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# Cost-effectiveness of sitagliptin-based treatment regimens in European patients with type 2 diabetes and haemoglobin A1c above target on metformin monotherapy

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**Objective:** Sitagliptin is a novel oral incretin enhancer that acts by inhibiting the dipeptidyl peptidase 4 enzyme and is indicated in Europe as a treatment adjunct to metformin (MF), sulphonylurea (SU), MF plus SU and diet and exercise, in the management of type 2 diabetes mellitus. The objective of the current analysis was to evaluate the cost-effectiveness of adding sitagliptin to the regimens of patients with haemoglobin A1c (HbA1C) above the International Diabetes Federation goal (6.5%) while on MF in six European countries: Austria, Finland, Portugal, Scotland (United Kingdom), Spain and Sweden.

**Methods:** A discrete event simulation model, which employed the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model risk equations for predicting risks of diabetes-related complication, was used. Lifetime costs and benefits were projected for alternative treatment strategies of adding sitagliptin, compared with adding rosiglitazone or a SU to MF in patients not at HbA1C goal on MF monotherapy. Changes in HbA1C as well as side effects associated with these different treatment strategies were based on clinical trial data. Mean baseline values from local epidemiologic studies involving patients with type 2 diabetes not at HbA1C goal on MF monotherapy were included in the current analysis. Costs of medications, side effects and direct costs of diabetes-related complications were based on country-specific data. UKPDS-based disutility weights associated with diabetes complications were incorporated. Disutilities associated with medication side effects were based on published data. All future costs and benefits were discounted according to local guidelines on cost-effectiveness analysis. One-way sensitivity analyses were conducted by varying key input parameters.

**Findings:** The discounted incremental cost-effectiveness ratios (ICER) associated with the addition of sitagliptin to MF, compared with adding rosiglitazone, in the different countries analysed ranged from treatment with sitagliptin being dominant (cost saving with improved health outcome) to its being cost-effective [€4,766 per quality-adjusted life year (QALY)]. Treatment with sitagliptin added to MF was cost-effective compared with adding a SU, with discounted

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**Conflicts of interest:**
J. C. and J. C. are employees of Merck & Co., Inc. and hold stock in the company. E. A. and D. Y. are employees and share holders of Merck & Co. K. J. is an employee of Merck Sharp & Dohme Ltd. and holds shares in the company. G. N. is an employee of Merck Sharp & Dohme de Espâna. H. S. has acted as a paid consultant to MSD Finland Oy and has received funding for research carried out in this work. M. G. has acted as a paid consultant to Merck & Co. and has received funding for research carried out in this work. G. K. was an employee of Merck & Co. at the time the paper was written. B. S. has acted as a paid consultant for MSD and other pharmaceutical, governmental and public organizations.

ICER values ranging from €5949/QALY to €20 350/QALY across countries. Sensitivity analyses showed that these results were robust to changes in input parameters, including clinical efficacy, costs and utility weights for both diabetes-related complications and hypoglycaemia.

**Conclusions:** Compared with adding rosiglitazone or a SU to MF, adding sitagliptin to MF is projected to be either cost saving or cost-effective for patients with type 2 diabetes who are not at HbA1C goal on MF.

Keywords: cost-effectiveness, diabetes-related complications, discrete event simulation, economic modelling, economic evaluation, sitagliptin, type 2 diabetes, UKPDS

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## Introduction

The prevalence of type 2 diabetes mellitus continues to increase in Europe and is projected to reach epidemic dimensions in the future [1]. The worldwide prevalence of diabetes for all age groups is estimated to increase from 2.8% in 2000 to 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [2]. It is estimated that, by 2005, the global prevalence of diabetes will increase 1.2-fold in Europe, 1.6-fold in North America and almost twofold in other parts of the world [3].

Management of type 2 diabetes, along with its vascular and other complications (including hospitalization), is costly [4,5]. A conservative estimate of annual European healthcare expenditures for diabetes is €46 billion (2007), and this value is projected to exceed €55 billion in 2025 [5]. Diabetes is also a major cause of disability and reduced quality of life (QOL) [3,6,7]. By one estimate, diabetes accounted for 59% of all disability-adjusted life years lost across the world [4].

Studies have shown that improved glycaemic control improves health outcomes, including reducing the risks of complications in patients with type 2 diabetes [8,9] and costs associated with these complications [10,11]. However, most type 2 diabetic patients do not attain their haemoglobin HbA1c (HbA1C) treatment goals [12,13] with current treatments. In addition, intensification of current antihyperglycaemic therapies is limited by adverse events such as hypoglycaemia and weight gain with sulphonylureas (SUs) and insulin, and congestive heart failure (CHF) with thiazolidinediones. Hence, there is a need for new therapies that can be used in combination with existing antihyperglycaemic agents.

Dipeptidyl peptidase-4 (DPP-4) inhibition is a novel therapeutic approach to the management of type 2 diabetes. These incretin enhancers significantly lower glucose concentrations by preventing the enzymatic degradation and inactivation of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide [14]. Unlike many previous therapies, these agents target both $\alpha$ cells and $\beta$ cells within the endocrine pancreas [14] and thus control insulin secretion in a glucose-dependent manner.

Sitagliptin, an oral once daily, highly selective DPP-4 inhibitor, is now available in many countries [15–18]. The efficacy of sitagliptin and its role in therapy have been established via clinical trials [19]. However, the cost-effectiveness of a sitagliptin-based regimen in patients not at HbA1C goal while on metformin (MF) monotherapy has yet to be determined. The objective of the present analysis was to project the costs and benefits of adding sitagliptin, compared with a SU or the thiazolidinedione (TZD) rosiglitazone to MF in type 2 diabetes patients not at the HbA1C goal (<6.5%) of the International Diabetes Federation (IDF) in several countries in Europe [20].

## Methods

### Model Structure

The Januvia Diabetes Economic (JADE) Model is a discrete event simulation model developed to project the long-term impacts of different interventions on diabetes-related outcomes. Details of the model and its various components are described elsewhere in this supplement [21].

As a patient-level simulation model, the JADE Model addresses statistical variability by allowing each individual to have different values for clinical parameters (e.g. efficacy and weight) randomly drawn from distributions (with mean $\pm$ s.d.) based on observational or clinical trial data. When data were not available from such sources, assumptions that minimized the risk of introducing a bias to the analysis were used.

The JADE Model has a lifetime horizon and also allows users to specify shorter time horizons if needed. The model incorporates or takes into account: (i) mortality as a competing risk; (ii) common complications experienced by patients with type 2 diabetes, such as ischaemic heart disease, stroke, CHF, renal failure, amputation, and blindness; (iii) interdependence among multiple complications, including mortality as a competing risk (based on the risk equations and algorithms published in United Kingdom Prospective Diabetes Study (UKPDS) 68 [22]; and (iv) complex treatment algorithms, including up to six treatment regimen changes over a patient's lifetime. By using a complex modelling approach, the JADE

Model appropriately captures the progression of diabetes and its complications and hence minimizes uncertainty arising from model design. The JADE Model allows the user to project the effects of competing treatments on both life expectancy as well as QOL, which is in turn influenced by diabetes-related complications and medication side effects, such as hypoglycaemia and oedema.

### Treatment Strategy and Comparison Scenarios

In the current analysis, three scenarios were evaluated. The comparators used in these scenarios were the most commonly used approaches in clinical practice in the countries included in the analysis. Scenario 1 compared the costs and benefits of adding sitagliptin, with adding rosiglitazone, to ongoing MF therapy (and lifestyle modifications). This is depicted in figure 1. Scenarios 2 (figure 2) and 3 (figure 3) represented treatment strategies in which the addition of sitagliptin to ongoing MF treatment was compared with the addition of SU.

In all three scenarios, regimens of patients with secondary treatment failure on oral antihyperglycaemic treatments, that is, HbA1C exceeding treatment switching thresholds progressed to basal insulin with MF, whereas regimens of individuals with treatment failure on basal insulin with MF progressed to multiple-dose insulin (solid lines in figures 1–3). In scenarios 1 and 2, patients experiencing therapy intolerance or primary treatment failure (inadequate initial treatment response) received basal insulin co-administered with MF (figures 1 and 2; dotted lines). While, in scenario 3, patients experiencing intolerance or primary treatment failure on sitagliptin (or SU) received rosiglitazone coadministered with MF (figure 3; dotted lines).

### Model Inputs

#### *Patient Profiles*

Average profiles of type 2 diabetic patients not at HbA1C targets (>6.5%) while on MF monotherapy based on local observational studies were used in the analysis. In countries where the HbA1Cs were not available, HbA1Cs > 6.5% were considered. Table 1 provides a brief description of each of the studies by country. The average profiles by country are represented in table 2, with each profile being simulated 50 000 times.

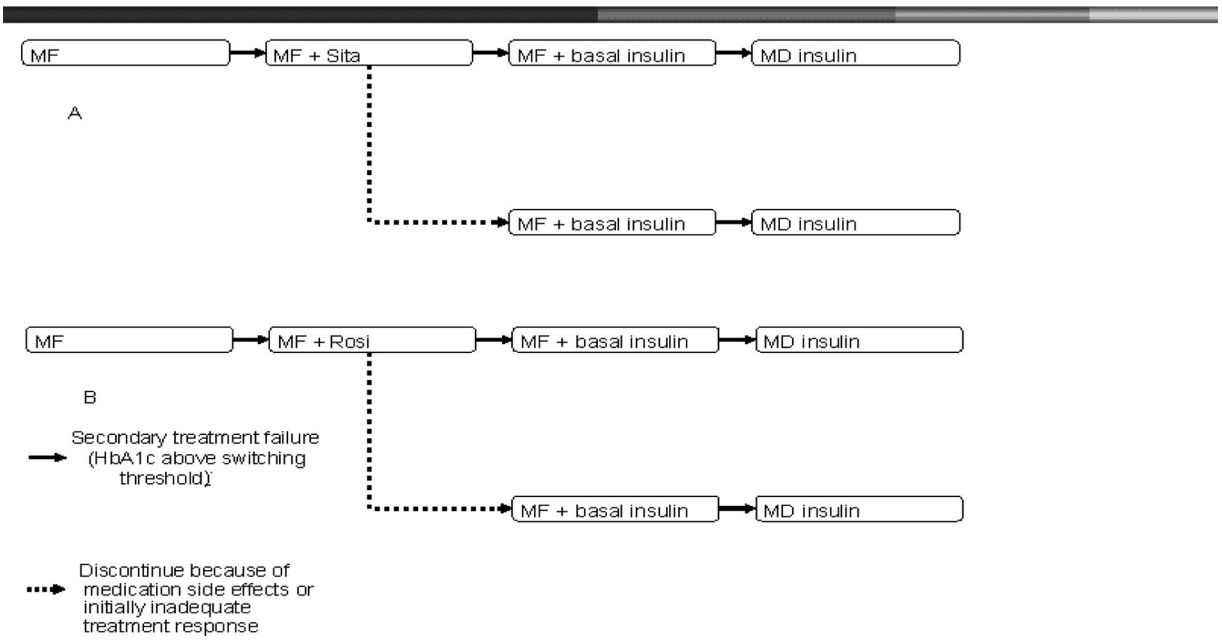


**Fig. 1** Scenario 1, comparing addition of sitagliptin (Sita; treatment arm A) vs. rosiglitazone (Rosi; treatment arm B) to ongoing metformin (MF) in patients not at HbA1C goals while receiving MF with or without recommendations for lifestyle modifications (diet and physical activity). Dotted lines indicate discontinuation (and switch to a different therapy) because of medication side effects or primary failure. Solid lines indicate secondary treatment failure (HbA1C exceeds treatment switching threshold). MD, multiple dose.

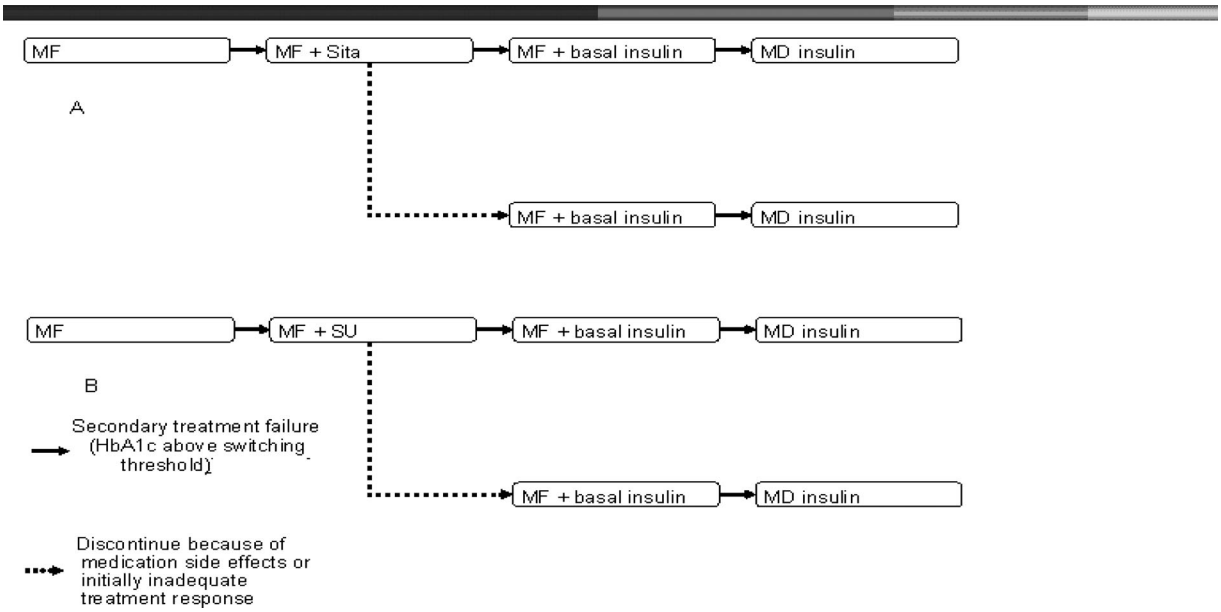


**Fig. 2** Scenario 2, comparing addition of sitagliptin (Sita; treatment arm A) vs. a sulphonylurea (SU; treatment arm B) to ongoing metformin (MF) in patients not at HbA1C goals while receiving metformin with or without recommendations for lifestyle modifications (diet and physical activity). Dotted lines indicate discontinuation (and switch to a different therapy) because of medication side effects or primary failure. Solid lines indicate secondary treatment failure (HbA1C exceeds treatment switching threshold). MD, multiple dose.

*Cost Inputs*

Three types of cost inputs were used: medication costs, diabetes and diabetes-related complication event costs and treatment-related side effect costs. Country-specific per-day drug costs were used in the analysis. The per-day drug costs were calculated based on daily costs (without value-added tax) for the different medications and doses available for SU, MF, rosiglitazone, basal insulin and multiple dose insulin (complex regimens of both short-acting and long-acting insulin), and weighting these costs by distribution of patient days on therapy for each of drug and dose. The distribution of patient days on therapy by drug and dose were derived using data from IMS Health (table 3). Also presented on a country-specific basis in table 3 are diabetes-related complication event costs for the first year as well as costs of treating medication side effects in the first event cycle. In addition to event cost in the year of the event, the analysis also was able to incorporate cost of events in subsequent years. Where country-specific data on costs of medication side effects in the first cycle were not available, they were assumed to be zero.

All future costs and benefits were discounted according to national guidelines on pharmacoeconomic analyses. Thus, discount rates varied from 3% for both cost and benefit in Sweden and Austria to 6% in Spain.

*Utility Weights*

Decrements in utility as a result of having diabetes as well as because of any diabetes-related complications [e.g. myocardial infarction (MI), stroke, CHF] are presented in table 4. The disutilities were based on the UKPDS Outcomes Model [7,23]. In addition, the disutilities associated with two or more diabetes-related complications were assumed to be additive as in the UKPDS Outcomes Model. Utility weights associated with each kilogram of change in body weight were from recommendations of the National Institute for Health and Clinical Excellence and were based on gender as well as baseline body mass index [24]. The utility decrements because of hypoglycaemia are based on a study by Lundkvist *et al.* [25]. No loss of utility was assumed because of the occurrence of oedema.

*Clinical Trial Data*

Antihyperglycaemic treatment strategies impact disease progression through HbA1C changes as well as effects on cardiovascular risk factors, such as lipids, hypertension, weight gain and oedema. In addition, side effects associated with these treatment strategies impact costs and patients' QOL.

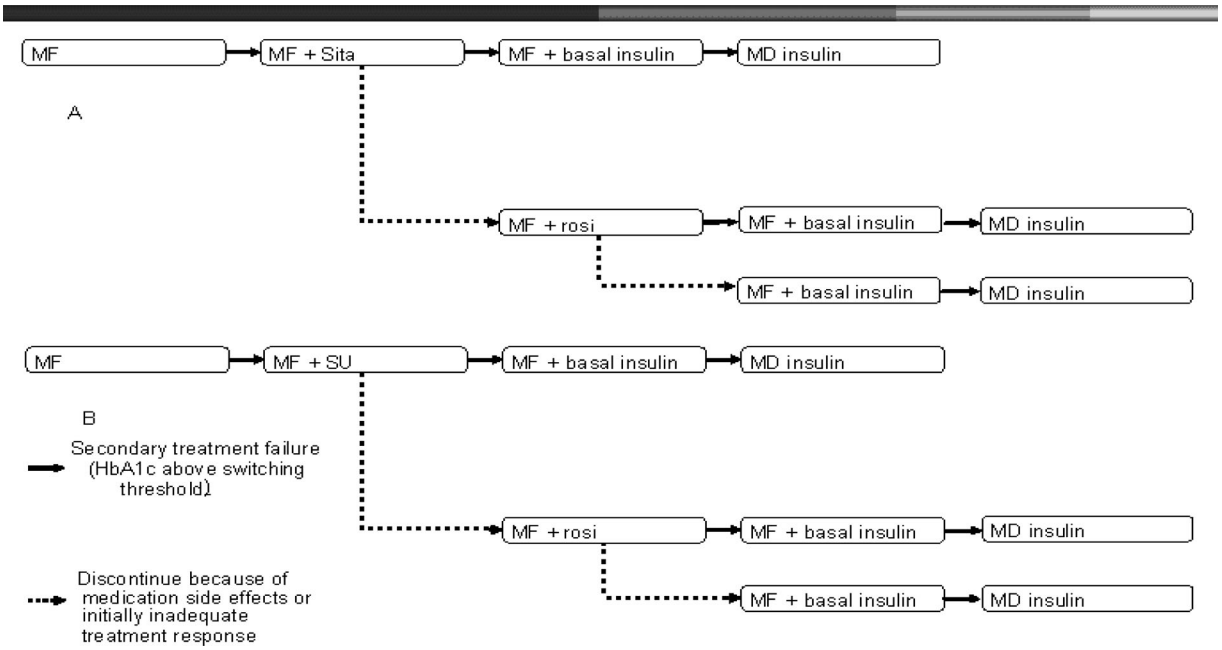


**Fig. 3** Scenario 3, comparing addition of sitagliptin (Sita; treatment arm A) vs. a sulphonylurea (SU; treatment arm B) to ongoing metformin (MF) in patients not at HbA1C goals while receiving MF with or without recommendations or lifestyle modifications (diet and physical activity). Dotted lines indicate discontinuation (and switch to a different therapy) because of medication side effects or primary failure. Solid lines indicate secondary treatment failure (HbA1C exceeds treatment switching threshold). MD, multiple dose.

The clinical and side effect impacts of different treatment strategies in the current analysis were based on either direct or indirect comparisons data from randomized clinical trials. The initial HbA1C drop because of sitagliptin-MF compared with rosiglitazone-MF are presented in table 5. These data were from a placebo controlled trial in which patients not at goal on MF monotherapy were randomized in a 1 : 1 : 1 ratio to one of following once-daily treatment groups: placebo, sitagliptin 100 mg, or rosiglitazone 8 mg [26]. Similarly, the initial 26-week HbA1C drop because of sitagliptin-MF compared with SU-MF is presented in table 6, and is based on an unpublished per-protocol analysis of the study by Nauck *et al.* [27].

The subsequent rise in HbA1C when patients continue on the medication, that is coefficient of durability (COD) (which has also been termed the coefficient of failure) is

**Table 1** Model inputs: local studies used to generate average patient profiles in the cost-effectiveness analysis

| Country | Study | Description |
|---|---|---|
| Austria | Public Health in Austria 2005 [35] | National health survey conducted by the Federal Ministry of Health and Women (BMGF) |
| Finland | FINRISK Study 2002 [36] | Cross-sectional population survey carried out in six provinces of Finland |
| Portugal | Portugal RECAP-DM [30] | European multicentre observational study involving outpatients with type 2 diabetes receiving oral antihyperglycaemic treatment in seven countries |
| Scotland (UK) | Scottish Health Survey [37] | Survey employing two-stage interview process involving a personal interview covering socioeconomic factors, self-assessed health and disability, health service use, diseases, and lifestyle; and a nurse interview covering medication use and anthropometric and biomedical measurements |
| Spain | Spain RECAP-DM [30] | European multicentre observational study involving outpatients with type 2 diabetes receiving oral antihyperglycaemic treatment in seven countries |
| Sweden | PROACTIVE [28] | European prospective randomized controlled trial involving patients with type 2 diabetes and evidence of macrovascular disease |

PROACTIVE, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECAP-DM, Real-Life Effectiveness and Care Patterns of Diabetes Management.

**Table 2** Model inputs: average patient profiles used in cost-effectiveness analysis by country

| | Spain | | Scotland | | Portugal | | Finland | | Sweden | | Austria | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | M | F | M | F | M | F | M | F | M | F | M | F |
| Age (years) | 61.8 | 63.9 | 64.9 | 64.9 | 59.8 | 62.8 | 58.5 | 56.7 | 61.6 | 61.6 | 60.0 | 60.0 |
| Age at diabetes diagnosis (years) | 53.7 | 55.5 | 54.9 | 54.9 | 51.7 | 55.3 | 53.5 | 51.7 | 53.6 | 53.6 | 50.0 | 50.0 |
| Height (cm) | 168.8 | 156.8 | 164.5 | 164.5 | 169.3 | 157.2 | 174.0 | 159.0 | 171.3 | 171.3 | 175.0 | 165.0 |
| Weight (kg) | 88.6 | 81.0 | 84.6 | 84.6 | 99.3 | 77.0 | 90.9 | 80.4 | 91.0 | 91.0 | 80.0 | 70.0 |
| TC (mmol/l) | 5.26 | 5.44 | 5.30 | 5.30 | 5.48 | 6.00 | 5.19 | 5.44 | 4.82 | 4.82 | 6.00 | 6.00 |
| HDL-C (mmol/l) | 1.18 | 1.33 | 1.33 | 1.33 | 1.06 | 1.34 | 1.22 | 1.45 | 1.10 | 1.10 | 1.00 | 1.00 |
| SBP (mmHg) | 139 | 139 | 142 | 142 | 138 | 143 | 140 | 143 | 143 | 143 | 143 | 143 |
| HbA1C (%) | 8.09 | 7.89 | 7.52 | 7.52 | 7.5 | 7.5 | 7.5 | 7.5 | 7.9 | 7.9 | 8.0 | 8.0 |
| % smokers | 21.3 | 5.1 | 0 | 0 | 22.6 | 3.2 | 29.5 | 12.8 | 0 | 0 | 0 | 0 |

F, female; HDL-C, high-density lipoprotein cholesterol; M, male; SBP, systolic blood pressure; TC, total cholesterol.

assumed to be the same for sitagliptin-MF vs. rosiglitazone-MF. The COD for the sitagliptin-MF compared with SU-MF is based on the Nauck *et al.* In this study, coefficients of durability were 0.394 for sitagliptin and rosiglitazone and 0.561 for SU.

As shown in figures 1–3, the treatment algorithms take into account that a portion of patients will need rescue therapies when they do not tolerate a treatment or when their initial treatment response to a treatment is not adequate. The proportion of patients who discontinue from

**Table 3** Model inputs: cost data (€) by country

| | Spain | UK*† | Portugal | Finland | Sweden† | Austria |
|---|---|---|---|---|---|---|
| Drug cost | | | | | | |
| Sulfonylurea | 0.42 | 0.19 | 0.31 | 0.25 | 0.16 | 0.37 |
| Metformin | 0.10 | 0.17 | 0.21 | 0.26 | 0.16 | 0.18 |
| Rosiglitazone | 1.91 | 1.66 | 2.04 | 1.57 | 1.50 | 2.01 |
| Sitagliptin | 1.91 | 1.71 | 1.86 | 1.96 | 1.63 | 2.15 |
| Basal insulin | 1.98 | 1.05 | 0.77 | 1.50 | 1.65 | 1.58 |
| Multiple dose insulin (basal + short acting insulin) | 2.13 | 2.41 | 2.47 | 1.68 | 1.65 | 3.17 |
| Event cost for first year | | | | | | |
| Diabetes without complication | 942 | 581 | 1254 | 3337 | 341 | 303 |
| Ischaemic heart disease | 901 | 4177 | 3981 | 5812 | 21 957 | 7660 |
| MI (nonfatal) | 3677 | 8055 | 10 059 | 7947 | 25 802 | 9155 |
| CHF | 2008 | 4659 | 4047 | 7554 | 14 763 | 5644 |
| Stroke | 1266 | 12 466 | 4742 | 17 593 | 34 929 | 5194 |
| Amputation (one leg) | 3322 | 16 042 | 16 383 | 27 168 | 14 876 | 8913 |
| Blindness (one eye) | 1709 | 10 551 | 1732 | 12 578 | 4572 | 1296 |
| Renal failure | 3594 | 28 965 | 4446 | 58 117 | 9765 | 48 500 |
| Fatal MI | 2758 | 2116 | 3818 | 1940 | 1966 | 9155 |
| Fatal stroke | 2896 | 10 909 | 2419 | 6842 | 1481 | 5194 |
| Fatal CHF | 2758 | 4659 | 2303 | 1940 | 1481 | 5644 |
| Fatal amputation | 2896 | 16 042 | 974 | 1940 | 7438 | 8913 |
| Fatal renal failure | 2895 | 28 965 | 5295 | 1940 | 4883 | 24 250 |
| Diabetes mortality | 2895 | 12 538 | 3160 | 5321 | 1966 | 6913 |
| Costs of medication side effects in first event cycle | | | | | | |
| Hypoglycaemia | 41.44 | 10.46 | 12.99 | 52.80 | 63.99 | 44.19 |
| Weight (per kg change) | 0‡ | 3.40 | 27.97 | 0‡ | 0‡ | 0‡ |

CHF, congestive heart failure; MI, myocardial infarction.

*Costing data were based on United Kingdom Prospective Diabetes Study [38], with costs scaled up to current price levels using local inflation indices. In other countries, costs were based on local data.

†1 GBP = € 1.43522; 1 SKr = € 0.109018. Source for conversion factors: www.xe.com/ucc. Accessed 24 September 2007.

‡Cost assumed to be 0 (conservative assumption).

**Table 4** Model inputs: disutilities because of diabetes, complications, and medication side effects

| Parameter | QALY weights (decrements) | Males | Females |
|---|---|---|---|
| Diabetes without complication* | 0.22 | | |
| Diabetes complications* | | | |
| Ischaemic heart disease | 0.090 | | |
| Myocardial infarction | 0.055 | | |
| Congestive heart failure | 0.108 | | |
| Stroke | 0.164 | | |
| Amputation | 0.280 | | |
| Blindness (one eye) | 0.074 | | |
| Renal failure | 0.265 | | |
| Medication side effects | | | |
| Hypoglycaemia† | 0.07 | | |
| Weight (per kg change)§ | | | |
| Baseline BMI 23–28 kg/m$^2$ | | 0.00062 | 0.00368 |
| Baseline BMI 28–35 kg/m$^2$ | | 0.00176 | 0.00209 |
| Baseline BMI 35–44 kg/m$^2$ | | −0.00205 | 0.00122 |

BMI, body mass index; QALY, quality-adjusted life year.
*Based on UKPDS Outcomes Model [22].
†Based on data from Lundkvist *et al.* [25].
§Based on data from an appraisal of weight loss products by the National Institute for Health and Clinical Excellence [24].

sitagliptin vs. rosiglitazone was 1.1 vs. 2.3% respectively [26]. Similarly, discontinuation rates of 22.3 vs. 16.9% based on per-protocol population from Nauck *et al.* [27] were used for sitagliptin vs. SU comparison.

The treatment effect on blood pressure, lipids and lipoproteins, and body weight are also collected from the above-mentioned trials, and were used to provide comparative treatment side effects of add-on sitagliptin compared with add-on rosiglitazone (table 7) or add-on SU (table 8). As shown in table 7, there was an upward adjustment in the risk of CHF with the rosiglitazone add-on regimen. This was based on a long-term clinical trial involving a TZD [28]. The model did not include any significantly increased risk of MI and heart failure associated with rosiglitazone treatment in patients with type 2 diabetes or impaired glucose tolerance, as suggested in a recent meta-analysis [29]. As shown in table 8, the model assumed an approximately sixfold higher risk of hypoglycaemia with SU-MF compared with sitagliptin-MF, based on a per-protocol analysis of the study by Nauck *et al.* [27]. No increased risk in CHF and a 0% risk of oedema was assumed for the comparison between sitagliptin-MF vs. SU-MF.

**Table 5** Efficacy of dual therapy with MF combined with either sitagliptin or rosiglitazone in lowering HbA1C, by baseline level used in the model

| | | MF + sitagliptin | | MF + rosiglitazone | |
|---|---|---|---|---|---|
| Baseline HbA1C (%) | | % HbA1C lowering | | % HbA1C lowering | |
| Lower | Upper | Mean | s.d. | Mean | s.d. |
| 0 | 7 | 0.460 | 0.320 | 0.10 | 0.490 |
| 7 | 8 | 0.630 | 0.390 | 0.77 | 0.460 |
| 8 | 9 | 1.040 | 0.870 | 0.86 | 0.760 |
| 9 | 99 | 1.640 | 1.180 | 1.98 | 1.260 |

HbA1C, haemoglobin HbA1C; MF, metformin.

**Table 6** Efficacy of dual therapy with MF combined with either sitagliptin or SU in lowering HbA1C, by baseline level used in the model

| | | MF + sitagliptin | | MF + SU | |
|---|---|---|---|---|---|
| Baseline HbA1C (%) | | % HbA1C lowering | | % HbA1C lowering | |
| Lower | Upper | Mean | s.d. | Mean | s.d. |
| 0 | 7 | 0.473 | 0.46 | 0.44 | 0.52 |
| 7 | 8 | 0.744 | 0.60 | 0.90 | 0.61 |
| 8 | 9 | 1.346 | 0.62 | 1.41 | 0.70 |
| 9 | 99 | 1.889 | 0.74 | 2.07 | 0.76 |

HbA1C, haemoglobin HbA1C; MF, metformin; SU, sulfonylurea.

### *Treatment Intensification Thresholds*

In clinical practice, physicians may have a range of HbA1C intervention points when changing treatment regimens for their diabetic patients. Some physicians may decide to switch patients to combination therapy at 6.5% and others at 8%, depending on the complexity of regimens, risks of hypoglycaemia, costs, etc. To capture this variation in physician behaviour, the analysis allowed different HbA1C thresholds for switching simulated. Distributions of switching thresholds were based on epidemiologic data from studies including the Real-Life Effectiveness and Care Patterns of Diabetes Management [30] wherever possible or on input from local clinical experts. These distributions are presented in table 9.

### *Sensitivity Analysis*

For one-way sensitivity analyses, we used scenario 1 as the base case and, in this, Finland had the highest incremental cost-effectiveness ratios (ICERs); hence, Finland was used as the base country in the analysis. In the one-way sensitivity analysis, the following parameters were varied: effects of rosiglitazone on total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure and CHF risk; efficacy of sitagliptin; COD of sitagliptin; utility values for changes in weight; the utility value associated with insulin treatment; costs and utility values associated with diabetes-related complications; and cost and utility values associated with hypoglycaemia.

**Table 7** Effects of dual therapy with MF combined with either sitagliptin or rosiglitazone on mean lipids, SBP and weight as well as on incidences of hypoglycaemic episodes, oedema, and CHF

| | MF + sitagliptin | | MF + rosiglitazone | |
|---|---|---|---|---|
| Mean (s.d.) change in SBP (mmHg) | −1.71 (13.34) | — | –3.29 | — |
| change in total cholesterol (%) | 5.2 | — | 15.7% | — |
| change in HDL-C (%) | 4.1 | — | 9.4 | — |
| Mean (s.d.) change in body weight (kg) | −0.4 (1.80) | | 1.5 (2.20) | |
| | **Probability of experiencing at least one episode** | **Episodes/year (conditional upon experiencing one episode)** | **Probability of experiencing at least one episode** | **Episodes/year (conditional upon experiencing one episode)** |
| Hypoglycaemia | 1.10% | 1.0 | 1.10% | 1.0 |
| Oedema | 1.10% | 1.0 | 4.60% | 1.0 |
| Adjustment in risk for CHF (RRR) | 1.0 | | 1.38 | |

CHF, congestive heart failure; HDL-C, high-density lipoprotein cholesterol; MF, metformin; RRR, relative risk reduction; SBP, systolic blood pressure.

## Results

Compared with adding rosiglitazone (scenario 1), adding sitagliptin to ongoing MF treatment was projected to provide 0.020–0.089 undiscounted incremental quality-adjusted life year (QALY) gained at a discounted incremental cost ranging from −€687 (cost saving) to €214 across different countries (table 10). The discounted ICER values associated with adding sitagliptin (vs. rosiglitazone) to ongoing MF treatment in patients not at HbA1C goals ranged (across countries) from being dominant (cost saving) to €4766/QALY.

When compared with adding SU by scenario 2 (figure 2), adding sitagliptin to ongoing MF therapy was projected to confer 0.037–0.110 undiscounted incremental QALY, at a discounted incremental cost ranging from €331 to €1097, across different countries (table 11). The discounted ICER for introducing sitagliptin (vs. SU by scenario 2) ranged from €5949/QALY to €20 350/QALY across countries.

Corresponding data for comparisons of add-on sitagliptin compared with add-on SU according to scenario 3 (figure 3) are presented in table 12. Under this scenario, sitagliptin treatment was projected to confer 0.049–0.118 undiscounted incremental QALY, at a discounted incremental cost of €339 to €1130, across different countries. The discounted ICER for introducing sitagliptin (vs. SU by scenario 3) ranged from €6029/QALY to €13 655/QALY across countries.

### Sensitivity Analyses

The above findings were robust to changes in model input parameters, including costs and utility weights for both diabetes-related complications and hypoglycaemia (table 13). Discounted ICER values in the sensitivity

**Table 8** Effects of dual therapy with MF combined with either sitagliptin or SU on mean lipids, SBP and weight change as well as on incidences of hypoglycaemic episodes, oedema and CHF

| | MF + sitagliptin | | MF + SU | |
|---|---|---|---|---|
| **Parameter** | **Mean** | **s.d.** | **Mean** | **s.d.** |
| Mean (s.d.) change in SBP (mmHg) | −0.563 (17.63) | — | 1.195 (17.70) | — |
| change in total cholesterol (%) | 4.8 (0.18) | — | 2.8 (0.16) | — |
| change in HDL-C (%) | 3.1 (0.14) | — | 0.9 (0.12) | — |
| Mean (s.d.) change in body weight (kg) | –1.426 (5.59) | | 1.07 (5.59) | |
| | **Probability of experiencing at least one episode** | **Episodes/year (conditional upon experiencing one episode)** | **Probability of experiencing at least one episode** | **Episodes/year (conditional upon experiencing one episode)** |
| Hypoglycaemia | 6.02% | 1.7 | 36.12% | 3.7 |
| Oedema | 0% | 0 | 0% | 0 |
| Adjustment in risk for CHF (RRR) | 1.00 | | 1.00 | |

CHF, congestive heart failure; HDL-C, high-density lipoprotein cholesterol; MF, metformin; RRR, relative risk reduction; SU, sulphonylurea.

**Table 9** HbA1C thresholds for changes in therapy and discount rates, by country

| | Spain (%) | | Scotland (%) | | Portugal (%) | | Finland (%) | | Sweden (%) | | Austria (%) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HbA1C | Dist. | HbA1C | Dist. | HbA1C | Dist. | HbA1C | Dist. | HbA1C | Dist. | HbA1C | Dist. |
| HbA1C thresholds for therapy change | 6.5 | 21 | 6.5 | 0 | 6.5 | 0 | 6.5 | 0 | 6.5 | 0 | 6.5 | 0 |
| | 7.3 | 18 | 7.0 | 0 | 7.0 | 100 | 7.0 | 0 | 7.0 | 0 | 7.0 | 100 |
| | 7.8 | 18 | 7.5 | 0 | 7.5 | 0 | 7.5 | 20 | 7.5 | 100 | 7.5 | 0 |
| | 8.3 | 15 | 8.0 | 100 | 8.0 | 0 | 8.0 | 30 | 8.0 | 0 | 8.0 | 0 |
| | 9.4 | 28 | 8.5 | 0 | 8.5 | 0 | 8.5 | 50 | 8.5 | 0 | 8.5 | 0 |
| Discount rates | | | | | | | | | | | | |
| Costs | 6 | | 3.5 | | 5 | | 5 | | 3 | | 3 | |
| Benefits | 6 | | 3.5 | | 5 | | 5 | | 3 | | 3 | |

HbA1C, haemoglobin HbA1C; Dist., % distribution.

analyses ranged from €2620/QALY, where the effect of TZDs on systolic blood pressure was assumed to be 0, to €6677/QALY, where the assumed effect of TZDs on CHF risk was reduced by 50%. Irrespective of 20% variations in the cost and utility weights associated with diabetes-related complications, discounted ICER values remained within a narrow range (€4060–€5473), as did values associated with 50% variations in costs and utility weights associated with hypoglycaemia (€5040–€5256).

## Discussion

Sitagliptin is the first major advance in oral antihyperglycaemic therapies since the introduction of TZDs. However, new antihyperglycaemic therapies are expensive compared with older generic medications, and payers are constantly confronted with evaluating whether the increased cost of the new agent is worth the additional benefits. In addition, decision makers (payers) are interested in determining the impact of therapy on endpoints such as mortality, morbidity and QOL rather than surrogate markers such as HbA1C [31]. Because such data take time to obtain, the use of modelling is increasingly being embraced by policymakers and practitioners to assist in decision making [31]. Therefore, our analysis may be of interest to healthcare policymakers and other decision makers, who are trying to evaluate the long-term costs and outcome benefits of sitagliptin vs. alternative treatment strategies.

Data across the evaluated countries for sitagliptin (vs. a SU or TZD), co-administered with MF, showed that it is cost-effective and comparable with other well-established cost-effective interventions reported in the literature [32]. Adding sitagliptin to ongoing MF treatment in patients with type 2 diabetes and HbA1C above consensus goal is projected to be a cost-effective strategy. In most evaluated countries, the addition of

**Table 10** Incremental cost, QALY and ICER values for adding sitagliptin to MF vs. adding rosiglitazone to MF in patients not at HbA1C targets on MF monotherapy (scenario 1)

| | Undiscounted incremental | | Discounted incremental | | Discounted ICER |
|---|---|---|---|---|---|
| Country | Cost (€) | QALY | Cost (€) | QALY | €/QALY |
| Spain | 34 | 0.051 | 5 | 0.033 | 149 |
| UK* | 66 | 0.020 | 36 | 0.016 | 2250 |
| Portugal | −828 | 0.089 | −687 | 0.063 | Sitagliptin dominates |
| Finland | 225 | 0.064 | 208 | 0.044 | 4766 |
| Sweden† | −270 | 0.066 | −214 | 0.052 | Sitagliptin dominates |
| Austria | −165 | 0.048 | −127 | 0.040 | Sitagliptin dominates |

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; MF, metaformin.
*1 GBP = € 1.43522
†1 SKr = € 0.109018
Source for conversion factors: www.xe.com/ucc. Accessed 24 September 2007.

**Table 11** Incremental cost, QALY and ICER values for adding sitagliptin to MF vs. adding sulfonylurea to MF in patients not at HbA1C targets on MF monotherapy (scenario 2)

| | Undiscounted incremental | | Discounted incremental | | Discounted ICER |
|---|---|---|---|---|---|
| Country | Cost (€) | QALY | Cost (€) | QALY | €/QALY |
| Spain | 1166 | 0.103 | 1046 | 0.078 | 13 440 |
| UK* | 1082 | 0.110 | 1097 | 0.095 | 11 547 |
| Portugal | 273 | 0.068 | 331 | 0.056 | 5949 |
| Finland | 1076 | 0.097 | 1073 | 0.078 | 13 737 |
| Sweden† | 846 | 0.075 | 830 | 0.068 | 12 219 |
| Austria | 747 | 0.037 | 760 | 0.037 | 20 350 |

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; MF, metaformin.
*1 GBP = € 1.43522
†1 SKr = € 0.109018
Source for conversion factors: www.xe.com/ucc. Accessed 24 September 2007.

**Table 12** Incremental cost, QALY and ICER values for adding sitagliptin to MF vs adding sulfonylurea to MF in patients not at HbA1C targets on MF monotherapy (scenario 3)

| | Undiscounted incremental | | Discounted incremental | | Discounted ICER |
|---|---|---|---|---|---|
| **Country** | **Cost (€)** | **QALY** | **Cost (€)** | **QALY** | **€/QALY** |
| Spain | 1149 | 0.110 | 1033 | 0.084 | 12 301 |
| UK* | 1086 | 0.118 | 1109 | 0.103 | 10 767 |
| Portugal | 275 | 0.068 | 339 | 0.056 | 6029 |
| Finland | 1220 | 0.109 | 1130 | 0.086 | 13 112 |
| Sweden† | 559 | 0.049 | 558 | 0.045 | 12 311 |
| Austria | 677 | 0.055 | 678 | 0.050 | 13 655 |

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; MF, metaformin.
*1 GBP = € 1.43522
†1 SKr = € 0.109018
Source for conversion factors: www.xe.com/ucc. Accessed 24 September 2007.

sitagliptin is a dominant (cost saving and superior health outcome) alternative to the addition of rosiglitazone, while in other countries the discounted incremental cost-effective ratio values were <€6000/QALY. When compared with adding SU to ongoing MF, sitagliptin resulted in incremental cost-effective ratio values ranging from €5949/QALY to €20 350/QALY (both by scenario 2) across the countries investigated. These data were robust to alterations in model assumptions.

Strengths of our analysis included the fact that the JADE Model incorporated risk equations/algorithm (from the UKPDS [22]) that allow simulation of a range of long-term outcomes while taking into account the association between different types of complications at an individual patient level. In addition, this is the only analysis that takes into account the complex treatment algorithm that patients with diabetes follow over their lifetime. This is an important aspect of the model because any evaluation of long-term cost and benefits of therapy in type 2 diabetes should incorporate not only the initial HbA1C drop because of therapy but also the subsequent rise when patients continue on the medication. Furthermore, allowing a treatment strategy to have more than one treatment regimen over a patient's remaining lifetime appropriately captures the impact of treatment on disease progression and thus long-term outcomes and cost of therapy more appropriately. In addition to comparing adjunctive sitagliptin with previous standards of care for oral therapies, the analysis incorporated international standard criteria for glycaemia goal attainment, while also taking into account local variations across countries in other clinical parameters.

The present study was, to our knowledge, unique in conducting cost-effectiveness analyses in six European countries. One methodological challenge inherent in such an ambitious undertaking is accounting for data heterogeneity across countries. A number of factors typically vary across countries, potentially limiting the generalizability (or transferability) of findings from one setting to another. For instance, drug and event costs varied substantially across countries, as did HbA1C thresholds

**Table 13** Sensitivity analysis

| | Discounted total cost difference | Discounted QALY difference | Discounted ICER, €/QALY |
|---|---|---|---|
| Base case | 208 | 0.044 | 4766 |
| Zero-out the effects of TZD on TC and HDL-C | 180 | 0.036 | 5012 |
| Zero-out the effect of TZD on SBP | 134 | 0.051 | 2620 |
| 50% reduction of increased CHF risk because of TZD | 275 | 0.041 | 6677 |
| Reduction in efficacy of sitagliptin by 10% | 206 | 0.027 | 7548 |
| Reduction in the COD of sitagliptin by 10% | 179 | 0.033 | 5455 |
| Utility associated with diabetes-related complications | | | |
| −20% | 208 | 0.043 | 4838 |
| +20% | 208 | 0.044 | 4698 |
| 50% reduction in NICE utility values for changes in weight | 208 | 0.037 | 5584 |
| Disutility of 0 for insulin treatment | 208 | 0.038 | 5512 |
| Hypoglycaemia utility reduced by 50% | 208 | 0.040 | 5256 |
| Cost of diabetes-related complications | | | |
| −20% | 239 | 0.044 | 5473 |
| +20% | 177 | 0.044 | 4060 |
| Hypoglycaemia cost reduced by 50% | 220 | 0.044 | 5040 |

CHF, congestive heart failure; COD, coefficient of durability; HDL-C, high-density lipoprotein cholesterol; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Clinical Excellence; QALY, quality-adjusted life year; SBP, systolic blood pressure; TC, total cholesterol; TZD, thiazolidinediones.

for switching to an alternative treatment (e.g. sitagliptin) in the event of intolerance or treatment failure using MF monotherapy or other regimens. Because of this limitation, comparisons across countries are not meaningful in this analysis.

In addition, although UKPDS disutilities (QALY weights) associated with diabetes and with different diabetes-related complications across countries based on data from a UK population (UKPDS [7]) were used in the model, these may not be representative of QALY weights determined by directly surveying patients in the other countries analysed. Finally, the model did not include data from a recent meta-analysis [29], suggesting that significantly increased risks of MI and heart failure with rosiglitazone may have led to an underestimation of the cost-effectiveness of sitagliptin (vs. rosiglitazone) added to ongoing MF therapy.

Another limitation of the current analysis involves the uncertainty associated with input parameters of clinical data for both efficacy and side effects, as these were based on short-term trials ranging to a maximum of 54 weeks with sample size of 100–600 patients. The impact of the uncertainty in the clinical input measures on the results were tested in sensitivity analysis, and we think that the overall conclusion of the analysis will not change by reducing the uncertainty in the parameter estimate through additional data on the clinical parameters. Certain limitations of the current analysis are because of the UKPDS Outcomes Model risk equations [22], upon which the JADE Model is based. For instance, risk equations and other parameters in the UKPDS Outcomes Model were based on data in a UK population and not validated in other countries. Furthermore, as with the UKPDS Outcomes Model, the JADE Model predicts only the first diabetes-related complication in any category of events, not subsequent diabetes-related complications. It may, therefore, underestimate the benefits of certain drugs that may prevent more than one episode of these complications. The UKPDS Outcomes Model also does not incorporate other complications of diabetes that are major causes of morbidity and reduced QOL. For instance, the model does not predict the occurrence of diabetic neuropathy or the effects of different treatments on this complication. Diabetic neuropathy is an independent risk factor for lower extremity amputation, which in turn significantly increases the risk of cardiac death [33]. In spite of these limitations, we consider the UKPDS Outcomes Model risk equations as the best to predict long-term outcomes in diabetes patients, as demonstrated in the Fourth Mount Hood Challenge (a previous validation exercise) where the UKPDS Model was among the best performing models in projecting long-term health outcomes from a recent clinical trial involving patients with type 2 diabetes [34]. For these reasons, it might be useful in the future to validate the JADE Model in other populations (e.g. by using it to project long-term outcomes in local clinical or epidemiological studies).

## Conclusions

In summary, across Europe, adding sitagliptin is projected to be either cost saving or cost-effective when compared with adding rosiglitazone or SU in patients with type 2 diabetes not at the IDF HbA1C goal (<6.5%) despite MF treatment.

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