF event | 14.964 | 14.891 | 0.073 |
| PVD onset | 17.437 | 17.347 | 0.09 |
| Angina | 17.043 | 17.01 | 0.033 |

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| | | | |
|---|---|---|---|
| Diabetes mortality | 26.541 | 26.505 | 0.036 |
| Stroke event | 29.425 | 29.465 | -0.04 |
| Event fatality | 36.563 | 36.694 | -0.131 |
| MI event | 39.239 | 39.43 | -0.191 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| UTI | 0.322 | 0.315 | 0.007 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.28 | 0.274 | 0.006 |
| GTI | 0.336 | 0.26 | 0.076 |

**Table 77 Complications: Empagliflozin 10mg Canagliflozin 300 (+MET)**

| | | | |
|---|---|---|---|
| CUMULATIVE INCIDENCE EYE DISEASE | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| BDR | 25.287 | 25.101 | 0.186 |
| PDR | 4.329 | 4.264 | 0.065 |
| ME | 22.508 | 22.462 | 0.046 |
| SVL | 19.678 | 19.693 | -0.015 |
| Cataract | 11.544 | 11.598 | -0.054 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| MA | 33.866 | 33.827 | 0.039 |
| GRP | 21.445 | 21.421 | 0.024 |
| ESRD | 9.806 | 9.708 | 0.098 |

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| CUMULATIVE INCIDENCE ULCER | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| Ulcer | 42.639 | 42.546 | 0.093 |
| Rec ulcer | 142.366 | 142.121 | 0.245 |
| Amputation ulcer | 27.564 | 27.52 | 0.044 |
| Amputation rec Ulcer | 15.362 | 15.449 | -0.087 |
| Neuropathy | 69.25 | 69.022 | 0.228 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| CHF event | 14.964 | 14.823 | 0.141 |
| PVD onset | 17.437 | 17.455 | -0.018 |
| Angina | 17.043 | 17.032 | 0.011 |
| Diabetes mortality | 26.541 | 26.474 | 0.067 |
| Stroke event | 29.425 | 29.441 | -0.016 |
| Event fatality | 36.563 | 36.443 | 0.12 |
| MI event | 39.239 | 38.922 | 0.317 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| UTI | 0.322 | 0.328 | -0.006 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.28 | 0.286 | -0.006 |
| GTI | 0.336 | 0.269 | 0.067 |

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**Table 78 Complications: Empagliflozin 25mg Canagliflozin 100 (+MET)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| BDR | 25.107 | 25.402 | -0.295 |
| PDR | 4.295 | 4.381 | -0.086 |
| ME | 22.536 | 22.564 | -0.028 |
| SVL | 19.667 | 19.719 | -0.052 |
| Cataract | 11.605 | 11.548 | 0.057 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| MA | 33.919 | 33.911 | 0.008 |
| GRP | 21.485 | 21.537 | -0.052 |
| ESRD | 9.786 | 9.793 | -0.007 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| Ulcer | 42.549 | 42.627 | -0.078 |
| Rec ulcer | 142.634 | 141.929 | 0.705 |
| Amputation ulcer | 27.546 | 27.474 | 0.072 |
| Amputation rec Ulcer | 15.443 | 15.279 | 0.164 |
| Neuropathy | 69.086 | 69.397 | -0.311 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| CHF event | 14.819 | 14.862 | -0.043 |
| PVD onset | 17.474 | 17.338 | 0.136 |
| Angina | 17.028 | 17.041 | -0.013 |

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| | | | |
|---|---|---|---|
| Diabetes mortality | 26.512 | 26.424 | 0.088 |
| Stroke event | 29.342 | 29.414 | -0.072 |
| Event fatality | 36.378 | 36.742 | -0.364 |
| MI event | 38.923 | 39.434 | -0.511 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| UTI | 0.313 | 0.302 | 0.011 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.189 | 0.183 | 0.006 |
| GTI | 0.43 | 0.26 | 0.17 |

### *5.6.2. 3rd line, patients who are no longer responding adequately to MET+SU*

**Table 79 Complications: Empagliflozin 10mg Sitagliptin 100mg (MET+SU)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| BDR | 25.147 | 25.324 | -0.177 |
| PDR | 4.356 | 4.473 | -0.117 |
| ME | 21.725 | 21.788 | -0.063 |
| SVL | 18.734 | 18.788 | -0.054 |
| Cataract | 10.836 | 10.847 | -0.011 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |

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| | | | |
|---|---|---|---|
| MA | 32.951 | 33.1 | -0.149 |
| GRP | 20.553 | 20.739 | -0.186 |
| ESRD | 9.165 | 9.284 | -0.119 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| Ulcer | 40.63 | 40.685 | -0.055 |
| Rec ulcer | 132.602 | 131.728 | 0.874 |
| Amputation ulcer | 25.609 | 25.461 | 0.148 |
| Amputation rec Ulcer | 13.596 | 13.532 | 0.064 |
| Neuropathy | 67.835 | 68.024 | -0.189 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| CHF event | 16.89 | 17.605 | -0.715 |
| PVD onset | 17.816 | 17.829 | -0.013 |
| Angina | 14.567 | 14.707 | -0.14 |
| Diabetes mortality | 24.608 | 24.675 | -0.067 |
| Stroke event | 29.408 | 29.818 | -0.41 |
| Event fatality | 34.373 | 34.926 | -0.553 |
| MI event | 34.294 | 35.353 | -1.059 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| UTI | 0.558 | 0.543 | 0.015 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 1.241 | 1.21 | 0.031 |
| GTI | 0.25 | 0 | 0.25 |

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**Table 80 Complications: Empagliflozin 25mg Sitagliptin 100mg (MET+SU)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| BDR | 25.097 | 25.324 | -0.227 |
| PDR | 4.347 | 4.473 | -0.126 |
| ME | 21.638 | 21.788 | -0.15 |
| SVL | 18.764 | 18.788 | -0.024 |
| Cataract | 10.862 | 10.847 | 0.015 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| MA | 32.877 | 33.1 | -0.223 |
| GRP | 20.638 | 20.739 | -0.101 |
| ESRD | 9.181 | 9.284 | -0.103 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| Ulcer | 40.654 | 0 | 40.654 |
| Rec ulcer | 132.192 | 131.728 | 0.464 |
| Amputation ulcer | 25.59 | 25.461 | 0.129 |
| Amputation rec Ulcer | 13.545 | 13.532 | 0.013 |
| Neuropathy | 67.818 | 68.024 | -0.206 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| CHF event | 16.916 | 17.605 | -0.689 |
| PVD onset | 17.851 | 17.829 | 0.022 |

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| | | | |
|---|---|---|---|
| Angina | 14.603 | 14.707 | -0.104 |
| Diabetes mortality | 24.624 | 24.675 | -0.051 |
| Stroke event | 29.243 | 29.818 | -0.575 |
| Event fatality | 34.37 | 34.926 | -0.556 |
| MI event | 34.4 | 35.353 | -0.953 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| UTI | 0.557 | 0.543 | 0.014 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.999 | 0.978 | 0.021 |
| GTI | 0.214 | 0 | 0.214 |

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**Table 81 Complications: Empagliflozin 10mg Canagliflozin 100mg (MET+SU)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| BDR | 25.147 | 25.036 | 0.111 |
| PDR | 4.356 | 4.375 | -0.019 |
| ME | 21.725 | 21.568 | 0.157 |
| SVL | 18.734 | 18.714 | 0.02 |
| Cataract | 10.836 | 10.872 | -0.036 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| MA | 32.951 | 32.928 | 0.023 |
| GRP | 20.553 | 20.516 | 0.037 |
| ESRD | 9.165 | 9.196 | -0.031 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| Ulcer | 40.63 | 0 | 40.63 |
| Rec ulcer | 132.602 | 132.339 | 0.263 |
| Amputation ulcer | 25.609 | 25.582 | 0.027 |
| Amputation rec Ulcer | 13.596 | 13.665 | -0.069 |
| Neuropathy | 67.835 | 67.777 | 0.058 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| CHF event | 16.89 | 17.106 | -0.216 |
| PVD onset | 17.816 | 17.817 | -0.001 |
| Angina | 14.567 | 14.565 | 0.002 |

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| | | | |
|---|---|---|---|
| Diabetes mortality | 24.608 | 24.6 | 0.008 |
| Stroke event | 29.408 | 29.279 | 0.129 |
| Event fatality | 34.373 | 34.226 | 0.147 |
| MI event | 34.294 | 34.114 | 0.18 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| UTI | 0.558 | 0.565 | -0.007 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 1.241 | 1.401 | -0.16 |
| GTI | 0.25 | 0.276 | -0.026 |

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**Table 82 Complications: Empagliflozin 25mg Canagliflozin 100mg (MET+SU)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| BDR | 25.097 | 25.036 | 0.061 |
| PDR | 4.347 | 4.375 | -0.028 |
| ME | 21.638 | 21.568 | 0.07 |
| SVL | 18.764 | 18.714 | 0.05 |
| Cataract | 10.862 | 10.872 | -0.01 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| MA | 32.877 | 32.928 | -0.051 |
| GRP | 20.638 | 20.516 | 0.122 |
| ESRD | 9.181 | 9.196 | -0.015 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| Ulcer | 40.654 | 0 | 40.654 |
| Rec ulcer | 132.192 | 132.339 | -0.147 |
| Amputation ulcer | 25.59 | 25.582 | 0.008 |
| Amputation rec Ulcer | 13.545 | 13.665 | -0.12 |
| Neuropathy | 67.818 | 67.777 | 0.041 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| CHF event | 16.916 | 17.106 | -0.19 |
| PVD onset | 17.851 | 17.817 | 0.034 |
| Angina | 14.603 | 14.565 | 0.038 |

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| | | | |
|---|---|---|---|
| Diabetes mortality | 24.624 | 24.6 | 0.024 |
| Stroke event | 29.243 | 29.279 | -0.036 |
| Event fatality | 34.37 | 34.226 | 0.144 |
| MI event | 34.4 | 34.114 | 0.286 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| UTI | 0.557 | 0.565 | -0.008 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.999 | 1.401 | -0.402 |
| GTI | 0.214 | 0.276 | -0.062 |

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**Table 83 Complications: Empagliflozin 10mg Canagliflozin 300mg (MET+SU)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| BDR | 25.147 | 24.892 | 0.255 |
| PDR | 4.356 | 4.289 | 0.067 |
| ME | 21.725 | 21.498 | 0.227 |
| SVL | 18.734 | 18.63 | 0.104 |
| Cataract | 10.836 | 10.801 | 0.035 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| MA | 32.951 | 32.797 | 0.154 |
| GRP | 20.553 | 20.328 | 0.225 |
| ESRD | 9.165 | 9.031 | 0.134 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| Ulcer | 40.63 | 0 | 40.63 |
| Rec ulcer | 132.602 | 131.984 | 0.618 |
| Amputation ulcer | 25.609 | 25.641 | -0.032 |
| Amputation rec Ulcer | 13.596 | 13.67 | -0.074 |
| Neuropathy | 67.835 | 67.488 | 0.347 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| CHF event | 16.89 | 16.876 | 0.014 |
| PVD onset | 17.816 | 17.853 | -0.037 |

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| | | | |
|---|---|---|---|
| Angina | 14.567 | 14.619 | -0.052 |
| Diabetes mortality | 24.608 | 24.525 | 0.083 |
| Stroke event | 29.408 | 29.614 | -0.206 |
| Event fatality | 34.373 | 34.052 | 0.321 |
| MI event | 34.294 | 33.589 | 0.705 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| UTI | 0.558 | 0.602 | -0.044 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 1.241 | 1.236 | 0.005 |
| GTI | 0.25 | 0.293 | -0.043 |

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**Table 84 Complications: Empagliflozin 25mg Canagliflozin 300mg (MET+SU)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| BDR | 25.097 | 24.892 | 0.205 |
| PDR | 4.347 | 4.289 | 0.058 |
| ME | 21.638 | 21.498 | 0.14 |
| SVL | 18.764 | 18.63 | 0.134 |
| Cataract | 10.862 | 10.801 | 0.061 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| MA | 32.877 | 32.797 | 0.08 |
| GRP | 20.638 | 20.328 | 0.31 |
| ESRD | 9.181 | 9.031 | 0.15 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| Ulcer | 40.654 | 0 | 40.654 |
| Rec ulcer | 132.192 | 131.984 | 0.208 |
| Amputation ulcer | 25.59 | 25.641 | -0.051 |
| Amputation rec Ulcer | 13.545 | 13.67 | -0.125 |
| Neuropathy | 67.818 | 67.488 | 0.33 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| CHF event | 16.916 | 16.876 | 0.04 |
| PVD onset | 17.851 | 17.853 | -0.002 |
| Angina | 14.603 | 14.619 | -0.016 |

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| | | | |
|---|---|---|---|
| Diabetes mortality | 24.624 | 24.525 | 0.099 |
| Stroke event | 29.243 | 29.614 | -0.371 |
| Event fatality | 34.37 | 34.052 | 0.318 |
| MI event | 34.4 | 33.589 | 0.811 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| UTI | 0.557 | 0.602 | -0.045 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.999 | 1.236 | -0.237 |
| GTI | 0.214 | 0.293 | -0.079 |

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### *5.6.3. 3rd line, patients who are no longer responding adequately to MET+TZD*

**Table 85 Complications: Empagliflozin 10mg Sitagliptin 100mg (MET+TZD)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| BDR | 25.405 | 25.08 | 0.325 |
| PDR | 4.486 | 4.364 | 0.122 |
| ME | 21.85 | 21.733 | 0.117 |
| SVL | 18.86 | 18.654 | 0.206 |
| Cataract | 10.914 | 10.83 | 0.084 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| MA | 33.234 | 32.902 | 0.332 |
| GRP | 20.851 | 20.55 | 0.301 |
| ESRD | 9.389 | 9.147 | 0.242 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| Ulcer | 40.836 | 40.643 | 0.193 |
| Rec ulcer | 132.918 | 132.454 | 0.464 |
| Amputation ulcer | 25.739 | 25.613 | 0.126 |
| Amputation rec Ulcer | 13.692 | 13.598 | 0.094 |
| Neuropathy | 67.99 | 67.711 | 0.279 |

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| CUMULATIVE INCIDENCE CVD (in %) | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| CHF event | 16.955 | 17.366 | -0.411 |
| PVD onset | 17.802 | 17.771 | 0.031 |
| Angina | 14.694 | 14.54 | 0.154 |
| Diabetes mortality | 24.751 | 24.625 | 0.126 |
| Stroke event | 28.903 | 29.148 | -0.245 |
| Event fatality | 34.506 | 34.214 | 0.292 |
| MI event | 34.869 | 34.204 | 0.665 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| UTI | 0.087 | 0.093 | -0.006 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.266 | 0.286 | -0.02 |
| GTI | 0.734 | 0 | 0.734 |

**Table 86 Complications: Empagliflozin 25mg Sitagliptin 100mg (MET+TZD)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| BDR | 25.163 | 25.08 | 0.083 |
| PDR | 4.374 | 4.364 | 0.01 |
| ME | 21.695 | 21.733 | -0.038 |
| SVL | 18.71 | 18.654 | 0.056 |
| Cataract | 10.91 | 10.83 | 0.08 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |

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| | | | |
|---|---|---|---|
| MA | 33.062 | 32.902 | 0.16 |
| GRP | 20.758 | 20.55 | 0.208 |
| ESRD | 9.308 | 9.147 | 0.161 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| Ulcer | 40.664 | 40.643 | 0.021 |
| Rec ulcer | 131.975 | 132.454 | -0.479 |
| Amputation ulcer | 25.575 | 25.613 | -0.038 |
| Amputation rec Ulcer | 13.488 | 13.598 | -0.11 |
| Neuropathy | 67.839 | 67.711 | 0.128 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| CHF event | 16.904 | 17.366 | -0.462 |
| PVD onset | 17.766 | 17.771 | -0.005 |
| Angina | 14.553 | 14.54 | 0.013 |
| Diabetes mortality | 24.648 | 24.625 | 0.023 |
| Stroke event | 29.031 | 29.148 | -0.117 |
| Event fatality | 34.423 | 34.214 | 0.209 |
| MI event | 34.539 | 34.204 | 0.335 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| UTI | 0.091 | 0.093 | -0.002 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.279 | 0.286 | -0.007 |
| GTI | 0.323 | 0 | 0.323 |

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**Table 87 Complications: Empagliflozin 10mg Canagliflozin 100mg (MET+TZD)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| BDR | 25.405 | 25.094 | 0.311 |
| PDR | 4.486 | 4.387 | 0.099 |
| ME | 21.85 | 21.719 | 0.131 |
| SVL | 18.86 | 18.728 | 0.132 |
| Cataract | 10.914 | 10.885 | 0.029 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| MA | 33.234 | 33.029 | 0.205 |
| GRP | 20.851 | 20.684 | 0.167 |
| ESRD | 9.389 | 9.211 | 0.178 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| Ulcer | 40.836 | 40.743 | 0.093 |
| Rec ulcer | 132.918 | 132.443 | 0.475 |
| Amputation ulcer | 25.739 | 25.64 | 0.099 |
| Amputation rec Ulcer | 13.692 | 13.692 | 0 |
| Neuropathy | 67.99 | 67.818 | 0.172 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| CHF event | 16.955 | 16.783 | 0.172 |
| PVD onset | 17.802 | 17.785 | 0.017 |
| Angina | 14.694 | 14.557 | 0.137 |

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| | | | |
|---|---|---|---|
| Diabetes mortality | 24.751 | 24.594 | 0.157 |
| Stroke event | 28.903 | 29.022 | -0.119 |
| Event fatality | 34.506 | 34.24 | 0.266 |
| MI event | 34.869 | 34.391 | 0.478 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| UTI | 0.087 | 0.092 | -0.005 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.266 | 0.282 | -0.016 |
| GTI | 0.734 | 0.268 | 0.466 |

**Table 88 Complications: Empagliflozin 25mg Canagliflozin 100mg (MET+TZD)**

| | | | |
|---|---|---|---|
| CUMULATIVE INCIDENCE EYE DISEASE | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| BDR | 25.163 | 25.094 | 0.069 |
| PDR | 4.374 | 4.387 | -0.013 |
| ME | 21.695 | 21.719 | -0.024 |
| SVL | 18.71 | 18.728 | -0.018 |
| Cataract | 10.91 | 10.885 | 0.025 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| MA | 33.062 | 33.029 | 0.033 |
| GRP | 20.758 | 20.684 | 0.074 |
| ESRD | 9.308 | 9.211 | 0.097 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |

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| | | | |
|---|---|---|---|
| Ulcer | 40.664 | 40.743 | -0.079 |
| Rec ulcer | 131.975 | 132.443 | -0.468 |
| Amputation ulcer | 25.575 | 25.64 | -0.065 |
| Amputation rec Ulcer | 13.488 | 13.692 | -0.204 |
| Neuropathy | 67.839 | 67.818 | 0.021 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| CHF event | 16.904 | 16.783 | 0.121 |
| PVD onset | 17.766 | 17.785 | -0.019 |
| Angina | 14.553 | 14.557 | -0.004 |
| Diabetes mortality | 24.648 | 24.594 | 0.054 |
| Stroke event | 29.031 | 29.022 | 0.009 |
| Event fatality | 34.423 | 34.24 | 0.183 |
| MI event | 34.539 | 34.391 | 0.148 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| UTI | 0.091 | 0.092 | -0.001 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.279 | 0.282 | -0.003 |
| GTI | 0.323 | 0.268 | 0.055 |

**Table 89 Complications: Empagliflozin 10mg Canagliflozin 300mg (MET+TZD)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| BDR | 25.405 | 25.106 | 0.299 |

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| | | | |
|---|---|---|---|
| PDR | 4.486 | 4.355 | 0.131 |
| ME | 21.85 | 21.573 | 0.277 |
| SVL | 18.86 | 18.677 | 0.183 |
| Cataract | 10.914 | 10.859 | 0.055 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| MA | 33.234 | 32.944 | 0.29 |
| GRP | 20.851 | 20.533 | 0.318 |
| ESRD | 9.389 | 9.173 | 0.216 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| Ulcer | 40.836 | 40.607 | 0.229 |
| Rec ulcer | 132.918 | 132.138 | 0.78 |
| Amputation ulcer | 25.739 | 25.658 | 0.081 |
| Amputation rec Ulcer | 13.692 | 13.653 | 0.039 |
| Neuropathy | 67.99 | 67.639 | 0.351 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| CHF event | 16.955 | 16.605 | 0.35 |
| PVD onset | 17.802 | 17.826 | -0.024 |
| Angina | 14.694 | 14.581 | 0.113 |
| Diabetes mortality | 24.751 | 24.607 | 0.144 |
| Stroke event | 28.903 | 29.336 | -0.433 |
| Event fatality | 34.506 | 34.156 | 0.35 |
| MI event | 34.869 | 34.028 | 0.841 |

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| CUMULATIVE ADVERSE EVENTS (in %) | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| UTI | 0.087 | 0.095 | -0.008 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.266 | 0.292 | -0.026 |
| GTI | 0.734 | 0.263 | 0.471 |

**Table 90 Complications: Empagliflozin 25mg Canagliflozin 300mg (MET+TZD)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| BDR | 25.163 | 25.106 | 0.057 |
| PDR | 4.374 | 4.355 | 0.019 |
| ME | 21.695 | 21.573 | 0.122 |
| SVL | 18.71 | 18.677 | 0.033 |
| Cataract | 10.91 | 10.859 | 0.051 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| MA | 33.062 | 32.944 | 0.118 |
| GRP | 20.758 | 20.533 | 0.225 |
| ESRD | 9.308 | 9.173 | 0.135 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| Ulcer | 40.664 | 40.607 | 0.057 |
| Rec ulcer | 131.975 | 132.138 | -0.163 |
| Amputation ulcer | 25.575 | 25.658 | -0.083 |

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| | | | |
|---|---|---|---|
| Amputation rec Ulcer | 13.488 | 13.653 | -0.165 |
| Neuropathy | 67.839 | 67.639 | 0.2 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| CHF event | 16.904 | 16.605 | 0.299 |
| PVD onset | 17.766 | 17.826 | -0.06 |
| Angina | 14.553 | 14.581 | -0.028 |
| Diabetes mortality | 24.648 | 24.607 | 0.041 |
| Stroke event | 29.031 | 29.336 | -0.305 |
| Event fatality | 34.423 | 34.156 | 0.267 |
| MI event | 34.539 | 34.028 | 0.511 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| UTI | 0.091 | 0.095 | -0.004 |
| Major hypo | 0 | 0 | 0 |
| Minor hypo | 0.279 | 0.292 | -0.013 |
| GTI | 0.323 | 0.263 | 0.06 |

### *5.6.4. Patients not responding adequately to INS*

**Table 91 Complications: Empagliflozin 10mg Dapagliflozin 10mg (INS)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Dapagliflozin 10mg | Incr. |
| BDR | 25.213 | 25.221 | -0.008 |
| PDR | 4.426 | 4.419 | 0.007 |

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| | | | |
|---|---|---|---|
| ME | 21.868 | 21.774 | 0.094 |
| SVL | 18.817 | 18.745 | 0.072 |
| Cataract | 10.881 | 10.849 | 0.032 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Dapagliflozin 10mg | Incr. |
| MA | 33.249 | 33.094 | 0.155 |
| GRP | 20.794 | 20.763 | 0.031 |
| ESRD | 9.343 | 9.326 | 0.017 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Dapagliflozin 10mg | Incr. |
| Ulcer | 40.821 | 40.787 | 0.034 |
| Rec ulcer | 132.726 | 132.564 | 0.162 |
| Amputation ulcer | 25.75 | 25.731 | 0.019 |
| Amputation rec Ulcer | 13.622 | 13.668 | -0.046 |
| Neuropathy | 68.116 | 68 | 0.116 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Dapagliflozin 10mg | Incr. |
| CHF event | 17.168 | 16.927 | 0.241 |
| PVD onset | 17.882 | 17.837 | 0.045 |
| Angina | 14.625 | 14.634 | -0.009 |
| Diabetes mortality | 24.754 | 24.678 | 0.076 |
| Stroke event | 29.156 | 29.163 | -0.007 |
| Event fatality | 34.575 | 34.48 | 0.095 |
| MI event | 34.9 | 34.66 | 0.24 |

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| CUMULATIVE ADVERSE EVENTS (in %) | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Dapagliflozin 10mg | Incr. |
| UTI | 0.435 | 0.503 | -0.068 |
| Major hypo | 0.172 | 0.177 | -0.005 |
| Minor hypo | 2.203 | 2.353 | -0.15 |
| GTI | 0.378 | 0.262 | 0.116 |

**Table 92 Complications: Empagliflozin 25mg Dapagliflozin 10mg (INS)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Dapagliflozin 10mg | Incr. |
| BDR | 25.229 | 25.221 | 0.008 |
| PDR | 4.418 | 4.419 | -0.001 |
| ME | 21.81 | 21.774 | 0.036 |
| SVL | 18.776 | 18.745 | 0.031 |
| Cataract | 10.872 | 10.849 | 0.023 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Dapagliflozin 10mg | Incr. |
| MA | 33.025 | 33.094 | -0.069 |
| GRP | 20.719 | 20.763 | -0.044 |
| ESRD | 9.211 | 9.326 | -0.115 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Dapagliflozin 10mg | Incr. |
| Ulcer | 40.697 | 40.787 | -0.09 |
| Rec ulcer | 132.208 | 132.564 | -0.356 |
| Amputation ulcer | 25.645 | 25.731 | -0.086 |

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| | | | |
|---|---|---|---|
| Amputation rec Ulcer | 13.637 | 13.668 | -0.031 |
| Neuropathy | 68.057 | 68 | 0.057 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Dapagliflozin 10mg | Incr. |
| CHF event | 17.098 | 16.927 | 0.171 |
| PVD onset | 17.848 | 17.837 | 0.011 |
| Angina | 14.631 | 14.634 | -0.003 |
| Diabetes mortality | 24.71 | 24.678 | 0.032 |
| Stroke event | 29.271 | 29.163 | 0.108 |
| Event fatality | 34.567 | 34.48 | 0.087 |
| MI event | 34.795 | 34.66 | 0.135 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Dapagliflozin 10mg | Incr. |
| UTI | 0.386 | 0.503 | -0.117 |
| Major hypo | 0.176 | 0.177 | -0.001 |
| Minor hypo | 2.632 | 2.353 | 0.279 |
| GTI | 0.859 | 0.262 | 0.597 |

**Table 93 Complications: Empagliflozin 10mg Sitagliptin 100mg (INS)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| BDR | 25.229 | 25.283 | -0.054 |
| PDR | 4.418 | 4.437 | -0.019 |
| ME | 21.81 | 21.888 | -0.078 |
| SVL | 18.776 | 18.815 | -0.039 |

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| | | | |
|---|---|---|---|
| Cataract | 10.872 | 10.866 | 0.006 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| MA | 33.025 | 33.351 | -0.326 |
| GRP | 20.719 | 20.9 | -0.181 |
| ESRD | 9.211 | 9.353 | -0.142 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| Ulcer | 40.697 | 40.812 | -0.115 |
| Rec ulcer | 132.208 | 132.194 | 0.014 |
| Amputation ulcer | 25.645 | 25.744 | -0.099 |
| Amputation rec Ulcer | 13.637 | 13.743 | -0.106 |
| Neuropathy | 68.057 | 68.386 | -0.329 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| CHF event | 17.098 | 17.544 | -0.446 |
| PVD onset | 17.848 | 17.825 | 0.023 |
| Angina | 14.631 | 14.823 | -0.192 |
| Diabetes mortality | 24.71 | 24.647 | 0.063 |
| Stroke event | 29.271 | 29.153 | 0.118 |
| Event fatality | 34.567 | 34.49 | 0.077 |
| MI event | 34.795 | 34.579 | 0.216 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Sitagliptin 100mg | Incr. |
| UTI | 0.386 | 0.39 | -0.004 |

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| | | | |
|---|---|---|---|
| Major hypo | 0.176 | 0.179 | -0.003 |
| Minor hypo | 2.632 | 2.661 | -0.029 |
| GTI | 0.859 | 0 | 0.859 |

**Table 94 Complications: Empagliflozin 25mg Sitagliptin 100mg (INS)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| BDR | 25.229 | 25.283 | -0.054 |
| PDR | 4.418 | 4.437 | -0.019 |
| ME | 21.81 | 21.888 | -0.078 |
| SVL | 18.776 | 18.815 | -0.039 |
| Cataract | 10.872 | 10.866 | 0.006 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| MA | 33.025 | 33.351 | -0.326 |
| GRP | 20.719 | 20.9 | -0.181 |
| ESRD | 9.211 | 9.353 | -0.142 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| Ulcer | 40.697 | 40.812 | -0.115 |
| Rec ulcer | 132.208 | 132.194 | 0.014 |
| Amputation ulcer | 25.645 | 25.744 | -0.099 |
| Amputation rec Ulcer | 13.637 | 13.743 | -0.106 |
| Neuropathy | 68.057 | 68.386 | -0.329 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |

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| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
|---|---|---|---|
| CHF event | 17.098 | 17.544 | -0.446 |
| PVD onset | 17.848 | 17.825 | 0.023 |
| Angina | 14.631 | 14.823 | -0.192 |
| Diabetes mortality | 24.71 | 24.647 | 0.063 |
| Stroke event | 29.271 | 29.153 | 0.118 |
| Event fatality | 34.567 | 34.49 | 0.077 |
| MI event | 34.795 | 34.579 | 0.216 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Sitagliptin 100mg | Incr. |
| UTI | 0.386 | 0.39 | -0.004 |
| Major hypo | 0.176 | 0.179 | -0.003 |
| Minor hypo | 2.632 | 2.661 | -0.029 |
| GTI | 0.859 | 0 | 0.859 |

**Table 95 Complications: Empagliflozin 10mg Canagliflozin 100mg (INS)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| BDR | 25.213 | 25.126 | 0.087 |
| PDR | 4.426 | 4.447 | -0.021 |
| ME | 21.868 | 21.699 | 0.169 |
| SVL | 18.817 | 18.75 | 0.067 |
| Cataract | 10.881 | 10.916 | -0.035 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |

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| | | | |
|---|---|---|---|
| MA | 33.249 | 33.043 | 0.206 |
| GRP | 20.794 | 20.659 | 0.135 |
| ESRD | 9.343 | 9.208 | 0.135 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| Ulcer | 40.821 | 40.678 | 0.143 |
| Rec ulcer | 132.726 | 132.232 | 0.494 |
| Amputation ulcer | 25.75 | 25.649 | 0.101 |
| Amputation rec Ulcer | 13.622 | 13.661 | -0.039 |
| Neuropathy | 68.116 | 67.761 | 0.355 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| CHF event | 17.168 | 16.936 | 0.232 |
| PVD onset | 17.882 | 17.921 | -0.039 |
| Angina | 14.625 | 14.67 | -0.045 |
| Diabetes mortality | 24.754 | 24.549 | 0.205 |
| Stroke event | 29.156 | 29.35 | -0.194 |
| Event fatality | 34.575 | 34.517 | 0.058 |
| MI event | 34.9 | 34.509 | 0.391 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 100mg | Incr. |
| UTI | 0.435 | 0.456 | -0.021 |
| Major hypo | 0.172 | 0.181 | -0.009 |
| Minor hypo | 2.203 | 3.247 | -1.044 |
| GTI | 0.378 | 0.268 | 0.11 |

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**Table 96 Complications: Empagliflozin 25mg Canagliflozin 100mg (INS)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| BDR | 25.229 | 25.182 | 0.047 |
| PDR | 4.418 | 4.397 | 0.021 |
| ME | 21.81 | 21.637 | 0.173 |
| SVL | 18.776 | 18.73 | 0.046 |
| Cataract | 10.872 | 10.938 | -0.066 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| MA | 33.025 | 33.038 | -0.013 |
| GRP | 20.719 | 20.68 | 0.039 |
| ESRD | 9.211 | 9.219 | -0.008 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| Ulcer | 40.697 | 40.736 | -0.039 |
| Rec ulcer | 132.208 | 132.227 | -0.019 |
| Amputation ulcer | 25.645 | 25.643 | 0.002 |
| Amputation rec Ulcer | 13.637 | 13.669 | -0.032 |
| Neuropathy | 68.057 | 67.916 | 0.141 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| CHF event | 17.098 | 17.041 | 0.057 |
| PVD onset | 17.848 | 17.891 | -0.043 |

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| | | | |
|---|---|---|---|
| Angina | 14.631 | 14.672 | -0.041 |
| Diabetes mortality | 24.71 | 24.638 | 0.072 |
| Stroke event | 29.271 | 29.319 | -0.048 |
| Event fatality | 34.567 | 34.479 | 0.088 |
| MI event | 34.795 | 34.549 | 0.246 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 100mg | Incr. |
| UTI | 0.386 | 0.394 | -0.008 |
| Major hypo | 0.176 | 0.181 | -0.005 |
| Minor hypo | 2.632 | 3.249 | -0.617 |
| GTI | 0.859 | 0.268 | 0.591 |

**Table 97 Complications: Empagliflozin 10mg Canagliflozin 300mg (INS)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| BDR | 25.213 | 25.069 | 0.144 |
| PDR | 4.426 | 4.366 | 0.06 |
| ME | 21.868 | 21.626 | 0.242 |
| SVL | 18.817 | 18.732 | 0.085 |
| Cataract | 10.881 | 10.897 | -0.016 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| MA | 33.249 | 32.942 | 0.307 |
| GRP | 20.794 | 20.53 | 0.264 |
| ESRD | 9.343 | 9.25 | 0.093 |

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| CUMULATIVE INCIDENCE ULCER | | | |
|---|---|---|---|
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| Ulcer | 40.821 | 40.656 | 0.165 |
| Rec ulcer | 132.726 | 132.293 | 0.433 |
| Amputation ulcer | 25.75 | 25.586 | 0.164 |
| Amputation rec Ulcer | 13.622 | 13.574 | 0.048 |
| Neuropathy | 68.116 | 67.758 | 0.358 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| CHF event | 17.168 | 16.825 | 0.343 |
| PVD onset | 17.882 | 17.849 | 0.033 |
| Angina | 14.625 | 14.603 | 0.022 |
| Diabetes mortality | 24.754 | 24.679 | 0.075 |
| Stroke event | 29.156 | 29.259 | -0.103 |
| Event fatality | 34.575 | 34.221 | 0.354 |
| MI event | 34.9 | 34.172 | 0.728 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 10mg | Canagliflozin 300mg | Incr. |
| UTI | 0.435 | 0.402 | 0.033 |
| Major hypo | 0.172 | 0.184 | -0.012 |
| Minor hypo | 2.203 | 3.215 | -1.012 |
| GTI | 0.378 | 0.259 | 0.119 |

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**Table 98 Complications: Empagliflozin 25mg Canagliflozin 300mg (INS)**

| CUMULATIVE INCIDENCE EYE DISEASE | | | |
|---|---|---|---|
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| BDR | 25.229 | 25.093 | 0.136 |
| PDR | 4.418 | 4.375 | 0.043 |
| ME | 21.81 | 21.591 | 0.219 |
| SVL | 18.776 | 18.658 | 0.118 |
| Cataract | 10.872 | 10.927 | -0.055 |
| CUMULATIVE INCIDENCE RENAL DISEASE | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| MA | 33.025 | 32.861 | 0.164 |
| GRP | 20.719 | 20.583 | 0.136 |
| ESRD | 9.211 | 9.187 | 0.024 |
| CUMULATIVE INCIDENCE ULCER | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| Ulcer | 40.697 | 40.656 | 0.041 |
| Rec ulcer | 132.208 | 132.614 | -0.406 |
| Amputation ulcer | 25.645 | 25.614 | 0.031 |
| Amputation rec Ulcer | 13.637 | 13.551 | 0.086 |
| Neuropathy | 68.057 | 67.696 | 0.361 |
| CUMULATIVE INCIDENCE CVD (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| CHF event | 17.098 | 16.761 | 0.337 |
| PVD onset | 17.848 | 17.86 | -0.012 |
| Angina | 14.631 | 14.649 | -0.018 |

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| | | | |
|---|---|---|---|
| Diabetes mortality | 24.71 | 24.548 | 0.162 |
| Stroke event | 29.271 | 29.236 | 0.035 |
| Event fatality | 34.567 | 34.213 | 0.354 |
| MI event | 34.795 | 34.079 | 0.716 |
| CUMULATIVE ADVERSE EVENTS (in %) | | | |
| | Empagliflozin 25mg | Canagliflozin 300mg | Incr. |
| UTI | 0.386 | 0.962 | -0.576 |
| Major hypo | 0.176 | 0.184 | -0.008 |
| Minor hypo | 2.632 | 3.218 | -0.586 |
| GTI | 0.859 | 0.26 | 0.599 |

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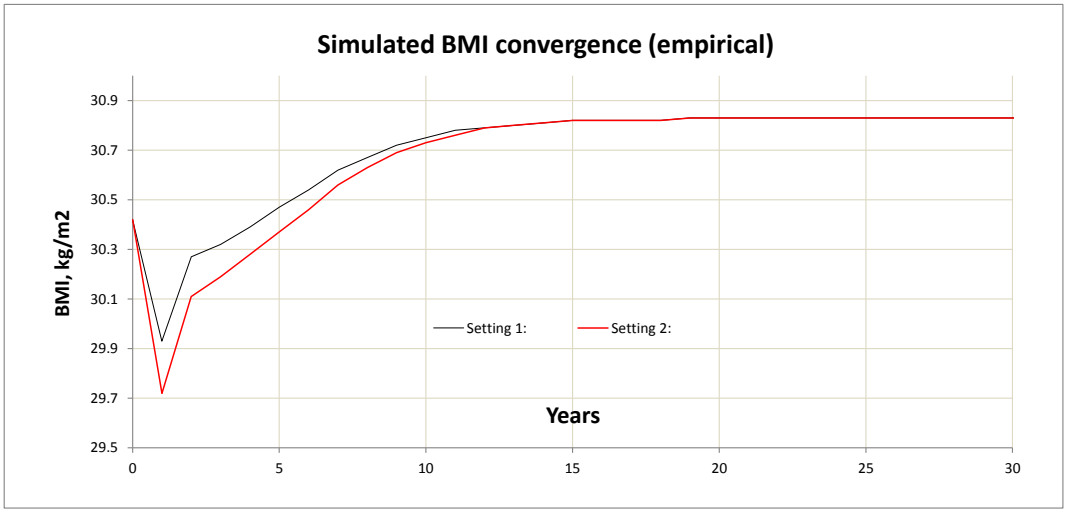
# 6. Sensitivity analyses (OWSA)

## 6.1. QWSA – 1: Convergence of BMI in the long run

A range of sensitivity analyses was conducted. In each of these analyses an empirical adjustment to weigh gain on full uptake of insulin was made in order to achieve a lifetime convergence of BMI in each of the treatment and comparator pairs. An example of such convergence that illustrates the method is shown below.




This section reports the impact of assumptions on BMI convergence on the costs and outcomes. These are shown in comparison with base case.

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## 6.2. Population I (OWSA – BMI convergence)

**Table 99 Impact of the BMI convergence assumptions on costs and outcomes (Tx added to MET)**

| | **Base case** | | | BMI Convergence | | |
|---|---|---|---|---|---|---|
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 61,761 | 7.963 | 13.32 | 61,761 | 7.963 | 13.32 |
| Dapagliflozin 10mg | 61,609 | 7.964 | 13.31 | 61,614 | 7.96 | 13.31 |
| Incrementals | 152 | -0.001 | 0.00 | 147 | 0.003 | 0.01 |
| | **Base case** | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 61,535 | 7.995 | 13.35 | 61,495 | 7.993 | 13.35 |
| Dapagliflozin 10mg | 61,609 | 7.964 | 13.31 | 61,582 | 7.964 | 13.31 |
| Incrementals | -74 | 0.031 | 0.00 | -87 | 0.029 | 0.04 |
| | **Base case** | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 61,761 | 7.963 | 13.32 | 61,783 | 7.944 | 13.31 |
| Sitagliptin 100mg | 61,778 | 7.899 | 13.25 | 61,778 | 7.899 | 13.25 |
| Incrementals | -18 | 0.064 | 0.00 | 5 | 0.045 | 0.07 |
| | **Base case** | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 61,535 | 7.995 | 13.35 | 61,557 | 7.97 | 13.35 |
| Sitagliptin 100mg | 61,778 | 7.899 | 13.25 | 61,778 | 7.899 | 13.25 |
| Incrementals | -243 | 0.096 | 0.00 | -221 | 0.071 | 0.10 |
| | **Base case** | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 61,535 | 7.995 | 13.35 | 61,535 | 7.995 | 13.35 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| Canagliflozin 300mg (vs Empagliflozin 25mg) | 61,829 | 7.986 | 13.34 | 61,829 | 7.986 | 13.34 |
| Incrementals | -294 | 0.009 | 0.00 | -294 | 0.009 | 0.02 |
| | **Base case** | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 61,761 | 7.963 | 13.32 | 61,761 | 7.963 | 13.32 |
| Canagliflozin 100mg (vs Empagliflozin 10mg) | 61,719 | 7.955 | 13.30 | 61,703 | 7.952 | 13.30 |
| Incrementals | 42 | 0.008 | 0.00 | 57 | 0.011 | 0.02 |
| | **Base case** | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 61,761 | 7.963 | 13.32 | 61,724 | 7.962 | 13.31 |
| Canagliflozin 300mg (vs Empagliflozin 10mg) | 61,912 | 7.99 | 13.34 | 61,877 | 7.984 | 13.34 |
| Incrementals | -151 | -0.027 | 0.00 | -154 | -0.022 | -0.03 |
| | **Base case** | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 61,535 | 7.995 | 13.35 | 61,532 | 7.993 | 13.35 |
| Canagliflozin 100mg (vs Empagliflozin 25mg) | 61,643 | 7.949 | 13.29 | 61,643 | 7.949 | 13.29 |
| Incrementals | -109 | 0.046 | 0.00 | -111 | 0.044 | 0.06 |

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**Table 100 Impact of the BMI convergence assumptions on cost-effectiveness (Tx added to MET)**

| ( Empagliflozin 10mg) vs. (Dapagliflozin 10mg ) | | | |
|---|---|---|---|
| Incr Cost | Incr QALY | ICER | Scenario |
| **152** | **-0.001** | **Dominated** | Base case |
| 147 | 0.003 | 49,000 | BMI convergence |
| ( Empagliflozin 25mg) vs. (Dapagliflozin 10mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-74** | **0.031** | **Dominant** | Base case |
| -87 | 0.029 | Dominant | BMI convergence |
| ( Empagliflozin 10mg) vs. (Sitagliptin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-18** | **0.064** | **Dominant** | Base case |
| 5 | 0.045 | 111 | BMI convergence |
| ( Empagliflozin 25mg) vs. (Sitagliptin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-243** | **0.096** | **Dominant** | Base case |
| -221 | 0.071 | Dominant | BMI convergence |
| ( Empagliflozin 25mg) vs. (Canagliflozin 300mg (vs Empagliflozin 25mg) ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-294** | **0.009** | **Dominant** | Base case |
| -294 | 0.009 | Dominant | BMI convergence [17] |
| ( Empagliflozin 10mg) vs. (Canagliflozin 100mg) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **42** | **0.008** | **5,250** | Base case |

[17] There is no difference in the BMI inputs in the base case and therefore no changes in the BMI convergence scenario for this treatment and comparator arm

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| | | | |
|---|---|---|---|
| 57 | 0.011 | 5,182 | BMI convergence |
| ( Empagliflozin 10mg) vs. (Canagliflozin 300mg (vs Empagliflozin 10mg) ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-151** | **-0.027** | **5,593** | Base case |
| -154 | -0.022 | 7,000 | BMI convergence |
| ( Empagliflozin 25mg) vs. (Canagliflozin 100mg (vs Empagliflozin 25mg) ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-109** | **0.046** | **Dominant** | Base case |
| -111 | 0.044 | Dominant | BMI convergence |

## 6.3. Population II (OWSA – BMI convergence)

Table 101 below shows present the comparison of absolute and incremental outcomes in the base case analysis. The next table (Table 102) shows a summary of cost effectiveness in base case settings and in the settings assuming convergence of BMI over time.

**Table 101 Impact of the BMI convergence assumptions on costs and outcomes (Tx added to MET+SU)**

| | **Base case** | | | BMI Convergence | | |
|---|---|---|---|---|---|---|
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 58,778 | 7.571 | 12.79 | 58,772 | 7.543 | 12.79 |
| Sitagliptin 100mg | 59,390 | 7.466 | 12.69 | 59,364 | 7.466 | 12.69 |
| Incrementals | -612 | 0.105 | 0.10 | -592 | 0.078 | 0.10 |
| | **Base case** | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 58,711 | 7.564 | 12.77 | 59,448 | 7.509 | 12.75 |
| Sitagliptin 100mg | 59,390 | 7.467 | 12.69 | 59,708 | 7.462 | 12.70 |
| Incrementals | -679 | 0.097 | 0.08 | -260 | 0.047 | 0.05 |

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| | **Base case** | | | BMI Convergence | | |
|---|---|---|---|---|---|---|
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 58,778 | 7.571 | 12.79 | 58,747 | 7.562 | 12.79 |
| Canagliflozin 100mg | 58,794 | 7.569 | 12.80 | 58,757 | 7.568 | 12.80 |
| Incrementals | -16 | 0.002 | -0.01 | -10 | -0.006 | -0.01 |
| | **Base case** | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 58,711 | 7.564 | 12.77 | 59,140 | 7.524 | 12.74 |
| Canagliflozin 100mg | 58,794 | 7.569 | 12.80 | 58,866 | 7.555 | 12.79 |
| Incrementals | -83 | -0.005 | -0.03 | 275 | -0.031 | -0.05 |
| | **Base case** | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 58,778 | 7.571 | 12.79 | 58,715 | 7.541 | 12.75 |
| Canagliflozin 300mg | 59,000 | 7.616 | 12.85 | 59,220 | 7.598 | 12.83 |
| Incrementals | -222 | -0.045 | -0.06 | -504 | -0.057 | -0.09 |
| | **Base case** | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 58,711 | 7.564 | 12.77 | 58,670 | 7.564 | 12.77 |
| Canagliflozin 300mg | 59,000 | 7.616 | 12.85 | 58,966 | 7.613 | 12.85 |
| Incrementals | -289 | -0.052 | -0.08 | -296 | -0.049 | -0.08 |

**Table 102 Impact of the BMI convergence assumptions on cost-effectiveness (Tx added to MET+SU)**

| ( Empagliflozin 10mg) vs. (Sitagliptin 100mg ) | | | |
|---|---|---|---|
| Incr Cost | Incr QALY | ICER | Scenario |

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| | | | |
|---|---|---|---|
| **-612** | **0.105** | **Dominant** | Base case |
| -592 | 0.078 | Dominant | BMI convergence |
| ( Empagliflozin 25mg) vs. (Sitagliptin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-679** | **0.097** | **Dominant** | Base case |
| -659 | 0.066 | Dominant | BMI convergence |
| ( Empagliflozin 10mg) vs. (Canagliflozin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-16** | **0.002** | **Dominant** | Base case |
| -10 | -0.006 | 1,667 | BMI convergence |
| ( Empagliflozin 25mg) vs. (Canagliflozin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-83** | **-0.005** | **16,600** | Base case |
| -61 | -0.014 | 4,357 | BMI convergence |
| ( Empagliflozin 10mg) vs. (Canagliflozin 300mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-222** | **-0.045** | **4,933** | Base case |
| -215 | -0.041 | 5,244 | BMI convergence |
| ( Empagliflozin 25mg) vs. (Canagliflozin 300mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-289** | **-0.052** | **5,558** | Base case |
| -296 | -0.049 | 6,041 | BMI convergence |

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## 6.4. Population III (OWSA – BMI convergence)

**Table 103 Impact of the BMI convergence assumptions on costs and outcomes (Tx added to MET+TZD)**

| | Base case | | | BMI Convergence | | |
|---|---|---|---|---|---|---|
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 59,166 | 7.542 | 12.75 | 59,137 | 7.516 | 12.74 |
| Sitagliptin 100mg | 58,644 | 7.553 | 12.80 | 58,610 | 7.553 | 12.80 |
| Incrementals | 522 | -0.011 | 0.00 | 527 | -0.037 | -0.05 |
| | Base case | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 58,854 | 7.561 | 12.77 | 58,896 | 7.54 | 12.77 |
| Sitagliptin 100mg | 58,644 | 7.553 | 12.80 | 58,610 | 7.553 | 12.80 |
| Incrementals | 210 | 0.008 | 0.00 | 286 | -0.012 | -0.02 |
| | Base case | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 59,166 | 7.542 | 12.75 | 59,146 | 7.542 | 12.74 |
| Canagliflozin 100mg | 58,751 | 7.579 | 12.78 | 58,722 | 7.574 | 12.78 |
| Incrementals | 415 | -0.037 | 0.00 | 424 | -0.032 | 0.00 |
| | Base case | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 58,854 | 7.561 | 12.77 | 58,838 | 7.56 | 12.77 |
| Canagliflozin 100mg | 58,751 | 7.579 | 12.78 | 58,721 | 7.573 | 12.78 |
| Incrementals | 103 | -0.018 | 0.00 | 117 | -0.013 | 0.00 |
| | Base case | | | BMI Convergence | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 59,166 | 7.542 | 12.75 | 59,146 | 7.542 | 12.74 |
| Canagliflozin 300mg | 59,106 | 7.614 | 12.81 | 59,110 | 7.598 | 12.81 |
| Incrementals | 60 | -0.072 | 0.00 | 36 | -0.056 | 0.00 |

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| | Base case | | | BMI Convergence | | |
|---|---|---|---|---|---|---|
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 58,854 | 7.561 | 12.77 | 58,838 | 7.56 | 12.77 |
| Canagliflozin 300mg | 59,106 | 7.614 | 12.81 | 59,111 | 7.597 | 12.81 |
| Incrementals | -252 | -0.053 | 0.00 | -273 | -0.037 | 0.00 |

**Table 104 Impact of the BMI convergence assumptions on incremental cost-effectiveness (Tx added to MET+TZD)**

| ( Empagliflozin 10mg) vs. (Sitagliptin 100mg ) | | | |
|---|---|---|---|
| Incr Cost | Incr QALY | ICER | Scenario |
| **522** | **-0.011** | **Dominated** | Base case |
| 527 | -0.037 | Dominated | BMI convergence |
| ( Empagliflozin 25mg) vs. (Sitagliptin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **210** | **0.008** | **26,250** | Base case |
| 286 | **-0.012** | Dominated | BMI convergence |
| ( Empagliflozin 10mg) vs. (Canagliflozin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **415** | **-0.037** | **Dominated** | Base case |
| 424 | -0.032 | Dominated | BMI convergence |
| ( Empagliflozin 25mg) vs. (Canagliflozin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **103** | **-0.018** | **Dominated** | Base case |
| 117 | -0.013 | Dominated | BMI convergence |
| ( Empagliflozin 10mg) vs. (Canagliflozin 300mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **60** | **-0.072** | **Dominated** | Base case |
| 36 | -0.056 | Dominated | BMI convergence |

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| ( Empagliflozin 25mg) vs. (Canagliflozin 300mg ) | | | |
|---|---|---|---|
| Incr Cost | Incr QALY | ICER | Scenario |
| **-252** | **-0.053** | **4,755** | Base case |
| -273 | -0.037 | 7,378 | BMI convergence |

## 6.5. Population IV (OWSA – BMI convergence)

**Table 105 Impact of the BMI convergence assumptions on costs and outcomes (Tx added to INS)**

| | **Base case** | | | **BMI Convergence** | | |
|---|---|---|---|---|---|---|
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 60,539 | 7.523 | 12.74 | 60,539 | 7.523 | 12.74 |
| Dapagliflozin 10mg | 60,360 | 7.545 | 12.76 | 60,372 | 7.538 | 12.76 |
| Incrementals | 179 | -0.023 | -0.02 | 166 | -0.015 | -0.02 |
| | **Base case** | | | **BMI Convergence** | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 60,428 | 7.534 | 12.74 | 60,394 | 7.534 | 12.76 |
| Dapagliflozin 10mg | 60,360 | 7.545 | 12.76 | 60,342 | 7.54 | 12.76 |
| Incrementals | 68 | -0.011 | -0.02 | 53 | -0.006 | 0.00 |
| | **Base case** | | | **BMI Convergence** | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 60,539 | 7.523 | 12.74 | 60,558 | 7.503 | 12.74 |
| Sitagliptin 100mg | 60,564 | 7.511 | 12.76 | 60,564 | 7.511 | 12.76 |
| Incrementals | -25 | -0.021 | -0.02 | -5 | -0.008 | 0.00 |
| | **Base case** | | | **BMI Convergence** | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 60,428 | 7.534 | 12.76 | 60,462 | 7.513 | 12.76 |
| Sitagliptin 100mg | 60,530 | 7.499 | 12.74 | 60,564 | 7.511 | 12.76 |

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| | Base case | | | BMI Convergence | | |
|---|---|---|---|---|---|---|
| Incrementals | -102 | 0.036 | 0.01 | -102 | 0.002 | -0.01 |
| | **Base case** | | | **BMI Convergence** | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 60,539 | 7.523 | 12.74 | 60,539 | 7.523 | 12.74 |
| Canagliflozin 100mg | 60,235 | 7.545 | 12.77 | 60,231 | 7.54 | 12.77 |
| Incrementals | 304 | -0.023 | -0.03 | 308 | -0.017 | -0.03 |
| | **Base case** | | | **BMI Convergence** | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 60,428 | 7.534 | 12.76 | 60,428 | 7.534 | 12.76 |
| Canagliflozin 100mg | 60,333 | 7.551 | 12.78 | 60,333 | 7.549 | 12.78 |
| Incrementals | 95 | -0.017 | -0.02 | 95 | -0.015 | -0.02 |
| | **Base case** | | | **BMI Convergence** | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 10mg | 60,539 | 7.523 | 12.74 | 60,539 | 7.523 | 12.74 |
| Canagliflozin 300mg | 60,599 | 7.583 | 12.81 | 60,592 | 7.573 | 12.81 |
| Incrementals | -60 | -0.061 | -0.07 | -53 | -0.05 | 0.00 |
| | **Base case** | | | **BMI Convergence** | | |
| | Cost | QALY | LY | Cost | QALY | LY |
| Empagliflozin 25mg | 60,428 | 7.534 | 12.76 | 60,428 | 7.534 | 12.76 |
| Canagliflozin 300mg | 60,476 | 7.584 | 12.81 | 60,479 | 7.576 | 12.81 |
| Incrementals | -48 | -0.049 | -0.05 | -51 | -0.042 | -0.06 |

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**Table 106 Impact of the BMI convergence assumptions on costs effectiveness (Tx added to INS)**

| ( Empagliflozin 10mg) vs. (Dapagliflozin 10mg ) | | | |
|---|---|---|---|
| Incr Cost | Incr QALY | ICER | Scenario |
| **179** | **-0.023** | **Dominated** | Base case |
| 166 | -0.015 | Dominated | BMI convergence |
| ( Empagliflozin 25mg) vs. (Dapagliflozin 10mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **68** | **-0.011** | **Dominated** | Base case |
| 53 | -0.006 | Dominated | BMI convergence |
| ( Empagliflozin 10mg) vs. (Sitagliptin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-25** | **-0.021** | **1,190** | Base case |
| -5 | -0.008 | 625 | BMI convergence |
| ( Empagliflozin 25mg) vs. (Sitagliptin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-102** | **0.036** | **Dominant** | Base case |
| -102 | 0.002 | Dominant | BMI convergence |
| ( Empagliflozin 10mg) vs. (Canagliflozin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **304** | **-0.023** | **Dominated** | Base case |
| 308 | -0.017 | Dominated | BMI convergence |
| ( Empagliflozin 25mg) vs. (Canagliflozin 100mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **95** | **-0.017** | **Dominated** | Base case |
| 95 | -0.015 | Dominated | BMI convergence |
| ( Empagliflozin 10mg) vs. (Canagliflozin 300mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |

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| | | | |
|---|---|---|---|
| **-60** | **-0.061** | **984** | Base case |
| -53 | -0.05 | 1,060 | BMI convergence |
| ( Empagliflozin 25mg) vs. (Canagliflozin 300mg ) | | | |
| Incr Cost | Incr QALY | ICER | Scenario |
| **-48** | **-0.049** | **980** | Base case |
| -51 | -0.042 | 1,214 | BMI convergence |

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## 6.6. OWSA - 2: Setting SBP change to 0 for Sitagliptin

This sensitivity analysis was conducted to explore the impact of an assumption made in the base case analysis, i.e. that the treatment effect on systolic blood pressure in sitagliptin arms was equal to the treatment effect in the respective empagliflozin arms. In this sensitivity analysis the impact of treatment on SBP in the sitagliptin arms in population III and population IV was assumed to be 0.

## 6.7. Population III

**Table 107: No SBP effect (=0) in the sitagliptin arm vs empagliflozin 10mg**

| **Base case**[18] | **Cost** | **QALY** | **LY** |
|---|---|---|---|
| Empagliflozin 10mg | 59,166 | 7.542 | 12.75 |
| Sitagliptin 100mg | 58,644 | 7.553 | 12.80 |
| Incremental | 522 | -0.011 | |
| **No SBP effect** | | | |
| Empagliflozin 10mg | 59,146 | 7.542 | 12.744 |
| Sitagliptin 100mg | 58,987 | 7.517 | 12.747 |
| Incrementals | 159 | 0.025 | |

**Table 108: No SBP effect (=0) in sitagliptin vs empagliflozin 25mg**

| **Base case** | **Cost** | **QALY** | **LY** |
|---|---|---|---|
| Empagliflozin 25mg | 58854 | 7.56 | 12.77 |
| Sitagliptin 100mg | 58644 | 7.553 | 12.80 |
| Incremental | 210 | 0.008 | |
| **No SBP effect** | | | |
| Empagliflozin 25mg | 58,838 | 7.56 | 12.77 |
| Sitagliptin 100mg | 58,987 | 7.517 | 12.747 |
| Incrementals | -149 | 0.043 | |

[18] Small variations in costs and outcomes are possible due to effect of randomness

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## 6.8. Population IV

**Table 109: No SBP effect (=0) in sitagliptin vs empagliflozin 10mg**

| **Base case** | **Cost** | **QALY** | **LY** |
|---|---|---|---|
| Empagliflozin 10mg | 60539 | 7.523 | 12.74 |
| Sitagliptin 100mg | 60,360 | 7.545 | 12.76 |
| Incremental | 179 | -0.023 | -0.0190 |
| **No SBP effect** | | | |
| Empagliflozin 10mg | 60511 | 7.522 | 12.74 |
| Sitagliptin 100mg | 60,719 | 7.481 | 12.716 |
| Incrementals | -208 | 0.04 | 0.0240 |

**Table 110: No SBP effect (=0) in sitagliptin vs empagliflozin 10m**

| **Base case** | **Cost** | **QALY** | **LY** |
|---|---|---|---|
| Empagliflozin 25mg | 60511 | 7.522 | 12.74 |
| Sitagliptin 100mg | 60719 | 7.481 | 12.716 |
| Incremental | -208 | 0.04 | |
| **No SBP effect** | | | |
| Empagliflozin 25mg | 60394 | 7.534 | 12.76 |
| Sitagliptin 100mg | 60828 | 7.476 | 12.71 |
| Incrementals | -434 | 0.058 | 0.05 |

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# 7. Probabilistic sensitivity analysis (PSA)

This section represents the results of the probabilistic sensitivity analysis (PSA) conducted for each treatment and comparator pair within each populations in the study. The scope of the PSA includes:

**For population I: Patients undergoing 2nd-line treatment who are no longer responding adequately to metformin (MET)**

| | |
|---|---|
| Empagliflozin 10mg | Dapagliflozin 10mg |
| Empagliflozin 25mg | Dapagliflozin 10mg |
| Empagliflozin 10mg | Sitagliptin 100mg |
| Empagliflozin 25mg | Sitagliptin 100mg |

**For population II: Patients undergoing 3rd line treatment who are no longer responding adequately to metformin (MET) plus sulfonylurea (SU)**

| | |
|---|---|
| Empagliflozin 10mg | Sitagliptin 100mg |
| Empagliflozin 25mg | Sitagliptin 100mg |
| Empagliflozin 10mg | Canagliflozin 100mg |
| Empagliflozin 25mg | Canagliflozin 100mg |
| Empagliflozin 10mg | Canagliflozin 300mg |
| Empagliflozin 25mg | Canagliflozin 300mg |

**For population III: Patients undergoing 3rd line treatment who are no longer responding adequately to metformin TZD**

| | |
|---|---|
| Empagliflozin 10mg | Sitagliptin 100mg |
| Empagliflozin 25mg | Sitagliptin 100mg |
| Empagliflozin 10mg | Canagliflozin 100mg |
| Empagliflozin 25mg | Canagliflozin 100mg |
| Empagliflozin 10mg | Canagliflozin 300mg |
| Empagliflozin 25mg | Canagliflozin 300mg |

**For population IV: Patients who are no longer responding adequately to backbone insulin therapy (INS)**

| | |
|---|---|
| Empagliflozin 10mg | Dapagliflozin 10mg |
| Empagliflozin 25mg | Dapagliflozin 10mg |
| Empagliflozin 10mg | Sitagliptin 100mg |
| Empagliflozin 25mg | Sitagliptin 100mg |

In this section we use abbreviated notation for the above populations, e.g. Population I-IV. The PSAs were conducted with both cost and clinical input parameters were samples the variation in unit costs were assumed to be 20% of the means; the sampling of the clinical inputs was based on standard deviations drawn from the network meta-analysis report (provided by BI).

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The results of the PSAs are presented as PSA scatterplot (plotting the incremental costs vs incremental QALYs) and cost-effectiveness acceptability curves. Please note that the PSA results below are always presented for Empagliflozin versus comparison regimen. In the PSA instances where the comparator regimen appears to be more effective than Empagliflozin, the scatterplot is shifted to the left-hand side of the chart, and the cost-effectiveness acceptability curve would have a downward slope.

The PSA data tables are accessible on the CDM website and are also available in Excel format.

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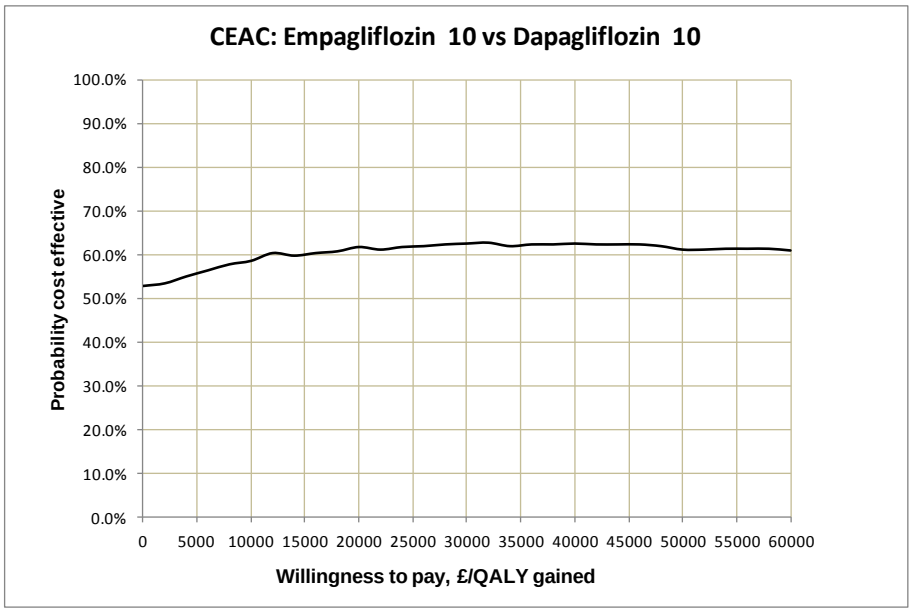
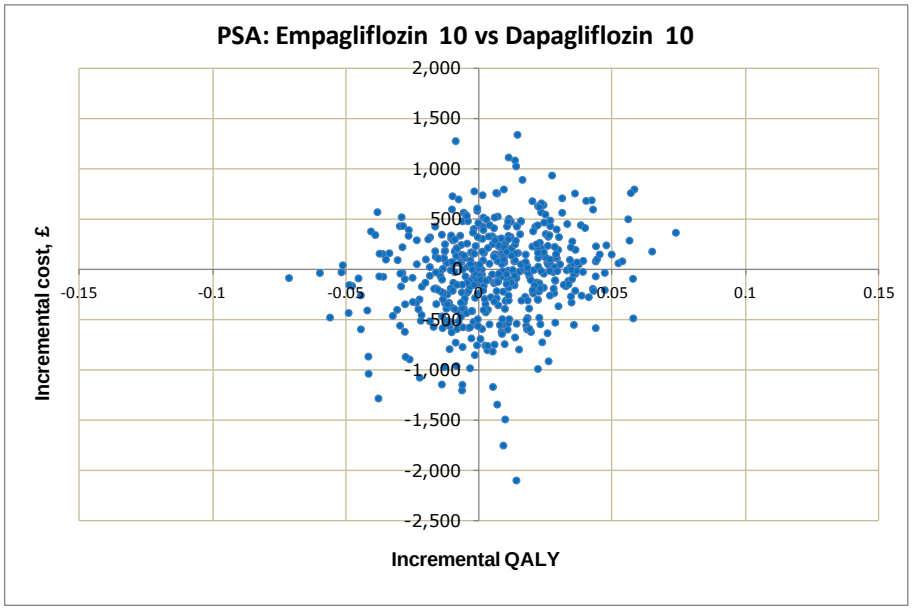
## 7.1. PSA in Population I

Patients undergoing 2nd-line treatment who are no longer responding adequately to metformin (MET)

### *7.1.1. Empagliflozin 10mg vs Dapagliflozin 10mg (Population I)*




### *7.1.2. Empagliflozin 25mg vs Dapagliflozin 10mg(Population I)*

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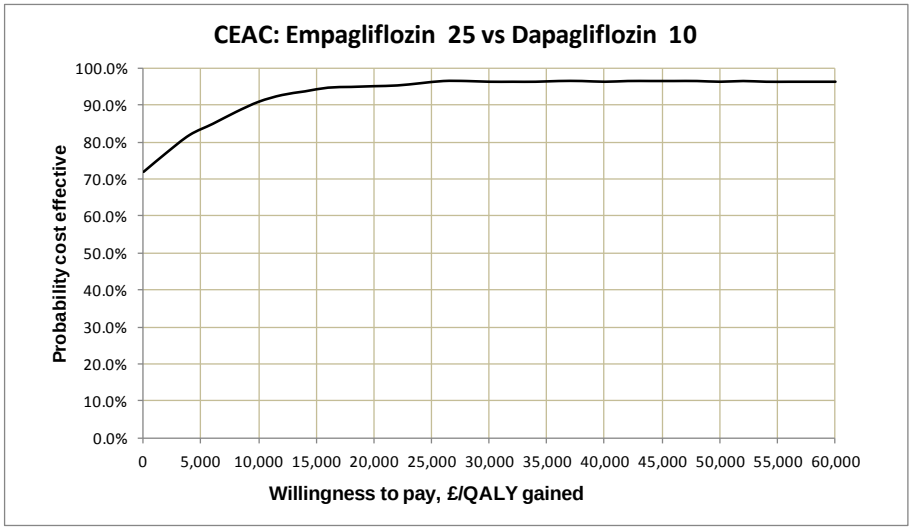


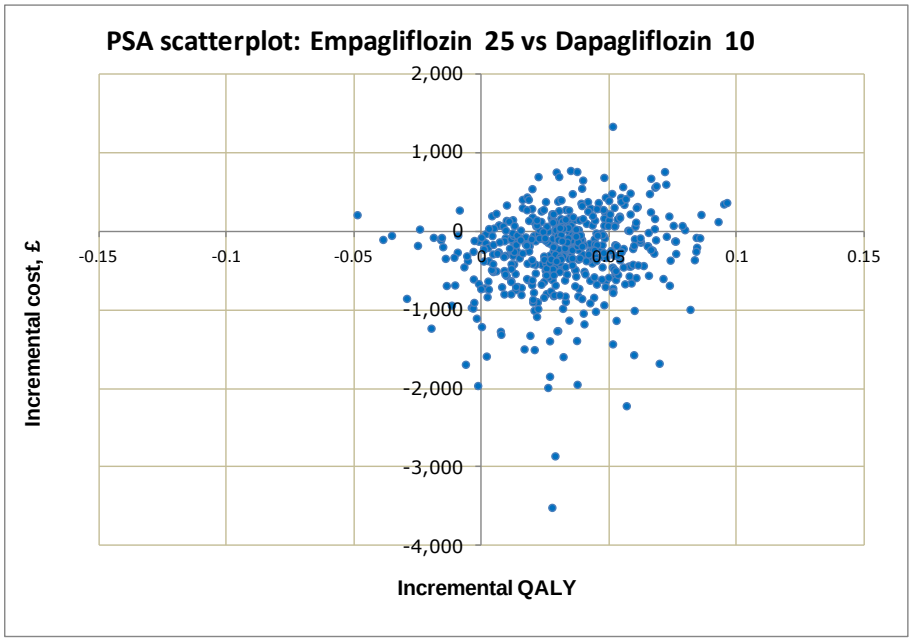


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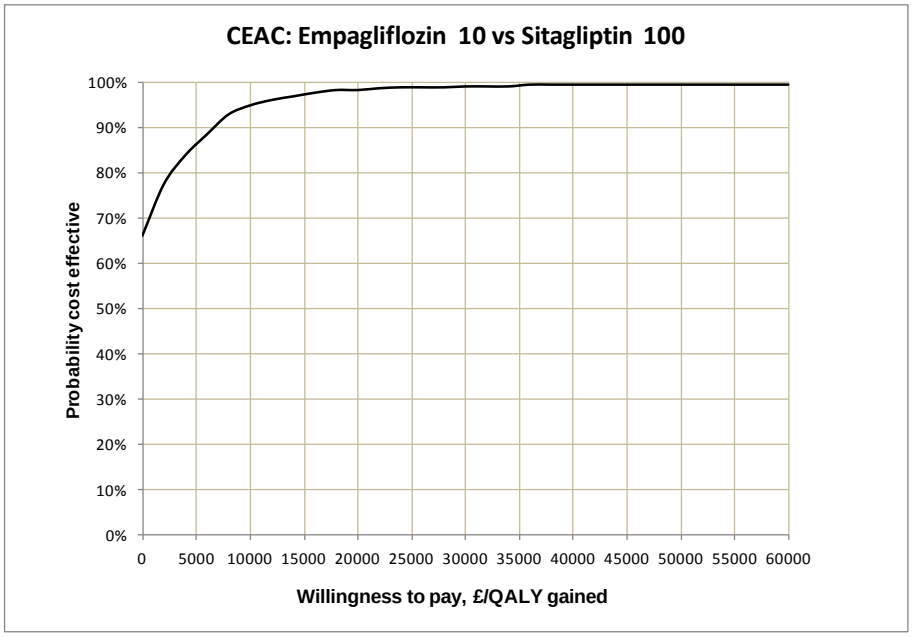
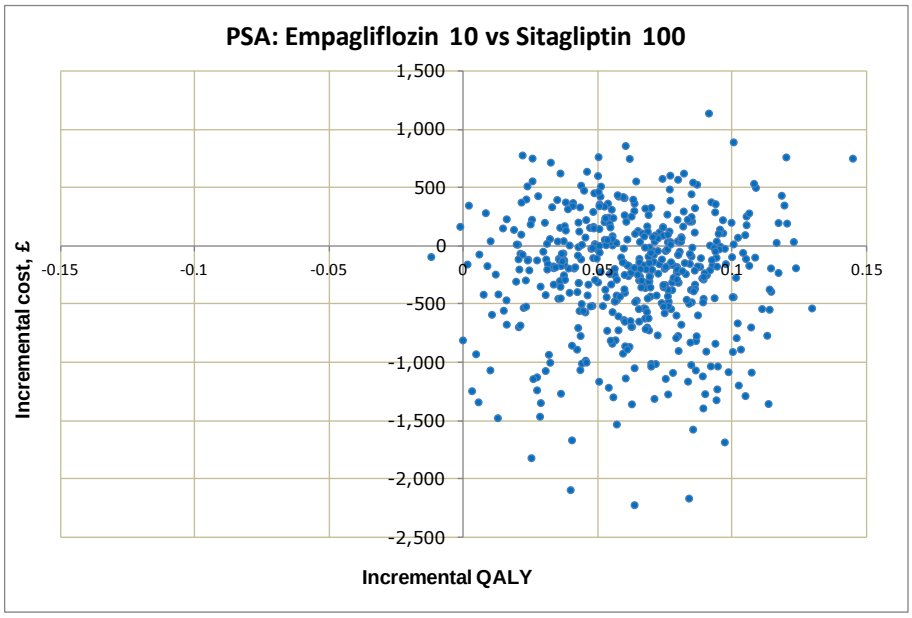
### 7.1.3. Empagliflozin 10mg vs Sitagliptin 100mg (Population I)

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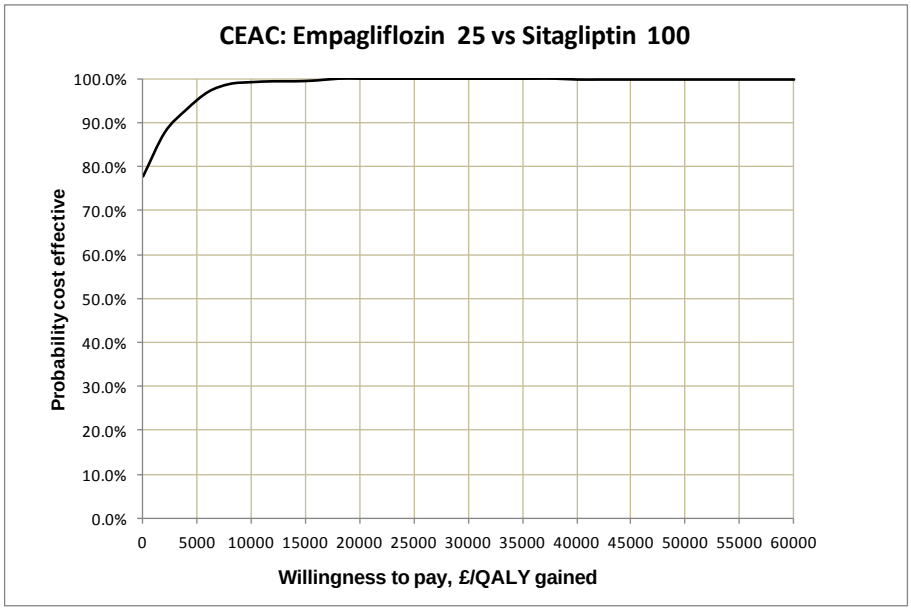
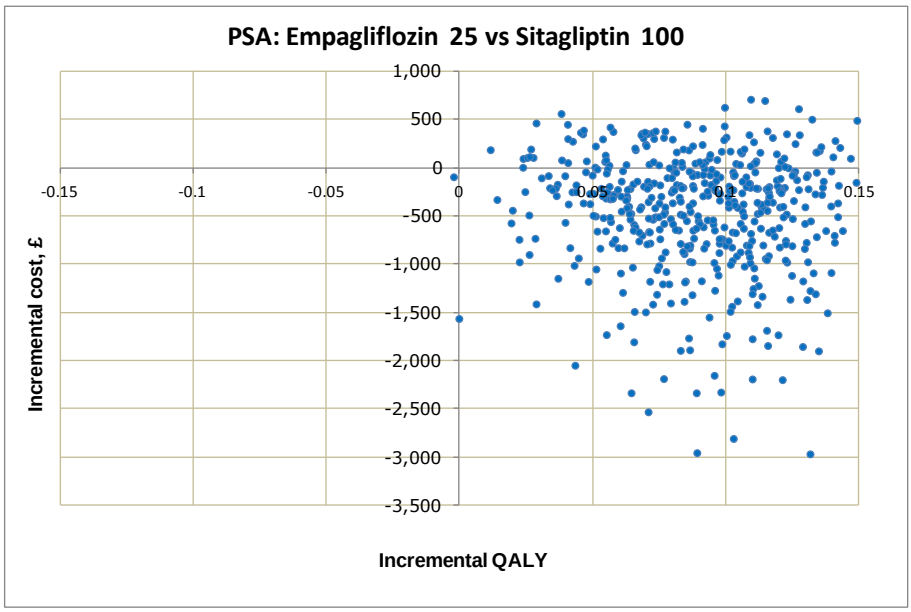
### 7.1.4. Empagliflozin 25mg vs Sitagliptin 100mg (Population I)

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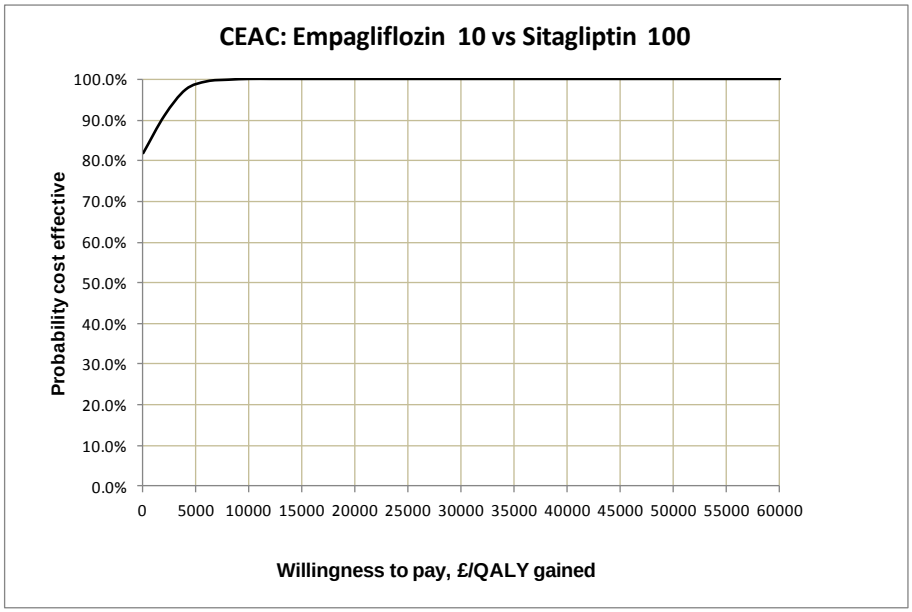
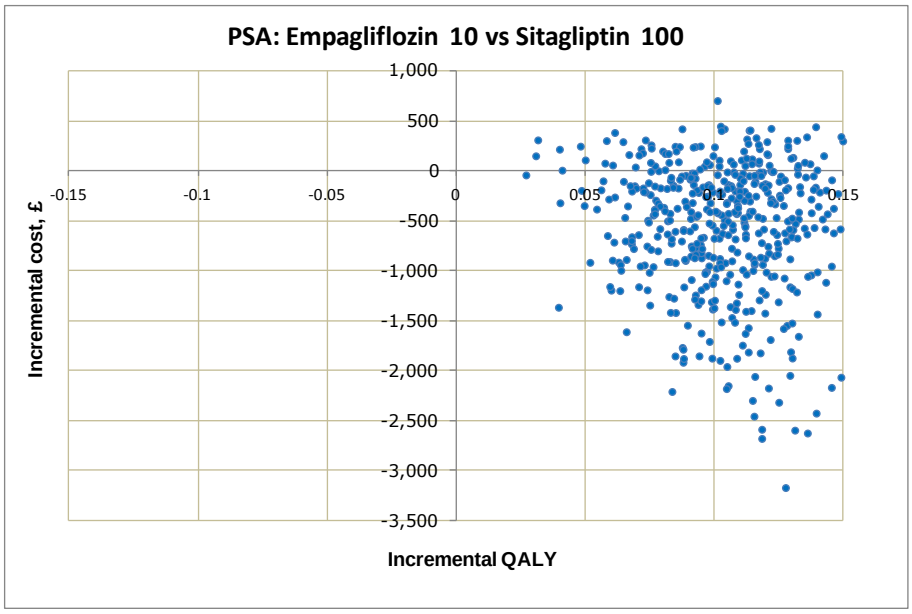
## 7.2. PSA in Population II

Patients undergoing 3rd line treatment who are no longer responding adequately to metformin (MET) plus sulfonylurea (SU)

### *7.2.1. Empagliflozin 10mg vs Sitagliptin 100mg (Population II)*

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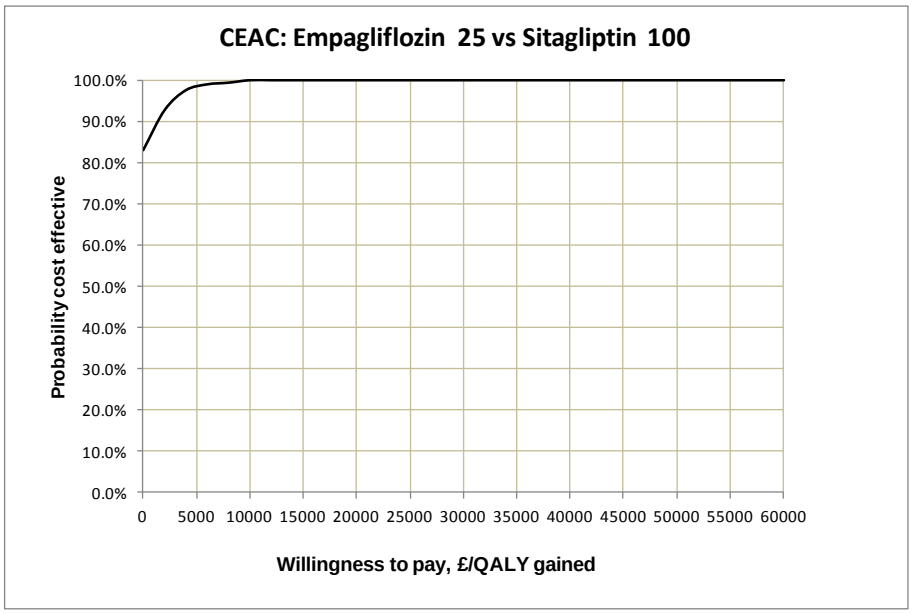
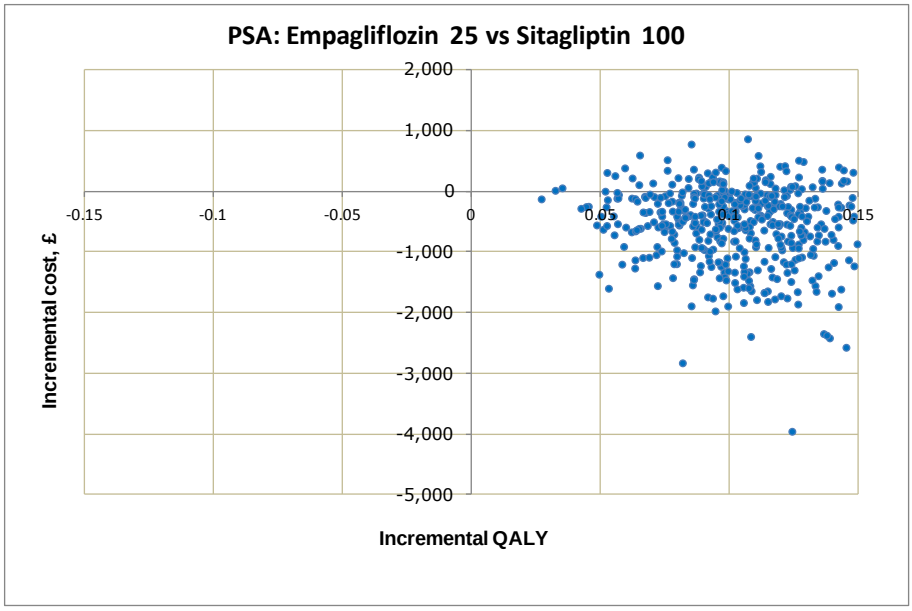
### 7.2.2. Empagliflozin 25mg vs Sitagliptin 100mg (Population II)

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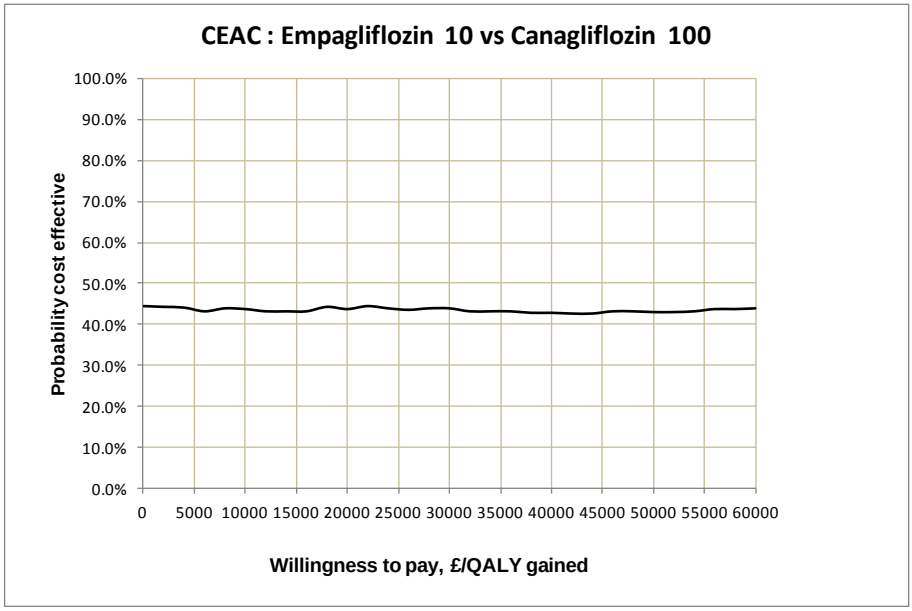
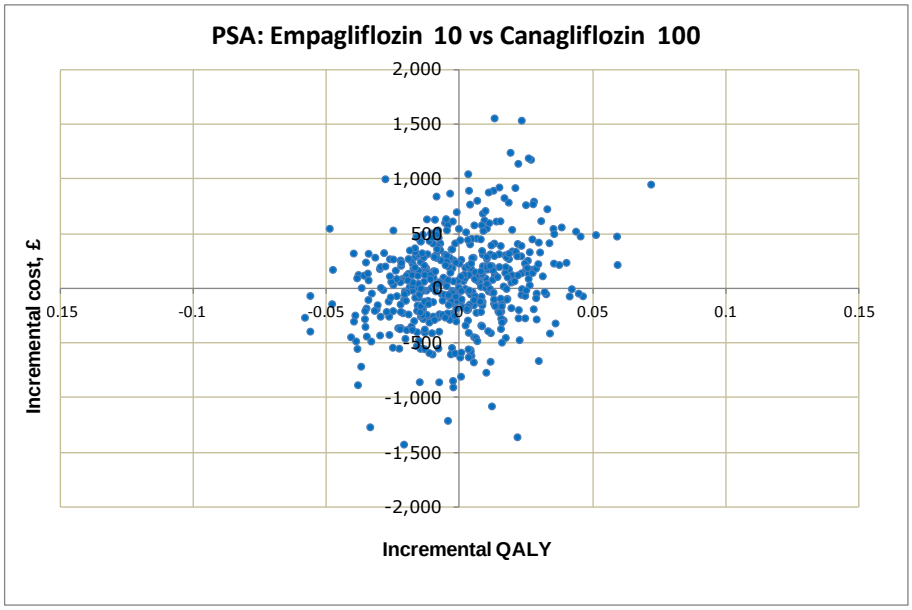
### *7.2.3. Empagliflozin 10mg vs Canagliflozin 100mg (Population II)*

Patients undergoing 3rd line treatment who are no longer responding adequately to metformin (MET) plus sulfonylurea (SU)

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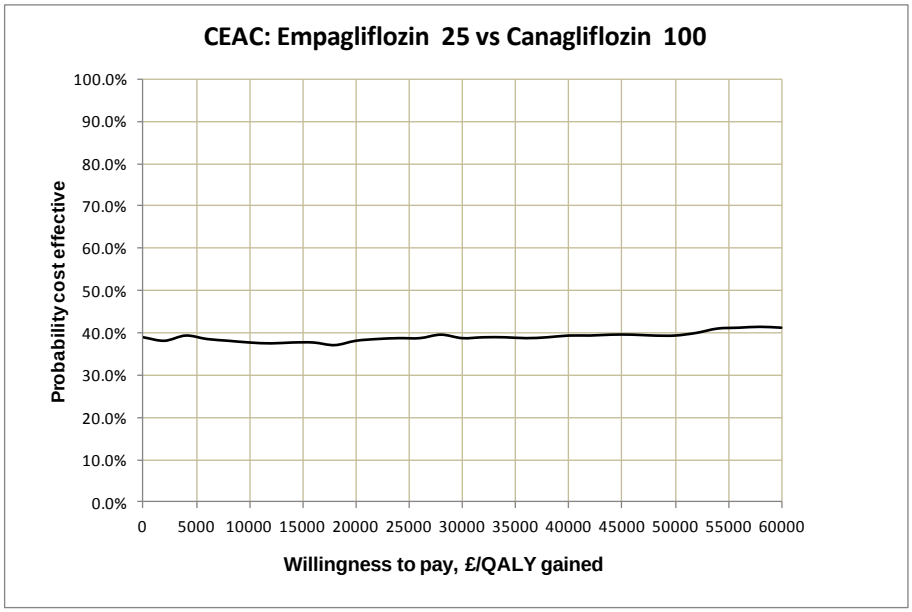
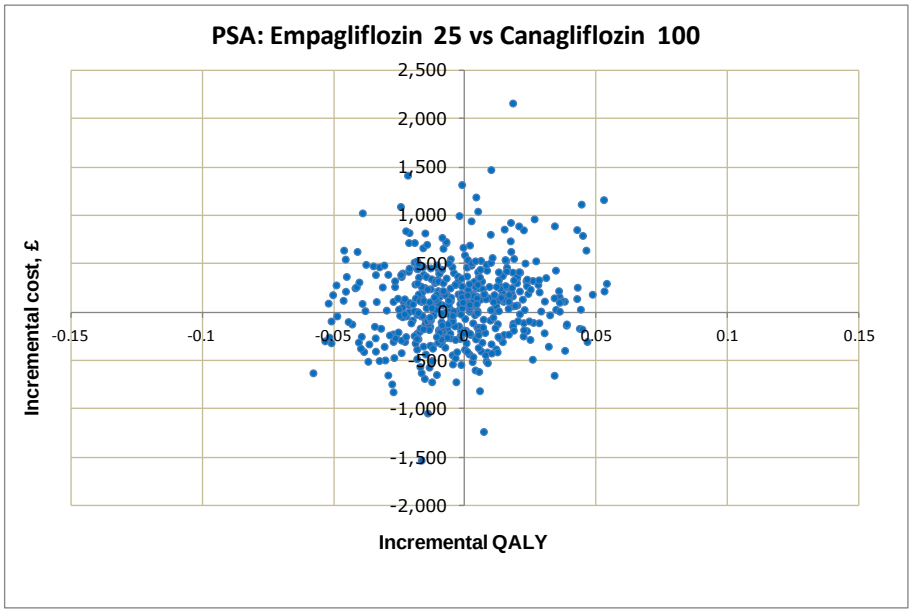
### 7.2.4. Empagliflozin 25mg vs Canagliflozin 100mg (Population II)

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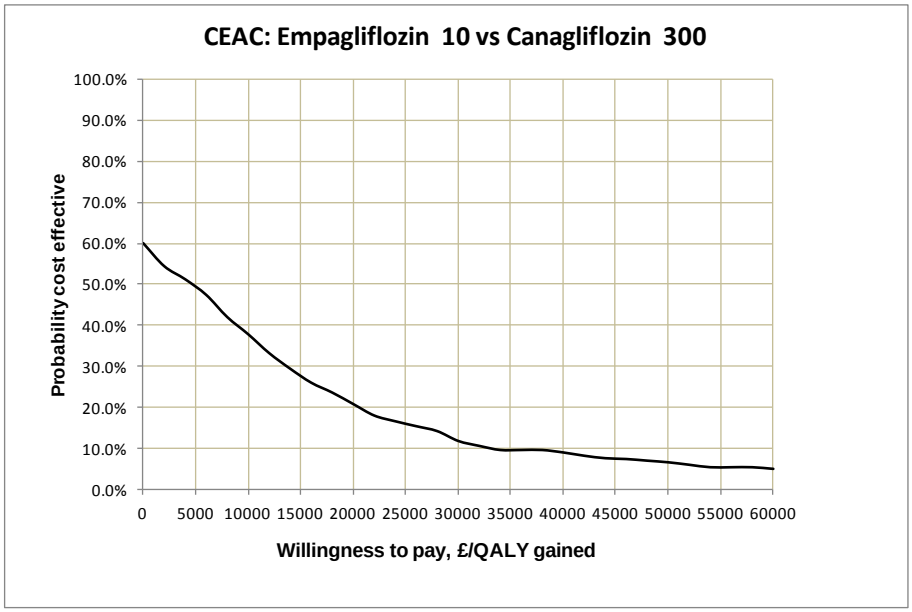
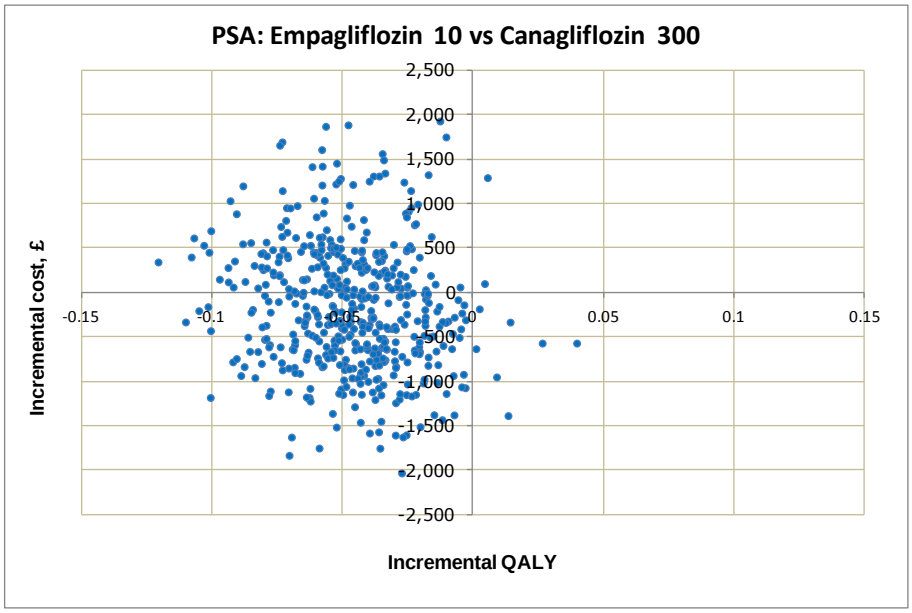
### 7.2.5. Empagliflozin 10mg vs Canagliflozin 300mg (Population II)

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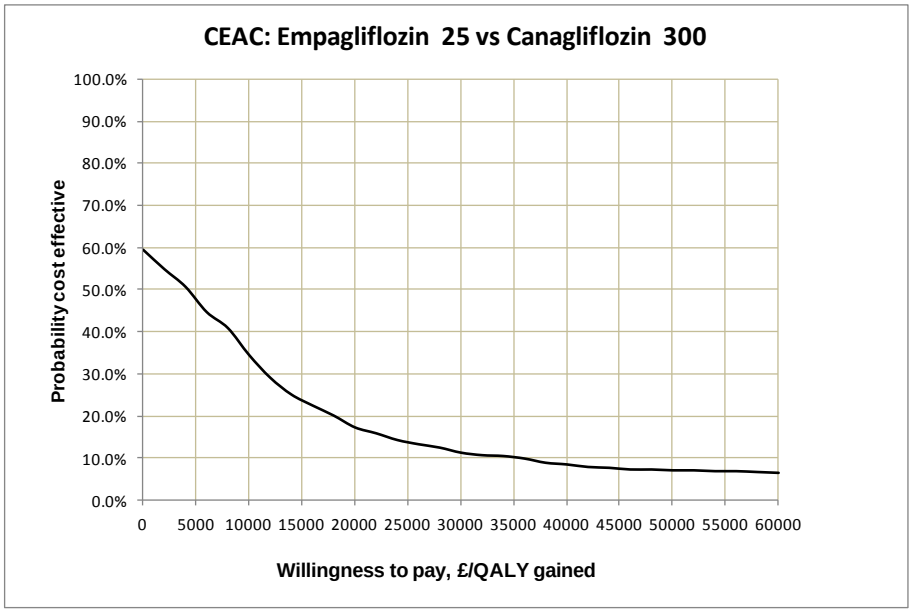
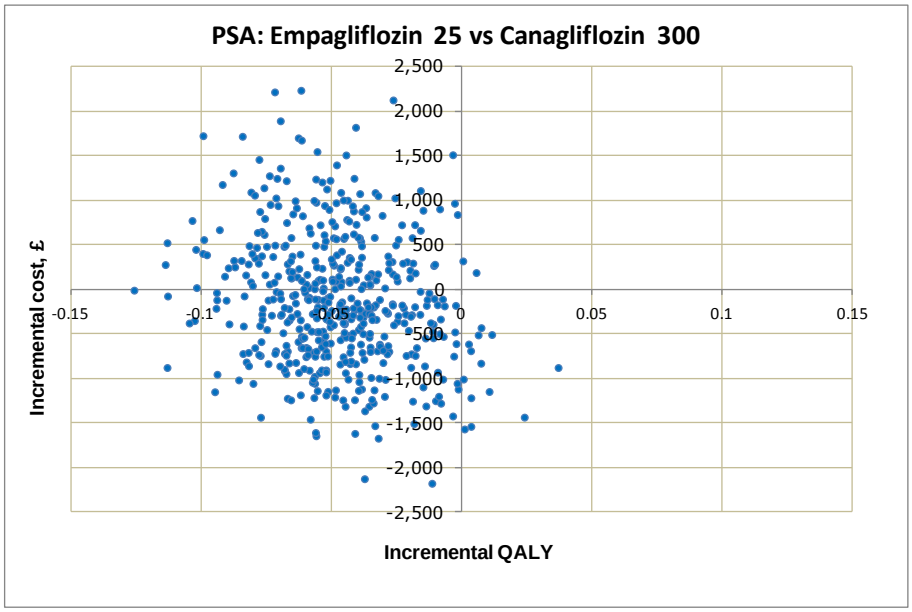
### 7.2.6. Empagliflozin 25mg vs Canagliflozin 300mg (Population II)

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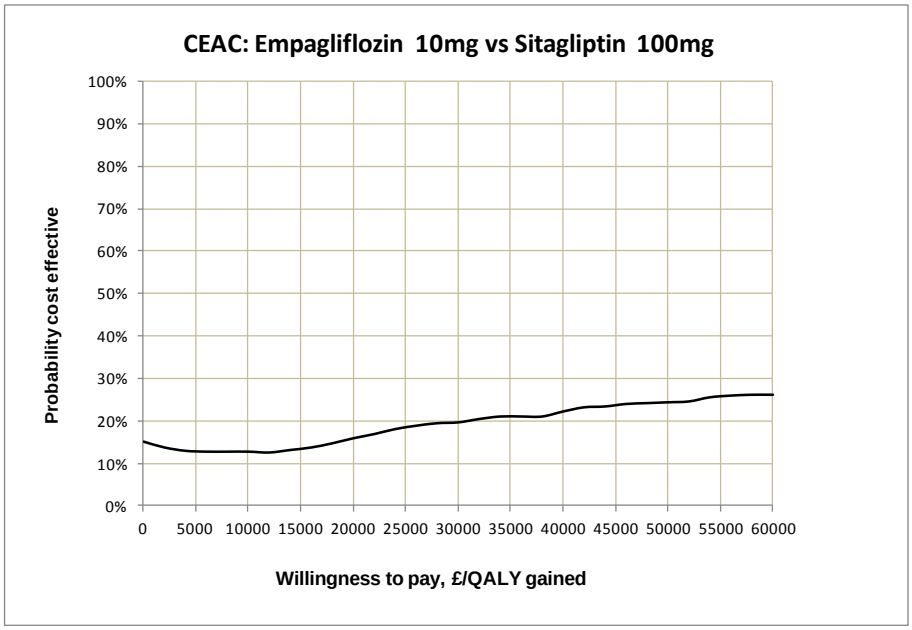
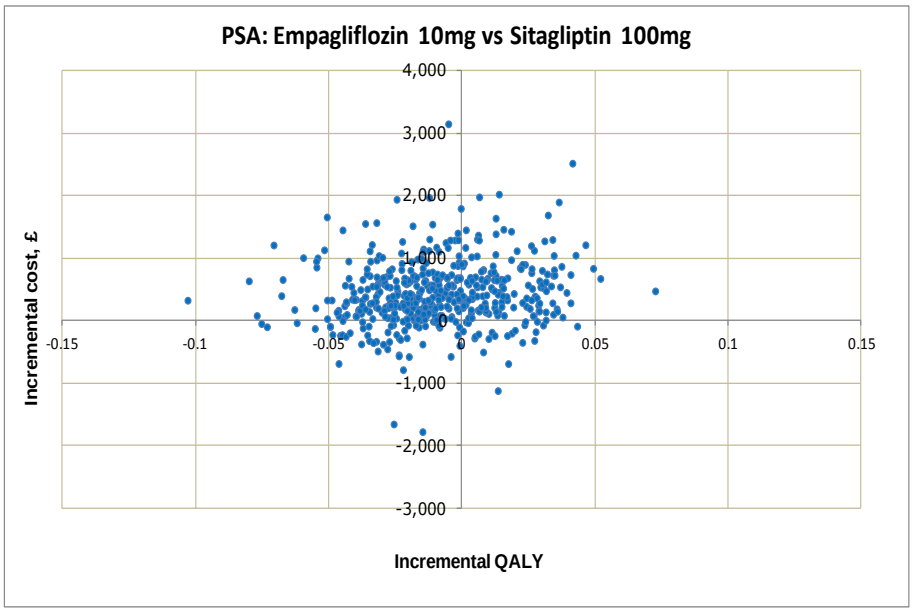
## 7.3. PSA in Population III

Patients undergoing 3rd line treatment who are no longer responding adequately to metformin TZD

### *7.3.1. Empagliflozin 10mg vs Sitagliptin 100mg (Population III)*

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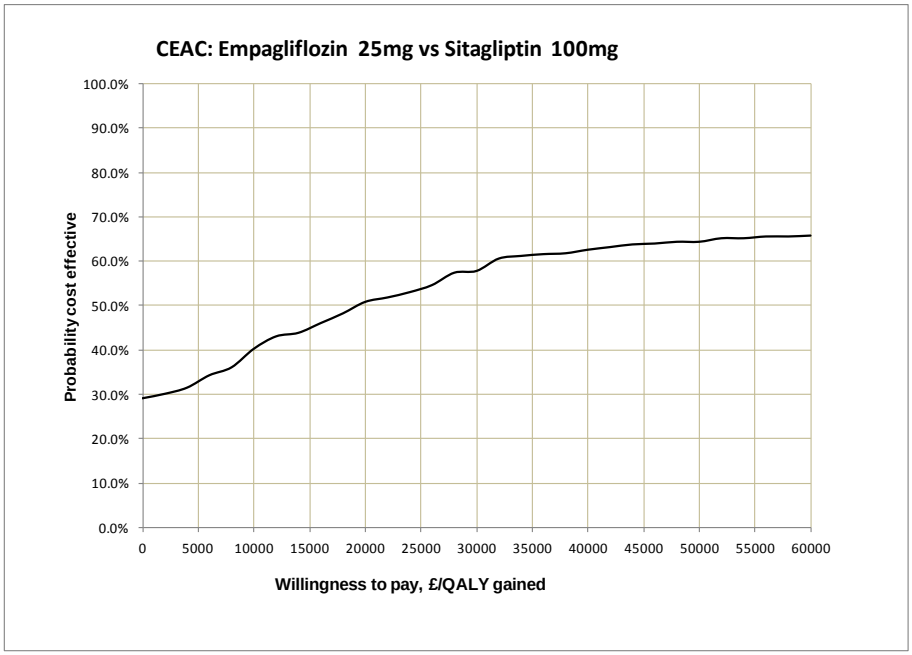
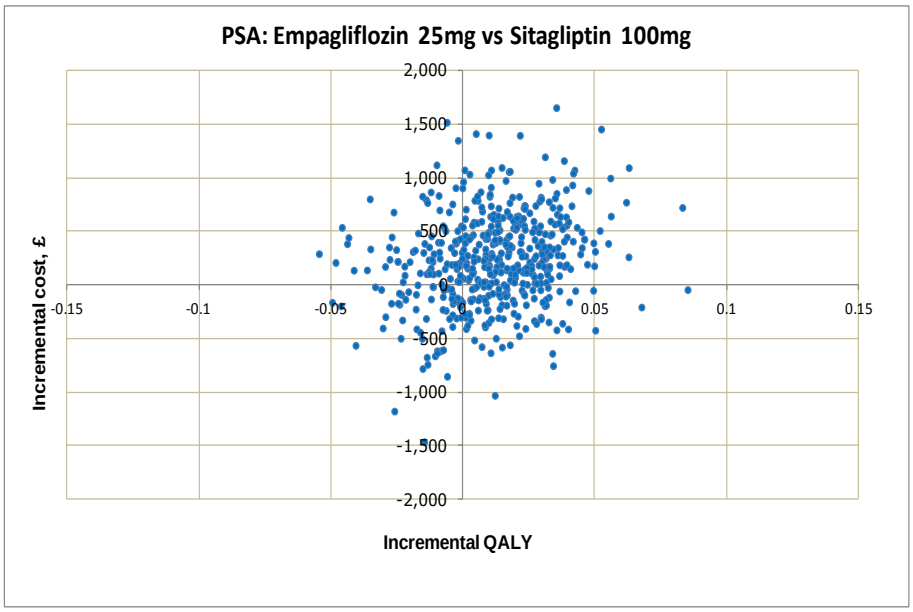
### 7.3.2. Empagliflozin 25mg vs Sitagliptin 100mg (Population III)

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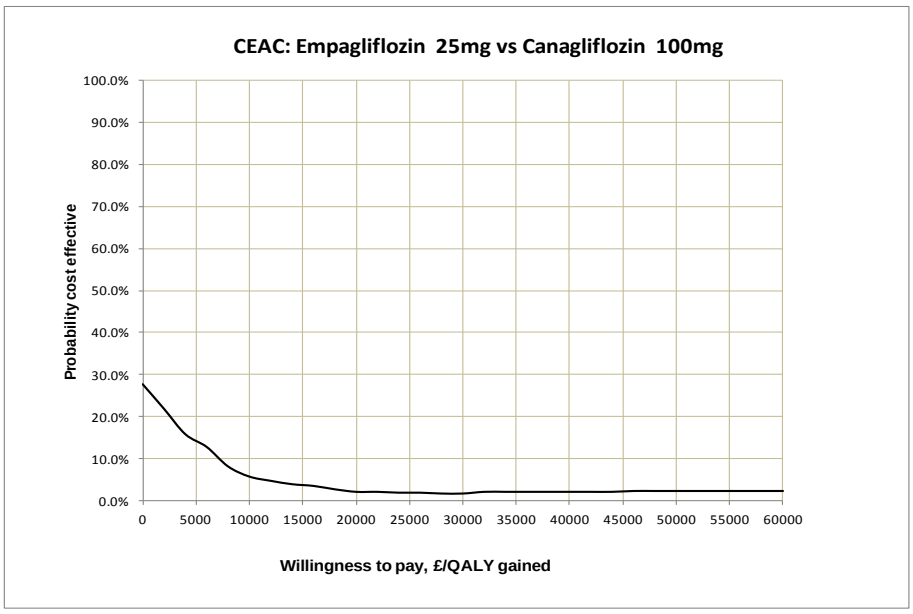
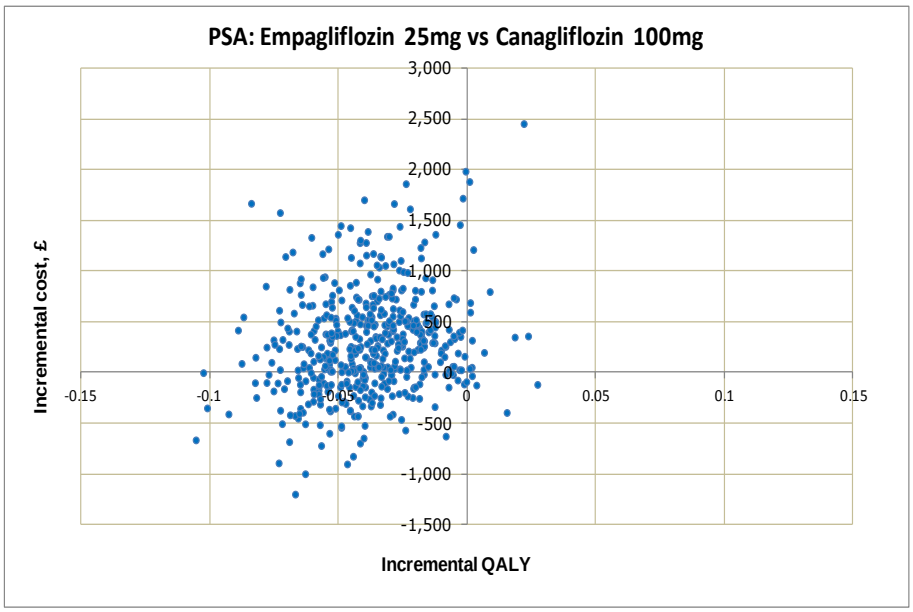
### 7.3.3. Empagliflozin 10mg vs Canagliflozin 100mg (Population III)

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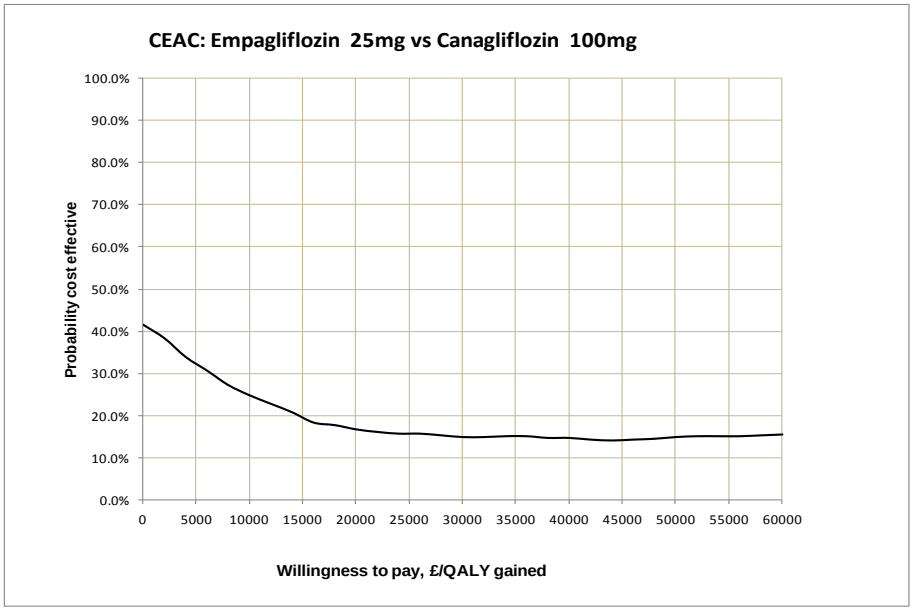
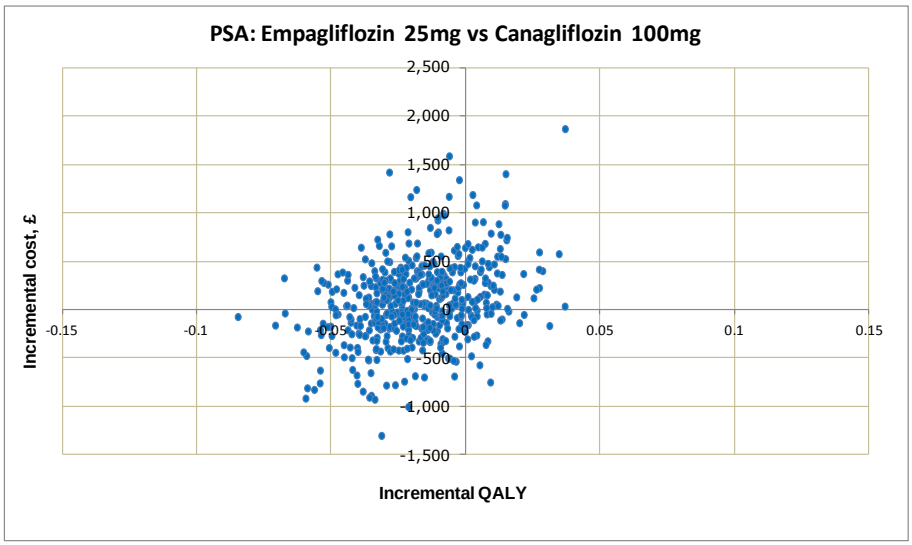
### 7.3.4. Empagliflozin 25mg vs Canagliflozin 100mg (Population III)

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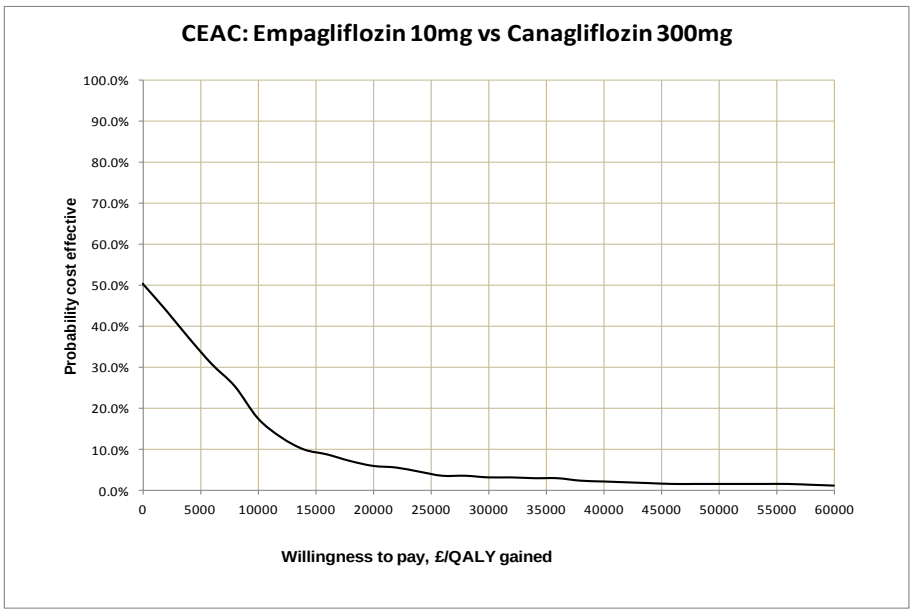
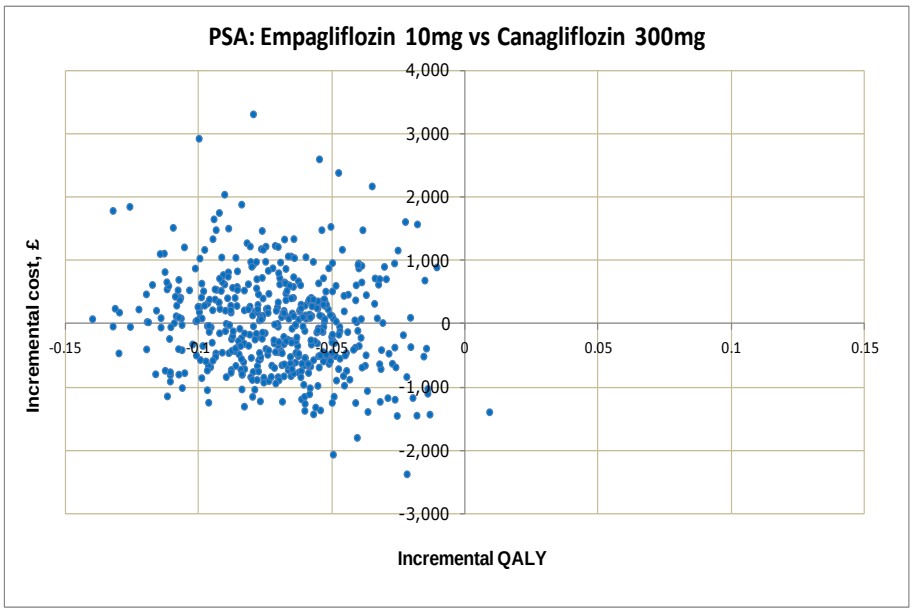
### 7.3.5. Empagliflozin 10mg vs Canagliflozin 300mg (Population III)

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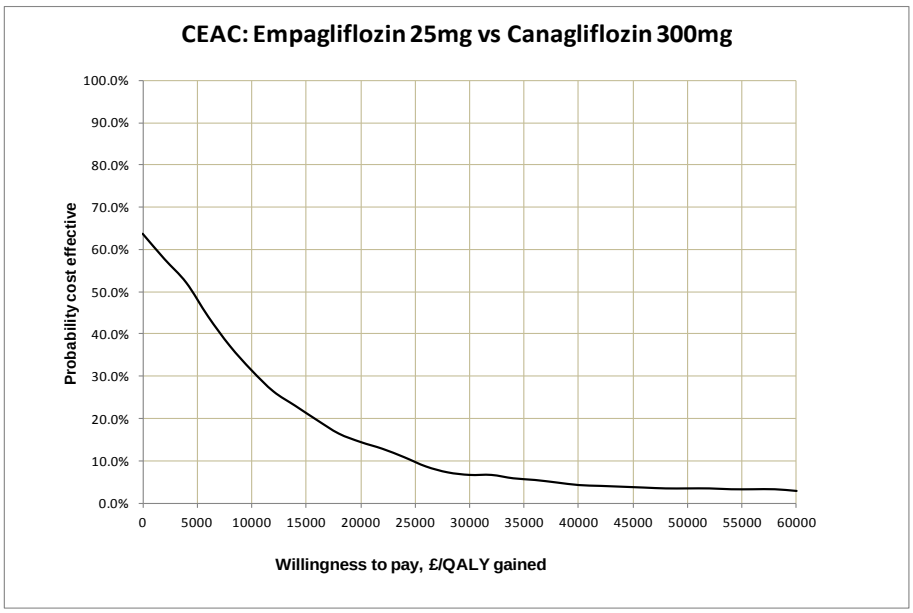
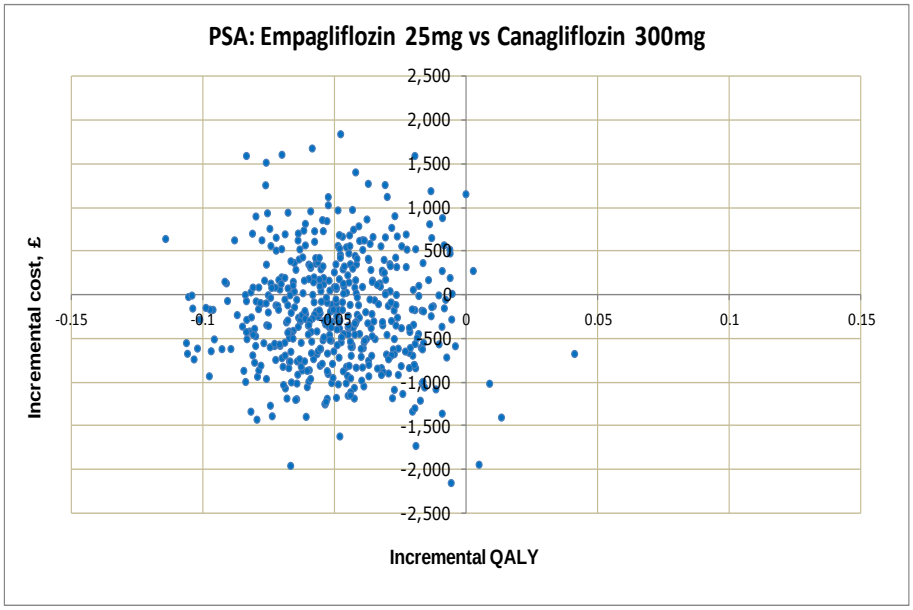
### 7.3.6. Empagliflozin 25mg vs Canagliflozin 300mg (Population III)

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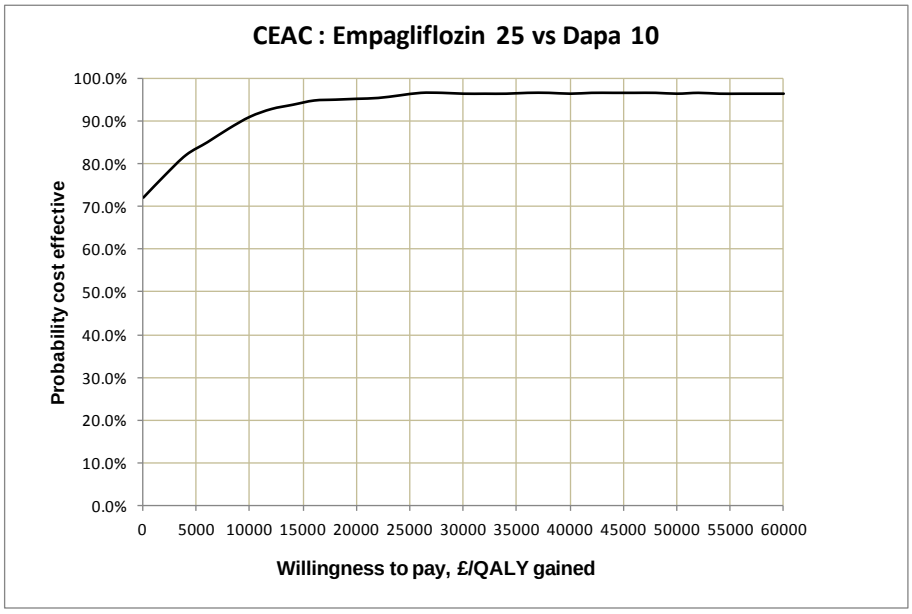
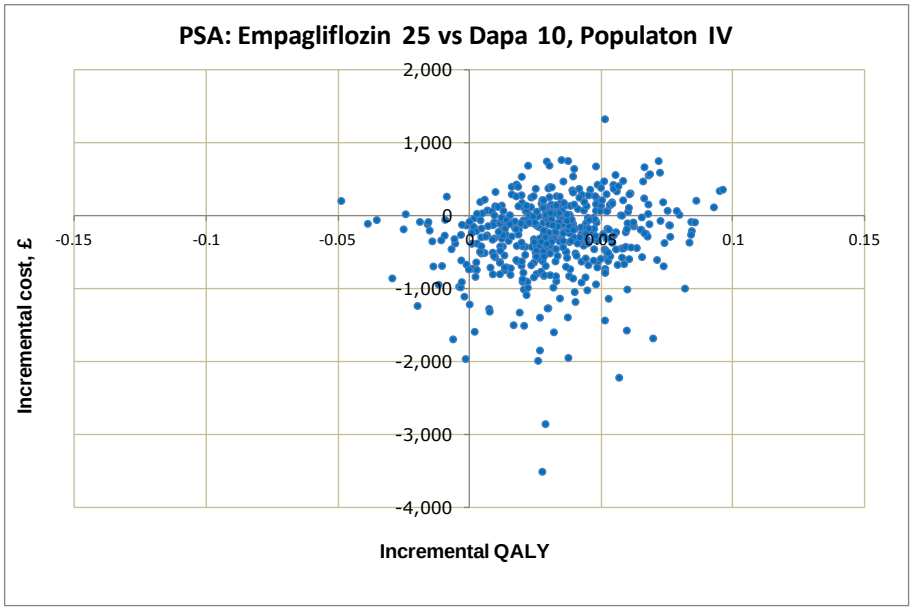
## 7.4. PSA in Population IV

Patients who are no longer responding adequately to backbone insulin therapy (INS)

### *7.4.1. Empagliflozin 10mg vs Dapagliflozin 10mg*

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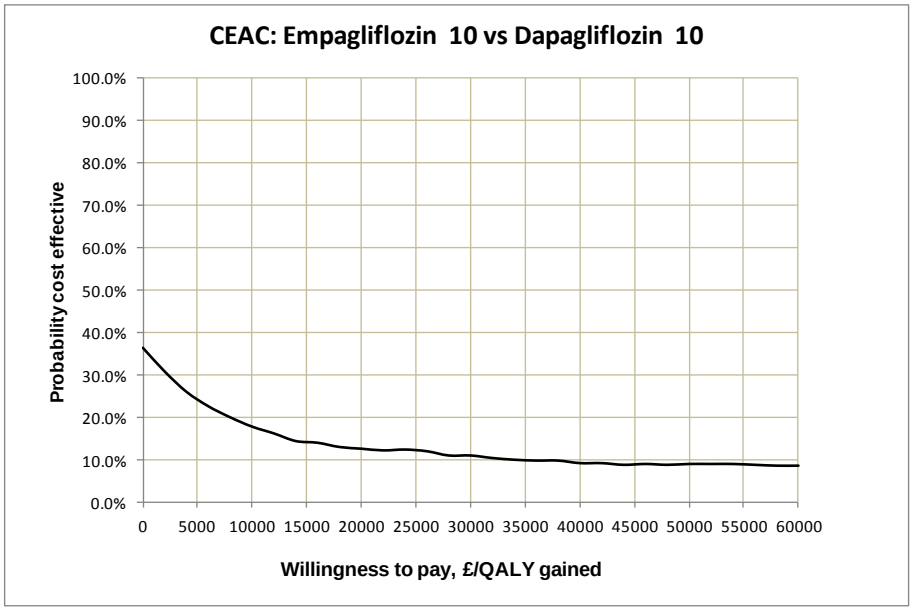
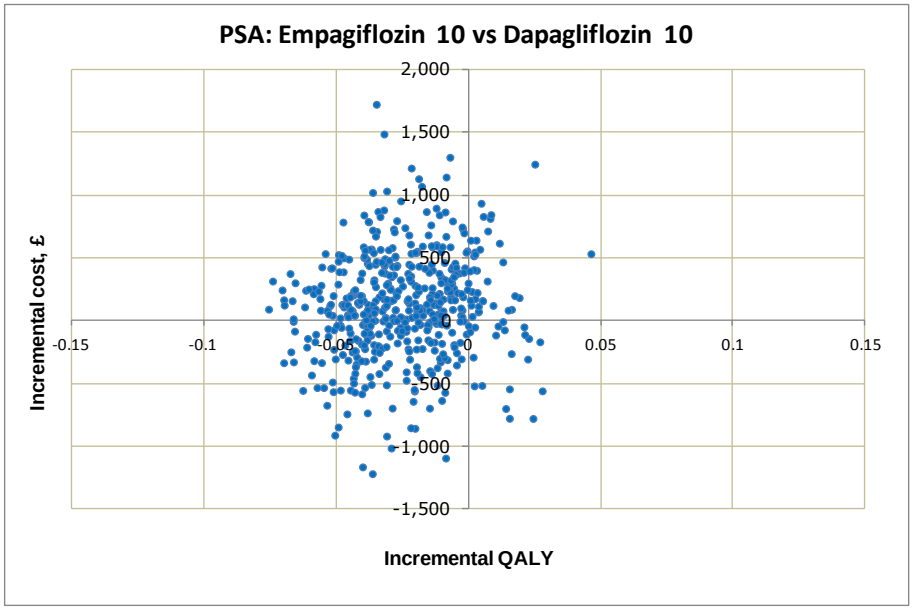
### 7.4.2. Empagliflozin 25mg vs Dapagliflozin 10mg

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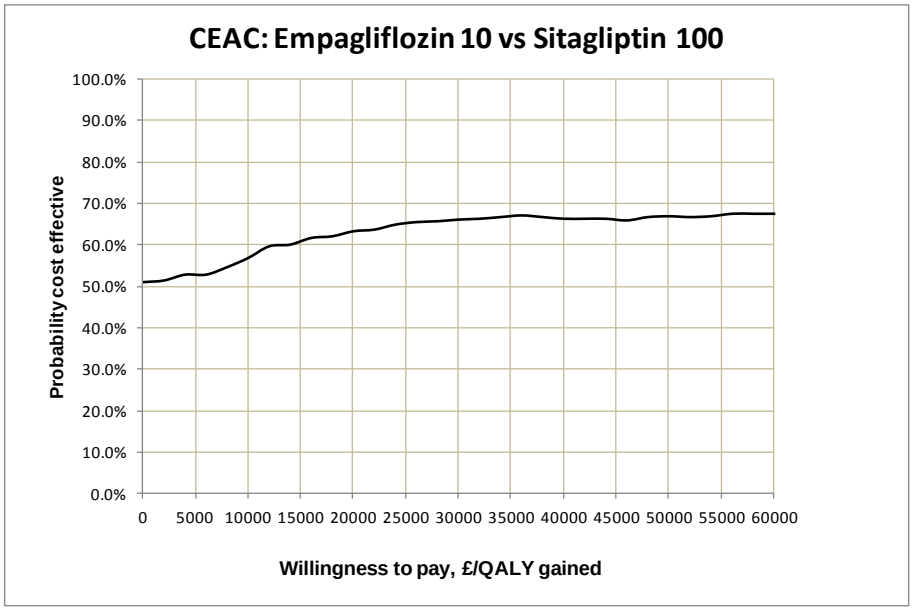
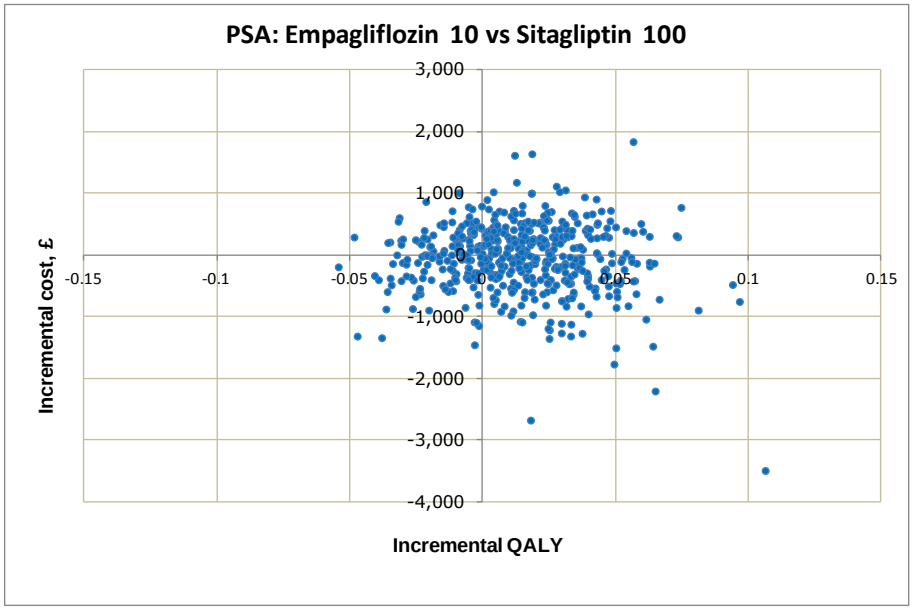
### 7.4.3. Empagliflozin 10mg vs Sitagliptin 100mg

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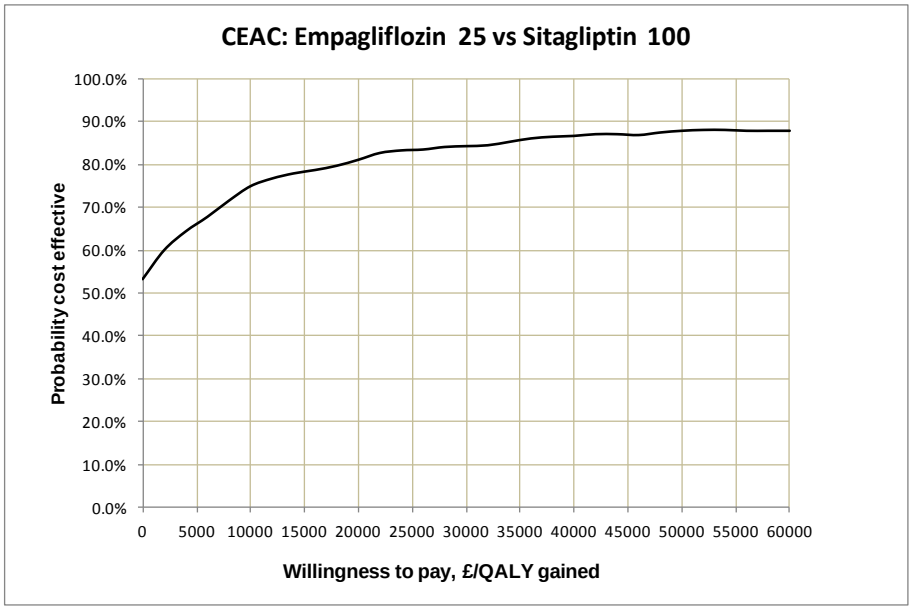
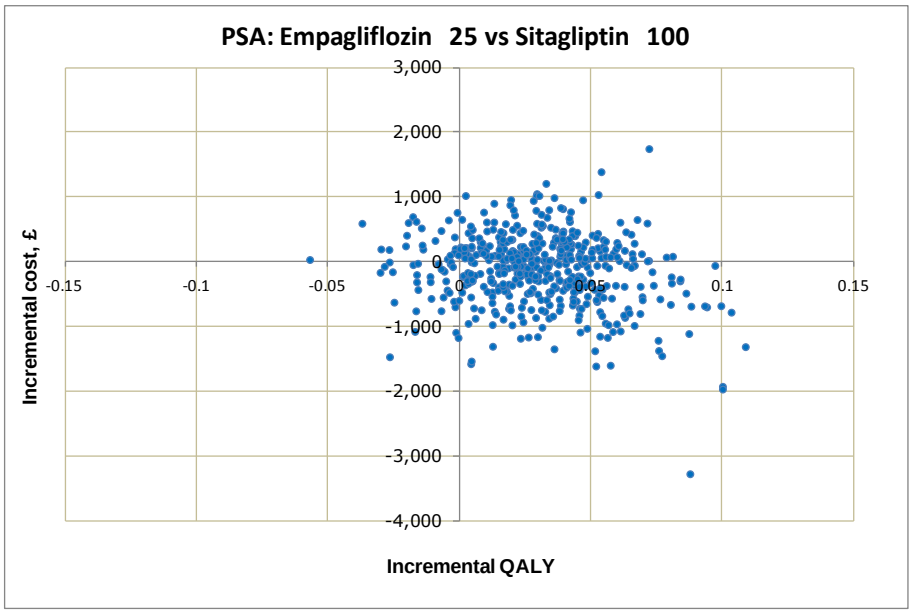
### 7.4.4. Empagliflozin 25mg vs Sitagliptin 100mg

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# Boehringer Ingelheim Response to Empagliflozin Appraisal Consultation document - Network meta-analysis report

## Introduction

The following report outlines the revised network meta-analysis (NMA) after the comments in the ACD (NICE 2014). The validated economic model chosen for the revised economic analysis was the IMS CORE model (Palmer et al 2004). Therefore, the primary purpose of this analysis is to produce estimates for the IMS CORE model. For safety outcomes it was necessary to produce placebo effects so relative risks can be applied to them to calculate rates of adverse events. It was further decided to simplify the NMA to only include the treatments of interest (empagliflozin, canagliflozin, dapagliflozin and sitagliptin). This greatly simplifies the validation and quality checking process without compromising the ability to make the necessary comparisons.

## Contents


Introduction ..... 1
List of tables ..... 2
List of Figures ..... 4
List of Abbreviations ..... 4
Study selection and literature search ..... 6
Search strategy ..... 7
PRISMA diagrams ..... 10
Studies identified ..... 11
Data extraction and conversion ..... 13
Network diagrams ..... 15
Statistical analysis ..... 18
Evaluation of consistency between direct and indirect comparisons ..... 18
Feasibility assessment ..... 19
Metformin background ..... 19
Metformin and sulphonylurea ..... 19
Metformin and thiazolidinediones ..... 19
Insulin ..... 20
Results ..... 20
Dual therapy - Metformin networks ..... 20
Triple therapy - Metformin and sulphonylurea networks ..... 25
Triple therapy - Metformin and thiazolidinediones networks ..... 29
Insulin networks ..... 30
Conclusions ..... 35
References ..... 36
Appendix A: Excluded studies ..... 42

Appendix B: Baseline characteristics of included studies ..... 45
Appendix C. data availability ..... 49
Appendix D. data extraction tables ..... 55
Appendix E: WinBUGs code ..... 66

## List of tables

Table 1: Patients, Intervention, Comparisons, Outcomes and Study Design ..... 6
Table 2 Studies included for dual therapy (metformin) ..... 12
Table 3 Studies included for triple therapy (metformin & SU) ..... 12
Table 4 Studies included for triple therapy (metformin & TZD) ..... 13
Table 5 Studies included for insulin combinations ..... 13
Table 6 Mean difference in HbA1c at 24 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET) ..... 20
Table 7 Mean difference in HbA1c at 52 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET) ..... 21
Table 8 Mean difference in Weight (kg) at 24 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET) ..... 21
Table 9 Mean difference in Weight (kg) at 52 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET) ..... 22
Table 10 Mean difference in systolic blood pressure at 24 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET) ..... 22
Table 11 Mean difference in systolic blood pressure at 52 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET) ..... 23
Table 12 Relative risks of hypoglycaemic events for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET) ..... 23
Table 13 Relative risks of overall hypoglycaemic events for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET) ..... 23
Table 14 Relative risk of non-severe hypoglycaemic events for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET) at 24 weeks ..... 24
Table 15 Relative risk of non-severe hypoglycaemic events for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET) at 52 weeks ..... 24
Table 16 Relative risks of urinary tract infections for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET) ..... 25
Table 17 Relative risks of urinary tract infection events for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET) at 52 weeks ..... 25
Table 18 Placebo response (proportion) in patients who are no longer responding adequately to metformin (MET) ..... 25
Table 19 Mean change in HbA1c for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) ..... 26
Table 20 Mean change in HbA1c for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) at 52 weeks ..... 26
Table 21 Mean change in Weight (kg) for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) ..... 26
Table 22 Mean change in body weight for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) at 52 weeks ..... 27
Table 23 Mean change in systolic blood pressure for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) ..... 27
Table 24 Mean change in systolic blood pressure for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) at 52 weeks ..... 27
Table 25 Relative risk of hypoglycaemic events for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) ..... 28
Table 26 Relative risk of non-severe hypoglycaemic events for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) ..... 28

Table 27 Placebo response (proportion) in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) ..... 28
Table 28 Mean change in HbA1c at 24 weeks for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any thiazolidinedione treatment (TZD) plus MET alone ..... 29
Table 29 Mean change in Weight (kg) at 24 weeks for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any thiazolidinedione treatment (TZD) plus MET alone ..... 29
Table 30 Mean change of systolic blood pressure at 24 weeks for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any thiazolidinedione treatment (TZD) ..... 30
Table 31 Placebo response (proportion in patients who are no longer responding adequately to metformin and thiazolidinedione treatment (TZD) ..... 30
Table 32 Mean change in HbA1c for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) ..... 31
Table 33 Mean change in HbA1c for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) at 52 weeks ..... 31
Table 34 Mean change in weight (kg) for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) ..... 31
Table 35 Mean change in body weight for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) at 52 weeks ..... 32
Table 36 Mean reduction in systolic blood pressure for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) ..... 32
Table 37 Mean change in systolic blood pressure for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) at 52 weeks ..... 32
Table 38 Relative risk of hypoglycaemic events for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) ..... 33
Table 39 Relative risk of non-severe hypoglycaemic events for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) ..... 33
Table 40 Relative risk of severe hypoglycaemic events for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) ..... 34
Table 41 Relative risk of urinary tract infections for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) ..... 34
Table 42 Placebo response (proportion) in patients who are no longer responding adequately to any insulin treatment (INS) ..... 34
Table 43 List of excluded studies from metformin background analysis ..... 42
Table 44 List of excluded studies from metformin and SU background analysis ..... 43
Table 45 List of excluded studies from metformin and TZD background analysis ..... 43
Table 46 List of excluded studies from insulin background analysis ..... 44
Table 47 Baseline characteristics of included studies - metformin networks ..... 45
Table 48 Baseline characteristics of included studies - metformin and sulphonylurea networks ..... 46
Table 49 Baseline characteristics of included studies - metformin and thiazolidinediones networks ..... 47
Table 50 Baseline characteristics of included studies - Insulin networks ..... 48
Table 51 Data availability - metformin networks 24 weeks ..... 49
Table 52 Data availability - metformin and sulphonylurea networks 24 weeks ..... 50
Table 53 Data availability - metformin and thiazolidinediones networks 24 weeks ..... 51
Table 54 Data availability - Insulin networks 24 weeks ..... 51
Table 55 Data availability - metformin networks 52 weeks ..... 52
Table 56 Data availability - metformin and sulphonylurea networks 52 weeks ..... 53
Table 57 Data availability - metformin and thiazolidinediones networks 52 weeks ..... 53
Table 58 Data availability - Insulin networks 52 weeks ..... 54
Table 59 HbA1c (%) change from baseline ..... 55
Table 60 Weight change (kg) from baseline ..... 55
Table 61 Systolic Blood Pressure (mmHg) change from baseline ..... 56
Table 62 Non severe hypoglycaemia ..... 57
Table 63 Severe Hypoglycaemia ..... 57
Table 64 Urinary tract infections ..... 58
Table 65 HbA1c (%) change from baseline ..... 59
Table 66 Weight (kg) change from baseline ..... 59
Table 67 Systolic Blood Pressure (mmHg) change from baseline ..... 59
Table 68 HbA1c (%) baseline change ..... 60
Table 69 Weight (kg) change from baseline ..... 60
Table 70 Systolic Blood Pressure (mmHg) change from baseline ..... 60

Table 71 Non-severe hypoglycaemia ..... 60
Table 72 Severe hypoglycaemia ..... 61
Table 73 Urinary tract infections ..... 61
Table 74 HbA1c (%) baseline change ..... 62
Table 75 Weight (kg) change from baseline ..... 62
Table 76 Systolic Blood Pressure (mmHg) change from baseline ..... 62
Table 77 HbA1c (%) baseline change ..... 63
Table 78 Weight (kg) change from baseline ..... 63
Table 79 Systolic Blood Pressure (mmHg) change from baseline ..... 63
Table 80 HbA1c (%) change from baseline ..... 64
Table 81 Weight (kg) change from baseline ..... 64
Table 82 Systolic Blood Pressure (mmHg) change from baseline ..... 64
Table 83 Overall hypoglycaemia ..... 64
Table 84 Non severe hypoglycaemia ..... 65
Table 85 Severe Hypoglycaemia ..... 65
Table 86 Urinary tract infections ..... 65

## List of Figures

Figure 1: PRISMA flow chart of RCTs included in 2nd line OAD failure analysis ..... 10
Figure 2: PRISMA flow chart of RCTs included in triple therapy (Metformin & SU) ..... 10
Figure 3: PRISMA flow chart of RCTs included in triple therapy (Metformin & TZD) ..... 11
Figure 4: PRISMA flow chart of RCTs included in insulin failure analysis ..... 11
Figure 5 24 week metformin background network diagram ..... 15
Figure 6 52 week metformin background network diagram ..... 15
Figure 7 24 week metformin and SU background network diagram ..... 16
Figure 8 52 week metformin and SU background network diagram ..... 16
Figure 9 24 week metformin and TZD background network diagram ..... 17
Figure 10 24 week insulin background network diagram ..... 17

## List of Abbreviations

| | |
|---|---|
| ACD | Appraisal consultation document |
| AE | Adverse event |
| BMI | Body mass index |
| BP | Blood pressure |
| CADTH | Canadian Agency for Drugs and Technologies in Health |
| CI | Confidence interval |
| DAPA | Dapagliflozin |
| DPP-4is | Dipeptidyl peptidase-4 inhibitors |
| FAD | Final appraisal determination |
| GLP-1 RAs | Glucagon-like peptide-1 receptor agonists |
| GTI | Genital infection |
| HbA1C | Glycated haemoglobin |
| HTA | Health Technology Assessment |
| ICER | incremental cost-effectiveness ratio |
| MDI | Multiple daily injections |
| NICE | National Institute for Health and Care Excellence |
| NMA | Network meta analysis |
| NPH | Neutral protamine Hagedorn |
| OAD | Oral antidiabetic drug |
| PSA | Probabilistic sensitivity analysis |
| QALY | Quality-adjusted life year |
| RR | Relative risk |
| SAE | Serious adverse event |
| SBP | Systolic blood pressure |
| SD | Standard deviation |
| SE | Standard error |

| | |
|---|---|
| SGLT2 | Sodium-glucose co-transporter 2 |
| SGLT2i | Sodium-glucose co-transporter 2 inhibitor |
| Sita | Sitagliptin |
| STA | Single technology appraisal |
| SU | Sulphonylureas |
| TZD | Thiazolidinedione |
| UTI | Urinary tract infection |

## Study selection and literature search

For these network meta-analyses, RCTs were required to meet the criteria outlined in the PICOS (Patients, Interventions, Comparisons, Outcomes, Study design) statement in **Table 1** below.

**Table 1: Patients, Intervention, Comparisons, Outcomes and Study Design**

| Criteria | Definition |
|---|---|
| **Population (P)** | Adult patients with type-2 diabetes experiencing inadequate (HbA1c) control despite a diet and exercise program and a stable regimen of metformin. |
| **Interventions (I)** | Interventions of interest for the primary comparisons:<br>• SGLT-2is: empagliflozin, canagliflozin, and dapagliflozin<br>• DPP-4is: sitagliptin |
| **Comparisons (C)** | Common control interventions consist of either placebo on top of backbone therapy or other anti-diabetic drugs on top of background therapy. |
| **Outcomes (O)** | Primary outcomes (efficacy)<br>• HbA1c change from baseline to end of study<br>• Weight change from baseline to end of study<br>• Systolic blood pressure (SBP) change from baseline to end of study<br>Adverse events<br>• Hypoglycaemic events (severe and non severe, separate and as a composite)<br>• Urinary tract infections (UTIs)<br>• Genital tract infection (GTIs) |
| **Study Design (S)** | Randomized controlled trials with randomized treatment duration of at least 6 months treatments reporting any of the stated outcomes at 6 and/or 12 months.<br>• *Note: some flexibility was allowed in the definition of treatment duration. In particular, outcomes reported +/- 4 weeks of the time point of interest were considered eligible.* |
| HbA1c - Glycated haemoglobin, Dpp-4is - Dipeptidyl peptidase-4 inhibitors, SGLT-2i - SGLT2i Sodium-glucose co-transporter 2 inhibitor | |

The literature search was performed in consultation with a trained librarian using the following databases: Medline (via PubMed), EMBASE, and Cochrane Central Register of Controlled Trials. In addition, the STA for canagliflozin (NICE TA315) was reviewed as it was the most recent STA to explore if any studies had been missed.

Study identification was achieved through multiple key sources and stages. First, for the analyses conducted as part of the submitted single technology appraisal (STA), a data set including SGLT-2is and DPP-4is was already available. Second, from analyses conducted for Boehringer Ingelheim Canada, another data set, based on the recent therapeutic review by the Canadian Agency for Drugs and Technologies in Health (CADTH) was also available. Both data sets were calibrated. Following calibration, a systematic literature review was performed to update both searches behind the two data sets

## Search strategy

| Search | | |
|---|---|---|
| 1 | Hypoglycemic drugs/ | 43672 |
| 2 | ((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or anti-diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or compounds)).ti,ab. | 18535 |
| 3 | Thiazolidinediones/ | 20045 |
| 4 | (glitazone* or thiazolidinedione* or pioglitazone* or rosiglitazone* or actos or avandia or avandamet or avandaryl).ti,ab. | 25169 |
| 5 | (122320-73-4 or 155141-29-0).rn. | 17617 |
| 6 | Dipeptidyl-Peptidase IV Inhibitors/ | 4826 |
| 7 | (sitagliptin or Januvia or Janumet or gliptin or incretin agent*).ti,ab. | 2494 |
| 8 | 486460-32-6.rn. | 3031 |
| 9 | (saxagliptin or Onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn. | 1486 |
| 10 | (361442-04-811 or 945667-22-111 or 361442-04-8 or 945667-22-1).rn. | 1047 |
| 11 | (linagliptin or Tradjenta or Trajenta or BI-1356 or alogliptin or SYR-322 or SYR322 or Nesina or dutogliptin).ti,ab,rn. | 1407 |
| 12 | (668270-12-0 or 850649-62-6 or 852329-66-9).rn. | 559 |
| 13 | (dpp adj IV adj inhibitor*).ti,ab. | 990 |
| 14 | (Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab. | 749 |
| 15 | DPP-4 inhibitors.ti,ab. | 1483 |
| 16 | dipeptidyl peptidase-4 inhibitors.ti,ab. | 676 |
| 17 | exp Sulfonylurea Compounds/ | 65823 |
| 18 | (sulfonylurea* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab. | 43809 |
| 19 | (64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn. | 49732 |
| 20 | exp insulin/ | 410653 |
| 21 | (long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab. | 2552 |
| 22 | (glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn. | 7550 |
| 23 | (detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn. | 2934 |
| 24 | (nph insulin or humulin or novolin).ti,ab. | 2276 |
| 25 | 11061-68-0.rn. | 3327 |
| 26 | (short acting insulin* or quick acting insulin* or rapid acting insulin* or rapidly acting insulin* or fast acting insulin* or quick acting analog* or rapid acting analog* or rapidly acting analog* or short acting analog* or fast acting analog*).ti,ab. | 2669 |
| 27 | (Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn. | 4859 |
| 28 | (Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn. | 4025 |
| 29 | (Glulisine or 207748-29-6 or Apidra).ti,ab,rn. | 1249 |
| 30 | or/1-29 | 519459 |
| 31 | exp Diabetes Mellitus, Type 2/ | 223869 |
| 32 | Diabetes mellitus/ | 433582 |
| 33 | ((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet$).ti,ab. | 224078 |
| 34 | (Mody or niddm or t2dm).ti,ab. | 33683 |
| 35 | or/31-34 | 680015 |
| 36 | Metformin/ | 39433 |
| 37 | Metformin.ti,ab. | 23798 |
| 38 | (dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab. | 246 |
| 39 | (657-24-9 or 1115-70-4).rn. | 36195 |
| 40 | (Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab. | 212 |
| 41 | (apo-metformin or apotex or genmetformin or glucophage or glumetza or novometformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab. | 341 |
| 42 | (Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or Dimethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab. | 475 |
| 43 | or/36-42 | 44538 |
| 44 | 30 and 35 and 43 | 24134 |
| 45 | Antidiabetic agent/ | 76876 |
| 46 | Oral Antidiabetic agent/ | 12870 |
| 47 | ((Antidiabetic or anti diabetic or antihyperglycemic or anti-hyperglycemic or oral hypoglycemic or anti- | 18535 |

| | | |
|---|---|---|
| | diabetes or antidiabetes) adj (agent or agents or drug or drugs or compound or compounds)).ti,ab. | |
| **48** | exp *glitazone derivative/ | 7532 |
| **49** | (glitazone* or thiazolidinedione* or pioglitazone or rosiglitazone or actos or avandia or avandamet or avandaryl).ti,ab. | 25156 |
| **50** | (122320-73-4 or 155141-29-0).rn. | 17617 |
| **51** | exp *Dipeptidyl Peptidase IV Inhibitor/ | 4254 |
| **52** | (sitagliptin or Januvia or Janumet or gliptin or incretin agent*).ti,ab. | 2494 |
| **53** | 486460-32-6.rn. | 3031 |
| **54** | (saxagliptin or Onglyza or bms 477118 or bms-477118 or bms477118 or 3-hydroxyadamantylglycine-4,5-methanoprolinenitrile).ti,ab,rn. | 1486 |
| **55** | (361442-04-811 or 945667-22-111 or 361442-04-8 or 945667-22-1).rn. | 1047 |
| **56** | (linagliptin or Tradjenta or Trajenta or BI-1356 or alogliptin or SYR-322 or SYR322 or Nesina or dutogliptin).ti,ab. | 886 |
| **57** | (668270-12-0 or 850649-62-6 or 852329-66-9).rn. | 559 |
| **58** | (dpp adj IV adj inhibitor*).ti,ab. | 990 |
| **59** | (Dipeptidyl-Peptidase adj IV adj inhibitor*).ti,ab. | 749 |
| **60** | DPP-4 inhibitors.ti,ab. | 1483 |
| **61** | dipeptidyl peptidase-4 inhibitors.ti,ab. | 676 |
| **62** | exp *sulfonylurea derivative/ | 18552 |
| **63** | (sulfonylurea* or tolbutamide or Orinase or glyconon or tolazamide or Tolinase or chlorpropamide or Diabinese or glymese or glipizide or Glucotrol or glyburide or glibenclamide or glybenclamide or Diabeta or Micronase or Glynase or gen-glybe or euglucon or glimepiride or Amaryl or gliclazide or Diamicron or diaglyk or glibenese or minodiab or gen-gliclazide).ti,ab. | 43809 |
| **64** | (64-77-7 or 1156-19-0 or 94-20-2 or 29094-61-9 or 10238-21-8 or 93479-97-1 or 21187-98-4).rn. | 49732 |
| **65** | *biphasic insulin/ or *human insulin/ or *insulin/ or *insulin aspart/ or *insulin detemir/ or *insulin glargine/ or *insulin glulisine/ or *insulin lispro/ or *isophane insulin/ or *long acting insulin/ or *monocomponent insulin/ or *neutral insulin/ or *recombinant human insulin/ or *synthetic insulin/ | 196348 |
| **66** | (long acting insulin* or long acting analog* or slow* acting insulin* or slow* acting analog*).ti,ab. | 2552 |
| **67** | (glargine or Lantus or Optisulin or hoe 901 or 160337-95-1).ti,ab,rn. | 7550 |
| **68** | (detemir or determir or Levemir or nn 304 or 169148-63-4).ti,ab,rn. | 2934 |
| **69** | (nph insulin or humulin or novolin).ti,ab. | 2276 |
| **70** | 11061-68-0.rn. | 3327 |
| **71** | (short acting insulin* or quick acting insulin* or rapid acting insulin* or rapidly acting insulin* or fast acting insulin* or quick acting analog* or rapid acting analog* or rapidly acting analog* or short acting analog* or fast acting analog*).ti,ab. | 2669 |
| **72** | (Lispro or Lyspro or Humalog or Liprolog or 133107-64-9).ti,ab,rn. | 4859 |
| **73** | (Insulin Aspart or 116094-23-6 or NovoLog or NovoRapid or NovoMix).ti,ab,rn. | 4025 |
| **74** | (Glulisine or 207748-29-6 or Apidra).ti,ab,rn. | 1249 |
| **75** | or/45-74 | 346418 |
| **76** | *Diabetes Mellitus/ | 232122 |
| **77** | *Maturity Onset Diabetes Mellitus/ | 70185 |
| **78** | *Non Insulin Dependent Diabetes Mellitus/ | 152205 |
| **79** | *Lipoatrophic Diabetes Mellitus/ | 296 |
| **80** | ((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet$).ti,ab. | 224078 |
| **81** | (Mody or niddm or t2dm).ti,ab. | 33683 |
| **82** | or/76-81 | 461651 |
| **83** | Metformin/ | 39433 |
| **84** | Metformin.ti,ab. | 23798 |
| **85** | (dimethylguanylguanidine or dimethylbiguanidine or glucophage).ti,ab. | 246 |
| **86** | (657-24-9 or 1115-70-4).rn. | 36195 |
| **87** | (apo-metformin or apotex or genmetformin or glucophage or glumetza or novometformin or nu-metformin or pms-metformin or ran-metformin or ratio-metformin or rhoxal-metformin or sandoz metformin).ti,ab. | 341 |
| **88** | (Glycon or Fortamet or Riomet or Venez or Diaformina or Dimefor or Glafornil or Glucaminol or Glucofage or Diabex or Diaformin or Glucohexal or Glucomet or Novomet or Metomin or Glucamet or Metsol or Orabet).ti,ab. | 212 |
| **89** | (Aron or Diabetosan or Diabex or Diformin or Diformin Retard or Dimethylbiguanide or Dmgg or Fluamine or Fortamet or Gliguanid or Glucoformin or Haurymellin or La 6023 or La6023 or Meguan or Mellittin or Metaformin or Methformin or Metiguanide or Metphormin or imethylguanylguanide or Nndg or Dimethylbiguanide or Dimethyl Biguanidine or Dimethylbiguanidine or Dimethyldiguanide).ti,ab. | 475 |
| **90** | or/83-89 | 44538 |
| **91** | 75 and 82 and 90 | 19170 |
| **92** | 44 or 91 | 24795 |
| **93** | limit 92 to english | 21717 |
| **94** | exp animals/ | 37343670 |
| **95** | exp animal experimentation/ | 1744223 |
| **96** | exp models animal/ | 1166747 |
| **97** | exp animal experiment/ | 1744223 |
| **98** | nonhuman/ | 4185230 |

| | | |
|---|---|---|
| **99** | exp vertebrate/ | 36373867 |
| **100** | exp animals/ | 37343670 |
| **101** | or/94-100 | 38557739 |
| **102** | exp humans/ | 28905541 |
| **103** | exp human experiment/ | 319239 |
| **104** | exp humans/ | 28905541 |
| **105** | or/102-104 | 28906982 |
| **106** | 101 not 105 | 9651736 |
| **107** | 93 not 106 | 20862 |
| **108** | meta-analysis.pt. | 52483 |
| **109** | meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ | 215994 |
| **110** | ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab. | 135391 |
| **111** | ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab. | 12204 |
| **112** | ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab. | 25714 |
| **113** | (data synthes* or data extraction* or data abstraction*).ti,ab. | 30792 |
| **114** | (handsearch* or hand search*).ti,ab. | 13433 |
| **115** | (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab. | 30567 |
| **116** | (met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab. | 7365 |
| **117** | (meta regression* or metaregression* or mega regression*).ti,ab. | 5772 |
| **118** | (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. | 308059 |
| **119** | (medline or Cochrane or pubmed or medlars).ti. | 6697 |
| **120** | (cochrane or (health adj2 technology assessment) or evidence report).jw. | 38564 |
| **121** | (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. | 308059 |
| **122** | or/108-121 | 413205 |
| **123** | Randomized Controlled Trial.pt. | 391739 |
| **124** | Randomized Controlled Trials as Topic/ | 146424 |
| **125** | Randomized Controlled Trial/ | 756048 |
| **126** | Randomization/ | 146068 |
| **127** | Random Allocation/ | 146068 |
| **128** | Double-Blind Method/ | 253826 |
| **129** | Double Blind Procedure/ | 121614 |
| **130** | Double-Blind Studies/ | 211513 |
| **131** | Single-Blind Method/ | 38330 |
| **132** | Single Blind Procedure/ | 18633 |
| **133** | Single-Blind Studies/ | 38330 |
| **134** | Placebos/ | 277080 |
| **135** | Placebo/ | 243259 |
| **136** | (random* or sham or placebo*).ti,ab,hw. | 2277165 |
| **137** | ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw. | 398665 |
| **138** | ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti. | 211 |
| **139** | or/123-138 | 2324861 |
| **140** | 107 and 122 | 1340 |
| **141** | 140 not conference abstract.pt. | 1226 |
| **142** | 107 and 139 | 7208 |
| **143** | 142 not conference abstract.pt. | 6568 |
| **144** | 141 or 143 | 6969 |

## PRISMA diagrams

Figure 1 to Figure 4 present the PRISMA diagrams for the various treatment networks.

**Figure 1: PRISMA flow chart of RCTs included in 2nd line OAD failure analysis**

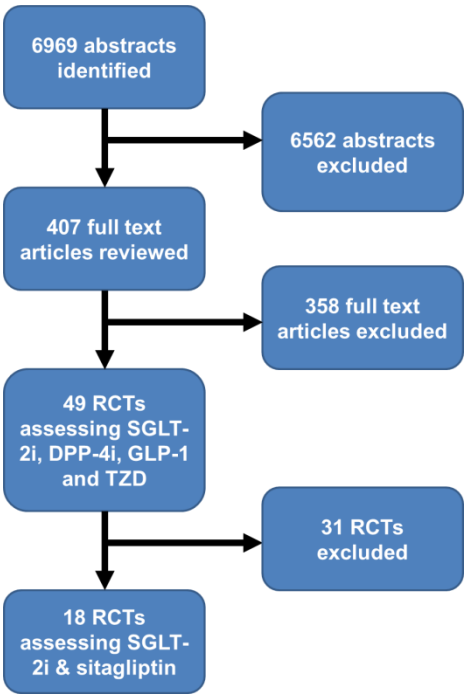



**Figure 2: PRISMA flow chart of RCTs included in triple therapy (Metformin & SU)**

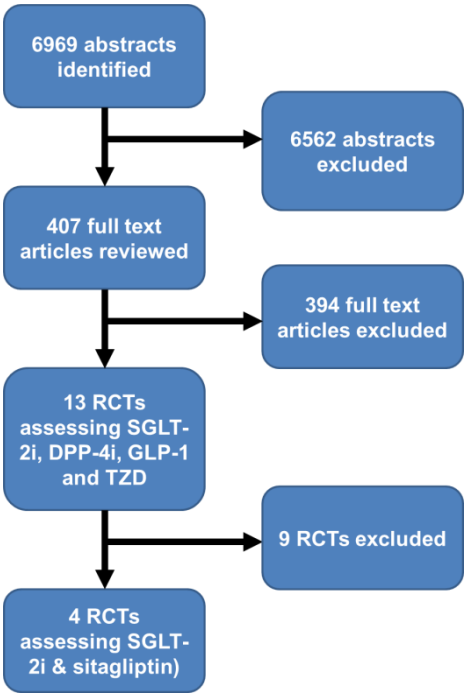


**Figure 3: PRISMA flow chart of RCTs included in triple therapy (Metformin & TZD)**

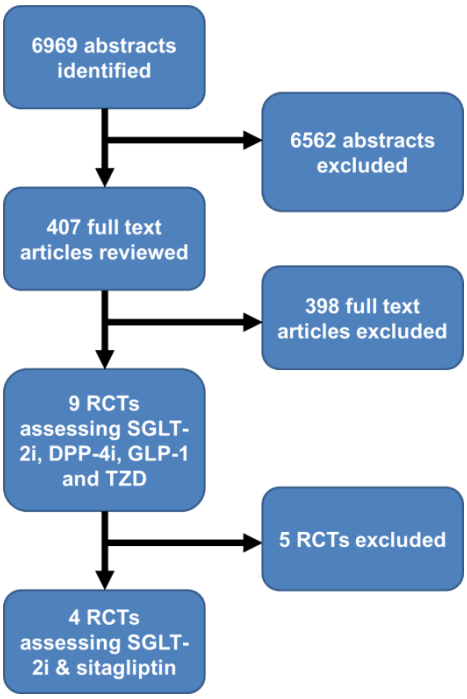
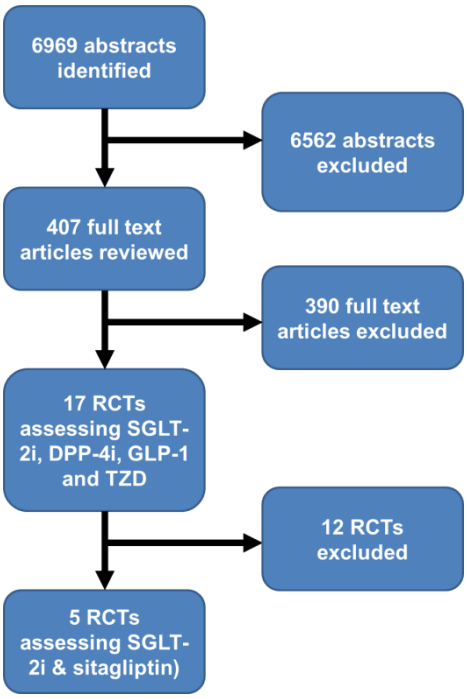



**Figure 4: PRISMA flow chart of RCTs included in insulin failure analysis**




## Studies identified

Of the studies identified only studies concerning the treatments of interest: empagliflozin, dapagliflozin, canagliflozin and sitagliptin. Table 2 to Table 5 summarise the studies identified for each treatment network. The full list of excluded studies is presented in appendix A. For the metformin

network it was decided to include trials with a metformin and sulphonylurea arm because it allowed it allowed linkage to 52 week data for sitagliptin (Nauck et al 2007).

### Table 2 Studies included for dual therapy (metformin)

| Author | Drugs (Metformin+) | n | Trial Duration (weeks) |
|---|---|---|---|
| **Arechavaleta et al 2011** | SU | 519 | 30 |
| | Sitagliptin 100 mg | 516 | |
| **Bailey et al 2010** | Placebo | 137 | 24 |
| | Dapagliflozin 5 mg | 137 | |
| | Dapagliflozin 10 mg | 135 | |
| **BI GMBH (1245-23) 2012 (Haring 2013)** | Placebo | 225 | 78 |
| | Empagliflozin 10mg | 225 | |
| | Empagliflozin 25 mg | 216 | |
| **BI GMBH (1245-28) 2-12 (Ridderstrale 2012)** | SU | 780 | 208 |
| | Empagliflozin 25 mg | 765 | |
| **Bolinder et al 2012** | Placebo | 91 | 102 |
| | Dapagliflozin 10 mg | 89 | |
| **Charbonnel et al 2006** | Placebo | 237 | 24 |
| | Sitagliptin 100 mg | 464 | |
| **Henry et al 2012a Study 2** | Placebo | 208 | 24 |
| | Dapagliflozin 10 mg | 211 | |
| **Henry et al 2012b Study 1** | Placebo | 201 | 24 |
| | Dapagliflozin 5 mg | 194 | |
| **Janssen (DIA3009) 2013 (Cefalu 2013)** | SU | 482 | 52 |
| | Canagliflozin 100 mg | 483 | |
| | Canagliflozin 300 mg | 485 | |
| **Janssen (DIA3006) 2013 (Lavalle-Gonzalez 2013)** | Placebo | 183 | 52 |
| | Canagliflozin 100 mg | 368 | |
| | Canagliflozin 300 mg | 367 | |
| | Sitagliptin 100 mg | 366 | |
| **Nauck et al 2007** | SU | 584 | 52 |
| | Sitagliptin 100 mg | 588 | |
| **Nauck et al 2011** | SU | 401 | 26 |
| | Dapagliflozin 10 mg | 400 | |
| **Raz et al 2008** | Placebo | 94 | 24 |
| | Sitagliptin 100 mg | 96 | |
| **Yang et al 2012** | Placebo | 198 | 24 |
| | Sitagliptin 100 mg | 197 | |
| **Retnakaran et al 2010** | Placebo | 11 | 48 |
| | Sitagliptin 100 mg | 10 | |
| **Bergenstal 2012** | Placebo | 90 | 156 |
| | Sitagliptin 100 mg | 177 | |
| **8354 Derosa 2012** | Placebo | 87 | 52 |
| | Sitagliptin 100 mg | 91 | |
| **Ljunggren 2012** | Placebo | 91 | 102 |
| | Dapagliflozin 10 mg | 89 | |

### Table 3 Studies included for triple therapy (metformin & SU)

| Author | Drugs (Metformin+SU+) | n | Trial Duration (weeks) |
|---|---|---|---|
| **Haring et al 2013** | Placebo | 225 | 52 |
| | Empagliflozin 10mg | 225 | |
| | Empagliflozin 25 mg | 216 | |
| **Hermansen et al 2007** | Placebo | 113 | 24 |
| | Sitagliptin 100 mg | 116 | |
| **Janssen (DIA3015) 2013 (Schernthaner 2013)** | Canagliflozin 300 mg | 377 | 52 |
| | Sitagliptin 100 mg | 378 | |
| **Janssen (DIA3002) 2013 (NCT01106625)** | Placebo | 156 | 52 |
| | Canagliflozin 100 mg | 157 | |
| | Canagliflozin 300 mg | 156 | |

**Table 4 Studies included for triple therapy (metformin & TZD)**

| Author | Drugs (Metformin+TZD+) | n | Trial Duration (weeks) |
|---|---|---|---|
| **Kovacs 2013**<br>**BI GMBH 1245.19 2013** | Placebo | 165 | 76 |
| | Empagliflozin 10mg | 165 | |
| | Empagliflozin 10mg | 168 | |
| **Rosenstock 2012** | Placebo | 139 | 48 |
| | Dapagliflozin 5 mg | 141 | |
| | Dapagliflozin 10 mg | 140 | |
| **DIA3012 2013** | Placebo | 115 | 52 |
| | Canagliflozin 100 mg | 113 | |
| | Canagliflozin 300 mg | 114 | |
| **Derosa et al 2010** | Placebo | 76 | 52 |
| | Sitagliptin 100 mg | 75 | |

**Table 5 Studies included for insulin combinations**

| Author | Drugs (Insulin+) | n | Trial Duration (weeks) |
|---|---|---|---|
| **1245-49 2013** | Placebo | 188 | 52 |
| | Empagliflozin 10mg | 186 | |
| | Empagliflozin 25 mg | 189 | |
| **1245-33 2013** | Placebo | 170 | 78 |
| | Empagliflozin 10mg | 169 | |
| | Empagliflozin 25 mg | 155 | |
| **Janssen DIA3008**<br>**(Neal 2013)** | Placebo | 565 | 104 |
| | Canagliflozin 100 mg | 566 | |
| | Canagliflozin 300 mg | 587 | |
| **Wilding 2012** | Placebo | 193 | 48 |
| | Dapagliflozin 2.5 mg | 202 | |
| | Dapagliflozin 5 mg | 211 | |
| | Dapagliflozin 10 mg | 194 | |
| **Vilsboli 2010** | Placebo | 319 | 24 |
| | Sitagliptin 100 mg | 322 | |

## Data extraction and conversion

Two reviewers independently extracted and recorded data in a Microsoft Excel spreadsheet. All data extractions were subsequently checked by a third reviewer. Trial characteristics, patient characteristics, treatment regimens and outcome data (identified in **Table 1**) were extracted from the selected RCTs. Trial characteristics included: study location, year of publication, primary author, metformin dose (mg/d); duration of stable background therapy dose (weeks); and criteria for defining treatment failure. Information regarding the following patient characteristics at baseline were extracted and used to assess comparability of studies: age (years), sex (% male), race/ethnicity (% Asian), weight (kg), body mass index (BMI) (kg/m$^2$), HbA1c (%), and duration of diabetes (years). In recent studies, HbA1c was occasionally presented in units of milli-mols of HbA1c per mole of Hb (mmol/mol) and converted to a percentage by multiplying by 0.0915 and adding 2.15%. These details are summarized in appendix B.

Treatment regimens were defined by the treatment as well as dosage. In this manner empagliflozin 10 mg was differentiated from empagliflozin 25 mg. All treatment arms included the background therapy i.e. all the dual therapy (metformin) trials included metformin in all arms. Inclusion of trials with

metformin and sulphonylurea was considered appropriate since it allowed the inclusion of relevant additional 52 week data.

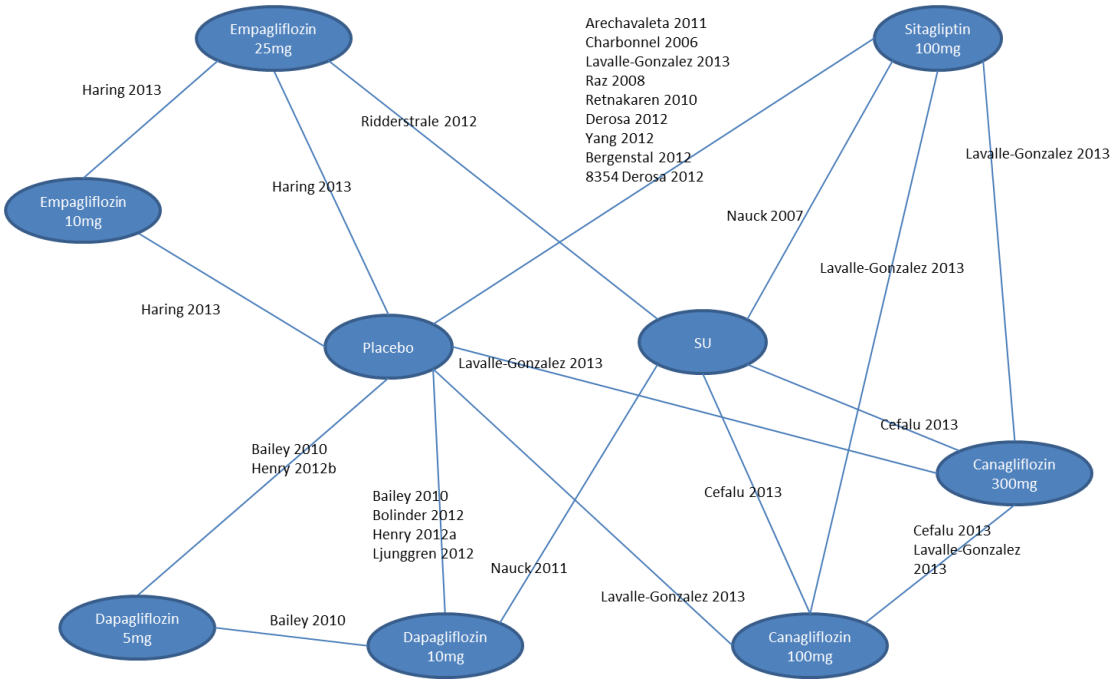
Dichotomous outcomes were recorded as the number of patients in each arm with the outcome in question. These outcomes included hypoglycaemic events, non-severe hypoglycaemic events, severe hypoglycaemic events, UTI and GTI. Severe hypoglycaemic events were defined as those requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative action. Continuous outcomes (Hb1Ac, weight, and systolic blood pressure) were recorded using mean or median difference from baseline. In cases where measurements at baseline and time of measurement were provided, rather than change from baseline, the difference in measures of location was used as a measure of change. In such cases, the standard error of change was estimated by combining the standard errors at both time points and assuming a correlation of 0.8 between baseline and follow-up measurements. In practice, the correlation for pre and post measurements tend to be above 0.8, so using 0.8 is a reasonable, conservative compromise to acknowledge a non-measurement. In cases where interquartile ranges (IQR) were provided, the length of the IQR was divided by 1.35 to estimate standard deviation. In cases where standard deviations were not provided, the average standard deviation among reported studies was used. Measures of dispersion were imputed for trials in which dispersion measures were not reported. Mean standard deviation was used for imputation and standard errors were derived from these.

A full summary of data availability and data extracted and at 24 (±4) weeks and 52 (±4) weeks are presented in appendix C and appendix D.

# Network diagrams

Figures 5 to 10 present the final networks chosen for each background therapy.

## Figure 5 24 week metformin background network diagram




## Figure 6 52 week metformin background network diagram

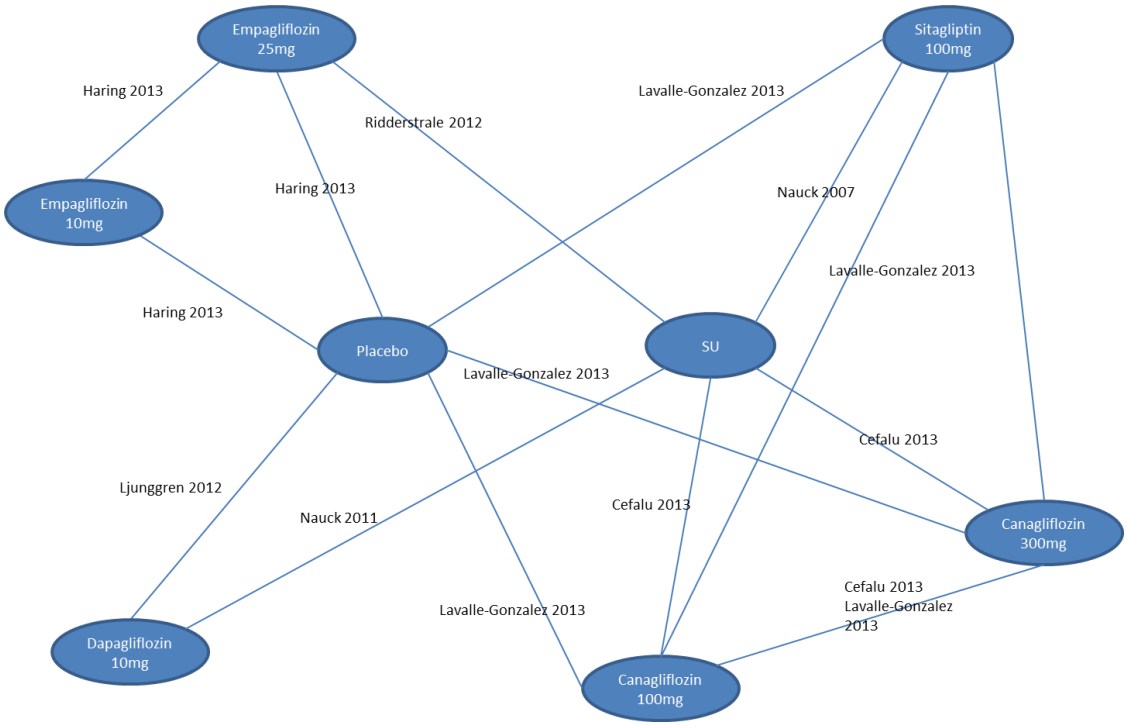


**Figure 7 24 week metformin and SU background network diagram**

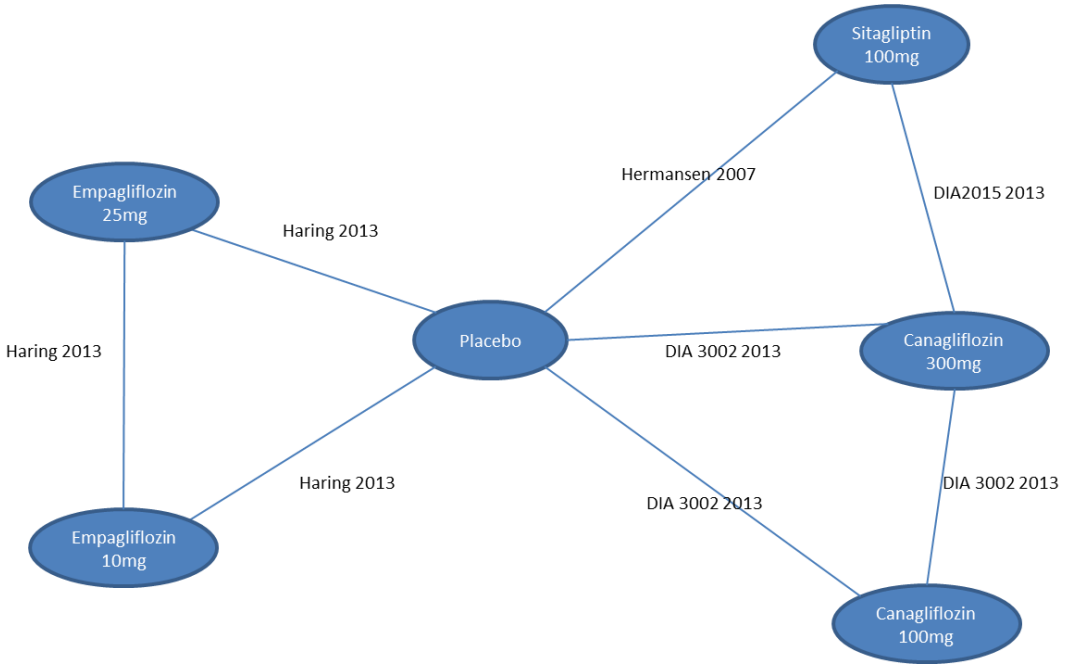
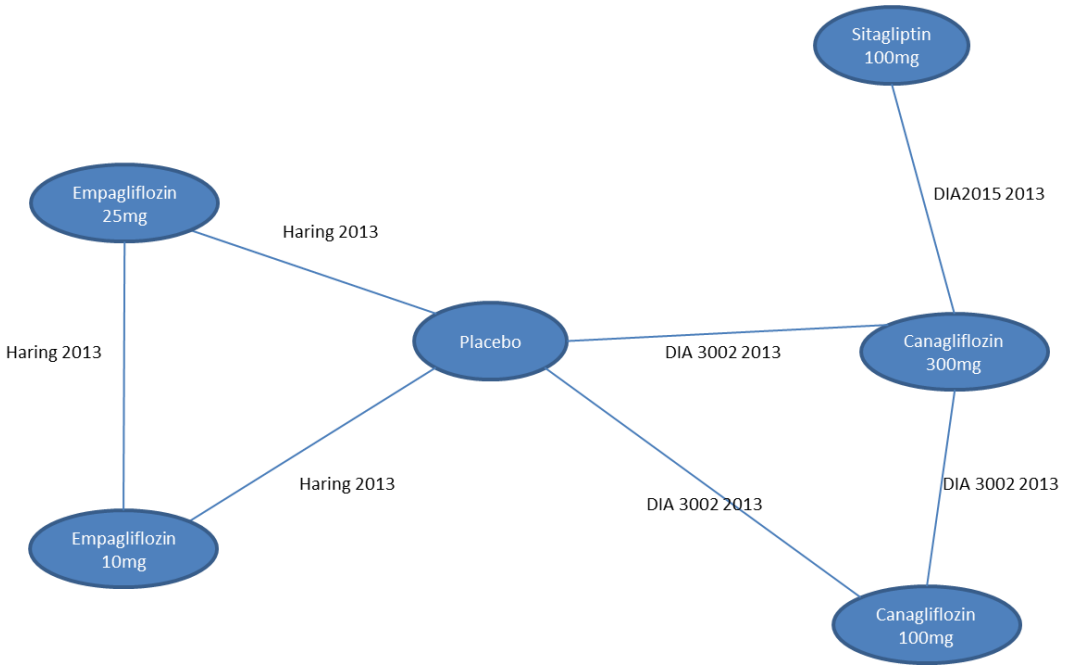
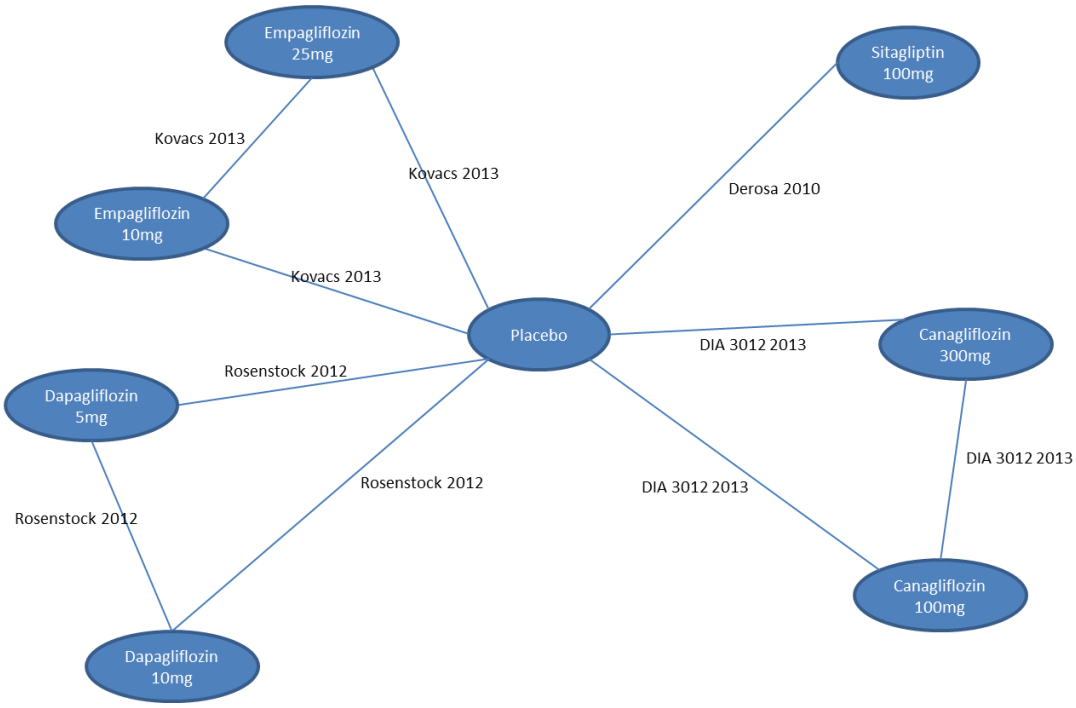


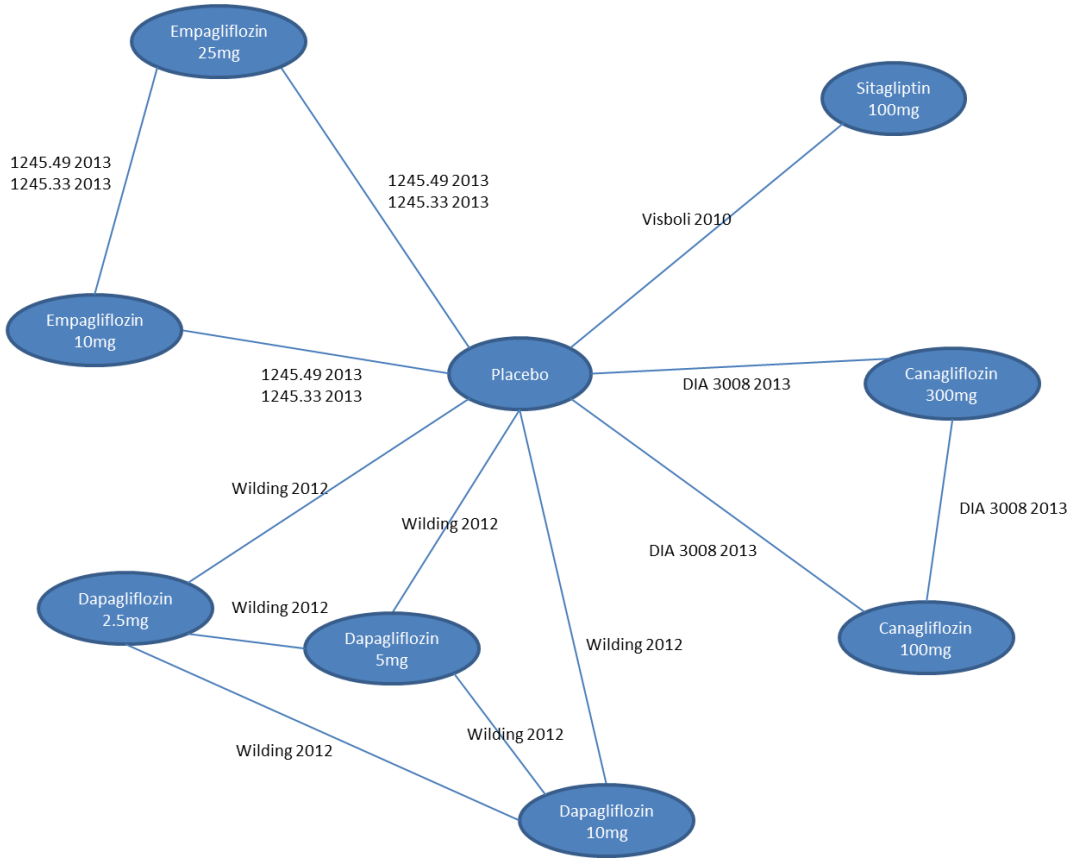

**Figure 8 52 week metformin and SU background network diagram**



## Figure 9 24 week metformin and TZD background network diagram




## Figure 10 24 week insulin background network diagram



Appendix C outlines the data available to populate each network and for which outcomes. As can be seen the metformin background therapy network has considerably more data than any of the other networks. In addition, it has the greatest likelihood for inconsistency due to the number if 'loops' created within the network. For triple therapy metformin and sulphonylurea 24 week there is one 'loop' in the network. However, for all other analysis there is generally only one trial for each treatment link.

## Statistical analysis

Bayesian network meta-analyses (NMA) were performed for all outcomes (Salanti et al 2008, Dias et al 2011 and Bucher et al 1997). For continuous outcomes (i.e., change from baseline [CFB] for HBA1C, Weight and SBP), a NMA model was employed assuming normality of mean differences between treatments (Dias et al 2011) For the binary outcomes (all adverse events), log odds ratios were modelled using the conventional logistic regression NMA setup. Log odds ratios were subsequently transformed to relative risks (RR) within the Bayesian Markov Chain Monte Carlo (MCMC) sampling using conventional methods established by the National Institute of health and Care Excellence (NICE) (Dias et al 2011). Convergence of the MCMC simulation was assessed using trace plots and time series plots. All results for the NMA analyses are reported as posterior median effects with corresponding 95% credible intervals (CrIs), the Bayesian equivalent of classical confidence intervals. All adverse events were analysed using an intention to treat approach.

Model fit was assessed using graphical and numerical methods. The difference in direct and indirect estimates in each loop was evaluated with the Bucher test for inconsistency (Bucher et al 1997). The deviance information criterion (DIC), a measure of model fit that penalizes for model complexity (Spiegelhalter et al 2002), was used for model selection. A smaller DIC indicates a better fit, and as such, the model with the smallest DIC was used. DICs are presented in the results section. Models were chosen based on DIC and conditions required for NMA. In all considered models, both a fixed and random effects approach were used and compared.

All analyses were conducted using WinBUGS version 1.4 (Medical Research Council Biostatistics Unit, Cambridge) and R version 3.1.1 (http://www.r-project.org/).

## Evaluation of consistency between direct and indirect comparisons

Evaluation of consistency was only required for the metformin network since this was the only network to include "loops", the other networks were all "star" networks and therefore, it was only necessary to compare the direct and indirect estimates to ensure they were consistent.

Evaluation of the consistency condition was conducted in two ways. First, using an iterative process to evaluate each closed loop, and second, using global tests for inconsistency by comparing the fit (DIC) in the NMA models with and without the assumption of consistency. The iterative process involved evaluating the consistency between direct and indirect comparisons for networks that consisted of closed loops. For each of the comparisons (i.e., contrasts) that were part of a closed loop

made up of more than 1 RCT, trials were separated into direct and indirect information. For each contrast in question, two (pooled) relative treatment effect estimates were obtained, one with independent-means models using only the studies providing direct comparisons, and one based on an NMA of the remaining studies providing only indirect evidence. This iterative technique is called edge-splitting (Dias et al 2010). The difference in direct and indirect estimates in each loop was evaluated with the Bucher test for inconsistency (Bucher et al 1997).

## Feasibility assessment

RCTs were found to be consistent with respect to most characteristics, as illustrated in appendix B. Nonetheless, some heterogeneity was observed in select baseline characteristics for certain analyses.

### Metformin background

For baseline disease duration, the RCT by Henry et al 2012 was found to have substantially shorter disease duration than the other included RCTs (2 years vs. ~6 years). Therefore, a sensitivity analysis excluding this study was performed. Second, with respect to ethnicity, the percentage of Asian patients ranged from 0 to 55%. The BI GMBH (1245-23) trial was found to have a higher percentage of Asian patients (more than 50%) in comparison to the other included RCTs. However, this higher percentage of Asian patients in the BI GMBH (1245-23) trial did not lead to lower baseline weight or BMI values on average. Similarly, considerable variation was observed in the percentage of males across comparisons in the network. However, meta-regression analyses adjusting for variations in sex percentages and ethnicity led to poorer fits than the unadjusted model. Therefore, no sensitivity analyses were required.

### Metformin and sulphonylurea

Trial and patient baseline characteristics were similar across comparisons. For disease duration, weight and BMI, trials that failed to report these values are reported as zeroes that should not be interpreted as heterogeneity. Nonetheless, some heterogeneity was observed. First, across comparisons there was some variation in race/ethnicity.

### Metformin and thiazolidinediones

RCTs were found to be consistent with respect to most characteristics. Nonetheless, some heterogeneity was observed in select baseline characteristics. Secondly, with respect to ethnicity, the percentage of Asian patients ranged from 5.4 to 62.4%. Kovacs et al (2013) had a higher percentage of Asian patients (more than 50%) in comparison to the other included RCTs However, this higher percentage of Asian patients did not correlate to a lower baseline weight or BMI values on average. Similarly, variation was observed in the mean baseline percentage of HbA1c across comparisons in the network.

## Insulin

RCTs were found to be consistent with respect to most characteristics, trials that failed to report these values are reported as zeroes that should not be interpreted as heterogeneity. Nonetheless, some heterogeneity was observed in select baseline characteristics. First, across comparisons there was some variation in race. In particular, the percentage of Asian patients ranged from 0 to 55%. However, no particular study stood out for conducting sensitivity analysis on.

# Results

The following tables present the results of the network meta-analysis for each of the background treatments, each outcome and where possible 24 and 52 weeks.

## Dual therapy - Metformin networks

Tables 6 and 7 present the results for the metformin background therapy networks for HbA1c. For 24 weeks the DIC estimates were 88.75 and 141.7 for the random effects and fixed effects models respectively, therefore the random effects model was preferred. For 52 weeks the DIC estimates were 31.98 and 30.8 for the random effects and fixed effects models respectively, therefore the fixed effects model was preferred.

All the treatments were statistically significantly superior to placebo at 24 and 52 week. At 24 weeks there were two statistically significant difference between the treatment regiments which were empagliflozin 25mg was statistically superior to dapagliflozin 5mg and 10mg. At 52 weeks empagliflozin 25mg remained statistically significantly superior to dapagliflozin 10mg. These results indicate that empagliflozin is comparable to the other oral treatments in terms of HbA1c reductions.

### *Reduction in HbA1c*

24 week data

**Table 6 Mean difference in HbA1c at 24 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Sulphonylurea** | **-0.72 (-0.79, -0.66)** | **-0.15 (-0.28, -0.02)** | **-0.08 (-0.16, -0.00)** |
| **Empagliflozin 10 mg** | **-0.57 (-0.70, -0.44)** | -- | 0.07 (-0.05, 0.20) |
| **Empagliflozin 25 mg** | **-0.64 (-0.73, -0.56)** | -0.07 (-0.20, 0.05) | -- |
| **Dapagliflozin 5 mg** | **-0.44 (-0.59, -0.29)** | 0.13 (-0.06, 0.33) | **0.21 (0.04, 0.37)** |
| **Dapagliflozin 10 mg** | **-0.52 (-0.60, -0.44)** | 0.05 (-0.09, 0.20) | **0.12 (0.02, 0.23)** |
| **Canagliflozin 100 mg** | **-0.58 (-0.67, -0.49)** | -0.01 (-0.16, 0.14) | 0.06 (-0.05, 0.17) |
| **Canagliflozin 300 mg** | **-0.70 (-0.79, -0.61)** | -0.13 (-0.28, 0.02) | -0.06 (-0.16, 0.05) |
| **Sitagliptin 100 mg** | **-0.58 (-0.64, -0.52)** | -0.01 (-0.14, 0.13) | 0.07 (-0.02, 0.15) |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row); All patients received metformin as a backbone (continuing) plus the above-stated interventions*

52 week data

**Table 7 Mean difference in HbA1c at 52 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Sulphonylurea** | **-0.52 (-0.64, -0.40)** | 0.06 (-0.08, 0.21) | 0.10 (0.02, 0.17) |
| **Empagliflozin 10mg** | **-0.58 (-0.72, -0.45)** | -- | 0.03 (-0.10, 0.16) |
| **Empagliflozin 25 mg** | **-0.62 (-0.73, -0.50)** | -0.03 (-0.16, 0.10) | -- |
| **Dapagliflozin 10 mg** | **-0.47 (-0.58, -0.36)** | 0.11 (-0.04, 0.27) | **0.15 (0.03, 0.26)** |
| **Canagliflozin 100 mg** | **-0.52 (-0.68, -0.37)** | 0.06 (-0.11, 0.23) | 0.09 (-0.03, 0.21) |
| **Canagliflozin 300 mg** | **-0.65 (-0.80, -0.50)** | -0.07 (-0.24, 0.10) | -0.03 (-0.15, 0.08) |
| **Sitagliptin 100 mg** | **-0.52 (-0.67, -0.37)** | 0.07 (-0.10, 0.24) | 0.10 (-0.02, 0.22) |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row). All patients received metformin as a backbone (continuing) plus the above-stated interventions*

## *Reduction in weight (kg)*

Tables 8 and 9 present the results for the metformin background therapy networks for weight change. For 24 weeks the DIC estimates were 70.58 and 72.6 for the random effects and fixed effects models respectively, therefore the random effects model was preferred. For 52 weeks the DIC estimates were 29.84 and 27.88 for the random effects and fixed effects models respectively, therefore the fixed effects model was preferred.

All the treatments were statistically significantly superior to placebo at 24 and 52 week except for sitagliptin which was weight neutral. Empagliflozin (10mg and 25mg) was statistically superior to sitagliptin and sulphonylurea.

24 week data

**Table 8 Mean difference in Weight (kg) at 24 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Sulphonylurea** | **2.34 (1.93, 2.68)** | **4.10 (3.30, 4.84)** | **4.62 (4.03, 5.11)** |
| **Empagliflozin 10 mg** | **-1.76 (-2.49, -1.02)** | -- | 0.52 (-0.22, 1.24) |
| **Empagliflozin 25 mg** | **-2.28 (-2.83, -1.72)** | -0.52 (-1.24, 0.22) | -- |
| **Dapagliflozin 5 mg** | **-1.81 (-2.40, -1.21)** | -0.05 (-0.99, 0.90) | 0.47 (-0.34, 1.29) |
| **Dapagliflozin 10 mg** | **-2.05 (-2.46, -1.63)** | -0.28 (-1.12, 0.54) | 0.23 (-0.43, 0.89) |
| **Canagliflozin 100 mg** | **-1.98 (-2.62, -1.42)** | -0.22 (-1.17, 0.66) | 0.29 (-0.49, 1.01) |
| **Canagliflozin 300 mg** | **-2.63 (-3.25, -2.06)** | -0.87 (-1.81, 0.01) | -0.36 (-1.14, 0.37) |
| **Sitagliptin 100 mg** | 0.16 (-0.28, 0.53) | **1.92 (1.07, 2.68)** | **2.44 (1.76, 3.01)** |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row)*

52 week data

**Table 9 Mean difference in Weight (kg) at 52 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Sulphonylurea** | **2.47 (1.91, 3.03)** | **4.22 (3.63, 4.80)** | **4.80 (4.50, 5.10)** |
| **Empagliflozin 10mg** | **-1.75 (-2.27, -1.22)** | -- | **0.58 (0.06, 1.10)** |
| **Empagliflozin 25 mg** | **-2.33 (-2.83, -1.83)** | **-0.58 (-1.10, -0.06)** | -- |
| **Dapagliflozin 10 mg** | **-2.21 (-2.87, -1.55)** | -0.47 (-1.17, 0.24) | 0.12 (-0.41, 0.65) |
| **Canagliflozin 100 mg** | **-1.98 (-2.71, -1.25)** | -0.24 (-0.99, 0.51) | 0.35 (-0.21, 0.90) |
| **Canagliflozin 300 mg** | **-2.33 (-3.06, -1.60)** | -0.59 (-1.34, 0.17) | -0.00 (-0.56, 0.55) |
| **Sitagliptin 100 mg** | 0.07 (-0.69, 0.83) | **1.81 (1.03, 2.60)** | **2.40 (1.80, 2.99)** |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row); All patients received metformin as a backbone (continuing) plus the above-stated interventions*

## *Reduction in systolic blood pressure*

Tables 10 and 11 present the results for the metformin background therapy networks for systolic blood pressure change. For 24 weeks the DIC estimates were 47.31and 46.13 for the random effects and fixed effects models respectively, therefore the fixed effects model was preferred. For 52 weeks we only had one study for each arm and therefore, the fixed effects model was preferred.

All the treatments were statistically significantly superior to placebo at 24 and 52 week except for sulphonylurea. Empagliflozin (10mg and 25mg) was statistically superior to sulphonylurea at both 24 and 52 weeks. In addition, at 24 weeks empagliflozin 25mg was statistically superior to dapagliflozin 5mg and sitagliptin. At 52 weeks both empagliflozin 10mg and 25mg was statistically superior to sitagliptin and empagliflozin 25mg was superior to canagliflozin 100mg.

24 week data

**Table 10 Mean difference in systolic blood pressure at 24 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Sulphonylurea** | 0.35 (-0.89, 1.59) | **4.55 (2.60, 6.51)** | **5.37 (4.16, 6.57)** |
| **Empagliflozin 10 mg** | **-4.21 (-6.02, -2.38)** | -- | 0.81 (-0.99, 2.63) |
| **Empagliflozin 25 mg** | **-5.01 (-6.42, -3.62)** | -0.81 (-2.63, 0.99) | -- |
| **Dapagliflozin 5 mg** | **-2.11 (-4.08, -0.16)** | 2.09 (-0.57, 4.70) | **2.91 (0.53, 5.25)** |
| **Dapagliflozin 10 mg** | **-3.91 (-5.28, -2.55)** | 0.30 (-1.84, 2.42) | 1.10 (-0.53, 2.73) |
| **Canagliflozin 100 mg** | **-3.89 (-5.30, -2.46)** | 0.32 (-1.84, 2.48) | 1.13 (-0.53, 2.77) |
| **Canagliflozin 300 mg** | **-5.19 (-6.60, -3.77)** | -0.99 (-3.13, 1.19) | -0.17 (-1.82, 1.46) |
| **Sitagliptin 100 mg** | **-2.15 (-3.65, -0.63)** | 2.06 (-0.22, 4.34) | **2.87 (1.01, 4.72)** |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row)*

52 week data

**Table 11 Mean difference in systolic blood pressure at 52 weeks +/- 4 weeks for SLGT-2 and DPP-4 inhibitors in patients who are no longer responding adequately to metformin (MET)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Sulphonylurea** | 1.31 (-1.06, 3.67) | **4.20 (1.79, 6.58)** | **5.80 (4.41, 7.19)** |
| **Empagliflozin 10mg** | **-2.89 (-4.84, -0.94)** | -- | 1.60 (-0.34, 3.56) |
| **Empagliflozin 25 mg** | **-4.49 (-6.44, -2.57)** | -1.60 (-3.56, 0.34) | -- |
| **Dapagliflozin 10 mg** | **-3.80 (-6.65, -0.94)** | -0.90 (-3.78, 1.91) | 0.70 (-1.41, 2.78) |
| **Canagliflozin 100 mg** | -2.25 (-5.05, 0.51) | 0.63 (-2.15, 3.42) | **2.23 (0.23, 4.24)** |
| **Canagliflozin 300 mg** | **-3.42 (-6.20, -0.66)** | -0.54 (-3.35, 2.26) | 1.07 (-0.94, 3.07) |
| **Sitagliptin 100 mg** | 0.60 (-2.55, 3.74) | **3.49 (0.34, 6.62)** | **5.09 (2.63, 7.56)** |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row)*

## *Overall Hypoglycaemia*

Tables 12 and 13 present the results for the metformin background therapy networks for the risk for overall hypoglycaemia. For 24 weeks the DIC estimates were 49.48 and 48.87 for the random effects and fixed effects models respectively, therefore the fixed effects model was preferred. For 52 weeks we only had one study for each arm and therefore, the fixed effects model was preferred. All the SGLT-2is at 24 weeks were equivalent to placebo. Sitagliptin was statistically superior to placebo and empagliflozin 10mg. At 52 weeks all the treatments were superior to sulphonylurea.

24 week data

**Table 12 Relative risks of hypoglycaemic events for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Sulphonylurea** | 1.68 (0.97, 2.98) | 0.62 (0.16, 3.45) | 0.82 (0.19, 5.36) |
| **Empagliflozin 10 mg** | 2.74 (0.54, 9.07) | -- | 1.32 (0.29, 6.79) |
| **Empagliflozin 25 mg** | 2.07 (0.34, 7.71) | 0.76 (0.15, 3.44) | -- |
| **Dapagliflozin 2.5 mg** | 0.85 (0.17, 3.12) | 0.32 (0.04, 2.50) | 0.42 (0.05, 3.81) |
| **Dapagliflozin 5 mg** | 2.03 (0.78, 5.08) | 0.75 (0.16, 4.80) | 1.00 (0.19, 7.38) |
| **Dapagliflozin 10 mg** | 1.24 (0.57, 2.68) | 0.46 (0.11, 2.74) | 0.61 (0.13, 4.17) |
| **Sitagliptin 100 mg** | **0.47 (0.26, 0.85)** | **0.17 (0.04, 0.98)** | 0.23 (0.05, 1.50) |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. All patients received metformin as a backbone (continuing) plus the above-stated interventions.*

52 week data

**Table 13 Relative risks of overall hypoglycaemic events for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET)**

| Treatment Regimen | Versus Sulphonylurea | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 25 mg** | **0.09 (0.05, 0.14)** | -- | -- |
| **Dapagliflozin 10 mg** | **0.06 (0.03, 0.11)** | -- | 0.72 (0.32, 1.57) |
| **Canagliflozin 100 mg** | **0.13 (0.09, 0.20)** | -- | 1.53 (0.78, 3.06) |
| **Canagliflozin 300 mg** | **0.12 (0.07, 0.18)** | -- | 1.35 (0.68, 2.75) |
| **Sitagliptin 100 mg** | **0.13 (0.08, 0.19)** | -- | 1.48 (0.77, 2.95) |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. All patients received metformin as a backbone (continuing) plus the above-stated interventions.*

## *Hypoglycaemia (non-severe)*

Tables 14 and 15 present the results for the metformin background therapy networks for the risk for non-severe hypoglycaemia. For 24 weeks the DIC estimates were 49.40 and 48.90 for the random effects and fixed effects models respectively, therefore the fixed effects model was preferred. For 52 weeks we only had one study for each arm and therefore, the fixed effects model was preferred. All the SGLT-2is at 24 weeks were equivalent to placebo. Sitagliptin was statistically superior to placebo and empagliflozin 10mg. At 52 weeks all the treatments were superior to sulphonylurea.

### 24 week data

**Table 14 Relative risk of non-severe hypoglycaemic events for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET) at 24 weeks**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Sulphonylurea** | 1.62 (0.92, 2.88) | 0.60 (0.16, 3.48) | 0.82 (0.19, 5.49) |
| **Empagliflozin 10 mg** | 2.71 (0.52, 9.04) | -- | 1.34 (0.30, 6.93) |
| **Empagliflozin 25 mg** | 1.99 (0.32, 7.57) | 0.75 (0.14, 3.34) | -- |
| **Dapagliflozin 2.5 mg** | 0.89 (0.18, 3.29) | 0.33 (0.04, 2.70) | 0.45 (0.05, 4.14) |
| **Dapagliflozin 5 mg** | 2.10 (0.80, 5.30) | 0.79 (0.16, 5.04) | 1.07 (0.20, 8.03) |
| **Dapagliflozin 10 mg** | 1.35 (0.61, 2.98) | 0.51 (0.12, 3.08) | 0.68 (0.14, 4.97) |
| **Sitagliptin 100 mg** | **0.45 (0.25, 0.83)** | **0.17 (0.04, 0.98)** | 0.23 (0.05, 1.57) |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. All patients received metformin as a backbone (continuing) plus the above-stated interventions.*

### 52 week data

**Table 15 Relative risk of non-severe hypoglycaemic events for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET) at 52 weeks**

| Treatment Regimen | Versus Sulphonylurea | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 25 mg** | **0.10 (0.05, 0.16)** | **--** | **--** |
| **Sitagliptin 100 mg** | **0.14 (0.09, 0.21)** | **--** | 1.49 (0.77, 2.99) |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. All patients received metformin as a backbone (continuing) plus the above-stated interventions.*

## *Urinary tract infections*

Tables 16 and 17 present the results for the metformin background therapy networks for the risk of urinary tract infections. For 24 weeks the DIC estimates were 27.26 and 28.96 for the random effects and fixed effects models respectively, therefore the random effects model was preferred. For 52 weeks we only had one study for each arm and therefore, the fixed effects model was preferred. All the SGLT-2is at 24 weeks were equivalent to placebo. At 52 weeks dapagliflozin, canagliflozin (100mg and 300mg) and sitagliptin were worse than sulphonylurea; however, given the low number of events (appendix D) these results are subject to significant uncertainty.

24 week data

**Table 16 Relative risks of urinary tract infections for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | 1.18 (0.31, 4.16) | -- | 0.01 (0.28, 3.70) |
| **Empagliflozin 25 mg** | 1.13 (0.31, 4.35) | 0.97 (0.27, 3.58) | -- |
| **Dapagliflozin 2.5 mg** | 0.58 (0.12, 2.20) | 0.47 (0.07, 2.95) | 0.49 (0.07, 3.18) |
| **Dapagliflozin 5 mg** | 1.05 (0.43, 2.51) | 0.89 (0.20, 4.13) | 0.94 (0.18, 4.34) |
| **Dapagliflozin 10 mg** | 1.55 (0.65, 3.55) | 1.35 (0.30, 5.95) | 1.39 (0.30, 6.43) |
| **Sitagliptin 100 mg** | 0.94 (0.41, 2.53) | 0.84 (0.18, 4.02) | 0.87 (0.16, 4.35) |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. All patients received metformin as a backbone (continuing) plus the above-stated interventions.*

52 week data

**Table 17 Relative risks of urinary tract infection events for SGLT-2is, sitagliptin and sulphonylurea in patients who are no longer responding adequately to metformin (MET) at 52 weeks**

| Treatment Regimen | Versus Sulphonylurea | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 25 mg** | 1.25 (0.90, 1.74) | -- | -- |
| **Dapagliflozin 10 mg** | **1.81 (1.01, 3.30)** | -- | 1.45 (0.75, 2.85) |
| **Canagliflozin 100 mg** | **2.25 (1.08, 4.59)** | -- | 1.80 (0.81, 3.95) |
| **Canagliflozin 300 mg** | 1.38 (0.61, 2.99) | -- | 1.10 (0.46, 2.54) |
| **Sitagliptin 100 mg** | **1.78 (1.10, 2.90)** | -- | 1.42 (0.80, 2.55) |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced.All patients received metformin as a backbone (continuing) plus the above-stated interventions.*

### *Placebo response rates*

The following table states the placebo response for the safety outcomes which are required for the IMS CORE model.

**Table 18 Placebo response (proportion) in patients who are no longer responding adequately to metformin (MET)**

| Treatment Regimen | | Overall hypoglycemia | Non severe hypoglycemia | Urinary tract infections |
|---|---|---|---|---|
| **Placebo** | Proportion | 0.01 | 0.01 | 0.03 |
| | 95% Credible interval | (0.01 to 0.02) | (0.01 to 0.02) | (0.02 to 0.04) |

*All patients received metformin as a backbone therapy to placebo*

## Triple therapy - Metformin and sulphonylurea networks

For the majority of analyses there was only one trial per arm available and therefore, the fixed effects model was used throughout.

### *Reduction in HbA1c*

Tables 18 and 19 present the results for the metformin and sulphonylurea background therapy networks for HbA1c. All the treatments were statistically significantly superior to placebo at 24 and 52 week. At 24 weeks canagliflozin 300mg was statistically superior to empagliflozin (10mg and 25mg), however at 52 weeks it was just statistically superior to empagliflozin 25mg.

24 week data

**Table 19 Mean change in HbA1c for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | **-0.65 (-0.79, -0.51)** | -- | -0.05 (-0.19, 0.09) |
| **Empagliflozin 25 mg** | **-0.60 (-0.74, -0.46)** | 0.05 (-0.09, 0.19) | -- |
| **Canagliflozin 100 mg** | **-0.76 (-0.96, -0.56)** | -0.11 (-0.35, 0.14) | -0.16 (-0.40, 0.09) |
| **Canagliflozin 300 mg** | **-1.01 (-1.16, -0.85)** | **-0.36 (-0.57, -0.15)** | **-0.41 (-0.62, -0.20)** |
| **Sitagliptin 100 mg** | **-0.81 (-0.97, -0.65)** | -0.16 (-0.37, 0.05) | -0.21 (-0.42, 0.00) |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row); All patients received Metformin plus Sulphonylurea as a backbone (continuing) plus the above-stated interventions*

52 week data

**Table 20 Mean change in HbA1c for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) at 52 weeks**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10mg** | **-0.71 (-0.88, -0.54)** | -- | -0.02 (-0.19, 0.15) |
| **Empagliflozin 25 mg** | **-0.69 (-0.86, -0.52)** | 0.02 (-0.15, 0.19) | -- |
| **Canagliflozin 100 mg** | **-0.75 (-0.96, -0.54)** | -0.04 (-0.31, 0.23) | -0.06 (-0.33, 0.21) |
| **Canagliflozin 300 mg** | **-0.97 (-1.18, -0.76)** | -0.26 (-0.53, 0.01) | **-0.28 (-0.55, -0.01)** |
| **Sitagliptin 100 mg** | **-0.60 (-0.85, -0.35)** | 0.11 (-0.19, 0.41) | 0.09 (-0.21, 0.39) |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row); All patients received Metformin plus Sulphonylurea as a backbone (continuing) plus the above-stated interventions*

## *Reduction in weight (kg)*

Tables 20 and 21 present the results for the metformin and sulphonylurea background therapy networks for reduction in weight. All the SGLT-2is were statistically significantly superior to placebo at 24 and 52 weeks except sitagliptin. Empagliflozin (10mg and 25mg) was statistically superior to sitagliptin at 24 and 52 weeks.

24 week data

**Table 21 Mean change in Weight (kg) for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | **-1.77 (-2.19, -1.36)** | -- | 0.23 (-0.20, 0.66) |
| **Empagliflozin 25 mg** | **-2.00 (-2.44, -1.57)** | -0.23 (-0.66, 0.20) | -- |
| **Canagliflozin 100 mg** | **-1.26 (-1.88, -0.63)** | 0.51 (-0.25, 1.26) | 0.74 (-0.02, 1.50) |
| **Canagliflozin 300 mg** | **-1.69 (-2.21, -1.15)** | 0.09 (-0.59, 0.76) | 0.32 (-0.36, 1.00) |
| **Sitagliptin 100 mg** | **0.99 (0.44, 1.54)** | **2.76 (2.06, 3.45)** | **2.99 (2.29, 3.68)** |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row); All patients received Metformin plus Sulphonylurea as a backbone (continuing) plus the above-stated interventions*

52 week data

**Table 22 Mean change in body weight for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) at 52 weeks**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10mg** | **-2.00 (-2.49, -1.51)** | -- | 0.05 (-0.49, 0.59) |
| **Empagliflozin 25 mg** | **-2.05 (-2.56, -1.55)** | -0.05 (-0.59, 0.49) | -- |
| **Canagliflozin 100 mg** | **-1.28 (-2.11, -0.44)** | 0.72 (-0.23, 1.68) | 0.77 (-0.19, 1.75) |
| **Canagliflozin 300 mg** | **-2.28 (-3.11, -1.46)** | -0.28 (-1.24, 0.68) | -0.22 (-1.20, 0.74) |
| **Sitagliptin 100 mg** | 0.37 (-0.53, 1.27) | **2.37 (1.35, 3.40)** | **2.42 (1.38, 3.45)** |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row); All patients received Metformin plus Sulphonylurea as a backbone (continuing) plus the above-stated interventions*

## *Reduction in systolic blood pressure*

Tables 22 and 23 present the results for the metformin and sulphonylurea background therapy networks for systolic blood pressure change. Only canagliflozin (100mg and 300mg) was not statistically superior compared to placebo at 24 weeks. At 52 weeks sitagliptin was the only treatment not statistically superior to placebo. The only treatment empagliflozin (10mg and 25mg) was statistically superior was sitagliptin. Overall the SGLT-2is were similar in efficacy.

24 week data

**Table 23 Mean change in systolic blood pressure for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | **-2.70 (-4.66, -0.73)** | -- | -0.58 (-2.55, 1.36) |
| **Empagliflozin 25 mg** | **-2.09 (-4.05, -0.17)** | 0.58 (-1.36, 2.55) | -- |
| **Canagliflozin 100 mg** | -2.30 (-4.92, 0.36) | 0.37 (-2.86, 3.65) | -0.22 (-3.46, 3.01) |
| **Canagliflozin 300 mg** | -1.70 (-4.27, 0.92) | 0.98 (-2.23, 4.26) | 0.40 (-2.82, 3.64) |
| **Sitagliptin 100 mg** | **4.33 (1.15, 7.43)** | **7.02 (3.23, 10.77)** | **6.42 (2.63, 10.10)** |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row); All patients received Metformin plus Sulphonylurea as a backbone (continuing) plus the above-stated interventions*

52 week data

**Table 24 Mean change in systolic blood pressure for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU) at 52 weeks**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10mg** | **-2.80 (-4.89, -0.72)** | -- | -0.09 (-2.19, 1.98) |
| **Empagliflozin 25 mg** | **-2.72 (-4.94, -0.48)** | 0.09 (-1.98, 2.19) | -- |
| **Canagliflozin 100 mg** | **-3.82 (-6.75, -0.85)** | -1.00 (-4.59, 2.59) | -1.10 (-4.77, 2.60) |
| **Canagliflozin 300 mg** | **-3.00 (-5.81, -0.21)** | -0.20 (-3.69, 3.28) | -0.28 (-3.88, 3.27) |
| **Sitagliptin 100 mg** | 2.99 (-0.35, 6.33) | **5.79 (1.86, 9.74)** | **5.70 (1.68, 9.69)** |

*Statistically significant results, i.e., comparisons where the 95% credible intervals do not overlap 0.00, are bold-faced. Negative Mean differences represent superiority of the interventions (left column), positive mean differences represent superiority of the comparator (first row); All patients received Metformin plus Sulphonylurea as a backbone (continuing) plus the above-stated interventions*

## *Overall Hypoglycaemia*

Tables 24 present the results for the metformin and sulphonylurea background therapy networks for the risk for overall hypoglycaemia. At 24 weeks empagliflozin 10mg is statistically significantly worse than placebo. This appears to be an inconsistent result since empagliflozin 25mg is not statistically worse than placebo. In addition, compared to each other the SGLT-2i has a similar effect.

### 24 week data

**Table 25 Relative risk of hypoglycaemic events for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | **1.67 (1.01, 2.75)** | -- | 1.31 (0.81, 2.13) |
| **Empagliflozin 25 mg** | 1.27 (0.74, 2.17) | 0.76 (0.47, 1.24) | -- |
| **Canagliflozin 100 mg** | 1.79 (0.72, 4.30) | 1.07 (0.38, 2.86) | 1.40 (0.50, 3.81) |
| **Canagliflozin 300 mg** | 1.48 (0.57, 3.73) | 0.89 (0.30, 2.52) | 1.16 (0.39, 3.36) |

*All patients received Metformin plus Sulphonylurea as a backbone (continuing) plus the above-stated interventions*

## *Hypoglycaemia (non-severe)*

Tables 25 present the results for the metformin and sulphonylurea background therapy networks for the risk for non-severe hypoglycaemia. There were no statistical differences.

### 24 week data

**Table 26 Relative risk of non-severe hypoglycaemic events for SGLT-2is and sitagliptin in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | 1.62 (0.97, 2.66) | -- | 1.21 (0.76, 2.00) |
| **Empagliflozin 25 mg** | 1.34 (0.78, 2.27) | 0.82 (0.50, 1.31) | -- |
| **Canagliflozin 100 mg** | 1.81 (0.74, 4.36) | 1.12 (0.40, 3.09) | 1.36 (0.47, 3.78) |
| **Canagliflozin 300 mg** | 1.51 (0.55, 3.84) | 0.93 (0.31, 2.66) | 1.12 (0.37, 3.26) |

*All patients received Metformin plus Sulphonylurea as a backbone (continuing) plus the above-stated interventions*

## *Urinary tract infections*

Lack of data

## *Placebo response rates*

The following table states the placebo response for the safety outcomes which are required for the IMS CORE model.

**Table 27 Placebo response (proportion) in patients who are no longer responding adequately to metformin (MET) plus Sulphonylurea (SU)**

| Treatment Regimen | | Overall hypoglycaemia | Non severe hypoglycaemia | Urinary tract infections |
|---|---|---|---|---|
| **Placebo** | Proportion | 0.08 | 0.08 | 0.06 |
| | 95% Credible interval | (0.04 to 0.13) | (0.04 to 0.13) | (0.05 to 0.09) |

*All patients received Metformin plus Sulphonylurea as a backbone therapy to placebo*

## Triple therapy - Metformin and thiazolidinediones networks

For the majority of analyses there was only one trial per arm available and therefore, the fixed effects model was used throughout.

### *Reduction in HbA1c*

Table 26 present the results for the metformin and thiazolidinedione background therapy networks for HbA1c. All the treatments were statistically significantly superior to placebo at 24 weeks. Canagliflozin 300mg was statistically superior to empagliflozin 10mg. Empagliflozin 25mg was equivalent to all treatments.

24 week data

**Table 28 Mean change in HbA1c at 24 weeks for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any thiazolidinedione treatment (TZD) plus MET alone**

| Treatment Regimen | Versus Control (TZD+MET) | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10mg** | **-0.44 (-0.66 to -0.22)** | -- | 0.15 (0.06 to 0.36) |
| **Empagliflozin 25 mg** | **-0.59 (-0.80 to -0.38)** | -0.15 (-0.36 to 0.06) | -- |
| **Canagliflozin 100 mg** | **-0.63 (-0.82 to -0.44)** | -0.19 (-0.49 to 0.10) | -0.04 (-0.32 to 0.24) |
| **Canagliflozin 300 mg** | **-0.77 (-0.93 to -0.61)** | **-0.33 (-0.61 to -0.06)** | -0.18 (-0.44 to 0.08) |
| **Sitagliptin 100 mg** | **-0.70 (-0.84 to -0.56)** | -0.26 (-0.52 to 0.00) | -0.11(-0.36 to 0.14) |

*All patients received TZD as a backbone (continuing) plus the above-stated Note: All patients receive backbone (continuing) TZD treatment (any type) with other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

### *Reduction in weight (kg)*

Table 27 present the results for the metformin and thiazolidinedione background therapy networks for reduction in weight. All the SGLT-2is were statistically significantly superior to placebo at 24 and 52 weeks. Empagliflozin (10mg and 25mg) was statistically superior to sitagliptin at 24 and 52 weeks. Canagliflozin was statistically superior to empagliflozin 10mg and 25mg.

24 week data

**Table 29 Mean change in Weight (kg) at 24 weeks for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any thiazolidinedione treatment (TZD) plus MET alone**

| Treatment Regimen | Versus Control (TZD+MET) | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10mg** | **-2.14 (-2.82 to -1.45)** | -- | -0.15 (0.86 to -0.54) |
| **Empagliflozin 25 mg** | **-1.98 (-2.68 to -1.28)** | 0.15 (-0.54 to 0.86) | -- |
| **Canagliflozin 100 mg** | **-2.55 (-3.36 to -1.74)** | -0.41 (-1.48 to 0.64) | -0.57 (-1.64 to 0.49) |
| **Canagliflozin 300 mg** | **-3.49 (-4.29 to -2.69)** | **-1.35 (-2.41 to -0.30)** | **-1.51 (-2.56 to -0.45)** |
| **Sitagliptin 100 mg** | 0.20 (-0.40 to 0.80) | **2.33 (1.42 to 3.24)** | **2.18 (1.26 to 3.09)** |

*All patients received TZD as a backbone (continuing) plus the above-stated Note: All patients receive backbone (continuing) TZD treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

### *Reduction in systolic blood pressure*

24 week data

**Table 30 Mean change of systolic blood pressure at 24 weeks for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any thiazolidinedione treatment (TZD)**

| Treatment Regimen | Versus Control (Met+TZD) | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10mg** | **-4.24 (-6.91 to -1.54)** | -- | -0.18 (-2.82 to 2.54) |
| **Empagliflozin 25 mg** | **-4.06 (-6.72 to -1.36)** | 0.18 (-2.54 to 2.82) | -- |
| **Canagliflozin 100 mg** | **-4.11 (-6.98 to -1.22)** | 0.10 (-3.87 to 4.13) | -0.05 (-4.02 to 3.93) |
| **Canagliflozin 300 mg** | **-3.54 (-6.46 to -0.54)** | 0.69 (-3.29 to 4.68) | 0.50 (-3.48 to 4.53) |

*All patients received TZD as a backbone (continuing) plus the above-stated Note: All patients receive backbone (continuing) TZD treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

### *Placebo response rates*

The following table states the placebo response for the safety outcomes which are required for the IMS CORE model. In addition given the

**Table 31 Placebo response (proportion in patients who are no longer responding adequately to metformin and thiazolidinedione treatment (TZD)**

| Treatment Regimen | | Overall hypoglycaemia | Non severe hypoglycaemia | Urinary tract infections |
|---|---|---|---|---|
| **Placebo** | Proportion | 0.03 | -- | 0.01 |
| | 95% Credible interval | (0.02 to 0.06) | -- | (0.00 to 0.02) |

*In addition to placebo, all patients received TZD as a backbone (continuing) with metformin*.

## Insulin networks

For the majority of analyses there was only one trial per arm available and therefore, the fixed effects model was used throughout.

### *Reduction in HbA1c*

Tables 29 and 30 present the results for the insulin background therapy networks for HbA1c. All the treatments were statistically significantly superior to placebo at 24 and 52 week. There was only one statistically significant difference between the treatment regiments which was that canagliflozin 300mg was statistically superior to empagliflozin 10mg.

24 week data

**Table 32 Mean change in HbA1c for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | **-0.50 (-0.61, -0.39)** | -- | 0.07 (-0.04, 0.19) |
| **Empagliflozin 25 mg** | **-0.57 (-0.69, -0.46)** | -0.07 (-0.19, 0.04) | -- |
| **Dapagliflozin 2.5 mg** | **-0.40 (-0.55, -0.25)** | 0.10 (-0.09, 0.29) | 0.17 (-0.02, 0.36) |
| **Dapagliflozin 5 mg** | **-0.50 (-0.65, -0.35)** | -0.00 (-0.19, 0.19) | 0.07 (-0.11, 0.26) |
| **Dapagliflozin 10 mg** | **-0.57 (-0.72, -0.42)** | -0.07 (-0.26, 0.12) | 0.00 (-0.18, 0.19) |
| **Canagliflozin 100 mg** | **-0.64 (-0.80, -0.47)** | -0.14 (-0.34, 0.06) | -0.07 (-0.26, 0.14) |
| **Canagliflozin 300 mg** | **-0.73 (-0.89, -0.57)** | **-0.23 (-0.43, -0.03)** | -0.15 (-0.35, 0.04) |
| **Sitagliptin 100 mg** | **-0.60 (-0.74, -0.46)** | -0.10 (-0.28, 0.08) | -0.03 (-0.20, 0.15) |

*Note: All patients received backbone (continuing) insulin treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

52 week data

**Table 33 Mean change in HbA1c for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) at 52 weeks**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10mg** | **-0.48 (-0.64, -0.33)** | -- | **0.16 (0.00, 0.32)** |
| **Empagliflozin 25 mg** | **-0.64 (-0.80, -0.49)** | **-0.16 (-0.32, -0.00)** | -- |
| **Dapagliflozin 2.5 mg** | **-0.40 (-0.55, -0.25)** | 0.08 (-0.14, 0.30) | **0.24 (0.02, 0.46)** |
| **Dapagliflozin 5 mg** | **-0.50 (-0.65, -0.35)** | -0.01 (-0.23, 0.20) | 0.14 (-0.07, 0.36) |
| **Dapagliflozin 10 mg** | **-0.57 (-0.72, -0.42)** | -0.08 (-0.30, 0.13) | 0.07 (-0.14, 0.29) |

*All patients received backbone (continuing) insulin treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

## *Reduction in weight (kg)*

Tables 31 and 32 present the results for the insulin background therapy networks for weight change. Empagliflozin 10mg, empagliflozin 25mg, dapagliflozin 10mg and canagliflozin 300mg were statistically significantly superior to placebo at 24 week. Empagliflozin (10mg and 25mg) and dapagliflozin (2.5mg, 5mg and 10mg) were statistically superior to placebo at 52 weeks. At all time points empagliflozin was not significantly different to any other treatment.

24 week data

**Table 34 Mean change in weight (kg) for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | **-1.44 (-3.10, -0.16)** | -- | 0.24 (-1.62, 1.41) |
| **Empagliflozin 25 mg** | **-1.68 (-3.01, 0.00)** | -0.24 (-1.41, 1.62) | -- |
| **Dapagliflozin 2.5 mg** | -1.36 (-3.24, 0.53) | 0.09 (-2.15, 2.64) | 0.33 (-2.22, 2.53) |
| **Dapagliflozin 5 mg** | -1.44 (-3.30, 0.43) | 0.01 (-2.18, 2.56) | 0.26 (-2.38, 2.45) |
| **Dapagliflozin 10 mg** | **-2.05 (-3.97, -0.14)** | -0.61 (-2.79, 1.92) | -0.36 (-2.99, 1.85) |
| **Canagliflozin 100 mg** | -1.84 (-3.74, 0.02) | -0.40 (-2.64, 2.21) | -0.15 (-2.78, 2.04) |
| **Canagliflozin 300 mg** | **-2.33 (-4.24, -0.48)** | -0.89 (-3.14, 1.68) | -0.65 (-3.28, 1.53) |
| **Sitagliptin 100 mg** | -0.00 (-1.88, 1.86) | 1.44 (-0.79, 4.03) | 1.69 (-0.91, 3.90) |

*All patients received backbone (continuing) insulin treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

52 week data

**Table 35 Mean change in body weight for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) at 52 weeks**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10mg** | **-1.41 (-1.82, -1.00)** | -- | 0.40 (-0.06, 0.86) |
| **Empagliflozin 25 mg** | **-1.81 (-2.26, -1.36)** | -0.40 (-0.86, 0.06) | -- |
| **Dapagliflozin 2.5 mg** | **-1.35 (-1.90, -0.81)** | 0.06 (-0.62, 0.74) | 0.46 (-0.25, 1.17) |
| **Dapagliflozin 5 mg** | **-1.43 (-1.97, -0.90)** | -0.02 (-0.70, 0.65) | 0.38 (-0.33, 1.08) |
| **Dapagliflozin 10 mg** | **-2.04 (-2.58, -1.49)** | -0.63 (-1.31, 0.05) | -0.23 (-0.93, 0.48) |

*All patients received backbone (continuing) insulin treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

## *Reduction in systolic blood pressure*

Tables 33 and 34 present the results for the insulin background therapy networks for systolic blood pressure change. The only statistically significant differences were empagliflozin (10mg and 25mg), dapagliflozin 10mg and canagliflozin 300mg versus placebo at 24 weeks. At 52 weeks empagliflozin (10mg and 25mg) and dapagliflozin 10mg were statistically superior to placebo. There were no statistically significant differences between empagliflozin and the other treatments.

24 week data

**Table 36 Mean reduction in systolic blood pressure for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | **-2.86 (-4.50, -1.17)** | -- | -0.59 (-2.30, 1.06) |
| **Empagliflozin 25 mg** | **-2.27 (-3.88, -0.51)** | 1.57 (-1.60, 4.74) | -- |
| **Dapagliflozin 2.5 mg** | -0.69 (-3.45, 2.00) | -0.11 (-3.14, 2.79) | 1.57 (-1.60, 4.74) |
| **Dapagliflozin 5 mg** | -2.40 (-4.98, 0.28) | -0.82 (-4.18, 2.30) | -0.11 (-3.14, 2.79) |
| **Dapagliflozin 10 mg** | **-3.13 (-5.85, -0.39)** | -0.36 (-3.68, 3.03) | -0.82 (-4.18, 2.30) |
| **Canagliflozin 100 mg** | -2.63 (-5.42, 0.18) | -2.18 (-5.61, 1.27) | -0.36 (-3.68, 3.03) |
| **Canagliflozin 300 mg** | **-4.40 (-7.34, -1.56)** | -2.14 (-4.54, 0.19) | -2.18 (-5.61, 1.27) |

*All patients received backbone (continuing) insulin treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

52 week data

**Table 37 Mean change in systolic blood pressure for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS) at 52 weeks**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10mg** | **-2.45 (-4.03, -0.88)** | -- | 0.05 (-1.52, 1.61) |
| **Empagliflozin 25 mg** | **-2.51 (-4.07, -0.93)** | -0.05 (-1.61, 1.52) | -- |
| **Dapagliflozin 2.5 mg** | -0.66 (-3.32, 2.06) | 1.79 (-1.28, 4.91) | 1.84 (-1.22, 4.97) |
| **Dapagliflozin 5 mg** | -2.38 (-5.01, 0.27) | 0.07 (-3.01, 3.16) | 0.12 (-2.95, 3.21) |
| **Dapagliflozin 10 mg** | **-3.11 (-5.76, -0.44)** | -0.65 (-3.74, 2.42) | -0.60 (-3.70, 2.47) |

*All patients received backbone (continuing) insulin treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

## *Overall Hypoglycaemia*

Tables 35 present the results for the insulin background therapy networks for the risk for overall hypoglycaemia. Dapagliflozin 2.5mg, canagliflozin (100mg and 300mg) and sitagliptin all statistically significantly increased the risk of overall hypoglycaemia. Empagliflozin 10mg was statistically significantly better than canagliflozin (100mg and 300mg) and sitagliptin. Empagliflozin 25mg was only statistically significantly better than sitagliptin.

### 24 week data

**Table 38 Relative risk of hypoglycaemic events for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | 1.03 (0.80, 1.32) | -- | 0.85 (0.67, 1.07) |
| **Empagliflozin 25 mg** | 1.22 (0.96, 1.53) | 1.18 (0.94, 1.50) | -- |
| **Dapagliflozin 2.5 mg** | **1.44 (1.10, 1.85)** | 1.40 (0.98, 2.01) | 1.18 (0.83, 1.66) |
| **Dapagliflozin 5 mg** | 1.18 (0.88, 1.55) | 1.14 (0.79, 1.66) | 0.97 (0.67, 1.38) |
| **Dapagliflozin 10 mg** | 1.09 (0.80, 1.45) | 1.05 (0.72, 1.55) | 0.89 (0.61, 1.29) |
| **Canagliflozin 100 mg** | **1.44 (1.22, 1.68)** | **1.39 (1.04, 1.88)** | 1.18 (0.90, 1.56) |
| **Canagliflozin 300 mg** | **1.41 (1.20, 1.65)** | **1.37 (1.02, 1.84)** | 1.15 (0.88, 1.53) |
| **Sitagliptin 100 mg** | **2.02 (1.67, 2.40)** | **1.96 (1.46, 2.66)** | **1.65 (1.25, 2.21)** |

*All patients received backbone (continuing) insulin treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

## *Hypoglycaemia (non-severe)*

Tables 36 present the results for the insulin background therapy networks for the risk for non-severe hypoglycaemia. Dapagliflozin 2.5mg and canagliflozin (100mg and 300mg) all statistically significantly increased the risk of non-severe hypoglycaemia. Empagliflozin 10mg was statistically significantly better than canagliflozin (100mg and 300mg).

### 24 week data

**Table 39 Relative risk of non-severe hypoglycaemic events for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | 1.03 (0.79, 1.32) | -- | 0.85 (0.66, 1.09) |
| **Empagliflozin 25 mg** | 1.20 (0.94, 1.54) | 1.17 (0.91, 1.51) | -- |
| **Dapagliflozin 2.5 mg** | **1.47 (1.10, 1.91)** | 1.43 (0.97, 2.08) | 1.22 (0.83, 1.77) |
| **Dapagliflozin 5 mg** | 1.18 (0.87, 1.58) | 1.15 (0.77, 1.70) | 0.98 (0.67, 1.44) |
| **Dapagliflozin 10 mg** | 1.09 (0.79, 1.47) | 1.06 (0.70, 1.59) | 0.9 (0.60, 1.34) |
| **Canagliflozin 100 mg** | **1.47 (1.23, 1.73)** | **1.43 (1.05, 1.94)** | 1.22 (0.91, 1.64) |
| **Canagliflozin 300 mg** | **1.42 (1.19, 1.68)** | **1.38 (1.02, 1.89)** | 1.18 (0.88, 1.60) |

*All patients received backbone (continuing) insulin treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

### *Hypoglycaemia (severe)*

Tables 37 present the results for the insulin background therapy networks for the risk for severe hypoglycaemia. There are no statistically significant differences between any of the treatments.

24 week data

**Table 40 Relative risk of severe hypoglycaemic events for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | 0.34 (0.02, 2.27) | -- | 0.26 (0.01, 2.46) |
| **Empagliflozin 25 mg** | 1.32 (0.25, 4.71) | 3.90 (0.41, 91.88) | -- |
| **Dapagliflozin 2.5 mg** | 0.04 (0.00, 1.66) | 0.14 (0.00, 14.80) | 0.03 (0.00, 1.83) |
| **Dapagliflozin 5 mg** | 1.83 (0.22, 7.27) | 5.37 (0.31, 154.05) | 1.39 (0.12, 11.88) |
| **Dapagliflozin 10 mg** | 0.04 (0.00, 1.77) | 0.14 (0.00, 15.05) | 0.03 (0.00, 1.85) |
| **Canagliflozin 100 mg** | 0.70 (0.30, 1.57) | 2.10 (0.25, 51.29) | 0.53 (0.11, 3.33) |
| **Canagliflozin 300 mg** | 1.10 (0.53, 2.27) | 3.33 (0.42, 80.29) | 0.84 (0.19, 5.04) |

*All patients received backbone (continuing) insulin treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

### *Urinary tract infections*

Tables 38 present the results for the insulin background therapy networks for the risk for urinary tract infections. There are no statistically significant differences between any of the treatments.

24 week data

**Table 41 Relative risk of urinary tract infections for SGLT-2is and sitagliptin in patients who are no longer responding adequately to any insulin treatment (INS)**

| Treatment Regimen | Versus Placebo | Versus Empagliflozin 10 mg | Versus Empagliflozin 25 mg |
|---|---|---|---|
| **Empagliflozin 10 mg** | 1.65 (0.78, 3.41) | -- | 1.14 (0.54, 2.43) |
| **Empagliflozin 25 mg** | 1.43 (0.65, 3.08) | 0.87 (0.41, 1.82) | -- |
| **Dapagliflozin 2.5 mg** | 1.67 (0.62, 4.59) | 1.02 (0.29, 3.56) | 1.16 (0.34, 4.15) |
| **Dapagliflozin 5 mg** | 1.90 (0.75, 5.24) | 1.17 (0.35, 3.91) | 1.34 (0.40, 4.79) |
| **Dapagliflozin 10 mg** | 1.86 (0.72, 5.20) | 1.15 (0.35, 3.90) | 1.32 (0.39, 4.85) |

*All patients received backbone (continuing) insulin treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to the above-stated interventions*

### *Placebo response rates*

The following table states the placebo response for the safety outcomes which are required for the IMS CORE model.

**Table 42 Placebo response (proportion) in patients who are no longer responding adequately to any insulin treatment (INS)**

| Treatment Regimen | | Overall hypoglycaemia | Non severe hypoglycaemia | Urinary tract infections |
|---|---|---|---|---|
| **Placebo** | Proportion | 0.26 | 0.24 | 0.03 |
| | 95% Credible interval | (0.25 to 0.28) | (0.23 to 0.26) | (0.02 to 0.05) |

*In addition to placebo, all patients receives backbone insulin treatment (any type) with or without other backbone (continuing) anti-diabetic drugs in addition to placebo*

## Conclusions

Across all the analyses it appears that the SGLT-2is are of similar efficacy and safety. Overall the SGLT-2i offer significant weight loss and blood pressure reductions compared to placebo and sulphonylurea. In addition, there is a numerical advantage compared to the DPP-4is in terms of weight loss and blood pressure as well.

The analysis has a number of advantages over previous NMAs in that more long-term data could be utilised such as in the metformin and sulphonylurea network. In addition, this is the first NMA for inclusion in a NICE appraisal that includes all the licensed SGLT-2is

There are some limitations to the analysis. In particular the lack of evidence for some of the networks and for particular outputs in particular the metformin and TZD network. In addition, the lack of long term evidence on a number of safety outcomes and for the metformin and TZD and Insulin background networks. This lack of evidence results in a limited amount of sensitivity analysis that could be conducted.

This analysis is consistent with the analysis conducted previously for NICE, however, there are small numerical differences. For the networks for metformin and TZD and insulin the estimates were almost identical due to the limited evidence base therefore, limiting the analysis to treatments had little impact.

Overall these analyses provide suitable estimates for inclusion in the economic analysis which will be outlined in the economic analysis.

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## Appendix A: Excluded studies

### Table 43 List of excluded studies from metformin background analysis

| Study | Treatment compared | Reason for exclusion |
|---|---|---|
| **Bosi et al 2007** | Placebo<br>Vildagliptin 50 mg<br>Vildagliptin 100 mg | No relevant treatments |
| **Charpentier et al 2001** | Placebo<br>SU | No relevant treatments |
| **Defronzo et al 2009** | Placebo<br>Saxagliptin 2.5 mg<br>Saxagliptin 5 mg<br>Saxagliptin 10 mg | No relevant treatments |
| **Ferrannini et al 2009** | SU<br>Vildagliptin 100 mg | No relevant treatments |
| **Filozof and Gautier 2010** | SU<br>Vildagliptin 100 mg | No relevant treatments |
| **Gallwitz et al 2012** | SU<br>Linagliptin 5 mg | No relevant treatments |
| **Goke et al 2010** | SU<br>Saxagliptin 5 mg | No relevant treatments |
| **Goodman et al 2009** | Placebo<br>Vildagliptin 100 mg | No relevant treatments |
| **Nauck et al 2009** | Placebo<br>SU<br>Liraglutide 0.6 mg<br>Liraglutide 1.2 mg<br>Liraglutide 1.8 mg | No relevant treatments |
| **Pan et al 2012** | Placebo<br>Vildagliptin 50 mg<br>Vildagliptin 100 mg | No relevant treatments |
| **Taskinen et al 2011** | Placebo<br>Linagliptin 5 mg | No relevant treatments |
| **Yang et al 2011** | Placebo<br>Saxagliptin 5 mg | No relevant treatments |
| **Gallwitz et al 2011** | Exenatide 20 mcg<br>Biphasic insulin aspart | No relevant treatments |
| **Pratley et al 2010** | Sitagliptin 100 mg<br>Liraglutide 1.2 mg<br>Liraglutide 1.8 mg | No link to common comparators (placebo, SU or SGLT-2is) |
| **Bolli et al 2009** | Vildagliptin 100 mg<br>Pioglitazone 30 mg | No relevant treatments |
| **Bunck et al 2009** | Exenatide 20 mcg<br>Insulin glargine | No relevant treatments |
| **Matthews et al 2010** | SU<br>Vildagliptin 100 mg | No relevant treatments |
| **Jeon et al 2011** | SU<br>Vildagliptin 100 mg | No relevant treatments |
| **Filozof et al 2010** | Placebo<br>Vildagliptin 100 mg | No relevant treatments |
| **Hermans et al 2012** | Placebo<br>Saxagliptin 5 mg | No relevant treatments |
| **Nauck et al 2009** | Placebo<br>Alogliptin 12.5mg<br>Alogliptin 25mg | No relevant treatments |
| **Defronzo et al 2012** | Placebo<br>Alogliptin 12.5mg<br>Alogliptin 25mg | No relevant treatments |
| **Bergenstal 2010** | Sitagliptin 100 mg<br>Exenatide 2 mg QWK<br>Pioglitazone 45 mg | No link to common comparators (placebo, SU or SGLT-2is) |
| **Bolli 2008** | Vildagliptin 100 mg<br>Pioglitazone 30 mg | No relevant treatments |
| **Defronzo 2005** | Placebo<br>Exenatide 10 mcg | No relevant treatments |

| | | |
|---|---|---|
| | Exenatide 20 mcg | |
| **8358 Derosa 2012** | Placebo | No relevant treatments |
| | Vildagliptin 100 mg | |
| **Derosa 2010** | SU | No relevant treatments |
| | Exenatide 20 mcg | |
| **Derosa 2011** | SU | No relevant treatments |
| | Exenatide 20 mcg | |
| **Papathanassiou 2009** | SU | No relevant treatments |
| | Pioglitazone 30 mg | |
| **Petrica 2011** | SU | No relevant treatments |
| | Pioglitazone 30 mg | |
| **Pfutzner 2011** | SU | No relevant treatments |
| | Pioglitazone 30 mg | |

### Table 44 List of excluded studies from metformin and SU background analysis

| Study | Treatment compared | Reason for exclusion |
|---|---|---|
| **Owens et al 2011** | Placebo | No relevant treatments |
| | Linagliptin 5 mg | |
| **Moses et al 2013** | Placebo | No relevant treatments |
| | Saxagliptin 5 mg | |
| **Bergenstal et al 2009** | Exenatide 20 mcg | No relevant treatments |
| | Biphasic insulin aspart (QD) | |
| | Biphasic insulin aspart (BID) | |
| **Heine et al 2005** | Exenatide 20 mcg | No relevant treatments |
| | Insulin glargine | |
| **Janka et al 2005** | Insulin glargine | No relevant treatments |
| | NPH Insulin | |
| **Kendall et al 2005** | Placebo | No relevant treatments |
| | Exenatide 10 mcg | |
| | Exenatide 20 mcg | |
| **Kalra et al 2010** | Insulin glargine | No relevant treatments |
| | Biphasic insulin aspart | |
| **Strojek et al 2009** | Insulin glargine | No relevant treatments |
| | Biphasic insulin aspart | |
| **Russell-Jones et al 2009** | Placebo | No relevant treatments |
| | Liraglutide 1.8 mg | |
| | Insulin glargine | |

### Table 45 List of excluded studies from metformin and TZD background analysis

| Study | Treatment compared | Reason for exclusion |
|---|---|---|
| **Pratley et al 2009** | Placebo | No relevant treatments |
| | Alogliptin 12.5mg | |
| | Alogliptin 25mg | |
| **Hollander et al 2009** | Placebo | No relevant treatments |
| | Saxagliptin 2.5 mg | |
| | Saxagliptin 5 mg | |
| **Garber et al 2007** | Placebo | No relevant treatments |
| | Vildagliptin 50 mg | |
| | Vildagliptin 100 mg | |
| **Bosi et al 2011** | Placebo | No relevant treatments |
| | Alogliptin 25mg | |
| **Defronzo et al 2012** | Placebo | No relevant treatments |
| | Alogliptin 12.5mg | |
| | Alogliptin 25mg | |

### Table 46 List of excluded studies from insulin background analysis

| Study | Treatment compared | Reason for exclusion |
|---|---|---|
| **Barnett 2012** | Placebo<br>Saxagliptin 5 mg | No relevant treatments |
| **Fonseca 2007** | Placebo<br>Vildagliptin 100 mg | No relevant treatments |
| **Mattoo 2005** | Placebo<br>Pioglitazone 30 mg | No relevant treatments |
| **Jacob 2007** | Placebo<br>Pioglitazone 30 mg<br>Placebo | No relevant treatments |
| **Davidson 2006** | Pioglitazone 30 mg<br>Pioglitazone 45 mg | No relevant treatments |
| **Kothny 2013** | Placebo<br>Vildagliptin 100 mg | No relevant treatments |
| **Rosenstock 2009** | Placebo<br>Alogliptin 12.5mg<br>Alogliptin 25mg | No relevant treatments |
| **Buse 2011** | Placebo<br>Exenatide 20 mcg | No relevant treatments |
| **Seino 2012** | Placebo<br>Lixisenatide | No relevant treatments |
| **Riddle 2013 (GetGoal-Duo 1)** | Placebo<br>Lixisenatide | No relevant treatments |
| **Riddle 2013 (GetGoal-L)** | Placebo<br>Lixisenatide | No relevant treatments |
| **Yki-Jarvinen 2013** | Placebo<br>Linagliptin 5 mg | No relevant treatments |

## Appendix B: Baseline characteristics of included studies

### *Dual therapy - Metformin networks - baseline characteristics*

**Table 47 Baseline characteristics of included studies - metformin networks**

| Author | Interventions /Comparators | N | Mean age, years | Male, % | Mean baseline HbA1c | Mean body weight, kg | Mean BMI, kg/m$^2$ | Mean disease duration, years | White, % | Black, % | Asian, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Arechavaleta et al 2011**[15] | SU | 519 | 56.2 | 54 | 7.5 | 82.0 | 30.2 | 6.7 | 57 | 1 | 21 |
| | Sitagliptin 100 mg | 516 | 56.3 | 55 | 7.5 | 80.6 | 29.7 | 6.8 | 58 | 1 | 21 |
| **Bailey et al 2010**[16] | Placebo | 137 | 53.7 | 55 | 8.1 | -- | 31.8 | 5.8 | -- | -- | -- |
| | Dapagliflozin 5 mg | 137 | 54.3 | 50 | 8.2 | -- | 31.4 | 6.4 | -- | -- | -- |
| | Dapagliflozin 10 mg | 135 | 52.7 | 57 | 7.9 | -- | 31.2 | 6.1 | -- | -- | -- |
| **Haring et al 2013**[42] | Placebo | 225 | 56.9 | 50 | 8.2 | 76.2 | 27.9 | -- | 39 | 3 | 56 |
| | Empagliflozin 10 mg | 225 | 57.0 | 50 | 8.1 | 77.1 | 28.3 | -- | 40 | 1 | 57 |
| | Empagliflozin 25 mg | 216 | 57.4 | 53 | 8.1 | 77.5 | 28.3 | -- | 39 | 1 | 58 |
| **Ridderstrale 2012** | SU | 780 | 55.7 | 54 | 7.92 | 83 | 30.3 | -- | 66.5 | 1 | 32.4 |
| | Empagliflozin 25 mg | 765 | 56.2 | 56.6 | 7.92 | 82.5 | 30.0 | -- | 65.1 | 1.6 | 33.2 |
| **Bolinder et al 2012**[19] | Placebo | 91 | 60.8 | 56 | 7.2 | 90.9 | 31.7 | 5.5 | 100 | 0 | 0 |
| | Dapagliflozin 10 mg | 89 | 60.6 | 55 | 7.2 | 92.1 | 32.1 | 6.0 | 100 | 0 | 0 |
| **Charbonnel et al 2006**[25] | Placebo | 237 | 54.7 | 60 | 8.0 | 89.6 | 31.5 | 6.6 | 67 | 6 | 11 |
| | Sitagliptin 100 mg | 464 | 54.4 | 56 | 8.0 | 86.7 | 30.9 | 6.0 | 63 | 7 | 11 |
| **Henry et al 2012a**[43] | Placebo | 208 | 52.7 | 47 | 9.1 | 87.2 | -- | 1.9 | -- | -- | -- |
| | Dapagliflozin 10 mg | 211 | 51.0 | 50 | 9.1 | 88.4 | -- | 2.2 | -- | -- | -- |
| **Henry et al 2012b**[43] | Placebo | 201 | 51.8 | 47 | 9.2 | 85.6 | -- | 1.6 | -- | -- | -- |
| | Dapagliflozin 5 mg | 194 | 51.7 | 40 | 9.2 | 84.1 | -- | 1.6 | -- | -- | -- |
| **Cefalu et al 2013**[24] | SU | 482 | 56.3 | 55 | 7.8 | 86.5 | 30.9 | 6.6 | 67 | 5 | 19 |
| | Canagliflozin 100 mg | 483 | 56.4 | 52 | 7.8 | 86.9 | 31.0 | 6.5 | 67 | 4 | 21 |
| | Canagliflozin 300 mg | 485 | 55.8 | 50 | 7.8 | 86.6 | 31.2 | 6.7 | 69 | 4 | 19 |
| **Lavalle-Gonzalez et al 2013**[46] | Placebo | 183 | 55.3 | 51 | 8.0 | 86.6 | 31.1 | 6.8 | 71 | 2 | 16 |
| | Canagliflozin 100 mg | 368 | 55.5 | 47 | 7.9 | 88.8 | 32.4 | 6.7 | 69 | 4 | 14 |
| | Canagliflozin 300 mg | 367 | 55.3 | 45 | 7.9 | 85.4 | 31.4 | 7.1 | 70 | 4 | 16 |
| | Sitagliptin 100 mg | 366 | 55.5 | 47 | 7.9 | 87.7 | 32.0 | 6.8 | 72 | 4 | 11 |
| **Nauck et al 2007**[52] | SU | 584 | 56.6 | 61 | 7.6 | 89.7 | 31.3 | 6.2 | 74 | 6 | 8 |
| | Sitagliptin 100 mg | 588 | 56.8 | 57 | 7.7 | 89.5 | 31.2 | 6.5 | 74 | 7 | 9 |
| **Nauck et al 2011**[49] | SU | 401 | 58.6 | 55 | 7.7 | -- | 31.2 | 7.0 | 81 | 6 | 9 |
| | Dapagliflozin 10 mg | 400 | 58.1 | 55 | 7.7 | -- | 31.7 | 6.0 | 82 | 7 | 7 |
| **Raz et al 2008**[58] | Placebo | 94 | 56.1 | 42 | 9.1 | 81.2 | 30.4 | 7.3 | 47 | 1 | -- |
| | Sitagliptin 100 mg | 96 | 53.6 | 51 | 9.3 | 81.5 | 30.1 | 8.4 | 42 | 3 | -- |
| **Yang et al 2012**[61] | Placebo | 198 | 55.1 | 55 | 8.5 | 68.9 | 25.3 | 7.3 | -- | -- | -- |
| | Sitagliptin 100 mg | 197 | 54.1 | 47 | 8.5 | 67.9 | 25.3 | 6.4 | -- | -- | -- |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Retnakaran et al 2010**[59] | Placebo | 11 | 60.8 | 73 | 6.1 | -- | 32.7 | 3.5 | 82 | 0 | 0 |
| | Sitagliptin 100 mg | 10 | 61.3 | 60 | 6.2 | -- | 34.3 | 2.8 | 40 | 0 | 0 |
| **Bergenstal et al 2012**[17] | Placebo | 90 | 56.1 | 52 | 8.0 | 91.1 | 32.5 | 5.5 | 77 | 6 | 10 |
| | Sitagliptin 100 mg | 177 | 55.5 | 59 | 7.9 | 92.5 | 32.4 | 6.0 | 76 | 6 | 11 |
| | Taspoglutide 10 mg | 182 | 55.3 | 56 | 8.0 | 93.6 | 32.7 | 6.1 | 79 | 7 | 8 |
| | Taspoglutide 20 mg | 187 | 56.8 | 52 | 8.0 | 91.8 | 32.3 | 5.7 | 82 | 4 | 7 |
| **Derosa et al 2012a**[30] | Placebo | 87 | 54.8 | 51 | 8.0 | 78.6 | 28.9 | 5.4 | 100 | 0 | 0 |
| | Sitagliptin 100 mg | 91 | 55.9 | 46 | 8.1 | 78.4 | 28.1 | 5.8 | 100 | 0 | 0 |
| **Ljunggren et al 2012**[47] | Placebo | 91 | 60.8 | 56 | 7.2 | 90.9 | 31.7 | 5.5 | 100 | 0 | 0 |
| | Dapagliflozin 10 mg | 89 | 60.6 | 55 | 7.2 | 92.1 | 32.1 | 6.0 | 100 | 0 | 0 |

## *Triple therapy - Metformin and sulphonylurea networks - baseline characteristics*

### Table 48 Baseline characteristics of included studies - metformin and sulphonylurea networks

| Author | Interventions /Comparators | N | Mean age, years | Male, % | Mean baseline HbA1c | Mean body weight, kg | Mean BMI, kg/m$^2$ | Mean disease duration, years | White, % | Black, % | Asian, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Haring et al 2013**[14] | Placebo | 225 | 56.9 | 50 | 8.2 | 76.2 | 27.9 | -- | 39 | 3 | 56 |
| | Empagliflozin 10 mg | 225 | 57.0 | 50 | 8.1 | 77.1 | 28.3 | -- | 40 | 1 | 57 |
| | Empagliflozin 25 mg | 216 | 57.4 | 53 | 8.1 | 77.5 | 28.3 | -- | 39 | 1 | 58 |
| **Hermansen et al 2007**[25] | Placebo | 113 | 57.7 | 52 | 8.3 | 86.7 | 30.7 | 10.6 | 72 | 8 | 12 |
| | Sitagliptin 100 mg | 116 | 56.6 | 53 | 8.3 | 87.2 | 31.3 | 9.3 | 65 | 3 | 14 |
| **Schernthaner et al 2013**[23] | Canagliflozin 300 mg | 377 | 56.6 | 55 | 8.1 | 87.4 | 31.5 | 9.4 | 65 | 11 | 18 |
| | Sitagliptin 100 mg | 378 | 56.7 | 57 | 8.1 | 89.1 | 31.7 | 9.7 | 64 | 12 | 17 |
| **Wilding et al 2013 (DIA3002)**[17] | Placebo | 156 | 56.7 | 49 | 8.1 | 91.2 | 32.7 | 10.3 | 82 | 6 | 1 |
| | Canagliflozin 100 mg | 157 | 57.3 | 48 | 8.1 | 93.8 | 33.3 | 9.0 | 84 | 3 | 1 |
| | Canagliflozin 300 mg | 156 | 56.0 | 56 | 8.1 | 93.5 | 33.2 | 9.4 | 81 | 7 | 0 |

## *Triple therapy - Metformin and thiazolidinediones networks - baseline characteristics*

**Table 49 Baseline characteristics of included studies - metformin and thiazolidinediones networks**

| Author | Interventions /Comparators | N | Mean age, years | Male, % | Mean baseline HbA1c | Mean body weight, kg | Mean BMI, kg/m$^2$ | Mean disease duration, years | White, % | Black, % | Asian, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Kovacs 2013**[18] | Placebo | 165 | 54.6 | 44.2 | 8.2 | 78.1 | 29.3 | -- | 36.4 | 0.6 | 62.0 |
| | Empagliflozin 10mg | 165 | 54.7 | 50.3 | 8.1 | 78.0 | 29.2 | -- | 41.8 | 2.4 | 55.0 |
| | Empagliflozin 10mg | 168 | 54.2 | 50.6 | 8.1 | 78.9 | 29.1 | -- | 40.5 | 3.6 | 56.0 |
| **Rosenstock 2012**[20] | Placebo | 139 | 53.5 | 51.1 | 8.3 | 86.4 | -- | 5.1 | 74.3 | 4.3 | 17.0 |
| | Dapagliflozin 5 mg | 141 | 53.2 | 55.3 | 8.4 | 87.8 | -- | 5.6 | 72.3 | 6.4 | 18.0 |
| | Dapagliflozin 10 mg | 140 | 53.8 | 42.1 | 8.3 | 84.8 | -- | 5.8 | 72.1 | 5.0 | 15.0 |
| **Forst (DIA3012) 2014**[15] | Placebo | 115 | 58.3 | 66.1 | 8.0 | 93.8 | 32.5 | 10.1 | 68.7 | 5.2 | 18.3 |
| | Canagliflozin 100 mg | 113 | 56.7 | 68.1 | 7.9 | 94.2 | 32.3 | 10.5 | 73.5 | 3.5 | 20.4 |
| | Canagliflozin 300 mg | 114 | 57.0 | 55.3 | 7.8 | 94.4 | 32.8 | 11.0 | 78.9 | 8.8 | 9.6 |
| **Derosa et al 2010**[14] | Placebo | 76 | 58.0 | 51.0 | 8.4 | 77.3 | 27.7 | 6.0 | -- | -- | -- |
| | Sitagliptin 100 mg | 75 | 57.0 | 49.0 | 8.5 | 78.7 | 27.9 | 5.0 | -- | -- | -- |

## *Triple therapy – Insulin networks - baseline characteristics*

### Table 50 Baseline characteristics of included studies - Insulin networks

| Author | Interventions /Comparators | N | Mean age, years | Male, % | Mean baseline HbA1c | Mean body weight, kg | Mean BMI, kg/m$^2$ | Mean disease duration, years | White, % | Black, % | Asian, % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1245-49 2013**[23] | Placebo | 188 | 55.3 | 40 | 8.3 | 95.5 | 34.7 | -- | 93 | 4 | 1 |
| | Empagliflozin 10mg | 186 | 56.7 | 52 | 8.4 | 96.7 | 34.7 | -- | 94 | 4 | 0 |
| | Empagliflozin 25 mg | 189 | 58.0 | 44 | 8.3 | 95.9 | 35.0 | -- | 96 | 2 | 1 |
| **1245-33 2013**[28] | Placebo | 170 | 58.1 | 53 | 8.2 | 90.5 | 31.8 | -- | 67 | 12 | 19 |
| | Empagliflozin 10mg | 169 | 58.6 | 55 | 8.3 | 91.6 | 32.1 | -- | 70 | 7 | 22 |
| | Empagliflozin 25 mg | 155 | 59.9 | 60 | 8.3 | 94.7 | 32.7 | -- | 72 | 10 | 18 |
| **Janssen (DIA3008) 2013**[20] | Placebo | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| | Canagliflozin 100 mg | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| | Canagliflozin 300 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| **Wilding 2012**[27] | Placebo | 193 | 58.8 | 49 | 8.5 | 94.5 | 33.1 | 13.5 | 96 | 3 | 0 |
| | Dapagliflozin 2.5 mg | 202 | 59.8 | 50 | 8.5 | 93.0 | 33.0 | 13.6 | 94 | 2 | 4 |
| | Dapagliflozin 5 mg | 211 | 59.3 | 47 | 8.6 | 93.3 | 33.0 | 13.1 | 95 | 2 | 1 |
| | Dapagliflozin 10 mg | 194 | 59.3 | 45 | 8.6 | 94.5 | 33.4 | 14.2 | 95 | 3 | 2 |
| **Vilsboli 2010**[26] | Placebo | 319 | 57.2 | 53 | 8.6 | 87.3 | 31.0 | 12.0 | 69 | 7 | 19 |
| | Sitagliptin 100 mg | 322 | 58.3 | 49 | 8.7 | 86.5 | 31.0 | 13.0 | 71 | 6 | 17 |

## Appendix C. data availability

### *24 week data*

*Dual therapy - Metformin networks – data availability*

**Table 51 Data availability - metformin networks 24 weeks**

| Author | Drugs (Metformin +) | n | Change from baseline | | | Hypoglycaemia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | HbA1C | Weight | SBP | Overall | Non-severe | Severe | UTI | GTI |
| **Arechavaleta et al 2011** | SU | 519 | ✓ | ✓ | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ |
| | Sitagliptin 100 mg | 516 | ✓ | ✓ | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ |
| **Bailey et al 2010** | Placebo | 137 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| | Dapagliflozin 5 mg | 137 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| | Dapagliflozin 10 mg | 135 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| **BI GMBH (1245-28) 2-12 (Ridderstrale 2012)** | SU | 780 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Empagliflozin 25 mg | 765 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **BI GMBH (1245-23) 2012 (Haring 2013?) (Haring 2013)** | Placebo | 225 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Empagliflozin 10mg | 225 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Empagliflozin 25 mg | 216 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Bolinder et al 2012** | Placebo | 91 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| | Dapagliflozin 10 mg | 89 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| **Charbonnel et al 2006** | Placebo | 237 | ✓ | ✗ | ✗ | ✓ | ✓ | ✓ | ✓ | ✗ |
| | Sitagliptin 100 mg | 464 | ✓ | ✗ | ✗ | ✓ | ✓ | ✓ | ✓ | ✗ |
| **Henry et al 2012a Study 2** | Placebo | 208 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| | Dapagliflozin 10 mg | 211 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| **Henry et al 2012b Study 1** | Placebo | 201 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| | Dapagliflozin 5 mg | 194 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ |
| **Janssen (DIA3009) 2013 (Cefalu 2013)** | SU | 482 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Canagliflozin 100 mg | 483 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Canagliflozin 300 mg | 485 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Janssen (DIA3006) 2013 (Lavalle-Gonzalez 2013)** | Placebo | 183 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Canagliflozin 100 mg | 366 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Canagliflozin 300 mg | 368 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Sitagliptin 100 mg | 367 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Nauck et al 2007** | SU | 584 | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Sitagliptin 100 mg | 588 | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Nauck et al 2011** | SU | 401 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Dapagliflozin 10 mg | 400 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Raz et al 2008** | Placebo | 94 | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✓ | ✗ |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sitagliptin 100 mg | 96 | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✓ | ✗ |
| **Yang et al 2012** | Placebo | 198 | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Sitagliptin 100 mg | 197 | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Retnakaran et al 2010** | Placebo | 11 | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Sitagliptin 100 mg | 10 | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Bergenstal 2012** | Placebo | 90 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Sitagliptin 100 mg | 177 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **8354 Derosa 2012** | Placebo | 87 | ✓ | ✓ | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ |
| | Sitagliptin 100 mg | 91 | ✓ | ✓ | ✗ | ✓ | ✓ | ✓ | ✗ | ✗ |
| **Ljunggren 2012** | Placebo | 91 | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Dapagliflozin 10 mg | 89 | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |

## *Triple therapy - Metformin and sulphonylurea networks – data availability*

**Table 52 Data availability - metformin and sulphonylurea networks 24 weeks**

| | | | Change from baseline | | | Hypoglycaemia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Author** | **Drugs (Metformin +)** | **n** | **HbA1C** | **Weight** | **SBP** | **Overall** | **Non-severe** | **Severe** | **UTI** | **GTI** |
| **Haring et al 2013** | Placebo | 225 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Empagliflozin 10mg | 225 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Empagliflozin 25 mg | 216 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Hermansen et al 2007** | Placebo | 113 | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Sitagliptin 100 mg | 116 | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Janssen (DIA3015) 2013 (Schernthaner 2013)** | Canagliflozin 300 mg | 377 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Sitagliptin 100 mg | 378 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Janssen (DIA3002) 2013** | Placebo | 156 | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ |
| | Canagliflozin 100 mg | 157 | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ |
| | Canagliflozin 300 mg | 156 | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ |

## *Triple therapy - Metformin and thiazolidinediones networks – data availability*

**Table 53 Data availability - metformin and thiazolidinediones networks 24 weeks**

| Author | Drugs (Metformin+TZD+) | n | Change from baseline | | | Hypoglycaemia | | | UTI | GTI |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | HbA1C | Weight | SBP | Overall | Non-severe | Severe | | |
| **Kovacs 2013** | Placebo | 165 | ✓ | ✓ | ✓ | ✓ | × | × | ✓ | ✓ |
| **BI GMBH 1245.19 2013** | Empagliflozin 10mg | 165 | ✓ | ✓ | ✓ | × | × | × | × | × |
| | Empagliflozin 10mg | 168 | ✓ | ✓ | ✓ | × | × | × | × | × |
| **Rosenstock 2012** | Placebo | 139 | ✓ | ✓ | ✓ | × | × | × | × | × |
| | Dapagliflozin 5 mg | 141 | ✓ | ✓ | ✓ | × | × | × | × | × |
| | Dapagliflozin 10 mg | 140 | ✓ | ✓ | ✓ | × | × | × | × | × |
| **DIA3012 2013** | Placebo | 115 | ✓ | ✓ | ✓ | × | × | × | × | × |
| | Canagliflozin 100 mg | 113 | ✓ | ✓ | ✓ | × | × | × | × | × |
| | Canagliflozin 300 mg | 114 | ✓ | ✓ | ✓ | × | × | × | × | × |
| **Derosa et al 2010** | Placebo | 76 | ✓ | ✓ | × | × | × | × | × | × |
| | Sitagliptin 100 mg | 75 | ✓ | ✓ | × | × | × | × | × | × |

## *Insulin networks – data availability*

**Table 54 Data availability - Insulin networks 24 weeks**

| Author | Drugs (Insulin +) | n | Change from baseline | | | Hypoglycaemia | | | UTI | GTI |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | HbA1C | Weight | SBP | Overall | Non-severe | Severe | | |
| **BI GMBH (1245-49) 2013** | Placebo | 188 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Empagliflozin 10mg | 186 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Empagliflozin 25 mg | 189 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **BI GMBH (1245-33) 2013** | Placebo | 170 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Empagliflozin 10mg | 169 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Empagliflozin 25 mg | 155 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Janssen DIA3008 (Neal 2013)** | Placebo | 565 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × | × |
| | Canagliflozin 100 mg | 566 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × | × |
| | Canagliflozin 300 mg | 587 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × | × |
| **Wilding 2012** | Placebo | 193 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × |
| | Dapagliflozin 2.5 mg | 202 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × |
| | Dapagliflozin 5 mg | 211 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × |
| | Dapagliflozin 10 mg | 194 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × |
| **Vilsboli 2010** | Placebo | 319 | ✓ | ✓ | × | ✓ | × | × | × | × |
| | Sitagliptin 100 mg | 322 | ✓ | ✓ | × | ✓ | × | × | × | × |

## *52 week data*

### *Dual therapy - Metformin networks – data availability*

**Table 55 Data availability - metformin networks 52 weeks**

| Author | Drugs (Metformin +) | n | Change from baseline | | | Hypoglycaemia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | HbA1C | Weight | SBP | Overall | Non-severe | Severe | UTI | GTI |
| **BI GMBH (1245-28) 2-12 (Ridderstrale 2012)** | SU | 780 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Empagliflozin 25 mg | 765 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| **BI GMBH (1245-23) 2012 (Haring 2013)** | Placebo | 225 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Empagliflozin 10mg | 225 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Empagliflozin 25 mg | 216 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Janssen (DIA3009) 2013 (Cefalu 2013)** | SU | 482 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ |
| | Canagliflozin 100 mg | 483 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ |
| | Canagliflozin 300 mg | 485 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ |
| **Janssen (DIA3006) 2013 (Lavalle-Gonzalez 2013)** | Canagliflozin 100 mg | 366 | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ |
| | Canagliflozin 300 mg | 368 | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ |
| | Sitagliptin 100 mg | 367 | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ |
| **Nauck et al 2007** | SU | 584 | ✓ | ✓ | ✗ | ✓ | ✓ | ✓ | ✓ | ✗ |
| | Sitagliptin 100 mg | 588 | ✓ | ✓ | ✗ | ✓ | ✓ | ✓ | ✓ | ✗ |
| **Nauck et al 2011** | SU | 401 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ |
| | Dapagliflozin 10 mg | 400 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ |
| **Ljunggren 2012** | Placebo | 77 | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Dapagliflozin 10 mg | 79 | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |

## *Triple therapy - Metformin and sulphonylurea networks – data availability*

### Table 56 Data availability - metformin and sulphonylurea networks 52 weeks

| Author | Drugs (Metformin+SU+) | n | Change from baseline | | | Hypoglycaemia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | HbA1C | Weight | SBP | Overall | Non-severe | Severe | UTI | GTI |
| **Haring et al 2013** | Placebo | 225 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Empagliflozin 10mg | 225 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Empagliflozin 25 mg | 216 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **Janssen (DIA3015) 2013 (Schernthaner 2013)** | Canagliflozin 300 mg | 377 | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ |
| | Sitagliptin 100 mg | 378 | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ |
| **Janssen (DIA3002) 2013 (NCT01106625)** | Placebo | 156 | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ |
| | Canagliflozin 100 mg | 157 | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ |
| | Canagliflozin 300 mg | 156 | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ |

## *Triple therapy - Metformin and thiazolidinediones networks – data availability*

### Table 57 Data availability - metformin and thiazolidinediones networks 52 weeks

| Author | Drugs (Metformin+TZD) | n | Change from baseline | | | Hypoglycaemia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | HbA1C | Weight | SBP | Overall | Non-severe | Severe | UTI | GTI |
| **BI GMBH 1245.19 2013 (Kovacs 2013)** | Placebo | 165 | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Empagliflozin 10mg | 165 | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Empagliflozin 10mg | 168 | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **DIA3012 2013** | Canagliflozin 100 mg | 113 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✗ |
| | Canagliflozin 300 mg | 114 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✗ |

## *Insulin networks – data availability*

### Table 58 Data availability - Insulin networks 52 weeks

| Author | Drugs (Insulin) | n | Change from baseline | | | Hypoglycaemia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | HbA1C | Weight | SBP | Overall | Non-severe | Severe | UTI | GTI |
| **BI GMBH (1245-49) 2013** | Placebo | 188 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Empagliflozin 10mg | 186 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Empagliflozin 25 mg | 189 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| **BI GMBH (1245-33) 2013** | Placebo | 170 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ |
| | Empagliflozin 10mg | 169 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ |
| | Empagliflozin 25 mg | 155 | ✓ | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ |
| **Wilding 2012** | Placebo | 193 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Dapagliflozin 2.5 mg | 202 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Dapagliflozin 5 mg | 211 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |
| | Dapagliflozin 10 mg | 194 | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ |

# Appendix D. data extraction tables

## *Data extraction tables (24wks) - Metformin background treatments*

**Accroynms:** Met - Metformin; SU –Sulphonylurea; Sita – Sitagliptin; Empa – Empagliflozin; Cana – Canagliflozin; Dapa - Dapagliflozin

### Table 59 HbA1c (%) change from baseline

| Trial | Time Point | Treatment arms | | | | Change from Baseline | | | | Standard Error (SE) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **Arechavaleta et al 2011** | 24 | SU | Sita 100mg | | | -0.54 | -0.40 | | | 0.03 | 0.02 | | |
| **Bailey et al 2010** | 24 | Placebo | Dapa 5mg | Dapa 10mg | | -0.32 | -0.69 | -0.98 | | 0.08 | 0.08 | 0.08 | |
| **BI GMBH (1245-23) 2012** | 24 | Placebo | Empa 10mg | Empa 25mg | | -0.13 | -0.70 | -0.77 | | 0.05 | 0.05 | 0.05 | |
| **BI GMBH (1245-28) 2012** | 28 | SU | Empa 25mg | | | -0.85 | -0.77 | | | 0.03 | 0.03 | | |
| **Bolinder et al 2012** | 24 | Placebo | Dapa 10mg | | | -0.10 | -0.39 | | | 0.09 | 0.09 | | |
| **Charbonnel et al 2006** | 24 | Placebo | Sita 100mg | | | -0.02 | -0.67 | | | 0.06 | 0.05 | | |
| **Henry et al 2012a** | 24 | Placebo | Dapa 10mg | | | -1.44 | -1.98 | | | 0.08 | 0.08 | | |
| **Henry et al 2012b** | 24 | Placebo | Dapa 5mg | | | -1.35 | -2.05 | | | 0.09 | 0.09 | | |
| **Janssen (DIA3006) 2013** | 26 | Placebo | Sita 100mg | Cana 100mg | Cana 300mg | -0.17 | -0.83 | -0.79 | -0.94 | 0.06 | 0.05 | 0.05 | 0.05 |
| **Janssen (DIA3009) 2013** | 26 | SU | Cana 100mg | Cana 300mg | | -0.81 | -0.94 | -0.91 | | 0.04 | 0.04 | 0.03 | |
| **Nauck et al 2007** | 24 | SU | Sita 100mg | | | -0.96 | -0.87 | | | 0.05 | 0.05 | | |
| **Nauck et al 2011** | 26 | SU | Dapa 10mg | | | -0.73 | -0.50 | | | 0.03 | 0.03 | | |
| **Raz et al 2008** | 24 | Placebo | Sita 100mg | | | 0.04 | -1.08 | | | 0.10 | 0.09 | | |
| **Yang et al 2012** | 24 | Placebo | Sita 100mg | | | -0.14 | -1.02 | | | 0.07 | 0.07 | | |
| **Retnakaran et al 2010** | 24 | Placebo | Sita 100mg | | | 0.27 | -0.22 | | | NR | NR | | |
| **Bergenstal 2012** | 24 | Placebo | Sita 100mg | | | -0.1 | -0.89 | | | 0.08 | 0.06 | | |
| **8354 Derosa 2012** | 26 | Placebo | Sita 100mg | | | -0.40 | -0.60 | | | 0.04 | 0.05 | | |
| **Ljunggren 2012** | 24 | Placebo | Dapa 10mg | | | -0.84 | -3.72 | | | 0.42 | 0.45 | | |

### Table 60 Weight change (kg) from baseline

| Trial | Time Point | Treatment arms | | | | Change from Baseline | | | | Standard Error (SE) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **Arechavaleta et al 2011** | 24 | SU | Sita 100mg | | | 1.20 | -0.62 | | | 0.15 | 0.16 | | |
| **Bailey et al 2010** | 24 | Placebo | Dapa 5mg | Dapa 10mg | | -0.90 | -3.00 | -2.90 | | 0.26 | 0.23 | 0.23 | |
| **BI GMBH (1245-23) 2012** | 24 | Placebo | Empa 10mg | Empa 25mg | | -0.45 | -2.08 | -2.46 | | 0.17 | 0.17 | 0.17 | |
| **BI GMBH (1245-28) 2012** | 28 | SU | Empa 25mg | | | 1.50 | -3.28 | | | 0.11 | 0.07 | | |
| **Bolinder et al 2012** | 24 | Placebo | Dapa 10mg | | | -0.88 | -2.96 | | | 0.28 | 0.28 | | |
| **Charbonnel et al 2006** | 24 | Placebo | Sita 100mg | | | | | | | | | | |
| **Henry et al 2012a** | 24 | Placebo | Dapa 10mg | | | -1.36 | -3.33 | | | 0.24 | 0.24 | | |
| **Henry et al 2012b** | 24 | Placebo | Dapa 5mg | | | -1.29 | -2.66 | | | 0.24 | 0.24 | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Janssen (DIA3006) 2013** | 26 | Placebo | Sita 100mg | Cana 100mg | Cana 300mg | -1.10 | -1.10 | -3.30 | -3.60 | 0.20 | 0.20 | 0.20 | 0.20 |
| **Janssen (DIA3009) 2013** | 26 | SU | Cana 100mg | Cana 300mg | | 0.87 | -3.38 | -4.33 | | 0.17 | 0.17 | 0.17 | |
| **Nauck et al 2007** | 24 | SU | Sita 100mg | | | 1.21 | -1.31 | | | 0.22 | 0.21 | | |
| **Nauck et al 2011** | 26 | SU | Dapa 10mg | | | 1.40 | -3.15 | | | 0.14 | 0.14 | | |
| **Raz et al 2008** | 24 | Placebo | Sita 100mg | | | | | | | | | | |
| **Yang et al 2012** | 24 | Placebo | Sita 100mg | | | -0.50 | 0.00 | | | 0.20 | 0.18 | | |
| **Retnakaran et al 2010** | 24 | Placebo | Sita 100mg | | | | | | | | | | |
| **Bergenstal 2012** | 24 | Placebo | Sita 100mg | | | -0.5 | -0.9 | | | 0.4 | 0.3 | | |
| **8354 Derosa 2012** | 26 | Placebo | Sita 100mg | | | -1 | -1 | | | 0.31 | 0.30 | | |
| **Ljunggren 2012** | 24 | Placebo | Dapa 10mg | | | -1.4 | -3.5 | | | -0.40 | 0.40 | | |

### Table 61 Systolic Blood Pressure (mmHg) change from baseline

| Trial | Time Point | Treatment arms | | | | Change from Baseline | | | | Standard Error (SE) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **Arechavaleta et al 2011** | 24 | SU | Sita 100mg | | | | | | | | | | |
| **Bailey et al 2010** | 24 | Placebo | Dapa 5mg | Dapa 10mg | | -0.20 | -4.30 | -5.10 | | 1.20 | 1.30 | 1.30 | |
| **BI GMBH (1245-23) 2012** | 24 | Placebo | Empa 10mg | Empa 25mg | | -0.40 | -4.50 | -5.20 | | 0.70 | 0.70 | 0.70 | |
| **BI GMBH (1245-28) 2012** | 28 | SU | Empa 25mg | | | 1.09 | -4.39 | | | 0.51 | 0.49 | | |
| **Bolinder et al 2012** | 24 | Placebo | Dapa 10mg | | | 0.10 | -2.70 | | | 1.30 | 1.30 | | |
| **Charbonnel et al 2006** | 24 | Placebo | Sita 100mg | | | | | | | | | | |
| **Henry et al 2012a** | 24 | Placebo | Dapa 10mg | | | -1.20 | -3.30 | | | 1.00 | 0.90 | | |
| **Henry et al 2012b** | 24 | Placebo | Dapa 5mg | | | -1.80 | -2.90 | | | 0.90 | 0.90 | | |
| **Janssen (DIA3006) 2013** | 26 | Placebo | Sita 100mg | Cana 100mg | Cana 300mg | 1.50 | -1.80 | -3.80 | -5.10 | 0.82 | 0.61 | 0.61 | 0.61 |
| **Janssen (DIA3009) 2013** | 26 | SU | Cana 100mg | Cana 300mg | | 0.20 | -3.30 | -4.60 | | 0.56 | 0.56 | 0.56 | |
| **Nauck et al 2007** | 24 | SU | Sita 100mg | | | | | | | | | | |
| **Nauck et al 2011** | 26 | SU | Dapa 10mg | | | 0.80 | -4.30 | | | 0.55 | 0.58 | | |
| **Raz et al 2008** | 24 | Placebo | Sita 100mg | | | | | | | | | | |
| **Yang et al 2012** | 24 | Placebo | Sita 100mg | | | | | | | | | | |
| **Retnakaran et al 2010** | 24 | Placebo | Sita 100mg | | | | | | | | | | |
| **Bergenstal 2012** | 24 | Placebo | Sita 100mg | | | -0.9 | -2.8 | | | 1.2 | 0.9 | | |
| **8354 Derosa 2012** | 26 | Placebo | Sita 100mg | | | | | | | | | | |
| **Ljunggren 2012** | 24 | Placebo | Dapa 10mg | | | | | | | | | | |

## Table 62 Non severe hypoglycaemia

| Trials | Treatments compared | | | | Population at Risk (N) | | | | Observed Cases (n) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **Arechavaleta et al 2011** | SU | Sita 100mg | | | 518 | 516 | | | 111 | 35 | | |
| **Bailey et al 2010** | Placebo | Dapa 5mg | Dapa 10mg | | 137 | 137 | 135 | | 4 | 5 | 5 | |
| **BI GMBH (1245-23) 2012** | Placebo | Empa 10mg | Empa 25mg | | 206 | 217 | 214 | | 1 | 4 | 3 | |
| **BI GMBH (1245-28) 2012** | SU | Empa 25mg | | | 780 | 765 | | | 164 | 15 | | |
| **Bolinder et al 2012** | Placebo | Dapa 10mg | | | 91 | 91 | | | 2 | 2 | | |
| **Charbonnel et al 2006** | Placebo | Sita 100mg | | | 237 | 464 | | | 5 | 6 | | |
| **Henry et al 2012a** | Placebo | Dapa 10mg | | | 208 | 211 | | | 6 | 7 | | |
| **Henry et al 2012b** | Placebo | Dapa 5mg | | | 201 | 194 | | | 0 | 5 | | |
| **Janssen (DIA3006) 2013** | Placebo | Sita 100mg | Cana 100mg | Cana 300mg | | | | | | | | |
| **Janssen (DIA3009) 2013** | SU | Cana 100mg | Cana 300mg | | 482 | 483 | 485 | | | | | |
| **Raz et al 2008** | Placebo | Sita 100mg | | | 94 | 96 | | | 0 | 1 | | |
| **8354 Derosa 2012** | Placebo | Sita 100mg | | | 87 | 91 | | | 0 | 0 | | |

## Table 63 Severe Hypoglycaemia

| Trials | Treatments compared | | | | Population at Risk (N) | | | | Observed Cases (n) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **Arechavaleta et al 2011** | SU | Sita 100mg | | | 518 | 516 | | | 3 | 1 | | |
| **Bailey et al 2010** | Placebo | Dapa 5mg | Dapa 10mg | | 137 | 137 | 135 | | 0 | 0 | 0 | |
| **BI GMBH (1245-23) 2012** | Placebo | Empa 10mg | Empa 25mg | | 206 | 217 | 214 | | 0 | 0 | 0 | |
| **BI GMBH (1245-28) 2012** | SU | Empa 25mg | | | 780 | 765 | | | 1 | 0 | | |
| **Bolinder et al 2012** | Placebo | Dapa 10mg | | | 91 | 91 | | | 0 | 0 | | |
| **Charbonnel et al 2006** | Placebo | Sita 100mg | | | 237 | 464 | | | 0 | 0 | | 0 |
| **Henry et al 2012a** | Placebo | Dapa 10mg | | | 208 | 211 | | | 0 | 0 | | |
| **Henry et al 2012b** | Placebo | Dapa 5mg | | | 201 | 194 | | | 0 | 0 | | |
| **Janssen (DIA3006) 2013** | Placebo | Sita 100mg | Cana 100mg | Cana 300mg | | | | | | | | |
| **Janssen (DIA3009) 2013** | SU | Cana 100mg | Cana 300mg | | 482 | 483 | 485 | | | | | |
| **Raz et al 2008** | Placebo | Sita 100mg | | | 94 | 96 | | | 0 | 0 | | |
| **8354 Derosa 2012** | Placebo | Sita 100mg | | | 87 | 91 | | | 0 | 0 | | |

## Table 64 Urinary tract infections

| Trials | Treatments compared | | | | Population at Risk (N) | | | | Observed Cases (n) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **Arechavaleta et al 2011** | SU | Sita 100mg | | | 518 | 516 | | | | | | |
| **Bailey et al 2010** | Placebo | Dapa 5mg | Dapa 10mg | | 137 | 137 | 135 | | | | | |
| **BI GMBH (1245-23) 2012** | Placebo | Empa 10mg | Empa 25mg | | 206 | 217 | 214 | | 8 | 9 | 9 | |
| **BI GMBH (1245-28) 2012** | SU | Empa 25mg | | | 780 | 765 | | | 67 | 81 | | |
| **Bolinder et al 2012** | Placebo | Dapa 10mg | | | 91 | 91 | | | 0 | 2 | | |
| **Charbonnel et al 2006** | Placebo | Sita 100mg | | | 237 | 464 | | | 13 | 22 | | |
| **Henry et al 2012a** | Placebo | Dapa 10mg | | | 208 | 211 | | | 4 | 6 | | |
| **Henry et al 2012b** | Placebo | Dapa 5mg | | | 201 | 194 | | | 10 | 10 | | |
| **Janssen (DIA3006) 2013** | Placebo | Sita 100mg | Cana 100mg | Cana 300mg | | | | | | | | |
| **Janssen (DIA3009) 2013** | SU | Cana 100mg | Cana 300mg | | 482 | 483 | 485 | | | | | |
| **Nauck et al 2007** | Placebo | Sita 100mg | | | 584 | 588 | | | 25 | 44 | | |
| **Nauck et al 2011** | Placebo | Sita 100mg | | | 408 | 406 | | | | | | |
| **Raz et al 2008** | Placebo | Sita 100mg | | | 94 | 96 | | | 3 | 4 | | |
| **8354 Derosa 2012** | Placebo | Dapa 5mg | Dapa 10mg | | | | | | | | | |

## *Data extraction tables (52wks) - Metformin background treatments*

**Accroynms:** Met - Metformin; SU –Sulphonylurea; Sita – Sitagliptin; Empa – Empagliflozin; Cana – Canagliflozin; Dapa - Dapagliflozin

### Table 65 HbA1c (%) change from baseline

| Trials | Time Point | Treatment arms | | | | Change from Baseline (y) | | | | Standard Error (SE) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **BI GMBH (1245-23) 2012** | 52 | Placebo | Empa 10mg | Empa 25mg | | -0.08 | -0.71 | -0.74 | | 0.06 | 0.05 | 0.06 | |
| **BI GMBH (1245-28) 2012** | 52 | SU | Empa 25mg | | | -0.66 | -0.73 | | | 0.03 | 0.03 | | |
| **Nauck et al 2007** | 52 | SU | Sita 100mg | | | -0.67 | -0.67 | | | 0.04 | 0.04 | | |
| **Janssen (DIA3009) 2013** | 52 | SU | Cana 100mg | Cana 300mg | | -0.81 | -0.82 | -0.93 | | 0.04 | 0.04 | 0.03 | |
| **Janssen (DIA3006) 2013** | 52 | Placebo | Sita 100mg | Cana 100mg | Cana 300mg | NR | -0.73 | -0.73 | -0.88 | NR | 0.04 | 0.04 | 0.05 |
| **Nauck et al 2011** | 52 | SU | Dapa 10mg | | | -0.52 | -0.52 | | | 0.04 | 0.04 | | |
| **Ljunggren 2012** | 50 | Placebo | Dapa 10mg | | | 0.02 | -0.38 | | | 0.05 | 0.05 | | |

### Table 66 Weight (kg) change from baseline

| Trials | Time Point | Treatment arms | | | | Change from Baseline (y) | | | | Standard Error (SE) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **BI GMBH (1245-23) 2012** | 52 | Placebo | Empa 10mg | Empa 25mg | | -0.58 | -2.27 | -2.89 | | 0.18 | 0.19 | 0.23 | |
| **BI GMBH (1245-28) 2012** | 52 | SU | Empa 25mg | | | 1.60 | -3.21 | | | 0.11 | 0.11 | | |
| **Nauck et al 2007** | 52 | SU | Sita 100mg | | | 1.10 | -1.50 | | | 0.28 | 0.28 | | |
| **Janssen (DIA3009) 2013** | 52 | SU | Cana 100mg | Cana 300mg | | 0.70 | -3.70 | -4.00 | | 0.20 | 0.20 | 0.20 | |
| **Janssen (DIA3006) 2013** | 52 | Placebo | Sita 100mg | Cana 100mg | Cana 300mg | NR | -1.20 | -3.30 | -3.70 | NR | 0.20 | 0.20 | 0.20 |
| **Nauck et al 2011** | 52 | SU | Dapa 10mg | | | 1.44 | -3.22 | | | 0.18 | 0.17 | | |
| **Ljunggren 2012** | 50 | Placebo | Dapa 10mg | | | -2.03 | -4.39 | | | 0.44 | 0.46 | | |

### Table 67 Systolic Blood Pressure (mmHg) change from baseline

| Trials | Time point | Treatment arms | | | | Change from Baseline (y) | | | | Standard Error (SE) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **BI GMBH (1245-23) 2012** | 52 | Placebo | Empa 10mg | Empa 25mg | | -0.40 | -3.70 | -5.30 | | 0.80 | 0.70 | 0.80 | |
| **BI GMBH (1245-28) 2012** | 52 | SU | Empa 25mg | | | 2.20 | -3.60 | | | 0.50 | 0.50 | | |
| **Nauck et al 2007** | 52 | SU | Sita 100mg | | | | | | | | | | |
| **Janssen (DIA3009) 2013** | 52 | SU | Cana 100mg | Cana 300mg | | 0.20 | -3.30 | -4.60 | | 0.56 | 0.56 | 0.56 | |
| **Janssen (DIA3006) 2013** | 52 | Placebo | Sita 100mg | Cana 100mg | Cana 300mg | NR | -0.70 | -3.50 | -4.70 | NR | 0.65 | 0.51 | 0.68 |
| **Nauck et al 2011** | 52 | SU | Dapa 10mg | | | 0.80 | -4.30 | | | 0.55 | 0.58 | | |
| **Ljunggren 2012** | 50 | Placebo | Dapa 10mg | | | | | | | | | | |

## *Data extraction tables (24wks) Metformin and SU background*

**Accroynms:** Met - Metformin; SU –Sulphonylurea; Sita – Sitagliptin; Empa – Empagliflozin; Cana – Canagliflozin; Dapa - Dapagliflozin

### Table 68 HbA1c (%) baseline change

| Trials | Time point | Treatment arms | | | Change from baseline | | | Standard error (SE) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **Haring et al 2012** | 24 | Placebo | Empa 10mg | Empa 25mg | -0.17 | -0.82 | -0.77 | 0.05 | 0.05 | 0.05 |
| **Hermansen et al 2007** | 26 | Placebo | Sita 100mg | | 0.3 | -0.59 | | 0.08 | 0.08 | |
| **Janssen (DIA3015) 2013** | 26 | Sita 100mg | Cana 300 mg | | -0.93 | -1.15 | | 0.04 | 0.04 | |
| **Janssen (DIA3002) 2013** | 26 | Placebo | Cana 100mg | Cana 300mg | -0.13 | -0.85 | -1.06 | 0.08 | 0.08 | 0.0765 |

### Table 69 Weight (kg) change from baseline

| Trials | Time point | Treatment arms | | | Change from baseline | | | Standard error (SE) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **Haring et al 2012** | 24 | Placebo | Empa 10mg | Empa 25mg | -0.39 | -2.16 | -2.39 | 0.15 | 0.15 | 0.16 |
| **Hermansen et al 2007** | 26 | Placebo | Sita 100mg | | -0.7 | 0.4 | | 0.33 | 0.26 | |
| **Janssen (DIA3015) 2013** | 26 | Sita 100mg | Cana 300 mg | | 0.26 | -2.38 | | 0.13 | 0.13 | |
| **Janssen (DIA3002) 2013** | 26 | Placebo | Cana 100mg | Cana 300mg | -0.65 | -1.94 | -2.41 | 0.24 | 0.24 | 0.24 |

### Table 70 Systolic Blood Pressure (mmHg) change from baseline

| Trials | Time point | Treatment arms | | | Change from baseline | | | Standard error (SE) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **Haring et al 2012** | 24 | Placebo | Empa 10mg | Empa 25mg | -1.4 | -4.1 | -3.5 | 0.70 | 0.70 | 0.70 |
| **Hermansen et al 2007** | 26 | Placebo | Sita 100mg | | | | | | | |
| **Janssen (DIA3015) 2013** | 26 | Sita 100mg | Cana 300 mg | | 0.9 | -5.1 | | 0.66 | 0.66 | |
| **Janssen (DIA3002) 2013** | 26 | Placebo | Cana 100mg | Cana 300mg | -2.6 | -4.9 | -4.3 | 0.92 | 0.97 | 0.97 |

### Table 71 Non-severe hypoglycaemia

| Trials | Time point | Treatment arms | | | Population at risk | | | Observed cases | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **Haring et al 2012** | 24 | Placebo | Empa 10mg | Empa 25mg | 225 | 224 | 217 | 22 | 35 | 28 |
| **Hermansen et al 2007** | 26 | Placebo | Sita 100mg | | 109 | 115 | | 1 | 19 | |
| **Janssen (DIA3015) 2013** | 26 | Sita 100mg | Cana 300 mg | | 378 | 377 | | 154 | 163 | |
| **Janssen (DIA3002) 2013** | 26 | Placebo | Cana 100mg | Cana 300mg | 156 | 157 | 156 | 24 | 43 | 47 |

### Table 72 Severe hypoglycaemia

| Trials | Time point | Treatment arms | | | Population at risk | | | Observed cases | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **Haring et al 2012** | 24 | Placebo | Empa 10mg | Empa 25mg | 225 | 224 | 217 | 0 | 0 | 0 |
| **Hermansen et al 2007** | 26 | Placebo | Sita 100mg | | 109 | 115 | | 0 | 0 | |
| **Janssen (DIA3015) 2013** | 26 | Sita 100mg | Cana 300 mg | | 378 | 377 | | | | |
| **Janssen (DIA3002) 2013** | 26 | Placebo | Cana 100mg | Cana 300mg | 156 | 157 | 156 | | | |

### Table 73 Urinary tract infections

| Trials | Time point | Treatment arms | | | Population at risk | | | Observed cases | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **Haring et al 2012** | 24 | Placebo | Empa 10mg | Empa 25mg | 225 | 224 | 217 | 18 | 23 | 18 |
| **Hermansen et al 2007** | 26 | Placebo | Sita 100mg | | 109 | 115 | | | | |
| **Janssen (DIA3015) 2013** | 26 | Sita 100mg | Cana 300 mg | | 378 | 377 | | | | |
| **Janssen (DIA3002) 2013** | 26 | Placebo | Cana 100mg | Cana 300mg | 156 | 157 | 156 | | | |

## *Data extraction tables (52wks) – Metformin and SU background*

Met - Metformin; SU –Sulphonylurea; Sita – Sitagliptin; Empa – Empagliflozin; Cana – Canagliflozin; Dapa - Dapagliflozin

### Table 74 HbA1c (%) baseline change

| Trial | Time point | Treatment arms | | | Change from baseline | | | Standard error (SE) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **BI GMBH (1245-23) 2012** | 52 | Placebo | Empa 10mg | Empa 25mg | -0.05 | -0.76 | -0.74 | 0.06 | 0.06 | 0.06 |
| **Janssen (DIA3015) 2013** | 52 | Sita 100mg | Cana 300 mg | | -0.66 | -1.03 | | 0.05 | 0.05 | |
| **Janssen (DIA3002) 2013** | 52 | Placebo | Cana 100mg | Cana 300mg | 0.01 | -0.74 | -0.96 | 0.08 | 0.60 | 0.08 |

### Table 75 Weight (kg) change from baseline

| Trial | Time point | Treatment arms | | | Change from baseline | | | Standard error (SE) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **BI GMBH (1245-23) 2012** | 52 | Placebo | Empa 10mg | Empa 25mg | -0.28 | -2.28 | -2.33 | 0.16 | 0.19 | 0.2 |
| **Janssen (DIA3015) 2013** | 52 | Sita 100mg | Cana 300 mg | | 0.2649 | -2.38 | | 0.13 | 0.13 | |
| **Janssen (DIA3002) 2013** | 52 | Placebo | Cana 100mg | Cana 300mg | -0.91 | -2.19 | -3.19 | 0.29 | 0.31 | 0.31 |

### Table 76 Systolic Blood Pressure (mmHg) change from baseline

| Trial | Time point | Treatment arms | | | Change from baseline | | | Standard error (SE) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **BI GMBH (1245-23) 2012** | 52 | Placebo | Empa 10mg | Empa 25mg | -0.2 | -3 | -2.9 | 0.80 | 0.70 | 0.80 |
| **Janssen (DIA3015) 2013** | 52 | Sita 100mg | Cana 300 mg | | 0.9 | -5.1 | | 0.66 | 0.66 | |
| **Janssen (DIA3002) 2013** | 52 | Placebo | Cana 100mg | Cana 300mg | 0.1 | -3.71 | -2.9 | 1.05 | 1.08 | 0.97 |

## *Data extraction tables (24wks) - Thiazolidinedione background*

Met - Metformin; SU –Sulphonylurea; Sita – Sitagliptin; Empa – Empagliflozin; Cana – Canagliflozin; Dapa - Dapagliflozin

### Table 77 HbA1c (%) baseline change

| Trials | Time point | Treatment arms | | | Change from baseline | | | Standard error | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **Kovacs 2013** | 24 | Placebo | Empa 10mg | Empa 25mg | -0.11 | -0.59 | -0.72 | 0.07 | 0.07 | 0.07 |
| **Rosenstock 2012** | 24 | Placebo | Dapa 5mg | Dapa 10mg | -0.42 | -0.82 | -0.97 | 0.08 | 0.08 | 0.08 |
| **DIA3012 2013** | 26 | Placebo | Cana 100mg | Cana 300mg | -0.26 | -0.89 | -1.03 | 0.07 | 0.07 | 0.04 |
| **Derosa et al 2010** | 26 | Placebo | Sita 100mg | | -0.60 | -0.80 | | 0.06 | 0.07 | |

### Table 78 Weight (kg) change from baseline

| Trials | Time point | Treatment arms | | | Change from baseline | | | Standard error | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **Kovacs 2013** | 24 | Placebo | Empa 10mg | Empa 25mg | 0.34 | -1.62 | -1.47 | 0.21 | 0.21 | 0.21 |
| **Rosenstock 2012** | 24 | Placebo | Dapa 5mg | Dapa 10mg | 1.64 | 0.09 | -0.14 | 0.28 | 0.28 | 0.28 |
| **DIA3012 2013** | 26 | Placebo | Cana 100mg | Cana 300mg | -0.09 | -2.64 | -3.58 | 0.29 | 0.29 | 0.29 |
| **Derosa et al 2010** | 26 | Placebo | Sita 100mg | | -1.40 | -1.10 | | 0.37 | 0.44 | |

### Table 79 Systolic Blood Pressure (mmHg) change from baseline

| Trials | Time point | Treatment arms | | | Change from baseline | | | Standard error | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 | Arm 1 | Arm 2 | Arm 3 |
| **Kovacs 2013** | 24 | Placebo | Empa 10mg | Empa 25mg | 0.7 | -3.1 | -4 | 0.90 | 0.80 | 0.90 |
| **Rosenstock 2012** | 24 | Placebo | Dapa 5mg | Dapa 10mg | 1.3 | -0.8 | -3.4 | 1.20 | 1.20 | 1.20 |
| **DIA3012 2013** | 26 | Placebo | Cana 100mg | Cana 300mg | -1.2 | -5.3 | -4.7 | 1.02 | 1.07 | 1.07 |
| **Derosa et al 2010** | 26 | Placebo | Sita 100mg | | 0.7 | -3.1 | -4 | 0.90 | 0.80 | 0.90 |

## *Data extraction tables (24wks) - Insulin background treatments*

**Accroynms:** Met - Metformin; SU –Sulphonylurea; Sita – Sitagliptin; Empa – Empagliflozin; Cana – Canagliflozin; Dapa – Dapagliflozin; Ins – Insulin

### Table 80 HbA1c (%) change from baseline

| Trials | Time point | Treatment arms | | | | Change from Baseline | | | | Standard Error (SE) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **1245-49 2013** | 18 | Placebo | Empa 10mg | Empa 25mg | | -0.49 | -0.96 | -1.00 | | 0.05 | 0.05 | 0.05 | |
| **1245-33 2013** | 18 | Placebo | Empa 10mg | | | -0.01 | -0.57 | -0.71 | | 0.07 | 0.07 | 0.07 | |
| **Janssen DIA3008** | 18 | Placebo | Cana 100mg | Cana 300mg | | 0.01 | -0.63 | -0.72 | | 0.06 | 0.06 | 0.06 | |
| **Wilding 2012** | 24 | Placebo | Dapa 2.5mg | Dapa 5mg | Dapa 10mg | -0.39 | -0.79 | -0.89 | -0.96 | 0.06 | 0.06 | 0.05 | 0.05 |
| **Vilsboli 2010** | 24 | Placebo | Sita 100mg | | | 0.00 | -0.60 | | | 0.07 | 0.07 | | |

### Table 81 Weight (kg) change from baseline

| Trials | Time point | Treatment arms | | | | Change from Baseline (y) | | | | Standard Error (SE) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **1245-49 2013** | 18 | Placebo | Empa 10mg | Empa 25mg | | 0.34 | -0.98 | -1.52 | | 0.16 | 0.17 | 0.21 | |
| **1245-33 2013** | 18 | Placebo | Empa 10mg | | | -0.05 | -2.09 | -0.92 | | 0.68 | 0.66 | 0.72 | |
| **Janssen DIA3008** | 18 | Placebo | Cana 100mg | Cana 300mg | | 0.10 | -1.75 | -2.23 | | 0.23 | 0.19 | 0.19 | |
| **Wilding 2012** | 24 | Placebo | Dapa 2.5mg | Dapa 5mg | Dapa 10mg | 0.43 | -0.92 | -1.00 | -1.61 | 0.20 | 0.20 | 0.19 | 0.19 |
| **Vilsboli 2010** | 24 | Placebo | Sita 100mg | | | 0.1 | 0.1 | | | 0.18 | 0.15 | | |

### Table 82 Systolic Blood Pressure (mmHg) change from baseline

| Trials | Time point | Treatment arms | | | | Change from Baseline | | | | Standard Error | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **1245-49 2013** | 18 | Placebo | Empa 10mg | Empa 25mg | | -1.20 | -3.60 | -2.90 | | 0.80 | 0.80 | 0.80 | |
| **1245-33 2013** | 18 | Placebo | Empa 10mg | | | -0.30 | -3.70 | -3.30 | | 0.90 | 0.90 | 1.00 | |
| **Janssen DIA3008** | 18 | Placebo | Cana 100mg | Cana 300mg | | -2.5 | -5.1 | -6.9 | | 1.07 | 1.035 | 1.10 | |
| **Wilding 2012** | 24 | Placebo | Dapa 2.5mg | Dapa 5mg | Dapa 10mg | -3.56 | -4.21 | -5.93 | -6.66 | 0.98 | 0.96 | 0.92 | 0.95 |
| **Vilsboli 2010** | 24 | Placebo | Sita 100mg | | | | | | | | | | |

### Table 83 Overall hypoglycaemia

| Trials | Time point | Treatment arms | | | | Change from Baseline (y) | | | | Standard Error (SE) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **1245-49 2013** | 18 | Placebo | Empa 10mg | Empa 25mg | | 188 | 186 | 189 | | 70 | 74 | 78 | |
| **1245-33 2013** | 18 | Placebo | Empa 10mg | | | 170 | 169 | 155 | | 18 | 20 | 27 | |
| **Janssen DIA3008** | 18 | Placebo | Cana 100mg | Cana 300mg | | 565 | 566 | 587 | | 208 | 279 | 285 | |
| **Wilding 2012** | 24 | Placebo | Dapa 2.5mg | Dapa 5mg | Dapa 10mg | 197 | 202 | 212 | 196 | 102 | 122 | 118 | 105 |
| **Vilsboli 2010** | 24 | Placebo | Sita 100mg | | | 319 | 322 | | | 76 | 155 | | |

### Table 84 Non severe hypoglycaemia

| Trials | Time point | Treatment arms | | | | Change from Baseline (y) | | | | Standard Error (SE) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **1245-49 2013** | 18 | Placebo | Empa 10mg | Empa 25mg | | 188 | 186 | 189 | | 69 | 73 | 77 | |
| **1245-33 2013** | 18 | Placebo | Empa 10mg | | | 170 | 169 | 155 | | 60 | 61 | 54 | |
| **Janssen DIA3008** | 18 | Placebo | Cana 100mg | Cana 300mg | | 565 | 566 | 587 | | 208 | 279 | 283 | |
| **Wilding 2012** | 24 | Placebo | Dapa 2.5mg | Dapa 5mg | Dapa 10mg | 197 | 202 | 212 | 196 | 99 | 118 | 113 | 99 |
| **Vilsboli 2010** | 24 | Placebo | Sita 100mg | | | | | | | | | | |

### Table 85 Severe Hypoglycaemia

| Trials | Time Point | Treatment arms | | | | Change from Baseline | | | | Standard Error (SE) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **1245-49 2013** | 18 | Placebo | Empa 10mg | Empa 25mg | | 188 | 186 | 189 | | 1 | 1 | 1 | |
| **1245-33 2013** | 18 | Placebo | Empa 10mg | | | 170 | 169 | 155 | | 0 | 0 | 2 | |
| **Janssen DIA3008** | 18 | Placebo | Cana 100mg | Cana 300mg | | 565 | 566 | 587 | | 14 | 10 | 16 | |
| **Wilding 2012** | 24 | Placebo | Dapa 2.5mg | Dapa 5mg | Dapa 10mg | 197 | 202 | 212 | 196 | 2 | 3 | 2 | 3 |
| **Vilsboli 2010** | 24 | Placebo | Sita 100mg | | | | | | | | | | |

### Table 86 Urinary tract infections

| Trials | Time point | Treatment arms | | | | Change from Baseline | | | | Standard Error | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arm 1 | Arm 2 | Arm 3 | Arm 4 |
| **1245-49 2013** | 18 | Placebo | Empa 10mg | Empa 25mg | | 188 | 186 | 189 | | 0 | 0 | 1 | |
| **1245-33 2013** | 18 | Placebo | Empa 10mg | | | 170 | 169 | 155 | | 13 | 21 | 16 | |
| **Janssen DIA3008** | 18 | Placebo | Cana 100mg | Cana 300mg | | | | | | | | | |
| **Wilding 2012** | 24 | Placebo | Dapa 2.5mg | Dapa 5mg | Dapa 10mg | 197 | 202 | 212 | 196 | 8 | 11 | 16 | 14 |
| **Vilsboli 2010** | 24 | Placebo | Sita 100mg | | | | | | | | | | |

## Appendix E: WinBUGs code

### *Random effects for metformin network for HbA1c, Weight change and SBP*

```
# Normal likelihood, identity link
# Random effects model for multi-arm trials
# Positive result is bad

model{                                                          # *** PROGRAM STARTS
for(i in 1:ns){                                                 # LOOP THROUGH STUDIES
   w[i,1] <- 0                                                  # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0                                              # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)                                       # vague priors for all trial baselines
   for (k in 1:na[i]) {                                         # LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)                                # calculate variances
      prec[i,k] <- 1/var[i,k]                                   # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k])                      # normal likelihood
      theta[i,k] <- mu[i] + delta[i,k]                          # model for linear predictor
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]     #Deviance contribution
    }
   resdev[i] <- sum(dev[i,1:na[i]])                             # summed residual deviance contribution for this trial
   for (k in 2:na[i]) {                                         # LOOP THROUGH ARMS
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])                     # trial-specific LOR distributions
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]               # mean of treat effects distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k                               # precision of treat effects distributions (with multi-arm trial correction)
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])            # adjustment for multi-arm RCTs
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)                          # cumulative adjustment for multi-arm trials
    }
 }
totresdev <- sum(resdev[])                                      # Total Residual Deviance
d[1]<-0                                                         # treatment effect is zero for reference treatment
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }                       # vague priors for treatment effects
sd ~ dunif(0,ub)                                                # ub=5*mse, mse is the median between trial for standard error
                                                                      # mse for HbA1c was calculated to be 0.073
                                        # mse for weight was calculated to be 0.324
                                                                      # mse for systolic blood pressure was calculated to be
1.08
tau <- pow(sd,-2)                                               # between-trial precision = (1/between-trial variance)


#Output
# pairwise treatment effect for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
        D[c,k] <- (d[k]-d[c])
                better[c,k]<- step(-D[c,k])                     # assumes a positive result is "bad"
                        }
    }

# ranking on relative scale
for (k in 1:nt) {
     rk[k] <- rank(d[],k)                                       # assumes events are "bad"
     best[k] <- equals(rk[k],1)                                 # calculate probability that treat k is best
            for (i in 1:nt) {
             prk[i,k] <- equals(rk[k],i)                        # calculate probability of treat k being each rank i
    }}

# Provide estimates of effects T[k]
# Absolute effects with placebo treatment based on number of placebo controlled trials
for (i in 1: ns){
                        mu1[i] <- mu[i]*equals(t[i,1],1)}
                        A<- sum(mu1[])/nt1

# Alternative: Given a Mean Effect, meanA, for 'standard' treatment 1, with precision (1/variance) precA
#A ~ dnorm(meanA,precA)

for (k in 1:nt) { T[k] <- A + d[k]  }


}                                                               # *** PROGRAM ENDS
```

## *Fixed effects model for HbA1c, Weight change and SBP*

```
# Normal likelihood, identity link
# Fixed effects model for multi-arm trials
# Events are bad

model{                                                          # *** PROGRAM STARTS
for(i in 1:ns){                                                 # LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)                                       # vague priors for all trial baselines
   for (k in 1:na[i]) {                                         # LOOP THROUGH ARMS
      var[i,k] <- pow(se[i,k],2)                                # calculate variances
      prec[i,k] <- 1/var[i,k]                                   # set precisions
      y[i,k] ~ dnorm(theta[i,k],prec[i,k])                      # normal likelihood
      theta[i,k] <- mu[i] + d[t[i,k]] - d[t[i,1]] # model for linear predictor
      dev[i,k] <- (y[i,k]-theta[i,k])*(y[i,k]-theta[i,k])*prec[i,k]     #Deviance contribution
    }
   resdev[i] <- sum(dev[i,1:na[i]])                             # summed residual deviance contribution for this trial
 }
totresdev <- sum(resdev[])                                      # Total Residual Deviance
d[1]<-0                                                         # treatment effect is zero for reference treatment
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }                       # vague priors for treatment effects


#Output
# pairwise treatment effect for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
        D[c,k] <- (d[k]-d[c])
                better[c,k]<- step(-D[c,k])                     # assumes a positive result is "bad"
                        }
    }

# ranking on relative scale
for (k in 1:nt) {
     rk[k] <- rank(d[],k)                                       # assumes events are "bad"
     best[k] <- equals(rk[k],1)                                 # calculate probability that treat k is best
            for (i in 1:nt) {
            prk[i,k] <- equals(rk[k],i)                         # calculate probability of treat k being each rank i
    }}

# Provide estimates of effects T[k]
# Absolute effects with placebo treatment based on number of placebo controlled trials
for (i in 1: ns){
                        mu1[i] <- mu[i]*equals(t[i,1],1)}
                        A<- sum(mu1[])/nt1

# Alternative: Given a Mean Effect, meanA, for 'standard' treatment 1, with precision (1/variance) precA
#A ~ dnorm(meanA,precA)

for (k in 1:nt) { T[k] <- A + d[k]  }


}                                                               # *** PROGRAM ENDS
```

## *Random effects model for safety outcomes*

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
# Events are bad
model{                                                          # *** PROGRAM STARTS
for(i in 1:ns){                                                 # LOOP THROUGH STUDIES
    w[i,1] <- 0                                         # adjustment for multi-arm trials is zero for control arm
    delta[i,1] <- 0                                     # treatment effect is zero for control arm
    mu[i] ~ dnorm(0,.0001)I(-6,6)                       # vague priors for all trial baselines
    for (k in 1:na[i])  {                       # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k])            # binomial likelihood
        logit(p[i,k]) <- mu[i] + delta[i,k]     # model for linear predictor
        rhat[i,k] <- p[i,k] * n[i,k]            # expected value of the numerators
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     }
    resdev[i] <- sum(dev[i,1:na[i]])                    # summed residual deviance contribution for this trial
    for (k in 2:na[i]) {                        # LOOP THROUGH ARMS
        delta[i,k] ~ dnorm(md[i,k],taud[i,k])# trial-specific LOR distributions
        md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]     # mean of LOR distributions (with multi-arm trial correction)
        taud[i,k] <- tau *2*(k-1)/k                     # precision of LOR distributions (with multi-arm trial correction)
        w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])# adjustment for multi-arm RCTs
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)        # cumulative adjustment for multi-arm trials
       }
 }
totresdev <- sum(resdev[])                              # Total Residual Deviance
d[1] <- 0                                               # treatment effect is zero for reference treatment
for (k in 2:nt){  d[k] ~ dnorm(0,.0001)I(-6,6) }        # vague priors for treatment effects
sd ~ dunif(0,5)                                                 # vague prior for between-trial SD. ALTERNATIVES
BELOW
tau <- pow(sd,-2)                                       # between-trial precision = (1/between-trial variance)

#Alternative prior distributions can be used for the Random Effects Variance
#tau ~ dgamma(.001,.001)                                # vague gamma prior on the precision
#sd <- pow(tau,-0.5)

#Output
# pairwise OR, LORs, RR, RD for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
        OR[c,k] <- exp(d[k] - d[c])
        lor[c,k] <- (d[k]-d[c])

                better[c,k]<- step(-lor[c,k])           # assumes events are "bad"

                        RR[c,k] <-T[k]/T[c]
                        RD[c,k] <-T[k]-T[c]
                        }
    }
# ranking on relative scale
for (k in 1:nt) {

     rk[k] <- rank(d[],k)                               # assumes events are "bad"
     best[k] <- equals(rk[k],1)                         # calculate probability that treat k is best
            for (i in 1:nt) {
            prk[i,k] <- equals(rk[k],i)                 # calculate probability of treat k being each rank i
    }}

# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Absolute log odds on placebo treatment based on number of placebo controlled trials
for (i in 1: ns){
                        mu1[i] <- mu[i]*equals(t[i,1],1)}
                        A<- sum(mu1[])/nt1
# Alternative: Given a Mean Effect, mean A, for 'standard' treatment 1, with precision (1/variance) precA
#A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }
# Provide estimates of number needed to treat NNT[k] for each treatment, relative to treatment 1
for (k in 2:nt) {
   NNT[k] <- 1/(T[1]- T[k])        # assumes events are "bad"
     }

}                                                       # *** PROGRAM ENDS
```

## *Fixed effects model for safety outcomes*

```
# Binomial likelihood, logit link
# Fixed effects model
# Events are bad
model{                                                          # *** PROGRAM STARTS
for(i in 1:ns){                                                 # LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)I(-6,6)                               # vague priors for all trial baselines
    for (k in 1:na[i])  {                                       # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k])                            # binomial likelihood
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]# model for linear predictor
        rhat[i,k] <- p[i,k] * n[i,k]                            # expected value of the numerators
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))     #Deviance contribution
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
      }
    resdev[i] <- sum(dev[i,1:na[i]])                            # summed residual deviance contribution for this trial
    }
totresdev <- sum(resdev[])                                      # Total Residual Deviance
d[1]<-0                                                         # treatment effect is zero for reference treatment
for (k in 2:nt){  d[k] ~ dnorm(0,.0001)I(-6,6) }                # vague priors for treatment effects


#Output
# pairwise OR, LORs, RR, RD for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1)) {
    for (k in (c+1):nt)  {
        OR[c,k] <- exp(d[k] - d[c])
        lor[c,k] <- (d[k]-d[c])
                better[c,k]<- step(-lor[c,k])  # assumes events are "bad"

                        RR[c,k] <-T[k]/T[c]
                        RD[c,k] <-T[k]-T[c]
                        }
    }

# ranking on relative scale
for (k in 1:nt) {
                rk[k] <- rank(d[],k)                            # assumes events are "bad"
     best[k] <- equals(rk[k],1)                                 # calculate probability that treat k is best
            for (i in 1:nt){
            prk[i,k] <- equals(rk[k],i)                         # calculate probability of treat k being each rank i
    }}

# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Absolute log odds on placebo treatment based on number of placebo controlled trials
for (i in 1: ns){
                        mu1[i] <- mu[i]*equals(t[i,1],1)}
                        A<- sum(mu1[])/nt1

# Alternative: Given a Mean Effect, mean A, for 'standard' treatment 1, with precision (1/variance) precA
#A ~ dnorm(meanA,precA)

for (k in 1:nt) { logit(T[k]) <- A + d[k]  }

# Provide estimates of number needed to treat NNT[k] for each treatment, relative to treatment 1
for (k in 2:nt) {
   NNT[k] <- 1/(T[1]- T[k])                                     # assumes events are "bad"
     }

}                                                               # *** PROGRAM ENDS
```