Finerenone in combination with empagliflozin for the treatment of chronic kidney disease in type 2 diabetes

CONFIDENCE – A randomised controlled trial

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Disclaimer

- This presentation may contain information regarding indications and/or instructions which differ from the approved use of products available in Canada.

- The indication for which finerenone is currently approved for use in Canada can be found in the complete product monograph at: https://pdf.hres.ca/dpd_pm/00067806.PDF [accessed 03 APR 2024].

- Statements of fact and opinions expressed are those of the speaker and do not necessarily reflect the opinions or position of the sponsor (Bayer Inc).

CKD, chronic kidney disease; EMA, European Medicines Agency; FDA, US Food and Drug Administration; T2D, type 2 diabetes

Executive summary

CONFIDENCE — **CO**mbinatio**N** effect of **FI**nerenone an**D** **E**mpagliflozi**N** in participants with CKD and T2D using an UA**C**R **E**ndpoint study – [NCT05254002]

Objective

- To investigate the efficacy and safety of finerenone in combination with empagliflozin compared with either empagliflozin alone or finerenone alone in patients with CKD and T2D

Primary efficacy endpoints

- Relative change in UACR from baseline to 180 days for:
  - **Combination therapy** vs **empagliflozin**
  - **Combination therapy** vs **finerenone**

Key inclusion criteria

- Aged ≥18 years
- T2D with HbA1c <11%
- eGFR 40–90 ml/min/1.73 m²*
- UACR ≥300–<5000 mg/g (≥33.9–<565 mg/mmol)

Key safety endpoints

- Change in eGFR from baseline to 30 days
- Change in eGFR from 30 to 180 and 210 days
- eGFR decline >30% at 30 days
- Incidences (n, %) of:
  - AKI, hyperkalaemia, severe hypoglycaemia, symptomatic hypotension, genital mycotic events
- AEs, ECG, laboratory and vital signs

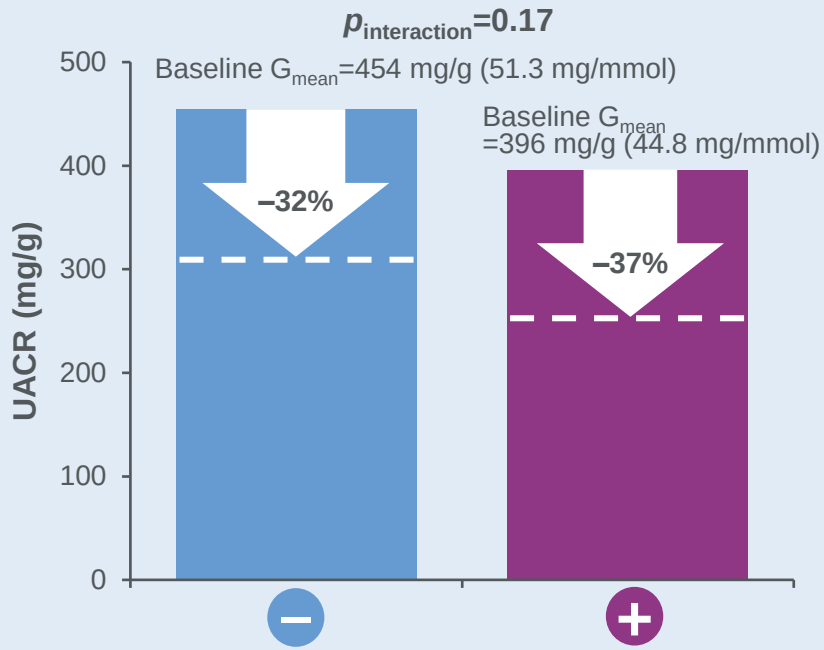
*Patients will require at least one value of eGFR <60 ml/min/1.73 m^2 within the previous 3 months or have registered diagnosis of CKD. Patients with an eGFR >75–90 ml/min/1.73 m² will be capped at 20%. Following feedback from DMC and safety analysis, participants with eGFR 30–90 ml/min/1.73 m² may also be recruited, with the same cap as in the first round of recruitment

AE, adverse event; AKI, acute kidney injury; DMC, data monitoring committee; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; UACR, urine albumin-to-creatinine ratio

Study rationale – Clinical background

- Guidelines recommend **SGLT-2is** as **first-line therapy for the management of CKD in T2D**[1,2], based on the results of the CREDENCE and DAPA-CKD trials[3,4]
  - **Empagliflozin** is currently being investigated in a dedicated CKD trial[5] and has significantly **reduced UACR** in phase III trials[6,7]
  - However, despite the kidney benefits of SGLT-2is, a **residual risk of decline** in kidney function remains[3,4]
- In phase III trials, **finerenone** demonstrated **kidney and CV benefits** in patients with CKD and T2D, including sustained **reductions in UACR**[8–10], a surrogate marker for kidney outcomes[11]
  - Subgroup analyses suggest that finerenone improves kidney and CV outcomes, and reduces UACR, **irrespective of SGLT-2i use at baseline**[12,13]
- More data are needed from randomised controlled trials on the potential **combination of finerenone and SGLT-2is**

Reduction in UACR (%) with finerenone vs placebo in FIDELITY[13]



CV, cardiovascular; G_{mean}, geometric mean; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

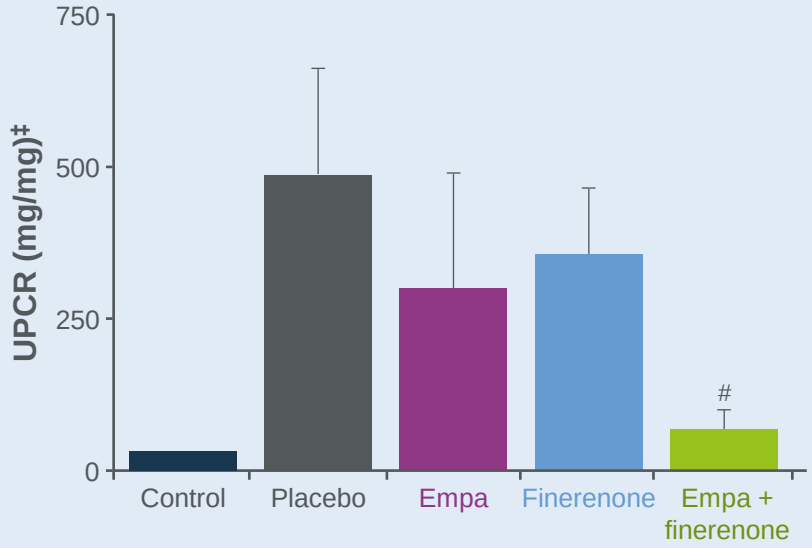
1. Kidney Disease Improving Global Outcomes. *Kidney Int Suppl* 2020;98:S1–S115; 2. American Diabetes Association. *Diabetes Care* 2022;45:S175–S184; 3. Perkovic V, *et al. N Engl J Med* 2019;380:2295–2306; 4. Heerspink HJL, *et al. N Engl J Med* 2020;383:1436–1446; 5. Herrington WG, *et al. Clin Kidney J* 2018;749–761; 6. Cherney D, *et al. Diabetologia* 2016;59:1860–1870; 7. Cherney D, *et al. Lancet Diabetes Endocrinol* 2017;5:610–621; 8. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 9. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263; 10. Agarwal R, *et al. Eur Heart J* 2021: doi:10.1093/eurheartj/ehab777; 11. Heerspink HJL, *et al. Lancet Diabetes Endocrinol* 2019;7:128–139; 12. Rossing P, *et al. Kidney Int Rep* 2021;7:36–45; 13. Rossing P, *et al.* ASN Kidney Week 2021; abstract SA-OR22

Study rationale – Preclinical data supporting finerenone + SGLT-2i combination therapy

- In a rodent model of hypertension-induced cardiorenal disease,* finerenone and empagliflozin **combination therapy** had a **significant additive effect** on **UPCR** versus either drug alone at low doses

- This evidence indicates a **potential synergistic effect** between finerenone and SGLT-2is that warrants further investigation

UPCR at Week 6 in a preclinical model of cardiorenal disease



CONFIDENCE study hypothesis: Finerenone + empagliflozin combination therapy is superior in reducing UACR compared with empagliflozin alone or finerenone alone

*Hypertensive L-NAME treated renin-transgenic (mRen2)27 rats; controls were normotensive renin-transgenic (mRen2)27 rats treated with captopril; #$p<0.05$ vs placebo; ‡Mean ± SEM
L-NAME, N(ω)-nitro-L-arginine methyl ester; SEM, standard error; UPCR, urine protein-to-creatinine ratio
Kolkhof P, *et al. Am J Nephrol* 2021;52:642–652

Objective

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To investigate the efficacy and safety of finerenone in combination with empagliflozin compared with either empagliflozin alone or finerenone alone in patients with CKD and T2D

Patient population

Key inclusion criteria

	**Aged ≥18 years**
	**T2D*** (with HbA1c <11% at screening visit)
	**eGFR 40–90 ml/min/1.73 m²#** and **UACR‡ ≥300–<5000 mg/g (≥33.9–<565 mg/mmol)** at screening visit
	Treated with **maximum tolerated dose of ACEi or ARB** for >1 month prior to screening visit

Key exclusion criteria

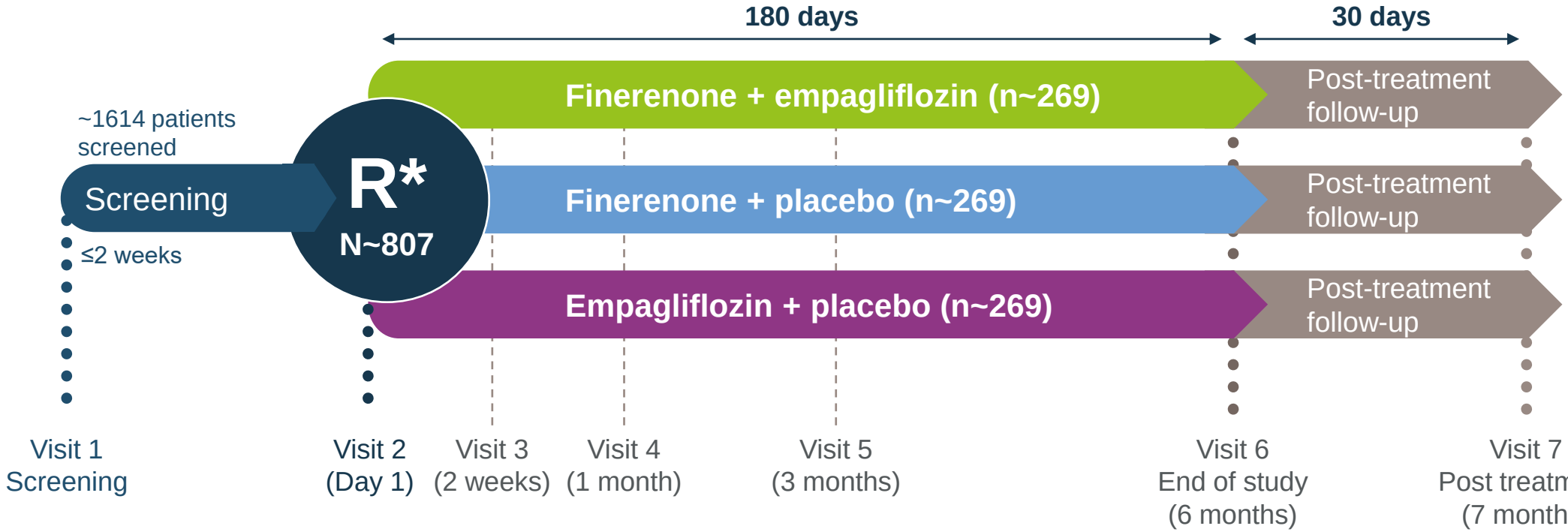
	**T1D**
	**Serum [K⁺] >4.8 mmol/l** at screening visit
	**BP >160/100 mmHg** or **SBP <90 mmHg** at baseline visit
	**Treatment with** the following **medications**§: • SGLT-2i or SGLT-1/2i • Finerenone or another MRA • Medications affecting serum [K⁺]
	**Hepatic insufficiency** classified as Child-Pugh C

*T2D diagnosed according to ADA guidelines[1]. Historical values of HbA1c within 3 months of screening visit accepted; #eGFR calculated according to CKD-EPI formula. Patients will require at least one value of eGFR <60 ml/min/1.73 m² within the previous 3 months or have registered diagnosis of CKD. Patients with an eGFR >75–90 ml/min/1.73 m² will be capped at 20%. Following feedback from DMC and safety analysis, participants with eGFR 30–90 ml/min/1.73 m² may also be recruited, with the same cap as in the first round of recruitment; ‡Mean value from three morning void samples; § Medications to be discontinued at least 8 weeks prior to screening visit and during study duration

ACEi, angiotensin-converting enzyme inhibitor; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; BP, blood pressure; CKD-EPI, chronic kidney disease epidemiology collaboration; [K⁺], potassium concentration; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; SGLT-1, sodium-glucose co-transporter-1; T1D, type 1 diabetes

American Diabetes Association. *Diabetes Care* 2022;45:S17–S38

Trial design – phase II, randomised, double-blind, multicentre prospective trial



Finerenone dosed at **10 to 20 mg od** based on serum [K^+] and eGFR. Dosage may be modified through the study#

Empagliflozin dosed at **10 mg od**

Assessments

- Blood and urine samples
- ECG
- BP
- Physical examination
- AEs

*Randomised patients stratified by eGFR (<60 and ≥60 ml/min/1.73 m²) and UACR (≤850 mg/g and >850 mg/g [≤96.1 mg/mmol and >96.1 mg/mmol]); #Finerenone (or its equivalent placebo) up-titration to the target dose of 20 mg allowed from Visit 4 onwards. Down-titration allowed at any time during the study for safety reasons
od, once daily; R, randomisation

Key efficacy and safety endpoints

Primary efficacy endpoints

Relative change in UACR from baseline to 180 days for:

finerenone + empagliflozin combination
vs
empagliflozin

OR

finerenone + empagliflozin combination
vs
finerenone

Key safety endpoints

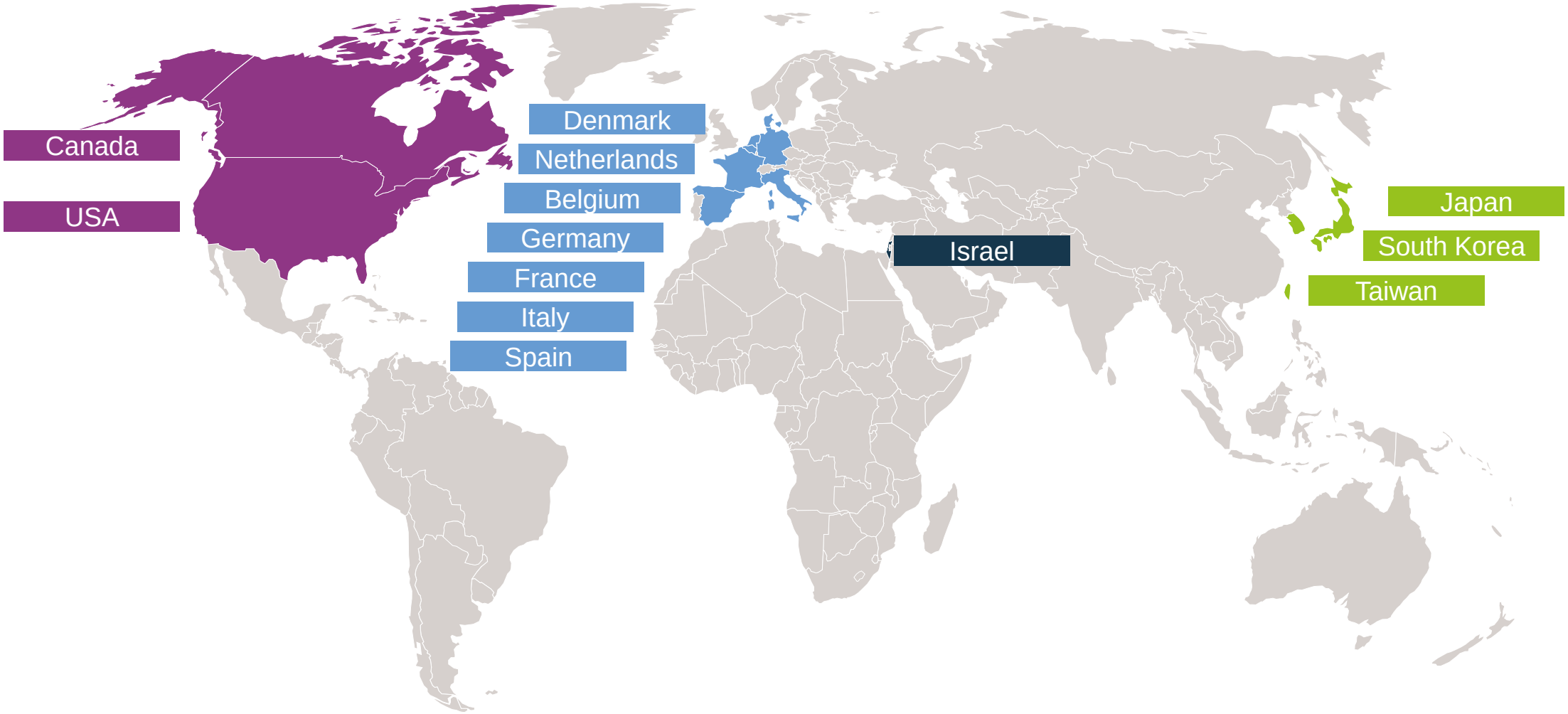
- Change in eGFR from baseline to 30 days
- Change in eGFR from 30 days to 180 and 210 days
- eGFR decline >30% from baseline to 30 days
- Incidences (n, %) of:
  - AKI
  - Hyperkalaemia*
  - Severe hypoglycaemia
  - Symptomatic hypotension
  - Genital mycotic events
- Monitoring of AEs, ECG, laboratory and vital signs

Primary objective

To assess whether the combination of finerenone and empagliflozin is superior in reducing UACR compared with empagliflozin alone **or** finerenone alone[#]

*Moderate hyperkalaemia defined as serum [K^+] >5.5–≤6.0 mmol/l; severe hyperkalaemia as >6.0 mmol/l; [#]Using a Bonferroni-Holm correction to adjust for multiplicity of the two endpoints

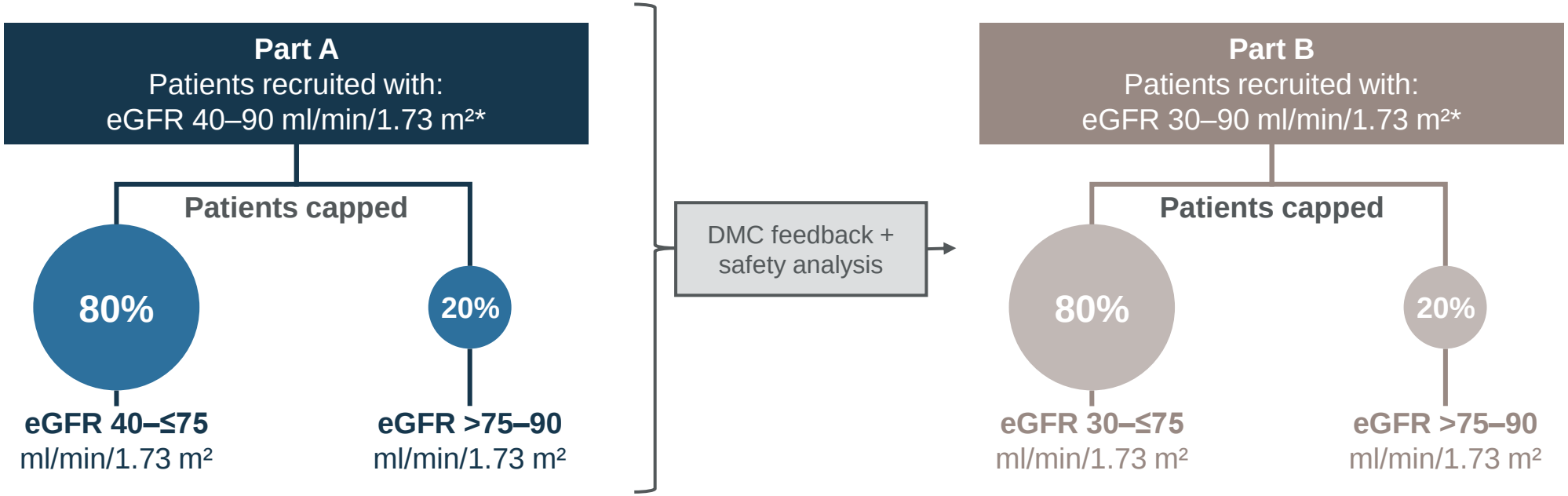
CONFIDENCE is a global trial conducted in 125 centres across 13 countries



Back-up

eGFR recruitment cap

An interactive web response system will allow capping of participants based on eGFR categories



*With at least one value of eGFR <60 ml/min/1.73 m² within previous 3 months or registered diagnosis of CKD

Study phase

- **CONFIDENCE was classified as a phase II trial as opposed to a phase IV trial due to the following factors:**
  - Finerenone has not yet been approved in all participating countries
  - Empagliflozin is not yet approved for CKD in any participating country
  - The hypothesis is exploratory in nature (despite the study being powered to address it)
  - The primary UACR endpoint is not recognised as an acceptable efficacy endpoint by the FDA or EMA*

*Accepted by the Pharmaceuticals and Medical Devices Agency