PREFACE

We, the staff members of the Division of Pharmacology have started half-yearly newsletter "Capsule". It will be supplied to all the divisions of our faculty.

It will give relevant information about the updated status of premarket drugs that are in various phases of clinical trial and also the recent advances / status of the drug in current use.

We sincerely hope that this data will be useful and informative to all the staff members of RMMC&H. Any constructive criticism or suggestions that would be warmly welcome. We also request Heads of the Division to send their feedback about this newsletter.

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Our sincere Thanks to

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VERICIGUAT

- ✓ Approved by FDA on 19th January, 2021.
- ✓ Indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic HF and ejection fraction (EF) less than 45%.

CHEMICAL DATA

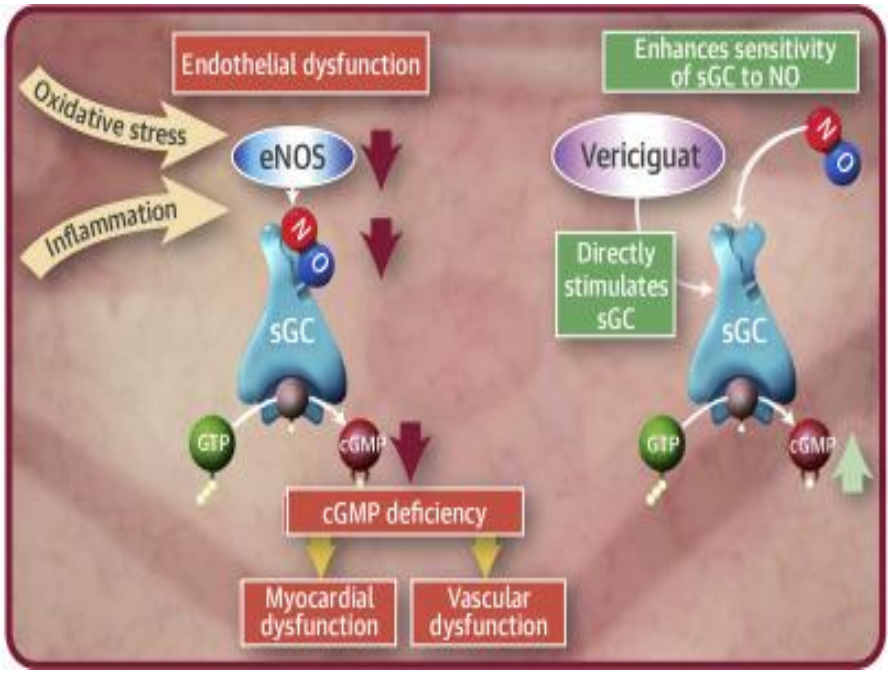
- ✓ Molecular formula: $C_{19}H_{16}F_2N_8O_2$
- ✓ Molecular weight: 426.39 g/mol.

PHARMACOKINETICS

- ✓ Route of administration-Oral
- ✓ Dosage-2.5mg,5mg,10mg
- ✓ Volume of distribution-44L
- ✓ Half life - 30 hours
- ✓ Bioavailability-93%(when taken with food)
- ✓ Plasma protein binding-98%
- ✓ Metabolism-UGT1A9
- ✓ Excretion-excreted as inactive metabolite in Urine

PHARMACODYNAMICS

- ✓ Vericiguat is an orally active drug used to treat patients with Heart Failure with reduced Ejection Fraction ie EF<45%
- ✓ It is a stimulator of soluble Guanylate cyclase (sGC)



CLINICAL STUDIES

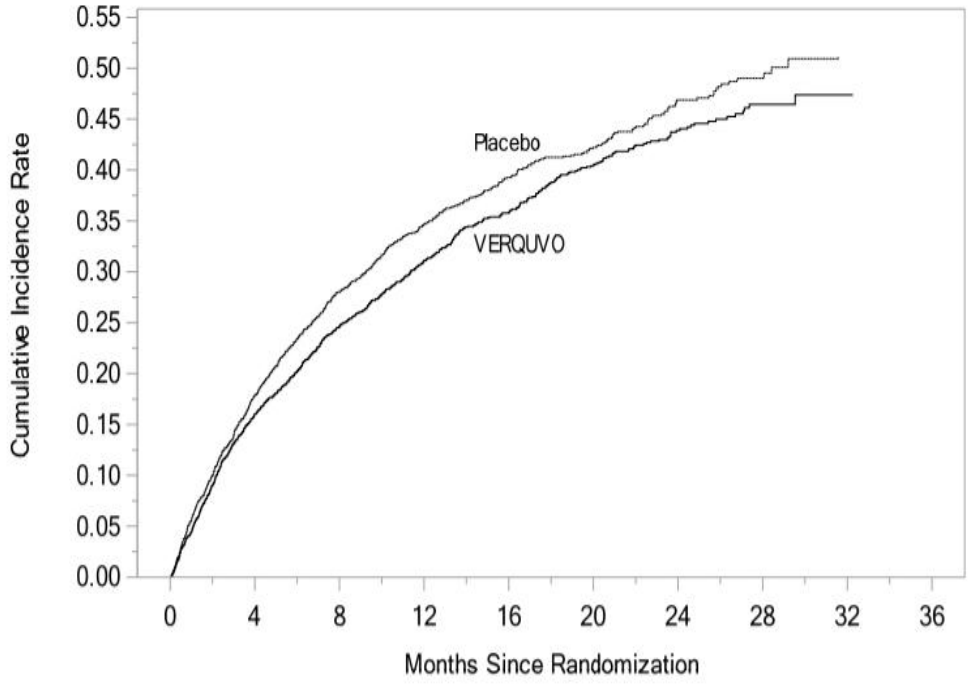
- ✓ VICTORIA was a randomized, parallel-group, placebo-controlled, double-blind, event-driven, multi-center trial.
- ✓ It compares VERICIGUAT and placebo in 5,050 adult patients with symptomatic chronic heart failure (New York Heart Association [NYHA] class II-IV) and left ventricular ejection fraction (LVEF) less than 45% following a worsening heart failure event.

- ✓ A worsening heart failure event was defined as heart failure hospitalization within 6 months before randomization or use of outpatient IV diuretics for heart failure within 3 months before randomization
- ✓ The primary endpoint was a composite of time to first event of CV death or hospitalization for heart failure.
- ✓ The median follow-up for the primary endpoint was 11 months.

Treatment Effect for the Primary Composite Endpoint and the Secondary Endpoints of Cardiovascular Death and Heart Failure Hospitalization

	VERQUVO N=2,526		Placebo N=2,524	
	n (%)	Event rate: % of patients per year*	n (%)	Event rate: % of patients per year*
Primary endpoint				
Composite of cardiovascular death or heart failure hospitalization¶	897 (35.5)	33.6	972 (38.5)	37.8
Secondary endpoints				
Cardiovascular death	414 (16.4)	12.9	441 (17.5)	13.9
Heart failure hospitalization	691 (27.4)	25.9	747 (29.6)	29.1

Figure 2: Kaplan-Meier Curve for the Primary Composite Endpoint



Number of subjects at risk

VERQUVO	2526	2099	1621	1154	826	577	348	125	1	0
Placebo	2524	2053	1555	1097	772	559	324	110	0	0

ADVERSE DRUG REACTIONS

- ✓ Hypotension (16%)
- ✓ Anemia (10%)

CONTRAINDICATION

- ✓ Contraindicated in Pregnancy.
- ✓ Contraindicated with concomitant use of other SGC stimulators and PDE-5 inhibitors.

DRUG INTERACTIONS

- ✓ Drugs which increase gastric pH like Proton pump inhibitors or antacids

- ✓ Severe hypotension occurs with PDE-5 inhibitors

SAFETY DATA

- ✓ PREGNANCY : No data on human study.
- ✓ LACTATION : No data on human study.
- ✓ REPRODUCTIVE AGE : Advised to verify pregnancy status before initial treatment.
- ✓ PAEDIATRIC : Safety and Efficacy had not been established.
- ✓ GERIATRIC : No dose adjustment required.
- ✓ RENAL AND HEPATIC IMPAIRMENT: No need of dose adjustment in patients with eGFR>15ml/min/1.73m² and with mild to moderate hepatic impairment (Child Pugh A or B) respectively

PHARMACOECONOMICS

- ✓ Each 2.5mg and 5 mg tablet costs 20.96$
- ✓ Each 10mg tablet costs 20.60$

DASIGLUCAGON

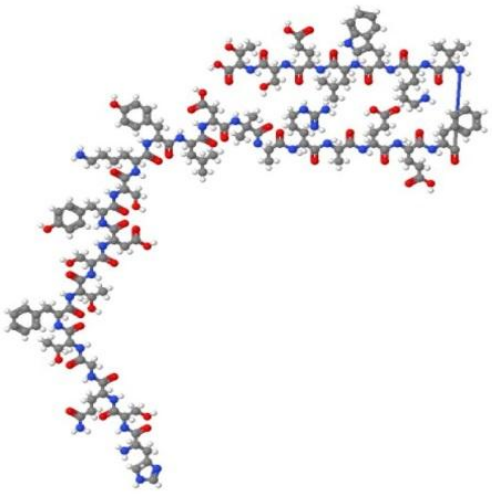
DESCRIPTION

DASIGLUCAGON hydrochloride.

- glucagon analogue.
- hyperglycaemic agent
- **29 amino acids.**

CHEMICAL DESCRIPTION

- **<u>MOLECULAR FORMULA</u>:**
- **$C_{152}H_{222}N_{38}O_{50}$**
- molecular mass - **3382 g/mol**.
- **<u>STRUCTURAL FORMULA</u>:**
- Dasiglucagon - 29 amino acids.



Dasiglucagon

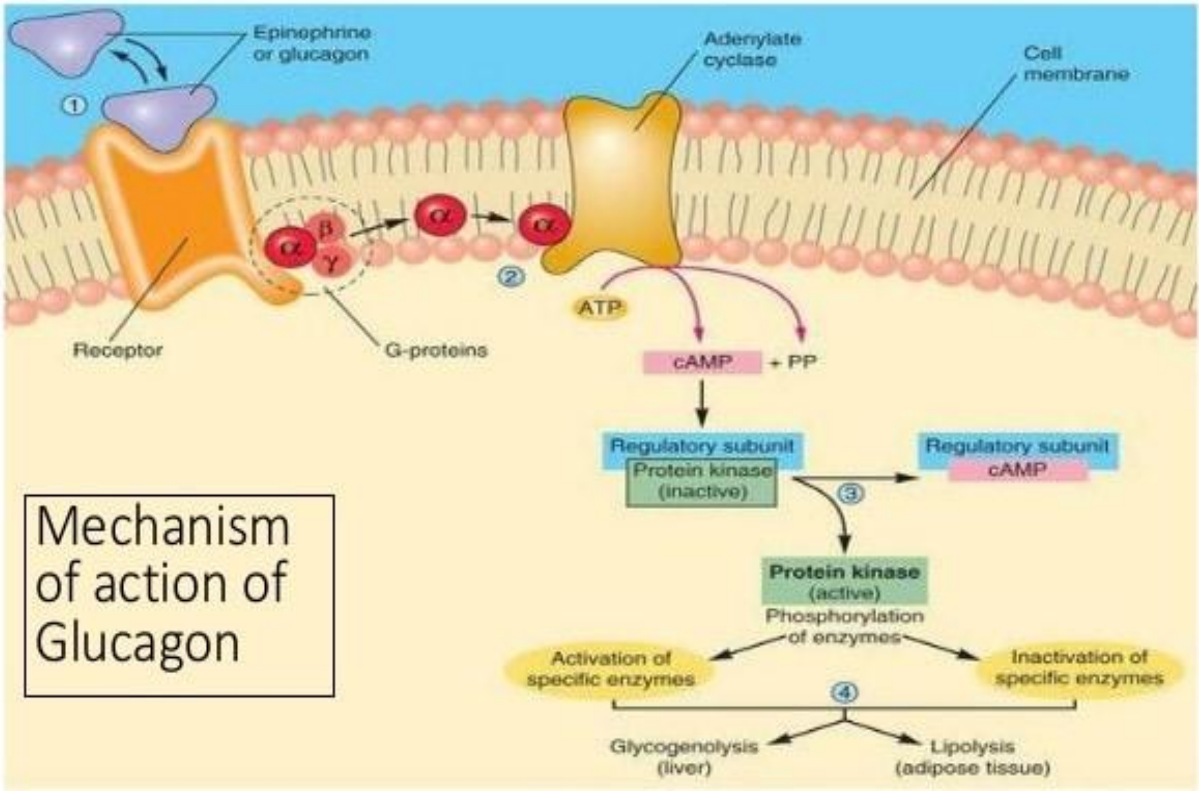
- Anti hypoglycemic agent

INDICATION

For hypoglycemia in pediatric (> 6 years) & adult diabetic patients.

- Approved by FDA on March 2021.

MECHANISM OF ACTION



Glucagon receptor agonist,

⬇

Activating hepatic glucagon receptors,

⬇

Stimulating glycogen breakdown

⬇

Release of glucose from the liver.

Hepatic stores of glycogen are necessary

PHARMACOKINETICS

- Administration :subcutaneous injection of 0.6 mg.
- Distribution :Apparent volume of distribution- 47 L to 57 L.
- Elimination : half-life - 30 minutes.
- Metabolism : cleared like native glucagon through proteolytic degradation pathways in blood, liver, and kidney.

	ADULTS	**CHILDREN**
mean peak plasma concentration	5110 pg/mL	3920 pg/mL
	At 35 minutes.	At 21 minutes

PHARMACODYNAMICS

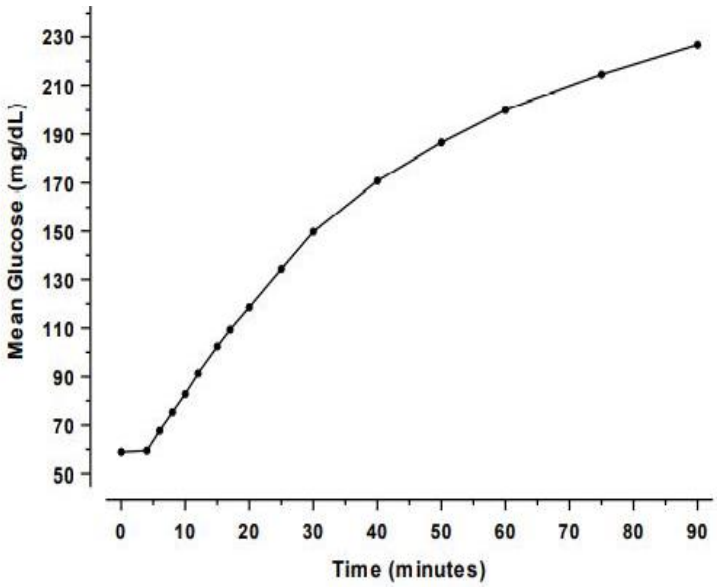


Figure 1 Mean plasma glucose over time in adults with type 1 diabetes administered 0.6 mg dasiglucagon

PHARMACODYNAMICS

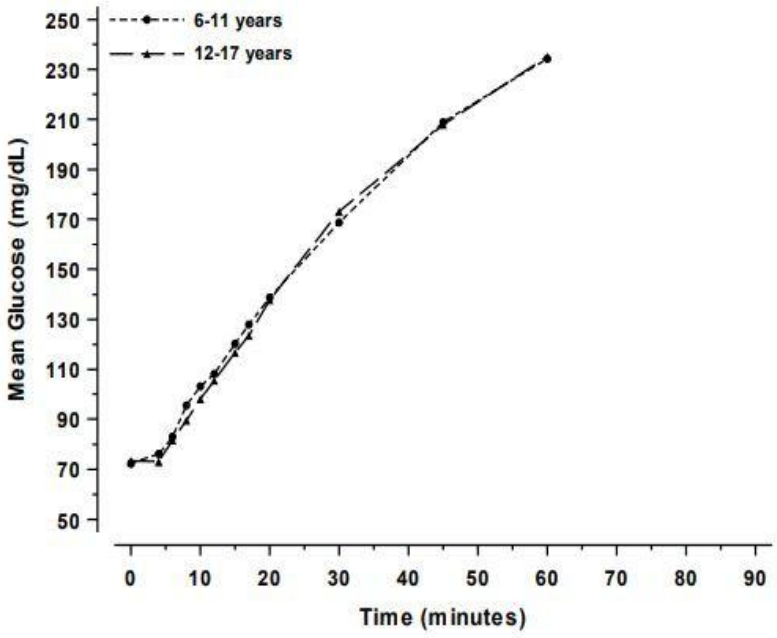


Figure 2 Mean plasma glucose over time in pediatric patients with type 1 diabetes administered 0.6 mg dasiglucagon

DOSAGE FORMS AND STRENGTHS

- 0.6 mg/0.6 mL single-dose autoinjector/prefilled syringe.
- That is 1mg/1ml – Subcutaneous route.

CONTRAINDICATIONS

- Pheochromocytoma.
- Insulinoma.

DRUG INTERACTIONS

- Beta blockers
- Indomethacin
- Warfarin

CLINICAL STUDIES

- Three randomized, double-blind, placebo-controlled, multicenter trials were conducted in patients with type 1 diabetes.
- Two trials - Trial A and Trial B - adult patients, one trial - Trial C - 6 to 17 years.
- Trial A – 170 patients
- Trial B - 45 patients
- Trial C - 42 patients

Trial A & Trial C - 2:1:1 -randomized to DASIGLUCAGON 0.6 mg, placebo, glucagon for injection 1.0 mg.

Trial B - 3:1 -patients were randomized to DASIGLUCAGON 0.6mg, placebo median time to plasma glucose recovery

Trial A – DASIGLUCAGON - 10 minutes

placebo - 40 minutes

GLUCAGON - 12 minutes

Trial B - DASIGLUCAGON - 10 minutes

placebo - 35 minutes

Trial C – DASIGLUCAGON - 10 minutes

placebo - 30 minutes

GLUCAGON - 10 minutes

ADVERSE REACTIONS

ADULTS & CHILDREN

- Nausea
- Vomiting
- Headache
- Diarrhea
- Injection site pain

Immunogenicity

- As with all therapeutic peptides, there is a potential for immunogenicity with Dasiglucagon.
- In clinical trials, 4/498 (<1%) of DASIGLUCAGON-treated patients developed treatment-emergent anti-drug antibodies (ADAs).

USE IN SPECIFIC POPULATIONS

- Pregnancy -no available human data on dasiglucagon. In animal reproduction studies - No adverse fetal developmental effects were observed.
- Lactation – no human data available
- Pediatric Use- safe above 6 years
- Geriatric Use- no difference in drug response
- Carcinogenesis- no human data available
- Mutagenesis- not mutagenic
- Impairment in fertility- no impairment of fertility in animal studies

PHARMACOECONOMICS

- Available in US
- $10 to $630 (single shot/multiple doses).

FINERENONE

- Non steroidal MR antagonist.
- Indication: To reduce the risk of sustained eGFR, End stage kidney disease, cardiovascular death, non-fatal myocardial infarction and hospitalization for heart failure in adult patients with CKD associated with type 2 diabetes.
- Approved by FDA on 09/July/2021.

Chemical description

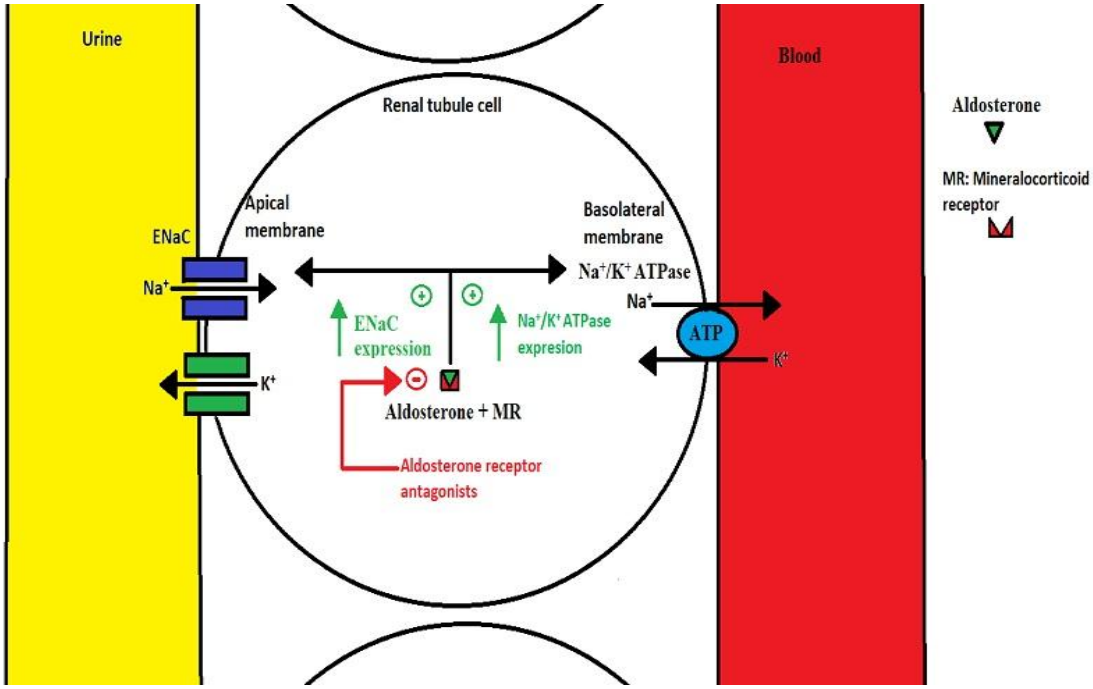
- Molecular formula:C21H22N4O3.
- Molecular formula:378.43g|mol

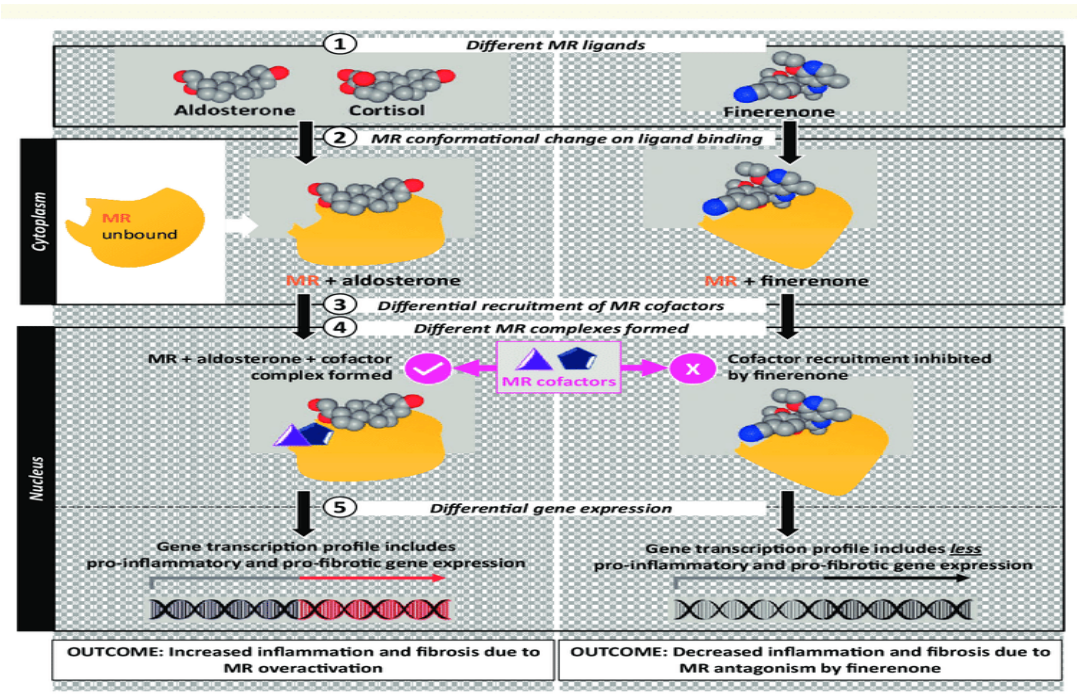
PHARMACOKINETICS:

- Recommended Dosage:10 mg,20 mg
- Route of administration :Oral
- Volume of distribution:52.6 L
- Half life:2-3hrs
- Bioavailability:44%
- Plasma protein binding:92%
- Metabolism:CYP3A4
- Excretion: Urine as inactive metabolite.

Pharmacodynamics

- **Mechanism of Action**:
- Blocks MR mediated sodium transport and blocks MR over activation.
- High potency and selectivity for MR & has no relative affinity for androgen, progesterone, estrogen and glucocorticoid receptor.





COMPARISON OF THREE MRA GENERATIONS

DRUG	AFFINITY TO MR	AFFINITY TO SHR	TISSUE DISTRIBUTION (HEART Vs KIDNEY)
SPIRONOLACTONE	HIGH	MODERATE	6 FOLD HIGHER IN KIDNEY
EPLERENONE	MODERATE	VERY LOW	3 FOLD HIGHER IN KIDNEY
FINERENONE	HIGH	VERY LOW	BALANCED BETWEEN HEART AND KIDNEY

CLINICAL STUDIES

- FIDELIO, was a double blinded, multicentre, randomized, controlled trial.
- It compares FINERENONE and placebo in 5674 adult patients with type 2 Diabetes and CKD.
- The primary composite outcome is kidney failure with >40% decrease in eGFR over a 4 week period or death from renal cause.

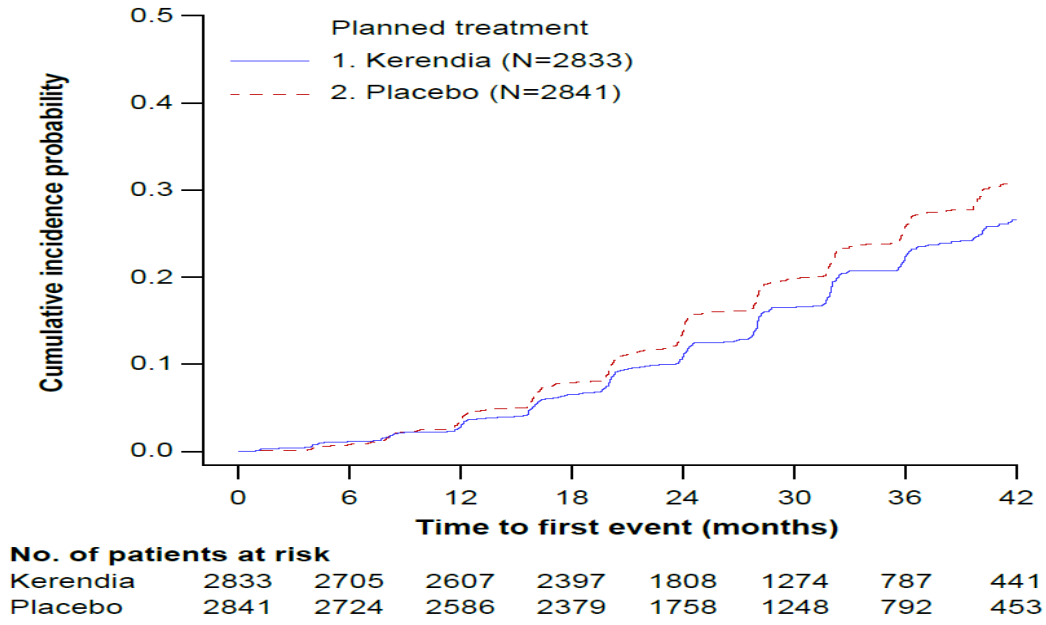
- The secondary outcome was death from cardiovascular cause or hospitalization for any cause.
- The median follow up period was 2.6 year.

Table 4: Analysis of the Primary and Secondary Time-to-Event Endpoints (and their Individual Components) in Phase 3 Study FIDELIO-DKD

	Kerendia N=2833		Placebo N=2841		Treatment Effect Kerendia / Placebo	
Primary and Secondary Time-to-event Endpoints:	**n (%)**	**Event Rate (100 pt-yr)**	**n (%)**	**Event Rate (100 pt-yr)**	**Hazard Ratio (95% CI)**	**p-value**
Primary composite of kidney failure, sustained eGFR decline ≥40% or renal death	504 (17.8%)	7.6	600 (21.1%)	9.1	0.82 [0.73; 0.93]	0.001
Kidney failure	208 (7.3%)	3.0	235 (8.3%)	3.4	0.87 [0.72; 1.05]	-
Sustained eGFR decline ≥40%	479 (16.9%)	7.2	577 (20.3%)	8.7	0.81 [0.72; 0.92]	-
Renal death	2 (<0.1%)	-	2 (<0.1%)	-	-	-
Secondary composite of CV death, non-fatal MI, non-fatal stroke or hospitalization for heart failure	367 (13.0%)	5.1	420 (14.8%)	5.9	0.86 [0.75; 0.99]	0.034
CV death	128 (4.5%)	1.7	150 (5.3%)	2.0	0.86 [0.68;1.08]	-
Non-fatal MI	70 (2.5%)	0.9	87 (3.1%)	1.2	0.80 [0.58;1.09]	-
Non-fatal stroke	90 (3.2%)	1.2	87 (3.1%)	1.2	1.03 [0.76;1.38]	-
Hospitalization for heart failure	139 (4.9%)	1.9	162 (5.7%)	2.2	0.86 [0.68;1.08]	-

p-value: two-sided p-value from stratified logrank test

CI = confidence interval, CV = cardiovascular, eGFR = estimated glomerular filtration rate, MI = myocardial infarction, N = number of subjects, n = number of subjects with event, pt-yr = patient year.
NOTE: Time to first event was analyzed in a Cox proportional hazards model. For patients with multiple events, only the first event contributed to the composite endpoint. Sums of the numbers of first events for the single components do not add up to the numbers of events in the composite endpoint.



Adverse Drug Reactions

- Hyperkalemia
- Hypotension
- Hyponatremia

CONTRAINDICATIONS

- *Cyp3A4 inhibitors.*
- *Adrenal insufficiency.*

DRUG INTERACTIONS

- CYP3A4 Inhibitors
- CYP3A4 Inducers
- Drugs that affect serum Potassium levels.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No data on human study.
- Lactation: No data on human study.
- Paediatric Use: Safety and efficacy has not been established.
- Geriatric: No dose adjustment required.
- Hepatic Impairment: No need dose adjustment in mild to moderate hepatic impairment. Avoid use in severe hepatic impairment.

Pharmacoeconomics

- 19$/tablet.