AstraZeneca
What science can do

Farxiga's DAPA-CKD trial at ESC

Conference call for investors and analysts

30th August 2020

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Agenda for today's conference call

1. Introduction by Pascal Soriot
2. Presentation by Prof. Hiddo L. Heerspink
3. Q&A

Presenters

Pascal Soriot
Executive Director and
Chief Executive Officer

Hiddo L. Heerspink
Professor Clinical Trials and Personalized Medicine
University Medical Center Groningen

Available for Q&A

David Wheeler
Professor of Kidney Medicine
University College London

Ruud Dobber
Executive Vice President
BioPharmaceuticals Business Unit

Mene Pangalos
Executive Vice President
BioPharmaceuticals R&D

Elisabeth Björk
Senior Vice President
Late CVRM

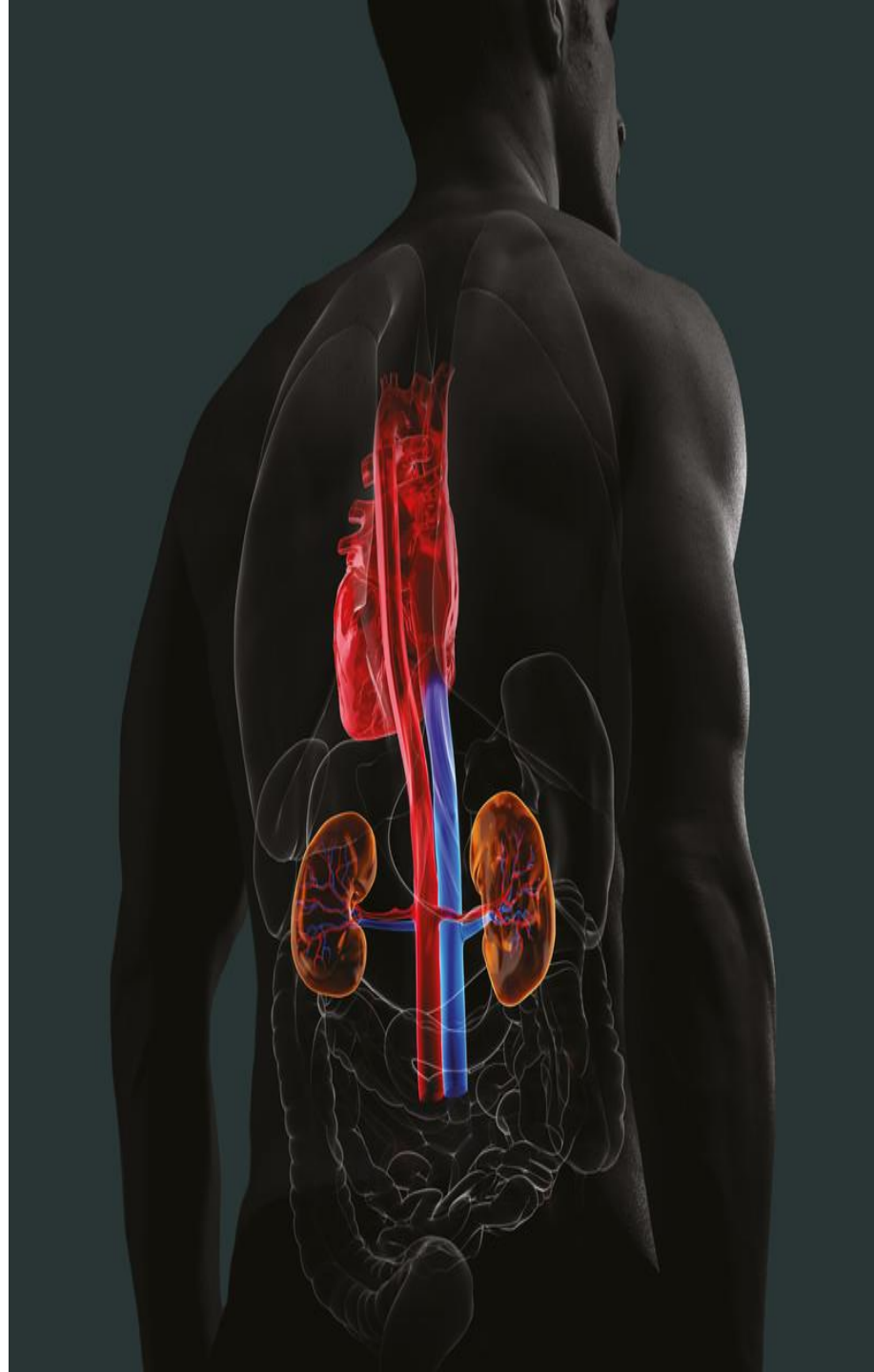
Farxiga continues to deliver

DAPA-CKD yet another important milestone
Follows successful US launch in heart failure

- **2018:** Positive DECLARE data in a broad patient population with **type-2 diabetes**
- **2019:** Ground breaking results in **heart failure** (HFrEF) patients with and without type-2 diabetes
- **2020:** Unprecedented data in **chronic kidney disease** (CKD) in patients with and without type-2 diabetes. First SGLT2 inhibitor to show positive data in a broad CKD population

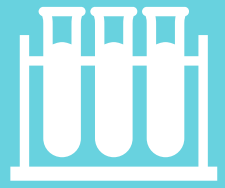
Future data readouts:

- **2021:** Additional **heart failure** data: DELIVER (HFpEF)
- **2021+:** Combination data including AZD9977 combo



CKD is currently highly underdiagnosed with significant morbidity & mortality

Increase awareness



Expand early diagnosis

Transform CKD management

CKD - low awareness and many undiagnosed patients

- 1 in 10 people around the world is living with CKD[1]
- Most adults (90%) with CKD in the US do not know they have it[2]
- Only ~12% of Stage 3 CKD patients are diagnosed in the US[3]
- Overall Medicare costs for people with CKD were over $84 billion in the US in 2017[4]

Sources; 1. Global Kidney Health Atlas 2019: A report by the International Society of Nephrology on the Global Burden of End-stage Kidney Disease and Capacity for Kidney Replacement Therapy and Conservative Care across World Countries and Regions. International Society of Nephrology. Available at www.theisn.org/global-atlas (accessed August 2020). 2. CDC National Chronic Kidney Disease Fact Sheet 2019. Available at https://www.cdc.gov/kidneydisease/pdf/2019_National-Chronic-Kidney-Disease-Fact-Sheet.pdf (accessed August 2020). 3. Analysis based on 2015 NHANES data. 4. CDC Chronic Kidney Disease: Common – Serious – Costly Fact Sheet. Available at https://www.cdc.gov/kidneydisease/pdf/CKD-common-serious-costly-h.pdf (accessed August 2020).

Innovative, complementary CVRM portfolio

Diabetes

farxiga (dapagliflozin) 5mg tablets

BRILINTA ticagrelor tablets

Roxadustat roxadustat

Once-weekly BYDUREON® BCise™ exenatide extended-release injectable suspension 2 mg

Heart Failure

farxiga (dapagliflozin) 5mg tablets

LOKELMA™▼* powder for oral suspension Sodium zirconium cyclosilicate

* Enabling effective treatment for HF

Cardiovascular

farxiga (dapagliflozin) 5mg tablets

BRILINTA ticagrelor tablets

Kidney Disease

farxiga (dapagliflozin) 5mg tablets

LOKELMA™▼ powder for oral suspension Sodium zirconium cyclosilicate

Roxadustat roxadustat

Pipeline includes:

cotadutide (GLP-1[1]/glucagon co-agonist) NASH[2]
AZD4831 (MPO[3] inhibitor) HFpEF[4]
AZD5718 (FLAP[5] inhibitor) CAD
AZD9977 + *Farxiga* (MCR[6] modulator/SGLT2) HF with CKD
AZD2693 (PNPLA3[7] inhibitor) NASH

1. Glucagon-like peptide-1 2. Non-alcoholic steatohepatitis 3. Myeloperoxidase 4. Heart failure with preserved ejection fraction 5. 5-Lipoxygenase activating protein 6. Mineralocorticoid receptor 7. Patatin-like phospholipase domain-containing protein 3.

Dapagliflozin in Patients with Chronic Kidney Disease DAPA-CKD

Hiddo L. Heerspink

Department of Clinical Pharmacy and Pharmacology

University Medical Center Groningen

DAPACKD

umcg

UCL DEPARTMENT OF RENAL MEDICINE

Disclosures

- HJLH is a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Gilead, Janssen, Merck, Mundi Pharma, Mitsubishi Tanabe, Novo Nordisk, and Retrophin.
  He has received research support from Abbvie, AstraZeneca, Boehringer Ingelheim and Janssen.

DAPACKD

Rationale for the DAPA-CKD trial

- Chronic kidney disease (CKD) is an important contributor to cardiovascular (CV) morbidity, all-cause mortality and diminished quality of life[1]
- Until recently, the only classes of medication specifically proven to slow progression of CKD were ACE inhibitors or ARBs
- Sodium glucose cotransporter 2 (SGLT2) inhibitors, including dapagliflozin, have shown favorable effects on CV and kidney outcomes in large clinical trials in patients with type 2 diabetes[2-5]
- The DAPA-HF trial showed that dapagliflozin reduced the risk of worsening heart failure or death from CV causes, independently of the presence of diabetes[6]
- We hypothesized that dapagliflozin could also preserve kidney function and improve outcomes in people with chronic kidney disease, independently of the presence of diabetes

1. GBD Chronic Kidney Disease Collaboration. Lancet 2020;395:709-733. 2. Zinman B. et al. N Engl J Med 2015;373:2117-2128. 3. Neal B. et al. N Engl J Med 2017;377:644-657. 4. Wiviott SD. et al. N Engl J Med 2019;380:347-357. 5. Perkovic V. et al. N Engl J Med 2019; 380:2295-2306. 6. McMurray J. et al. N Engl J Med 2019; 381:1995-2008.

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Objectives

- To assess whether treatment with dapagliflozin, compared with placebo, reduced the risk of renal and CV events in people with CKD with or without type 2 diabetes, and who are receiving standard of care including a maximum tolerated dose of an ACE inhibitor or ARB

- **Primary outcome**
  - Composite outcome of sustained ≥50% eGFR decline, ESKD, renal or CV death

- **Secondary outcomes (in hierarchical order)**
  - Composite outcome of sustained ≥50% eGFR decline, ESKD or renal death
  - CV death or hospitalizations for heart failure
  - All-cause mortality

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.

Heerspink HJL. et.al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282.

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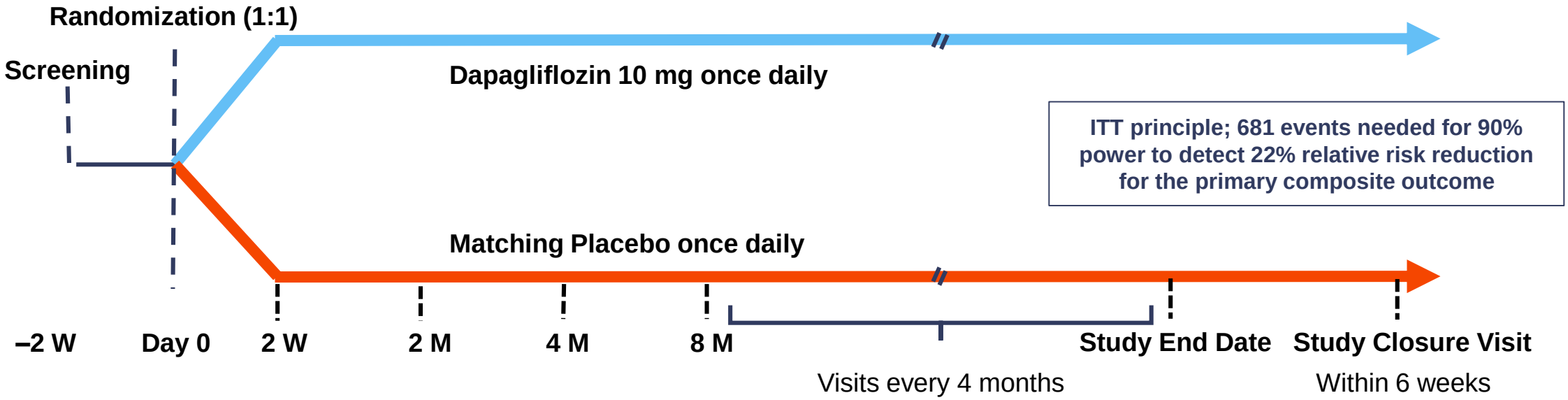
Study Design

Key inclusion criteria:
- ≥18 years of age
- eGFR 25 to 75 mL/min/1.73m^2
- UACR 200 to 5000 mg/g (22.6 to 565 mg/mmol)
- Stable maximum tolerated labelled dose of ACEi or ARB for ≥4 weeks (if not contraindicated)

Key exclusion criteria:
- Type 1 diabetes
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy within 6 months prior to enrollment



- Outcome analysis based on Cox proportional hazard model stratified by type 2 diabetes and UACR and adjusted for eGFR

ANCA, anti-neutrophil cytoplasmic antibody; ITT, intention-to-treat; UACR, urinary albumin-to-creatinine ratio.

Heerspink HJL. et.al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282; Wheeler DC. et.al. Nephrol Dial Transplant. 2020 DOI 10.1093/ndt/gfaa234.

DAPA-CKD: 21 countries, 386 sites, 4304 participants

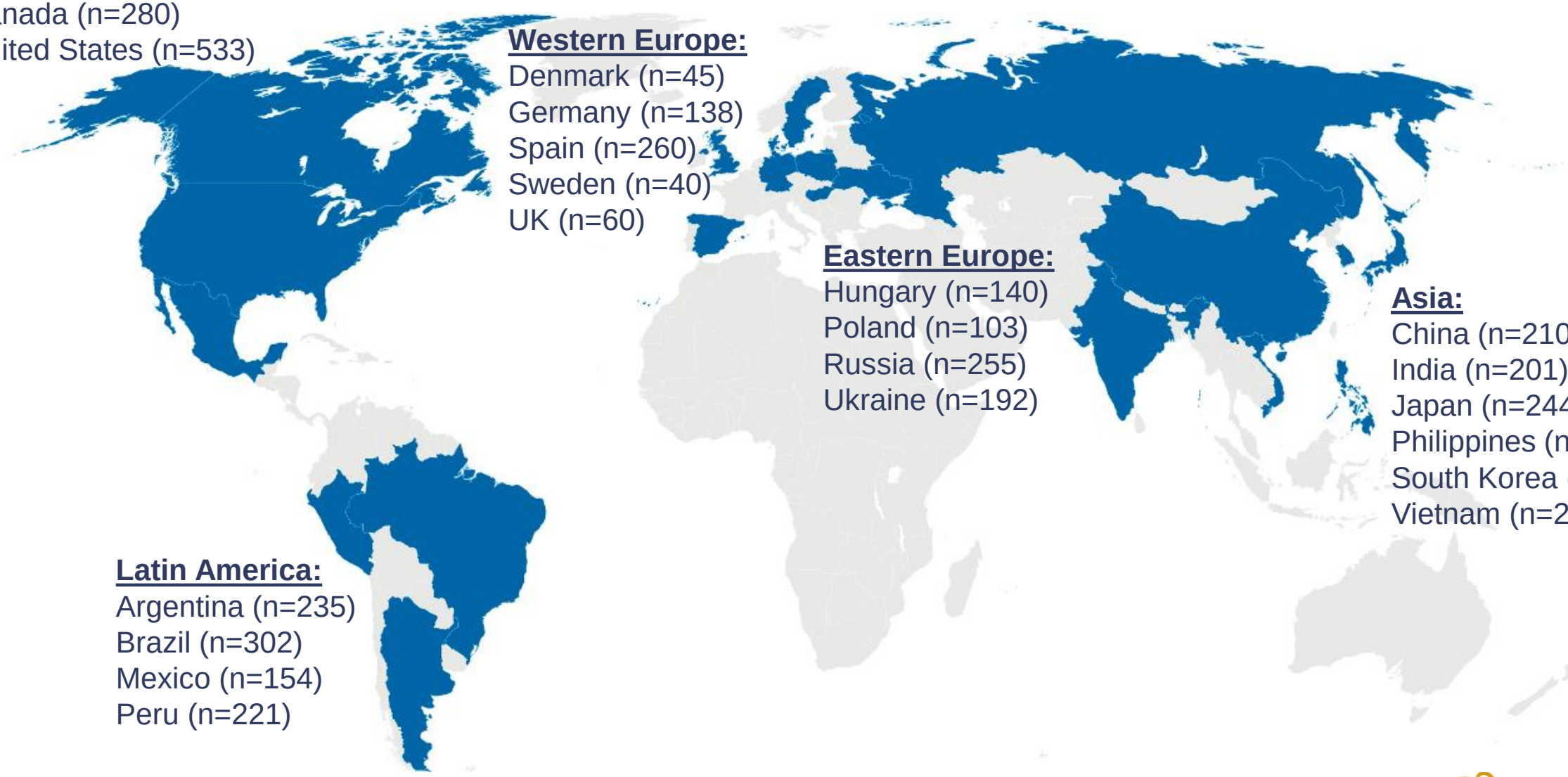
North America:
Canada (n=280)
United States (n=533)

Western Europe:
Denmark (n=45)
Germany (n=138)
Spain (n=260)
Sweden (n=40)
UK (n=60)

Eastern Europe:
Hungary (n=140)
Poland (n=103)
Russia (n=255)
Ukraine (n=192)

Asia:
China (n=210)
India (n=201)
Japan (n=244)
Philippines (n=115)
South Korea (n=294)
Vietnam (n=282)

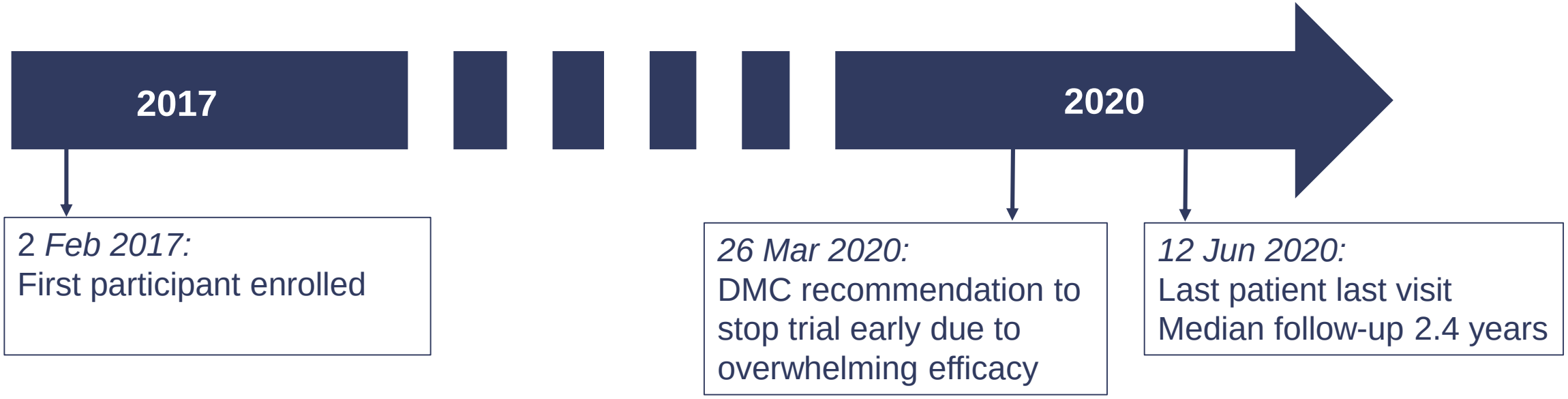
Latin America:
Argentina (n=235)
Brazil (n=302)
Mexico (n=154)
Peru (n=221)



DAPACKD

 Heerspink HJL. et.al. Nephrol Dial Transplant. 2020 Feb 1;35(2):274-282.

Study timeline

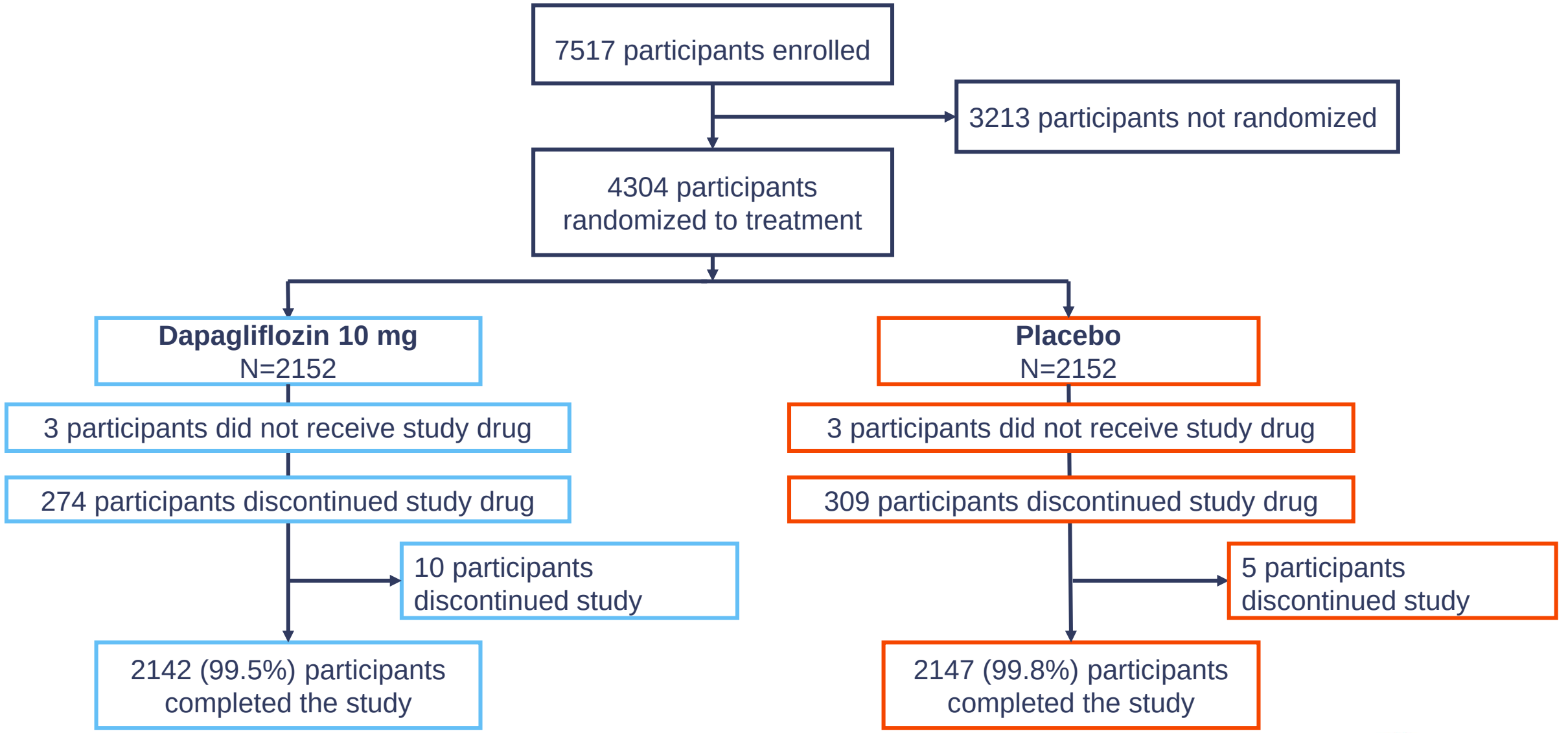


After a regular review meeting, the Independent DMC recommended on 26 March that the trial be stopped due to overwhelming efficacy, based on 408 primary endpoint events (60% of planned events)

DMC, data monitoring committee

 Heerspink HJL. et.al. Presented at ESC 2020.

Patient disposition



4299 (99.9%) vital status known; 4289 (99.7%) completed study

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 Heerspink HJL. et.al. Presented at ESC 2020.

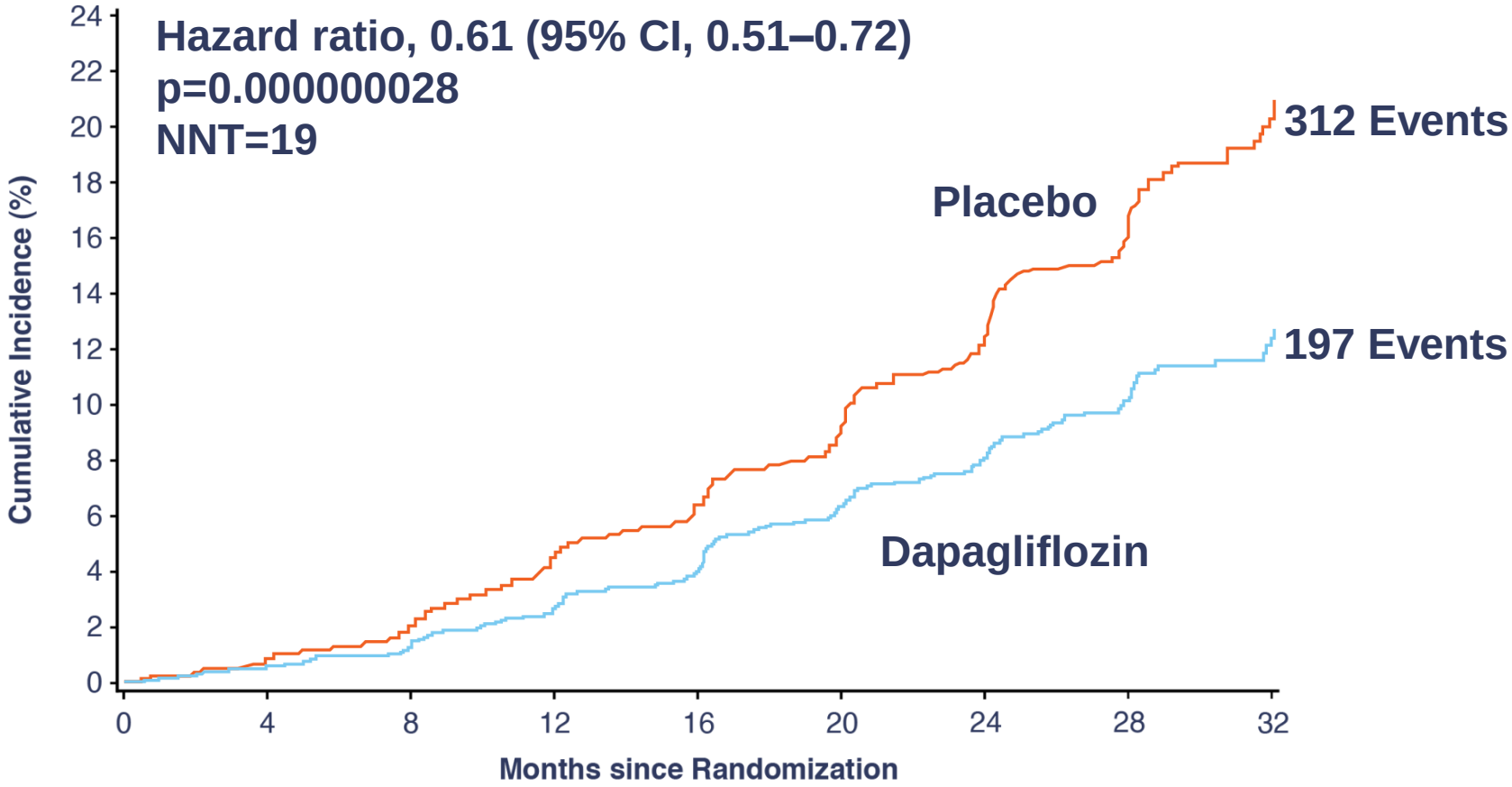
Baseline characteristics

	Dapagliflozin (N=2152)	Placebo (N=2152)
Age, years, mean	62	62
Sex, female, %	33	33
Race, %		
White	52	54
Black or African-American	5	4
Asian	35	33
Other	8	8
Type 2 diabetes, %	68	67
Systolic blood pressure, mmHg, mean	137	137
eGFR, mL/min/1.73m^2, mean	43	43
UACR, mg/g, median	965	934
ACEi or ARB, %	97	97

DAPACKD

 Wheeler DC. et.al. Nephrol Dial Transplant. 2020 DOI 10.1093/ndt/gfaa234.

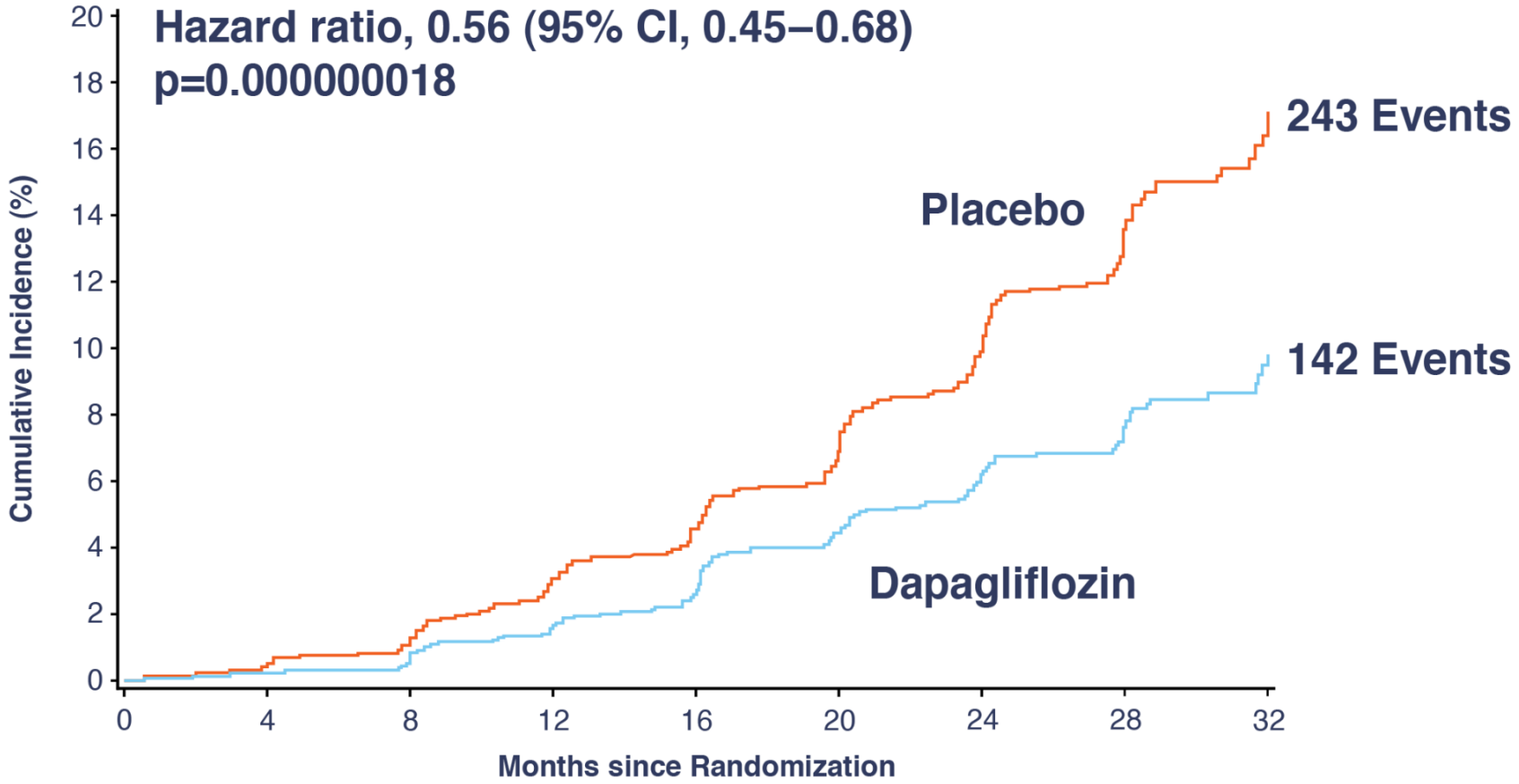
Primary outcome:
Sustained ≥50% eGFR decline, ESKD, renal or CV death



No. at Risk									
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

DAPACKD

Secondary outcome:
Sustained ≥50% eGFR decline, ESKD, renal death



No. at Risk									
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

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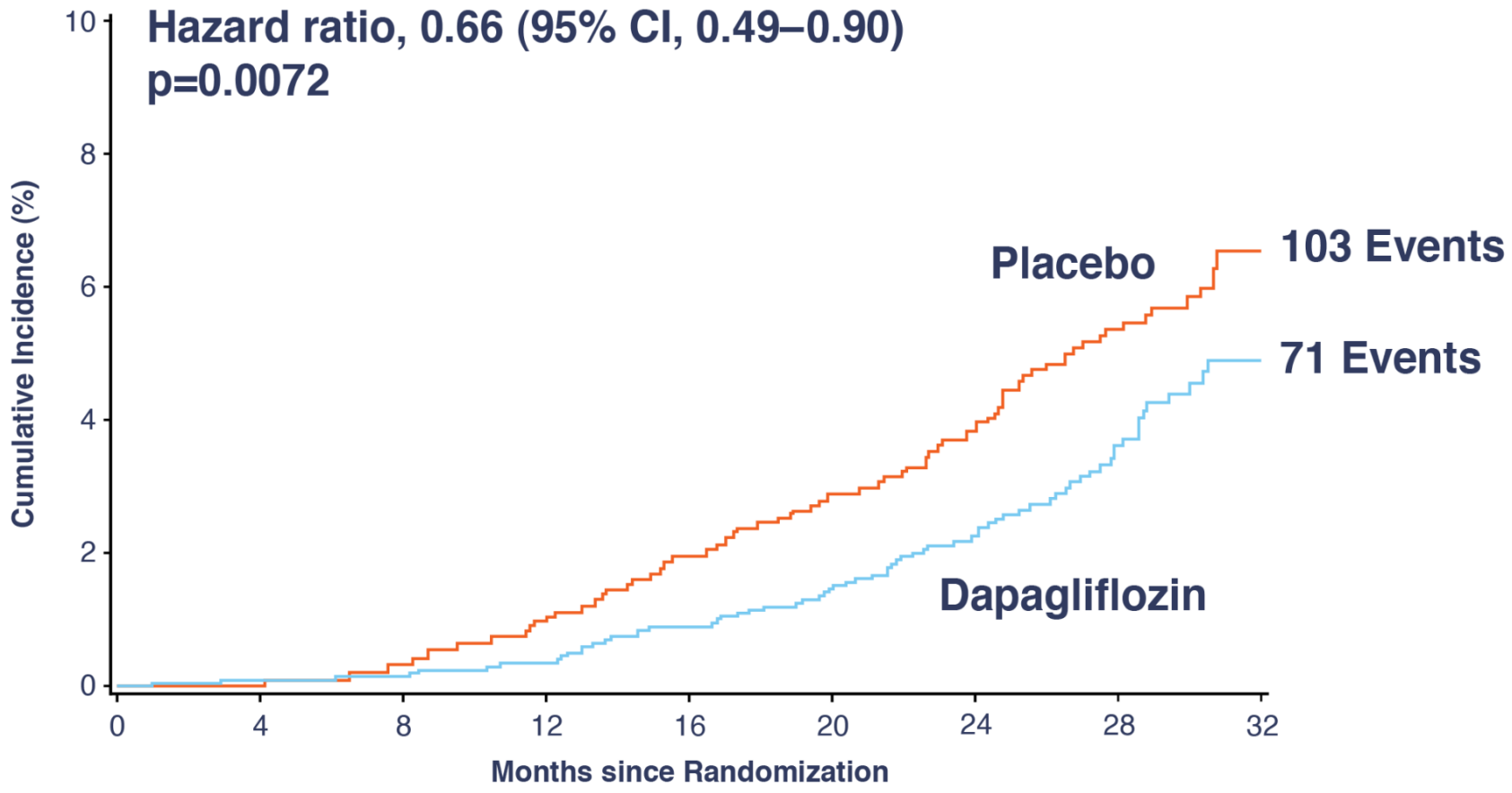
Chronic dialysis, kidney transplantation, renal death



No. at Risk									
Dapagliflozin	2152	2035	2021	2004	1977	1887	1481	985	373
Placebo	2152	2031	2006	1971	1936	1849	1444	955	356

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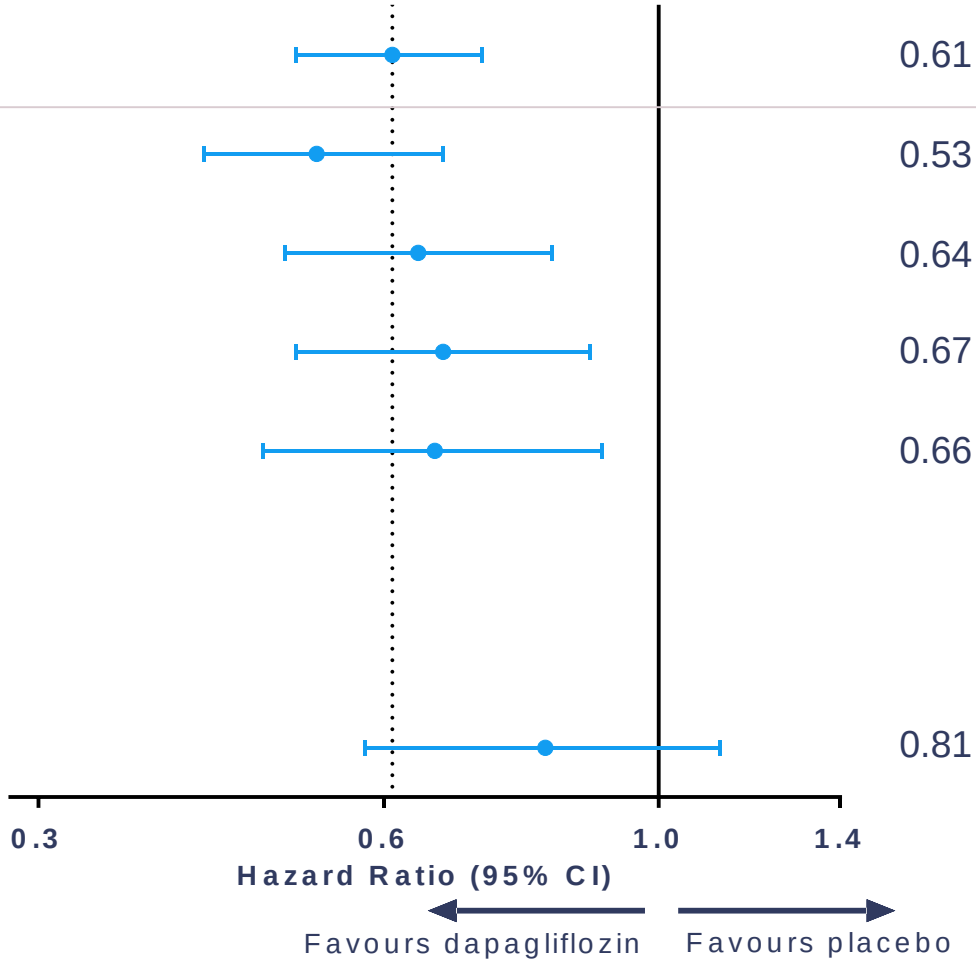
Summary of the primary outcome and its components

	Dapagliflozin events	Placebo events	Hazard Ratio (95% CI)	p-value
Primary composite endpoint	197	312	0.61 (0.51, 0.72)	0.000000028
≥50% eGFR decline	112	201	0.53 (0.42, 0.67)	<0.0001
ESKD	109	161	0.64 (0.50, 0.82)	0.0004
eGFR <15 mL/min/1.73m^2	84	120	0.67 (0.51, 0.88)	0.0045
Chronic dialysis	68	99	0.66 (0.48, 0.90)	0.0080
Transplantation	3	8	NC	
Renal death	2	6	NC	
CV death	65	80	0.81 (0.58, 1.12)	0.2029

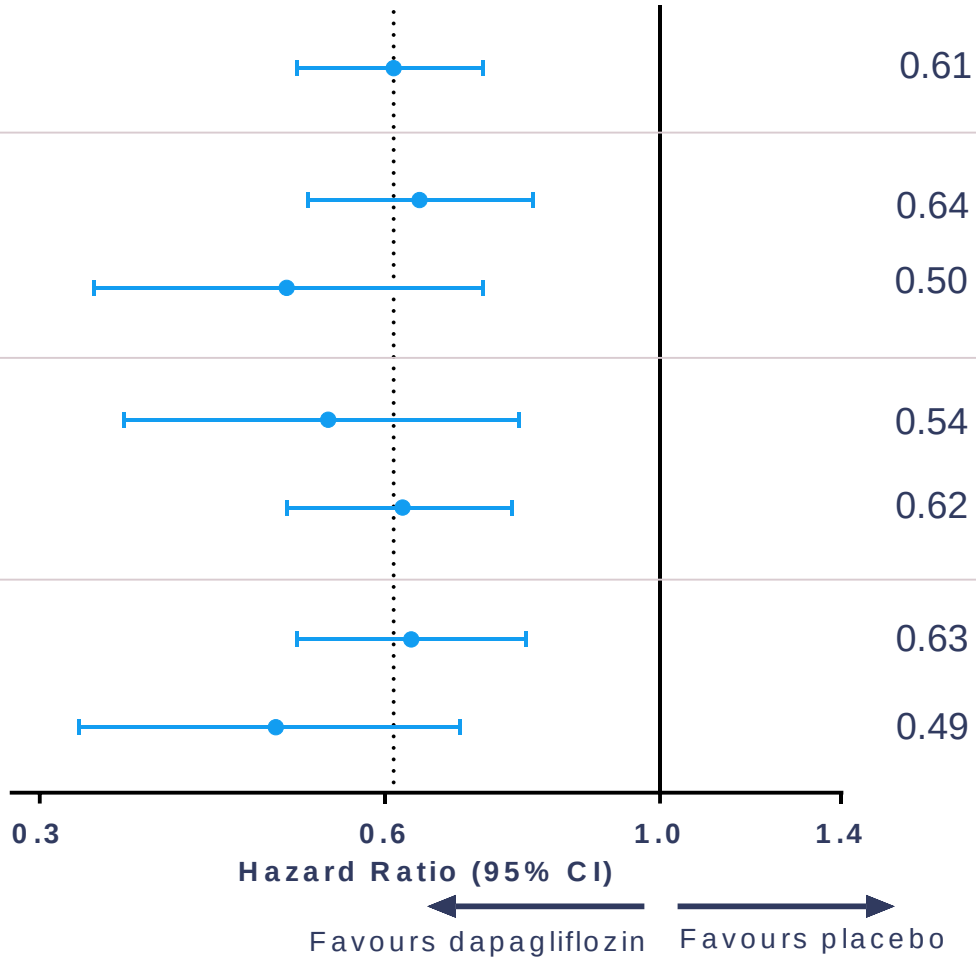


NC, not calculable

Heerspink HJL. et.al. Presented at ESC 2020.

Primary outcome – pre-specified subgroup analysis

	Dapagliflozin events	Placebo events	Hazard Ratio (95% CI)	p-value interaction
All patients	197	312	0.61 (0.51, 0.72)	
With type 2 diabetes	152	229	0.64 (0.52, 0.79)	
Without type 2 diabetes	45	83	0.50 (0.35, 0.72)	0.24
UACR ≤1000 mg/g	44	84	0.54 (0.37, 0.77)	
UACR >1000 mg/g	153	228	0.62 (0.50, 0.76)	0.52
eGFR <45 mL/min/1.73m²	152	217	0.63 (0.51, 0.78)	
eGFR ≥45 mL/min/1.73m²	45	95	0.49 (0.34, 0.69)	0.22



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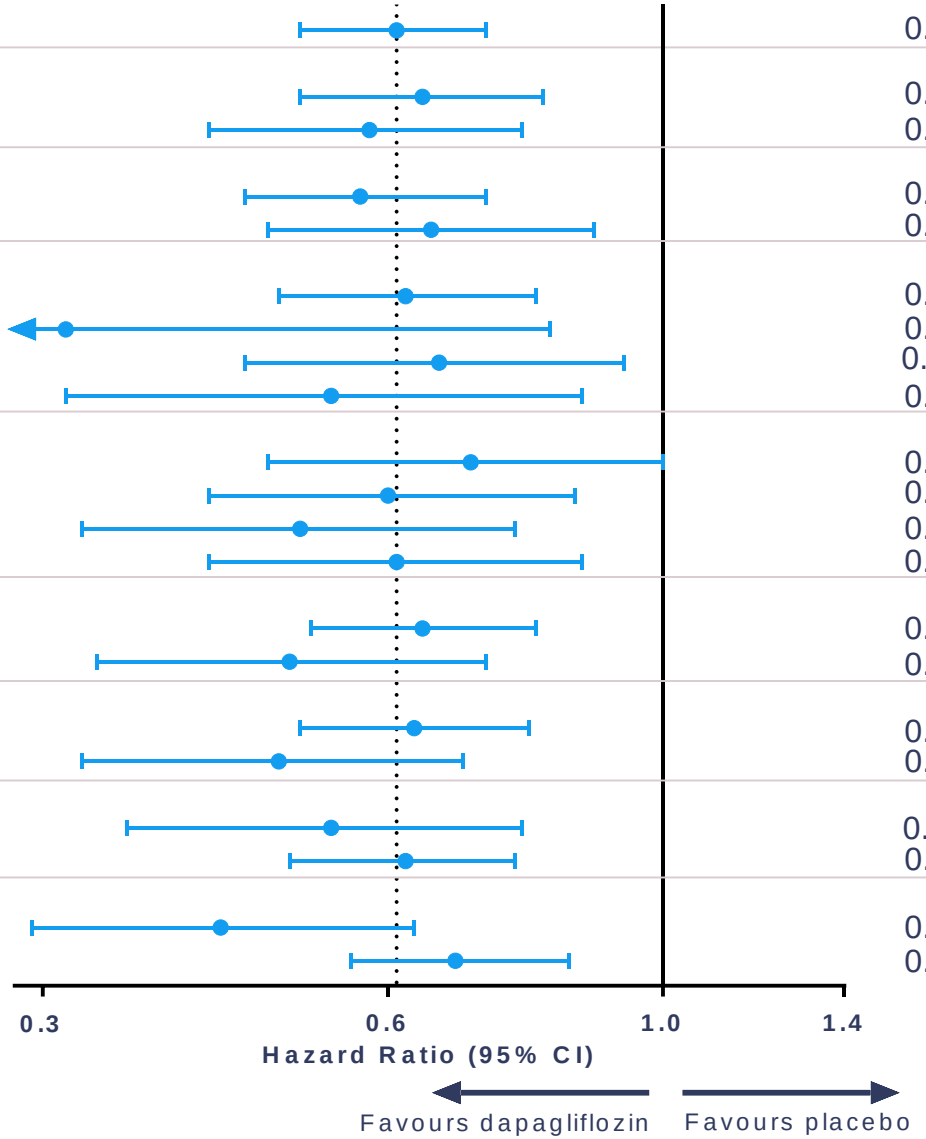
Primary outcome – pre-specified subgroup analysis

	Dapagliflozin events	Placebo events	Hazard ratio (95% CI)	p-value interaction
All patients	197	312	0.61 (0.51, 0.72)	
Age				
≤65 years	122	191	0.64 (0.51, 0.80)	
>65 years	75	121	0.58 (0.43, 0.77)	0.53
Sex				
Male	126	209	0.57 (0.46, 0.72)	
Female	71	103	0.65 (0.48, 0.88)	0.50
Race				
White	110	174	0.62 (0.49, 0.79)	
Black	7	14	0.33 (0.13, 0.81)	
Asian	53	77	0.66 (0.46, 0.93)	
Other	27	47	0.54 (0.33, 0.86)	0.68
Region				
Asia	50	69	0.70 (0.48, 1.00)	
Europe	57	89	0.60 (0.43, 0.85)	
North America	35	69	0.51 (0.34, 0.76)	
Latin America	55	85	0.61 (0.43, 0.86)	0.77
Diabetes				
With type 2 diabetes	152	229	0.64 (0.52, 0.79)	
Without type 2 diabetes	45	83	0.50 (0.35, 0.72)	0.24
eGFR				
<45 mL/min/1.73m^2	152	217	0.63 (0.51, 0.78)	
≥45 mL/min/1.73m^2	45	95	0.49 (0.34, 0.69)	0.22
UACR				
≤1000 mg/g	44	84	0.54 (0.37, 0.77)	
>1000 mg/g	153	228	0.62 (0.50, 0.76)	0.52
SBP				
≤130 mmHg	46	96	0.44 (0.31, 0.63)	
>130 mmHg	151	216	0.68 (0.56, 0.84)	0.04



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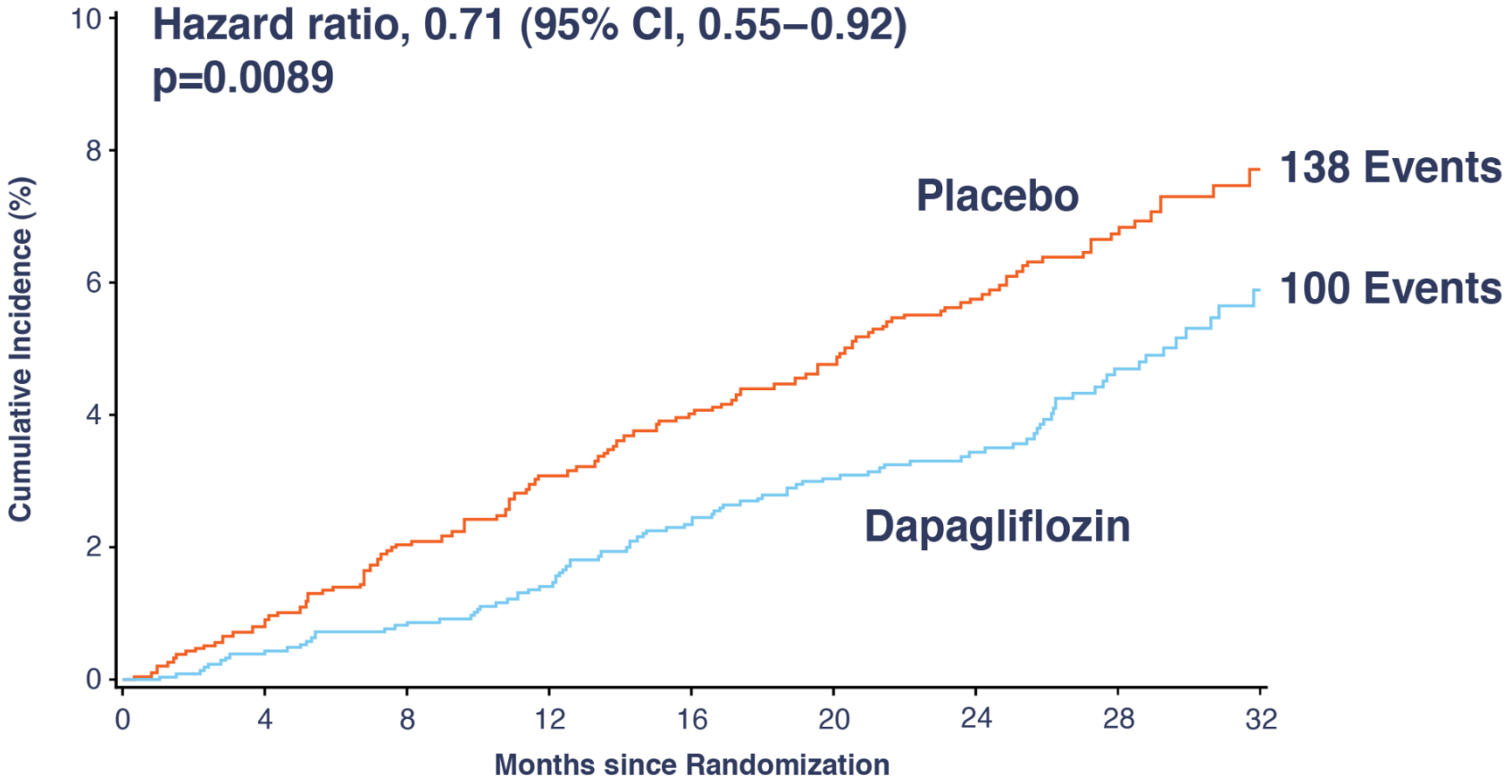
 Heerspink HJL. et.al. Presented at ESC 2020.

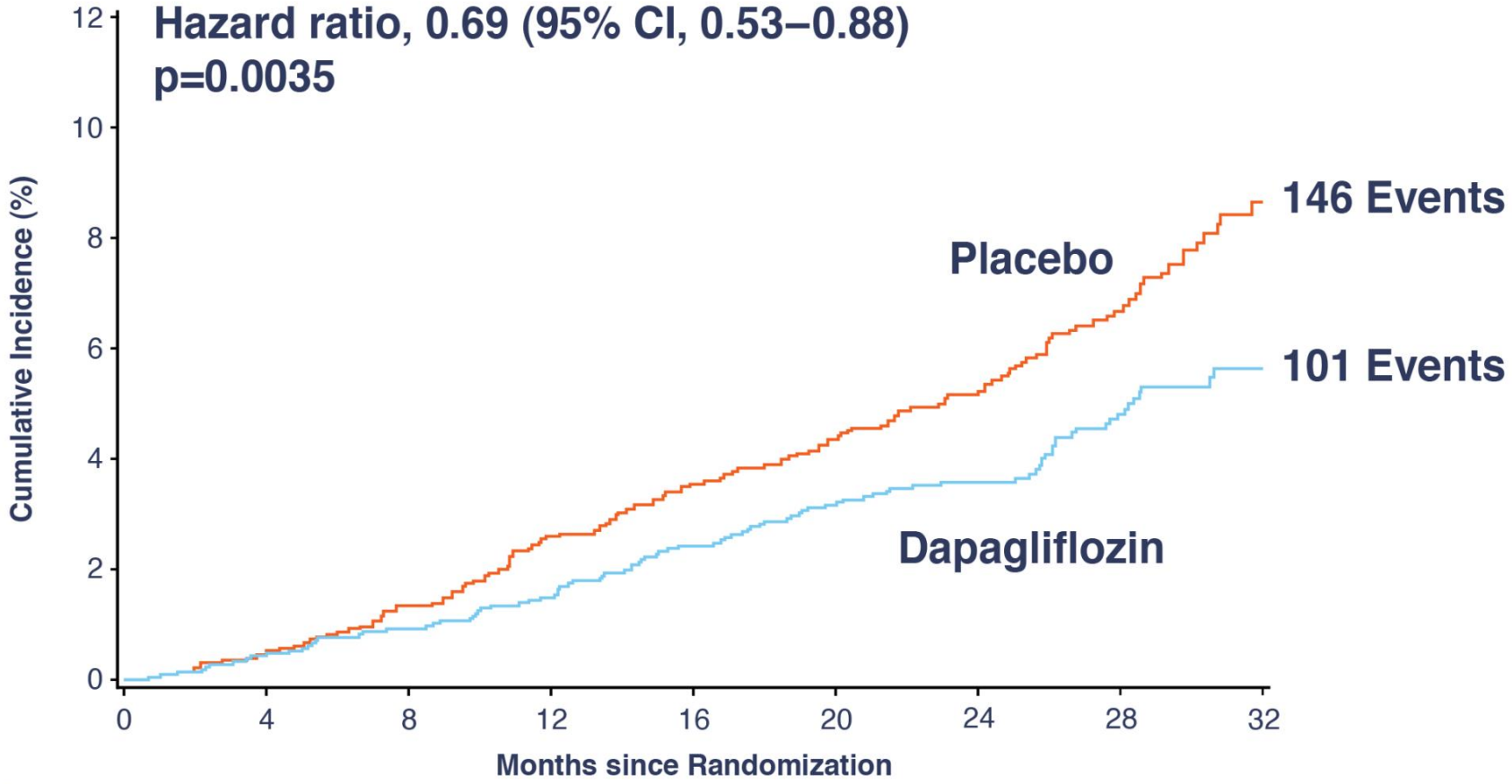
Secondary outcome:
CV death or heart failure hospitalization



No. at Risk									
Dapagliflozin	2152	2035	2021	2003	1975	1895	1502	1003	384
Placebo	2152	2023	1989	1957	1927	1853	1451	976	360

DAPACKD

Secondary outcome: All-cause mortality



No. at Risk									
Dapagliflozin	2152	2039	2029	2017	1998	1925	1531	1028	398
Placebo	2152	2035	2018	1993	1972	1902	1502	1009	379

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 Heerspink HJL. et.al. Presented at ESC 2020.

Safety

Safety outcomes*, n (%)	Dapagliflozin (N=2149)	Placebo (N=2149)
Discontinuation of study drug	274 (12.8)	309 (14.4)
Discontinuation due to adverse event	118 (5.5)	123 (5.7)
Any serious adverse event	633 (29.5)	729 (33.9)
Adverse events of interest		
Amputation†	35 (1.6)	39 (1.8)
Any definite or probable diabetic ketoacidosis	0	2 (0.1)
Fracture‡	85 (4.0)	69 (3.2)
Renal related adverse event‡	155 (7.2)	188 (8.7)
Major hypoglycaemia §	14 (0.7)	28 (1.3)
Volume depletion‡	127 (5.9)	90 (4.2)
Serious adverse events of volume depletion	22 (1.0)	18 (0.8)

*Safety outcomes reported in participants on and off treatment; †surgical or spontaneous/non-surgical amputation, excluding amputation due to trauma; ‡based on pre-defined list of preferred terms; §AE with the following criteria confirmed by the investigator: i) symptoms of severe impairment in consciousness or behaviour, ii) need of external assistance, iii) intervention to treat hypoglycaemia, iv) prompt recovery of acute symptoms following the intervention

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Conclusion

- In patients with CKD, with and without type 2 diabetes, dapagliflozin compared to placebo:
  - Reduced the risk of kidney failure
  - Reduced the risk of death from CV causes or hospitalization for heart failure
  - Prolonged survival

- Dapagliflozin was well tolerated, in keeping with its established safety profile

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DAPA-CKD
21 countries, 386 sites, 4304 participants

Thank You

The DAPA-CKD team would like to thank the following:

Members of the DAPA-CKD Executive Committee
Hiddo J.L. Heerspink, David C. Wheeler, Glenn Chertow, Ricardo Correa-Rotter, Tom Greene, Fan Fan Hou, John McMurray, Peter Rossing, Robert Toto, Bergur Stefansson, and Anna Maria Langkilde

Members of the DAPA-CKD Independent Data Monitoring Committee
Marc A. Pfeffer, Stuart Pocock, Karl Swedberg, Jean L. Rouleau, Nishi Chaturvedi, Peter Ivanovich, Andrew S. Levey, and Heidi Christ-Schmidt

Members of the DAPA-CKD Event Adjudication Committee
Claes Held, Christina Christersson, Johannes Mann, and Christoph Varenhorst

The DAPA-CKD team would also like to thank all participating investigators, the patients and their families!

Q&A

Use of AstraZeneca conference call, webcast and presentation slides