ΕΛΛΗΝΙΚΗ ΝΕΦΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
HELLENIC SOCIETY OF NEPHROLOGY

25ο Πανελλήνιο Συνέδριο
ΝΕΦΡΟΛΟΓΙΑΣ

19-21 ΙΟΥΝΙΟΥ 2024

ΜΕΓΑΡΟ ΔΙΕΘΝΕΣ ΣΥΝΕΔΡΙΑΚΟ ΚΕΝΤΡΟ - ΑΘΗΝΑ

Νεότερα δεδομένα στη θεραπεία της IgA νεφροπάθειας

Σ.Μαρινάκη

Αναπληρώτρια Καθηγήτρια Νεφρολογίας

Διευθύντρια Κλινικής Νεφρολογίας και Μεταμόσχευσης Νεφρού

ΕΚΠΑ, Ιατρική Σχολή, Λαϊκό Νοσοκομείο

ΔΟΡΥΦΟΡΙΚΟ ΣΥΜΠΟΣΙΟ ΕΤΑΙΡΕΙΑΣ FARAN

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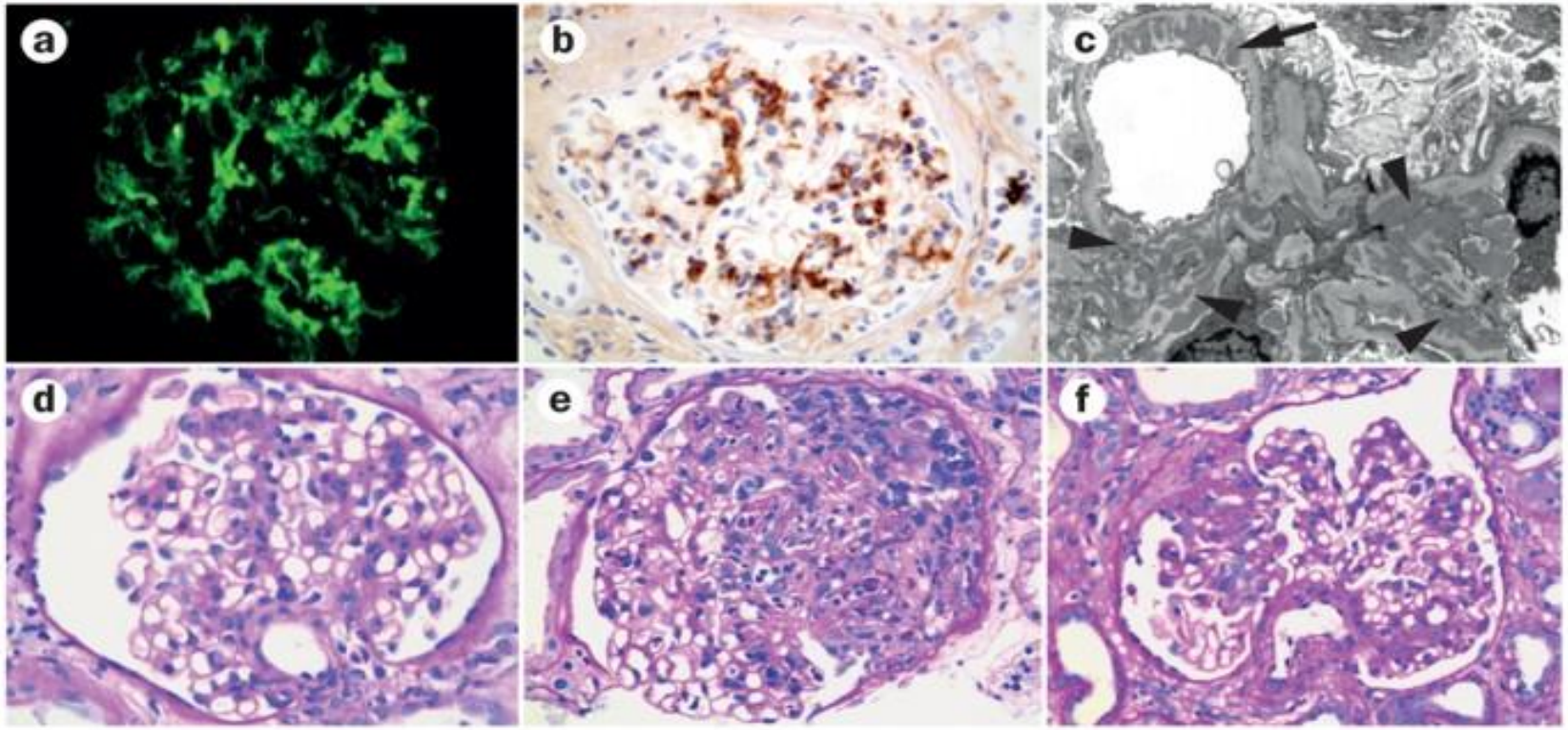
IgAN



Progression to ESRD in 10-20 years >50%

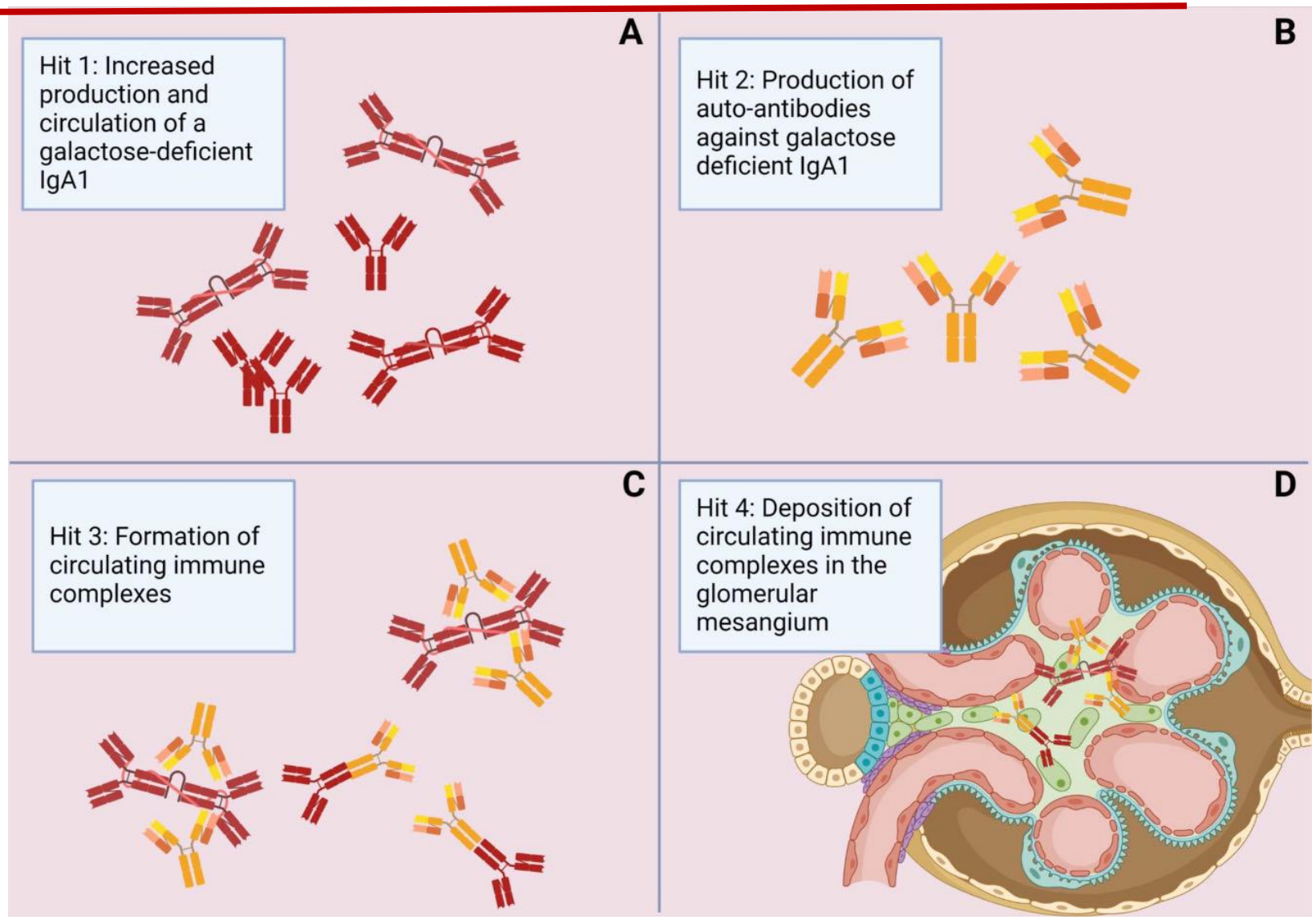
High risk of progression even with proteinuria <500mg/d

Immune abnormalities in IgA nephropathy

IgA1 mucosal surfaces
systemic circulation

IgA2 mucosal surfaces

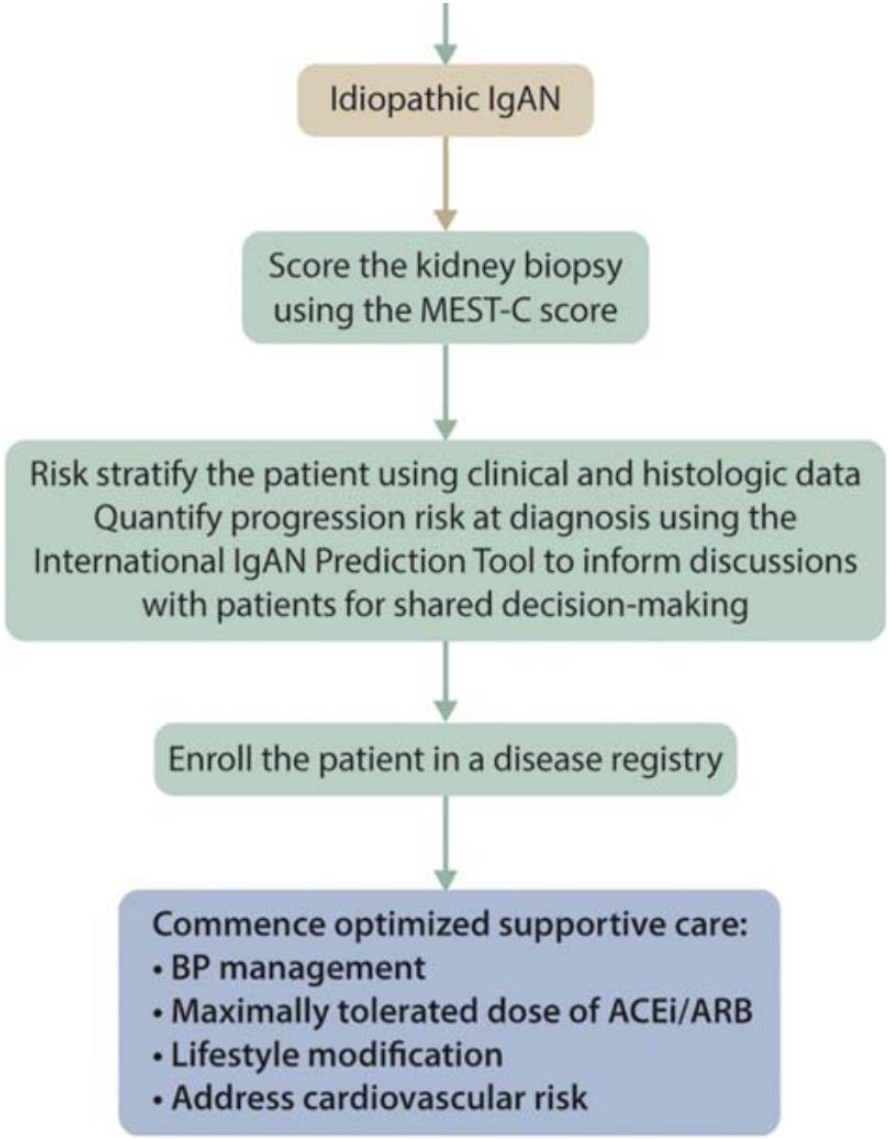
1. ↑Circulating levels of Gd-IgA1
2. Antiglycan autoantibodies against Gd-IgA1
3. Circulating immune complexes contain Gd-IgA
4. The Gd-IgA1-antiglycan IgG immune complexes deposit in the mesangium



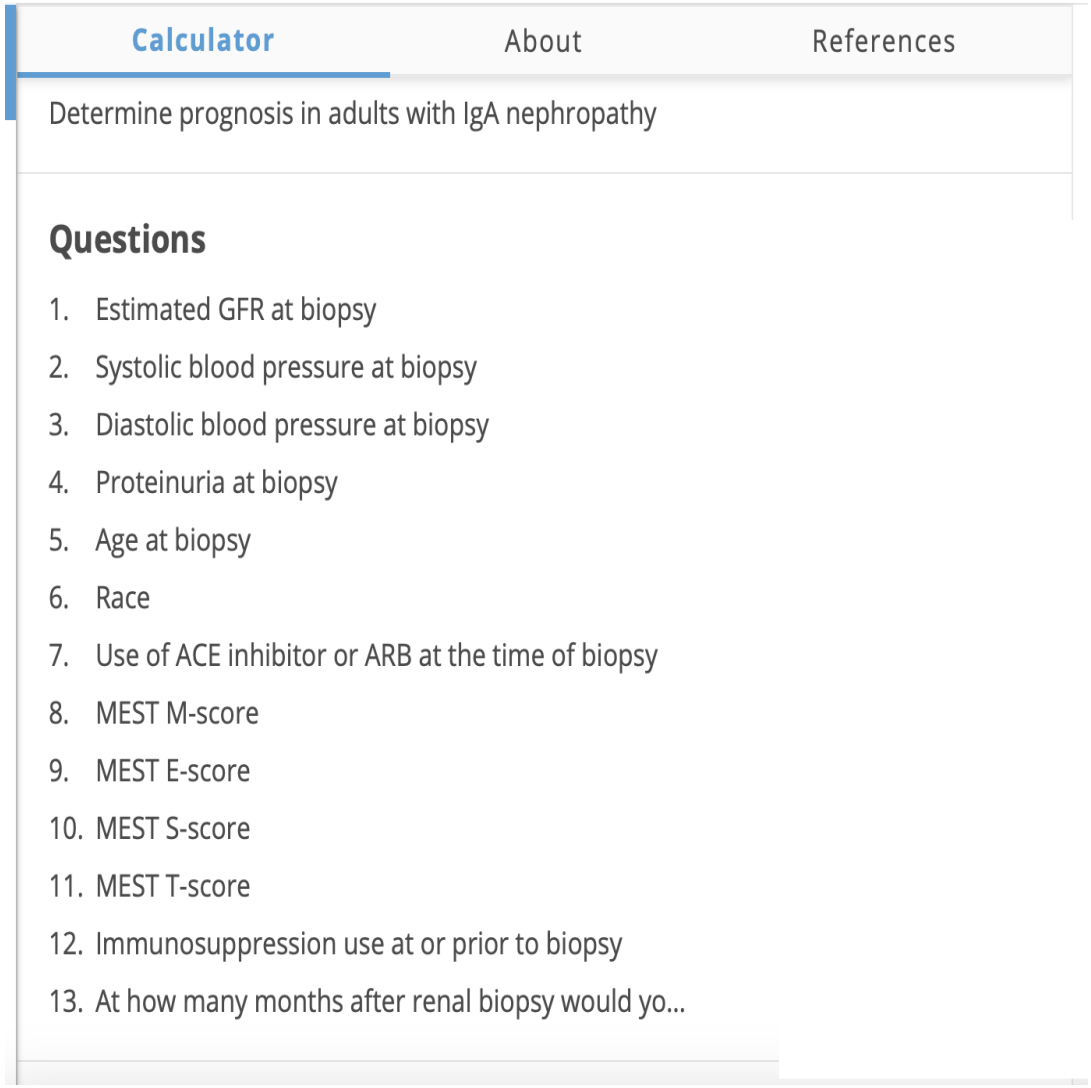
Clinical Kidney Journal, 2023

Until 2015

KDIGO Guidelines



International IgAN Prediction tool



IgAN Therapy

Treat immune mediated damage "activity"

- Reduce pathogenic IgA
- Reduce glomerular inflammation

Treat CKD component "chronicity"

- BP control
- Reduce glomerular hyperfiltration/ proteinuria
- Reduce CV risk factors

IgAN Therapy

Treat Immune Mediated damage

- **Reduce pathogenic IgA**
  - NEFECON (targeted release butesonide)
  - B-cell Modulation
    - Atacicept
    - APRIL inhibitors
- **Reduce glomerular inflammation**
  - Glucocorticoids
  - Complement inhibition
    - Factor B-i Iptacopan
    - MASP-2 i Narsoplimab
    - C5a receptor i (Avacopan)
    - C5 inhibitor:Ravulizumab

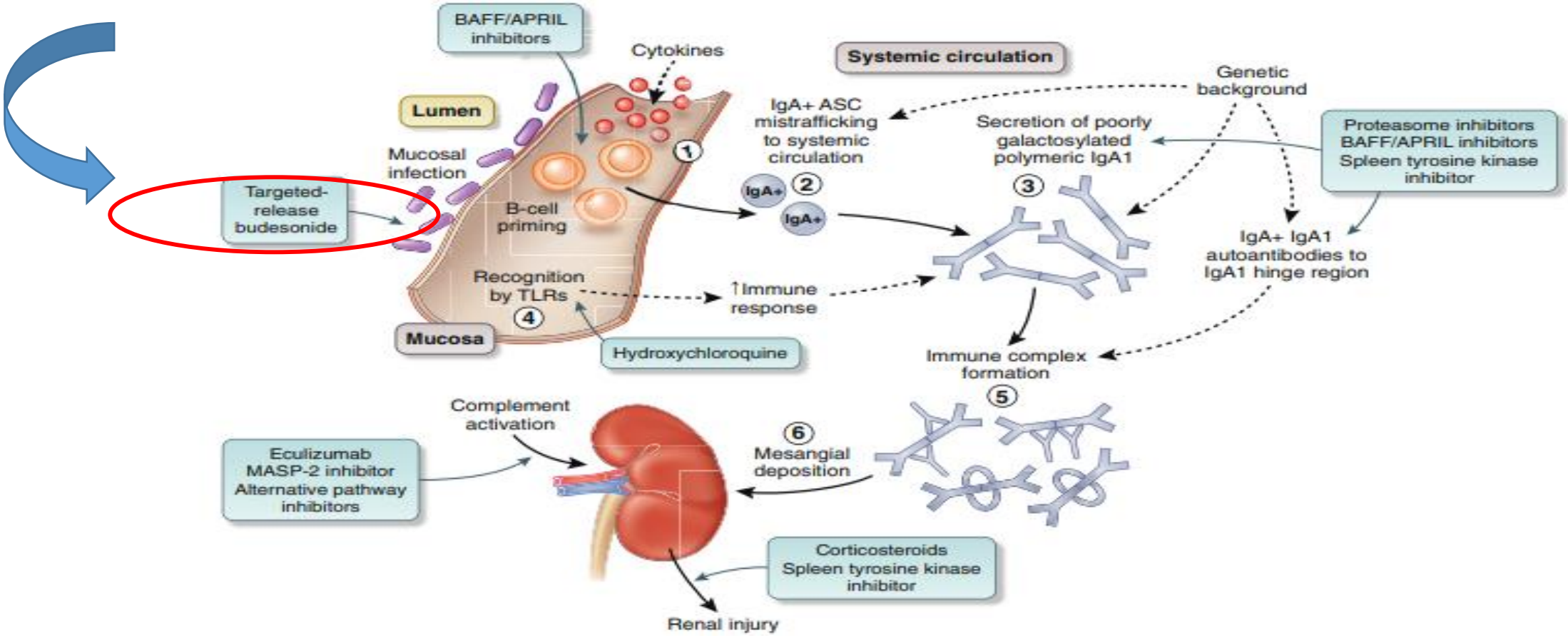
Treat CKD component

- **BP control**
  - Lifestyle modifications
  - RAASi
  - SGLT2
  - DEARA (Sparsentan)
  - MRA(finerenone), GLP1…
- **Reduce glomerular hyperfiltration/ proteinuria**
- **Reduce CV risk factors**

2024...

Reduce pathogenic IgA1 production

NEFECON (targeted release butesonide)

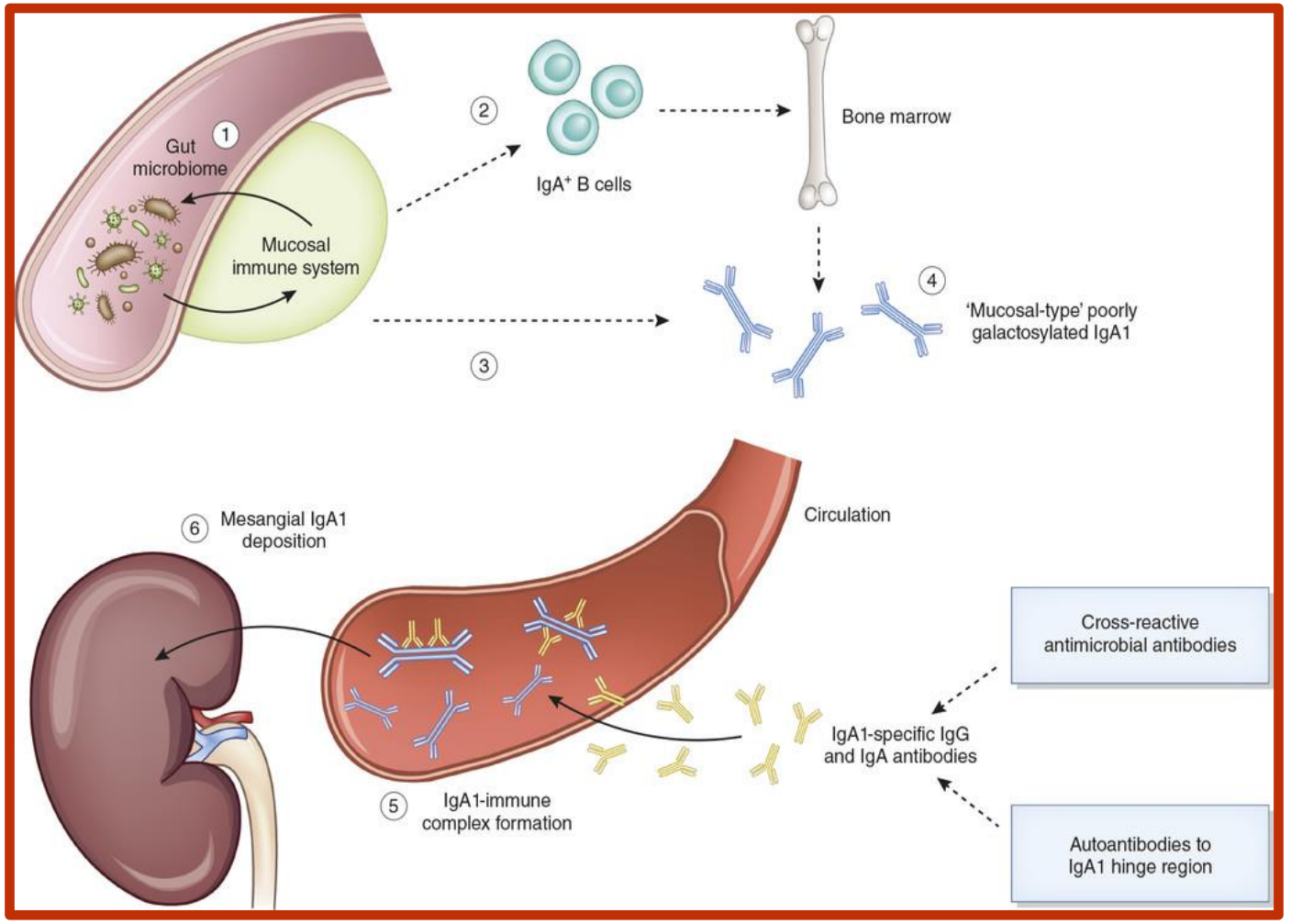


Boyd JK et al. Kidney Int 2019;281:833-843

Nefecon: Targeted-Release Budesonide

pH dependent and time delayed release

- Nefecon is designed to achieve a **high dose delivery of budesonide to the distal ileum** where Peyer's patches are highly concentrated.
- Approximately **46% of all Peyer's patches** are located in the **final 25cm segment of the distal ileum**
- **90% first pass effect** reduces systemic exposure and the risk of AEs typically associated with the systemic administration of corticosteroids.



Nefecon: Targeted-Release Budesonide

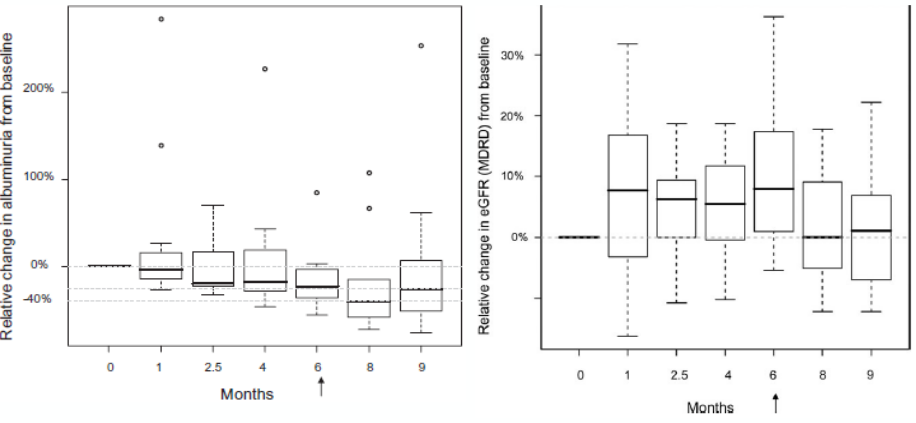
Trials overview

2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024

Phase 2A Pilot Study

N=16 IgAN

↓Uprot 23%



◇ NDT 2011

NEFIGAN
Phase 2B Study

◇ Lancet 2017

NEFIGARD
Phase 3A

◇ Kidney Int 2022

Phase 3B

◇ Lancet 2023

Phase 3 OLE

Last patient out: Q1 2024

◇ Publication

Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

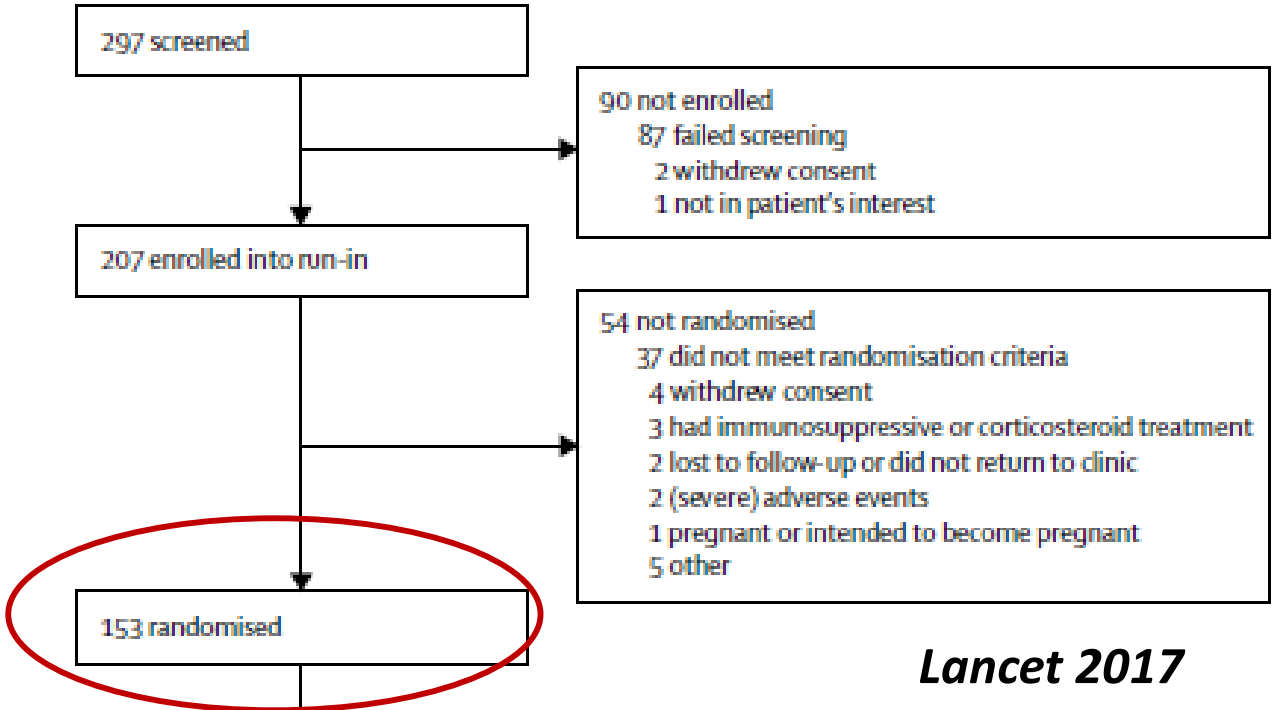
NEFIGAN
Phase 2B Study

Double-blind, placebo-controlled phase 2b trial, 6-month run-in,
9-month treatment,
3-month follow-up (62 nephrology clinics across 10 European countries)

Randomised **1:1:1 ratio to 16 mg/day TRF-budesonide, 8 mg/day TRF-budesonide, or placebo**

Inclusion criteria

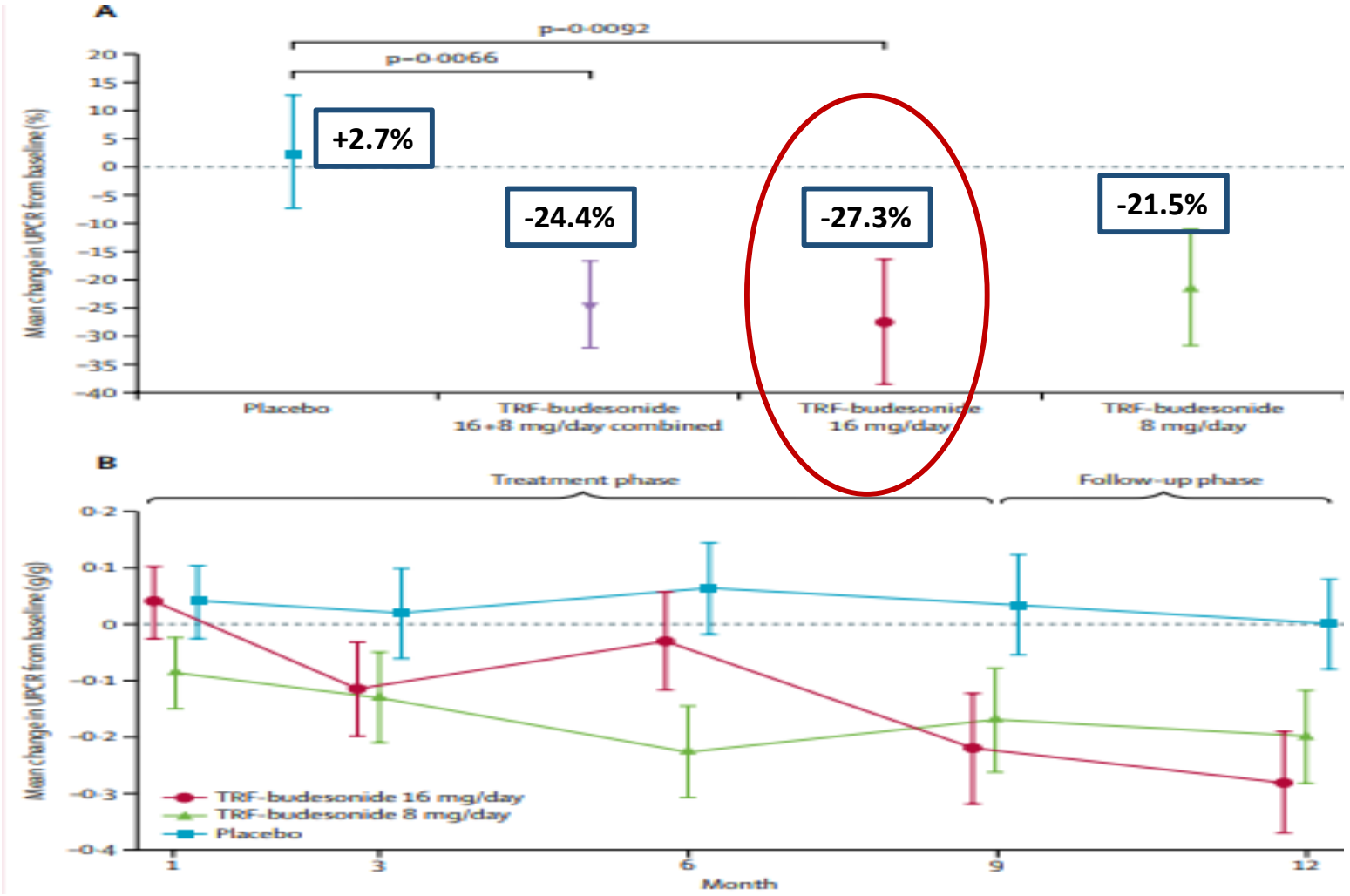
- GFR **(eGFR) ≥ 45 mL /min/1.73m²**
- **UPCR ≥ 0.5 g/g or Uprot ≥ 0.75 g/day**
- Target blood pressure <130/80mmHg (ACEIs or ARBs to a maximum recommended dose or maximum tolerated dose)



Lancet 2017

Primary outcome
9-months: Mean change in UPCR

NEFIGAN
Phase 2b



ΔUPCR at 9 months **significant for 16mg/d**, not for 8 mg/d

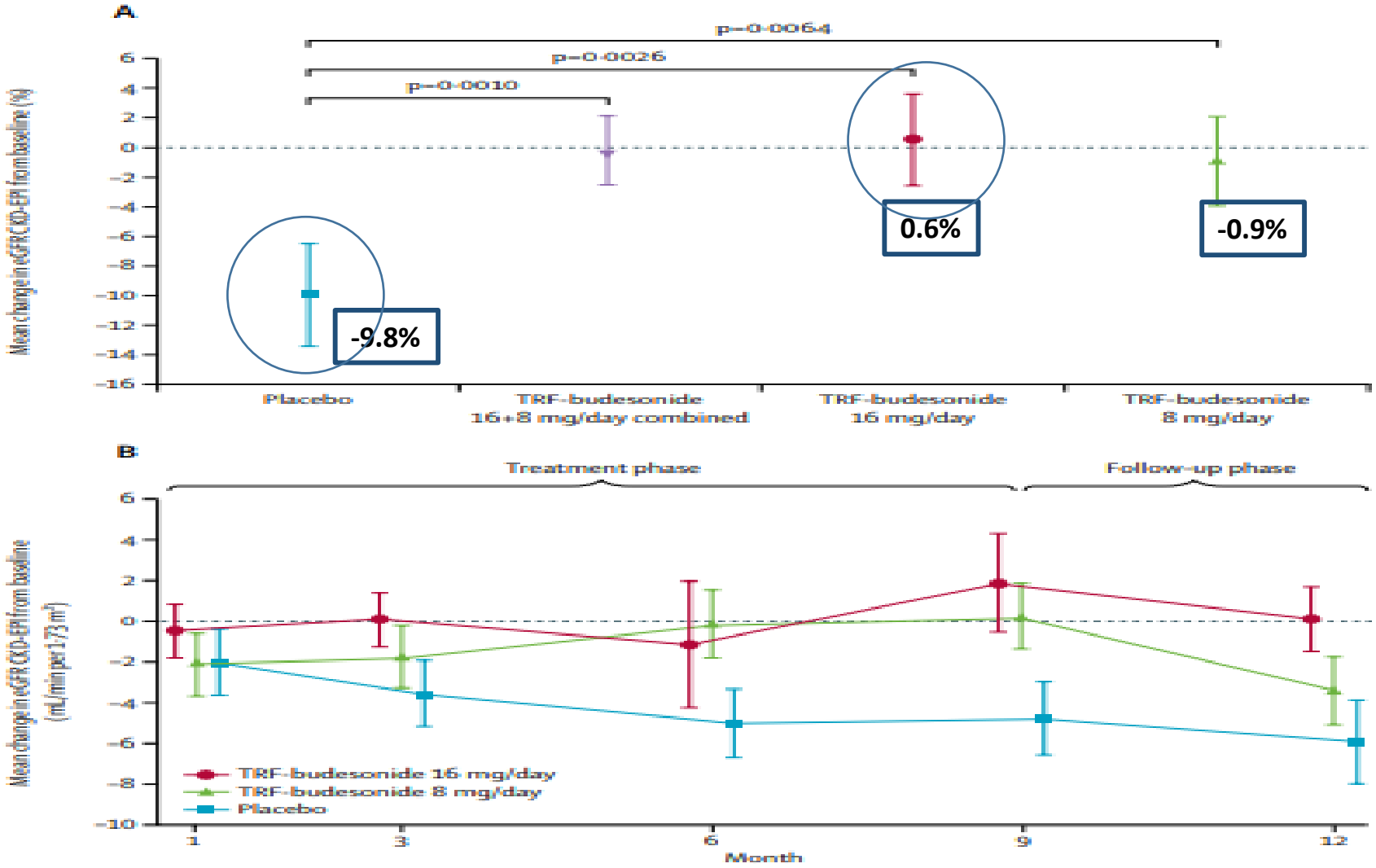
UPCR reduction sustained up to **12 months** in the 8mg/d group, **further decreased in the 16mg/d** group

Fellstrom BC et al. The Lancet 2017;389(10084):2117-27

Secondary outcomes

12 months**: Mean changes from baseline in eGFR, (**UPCR, Uprot (g/24hr), UACR, Ualb (g/24hr)

NEFIGAN
Phase 2b



eGFR levels in the **16mg/d** group **sustained throughout the trial**

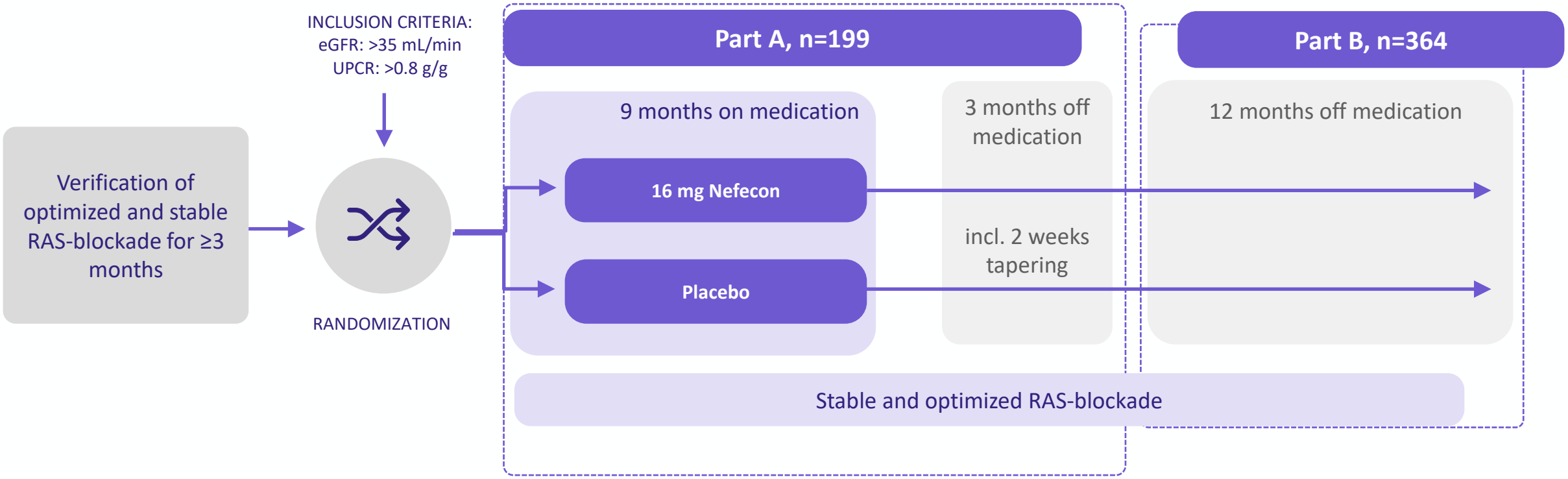
Decreased in the placebo group

Stabilisation of eGFR in budesonide groups was independent of baseline UPCR and eGFR

Fellstrom BC et al. The Lancet 2017;389(10084):2117-27

NeflgArd: Study Design

Efficacy and safety of Nefecon in patients with primary IgA Nephropathy



Kidney Int 2022

NEFIGARD
Phase 3A

Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

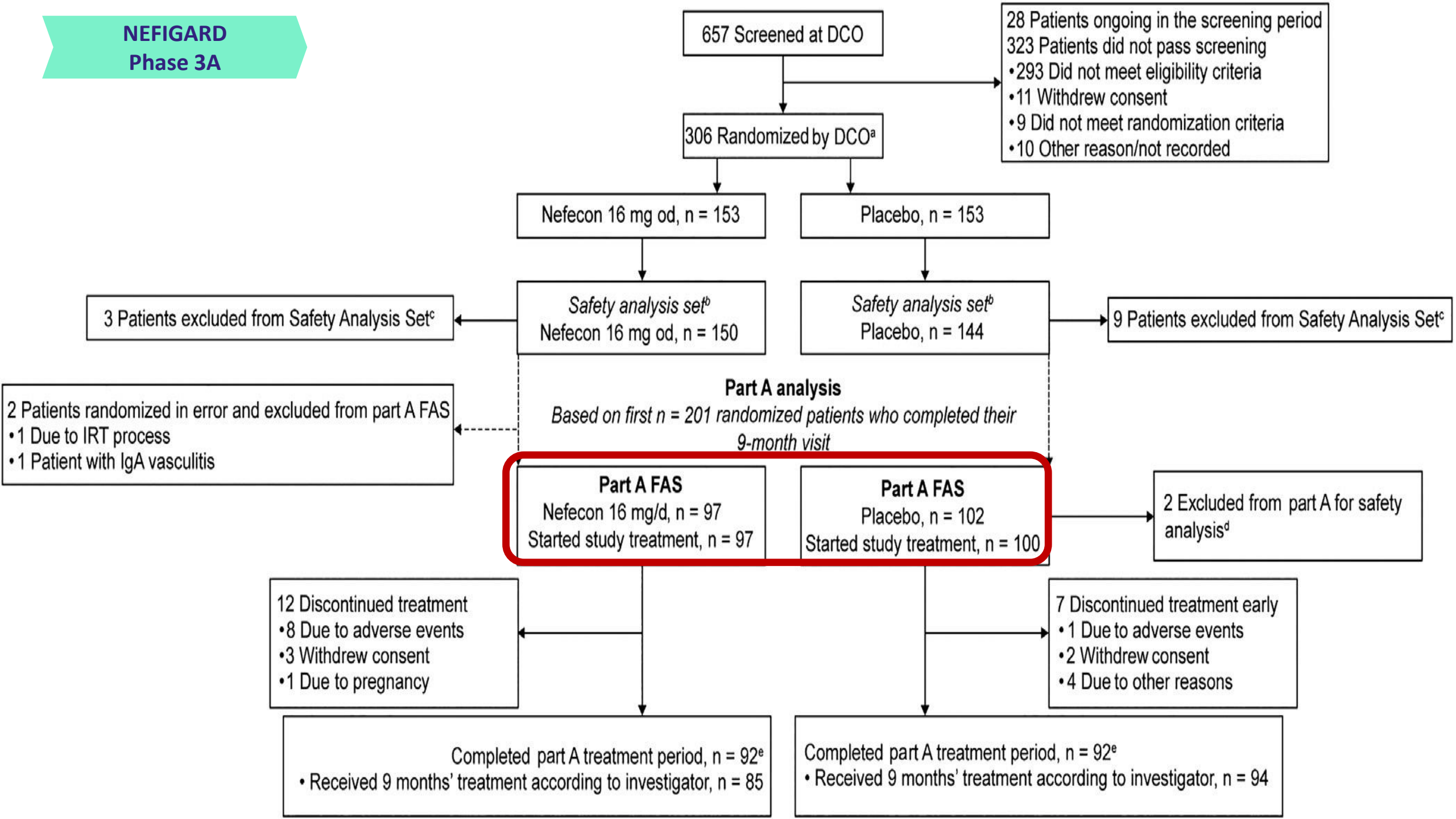
Inclusion criteria

- Persistent proteinuria (**UPCR > 0.8 g/g or Uprot >1 g/24 h**)
- **eGFR 35 - 90 ml/min/1.73 m2** using CKD-EPI
- Maximum tolerated or maximum allowed of an RAAS inhibitors for at least 3 months
- Patients with type 1 or type 2 diabetes were eligible provided their diabetes was adequately controlled

Exclusion criteria

- All secondary forms of IgAN or any non-IgAN glomerulonephritis
- Inadequately controlled BP>140/90 mm Hg
- Kidney transplant
- Treatment with systemic glucocorticoids or immunosuppressants in the 12 months

NEFIGARD
Phase 3A

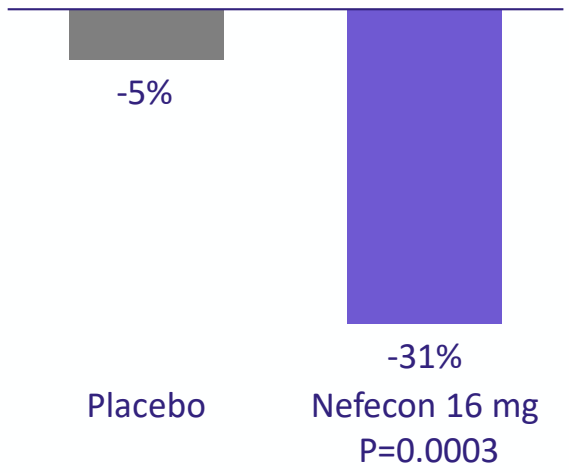


NEFIGARD
Phase 3A

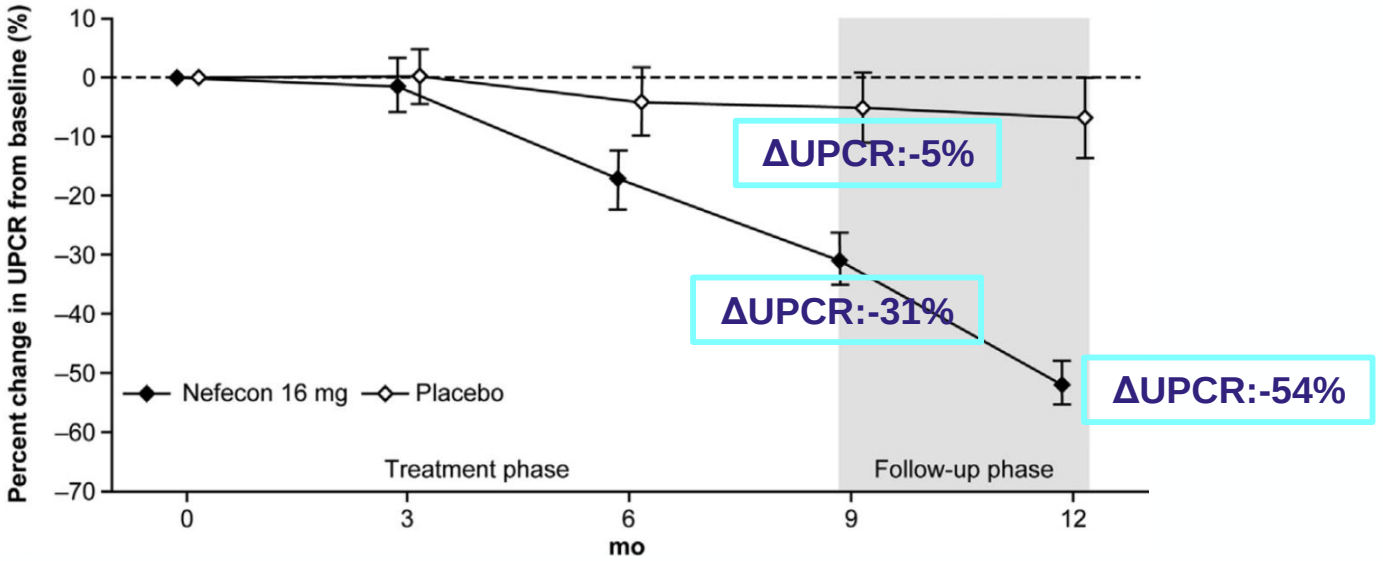
NeflgArd Part A: Results

Change in UPCR at 9 and 12 months vs. baseline

Primary endpoint: change in UPCR from baseline at 9 months



Change in UPCR from baseline over 9 and 12 months



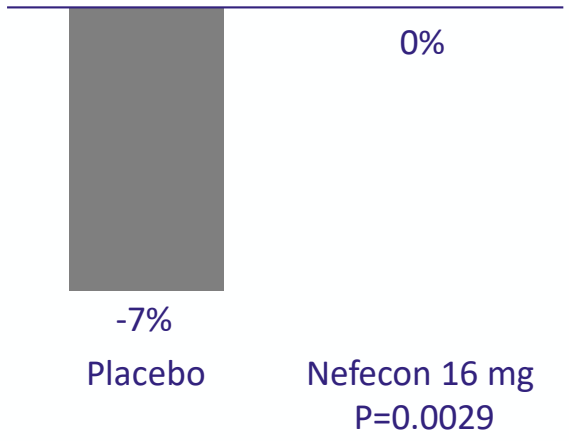
Barratt J et al. (2023) Kidney Int. 103(2):391-402

NEFIGARD
Phase 3A

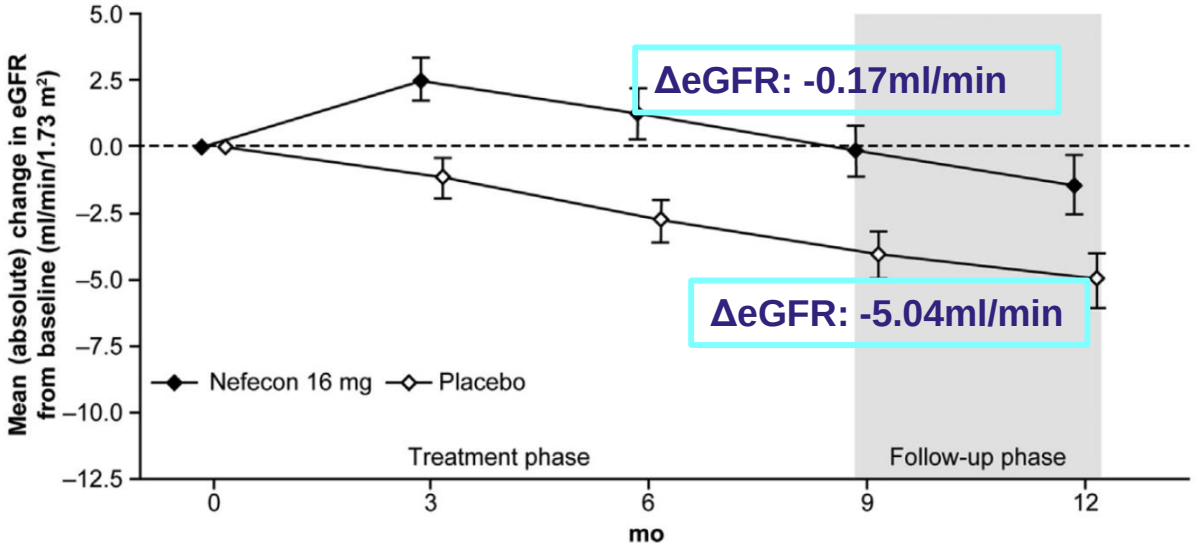
NefIgArd Part A: Results

Change in eGFR at 9 months vs. baseline

Secondary endpoint: change in eGFR from baseline at 9 months



Change in eGFR from baseline over 9 and12 months



Barratt J et al. (2023) Kidney Int. 103(2):391-402

NEFIGARD
Phase 3A

Safety

Adverse event descriptors	Placebo (n = 100) n (%)	Events	Nefecon 16 mg/d (n = 97) n (%)	Events
All TEAEs	73 (73.0)	300	84 (86.6)	429
Maximum severity of TEAEs				
Mild	46 (46.0)	243	49 (50.5)	330
Moderate	26 (26.0)	56	31 (32.0)	95
Severe	1 (1.0)	1	4 (4.1)	4
AE of infection	41 (41.0)	–	38 (39.2)	–
Any AESI	0 (0.0)	–	2 (2.1)	–
Severe infection that required hospitalization	0 (0.0)	–	0 (0.0)	–
New onset of diabetes mellitus[a]	0 (0.0)	–	2 (2.1)	–
Confirmed fracture	0 (0.0)	–	0 (0.0)	–
New osteonecrosis	0 (0.0)	–	0 (0.0)	–
GI bleeding requiring hospitalization	0 (0.0)	–	0 (0.0)	–
Reported occurrence of cataract formation	0 (0.0)	–	0 (0.0)	–
Reported onset of glaucoma	0 (0.0)	–	0 (0.0)	–
Any treatment-emergent SAE	5 (5.0)	5	11 (11.3)	16
Any study treatment related treatment-emergent SAE	2 (2.0)	2	2 (2.1)	2
Any AE leading to death	0 (0.0)	0	0 (0.0)	0
Any TEAE leading to discontinuation of study treatment[b]	1 (1.0)	5	9 (9.3)	27

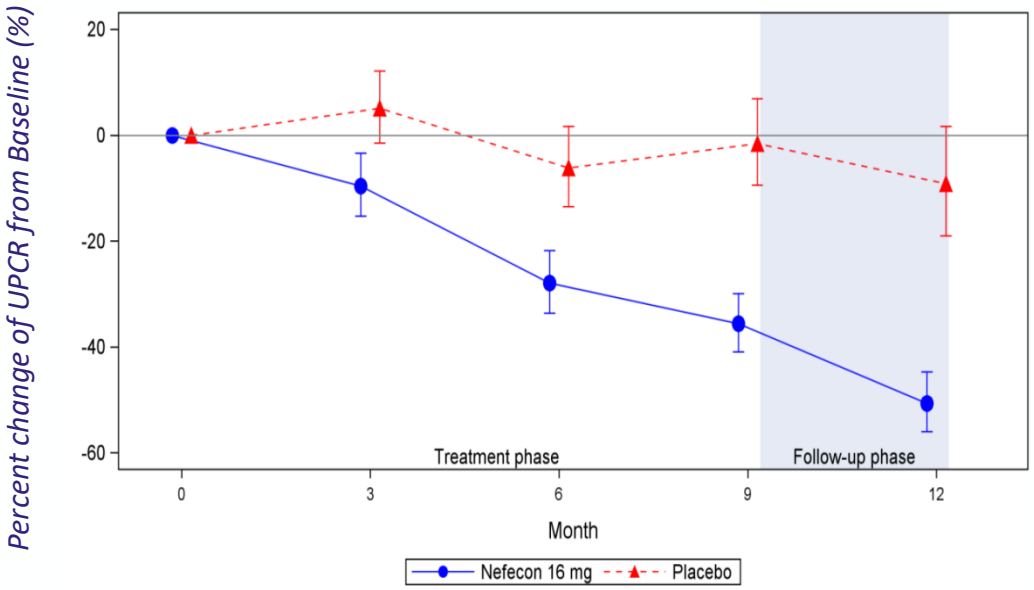
Barratt J et al. Kidn Int 2023;103(2):391-402

NEFIGARD
Phase 3A

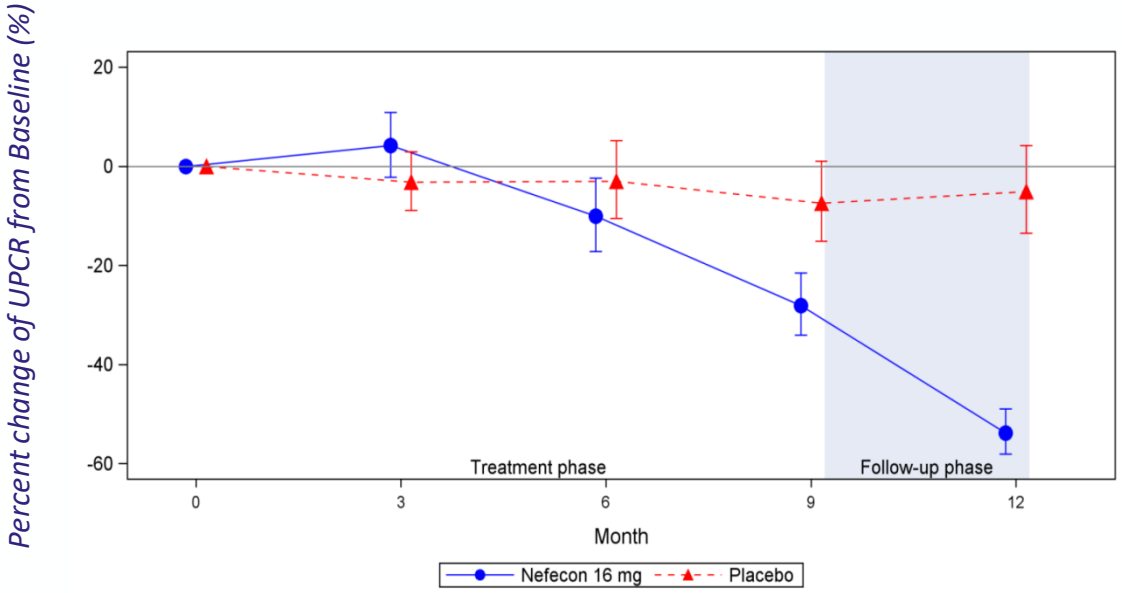
NefIgArd Part A: Results

Subgroup analysis: UPCR change in patients based on baseline UPCR

Baseline UPCR subgroup ≥1.5 g/g



Baseline UPCR subgroup <1.5 g/g



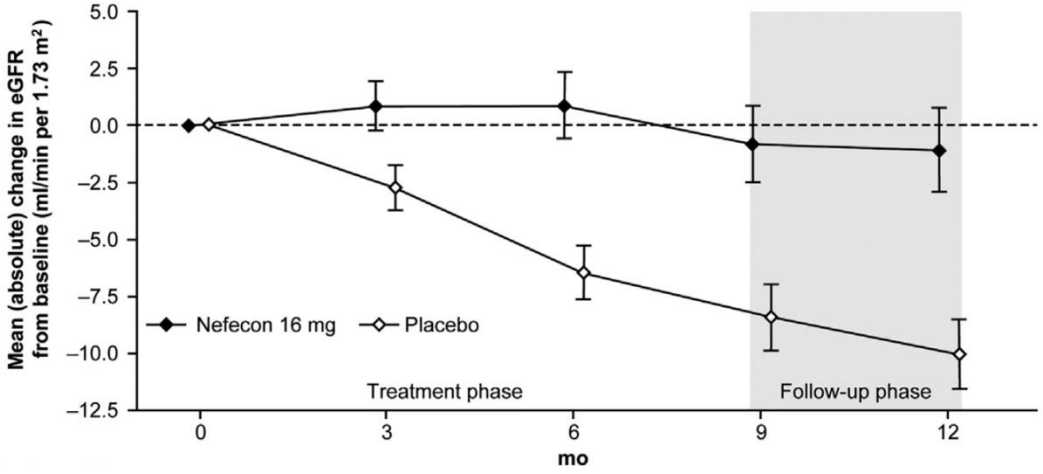
Barratt J et al. (2023) Kidney Int. 103(2):391-402

NEFIGARD
Phase 3A

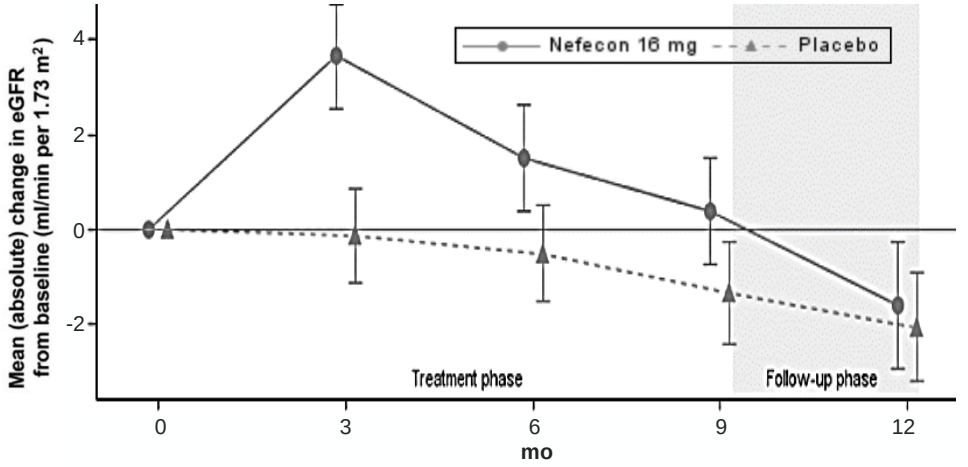
NeflgArd Part A: Results

Subgroup analysis: eGFR change in patients based on baseline UPCR

Baseline UPCR subgroup ≥1.5 g/g



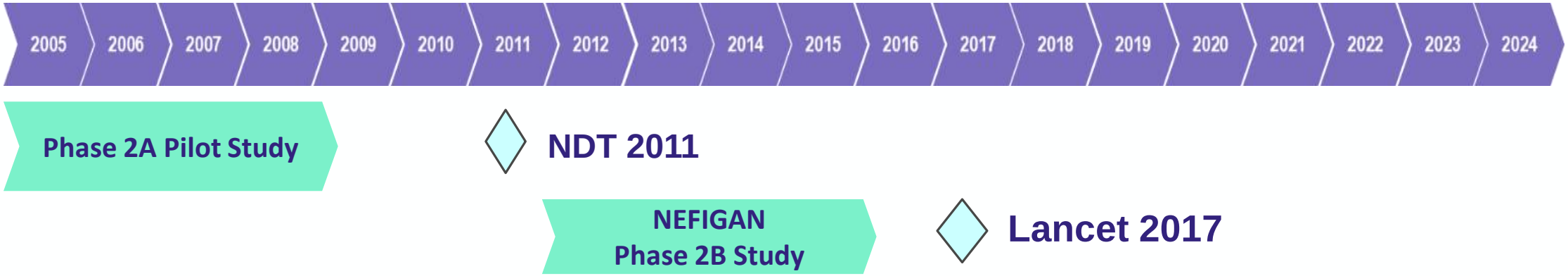
Baseline UPCR subgroup <1.5 g/g



Barratt J et al. (2023) Kidney Int. 103(2):391-402

Nefecon: Targeted-Release Budesonide

Trials overview



Phase 3B

- Analysis of full trial population of 364 patients
- **Safety and efficacy of Nefecon over 2 years**

Phase 3B

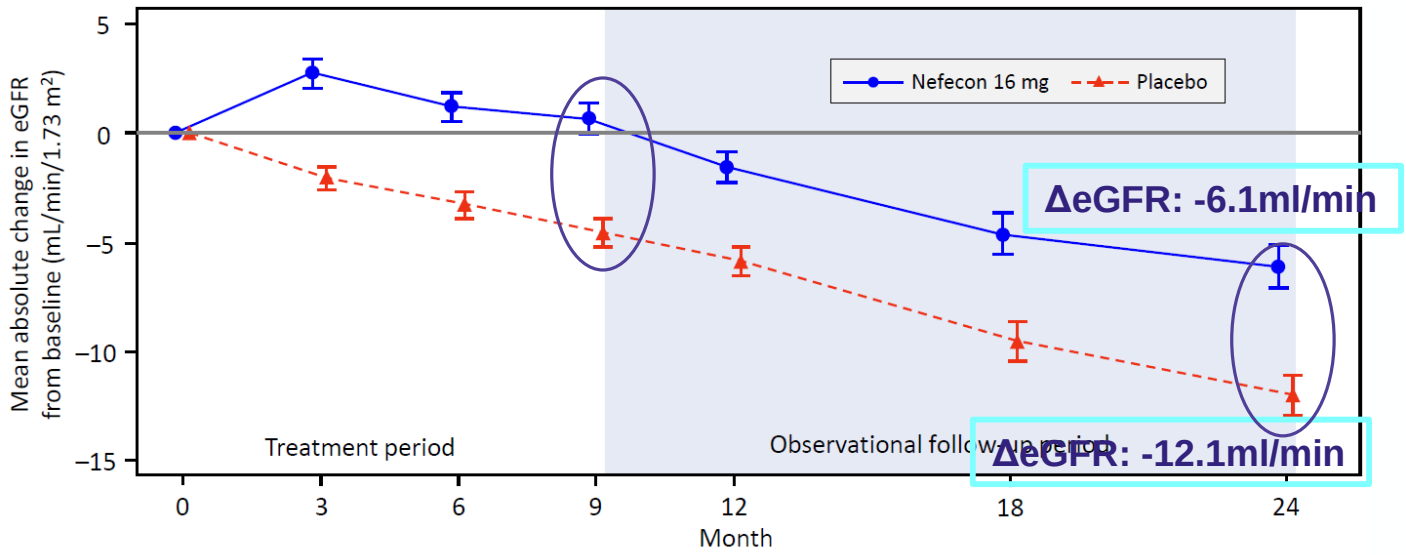
NefIgArd Part B: Results

Time-weighted average of eGFR over 2 years

- **Primary endpoint:** time-weighted average of eGFR over 2 years showed a statistically **significant benefit with Nefecon vs. Placebo of 5.05 mL/min/1.73 m²** (p<0.0001).

- The eGFR **benefit** at the end of the 9-month treatment period with Nefecon **was maintained** during the 15-month of observational follow-up.

Mean absolute change in eGFR from baseline to 24 months in the overall study population



Lafayette R. Lancet 2023;402(10405):859-870

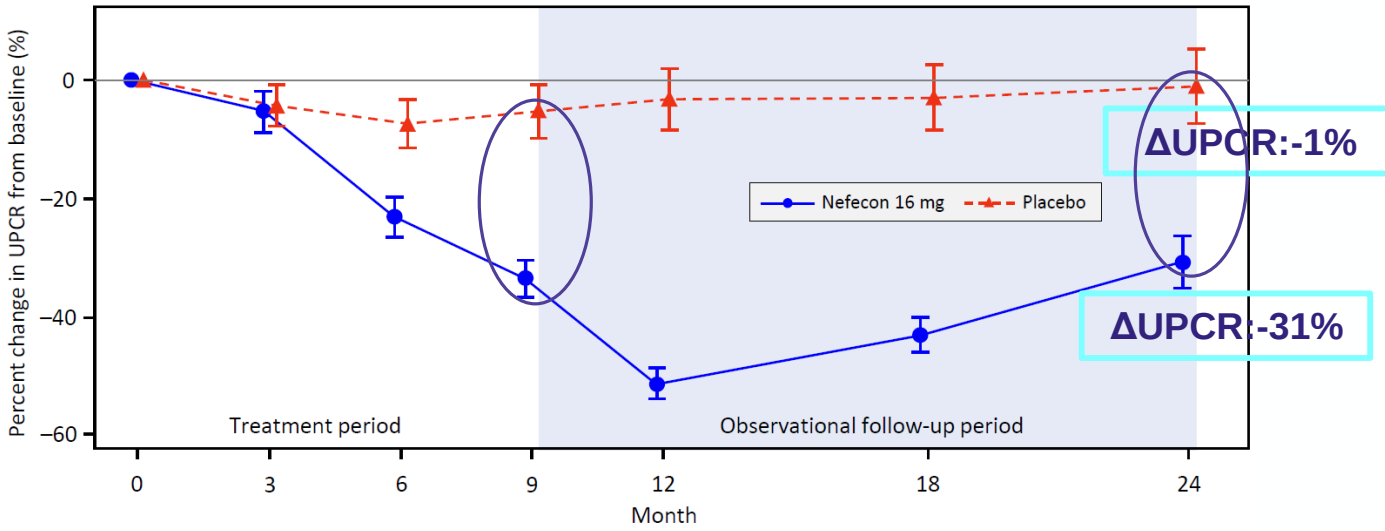
Phase 3B

NefIgArd Part B: Results

UPCR change over 24 months

- Mean relative **change in UPCR at 24 months was -30.7%** with Nefecon vs. -1.0 % with Placebo
- **At 24 months**, the percentage reduction in UPCR in the Nefecon vs placebo arm was **similar to the end of the 9-month treatment period**

Mean relative change in UPCR from baseline to 24 months in the overall study population



Lafayette R. Lancet 2023;402(10405):859-870

Phase 3B

Adverse events

Good safety and tolerability profile

	Treatment period		Follow up	
Adverse events	**Placebo (n = 182)**	**Nefecon 16 mg (n = 182)**	**Placebo (n = 174)**	**Nefecon 16 mg (n = 175)**
All AEs (%)	69	87	71	73
Mild (%)	41	51	42	35
Moderate (%)	25	31	25	28
Serious (%)	2	5	5	9
SAEs, deaths, treatment discontinuations				
All SAEs (%)	5	10	8	8
Any treatment-related SAE (%)	2	2	1	0
SAE leadind to death (%)*	0	1	0	1
AE leading to treatment discontinuation (%)	2	9	NA	NA

Lafayette R. Lancet 2023;402(10405):859-870

Phase 3B

NefIgArd Part B: AEs related to systemic steroid exposure

Infections: the incidence of infections was the same between the Nefecon arm (35%) and the Placebo arm (31%).

No clinically relevant differences in body weight and blood pressure measurements were observed between treatment groups.

New events of diabetes: **4 patients (2.1%) in the Nefecon** arm vs. 0% in the placebo arm developed new events. **All patients were prediabetic at baseline**. *HbA1c returned to baseline levels in all four patients at two years.*

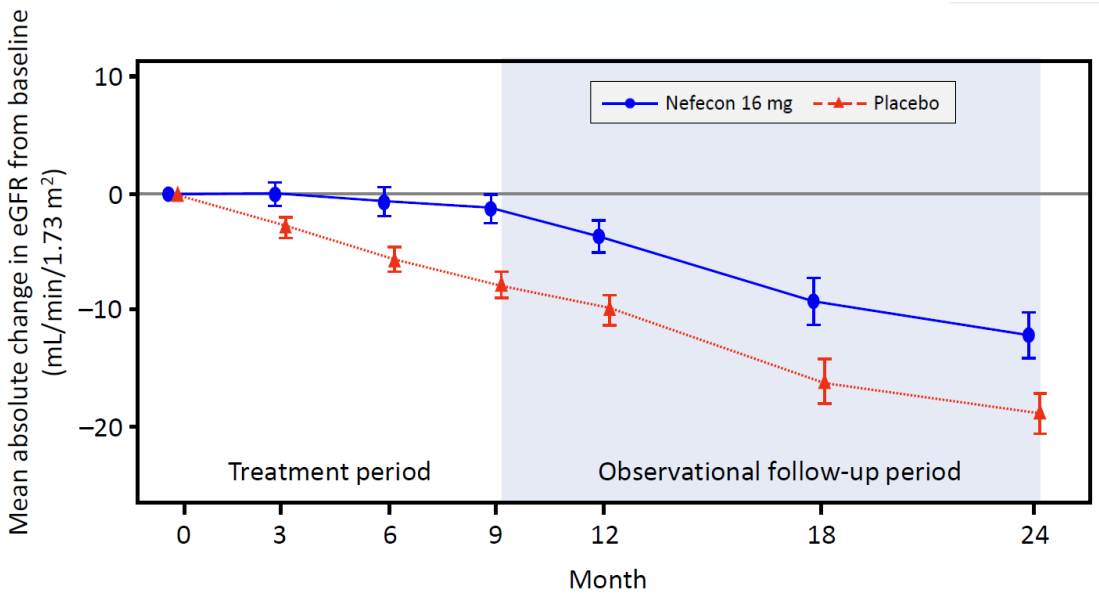
Lafayette R. Lancet 2023;402(10405):859-870

Phase 3B

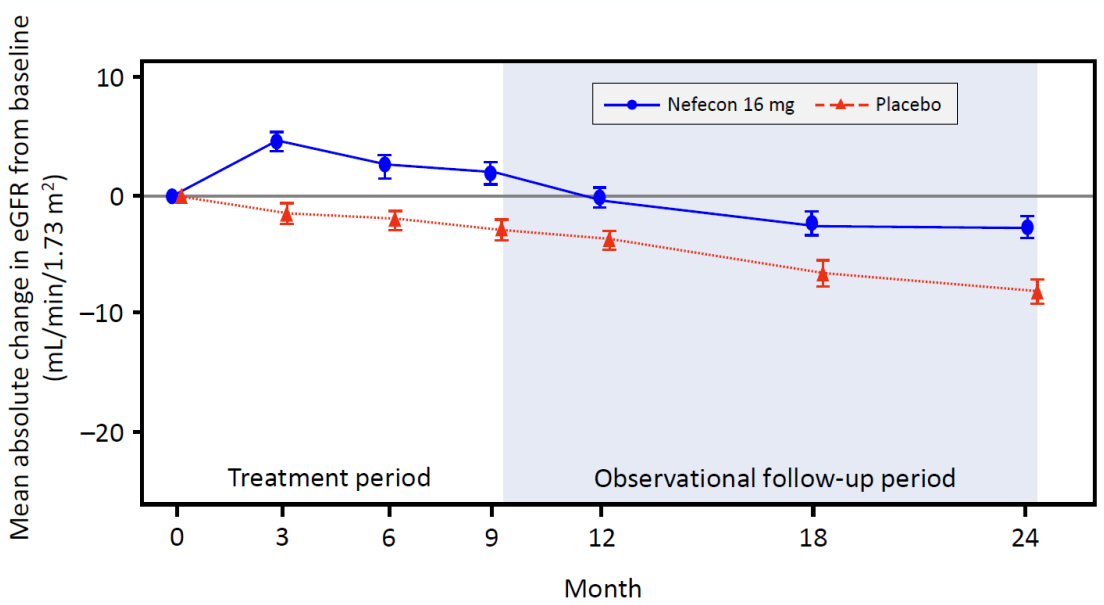
NefIgArd Part B: Results

Subgroup analysis: eGFR change in patients based on baseline UPCR

Baseline UPCR subgroup ≥ 1.5 g/g

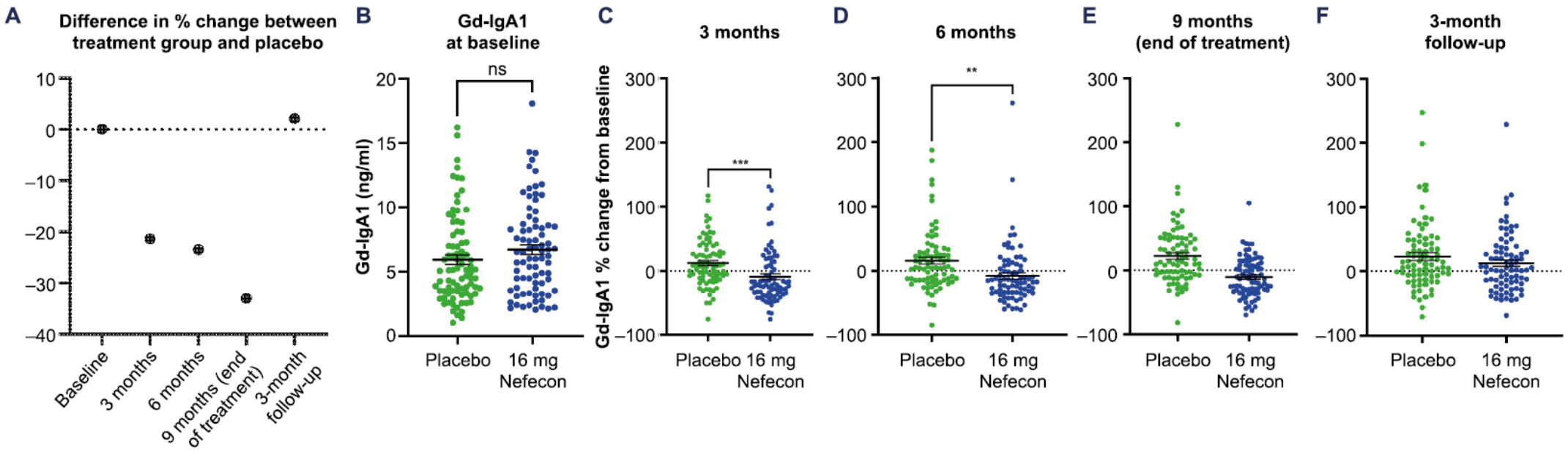


Baseline UPCR subgroup <1.5 g/g



Lafayette R. Lancet 2023;402(10405):859-870

Treatment with Nefecon reduces circulating levels of gd-IgA1



	3 months	6 months	9 months
Mean reduction in gd-IgA1 vs. placebo	-21.4%	-23.5%	-34%
P-value	<0.0005	<0.0017	<0.0001

Molyneux et al., ASN 2022 Orlando, poster SA-PO654

Phase 3B

Summary

NefIgArd Part B

- The NefIgArd study **met its 2-year primary endpoint**, demonstrating that 9 months of treatment with Nefecon on top of optimized standard of care provided a **statistically significant and clinically relevant preservation of eGFR** compared with optimized standard of care alone.

- The size of the **eGFR benefit was maintained over the 15-month off-drug** observational follow-up period.

- The observed eGFR benefit was **independent of baseline UPCR.**

- Nefecon 16 mg was generally **well tolerated**, and the AE profile was consistent with that reported in the previous interim analysis.

U.S. FOOD & DRUG ADMINISTRATION

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17/12/2021

FDA approves first drug to decrease urine protein in IgA nephropathy, a rare kidney disease

FDA has granted accelerated approval for Tarpeyo (budesonide) delayed release capsules to reduce proteinuria (increased protein levels in the urine) in adults with primary immunoglobulin A (IgA) nephropathy at risk of rapid disease progression. It has not been established whether Tarpeyo slows kidney function decline in patients with IgA nephropathy.

15/07/2022

EMA approval for the treatment of primary IgA nephropathy in adults at risk of rapid disease progression with a UPCR ≥1.5g/g.

21/12/2023

FDA approval to reduce kidney function loss in IgAN patients at risk of disease progression.

30/05/2024

EMA approval for the treatment of adults with primary IgA nephropathy with a urine protein excretion ≥1.0g/day (or UPCR≥0.8g/g).

Conclusions

- The gut-kidney axis is implicated in the pathogenesis and progression of IgAN
- Increased levels of Gd-IgA1 lead to immune-complex formation and deposition into the mesangium
- Active (inflammation, hyperplasia) and chronic renal lesions (sclerosis, fibrosis, atrophy)
- Steroid treatment reduces inflammation, but it is not specific and followed by frequent relapses and side-effects
- Budesonide aims to reduce production of Gd-IgA1
- It is proved safe and efficient to reduce proteinuria and sustain/improve renal function

Time has come to change the aspect of therapeutic approach

from symptomatic treatment to precision medicine


Thank you
for your attention