Slides for public observers-contains no ACIC

NICE National Institute for Health and Care Excellence

Ertugliflozin in triple therapy for treating type 2 diabetes

Lead Team presentation

1st appraisal committee meeting
Clinical effectiveness
Committee A
Lead team: Graham Ash and Olivia Wu
ERG:University of Warwick Medical School
NICE technical team: Sana Khan, Zoe Charles
Company: MSD
8 January 2019

Definition of terms

Sodium–glucose co-transporter 2 inhibitors (SGLT-2 inhibitors)	
Ertugliflozin (ERTU)	**Referred to collectively hereafter as ‘flozins’**
Canagliflozin (CANA)	
Dapagliflozin (DAPA)	
Empagliflozin (EMPA)	
Dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors)	
Such as sitagliptin, saxagliptin and linagliptin	**Referred to collectively hereafter as ‘gliptins’**

Key issues

- The company's submission focusses on a triple therapy regimen of a flozin with metformin and a gliptin because ertugliflozin (ERTU) has been studied in this combination
  - the combination of a flozin with metformin and a gliptin has not been considered or approved previously by NICE
  - the company believes that this regimen is sufficiently used in the UK for it to be regarded as standard therapy, and therefore no other triple therapy regimens are included as comparators
  - does the committee accept the company's approach?
- The key clinical trial data come from VERTIS SITA 2. Is the committee satisfied with the evidence for the efficacy and safety of ERTU compared with placebo?

[redacted]

Background

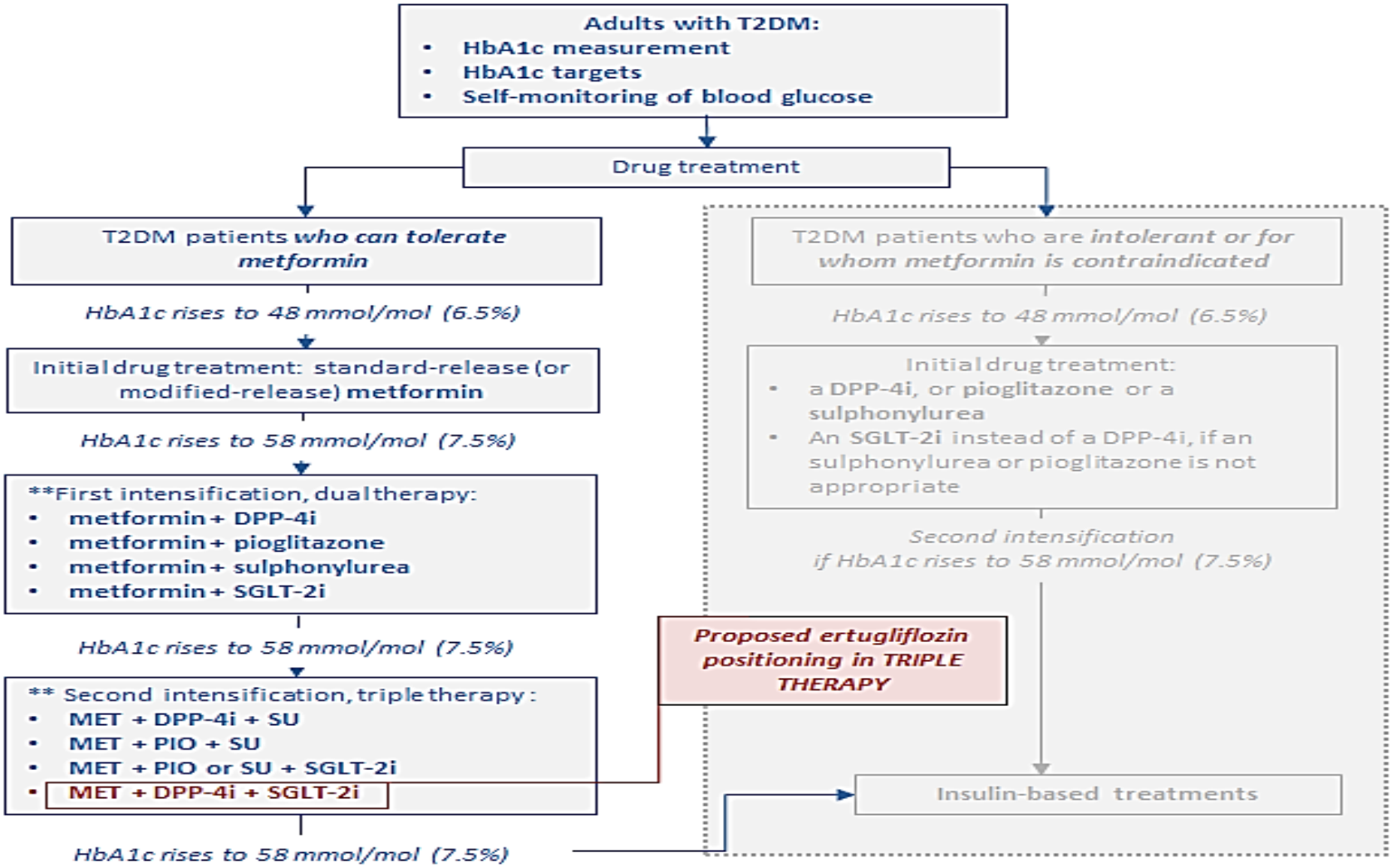
- Type 2 diabetes mellitus is a chronic metabolic disorder characterised by elevated blood glucose levels (hyperglycaemia) resulting from reduced secretion of the hormone insulin or reduced tissue sensitivity to insulin (known as insulin resistance)
- If not managed effectively, type 2 diabetes can lead to kidney failure, blindness, limb amputation, hypertension, damage to the nervous system, peripheral vasculature and skin. Cardiovascular disease is the most common complication and is the greatest cause of morbidity and premature death
  - life expectancy is reduced by up to 10 years in people with diabetes
- There are over 3 million people aged 17 and over in England with type 2 diabetes, however many people are undiagnosed so this may be conservative
- Prevalence is rising because of increased prevalence of obesity, low physical activity and higher life expectancy after diagnosis because of better cardiovascular risk protection
  - particularly prevalent in people of African, South Asian and Caribbean family origin

Details of the technology

Technology	Ertugliflozin (Steglatro, MSD)
Marketing authorisation	Adults aged 18 years and older with type 2 diabetes to improve glycaemic control: • as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications; • in addition to other medicinal products for the treatment of diabetes **This STA covers the triple therapy indication only. Monotherapy and dual therapy indications to be appraised in subsequent FTA**
Mechanism of action	Sodium–glucose co-transporter 2 inhibitor (SGLT2i): Reduces conservation of glucose by kidneys, leading to loss of glucose in urine
Administration & dosage	5 mg once daily for monotherapy, increasing to 15 mg once daily if additional glycaemic control is needed. In combination therapy, dosage should be individualised using the recommended daily dose of 5 mg or 15 mg
List price and average cost of treatment	Ertugliflozin (Steglatro®) 5 mg * 28 tablets: £[redacted] per pack Ertugliflozin (Steglatro®) 15 mg * 28 tablets: £[redacted] per pack

Treatment Pathway for type 2 diabetes

Current clinical pathway (NG28) and proposed positioning of ertugliflozin (ERTU) combination therapy with metformin and a gliptin



Abbreviations: T2DM, type 2 diabetes mellitus; HbA1c, haemoglobin A1c; MET, metformin; DPP4-I (gliptin), dipeptidyl peptidase 4 inhibitor; SGLT-2i (flozin), sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea; PIO, pioglitazone

Current management of type 2 diabetes

- NICE guideline (NG) 28 ‘Type 2 diabetes in adults: management’ recommends reinforcing advice on diet, lifestyle and adherence to drug treatment
- If there is still inadequate glycaemic control, NG28 recommends several options as monotherapy. Following this initial therapy, if there is still inadequate glycaemic control, dual therapy is recommended
- This appraisal focuses on **triple therapy options** if there is inadequate glycaemic control following dual therapy
  - NG28 recommends triple therapy (metformin plus a sulfonylurea plus either a gliptin or pioglitazone), or insulin based treatment
  - TAs 315, 336 and 418 recommend the flozins CANA, EMPA and DAPA either with metformin plus a sulphonylurea or metformin plus pioglitazone. The flozins are also recommended with insulin, with or without other antidiabetic drugs

[redacted]

Decision problem

	NICE scope	Company submission	Rationale if different from scope
Population	Adults with type 2 diabetes that is inadequately controlled on combination therapy with anti-diabetic agents	As per scope	
Intervention	ERTU in triple therapy	As per scope	
Comparator	• Sulfonylureas • DPP-4is • Pioglitazone • SGLT-2is • GLP-1 mimetics • Insulin	SGLT-2is (flozins)	Evidence base for ERTU in triple therapy is with metformin + a gliptin only. The company believes the only relevant comparators are other flozins used in a triple therapy regimen with the same background therapies
Outcomes	• Mortality • Complications of diabetes • HbA1c/glycaemic control • Changes in cardiovascular risk factors • Adverse events • Health-related quality of life	As per scope	
Economic analysis	Cost-utility analysis	Cost-minimisation analysis	An indirect comparison showed similar efficacy and safety of all flozins. Company considered cost-minimisation analysis the most appropriate form of economic evaluation

Anti-hyperglycaemic agents used in triple therapy in the UK (moving annual total)

- Company reports that flozins are only used in triple therapy as add on to metformin with a sulfonylurea/gliptin, based on data from a panel of 150 general practices (800 GPs) in the UK
- The metformin + gliptin+ flozin combination already accounts for [redacted] of triple therapy (equating to about 1.2 million people in the UK)
- Based on this, the company's proposed positioning of ERTU in triple therapy is with metformin and a gliptin compared with other flozins with the same background therapy

Triple therapy	Moving annual total 2017	
	patients	%
MET + SU + PIO	23,806	7.8
MET + SU + gliptin	138,287	45.1
MET + SU + GLP-1	21,172	6.9
MET + SU + flozin	45,792	15.0
MET + gliptin + PIO	10,059	3.3
MET + gliptin + GLP-1	1,724	0.5
MET + gliptin + flozin	34,775	[redacted]
Other	30,656	10.0
Total	306,271	100

Abbreviations:
SU: sulphonylureas
MET: metformin
PIO: thiazolidinedione
GLP-1: glucagon-like peptide-1
Gliptin: DPP-4 inhibitor
Flozin: SGLT-2 inhibitor

[redacted]

Clinical expert comments

- Aim of treatment is to maintain control of blood glucose levels so that glycated haemoglobin (HbA1c) is 53 mmol/mol or less. Treatment should reduce the incidence and progression of complications of diabetes and minimise adverse events
- Pathway of care well defined in the NHS and based on NG28 – the treatment options after metformin, and before insulin is required, can vary depending on the clinical condition of the patient and co-morbidities
  - NG28 does not reflect new cardiovascular outcome data with flozins that has led to changes in most other international guidelines that support use of flozins in patients with pre-existing CV disease
- ERTU in triple therapy is likely to add another option to the flozins currently available in the NHS and is likely to work in the same way as other flozins
- Flozins can be more effective in people with type 2 diabetes who have normal kidney function but elevated Hba1c and are overweight or obese
- Treatment is likely to be less effective in people with renal impairment and stopped when estimated glomerular filtration rate (eGFR) falls below 30 mls/min. As eGFR is routinely monitored in patients with diabetes, additional monitoring is unlikely to be required
- Adverse effects are polyuria and UTIs / genital infections. These are unpleasant but not usually severe. Rare events such as diabetic ketoacidosis not reported in trials for ERTU and CV outcomes not yet available
- Emerging data also suggest flozins have a protective effect on kidney function

[redacted]

Company's clinical evidence: VERTIS SITA 2

Design	Randomised, double-blind, placebo-controlled, phase III study: Part A: 26–week, double-blind, placebo–controlled treatment period Part B: 26-week active placebo extension treatment period
Population (Part A only) (n=462)	Adults with type 2 diabetes who have inadequate glycaemic control (HbA1c 7.0-10.5% [53-91 mmol/mol]) on metformin at a dose ≥1500 mg/day and on sitagliptin at a dose of 100 mg/day
Intervention	ERTU 5 mg (n=156) ERTU 15 mg (n=153)
Comparator	Placebo (n=153)
Location	104 international study sites in 12 countries from Europe, North America and selected other countries. No UK sites or patients included in the trial
Primary outcome	• Change in HbA1c from baseline to week 26
Other outcomes	• Change in fasting plasma glucose, body weight and blood pressure • Proportion of patients with HbA1c <7.0% • Proportion receiving glycaemic rescue therapy • Adverse events • Health related quality of life
Duration of study	52 weeks

[redacted]

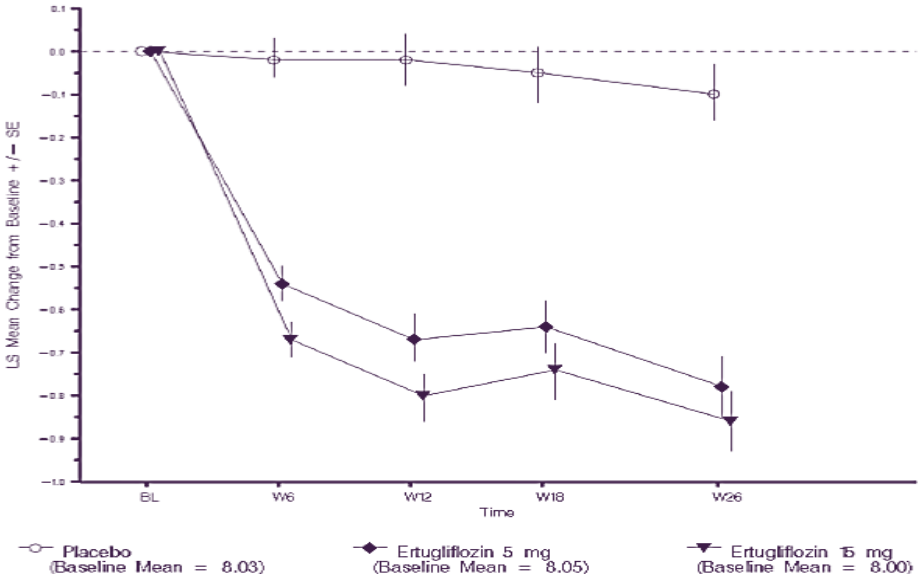
Baseline characteristics in VERTIS SITA 2

VERTIS SITA 2	PBO	ERTU 5 mg	ERTU 15 mg	TOTAL
n	153	156	153	462
Age, mean (SD) years	58.3 (9.2)	59.2 (9.3)	59.7 (8.6)	59.1 (9.0)
Sex, %	Male: 65.4 Female: 34.6	Male: 51.9 Female: 48.1	Male: 53.6 Female: 46.4	Male: 56.9 Female: 43.1
Body weight (kg), mean (SD)	86.4 (20.8)	87.6 (18.6)	86.6 (19.5)	86.9 (19.6)
BMI, mean (SD) kg/m^2	30.3 (6.40)	31.2 (5.5)	30.9 (6.1)	30.8 (6.0)
Disease duration (years), mean (SD)	9.44 (5.55)	9.88 (6.13)	9.20 (5.32)	9.51 (5.68)

Abbreviations: BMI, body mass index; kg, kilogram; PBO; placebo, SD, standard deviation

Clinical effectiveness results (1)

<u>Primary efficacy outcome</u>: HbA1c change from baseline to week 26 - Least Squares mean change (constrained longitudinal data analysis [cLDA] using full analysis set [FAS] population



Treatment	Differences in LS means vs. PBO at W26 (95% CI; p-value)
ERTU 5 mg	-0.69 (-0.87, -0.50);<0.001
ERTU 15 mg	-0.76 (-0.95, -0.58); <0.001)

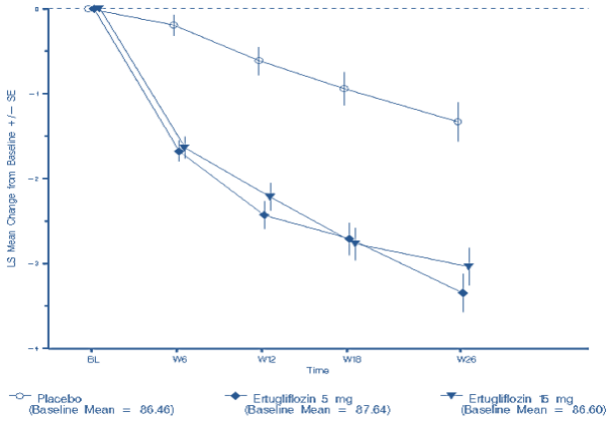
<u>Secondary efficacy outcome</u>: Analysis of patients with HbA1c <7% (<53 mmol/mol) at week 26 – Logistic regression using multiple imputations (FAS)

Treatment	n	Number (%) with HbA1c <7.0% at W26	Adjusted Odds Ratio (OR) relative to PBO 95%% CI; p-value)
PBO	153	26 (17.0)	-
ERTU 5 mg	156	50 (32.1)	3.16 (1.74, 5.72; <0.001)
ERTU 15 mg	153	61 (39.9)	4.43 (2.44, 8.02; <0.001)

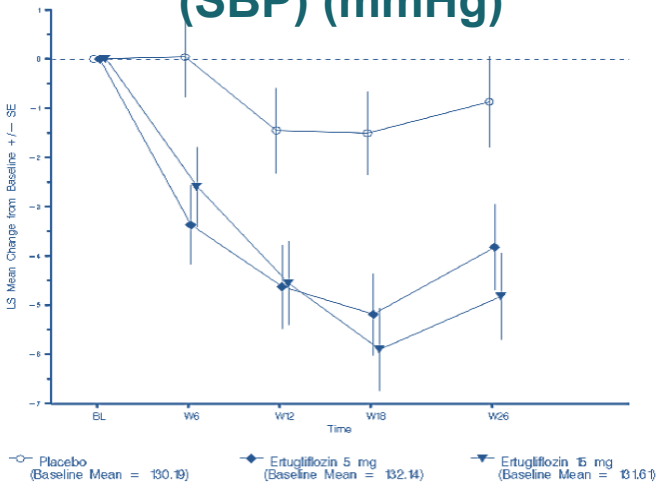
Clinical effectiveness results (2)

Other continuous efficacy outcomes – change from baseline at week 26 - Least Squares mean change (cLDA, FAS)

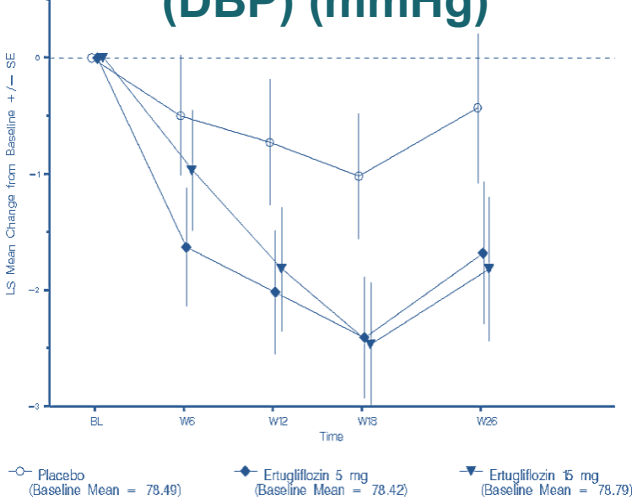
Body Weight (kg)



Systolic blood pressure (SBP) (mmHg)



Diastolic blood pressure (DBP) (mmHg)



Outcome	Differences in LS means vs. PBO at wk 26 (95% CI; p-Value)	
	ERTU 5 mg	ERTU 15 mg
Body Weight (kg)	-2.03 (-2.65, -1.40); <0.001	-1.72 (-2.35, -1.09) ; <0.001
SBP (mmHg)	-2.93 (-5.36, -0.49); 0.019	-3.94 (-6.39, -1.50); 0.002
DBP (mmHg)	-1.24 (-2.97, 0.48); 0.157	-1.38 (-3.11, 0.36); 0.119

Abbreviations: cLDA, constrained longitudinal data analysis; LS, least squares; SE, standard error; W= week; FAS, full analysis set

[redacted]

Adverse events (AEs)

VERTIS SITA 2	PBO N = 153	ERTU5 N = 156	ERTU15 N = 153
Overall Safety (excluding rescue and including rescue)[a], n (%)			
AEs related to study drug [b]	13 (8.5)	17 (10.9)	22 (14.4)
SAE related to study drug [b]	0 (0)	0 (0)	1 (0.7)
Genital mycotic infection (women)	1 (1.9)	6 (8.0)	**9 (12.7)***
Genital mycotic infection (men)	0 (0)	**4 (4.9)***	3 (3.7)
Urinary tract infection	3 (2.0)	4 (2.6)	7 (4.6)

* p< 0.05 versus placebo

[a] week 26 safety analyses, data following initiation of glycaemic rescue were excluded from incidence of 'one or more AEs' and from 'AEs related to study drug'

[b] investigator assessed

Abbreviations: PBO, placebo; AE, adverse event; SAE, serious adverse event

ERG critique: VERTIS SITA 2

- Good quality trial showing that ERTU is effective in improving glycaemic control vs placebo
- Key issue is that the triple therapy regimen of a flozin with metformin + gliptin has not been considered previously by NICE (only flozin with metformin + sulfonylurea/pioglitazone)
  - ERG considers it reasonable to extrapolate from clinical equivalence shown in trials of triple therapy with metformin + gliptin, to triple therapy with metformin and either sulfonylurea/pioglitazone
- The company used the full analysis set (FAS) population (defined as patients who received at least one dose of study treatment and who had at least one measurement of the outcome. This could result in unhealthier patients being underrepresented in the FAS population
  - ERG noted there were no major imbalances of baseline characteristics across the arms of VERTIS SITA 2 in the FAS population
- VERTIS FACTORIAL trial not included by the company its submission provides further evidence on the effectiveness of ERTU in triple therapy. Results were comparable to VERTIS-SITA 2 results at 26 and 52 weeks

[redacted]

Key issues

- The company's submission focusses on a triple therapy regimen of a flozin with metformin and a gliptin because ertugliflozin (ERTU) has been studied in this combination
  - the combination of a flozin with metformin and a gliptin has not been considered or approved previously by NICE
  - the company believes that this regimen is sufficiently used in the UK for it to be regarded as standard therapy, and therefore no other triple therapy regimens are included as comparators
  - does the committee accept the company's approach?
- The key clinical trial data come from VERTIS SITA 2. Is the committee satisfied with the evidence for the efficacy and safety of ERTU compared with placebo?

[redacted]