PART 1
AIC redacted

NICE National Institute for Health and Care Excellence

Dapagliflozin for treating chronic kidney disease [ID3866]

Lead team presentation

Chair: Megan John

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ERG: ScHARR

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Company: AstraZeneca

ACM1: 14th October 2021

Unresolved issues

Key issues unresolved post technical engagement	Status	Impact	Slide
Issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in people excluded from DAPA-CKD. These include those:			
a. With uACR less than 22.6mg/mmol	To discuss		22-25
b. With eGFR less than 25 ml/min/1.73m^2 or more than 75 ml/min/1.73m^2	To discuss		
c. With prior organ transplant	To discuss		
d. Not having optimised ACE inhibitor/ARB background therapy	To discuss		
Issue 2: Modelling approach and overall survival predictions	To discuss		32-34
Other unresolved issues			
Is canagliflozin a relevant comparator in people with co-morbid T2DM?	To discuss		19
What mean age should be used in the model?	To discuss		27-31

Key: Large impact  Small/moderate impact  Unknown impact 

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate; T2DM: Type 2 diabetes mellitus; uACR: Urine albumin-to-creatinine ratio

Chronic kidney disease (CKD)

- Complex progressive disorder with abnormal kidney function present for at least 3 months
- Loss of nephrons causes kidney function to decline over time, eventually leading to end-stage renal disease and considerable health-related quality of life (HRQoL) impact
- Symptoms including fatigue, weight loss, itching, swelling, restless leg syndrome, muscle cramps and sleep problems
- CKD may result from:
  - Systemic disease affecting the kidney, such as type 2 diabetes mellitus (T2DM), hypertension or cardiovascular disease (CVD)
  - Primary kidney disease such as glomerulonephritis (inflammation of glomeruli)
- T2DM, hypertension and CVD can also result from CKD, and commonly co-occur:
  - [redacted] of people with CKD have T2DM, [redacted] have prior heart failure, [redacted] have prior myocardial infarction, [redacted] have prior stroke
- CKD varies in severity and is classified based on estimated glomerular filtration rate (eGFR [categories G1 to G5]) and urine albumin:creatinine ratio (uACR [categories A1 to A3])
- Often asymptomatic in early disease, but risks of cardiovascular (CV) events and acute kidney injury are considerably increased in later disease stages. Associated impact on mortality and resource use
- Around 1.9 million adults in the UK have CKD with an eGFR category of G3a to G5, with likely many more undiagnosed

CKD classification

- NICE guidelines (NG203) recommend CKD be classified based on combination of:
  1. **Glomerular filtration rate (GFR):** measures level of kidney function and is usually estimated (eGFR) using a creatinine blood test
  2. **Albumin-to-creatinine ratio (ACR):** measured from a urine sample (uACR), as a marker of kidney damage

eGFR (category, range [ml/min/1.73m^2], kidney function reduction†)			**uACR** (category, range [mg/mmol], kidney function reduction†)		
			A1	**A2**	**A3**
			Less than 3	3 to 30	Greater than 30
			Normal/Mild	Moderate	Severe
G1	90 or more	None	Low (risk)*	Moderate	High
G2	60 to 89	Mild	Low*	Moderate	High
G3a	45 to 59	Mild/moderate	Moderate	High	Very high
G3b	30 to 44	Moderate/severe	High risk	Very high	Very high
G4	15 to 29	Severe	Very high	Very high	Very high
G5	Less than 15	Kidney failure	Very high	Very high	Very high

* No CKD if there are no other markers of kidney damage
† Compared to a healthy adult

CKD treatment algorithm (NICE CG203 [Aug 2021])

uACR category (mg/mmol)	CKD +/-	Hypertension +/-	Diabetes +/-	CVD (secondary prevention)
A1 (less than 3)	• Education • Lifestyle changes (exercise, weight loss, smoking cessation) • Dietary advice • Statins	• Lifestyle changes • Anti-hypertensive drugs (ACEi / ARB / calcium channel blockers)	Antidiabetics (e.g., insulin)	• Antiplatelets • Anticoagulants
A2 (3 to 30)			Antidiabetics + ACEi / ARB at highest tolerated dose* *(type 2 diabetes)*	
A3 (more than 30)		ACEi / ARB at highest tolerated dose +/-	Antidiabetics + ACEi / ARB at highest tolerated dose + SGLT2i *(type 2 diabetes)*	
70 or more	+ ACEi / ARB at highest tolerated dose			

Management of other complications:

- Erythropoietin stimulating agents therapy
- Phosphate binders
- Bisphosphonates
- Colecalciferol/ergocalciferol
- Alfacalcidol/calcitriol
- Sodium bicarbonate

* plus consider SGLT2 inhibitor, based on draft type 2 diabetes guideline for consultation

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CVD: Cardiovascular disease; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; Urine albumin-to-creatinine ratio

Dapagliflozin (Forxiga, AstraZeneca)

Marketing authorisation[1,2]	'Forxiga is indicated in adults for the treatment of chronic kidney disease' (granted by the European Medicines Agency 5th August 2021)
Mechanism of action	Highly potent, selective and reversible sodium-glucose cotransporter-2 inhibitor (SGLT2i)
Administration	Orally, 10 mg once daily
List price†	£1.31 per 1 tablet of 10 mg or £36.59 per pack of 28 tablets or £477.30 per annum

[1] Dapagliflozin also has a marketing authorisation for type 2 diabetes mellitus and heart failure
[2] Summary of product characteristics states that "there is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m^2, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m^2. Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m^2". Dapagliflozin is also not recommended for treating chronic kidney disease in people with type 1 diabetes mellitus
† There is **no** patient access scheme (PAS) applicable to dapagliflozin for this appraisal

Marketing authorisation: there is no experience with dapagliflozin for the treatment of CKD in patients without diabetes who do not have albuminuria

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eGFR: Estimated glomerular filtration rate

Existing NICE recommendations for dapagliflozin

Dapagliflozin recommended for treating chronic heart failure and diabetes

TA679 (2021)	Recommended for treating symptomatic chronic heart failure with reduced ejection fraction in adults, only if used as add-on to optimised standard care with: • ACE inhibitors or ARBs, with beta blockers, and, if tolerated, MRAs, or • sacubitril valsartan, with beta blockers, and, if tolerated, MRAs
TA597 (2019)	Recommended with insulin for treating type 1 diabetes in adults with BMI of at least 27 kg/m^2, when optimal insulin does not provide adequate glycaemic control, only if they are on insulin doses of 0.5 units/kg body weight/day or more
TA418 (2016)	Recommended in triple therapy regimen for treating type 2 diabetes in adults, in combination with metformin and a sulfonylurea
TA390 (2016)	Recommended as monotherapy for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if: • a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and • a sulfonylurea or pioglitazone is not appropriate
TA288 (2013)	Recommended with metformin as an option for treating type 2 diabetes, only if: • a sulfonylurea is contraindicated or not tolerated or • the person is at significant risk of hypoglycaemia or its consequences. Recommended with insulin with or without other antidiabetic drugs for treating type 2 diabetes

ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; BMI: Body mass index; MRA: Mineralocorticoid receptor antagonist; TA: Technology appraisal

Decision problem

	Final Scope	Company submission	ERG comment
P	Adults with CKD who are having optimised standard of care (including ACEi or ARBs), irrespective of eGFR/uACR	**Post technical engagement:** As per scope, updated to restrict to people having ACEi /ARBs as part of standard of care	Some patient groups not represented in DAPA-CKD (e.g. uACR less than 22.6 mg/mmol, end-stage renal disease)
I	Dapagliflozin plus optimised standard of care	As per scope	In line with final scope
C	Established clinical management without dapagliflozin	As per scope. Company did not consider canagliflozin a relevant comparator in people with T2DM, but company did scenario based on indirect comparison	
O	Morbidity, mortality, adverse events and HRQoL	As per scope	
S	People with diabetes, CVD and other causes of CKD	People with comorbid T2DM, comorbid CVD and no comorbid T2DM/CVD	Definition of subgroups based on comorbidity agreed with NICE

C: Comparators; CV: Cardiovascular; I: Interventions; P: Population; O: Outcomes; S: Subgroups

Patient expert perspectives

Submission from Kidney Care UK

- Diagnosis of CKD and adjusting to new treatments is challenging
- CKD has huge implications on quality of life:
  - Affects mental health and emotional wellbeing, capacity to stay in work and maintain relationships. Significant amount of time spent in hospitals for people having dialysis

"I live with physical and emotional impact of suffering with CKD and its complications that many endure. Loss of my beloved father, my job, impact on my family, fatigue, medication regime. Fear/anxiety of knowledge of what's ahead, as well as being physically debilitated"

- Patients often require help with daily activities and support with treatment, in particular dialysis
- CKD is incurable with limited pharmacological options for delaying progression
  - Current management includes lifestyle changes, diet and treatments for co-morbidities
  - Kidney transplant is gold standard but access is limited

"Many patients arrive at the point of dialysis without any prior knowledge. Diet and lifestyle changes, medical interventions year's before could prevent or delay progression"

- Dapagliflozin offers a step change in treatment of CKD, as delay in progression in patients with and without diabetes offers real hope

"As a transplantee quality of life is important, as is quantity. The longer we can put off the inevitable the better. I think this is the main advantage of this technology"

Clinical expert perspectives (1/2)

Submissions from London Kidney Network, St George's University Hospital NHS Foundation, University Hospitals of Leicester and Leeds Teaching Hospitals Trust

- Aims of treatment are to delay CKD progression, reduce CV morbidity and mortality
- Current treatment pathway not well defined, though there is general alignment with NICE CKD guidelines (NG203)
  - Rapidly changing evidence, primary care referrals differ between practices
  - Pathway clear for people with diabetes but less clear for people without diabetes or heart failure
  - ACEi/ARBs are mainstay of clinical management
  - SGLT2 inhibitors widely accepted by renal community following DAPA-CKD trial
- Unmet need as current management only slows CKD progression
- Current therapies for CKD target multiple pathogenic pathways, but only retard disease progression
- Increasingly ageing population, and increasing rates of type 2 diabetes
- Measurement of albuminuria (uACR levels) in people with CKD is rarely being done.

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CV: Cardiovascular; eGFR: Estimated glomerular filtration rate; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; uACR: Urine albumin-to-creatinine ratio

Clinical expert perspectives (2/2)

- Impact of potential dapagliflozin recommendation on current treatment pathway:
  - Enables use down to eGFR 15ml/min/1.73m^2 and widens use in people without diabetes
  - If CKD is primary diagnosis dapagliflozin is likely be introduced where there are existing co-morbidities in addition to CKD
  - Would be preferred choice of SGLT2 inhibitor
- Education is imperative for this to be embedded in the current pathway of care
- Evidence suggests dapagliflozin offers significant therapeutic breakthrough:
  - Greater benefits compared to ACE inhibitors/ARBs, though unclear if this is a SGLT2i class effect or specific to dapagliflozin
  - Reduces renal disease, developing diabetes, hospitalisation due to heart failure and cardiovascular mortality
  - Benefit distinct from just a blood glucose reduction i.e. benefits in non-diabetic patients
  - Reducing progression to end stage renal disease will increase quality of life

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; uACR: Urine albumin-to-creatinine ratio

Key dapagliflozin clinical trials

Trial	DAPA-CKD (pivotal trial)	DECLARE-TIMI 58	DAPA-HF
Design		Double-blind, randomised	
Population	Adults with CKD, with/without comorbid T2DM	Adults with T2DM	Adults with chronic heart failure
Interventions	• Dapagliflozin (n=2,152) • Placebo (n=2,152)	• Dapagliflozin (n=8,582) • Placebo (n=8,578)	• Dapagliflozin (n=2,373) • Placebo (n=2,371)
Key inclusion criteria	• eGFR: ≥25 to ≤75 ml/min/1.73m^2 • uACR: ≥22.6 to ≤565 mg/mmol • Max tolerated ACEi/ARBs • No type 1 diabetes • No prior transplants	• Aged ≥40 years • Diagnosed with T2DM • High risk for CVE • No restriction by uACR • No type 1 diabetes	• Symptomatic HFrEF present for ≥ 2 months • LVEF≤40% • Elevated NT-proBNP • eGFR ≥30 ml/min/1.73 m^2 • No type 1 diabetes
Primary outcome	Composite outcome of sustained decline in eGFR ≥ 50%, ESRD or death from renal/CV causes	Composite outcomes: • CV death, MI or ischemic stroke • CV death or hHF	Composite outcome of CV death, hHF or urgent visit due to heart failure
Use in model (post TE)	Yes	Yes	No

Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CV: Cardiovascular; eGFR: Estimate glomerular filtration rate; hHF: Hospitalisation due to heart failure; MI: Myocardial infarction; TE: Technical engagement; T2DM: Type 2 diabetes mellitus; uACR: Urine albumin-to-creatinine ratio

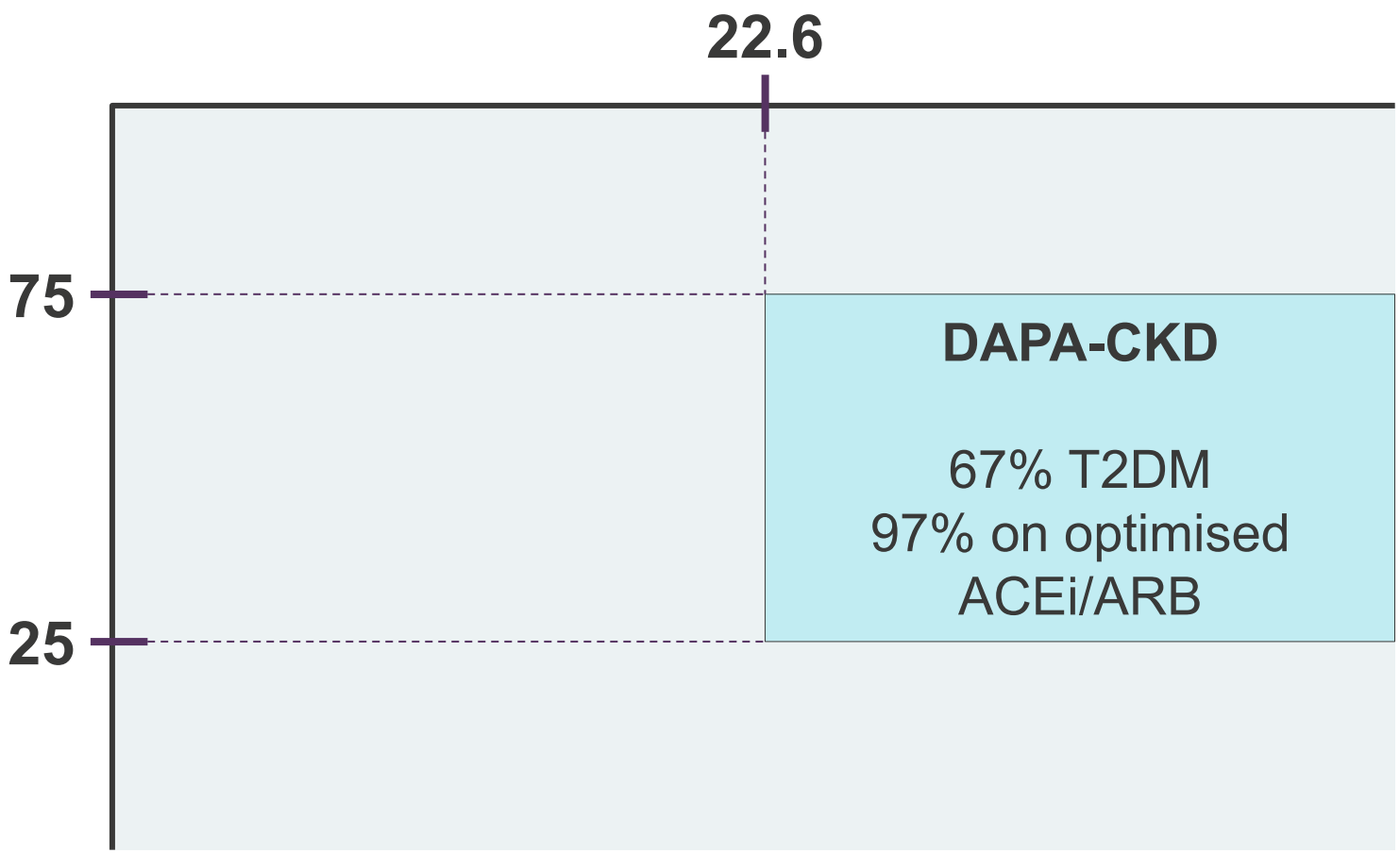
Pivotal trial coverage of eligible population

Urine albumin:creatinine ratio (mg/mmol)

A1	A2	A3
<3 (norm/mild)	3-30 (mod)	>30 (severe)

eGFR
(mL/min/1.73 m^2)

G1	>90	Norm/ high
G2	60-89	Mild
G3a	45-59	Mild/ mod
G3b	30-44	Mod/ severe
G4	15-29	Severe
G5	<15	Kidney failure



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ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; T2DM: Type 2 diabetes mellitus

Supporting data: DECLARE-TIMI 58

Urine albumin:creatinine ratio (mg/mmol)

A1	A2	A3
<3 (norm/mild)	3-30 (mod)	>30 (severe)

eGFR
(mL/min/1.73 m^2)

G1	>90	Norm/ high
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G3a	45-59	Mild/ mod
G3b	30-44	Mod/ severe
G4	15-29	Severe
G5	<15	Kidney failure

DECLARE-TIMI 58

T2DM ±CKD
[redacted]% on optimised ACEi/ARB

Around 7% (n>1,100) had eGFR less than 60

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ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; T2DM: Type 2 diabetes mellitus

Supporting data: DAPA-HF

Urine albumin:creatinine ratio (mg/mmol)

A1	A2	A3
<3 (norm/mild)	3-30 (mod)	>30 (severe)

eGFR
(mL/min/1.73 m^2)

G1	>90	Norm/ high
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G3a	45-59	Mild/ mod
G3b	30-44	Mod/ severe
G4	15-29	Severe
G5	<15	Kidney failure

DAPA-HF

Heart failure ±CKD ±T2DM
(uACR not measured)
[redacted]% on optimised ACEi/ARB
Around 41% had eGFR less than 60

NICE

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; T2DM: Type 2 diabetes mellitus

Dapagliflozin data gaps compared with marketing authorisation

Subgroups without data from DAPA-CKD

- eGFR less than 25ml/min/1.73m^2 or more than 75ml/min/1.73m^2
- uACR less than 22.6 mg/mmol
- Not having maximally tolerated ACE inhibitors/ARBs
- With prior transplants

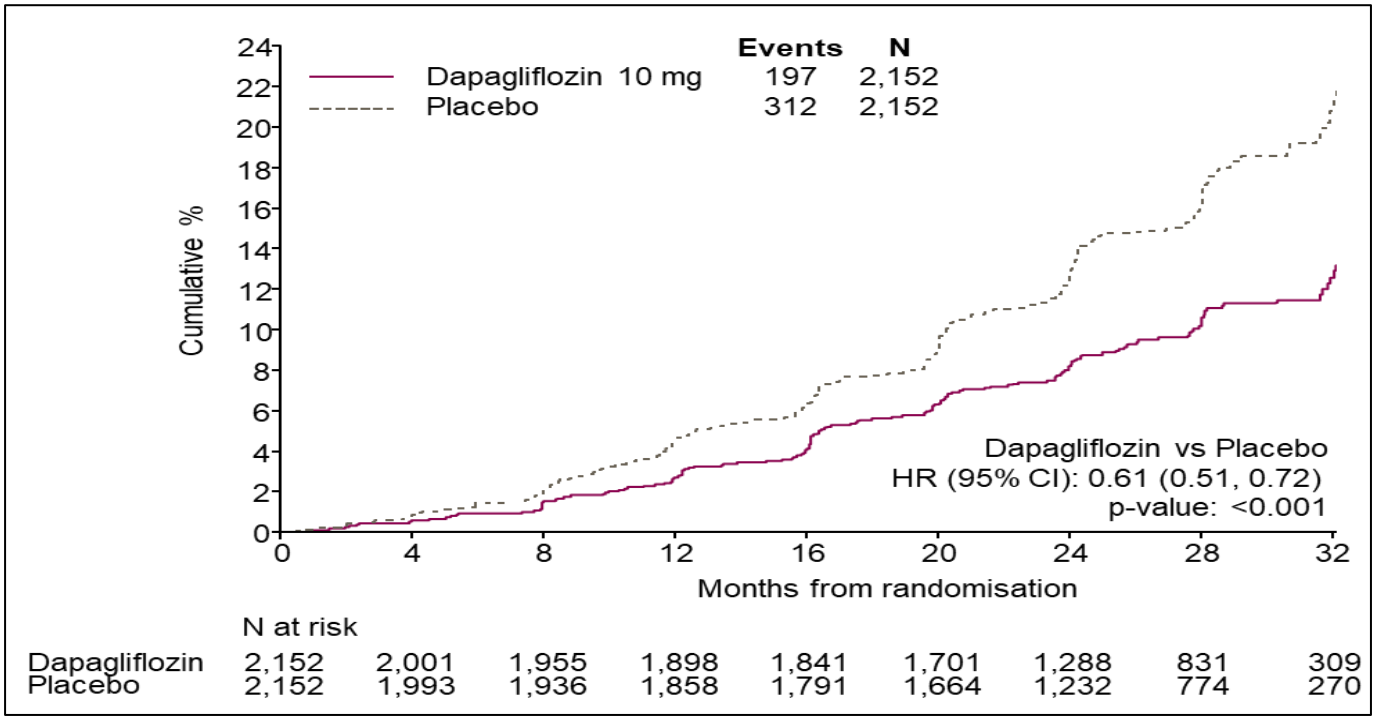
Subgroups without any data

- CKD + no type 2 diabetes + uACR less than 22.6 mg/mmol
- CKD + prior organ transplants

Clinical evidence summary (1): DAPA-CKD

- Double-blind, placebo-controlled, randomised controlled trial that examined the effects of dapagliflozin on renal and cardiovascular outcomes in patients with CKD, with or without T2DM
- 386 study sites: 9 UK sites (n=60, dapagliflozin arm, n=28; placebo arm, n=32)
  - **ERG comment:** clinical advice suggests management of CKD across study sites likely to be broadly generalisable to UK clinical practice
- Dapagliflozin associated with statistically significant risk reduction of 39% (HR 0.61; 95% CI: 0.51, 0.72; p<0.001) in primary composite outcome

Kaplan-Meier plot of composite outcome of ≥50% eGFR decline, ESRD and renal CV death



Source: company submission, Figure 7

CI: Confidence interval; CV: cardiovascular; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; HR: Hazard ratio; T2DM: Type 2 diabetes mellitus

Clinical evidence summary (2): DAPA-CKD

Exploratory analysis – individual components of primary outcome

Outcome, N (%)	Dapagliflozin (n=2,152)	Placebo (n=2,152)	Hazard ratio (95% CI)	p value
Sustained ≥50% decline in eGFR	112 (5.2)	201 (9.3)	0.53 (0.42, 0.67)	[redacted]
End-stage renal disease	109 (5.1)	161 (7.5)	0.64 (0.50, 0.82)	[redacted]
eGFR <15 ml/min/1.73 m^2	84 (3.9)	120 (5.6)	0.67 (0.51, 0.88)	[redacted]
Chronic dialysis	68 (3.2)	99 (4.6)	0.66 (0.48, 0.90)	[redacted]
Kidney transplantation	3 (0.1)	8 (0.4)	N/A	N/A
Death from renal causes	2 (<0.1)	6 (0.3)	N/A	N/A
Death from CV causes	65 (3.0)	80 (3.7)	0.81 (0.58, 1.12)	[redacted]

CI: confidence interval; CV: Cardiovascular; eGFR: estimate glomerular filtration rate; n: number; N/A: not applicable

- [redacted]
- Post hoc subgroup analyses of relevant subgroups in line with NICE scope showed consistent treatment benefit with dapagliflozin in patients regardless of comorbid CVD, and those without comorbid T2DM and CVD versus those with comorbid CVD and/or T2DM.

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T2DM: Type 2 diabetes mellitus

Indirect treatment comparison with canagliflozin

- Canagliflozin is another SGLT2 inhibitor with a marketing authorisation for treating T2DM. Company does not consider canagliflozin a relevant comparator
- Company did indirect treatment comparison (ITC) to estimate efficacy of dapagliflozin versus canagliflozin for people with CKD and T2DM. Used anchored matching adjusted indirect comparison (MAIC) with data from DAPA-CKD and CREDENCE trials
- [redacted]

Outcome	Analysis set	
	Unweighted	Primary
CREDENCE composite primary outcome	[redacted]	[redacted]
Cardiovascular death	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]
End-stage renal disease	[redacted]	[redacted]
Hospitalisation for heart failure	[redacted]	[redacted]
Doubling of serum creatinine	[redacted]	[redacted]
CREDENCE renal composite	[redacted]	[redacted]
CREDENCE exploratory renal	[redacted]	[redacted]

ERG comments:

- Selection of covariates overly complex
- [redacted]
- [redacted]

Question for committee:

- Is canagliflozin a relevant comparator in people with CKD and comorbid T2DM?

Results: DECLARE-TIMI 58 and DAPA-HF

- **Company:** Treatment benefit of dapagliflozin versus placebo is generalisable to the broad population of patients with CKD, regardless of uACR and eGFR category

Subgroup	Dapagliflozin (n/N)	Placebo (n/N)	HR (95% CI)	P-value	DAPA-CKD data gap addressed
Co-primary endpoint from DECLARE-TIMI 58 (hospitalisation for HF or CV death)					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	• uACR < 22.6 mg/mmol (with T2DM) • eGFR > 75 ml/min/1.73m^2 (with T2DM)
[redacted]	[redacted]	[redacted]	[redacted]		
Overall	[redacted]	[redacted]	[redacted]		
eGFR ≥ 90ml/min/1.73m^2	163/4,137	163/4025	0.96 (0.77-1.19)	**0.37**	
eGFR ≥ 60 to < 90ml/min/1.73m^2	199/3838	252/3894	0.79 (0.66-0.95)		
eGFR < 60ml/min/1.73m^2	55/606	81/659	0.78 (0.55-1.09)		
Overall	**417/8581**	**496/8578**	**0.84 (0.74-0.96)**		
Co-primary endpoint from DAPA-HF (hospitalisation/urgent visit for HF, or CV death)					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	• eGFR > 75 ml/min/1.73m^2 (with heart failure)
[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]		
Overall	[redacted]	[redacted]	[redacted]		

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CV: Cardiovascular; eGFR: Estimated glomerular filtration rate; HF: Heart failure; uACR: Urine albumin-to-creatinine ratio

Unresolved issues

Key issues unresolved post technical engagement	Status	Impact	Slide
Issue 1: Uncertainty surrounding the target population and the effectiveness of dapagliflozin in people excluded from DAPA-CKD. These include those:			
a. With uACR less than 22.6mg/mmol	To discuss		22-25
b. With eGFR less than 25 ml/min/1.73m^2 or more than 75 ml/min/1.73m^2	To discuss		
c. With prior organ transplant	To discuss		
d. Not having optimised ACE inhibitor/ARB background therapy	To discuss		
Issue 2: Modelling approach and overall survival predictions	To discuss		32-34
Other unresolved issues			
Is canagliflozin a relevant comparator in people with co-morbid T2DM?	To discuss		19
What mean age should be used in the model?	To discuss		27-31

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ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate; T2DM: Type 2 diabetes mellitus; uACR: Urine albumin-to-creatinine ratio

Issue 1: Dapagliflozin efficacy in people outside DAPA-CKD

Background:

- Dapagliflozin marketing authorisation in CKD includes all CKD populations irrespective of uACR levels and comorbid T2DM.
  - ACE inhibitors/ARBs not specified as part of marketing authorisation
- Dapagliflozin expected to be used in addition to optimised standard of care, which may or may not include ACE inhibitors/ARBs
- Company's economic analysis uses CPRD dataset to reflect the UK population characteristics and to adjust event risks from DAPA-CKD

ERG comments:

- DAPA-CKD does not provide evidence of dapagliflozin efficacy for some CKD populations:
  a. uACR less than 22.6mg/mmol,
  b. eGFR less than 25ml/min/1.73m^2 or more than 75ml/min/1.73m^2
  c. Prior organ transplant
  d. not having ACE inhibitor/ARB therapy
- Evidence from DAPA-HF and DECLARE-TIMI 58 not used in original economic model
- Adjusting baseline characteristics and event risks to CPRD data questionable
  - 97% of patients in DAPA-CKD were having ACE inhibitor or ARB therapy at baseline ➔ however, only [redacted] of people in the CPRD dataset were having these therapies
  - none of the CKD transition probabilities are adjusted to reflect CPRD population

ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; CPRD: Clinical practice research datalink; CVD: Cardiovascular disease; eGFR: Estimated glomerular filtration rate; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; SoC: Standard of care; T1DM: Type 1 diabetes mellitus; uACR: Urine albumin-to-creatinine ratio

Issue 1: Dapagliflozin efficacy in people outside DAPA-CKD

Clinical expert comments

General comments:

- NICE recommendations should reflect existing evidence base, mainly from DAPA-CKD
- Recommendations based on uACR would significantly limit access. uACR testing not consistently done across country; more common in severe CKD treated in secondary care

Dapagliflozin efficacy in ACR and GFR levels outside of DAPA-CKD:

- Dapagliflozin mechanism of action should work across range of GFR levels, although less so in more advanced disease
  - Mechanisms providing cardiovascular benefits beyond renal physiology will benefit those with eGFR/uACR levels outside DAPA-CKD ➔ supported by evidence from DAPA-HF, which likely included some people with uACR levels lower than DAPA-CKD
- Dapagliflozin likely to be effective in people irrespective of uACR levels due to effect on reducing intraglomerular hypertension
- Reducing hyperfiltration, decreasing inflammation and fibrotic response of proximal tubules are all beneficial in maintaining renal function irrespective of uACR level

Dapagliflozin efficacy in people with prior organ transplant:

- Further studies needed of safety of dapagliflozin in people who are immunosuppressed

Issue 1: Dapagliflozin efficacy in people outside DAPA-CKD

Company comments

- MHRA, EMA and FDA have all granted marketing authorisation for dapagliflozin in CKD, irrespective of uACR levels and diabetes status
  - Evidence from DECLARE-TIMI 58 and DAPA-HF trials sufficient to demonstrate efficacy of dapagliflozin beyond DAPA-CKD
- Revised positioning to reflect people with CKD who are currently having ACE inhibitor/ARB therapy ➔ amended CPRD population to reflect this in economic model
- Provided additional analyses to address uncertainty of clinical and cost-effectiveness of dapagliflozin in people with uACR/eGFR outside of DAPA-CKD:
  1. Estimated outcomes in people with low uACR, stratified by T2DM status
  2. Updated model to use data from CKD subgroup of DECLARE-TIMI 58, and split population into 3 weighted subgroups based on uACR level and T2DM status – discussed alongside key issue 2.

eGFR: Estimated glomerular filtration rate; EMA: European Medicines Agency; FDA: Food and Drug Administration; MHRA: Medicines and Healthcare products Regulatory Agency; T2DM: Type 2 diabetes mellitus; uACR: Urine albumin-to-creatinine ratio

Issue 1: Estimating outcomes in people with low uACR

- Company did simulated treatment outcomes analysis, using Poisson model to fit estimated annual event rate conditional on uACR as continuous variable from DAPA-CKD data
- uACR range extended to 3.39-565 mg/mmol (30 to 5,000 mg/g), beyond DAPA-CKD
- Dapagliflozin treatment effect maintained in low uACR region (<22.6 mg/mmol)

Ratio of annual event rates per 100 patients with dapagliflozin versus placebo

Source: Dapagliflozin ERG technical engagement response, Figure 1

ERG comments

- Analysis supports hypothesis that dapagliflozin might work in this population. However, event rates extrapolated to population for whom there is no evidence of efficacy

Question for committee: Is the evidence for dapagliflozin in a broader population beyond DAPA-CKD sufficient? If so, which population?

Unresolved issues

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b. With eGFR less than 25 ml/min/1.73m^2 or more than 75 ml/min/1.73m^2	To discuss		
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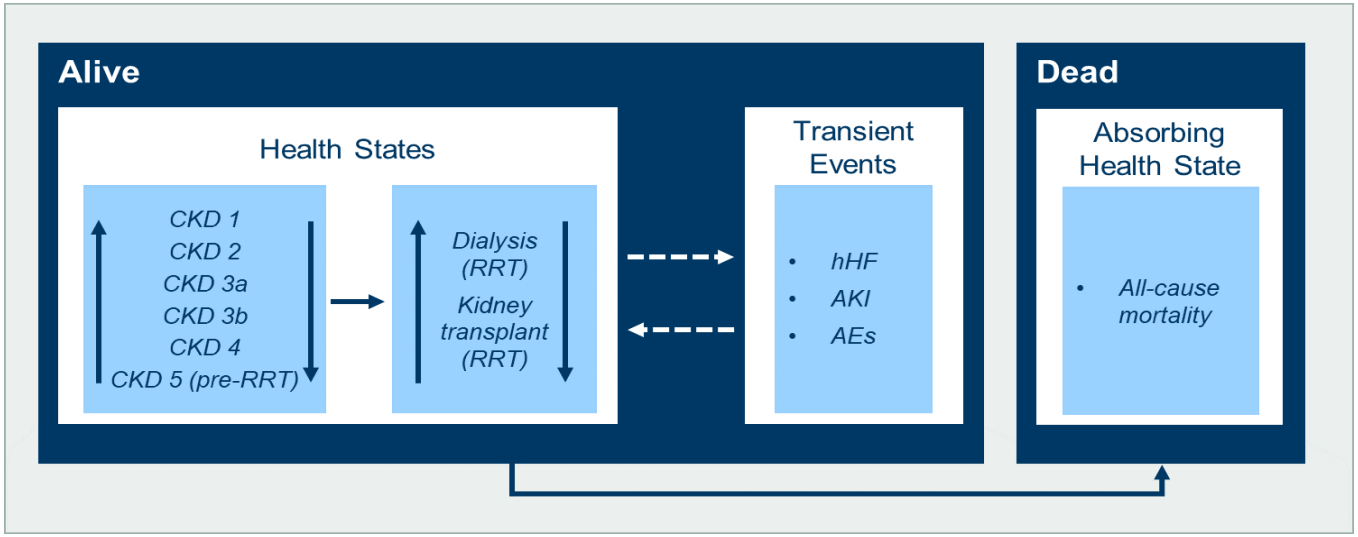
Issue 2: Modelling approach and overall survival predictions	To discuss		32-34
Other unresolved issues			
Is canagliflozin a relevant comparator in people with co-morbid T2DM?	To discuss		19
What mean age should be used in the model?	To discuss		27-31

Key: Large impact  Small/moderate impact  Unknown impact 

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate; T2DM: Type 2 diabetes mellitus; uACR: Urine albumin-to-creatinine ratio

Cost effectiveness summary – Economic model



Source: company submission, Figure 22

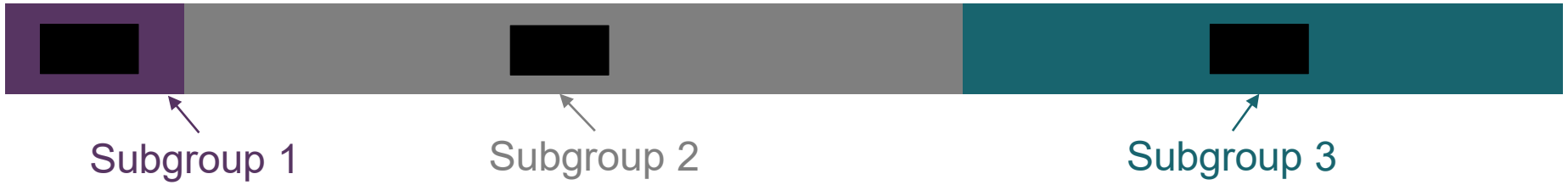
Population	People with CKD ([redacted]) having background ACEi/ARB therapy unless not tolerated (added at TE)
Model Type	Cohort-level state transition approach with health states based on CKD stages 1, 2, 3a, 3b, 4 and 5 and need for dialysis or RRT
Time horizon	Lifetime ([redacted] years)
Interventions	Dapagliflozin plus standard of care versus standard of care alone
Approach	Cost-utility analysis
Perspective	NHS and personal social services (PSS)
Discount rate	3.5% for health outcomes and costs

- Clinical Practice Research Datalink (CPRD) informed patient baseline characteristics with event risks from DAPA-CKD adjusted to reflect CPRD population
- **ERG** and its clinical advisors consider company's overall model structure and modelling approach to be reasonable

Company updated model using data from DECLARE-TIMI 58 (1/4)

- Company submitted updated economic model post technical engagement. Aims to address uncertainty in people with uACR/eGFR outside DAPA-CKD (Issue 1)
  - reflects people with CKD currently having ACEi/ARB, irrespective of uACR
  - used weighted economic analysis across 3 subgroups according to prevalence in updated CPRD dataset:
    i. Subgroup 1: uACR≥22.6 mg/mmol, with or without T2DM
       - **ERG:** Subgroup 1 most closely reflects the DAPA-CKD population
    ii. Subgroup 2: uACR<22.6 mg/mmol, with T2DM
    iii. Subgroup 3: uACR<22.6 mg/mmol, without T2DM
- Updated model uses data from subset of patients with CKD from DECLARE TIMI 58 (company excluded people with eGFR>60 ml/min/1.73 m^2 and uACR<3 mg/mmol). Dataset referred to as "$DECLARE_{CKD}$"
- Model re-estimates patient characteristics, transition probabilities, mortality risks and transient event risks for each subgroup

Subgroup weighting in updated company model



ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate; T2DM: Type 2 diabetes mellitus; uACR: Urine albumin-to-creatinine ratio

Company updated model using data from DECLARE-TIMI 58 (2/4)

Summary of company's weighted subgroup approach:

	Survival	Transition probabilities
Subgroup 1 uACR≥22.6mg/mmol Weighting: [redacted]% *(based on CPRD data)*	• Multivariable Weibull model fitted to pooled data from DAPA-CKD and $DECLARE_{CKD}$, including covariates for treatment group, uACR, T2DM	• DAPA-CKD used to inform all transitions out of CKD stages 1-5 (original model) • Not adjusted by CPRD
Subgroup 2 uACR<22.6mg/mmol with T2DM Weighting: [redacted]%	• Weibull model selected on basis of statistical goodness of fit and through reference to clinical experts' expectations of survival for patients with CKD and albuminuria*	• $DECLARE_{CKD}$ used to inform transitions out of CKD stages 1-3b and DAPA-CKD for CKD stages 4-5 • Not adjusted by CPRD
Subgroup 3 uACR<22.6mg/mmol without T2DM Weighting: [redacted]%	• Same survival model as subgroups 1 and 2, but including non-T2DM mortality adjustment factor of [redacted] (lower event rate compared with diabetic patients)	• Assumed to be the same as subgroup 2 • Not adjusted by CPRD

* This approach was taken because the models fitted individually to $DECLARE_{CKD}$ and DAPA-CKD suggested counter-intuitive results, with lower mortality risks in the DAPA-CKD population than the $DECLARE_{CKD}$ population, despite the former representing a more severe CKD population

- Company used mean age of [redacted] years in all subgroups based on separate CPRD query including people with eGFR less than 90 ml/min/1.73m^2, without formal diagnosis of CKD
- Company explored 3 other approaches for transition probabilities and survival modelling. Broadly varied according to whether datasets were combined or used separately
- **ERG:** Subgroup 1 most closely reflects the DAPA-CKD population

Company updated model using data from DECLARE-TIMI 58 (3/4)

ERG's comments (1/2):

- Reiterates that there is no evidence of efficacy in patients without T2DM and with uACR less than 22.6mg/mmol (subgroup 3 in company's updated model) ➔ this group represents large proportion of target population ([redacted])
  - [redacted] of weighting of QALYs and costs in updated model comes from patients ineligible for DAPA-CKD (i.e. subgroups 2 and 3)
- Inappropriate to include a mix of patient characteristics from 2 separate groups of patients in the CPRD
  - Analysis using older mean age ([redacted] years) from CKD patients having ACE inhibitor/ARB therapy rather than patients without formal CKD diagnosis ([redacted] years) increases subgroup 3 ICER to >£30k/QALY
- More appropriate to consider analysis within the individual subgroups that make up the overall proposed target population rather than weighted analysis
- Results from ERG's double-programmed model different to those from company's post technical engagement model ➔ does not necessarily indicate errors in the model
- Company used the same transition probabilities for subgroups 2 and 3 ➔ the ERG's clinical advisors noted this is probably not appropriate, as rapid CKD progression is more common in people with T2DM

Company updated model using data from DECLARE-TIMI 58 (4/4)

ERG's comments (2/2):

- Company's technical engagement response argues that the amended CPRD dataset is not representative of target CKD population in whom dapagliflozin would be used
  - Raises questions regarding justification for undertaking an adjusted analysis
  - Concerns apply to all company's CPRD-adjusted analyses, including original submission
- Several concerns regarding the company's use of CPRD data and new multivariable survival model using pooled data from $DECLARE_{CKD}$ and DAPA-CKD:
  - Simple pooling of data from separate trials will break randomisation, which may lead to bias in the survival modelling and the group-specific transition probabilities
  - Updated model assumes that same covariates identified from analysis of DAPA-CKD should also apply in pooled dataset of DAPA-CKD and $DECLARE_{CKD}$. ERG unclear whether this would be the case, had original selection procedure been repeated
  - Given the differences between the populations considered in elicitation exercise and economic model, unclear whether new Weibull OS model provides plausible estimates

Questions for committee:

- What mean age should be used in the model?
- Is the company's weighted approach appropriate, or should the subgroups be considered separately?

Issue 2: Modelling approach and OS predictions

Background

- Treatment effects for dapagliflozin on overall survival (OS) are modelled via 2 mechanisms:
  i. Directly – applying treatment-related hazard ratio for OS to each CKD state, from the multivariable survival model to each state-specific OS model except transplant
  ii. Indirectly – applying transition matrices which lead to slower disease progression for dapagliflozin compared with standard of care

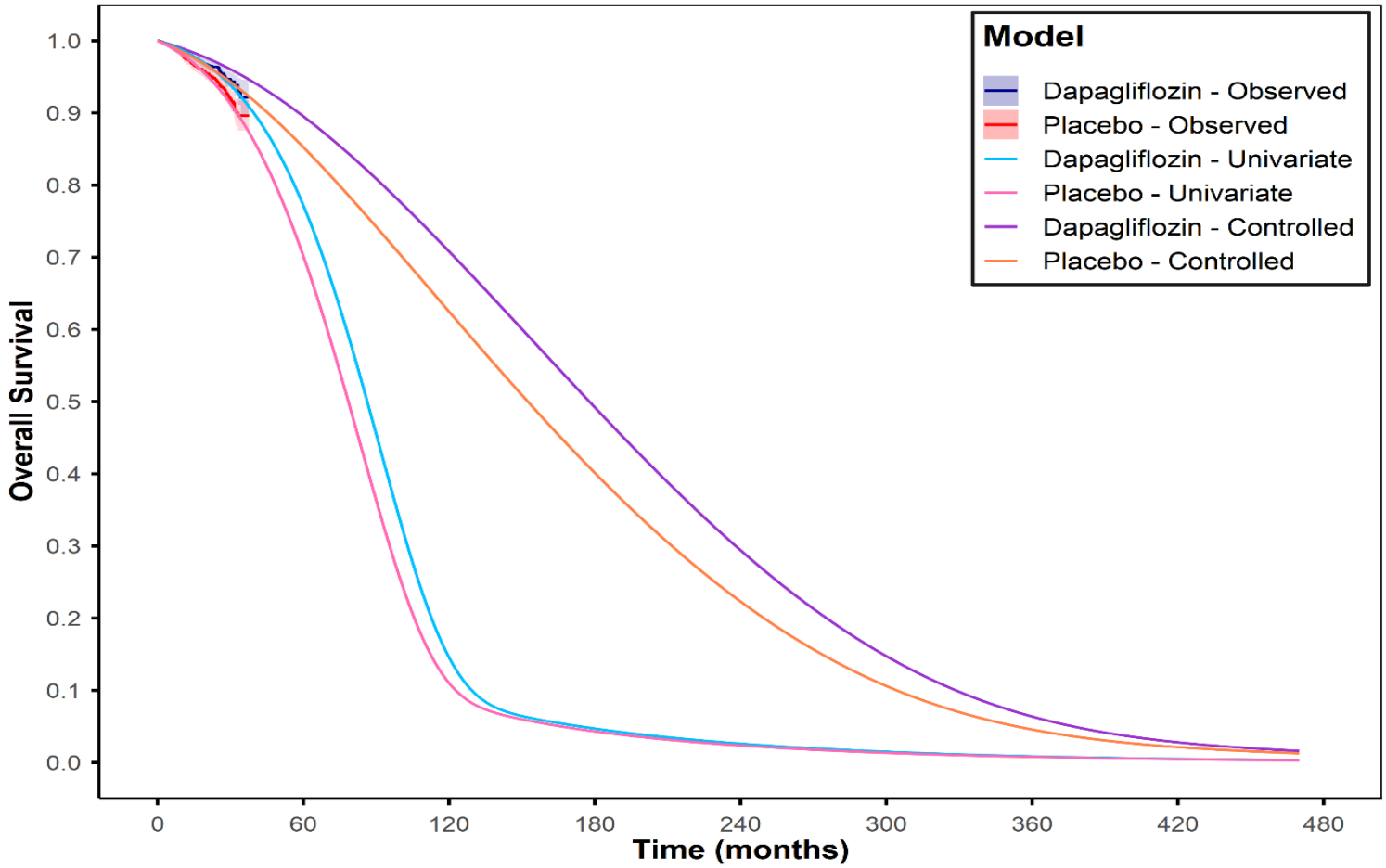
ERG comments - issue of the poor fit of the multivariable OS model unresolved

- Using post-randomisation covariates (CKD stage) is unconventional and can lead to problems in determining causality
  - EMA's guidance cautions against adjusting for post-randomisation covariates because they may be affected by treatments included in the trial. Suggests such analyses might be considered in secondary
- Company's multivariable survival model uses a "mean of covariates" approach which has been shown to lead to bias when estimating survival distributions
  - Prefers that predicted OS be estimated using 'corrected group prognosis' method
- Company's unadjusted economic model for DAPA-CKD population, excluding adjustment to the CPRD population, overestimates OS in both treatment groups ➔ raises some doubts regarding the confidence in results from the company's economic model
  - Suggests a different modelling approach (e.g. multi-state model) as alternative

CPRD: Clinical Practice Research Datalink; EMA: European Medicines Agency; OS: Overall survival

Issue 2: Modelling approach and OS predictions

Observed survival in DAPA-CKD, univariate unadjusted survival curves (Gompertz) and multivariable adjusted survival curves (Gompertz)



Source: Dapafliflozin clarification response B31 update, Figure 1
"Observed" – Kaplan-Meier estimator of OS from DAPA-CKD. "Univariate" – Gompertz model of OS dependent only upon time and treatment status (i.e. without baseline or time-varying CKD adjustment). "Controlled" – Company base case Gompertz model with adjustment cofactors, configured for the DAPA-CKD population. OS predictions from models are economic model output and are dependent upon the time-varying CKD state occupation, including non-Gompertz mortality hazard in transplant and dialysis states

Issue 2: Modelling approach and OS predictions

Company comments:

- No assumption about causality in the cost-effectiveness model
- Modelled overall survival (OS) predictions were validated through expert elicitation
- Multi-state modelling approach proposed by ERG likely to lead to implausible OS predictions
- Last observed eGFR included as a covariate in the multivariable OS model – this means impact of CKD stage on mortality is taken into account
- ***Mean of covariates issue:***
  - Applying "corrected group prognosis" method to the model would be very complex
  - CREDEM-DKD microsimulation suggests that canagliflozin associated with QALY gains. Microsimulation model also considered for dapagliflozin, but deprioritised

ERG's comments:

- Fully specified survival model and code used to fit multivariable OS model not provided by the company. This limits extent to which cause of poor fit could be established by ERG
- Agree that multi-state modelling approach likely leads implausible OS predictions
- Unclear how CREDEM-DKD model QALY estimates are relevant to the OS prediction issue
- Unsure why the company prefers the multivariable model. Agrees that SMR, simple Gompertz and ERG's exploratory analysis 7 provide a better fit OS data in DAPA-CKD
- ICER is unlikely to be >£20,000/QALY even if all the issues with OS prediction are corrected

Question for committee:

- How appropriate is the company's updated modelling approach in predicting OS?

Other considerations

Innovation

- Company submission highlights the following:
  - CKD is associated with a significant clinical and economic burden
  - Current standard of care is inadequate for many patients with CKD, and is associated with clinically relevant adverse events which may limit upward dose titration
  - Dapagliflozin offers a substantial treatment benefit above current standard of care
- During technical engagement, clinical expert feedback suggests there is clear evidence that dapagliflozin can modulate the disease process across the spectrum of CKD, and certainly has the potential to make a significant and substantial impact

Equality

- Patient and clinical expert submissions highlighted that CKD impacts most on people from Black, Asian, and minority ethnic (BAME) backgrounds and socio-economically deprived groups. People from these groups are also more likely to progress quicker to kidney failure and die earlier with CKD

Questions for committee:

- Is dapagliflozin an innovative treatment for CKD?
- Are there any additional benefits with dapagliflozin that have not been captured adequately in the economic model?
- Are there any equality issues relevant to this appraisal?

Company's base-case deterministic cost-effectiveness results

Company's base case deterministic cost-effectiveness results (weighted)*

	Treatment	Inc. QALYs	Inc. costs	ICER
CKD population, treated with ACEi/ARBs, mean age = [redacted]	Dapagliflozin	0.45	£2,069	£4,557
	SoC	-	-	
Derived from weighted analysis of subgroups 1-3 (below) from company's post TE model				

Company's base case deterministic cost-effectiveness results by subgroup*

Subgroup / population	Weighting	Treatment	Inc. QALYs	Inc. costs	ICER
1. Patients with uACR≥22.6mg/mmol	[redacted]	Dapagliflozin	0.59	-£1,183	Dominant
		SoC	-	-	-
2. Patients with uACR<22.6mg/mmol with T2DM	[redacted]	Dapagliflozin	0.52	£2,801	£5,418
		SoC	-	-	-
3. Patients with uACR<22.6mg/mmol without T2DM	[redacted]	Dapagliflozin	0.33	£2,091	£6,285
		SoC	-	-	-

*** Results do not include confidential commercial discounts for comparators/subsequent treatments**

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ICER: Incremental cost-effectiveness ratio; QALYs: Quality adjusted life years; SoC: Standard of care; TE: Technical engagement; T2DM: Type 2 diabetes mellitus; uACR: Urine albumin-to-creatinine ratio

ERG's deterministic cost-effectiveness results

ERG updates to company base case post technical engagement*:

- Considers subgroup results separately rather than company's weighted approach
- Uses older mean age from CPRD: Subgroup 1 = [redacted] years, subgroup 2 = [redacted] years, subgroup 3 = [redacted] years. Company uses [redacted] years

Subgroup	Treatment	QALYs	Costs	ICER
1. Patients with uACR≥22.6mg/mmol	Dapagliflozin	6.00	£48,426	-
	SoC	5.51	£49,389	-
	Incremental	0.49	-£962	**Dominant**
2. Patients with uACR<22.6mg/mmol with T2DM	Dapagliflozin	6.34	£21,016	-
	SoC	6.02	£18,771	-
	Incremental	0.31	£2,245	**£7,189**
3. Patients with uACR<22.6mg/mmol without T2DM	Dapagliflozin	6.29	£21,229	-
	SoC	6.27	£20,060	-
	Incremental	0.03	£1,169	**£44,748**

[redacted]*

*** Results do not include confidential commercial discounts for comparators/subsequent treatments**

CPRD: Clinical practice research datalink; ICER: Incremental cost-effectiveness ratio; QALYs: Quality adjusted life years; SoC: Standard of care; T2DM: Type 2 diabetes mellitus; uACR: Urine albumin-to-creatinine ratio

Back-up slides

Clinical evidence summary (4): DAPA-CKD subgroup results

- Post hoc subgroup analyses were undertaken to obtain effectiveness data for all the relevant subgroups in line with the final NICE scope
- Consistent treatment benefit for dapagliflozin in the analyses of patients with or without comorbid CVD and in patients without comorbid T2DM and without comorbid CVD versus those with comorbid CVD and/or T2DM

Post hoc subgroup analyses of primary efficacy outcome for DAPA-CKD

Source: ERG report post FAC, Figure 6
CVD: Cardiovascular disease; HR: Hazard ratio; T2DM: Type 2 diabetes mellitus

CVD: Cardiovascular disease; T2DM: Type 2 diabetes mellitus

Additional areas of uncertainty

Issue	Description of issue
CPRD adjustment	• Inconsistent to adjust some model parameters to target population using CPRD data while leaving others unadjusted • Implausible that transition probabilities estimated for overall DAPA-CKD population would be identical in CPRD population
Transition probabilities	• Some transition probabilities appear to be clinically implausible
Survival models	• Limited information provided regarding selection of covariables and the selected survival models • Assumption of proportional hazards not well justified, and survival models for dialysis/transplant states based on Sugrue not well justified
Health related quality of life	• Mixture model rather than linear model would have been more appropriate to derive utility values
Costs	• Drug acquisition costs are not adjusted for observed RDI in DAPA-CKD and wastage is not included • Kent et al. and the DISCOVER CKD study likely to underestimate costs for managing CKD stages 1-5 (pre-RRT) • Maintenance costs following transplant from NHS Blood and Transplant fact-sheet may not be reasonable

CPRD: Clinical practice research datalink; RDI: Recommended daily intake; RRT: Renal replacement therapy

NICE recommendations for SGLT2is in CKD

- **NG203 (published Aug 2021):** For adults with CKD and T2DM, offer an SGLT2i, in addition to ARB/ACE inhibitor at optimised dose, if uACR is more than 30 mg/mmol and they meet criteria in MA (including eGFR thresholds)
- ***Type 2 diabetes management - SGLT2is for CKD (sent for consultation Sep 2021):***
  - *i. For adults with CKD and T2DM, offer an SGLT2i, in addition to ARB/ACE inhibitor at optimised dose, if uACR is greater than 30 mg/mmol,*
  - *ii. For adults with CKD and T2DM, consider an SGLT2i, in addition to ARB/ACE inhibitor at optimised dose, if uACR is 3 to 30 mg/mmol,*
  - *For both i and ii, 'and they meet criteria in MA (including eGFR thresholds)'*

Committee considerations:

NG203	T2DM in adults: management
• Noted high costs of SGLT2is and lack of CE evidence. But with positive TA guidance in diabetes without CKD, agreed that with additional renal benefits in CKD, SGLT2is likely to be CE in this population • SGLT2is reduced risk of ESRD, mortality, hospitalisation in T2DM; likely class effect • uACR of 30 mg/mmol = appropriate and consistent criteria based on trial evidence • Evidence of SGLT2is in people with CKD without diabetes not yet strong enough to make recommendation	• Strong evidence that SGLT2is reduced the risk of CKD progression, mortality and CVEs in adults with T2DM and CKD • uACR above 30 mg/mol: SGLT2is likely more effective and cost saving. • uACR of 3 to 30 mg/mmol = SGLT2is likely more effective and cost saving but would prevent fewer events in absolute terms in this group. • No evidence for effectiveness of SGLT2is for people with a baseline uACR of less than 3 mg/mol = research recommendation

CE: Cost-effectiveness; CVE: Cardiovascular event; TA: Technology appraisal

Cost-effectiveness results

Company's original base case deterministic cost-effectiveness results (post clarification)*

Intervention	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
Dapagliflozin	6.21	£53,366	0.50	£3,095	£6,158
SoC	5.71	£50,271	-	-	

LYG: Life year gained; QALY: Quality-adjusted life year; ICER: Incremental cost-effectiveness ratio; Inc.: Incremental; SoC: Standard of care

*** Company's post clarification model and economic analysis reflects a population in whom [redacted] of patients from CPRD dataset were receiving ACEi/ARB therapy**

ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; CPRD: Clinical practice research datalink