

Dapagliflozin, in combination with insulin, for
treating type 1 diabetes

Chair's presentation

2nd appraisal committee B meeting

1st appraisal committee B meeting (26th March 2019)

Chair: Amanda Adler

Lead team: Nicholas Latimer, Nigel Westwood, Sarah Wild

ERG: Warwick Evidence

NICE technical team: Sharlene Ting, Ross Dent, Nicole Elliott

Company: AstraZeneca

30th May 2019

Appraisal consultation document: preliminary recommendation

‘...not to recommend dapagliflozin with insulin as an option for treating type 1 diabetes in adults with a body mass index (BMI) of at least 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.’

Key issues

- Trials shows no increase in length of life and small increase in quality of life – model results show that dapagliflozin increases both length and quality of life
- Does the company's scenario restricting benefit from lowering HbA1c to the duration of the trial address uncertainties about extrapolating benefit into future?
- Which of the treatment waning scenarios modelled by the company are most appropriate?
- Which of the company's scenarios modelling stopping treatment are most appropriate?
- Is dapagliflozin innovative? Are there any benefits not captured in the QALY calculation?

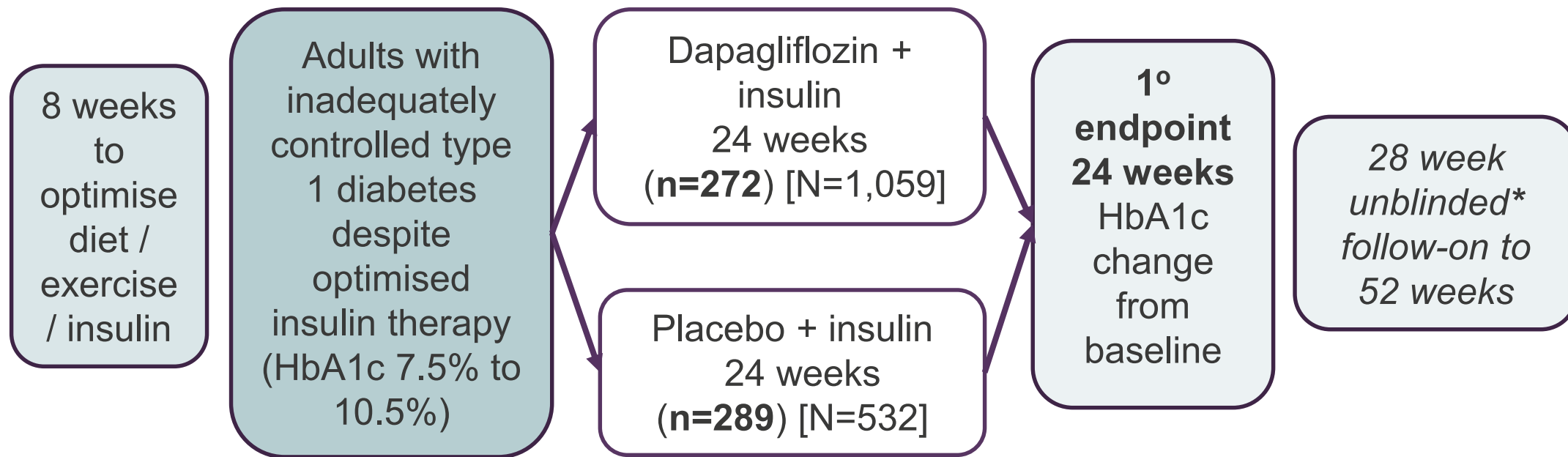
Recap 1st committee meeting and committee's conclusions

Background

- **Type 1 diabetes**
 - Autoimmune → characterised by hyperglycaemia → measured with HbA1c which drives risk of complications
 - Complications decrease quality of life and can increase risk of death
 - In England, 70% have high HbA1c
- **Dapagliflozin – 5 mg once daily orally**
 - Prevents glucose reabsorption in kidneys
- **Marketing authorisation:** “type 1 diabetes mellitus as an adjunct to insulin in patients with body mass index (BMI) ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy”
 - BMI cut-off reflects concern about diabetic ketoacidosis
 - Not recommended in patients with low insulin needs defined by clinicians in 1st meeting as <0.5 units per kg body weight
 - Patients should be able and committed to control blood ketones – see later slide

Clinical evidence: DEPICT-1 + DEPICT-2

Double-blind, randomised, placebo-controlled



*“Indicated” population (n):
BMI ≥27kg/m²*

Key 2° endpoints:

- % with fall in HbA1c ≥0.5% without severe hypoglycaemia
- % change in body weight
- change in mean 24-hour blood glucose
- change in % of blood glucose readings outside range
- % change in total daily insulin

Exploratory endpoints: EQ-5D-3L, Diabetes Treatment Satisfaction Questionnaire

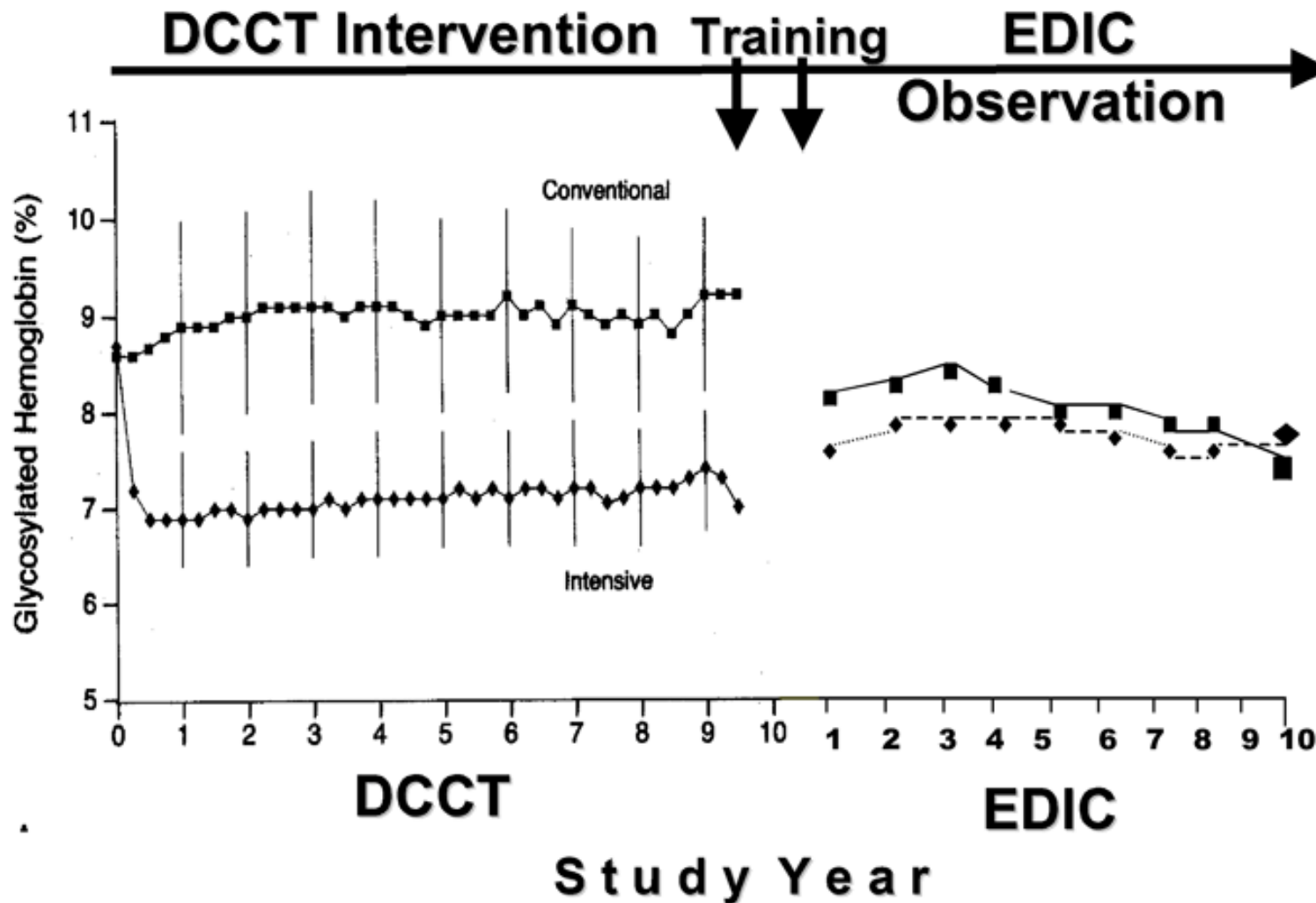
*HbA1c values unmasked

Trial evidence underlying modelling

Diabetes Control and Complications Trial (DCCT)

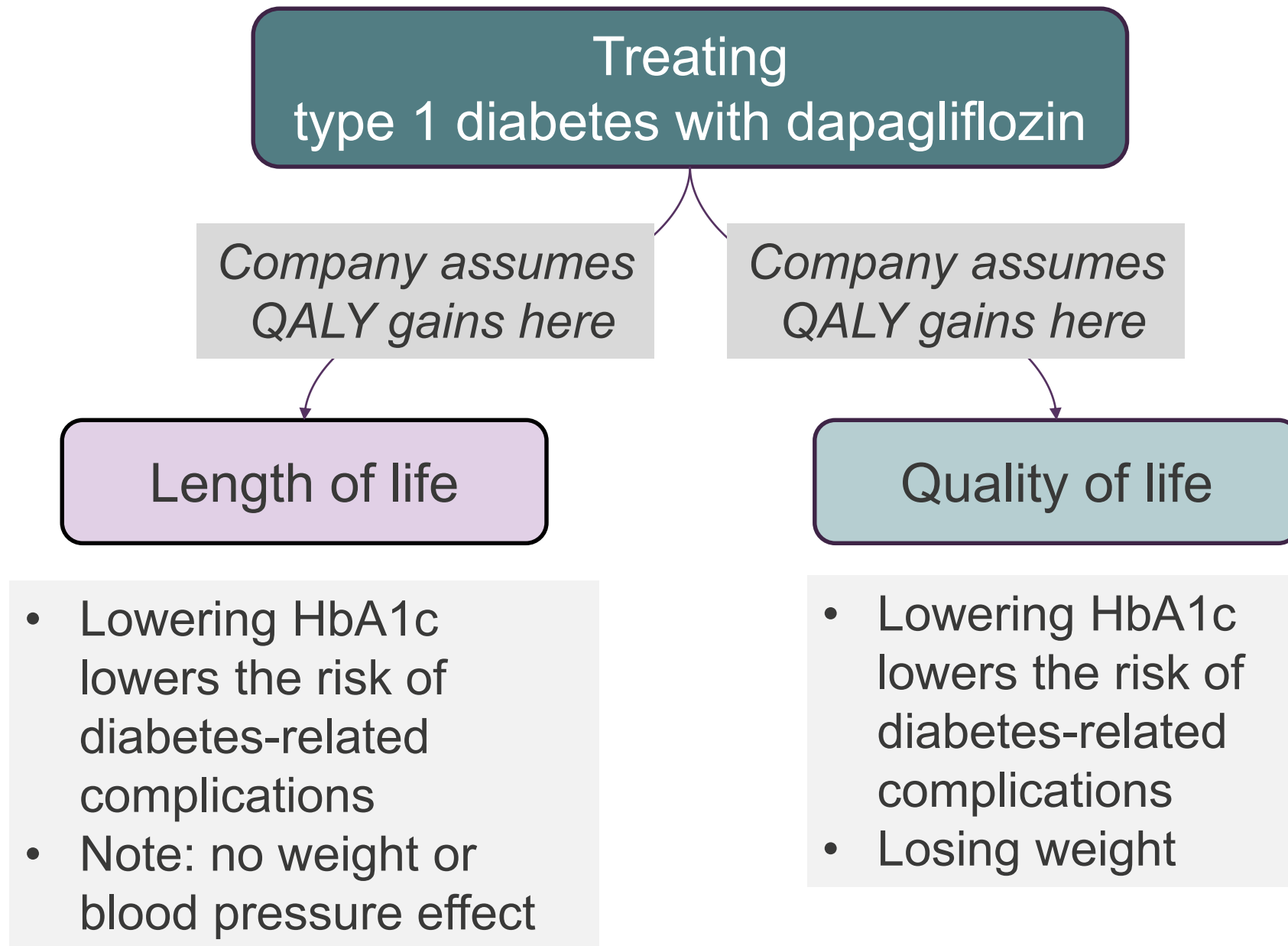
Epidemiology of Diabetes Interventions and Complications (EDIC)

Metabolic Results



Randomisation to intensive compared with conventional glycaemic control associated with decreased risk of complications

Where do gains come from in company's model?



Company's base case, committee conclusions

Population

subgroup of DEPICT 1+2, BMI $\geq 27\text{kg/m}^2$:

- Low insulin needs not defined in marketing authorisation (suggest <0.5 units/kg)
- Does not reflect NHS patients (where fewer use insulin pump, more smoke and baseline risk of DKA higher)

Dapagliflozin + insulin

Placebo + insulin

1° outcome

ΔHbA1c baseline to 24 weeks:

- Reduction modest at 0.44%
- Unclear whether sustained and clinically meaningful over lifetime (0.34% at 52 weeks)

52 week data: uncertainty using DCCT/EDIC to extrapolate DEPICT results (larger effect, longer duration)

Lifetime risk of complications: increased length of life & quality of life

Company's Cardiff type 1 diabetes model

- Simulates disease progression using risk equations over life-time
 - links HbA1c from trials with diabetic complications
- Company chose risk equations from DCCT/EDIC for microvascular complications and Swedish National Diabetes Registry for macrovascular complications
- Patient cohort enters model with baseline characteristics (some modifiable) from dapagliflozin trials → risk factors change over time affecting modelled incidence of complications
- Company assumed no progressive increase in values for risk factors (for example, HbA1c and body weight) based on clinical advice
- Model includes increased risk of DKA with dapagliflozin

Committee requested from company (1)

Issue	Committee requested	Company provided?
Face validity model output: greater length and quality of life (ACD 3.11, 3.13, 3.14)	<ul style="list-style-type: none"> • Risk equations, their sources, their impact on diabetic complications in model • Scenario analysis varying risk equation for macrovascular disease 	Yes
Extrapolating benefits from DEPICT using DCCT/EDIC equations – larger drop in HbA1c for longer (ACD 3.13, 3.14)	Scenario analyses varying benefit of HbA1c in DEPICT including: <ul style="list-style-type: none"> • not proportional to DCCT/EDIC • no immediate benefit • no benefit after 52 week trial period 	Partially
Generalisability (ACD 3.3, 3.15)	Population in model should reflect people in England with type 1 diabetes likely to have dapagliflozin (including insulin dose)	Yes
Natural history of disease (ACD 3.16)	Model progressive increase in HbA1c and weight over time	Yes

Committee requested from company (2)

Issue	Committee requested	Company provided?
Dapagliflozin: waning of effect (ACD 3.17)	Scenario analyses including waning in model: <ul style="list-style-type: none"> • rate informed by other trials • same rate as in DEPICT between 24 and 52 weeks • treatment effect stops at 52 weeks 	Yes
Stopping for lack of benefit (ACD 3.18)	Scenario analyses using a range of HbA1c at different timepoints	Yes
Annual rate stopping for any reason (ACD 3.19)	<ul style="list-style-type: none"> • Dapagliflozin: stopping rate for any reason in year 1; lower rate in subsequent years • Standard of care: no stopping treatment 	Yes
Adverse events (ACD 3.20)	Include disutility and risk of death from Fournier's gangrene, severe hypoglycaemia and diabetic ketoacidosis	Yes

Committee requested from company (3)

Issue	Committee requested	Company provided?
Utility values (ACD 3.21, 3.22)	<ul style="list-style-type: none">• Use most robust literature source (can be from different sources)• Use both additive and multiplicative approaches for disutilities• Scenario analyses including EQ-5D from DEPICT, using disutilities with face validity for amputation	Yes
Costs (ACD 3.23)	Analyses include additional: ketone + blood glucose testing, and visits to diabetes clinic	Yes

Consultation on Appraisal Consultation Document (ACD)

Responses

Consultee comments from:

- AstraZeneca (Company)
 - **new evidence, revised model**
- Association of British Clinical Diabetologists

Web comments from:

- 2 clinical experts present at 1st meeting

Order of points from consultation

1. Population in model – trial or NHS?
2. Clinical benefit seen in trials modelled over a lifetime
 - a) relationship between HbA1c and complications
 - b) source of risk equations in model
3. Diabetic ketoacidosis (DKA)
 - a) risk and costs
 - b) defining subgroups
4. Utility (health related quality of life)
5. Company's revised base case and scenario analyses

1. Population

Committee: population did not reflect patients who would be offered dapagliflozin in NHS → fewer people use an insulin pump and more smokers in NHS → unlikely to be treatment-effect modifier but baseline level of risk of DKA could be higher in NHS

Consultation comments from company:

- ERG and clinical experts: DEPICT generalisable to UK practice
- Cost-effectiveness conclusions unaffected by sensitivity analyses including:
 - changing proportions smoking, using RAASi, or with microalbuminuria, hypertension, dyslipidaemia or other comorbidities
 - DKA incidence increased by a factor of 2, 3, 4, or 5 relative to base case

© ***Which population should company model – DEPICT or NHS?***

2. Clinical benefit of dapagliflozin over time

Committee: any decrease in HbA1c without substantial hypoglycaemia or weight gain desirable. Unclear whether small change in HbA1c in DEPICT important, and whether they would last over a lifetime

Consultation comments from company and 2 clinical experts:

- Should use difference in HbA1c at 24 weeks rather than 52 weeks (*n.b. company used 52 week value in model*)
 - 24 weeks = 1° endpoint, 52 weeks results unblinded and “exploratory”
 - 0.44% decrease in HbA1c at 24 weeks is clinically meaningful
- DEPICT allowed insulin dose titration, but EMA recommends reducing dose only to avoid hypoglycaemia → results are a conservative estimate of efficacy
- Benefits on **glycaemic variability** important (but not in model)
 - DCCT: 10% less time in range increases risk of retinopathy/microalbuminuria
 - DEPICT: 9.7% more values in target with dapagliflozin than placebo (24 wks)
- Preventing weight gain may affect long-term complications (not in model)
 - *n.b. but not included in Swedish risk equation*
- Misleading and inaccurate to compare naively results from DEPICT and REMOVAL (metformin) trials (*n.b. not compared*)

ERG: 52 week data provides longer follow up; post-hoc subgroup already breaks randomisation; unblinding of HbA1c (objective measure) → minimal risk of bias

2a. Relationship between HbA1c & complications

Committee: uncertain if smaller and shorter improvement in HbA1c with dapagliflozin should be extrapolated using DCCT/EDIC. Prefer scenario where risk of complications does not improve immediately when HbA1c decreases

Consultation comments from company:

- In DCCT/EDIC, a 'legacy effect' was seen
- DECLARE-TIMI 58 trial in type 2 diabetes shows dapagliflozin "has an impact on hard endpoints" over median 4.2 year follow up
 - *n.b. "dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; hazard ratio, 0.93; 95% CI, 0.84 to 1.03; P=0.17" (N Engl J Med 2019; 380:347-357)*
- DCCT: "for a proportionate reduction in HbA1c, there is a constant proportionate reduction in risk for retinopathy and nephropathy complications" and "there is a constant relative risk relationship over the entire range of HbA1c values"
- Other models do not include delays in benefit related to HbA1c
- Scenario analysis presented where no HbA1c benefits modelled beyond trial

2b. Source of risk equations

Committee:

- Company presented no clinical evidence that dapagliflozin extends life, but model predicts that dapagliflozin increased length of life, and substantially improved quality of life → questionable face validity
- Uncertain whether model predicted what might occur after a short period of improved glycaemic control yet an increased risk of adverse events

Consultation comments from company:

- DCCT/EDIC shows duration of diabetes and HbA1c key predictors of complications
 - In company's risk equations with other predictors e.g. blood pressure
- Risk equations for macrovascular complications from Swedish National Diabetes registry → robustly derived, used in other models (Sheffield and PRIME), produce results consistent with other published risk equations:
 - 1-year risk of CVD for non-smoking patient with risk factor levels of DEPICT
 - is 0.4% [no history of CVD] and 1.4% [history of CVD]
vs 0.9% and 1.0% using QRisk320 and STENO19 risk equations
- Company did not have access to patient level data to derive new risk equation for macrovascular complications from DCCT/EDIC; studies do not provide enough information (Ontario model, Wolowacz et al, CORE)
- Scenario analyses: CVD risks from Swedish National Diabetes registry \pm 20% and when HbA1c did not affect CVD → did not change cost-effectiveness conclusions

3a. Dapagliflozin – risk of DKA

Committee: dapagliflozin doubles incidence of diabetic ketoacidosis and baseline risk higher in NHS than DEPICT. Heard from clinical experts that would offer dapagliflozin only to people who had undergone structured education

Consultation comments from company:

- DKA is serious; EMA details guidance to reduce risk
- Absolute risk low even though relative risk high – 1.7% dapagliflozin vs 1.0% placebo
- Benefits likely to outweigh risks
- Risk in NHS similar to DEPICT → systematic review showed incidence ranges from 8 (UK) to 51 (Germany & Austria) cases per 1,000 patient years in type 1 diabetes
- Scenario analyses increasing incidence of DKA by 2, 3, 4 or 5-fold: dapagliflozin remains cost effective

⊙ ***Which baseline risk of DKA to use in model? DEPICT or a scenario analysis where risk is increased?***

3a. Summary of product characteristics: DKA

Committee: company underestimates costs associated with risk of DKA

“Before starting treatment with dapagliflozin:

- Assess risk factors for DKA
- Ensure ketone levels are normal. If ketones are elevated (blood beta-hydroxybutyrate reading >0.6 mmol/L or urine ketones one plus), do not start treatment with dapagliflozin until the ketone levels are normal
- Ensure that patient demonstrates ability to monitor ketone levels
- Patients should obtain several baseline ketone levels over 1 to 2 weeks before starting dapagliflozin and should become familiar with how their behaviours and circumstances affect their ketone levels
- Inform patients in a dedicated education session, on the risk of DKA, how to recognise DKA risk factors, signs or symptoms, how and when to monitor ketone levels and what actions to take at elevated ketone readings
- Correction of volume depletion prior to starting dapagliflozin is recommended

3a. EMA's advice on DKA (continued)

Clinical stage	Blood ketones	Urine ketone	Actions
Ketonaemia	0.6-1.5 mmol/L	Trace or Small +	... patient should measure blood glucose and consider taking extra carbohydrates if glucose levels are normal or low. Ketone levels should be measured again after 2 hours. Patient should immediately seek medical advice and stop taking dapagliflozin if levels persist and symptoms present
Impending DKA	> 1.5-3.0 mmol/L	Moderate ++	Patient should immediately seek medical advice and stop taking dapagliflozin ...
Probable DKA	> 3.0 mmol/L	Large to very large +++ / +++++	Patient should go to emergency department without delay and stop taking dapagliflozin

ERG: additional needs for education of specialists and patients not included in costs

⦿ ***Company has tripled costs of monitoring for ketones; £238.62 applied to dapagliflozin for increased blood glucose self-monitoring and visits – is this sufficient?***

3b. Defining 'low-insulin needs' specified in marketing authorisation

Committee: "low insulin needs" not defined in marketing authorisation. Clinical experts suggest threshold <0.5 units/kg

Consultation comments from company:

- Accepts committee's reasons for defining 'low insulin needs'
- Absolute DKA risk for subgroup without "low insulin needs <0.5 units/kg" is lower than indicated population **xxx** vs 0.7%
- Clinically questionable → people with newly diagnosed type 1 diabetes may have low insulin doses because of residual insulin production
 - *n.b. DEPICT-1 excluded people on insulin <12 months*
- Difficult to implement → insulin doses vary daily
- Included in updated company base case
 - small effect on cost effectiveness results

⊙ ***Has committee seen new evidence why it would not be appropriate to define 'low insulin needs'?***

4. Company revised utility values – same source

Event	Used in company base case	
	Original	Revised
Baseline utility	0.878*	0.865*
Disutilities		
Cardiovascular disease	0.075**	No change
Background diabetic retinopathy	0.027	No change
Proliferative diabetic retinopathy	0.070	0.029
Severe vision loss	0.074	0.059
Macular oedema	0.040	No change
Microalbuminuria	0	0.011
Macroalbuminuria	0.017	No change
Dialysis	0.169#	0.010
Renal transplant	0.023	0.010
Neuropathy	0.084	No change
Uncomplicated foot ulcer	0.125	No change
Deep foot infection	0.170	No change
Foot ulcer and critical ischaemia	0.170	No change
Minor amputation	0.117	0.080
Major amputation	0.117	0.200
Body mass index, per unit change	±0.008	0.003
Hypoglycaemia	Currie equations	No change
Diabetic ketoacidosis	0	0.0091
Urinary tract / genital infection	0.003	No change

*Value derived from Peasgood RE model; **Weighted average of MI (-0.55; 57%), angina (-0.09; 37%) and stroke (-0.164; 7%); weightings derived from DCCT; # Weighted average of HD (-0.164; 385 pmp) and PD (-0.204; 55 pmp); weighted by UK prevalence from Renal Registry

5. Company's revised base case

Issue	Company changes	Committee preference
Population	insulin dose >0.5 unit/kg body weight	Yes
Natural history of disease	Progressive annual increases in HbA1c (+0.045%) and weight (+0.1 kg) in both arms	Yes
Annual rate stopping for any reason	<ul style="list-style-type: none"> • Dapagliflozin: year 1 based on DEPICT – any reason; year 2+ based on DEPICT – adverse events • No stopping in standard of care 	Partially
Adverse events	<ul style="list-style-type: none"> • Mortality: 4% DKA + 4.45% severe hypoglycaemia • Fournier's gangrene: £2,455 and 0.17 disutility at annual probability 0.00001 for dapagliflozin vs 0 for standard care 	Yes
Costs	Dapagliflozin: ketone monitoring cost tripled + £238.62 for increased blood glucose self-monitoring and visits	?
Utility	<ul style="list-style-type: none"> • Disutility values from Peasgood (except amputation); including 0.0091 for DKA • Disutilities of 0.08 and 0.20 for minor and major amputation 	Yes
Stopping rule	No change – no stopping rules based on treatment effectiveness (HbA1c) applied	No
Other	Intention-to-treat dataset	Yes

Company revised base case deterministic results, list price

	Δ cost	Δ QALY	Δ LY	ICER £/QALY
Original base case	£2,026	0.31	0.32	£6,618
Revised base case	£5,474	0.40	0.43	£13,775

Scenario and sensitivity analyses

Scenarios

1. Risk equations
2. Waning of dapagliflozin effect
3. Stopping rules
4. Utility – different source of values
5. Company's scenarios combined

Scenarios 1. Risk equations

Committee requested: analyses varying benefit of HbA1c in DEPICT including benefit not proportional to DCCT/EDIC and no benefit after 52 week trial period

Company scenarios	Δ cost	Δ QALY	Δ LY	ICER £/QALY
1. No HbA1c effect after 52 weeks	£3,791	0.20	0.24	£19,122
2. No HbA1c or weight effect after 52 weeks (and all stop dapagliflozin)	£313	0.05	0.05	£6,385

ERG comments:

- QALY gains in scenario 1 driven by weight loss
- There is a “legacy effect”* of lower HbA1c – people experience benefit in future of having had lower HbA1c for 52 weeks
- Removing all benefits of “legacy effect” for scenario where no HbA1c or weight benefits after 52 weeks → ICER £119,095 (Δ cost £671, Δ QALY 0.0056)

⊙ ***Is a legacy effect of lower risk of complications in future from 52 weeks of lower HbA1c plausible?***

DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year

*At the committee meeting, the company explained that it believed that this was a factual inaccuracy because no legacy effect has been modelled. The QALY gains in the ERG’s analysis are driven by the differences in mortality associated with severe hypoglycaemia in year 1.

Scenarios 2. Waning of dapagliflozin's effect

Committee: after initially dropping, HbA1c increases in people on (or not on) dapagliflozin up to 52 weeks in DEPICT. Unclear if HbA1c drop with dapagliflozin will be sustained

Consultation comments company and 1 clinical expert:

- “Commonly observed pattern in trials of effective anti-hyperglycaemic agents”: initial drop followed by gradual increase, then long-term stabilisation
 - no biological basis for waning of effect
 - clinicians on advisory board suggest “most” patients who respond would maintain benefit
 - *n.b. average would still increase?*
 - UK observational data of dapagliflozin in 5,228 patients with type 2 diabetes show sustained treatment effect over 2 years (Prim Care Diabetes 2017; 437-444)
- Endpoints at 52 weeks were “exploratory”

© *Is there evidence of a waning in treatment effect?*

Company's waning scenarios – HbA1c, weight

- In all scenarios, weight effects assumed constant while on treatment
 - conservative: trajectory using DEPICT 24 and 52 week data suggest weight continues to fall in dapagliflozin but increases in placebo
- HbA1c waning from DCCT: after initial change in HbA1c, trajectories in each arm were almost parallel → applied rate of HbA1c progression of 0.045% per year
- Waning effect informed by DEPICT 24 and 52 week results:
 - extrapolation suggest HbA1c would return to baseline by year 2 of treatment
 - HbA1c benefit still expected for dapagliflozin relative to placebo until year 3

☉ Which scenario is most appropriate?

	Δ cost	Δ QALY	Δ LY	ICER £/QALY
Original base case	£2,026	0.31	0.32	£6,618
A: HbA1c effect lost over 2nd year	£823	0.09	0.10	£9,117
C: HbA1c effect lost over 2nd year; natural annual progression of HbA1c and weight after stopping at year 2	£930	0.07	0.08	£12,621
F: HbA1c effect in 2nd year extrapolated using 24/52 week results; natural annual progression of HbA1c and weight after stopping at year 2	£788	0.09	0.10	£8,938
G: HbA1c effect in 2nd and 3rd year extrapolated using 24/52 week results; natural annual progression of HbA1c and weight after stopping at year 3	£1,137	0.11	0.12	£10,005

Scenarios 3. Stopping rules

Committee: it may be difficult to stop treatment for people who had lost weight only but dapagliflozin does not have a marketing authorisation for weight loss. Preferred to see scenarios using a range of treatment stopping rules (HbA1c at different timepoints)

Consultation comments from company:

- Stopping treatment should consider glycaemic variability, hypoglycaemia, weight, renal function, risk factors and adverse events (supported by clinical experts) → no stopping rule should be applied in practice → decision left to physician and made on individual basis
- Scenario analyses:
 - stop dapagliflozin when waning treatment effects results in no improvement in HbA1c – see previous slide
 - stop dapagliflozin when $eGFR < 45 \text{ ml/min/1.73m}^2$ → ICER = £6,747
- Dapagliflozin still cost effective in these scenarios

⊙ ***Should a stopping rule apply? If so, what should it be?***

Scenarios 4. Source of utility values

Committee:

- Company should model additive and multiplicative approach to disutilities
- Use most robust literature source for values (can be from different sources)
- Wish to see a scenario analysis including EQ-5D data from DEPICT

Consultation comments from company:

- Scenario analyses addressing above do not alter cost-effectiveness conclusions
- Scenario analysis using non-significant disutility values from Peasgood et al. → replaced with estimates from other sources (in original company submission)

	Δ cost	Δ QALY	Δ LY	ICER £/QALY
Original base case	£2,026	0.31	0.32	£6,618
Multiplicative approach to utilities	£2,026	0.29	0.32	£7,018
DEPICT baseline EQ-5D (0.875)	£2,026	0.31	0.32	£6,550
DEPICT baseline EQ-5D (0.875) and change associated with BMI (0.0026 per unit)	£2,026	0.31	0.32	£6,615
Upper values from review of utilities	£2,026	0.41	0.32	£4,904
Lower values from review of utilities	£2,026	0.25	0.32	£8,266
Alternative utilities instead of non-significant values from Peasgood et al.	£2,026	0.31	0.32	£6,508

Scenarios 5. Company's combined results

Description	Δ cost	Δ QALY	Δ LY	ICER £/QALY
Revised base case	£5,474	0.40	0.43	£13,775
+ Waning of HbA1c over 2nd year of treatment, by extrapolating of 24/52-week results	£1,328	0.10	0.11	£13,820
+ Stopping after 2 years (HbA1c stopping rule)				
+ Probabilistic sensitivity analysis	£6,420	0.45	0.49	£14,344
+ Multiplicative approach to utilities (except Fournier's gangrene applied additively)	£5,474	0.38	0.43	£14,405
+ DEPICT baseline EQ-5D (0.875)	£5,474	0.40	0.43	£13,656
+ DEPICT baseline EQ-5D (0.875) and change associated with BMI (0.0026 per unit)	£5,474	0.40	0.43	£13,781
+ Upper values from review of utilities	£5,474	0.51	0.43	£10,817
+ Lower values from review of utilities	£5,474	0.32	0.43	£17,334
+ alternative utilities in place of non-significant values from Peasgood et al.	£5,474	0.40	0.43	£13,602

Committee: unmet need for people with type 1 diabetes inadequately controlled despite optimised insulin therapy. Dapagliflozin is innovative but may not be considered a step change in managing type 1 diabetes because of the modest benefits seen in clinical trials. It did not hear that there were any additional gains in health-related quality of life over those already included in QALY calculations.

Consultation comments

Company:

- QALY estimates does not capture additional benefit of improvement in weight and glycaemic variability (effect on complications not modelled)
 - *n.b. weight benefits on complications?*

Association of British Clinical Diabetologists*

- “ABCD recognises that SGLT2 inhibitors may be helpful in a small cohort of patients with type 1 diabetes whilst under specialist care, having been made aware of potential risks. These patients should receive education on how to mitigate the risks and deal with any consequences of such use. ABCD is aware that Dapagliflozin is now licensed for patients with type 1 diabetes with BMI ≥ 27 kg/m² and not on small dose of insulin.”

⊙ ***Has committee seen evidence of additional gains in health-related quality of life not captured in QALY calculation?***