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ORIGINAL RESEARCH

# The Cost-Effectiveness of Alogliptin Versus Sulfonylurea as Add-on Therapy to Metformin in Patients with Uncontrolled Type 2 Diabetes Mellitus

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## ABSTRACT

***Introduction***: ENDURE (ClinicalTrials.gov identifier, NCT00856284), a multicenter, double-blind, active-controlled study of 2639 patients with uncontrolled type 2 diabetes mellitus (T2DM), found that metformin in combination with alogliptin (12.5 and 25 mg doses), when compared to standard add-on therapy (sulfonylurea, SU), exerted sustained antihyperglycemic effects over 2 years. This economic analysis of ENDURE aimed to quantify the relationship between increased glycemic durability and cost-effectiveness of alogliptin in the UK clinical setting, and communicate its sustained glycemic benefit in economic terms.

***Methods***: Using baseline characteristics and treatment effects from the ENDURE trial population, between-group cost-effectiveness analyses compared the combined use of metformin and alogliptin (MET + $ALO_{12.5/25}$) in patients with inadequately controlled T2DM, as an alternative to metformin and SU (MET + SU). In scenario analyses, an intragroup cost-effectiveness analysis compared MET + $ALO_{12.5/25}$ with MET + SU; a between-group cost-effectiveness analysis also compared MET + $ALO_{12.5/25}$ versus MET + SU within a subpopulation of patients who achieved HbA1c control (<7.5%) at 2 years on study drug.

***Results***: Compared with baseline profiles of patients, combination therapies with

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alogliptin or SU were associated with improvements in length and quality of life and were cost-effective at established norms. Despite increased drug acquisition costs, alogliptin at 12.5 mg and 25 mg doses resulted in greater predicted lifetime quality-adjusted life year (QALY) gains with associated incremental cost-effectiveness ratios (ICERs) of £10,959/QALY and £7217/QALY compared to SU, respectively.

***Conclusion***: The ENDURE trial and the present cost-effectiveness analysis found that the glycemic durability of alogliptin therapy was associated with improved long-term patient outcomes, QALY gains, and ICERs that were cost-effective when evaluated against standard threshold values. Alogliptin therefore represents a cost-effective treatment alternative to SU as add-on therapy to metformin in patients with poorly managed T2DM.

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**Keywords:** Alogliptin; Cost-effectiveness analysis; Glycemic durability; Sulfonylurea; Second-line therapy; Type 2 diabetes mellitus

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that imposes major social and economic burdens on public health in the UK. In addition to the direct healthcare costs associated with managing T2DM, the societal and productivity consequences of T2DM also incur significant indirect costs. In 2010–11, it was estimated that T2DM affected 3.4 million adults in the UK, the cost of which exceeded £21.7 billion [1]. This was made up of £13 billion in indirect expenses and £8.7 billion in direct healthcare costs [1], which account for up to 10% of all NHS expenditure [2]. Economic projections have hypothesized that the prevalence of T2DM in the UK will rise to 5.6 million adults in 2035–36, and will incur direct NHS costs exceeding £15.1 billion. The indirect costs of the morbidity and mortality associated with T2DM were also projected to rise, to £20.5 billion by 2035–36 [1].

More than 75% of NHS expenditure on T2DM is related to the costs of treating the complications of T2DM, rather than the ongoing management of the condition itself [1]. These complications include cardiovascular events, neuropathy, renal disorders, visual impairment, and amputations, many of which are avoidable consequences of suboptimal glycemic control. The National Institute for Health and Care Excellence (NICE) recommends that T2DM therapy ought to lower glycated hemoglobin A1c (HbA1c) levels to 48 mmol/mol (6.5%) [2]; however, approximately 30% of patients fail to reach and maintain this goal [3]. Effective management of T2DM, through improvements to current treatment strategies, has the potential to reduce adverse micro- and macrovascular complications, and their associated burden.

Clinical guidelines for the management of T2DM initially advocate metformin, in combination with diet and lifestyle changes [2, 4]. However, given the progressive nature of T2DM due to declining beta cell function, long-term glycemic management is invariably associated with the requirement for therapy escalation [5, 6]. In patients suboptimally controlled on metformin monotherapy, sulfonylurea (SU) is a common second-line treatment option [2]. Whilst combination therapy with drugs of this class is associated with significant reductions in HbA1c, SUs are

additionally associated with weight gain and an increased risk of hypoglycemia [7]. The risk of these adverse events is further exacerbated when secondary treatment failure progressively necessitates the addition of further oral therapies and/or insulin initiation [6].

Inhibitors of dipeptidyl peptidase-4 (DPP-4) exert antihyperglycemic effects in T2DM, without increased risk of weight gain or hypoglycemic events [7]. Alogliptin is a selective inhibitor of DPP-4, and its antidiabetic efficacy in monotherapy and combination therapy has been established in clinical studies over 1 year [8–10]. To investigate the long-term glycemic durability of alogliptin, ENDURE (Efficacy and safety of alogliptin plus metformin compared to glipizide plus metformin in subjects with type 2 diabetes mellitus; ClinicalTrials.gov identifier, NCT00856284) was a multicenter, double-blind, active-controlled trial that compared alogliptin with an SU (glipizide) in combination with metformin in poorly managed T2DM over 2 years [11]. The trial found that, in patients with inadequate glycemic control following stable-dose metformin treatment, combination therapy with alogliptin (12.5 and 25 mg once daily) was associated with significant improvements in HbA1c, fasting plasma glucose, and the incidence of weight gain, hyperglycemic rescue, and hypoglycemic events over 2 years [11]. In a post hoc analysis of ENDURE, a significantly greater proportion of the alogliptin cohort achieved the composite endpoint of glycemic control, without weight gain or hypoglycemia [12].

Although ENDURE demonstrated the clinical effectiveness of alogliptin compared to SU as a second-line therapy for T2DM, further studies are required to determine whether its durability benefits may translate to improved cost-effectiveness. The present economic analysis of ENDURE aimed to evaluate the relative cost-effectiveness of alogliptin compared to SU in the UK clinical setting.

## METHODS

### Patient Population

Baseline characteristics and treatment effects were sourced from the ENDURE trial population ($N = 2639$) [11]. Patients were randomized to receive 12.5 mg alogliptin once daily ($n = 880$), 25 mg alogliptin once daily ($n = 885$), or 5 mg glipizide once daily ($n = 874$) for 104 weeks, in combination with at least 1500 mg open-label metformin once daily (or maximum tolerated dose). The model cohort was considered to be representative of UK patients who would be eligible to receive alogliptin as part of a UK treatment strategy.

### Cost-Effectiveness Model

Economic analysis of ENDURE trial data was performed using the widely published and validated IMS Core Diabetes Model (CDM), a generic (non-product-specific) computer simulation model used to predict the long-term incidence of adverse events and the economic consequences of interventions in the management of T2DM [13].

The CDM is a fixed-time increment stochastic model comprised of 17 interrelated state transition Markov submodels, with each submodel using time, state, and patient-dependent probabilities. Monte Carlo simulations are performed at the individual patient level using tracker variables to accommodate complex interactions between individual complication submodules. The CDM simulates diabetes-related micro- and

macrovascular complications (angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular edema, cataract, hypoglycemia [nocturnal, severe, and symptomatic], ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, and amputation), cardiovascular, and non-specific mortality. It accommodates direct and indirect costs, adjusts for quality of life, and performs cost-effectiveness and cost–utility analyses. Separate transition probabilities and management strategies for type 1 and type 2 diabetes are utilized within the model, and source data for model parameters are obtained from a broad range of published clinical and epidemiological studies, predominantly the Diabetes Control and Complications Trial (DCCT) [14] and Framingham studies [15] for type 1 diabetes and UKPDS studies [16, 17] for T2DM.

Patient progression through the model is determined by baseline clinical and demographic characteristics. The progression of T2DM is modelled using annual time increments. As the simulation progresses, time-dependent risk factors are updated or modified according to a therapy change, thereby altering the likelihood of event occurrence.

## Analyses

Within each analysis, a cohort of 1000 patients was simulated for each treatment arm based on the baseline profile and treatment effect adjusted for distributions in the deviation of CDM inputs. Each patient was simulated for a lifetime time horizon (excluding where model inputs were fluctuating as part of a sensitivity analysis) up to a maximum of 50 years on a yearly cycle. Discount rates for both cost and utilities were set to 3.5%.

Costs were adjusted for inflation (where necessary), set against 2015 using the hospital and community health services (HCHS) index compiled by the Personal Social Services Research Unit (PSSRU) [18]. The annual cost of each regimen was input into the CDM as an annual cost encompassing both the treatment and consumables (test strips, lancets, and needles) required to administer and manage the treatment. The treatment and consumables were calculated using both the daily cost obtained from the latest Monthly Index of Medical Specialties (MIMS) [19] and daily usage guidelines for all individual drug regimens and consumables obtained from either the ENDURE study protocol [11] or daily usage guidelines from NICE [2]. Where relevant, an average cost of all relevant products was applied unless explicitly defined within the treatment arm (including metformin, alogliptin, and glipizide). Additional complication specific costs and overall utility consequences were applied on a per cycle basis based on the predicted occurrence of diabetes-related complications. All utilities and disutility rates were sourced from relevant literature of patients with T2DM (see appendix in the Supplementary Material). Modelled costs and utilities are provided in Tables S1–S8 in the Supplementary Material.

Across all analyses, CDM input data for the baseline cohort profile and treatment effect were sourced from published trial data [11] supplemented with validated patient level ENDURE data where required. The baseline profiles used are presented in Table 1; the treatment effects for both the overall population and subpopulation of patients with HbA1c less than 7.5% at week 104 that were input into the CDM are presented in Tables 2 and 3, respectively.

**Table 1** Baseline demographics and clinical characteristics of ENDURE study population input into the CDM

| | Overall population | | | | HbA1c control | Source |
|---|---|---|---|---|---|---|
| **Applied to:** | **Total ($N = 2639$) BC, ScA-2** | **MET + $ALO_{12.5}$ ($n = 880$) ScA-1** | **MET + $ALO_{25}$ ($n = 885$) ScA-1** | **MET + SU ($n = 874$) ScA-1** | **Total ($N = 1177$) SA-1** | |
| Patient demographics | | | | | | |
| Age (years) | 55.40 ± 0.19 | 55.22 ± 0.32 | 55.52 ± 0.33 | 55.44 ± 0.32 | 56.46 ± 0.27 | ENDURE PLD [11] |
| Diabetes duration (years) | 5.52 ± 0.10 | 5.65 ± 0.18 | 5.42 ± 0.16 | 5.48 ± 0.17 | 5.42 ± 0.15 | ENDURE PLD [11] |
| Male (%) | 49.72 | 47.61 | 51.07 | 50.46 | 49.02 | ENDURE PLD [11] |
| Smoker (%)[a] | 13.94 | 15.34 | 13.79 | 12.70 | 11.55 | ENDURE PLD [11] |
| Cigarettes (units/day) | 12.10 | 12.10 | 12.10 | 12.10 | 12.10 | ONS Table 2 in [30] |
| Alcohol (oz/week) | 5.00[c] | 5.00[c] | 5.00[c] | 5.00[c] | 5.00[c] | WHO Fig. 2 in [31] |
| Race (%)[b] | | | | | | |
| White | 63.34 | 64.10 | 63.72 | 62.19 | 62.28 | ENDURE PLD [11] |
| Black | 8.51 | 8.52 | 7.58 | 9.45 | 7.23 | ENDURE PLD [11] |
| Hispanic | – | – | – | – | – | – |
| Native American | 4.54 | 4.60 | 4.82 | 4.20 | 4.70 | ENDURE PLD [11] |
| Asian/Pacific Islander | 23.60 | 22.78 | 23.88 | 24.15 | 25.78 | ENDURE PLD [11] |
| Clinical characteristics | | | | | | |
| HbA1c (%) | 7.60 ± 0.01 | 7.59 ± 0.02 | 7.61 ± 0.02 | 7.60 ± 0.02 | 7.42 ± 0.02 | ENDURE PLD [11] |
| SBP (mmHg) | 139.2 ± 0.23 | 139.2 ± 0.23 | 139.2 ± 0.23 | 139.2 ± 0.23 | 139.2 ± 0.23 | ACCORD Table 1 in [32] |
| DBP (mmHg) | 76.00 ± 0.15 | 76.00 ± 0.15 | 76.00 ± 0.15 | 76.00 ± 0.15 | 76.00 ± 0.15 | ACCORD Table 1 in [32] |
| TC (mg/dL) | 181.8 ± 0.79 | 182.8 ± 1.39 | 182.1 ± 1.38 | 180.7 ± 1.35 | 178.6 ± 1.15 | ENDURE PLD [11] |
| HDL (mg/dL) | 46.70 ± 0.22 | 46.93 ± 0.4 | 46.57 ± 0.36 | 46.60 ± 0.38 | 47.30 ± 0.31 | ENDURE PLD [11] |

**Table 1** continued

| | Overall population | | | | HbA1c control | Source |
|---|---|---|---|---|---|---|
| **Applied to:** | **Total ($N = 2639$) BC, ScA-2** | **MET + $ALO_{12.5}$ ($n = 880$) ScA-1** | **MET + $ALO_{25}$ ($n = 885$) ScA-1** | **MET + SU ($n = 874$) ScA-1** | **Total ($N = 1177$) SA-1** | |
| LDL (mg/dL) | 100.9 ± 0.66 | 100.7 ± 1.14 | 101.2 ± 1.14 | 101.0 ± 1.17 | 99.3 ± 0.98 | ENDURE PLD [11] |
| TRIG (mg/dL) | 175.5 ± 0.98 | 179.0 ± 1.75 | 176.6 ± 1.71 | 170.9 ± 1.64 | 163.1 ± 1.35 | ENDURE PLD [11] |
| BMI ($kg/m^2$) | 31.23 ± 0.11 | 31.3 ± 0.18 | 31.27 ± 0.18 | 31.11 ± 0.18 | 30.73 ± 0.15 | ENDURE PLD [11] |
| eGFR (mL/min/1.73 $m^2$) | 91.60 ± 0.42 | 91.60 ± 0.42 | 91.60 ± 0.42 | 91.60 ± 0.42 | 91.60 ± 0.42 | ACCORD Table 1 in [32] |

Data reported as mean ± SE or %

*HbA1c* glycated hemoglobin, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *TRIG* triglycerides, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *PLD* patient-level data, *BC* base case, *SA* sensitivity analysis, *ScA* scenario analysis, *ONS* Office for National Statistics, *WHO* World Heath Organization

[a] Patients coded as "Current smoker"

[b] Proportions adjusted to discard patients coded as "Multiracial"

[c] Based on 5.1 L pure alcohol consumption per year

**Table 2** Treatment effect of clinical characteristics for ENDURE study population

| **Δ from baseline to year 1 unless specified (mean ± SE)** | **Second-line therapy** | | | | | | **Rescue therapy** | |
|---|---|---|---|---|---|---|---|---|
| | **With treatment effect** | | | | **Without treatment effect** | | | |
| | **MET + $ALO_{12.5}$ ($n$ = 631/461[d])** | **MET + $ALO_{25}$ ($n$ = 644/482[d])** | **MET + SU ($n$ = 588/424[d])** | **Source** | **MET + $ALO_{12.5/25}$/MET + SU** | **Source** | **MET + NPH** | **Source** |
| **Applied to:** | **BC, ScA-1, SA-1** | **BC, ScA-1, SA-1** | **BC, ScA-1, SA-1** | | **ScA-1** | | **BC, ScA-1, SA-1** | |
| Clinical characteristics | | | | | | | | |
| Δ HbA1c (%) | – | – | – | – | – | – | −0.54 ± 0.00 | NICE [2] |
| Baseline to year 1 | −0.81 | −0.76 | −0.73 | ENDURE Fig. 2 in [11][c] | 0.00 | – | – | – |
| Year 1 to year 2 | 0.13 | 0.04 | 0.14 | ENDURE Fig. 2 in [11][c] | 0.00 | – | – | – |
| Δ SBP (mmHg) | – | – | – | – | – | – | | |
| Δ TC (mg/dL) | 4.29 ± 1.30 | 1.11 ± 1.3 | 6.62 ± 1.34 | ENDURE PLD [11] | 0.00 ± 0.00 | – | 0.00 ± 0.00 | – |
| Δ LDL (mg/dL) | 3.88 ± 1.11 | 0.15 ± 1.13 | 3.58 ± 1.17 | ENDURE PLD [11] | 0.00 ± 0.00 | – | 0.00 ± 0.00 | – |
| Δ HDL (mg/dL) | 1.40 ± 0.29 | 1.9 ± 0.28 | 1.28 ± 0.31 | ENDURE PLD [11] | 0.00 ± 0.00 | – | 0.00 ± 0.00 | – |
| Δ TRIG (mg/dL) | −1.51 ± 3.54 | −7.84 ± 3.54 | 6.59 ± 3.03 | ENDURE PLD [11] | 0.00 ± 0.00 | – | 0.00 ± 0.00 | – |
| Δ BMI ($kg/m^2$) | −0.26 ± 0.05 | −0.37 ± 0.05 | 0.35 ± 0.05 | ENDURE PLD [11] | 0.00 ± 0.00 | – | 0.62 ± 0.00 | NICE [2][a] |

**Table 2** continued

| Δ from baseline to year 1 unless specified (mean ± SE) | Second-line therapy | | | | | | Rescue therapy | |
|---|---|---|---|---|---|---|---|---|
| | With treatment effect | | | | Without treatment effect | | | |
| | MET + $ALO_{12.5}$ ($n$ = 631/461[d]) | MET + $ALO_{25}$ ($n$ = 644/482[d]) | MET + SU ($n$ = 588/424[d]) | Source | MET + $ALO_{12.5/25}$/MET + SU | Source | MET + NPH | Source |
| **Applied to:** | **BC, ScA-1, SA-1** | **BC, ScA-1, SA-1** | **BC, ScA-1, SA-1** | | **ScA-1** | | **BC, ScA-1, SA-1** | |
| Adverse events | | | | | | | | |
| Minor hypo event rate (/100 pt years) | 2.32[b] | 1.28[b] | 21.86[b] | ENDURE PLD [11] | 0.00 | – | 196.40 | NICE [2] |
| Major hypo event rate (/100 pt years) | 0.11[b] | 0.00[b] | 0.54[b] | ENDURE PLD [11] | 0.00 | – | – | – |

*HbA1c* glycated hemoglobin, *SBP* systolic blood pressure, *TC* total cholesterol, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *TRIG* triglycerides, *BMI* body mass index, *hypo* hypoglycemic, *PLD* patient-level data, *BC* base case, *SA* sensitivity analysis, *ScA* scenario analysis, *pt* patient

[a] Δ BMI calculated on the basis of +1.703 (guidelines) weight change and baseline height

[b] Searched within on-treatment adverse event dataset (minor = hypoglycemia, major = hypoglycemic seizure)

[c] Adjusted for co-variates as outlined in Fig. 2 of source data

[d] $N$ = 12 months/24 months. Data reported as mean ± SE or %

**Table 3** Treatment effect of clinical characteristics for HbA1c control (<7.5%) subpopulation

| **Δ from baseline to year 1 unless specified (mean ± SE)** | **Second-line therapy** | | | | | | **Rescue therapy** | |
|---|---|---|---|---|---|---|---|---|
| | **With treatment effect** | | | | **Without treatment effect** | | | |
| | **MET + $ALO_{12.5}$ ($n$ = 397/397[c])** | **MET + $ALO_{25}$ ($n$ = 430/430[c])** | **MET + SU ($n$ = 347/347[c])** | **Source** | **MET + $ALO_{12.5/25}$/MET + SU** | **Source** | **MET + NPH** | **Source** |
| **Applied to:** | **ScA-2** | **ScA-2** | **ScA-2** | | | | **ScA-2** | |
| Clinical characteristics | | | | | | | | |
| Δ HbA1c (%) | – | – | – | – | – | – | −0.54 ± 0.00 | NICE [2] |
| Baseline to year 1 | −0.77 | −0.75 | −0.70 | ENDURE PLD [11] | 0.00 | – | – | – |
| Year 1 to year 2 | 0.03 | −0.04 | −0.01 | ENDURE PLD [11] | 0.00 | – | – | – |
| Δ SBP (mmHg) | – | – | – | – | – | – | – | – |
| Δ TC (mg/dL) | 5.61 ± 1.60 | 0.28 ± 1.61 | 4.58 ± 1.75 | ENDURE PLD [11] | 0.00 ± 0.00 | – | 0.00 ± 0.00 | – |
| Δ LDL (mg/dL) | 5.32 ± 1.40 | −0.76 ± 1.41 | 2.18 ± 1.53 | ENDURE PLD [11] | 0.00 ± 0.00 | – | 0.00 ± 0.00 | – |
| Δ HDL (mg/dL) | 2.14 ± 0.36 | 1.94 ± 0.35 | 1.59 ± 0.38 | ENDURE PLD [11] | 0.00 ± 0.00 | – | 0.00 ± 0.00 | – |
| Δ TRIG (mg/dL) | −8.22 ± 4.67 | −3.87 ± 4.23 | 0.68 ± 3.50 | ENDURE PLD [11] | 0.00 ± 0.00 | – | 0.00 ± 0.00 | – |

**Table 3** continued

| Δ from baseline to year 1 unless specified (mean ± SE) | Second-line therapy | | | | | | Rescue therapy | |
|---|---|---|---|---|---|---|---|---|
| | With treatment effect | | | | Without treatment effect | | | |
| | MET + $ALO_{12.5}$ ($n$ = 397/397[c]) | MET + $ALO_{25}$ ($n$ = 430/430[c]) | MET + SU ($n$ = 347/347[c]) | Source | MET + $ALO_{12.5/25}$/MET + SU | Source | MET + NPH | Source |
| **Applied to:** | **ScA-2** | **ScA-2** | **ScA-2** | | | | **ScA-2** | |
| Δ BMI ($kg/m^2$) | −0.41 ± 0.07 | −0.54 ± 0.07 | 0.21 ± 0.07 | ENDURE PLD [11] | 0.00 ± 0.00 | – | 0.63 ± 0.00 | NICE [2][a] |
| Adverse events | | | | | | | | |
| Minor hypo event rate (/100 pt years) | 2.32[b] | 1.28[b] | 21.86[b] | ENDURE PLD [11] | 0.00 | – | 196.40 | NICE [2] |
| Major hypo event rate (/100 pt years) | 0.11[b] | 0.00[b] | 0.54[b] | ENDURE PLD [11] | 0.00 | – | – | – |

*HbA1c* glycated hemoglobin, *SBP* systolic blood pressure, *TC* total cholesterol, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *TRIG* triglycerides, *BMI* body mass index, *hypo* hypoglycemic, *PLD* patient-level data, *ScA* scenario analysis

[a] Δ BMI calculated on the basis of +1.703 (guidelines) weight change and baseline height

[b] Obtained from overall population

[c] $N$ = 12 months/24 months. Data reported as mean ± SE or %

### Base Case Analyses

The base case analysis considered the combined use of metformin and alogliptin (MET + $ALO_{12.5/25}$) in patients with inadequately controlled T2DM, as an alternative to metformin and glipizide (MET + SU). In line with UK guidelines, therapy intensification occurred when HbA1c reached 7.5%; at this point patients were escalated to insulin therapy: metformin and neutral protamine Hagedorn insulin (MET + NPH) [2].

### Probabilistic and Deterministic Sensitivity Analyses

Additional analyses were performed for the base case including both probabilistic and a deterministic sensitivity analysis. For the probabilistic sensitivity analysis, 1000 runs were performed in which input parameters were sampled using the CDM's default distribution; for the deterministic sensitivity analysis, model inputs were fluctuated (10- and 20-year time horizons; complication costs ±20%; utilities ±20%; discount rates (costs/utilities) 0% and 7%; duration switch of 5 years).

### Scenario Analyses (ScA)

#### *ScA-1*

Scenario analyses assessed within-group comparisons using treatment arm-specific baseline profiles: MET + SU with no treatment effect versus MET + SU with treatment effect; MET + $ALO_{12.5}$ with no treatment effect versus MET + $ALO_{12.5}$ with treatment effect; MET + $ALO_{25}$ with no treatment effect versus MET + $ALO_{25}$ with treatment effect.

#### *ScA-2*

A secondary scenario analysis replicated the base case simulations using a subpopulation of patients who achieved an HbA1c of 7.5% or less at 2 years, in line with NICE guidelines [2].

### Compliance with Ethics Guidelines

This study was based on a previously conducted trial, and does not involve any new studies of human or animal subjects performed by any of the authors.

## RESULTS

### Base Case Analyses

The base case economic evaluation compared alogliptin (12.5 and 25 mg doses) to SU, as add-on therapies to metformin (Table 4, Fig. 1).

Treatment with alogliptin 12.5 mg was estimated to incur additional total costs (£1131) but gains in quality-adjusted life years (0.103 QALYs) and life expectancy (0.044 years). The additional total costs were driven by increased drug acquisition costs (£1399), which were partly offset by a reduction in complication costs (£263) from fewer predicted events. The largest cost offset in the analysis was attributable to a reduction in the incidence of CVD. Treatment with alogliptin 12.5 mg compared with SU was associated with an incremental cost-effectiveness ratio (ICER) of £10,959/QALY.

Treatment with alogliptin 25 mg was estimated to incur additional total costs (£1012) but gains in QALYs (0.140) and life expectancy (0.081 years). The additional total costs were driven by increased drug acquisition costs (£1421), which were partly offset by a reduction in complication costs (£382) from

**Table 4** Base case event rate and economic analysis of alogliptin as a second-line antidiabetic therapy

| | MET + SU | MET + $ALO_{12.5}$ | MET + $ALO_{25}$ |
|---|---|---|---|
| Macrovascular complications (cumulative incidence %) | | | |
| CHF death | 39.48 | 40.46 | 40.80 |
| CHF event | 15.72 | 15.23 | 15.19 |
| PVD onset | 19.26 | 19.07 | 18.79 |
| Angina | 13.72 | 13.39 | 13.06 |
| Diabetes mortality | 26.97 | 26.73 | 26.81 |
| Stroke event | 7.66 | 7.64 | 7.53 |
| Event fatality | 33.36 | 32.64 | 32.21 |
| MI event | 18.42 | 17.85 | 17.63 |
| Microvascular complications (cumulative incidence %) | | | |
| Background diabetic retinopathy | 29.62 | 29.29 | 29.35 |
| Proliferative diabetic retinopathy | 2.56 | 2.49 | 2.48 |
| Macular edema | 25.47 | 25.14 | 25.19 |
| Severe vision loss | 12.83 | 12.55 | 12.56 |
| Cataract | 13.09 | 13.05 | 13.08 |
| Microalbuminuria | 41.25 | 41.00 | 40.88 |
| Gross proteinuria | 14.80 | 14.59 | 14.48 |
| ESRD | 4.86 | 4.78 | 4.66 |
| Nephropathy (death) | 0.00 | 0.00 | 0.00 |
| Ulcer | 41.9 | 41.52 | 41.57 |
| Recurrent ulcer | 89.6 | 88.72 | 88.88 |
| Amputation due to ulcer | 19.53 | 19.34 | 19.43 |
| Amputation due to recurrent ulcer | 13.41 | 13.30 | 13.38 |
| Neuropathy | 72.8 | 72.53 | 72.49 |
| Absolute results (discounted) | | | |
| Total cost (£) | 27,835 | 28,966 | 28,847 |
| Treatment | 6644 | 8043 | 8065 |
| Management | 462 | 463 | 465 |
| CVD | 7450 | 7358 | 7259 |
| ESRD | 1245 | 1186 | 1164 |
| Ulcer/amputation/neuropathy | 10,130 | 10,038 | 10,043 |
| Eye | 1851 | 1831 | 1828 |

**Table 4** continued

| | MET + SU | MET + $ALO_{12.5}$ | MET + $ALO_{25}$ |
|---|---|---|---|
| Hypoglycemia | 0 | 0 | 0 |
| Total LE | 14.833 | 14.878 | 14.914 |
| Total QALY | 9.720 | 9.824 | 9.861 |
| Between groups analysis (MET + SU vs MET + $ALO_{12.5/25}$) | | | |
| Incremental cost | | 1131 | 1012 |
| Incremental LE | | 0.044 | 0.081 |
| Incremental QALY | | 0.103 | 0.14 |
| ICER (cost/LE) | | 25,588 | 12,476 |
| ICER (cost/QALY) | | 10,959 | 7217 |
| CE? (£30,000 ICER) | | 67.6 | 77.1 |

*MI* myocardial infarction, *CVD* cardiovascular disease, *ESRD* end-stage renal disease, *LE* life expectancy, *QALY* quality-adjusted life year, *ICER* incremental cost-effectiveness ratio, *CE?* probability of cost-effectiveness

fewer predicted events. The largest cost offset in the analysis was attributable to a reduction in the incidence of CVD. Treatment with alogliptin 25 mg compared with SU was associated with an ICER of £7217/QALY.

Results of the probabilistic sensitivity analysis support the base case results and give an indication as to the likelihood of cost-effectiveness at various willingness to pay thresholds. ICER scatterplots (Figs. 2, 3) demonstrate that in the comparison of alogliptin 12.5 mg and SU, alogliptin 12.5 mg was cost-effective at a threshold of £30,000/QALY with a probability of cost-effectiveness of 67.6%. Similarly, in the analysis of alogliptin 25 mg and SU, the probability of cost-effectiveness of alogliptin 25 mg was 77.1% at a £30,000/QALY willingness to pay threshold.

Results of the deterministic sensitivity analysis are reported in Table 5. The cost-effectiveness of alogliptin 12.5 and 25 mg was insensitive to change in key model input parameters and remained cost-effective compared to SU across deterministic sensitivity analyses. For alogliptin 12.5 mg, ICERs across sensitivity analyses ranged from £6932/QALY to £24,143/QALY (base case ICER £10,959/QALY). For alogliptin 25 mg, ICERs across sensitivity analyses ranged from £4225/QALY to £19,056/QALY (base case ICER £7217/QALY). ICERs improved with increased time horizon driven by increased accumulation of QALYs. However, even at a 10-year time horizon, alogliptin was cost-effective compared with SU with ICERs less than £20,000/QALY at 12.5 and 25 mg doses.

## Scenario Analysis (ScA)

### *ScA-1*

A within-arm cost-effectiveness analysis was undertaken for each treatment group: SU, alogliptin 12.5 mg, and alogliptin 25 mg. In each analysis, patient baseline profiles were

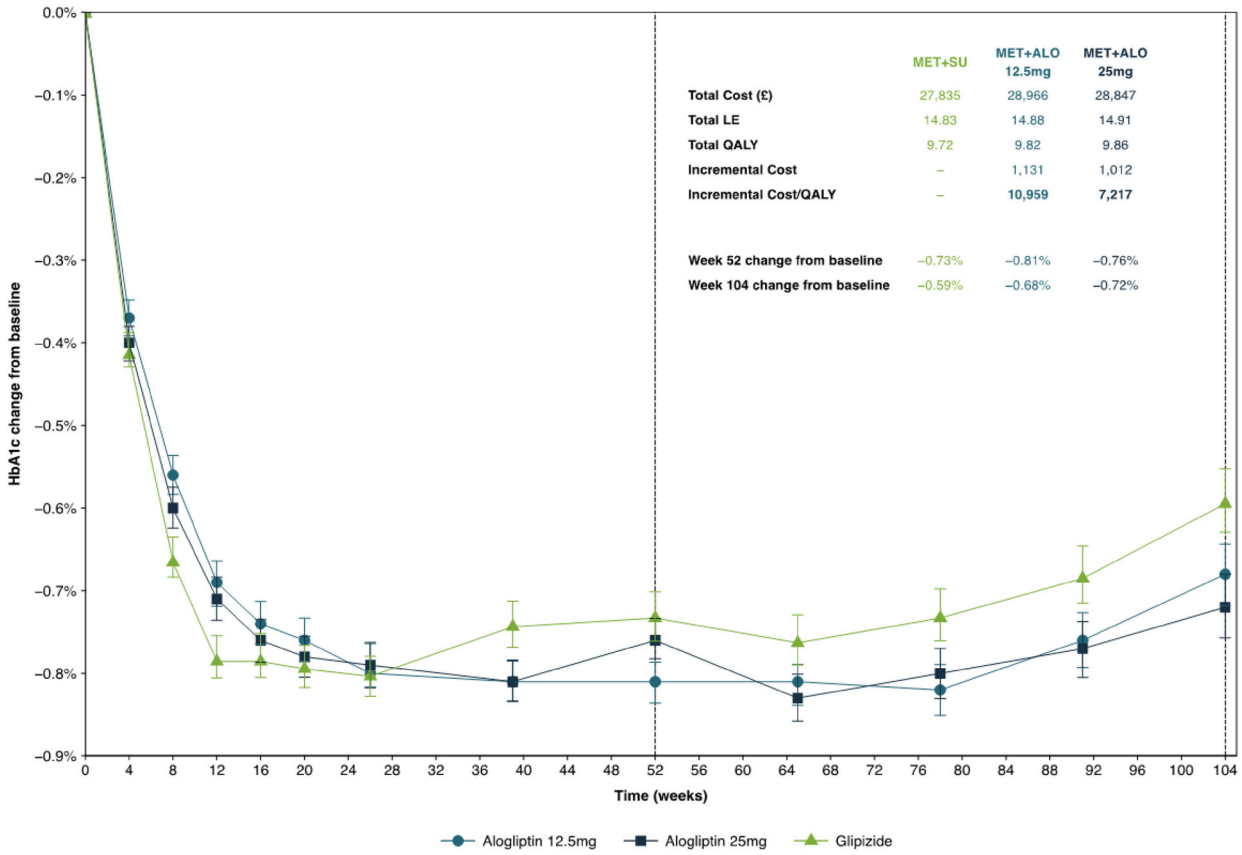


**Fig. 1** Relationship between sustained antihyperglycemic efficacy (HbA1c) and cost-effectiveness of alogliptin 12.5 mg and 25 mg vs SU ([adapted from [11])

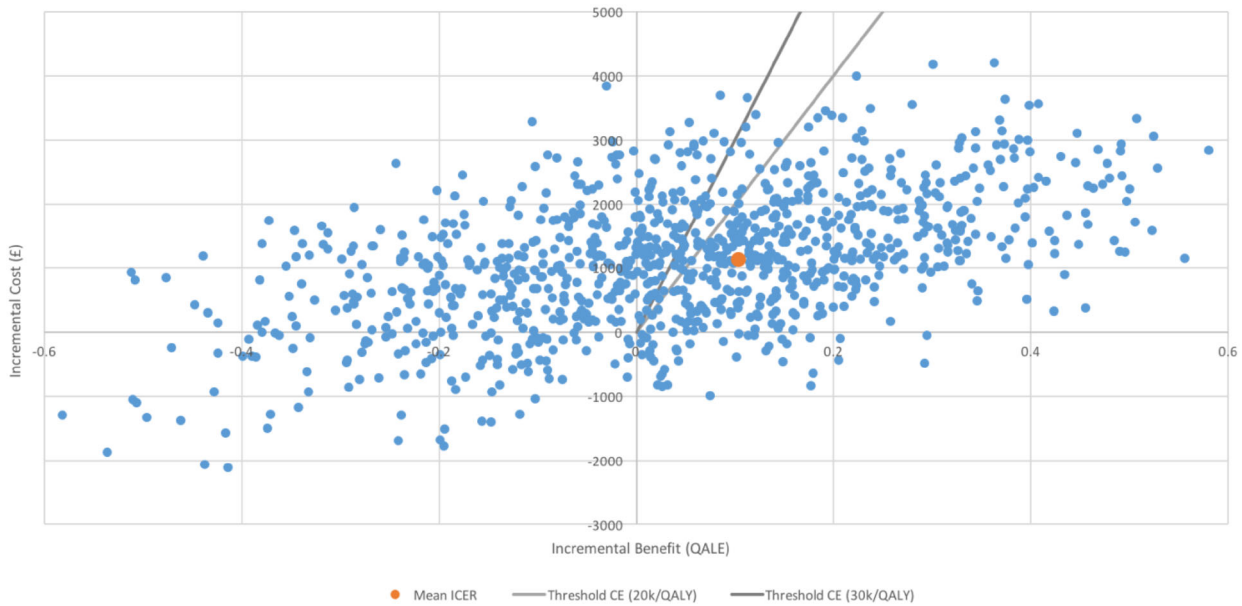


**Fig. 2** Incremental cost-effectiveness ratio scatterplot (SU vs alogliptin 12.5 mg)

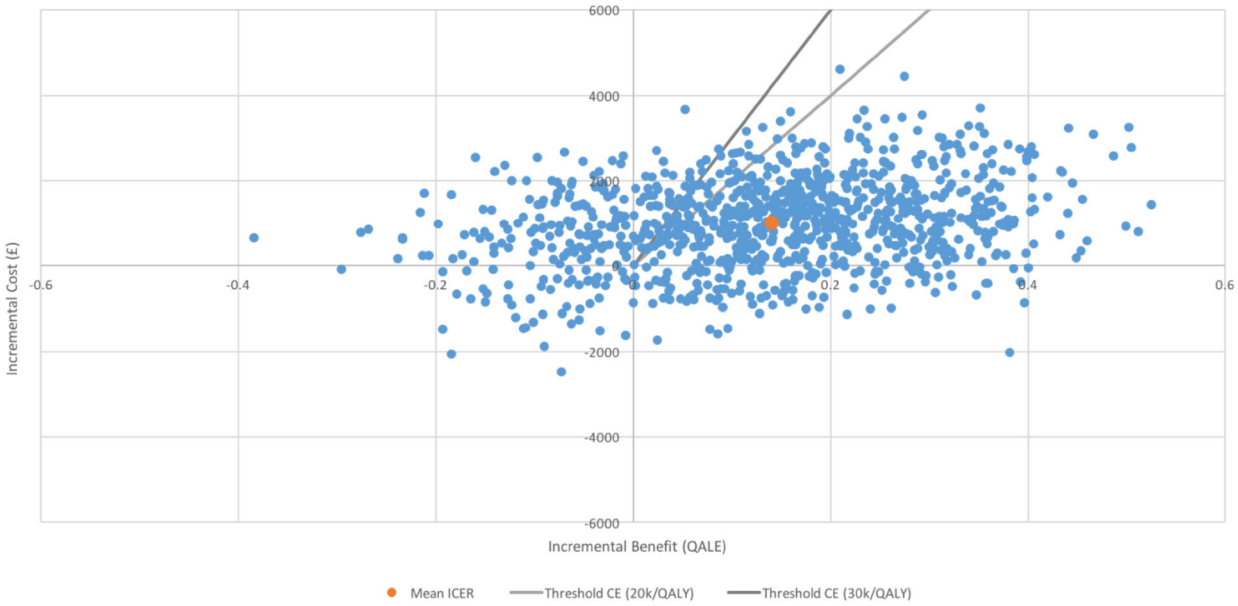


**Fig. 3** Incremental cost-effectiveness ratio scatterplot (SU vs alogliptin 25 mg)

compared to 12-month profiles (12 and 24 months for HbA1c), to evaluate the cost-effectiveness of each treatment allocation.

Treatment with SU was estimated to incur higher total costs (£2194) but gains in QALYs (0.211) and life expectancy (0.291 years) as an add-on to metformin. The higher total costs were driven by an increase in drug acquisition costs, but partly offset by a corresponding decrease in complication costs from fewer predicted events. The largest cost components in the analysis were attributable to the incidence of ulcer, amputation, and neuropathy. The addition of an SU to metformin was associated with an ICER of £10,398/QALY (Table 6).

Treatment with alogliptin 12.5 mg was estimated to incur additional total costs (£3325) but gains in QALYs (0.315) and life expectancy (0.336 years). The additional total costs were driven by increased drug acquisition costs, which were partly offset by a reduction in complication costs from fewer predicted events. The largest cost offsets in the analysis were attributable to CVD and renal disease, and the incidence of ulcer amputation and neuropathy. The addition of alogliptin 12.5 mg to metformin was associated with an ICER of £10,556/QALY (Table 6).

Treatment with alogliptin 25 mg was estimated to incur additional total costs (£3206) but gains in QALYs (0.352) and life expectancy (0.372 years). The additional total costs were driven by increased drug acquisition costs, which were partly offset by a reduction in complication costs from fewer predicted events. The largest cost offsets in the analysis were attributable to CVD and renal disease, and the incidence of ulcer amputation and neuropathy. The addition of alogliptin 25 mg to metformin was associated with an ICER of £9108/QALY (Table 6).

### *ScA-2*

A subgroup economic evaluation was undertaken of the base case population (between-arm comparison of SU and

**Table 5** Deterministic sensitivity analysis results (SU vs alogliptin 12.5 mg and 25 mg)

| Strategy vs MET + SU | Incremental cost (£) | Incremental benefit (QALY) | Incremental cost-effectiveness (£/QALY) |
|---|---|---|---|
| MET + $ALO_{12.5\ mg}$ | | | |
| Base case | 1131 | 0.103 | 10,959 |
| 10-year horizon | 1297 | 0.054 | 24,143 |
| 20-year horizon | 1109 | 0.082 | 13,571 |
| Costs −20% | 1184 | 0.103 | 11,477 |
| Utilities −20% | 1131 | 0.094 | 11,993 |
| Costs +20% | 1078 | 0.103 | 10,441 |
| Utilities +20% | 1131 | 0.112 | 10,098 |
| Discount rate 0% | 1121 | 0.162 | 6932 |
| Discount rate 7% | 1074 | 0.072 | 14,961 |
| Duration switch 5 years | 1008 | 0.082 | 12,252 |
| MET + $ALO_{25\ mg}$ | | | |
| Base case | 1012 | 0.140 | 7217 |
| 10-year horizon | 1201 | 0.063 | 19,056 |
| 20-year horizon | 1000 | 0.109 | 9200 |
| Costs −20% | 1093 | 0.140 | 7799 |
| Utilities −20% | 1012 | 0.125 | 8101 |
| Costs +20% | 930 | 0.140 | 6635 |
| Utilities +20% | 1012 | 0.155 | 6515 |
| Discount rate 0% | 1022 | 0.242 | 4225 |
| Discount rate 7% | 978 | 0.091 | 10,721 |
| Duration switch 5 years | 877 | 0.120 | 7306 |

alogliptin), to assess the cost-effectiveness profile of subjects who maintained a level of HbA1c at 2 years (104 weeks) of less than 7.5%. Results of this scenario analysis were similar to the base case analysis in terms of absolute costs and health benefits, with ICERs (probability of cost-effectiveness at £30,000/QALY) of £13,326/QALY (61.0%) and £6771/QALY (72.4%) for the comparison of SU and alogliptin 12.5 mg and 25 mg, respectively (Table 7).

## DISCUSSION

As a result of both the incidence and increasing prevalence of T2DM in the UK, the consequences of suboptimal glycemic control impose a considerable economic burden on patients and the NHS. These costs are further exacerbated when current treatment strategies lack the glycemic durability required to manage the progressive nature of the condition. When

**Table 6** Intragroup economic analysis of SU, alogliptin 12.5 mg, and alogliptin 25 mg as a second-line antidiabetic therapy

| | MET + SU | | MET + $ALO_{12.5}$ | | MET + $ALO_{25}$ | |
|---|---|---|---|---|---|---|
| | Baseline | Month 12 | Baseline | Month 12 | Baseline | Month 12 |
| Absolute results (discounted) | | | | | | |
| Total cost (£) | 25,641 | 27,835 | 25,641 | 28,966 | 25,641 | 28,847 |
| Total LE | 14.542 | 14.833 | 14.542 | 14.878 | 14.542 | 14.914 |
| Total QALY | 9.509 | 9.720 | 9.509 | 9.824 | 9.509 | 9.861 |
| Incremental cost | | 2194 | | 3325 | | 3206 |
| Incremental LE | | 0.291 | | 0.336 | | 0.372 |
| Incremental QALY | | 0.211 | | 0.315 | | 0.352 |
| ICER (cost/LE) | | 7540 | | 9896 | | 8618 |
| ICER (cost/QALY) | | 10,398 | | 10,556 | | 9108 |

*LE* life expectancy, *QALY* quality-adjusted life year, *ICER* incremental cost-effectiveness ratio

**Table 7** Economic analysis of SU, alogliptin 12.5 mg, and alogliptin 25 mg for HbA1c control (<7.5%) subpopulation

| | MET + SU | MET + $ALO_{12.5}$ | MET + $ALO_{25}$ |
|---|---|---|---|
| Absolute results (discounted) | | | |
| Total cost (£) | 28,688 | 29,565 | 29,435 |
| Total LE | 14.641 | 14.663 | 14.708 |
| Total QALY | 9.603 | 9.688 | 9.713 |
| Between groups analysis (MET + SU vs MET + $ALO_{12.5/25}$) | | | |
| Incremental cost | | 877 | 746 |
| Incremental LE | | 0.022 | 0.068 |
| Incremental QALY | | 0.066 | 0.110 |
| ICER (cost/LE) | | 39,856 | 11,039 |
| ICER (cost/QALY) | | 13,326 | 6771 |
| CE? (£30,000 ICER) | | 61.0 | 72.4 |

*LE* life expectancy, *QALY* quality-adjusted life year, *ICER* incremental cost-effectiveness ratio, *CE?* probability of cost-effectiveness

compared to standard second-line SU therapy, the ENDURE trial showed that DPP-4 inhibition by alogliptin elicited sustained antihyperglycemic effects, without weight gain and hypoglycemia, in T2DM patients who had failed first-line metformin monotherapy [11, 12].

The present economic analysis of ENDURE aimed to quantify the relationship between improved glycemic durability and

cost-effectiveness of alogliptin in the UK clinical setting. This study estimated that in patients inadequately managed on metformin monotherapy, the addition of alogliptin (12.5 and 25 mg) was associated with improvements in length and quality of life and was cost-effective at established norms. Compared with baseline profiles of suboptimal management on metformin monotherapy (intragroup analysis), combination therapies with alogliptin or SU were associated with improvements in length and quality of life and were cost-effective at established norms. However, the increased glycemic durability associated with alogliptin translated to larger health (QALY) gains predicted across analyses compared with SU.

Improvements in glycemic control and durability of antihyperglycemic effects observed in ENDURE subjects translates to favorable cost-effectiveness profiles for alogliptin compared with SU, as add-on therapies to metformin when analyzed with an established diabetes model. These cost-effectiveness conclusions were robust across a number of scenarios, including intragroup analyses that confirmed the cost-effectiveness of the addition of SU and alogliptin in analyses where patients within each study arm formed their own control group. In patients who had HbA1c levels less than 7.5% after 2 years, alogliptin was estimated to be cost-effective compared with SU at established norms. In deterministic and probabilistic sensitivity analyses where the joint uncertainty in parameter values was evaluated in terms of its impact on estimates of cost-effectiveness, base case cost-effectiveness conclusions were shown to be robust. In comparison with SU, the probability that combination therapy with alogliptin (12.5 and 25 mg) was cost-effective was 67.6% and 77.1% at a willingness to pay threshold of £30,000 per QALY gained, respectively.

This economic evaluation of ENDURE provides further evidence supporting the cost-effectiveness of DPP-4 inhibitors as a second-line therapy for T2DM [20]. Previous analyses have indicated that, in T2DM patients who were no longer responsive to first-line metformin monotherapy, the addition of DPP-4 inhibitors was cost-effective compared to add-on SU [21–25], thiazolidinediones [25, 26], and insulin [27, 28]. The DPP-4 inhibitors investigated in these studies were either sitagliptin or saxagliptin; however, a pharmacoeconomic analysis of antidiabetic therapies in the Japanese clinical setting found that alogliptin was a more cost-effective DPP-4 inhibitor than sitagliptin [29]. The ENDURE trial and its subsequent cost-effectiveness analysis suggest that the improved efficacy of second-line alogliptin therapy translated to improved cost-effectiveness compared to SU in patients with uncontrolled T2DM.

There are several strengths and limitations associated with this study. A UK perspective was adopted for costs and cost-effectiveness settings (e.g., discount rates), which may affect whether these findings are relatable to other country settings. However, the input profiles and treatment effects from ENDURE were based on subjects from North and South America, Europe, Asia, South Africa, Australia, and New Zealand [11] and are reported transparently such that country-specific settings for costs and utilities could be used to replicate this analysis to inform country-specific decision-making. Computer modelling in diabetes is an established and accepted paradigm, and is used to extrapolate beyond the trial follow-up period to obtain best estimates of downstream clinical and economic outcomes associated with individual

treatments. Nonetheless, a computer simulation model was used to evaluate how changes in subjects' short-term surrogate outcomes (risk factor profiles) translated to incidence of diabetes-related complications and mortality over a lifetime perspective. Given the lifetime nature of the analysis, assumptions regarding patient treatment escalation were made such that patients escalated (or intensified) to rescue therapy once their HbA1c value (following initial treatment-related change) returned to its starting (or baseline) HbA1c. This is a realistic assumption that may reflect treatment intensification practice in the clinical setting. In the base case analysis, the SU and alogliptin arms intensified to metformin and NPH insulin after 7–9 years across analyses; in the modelled lifetime analysis, discounted average life expectancy was approximately 14–15 years. Therefore, the comparison of alogliptin and SU contains the effects of therapy intensification for the period of the modelled time horizon, which should be acknowledged when interpreting the results. However, as the therapy intensification profile was applied equally to each arm, any incremental differences associated with therapy escalations should pertain to different times to escalation which were not substantially different.

## CONCLUSION

The use of SU as a second-line indication for uncontrolled T2DM is associated with weight gain and hypoglycemic events [7], the risks of which are further increased when doses are escalated to combat progressive treatment failure [6]. In comparison, the ENDURE trial showed that alogliptin, in combination with metformin, was associated with improved glycemic durability, without weight gain and hypoglycemia, over 2 years [11, 12]. With base case estimated ICERs of £10,959/QALY and £7217/QALY, evaluated against commonly used cost-effectiveness threshold values, this study demonstrated that alogliptin represents a cost-effective treatment alternative to SU as add-on therapy to metformin in patients with poorly managed T2DM. Cost-effectiveness conclusions were robust across a number of evaluated scenarios and in sensitivity analyses.

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***Compliance with Ethics Guidelines.*** This article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

***Data Availability.*** The datasets analyzed during the current study were sourced from and are available in the original trial publication [11].

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