Atrasentan for the Treatment of IgA Nephropathy: Interim Results from the AFFINITY Study

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Disclosures for Presenting Author:

Current Employer:	Concord Repatriation General Hospital, Sydney, Australia
Honoraria:	Baxter, Amgen, AstraZeneca, CSL Behring, Dimerix, Otsuka, Chinook and Travere
Scientific Advisor or Membership:	Member of the Steering Committee for PROTECT, DUPLEX and VISIONARY trials

Previous Employer, the George Institute for Global Health, holds research contracts for trials in cardiovascular and/or kidney disease in Asia Pacific region

IgA Nephropathy (IgAN): A Potentially Progressive, Chronic Glomerular Disease with Limited Treatment Options

#1

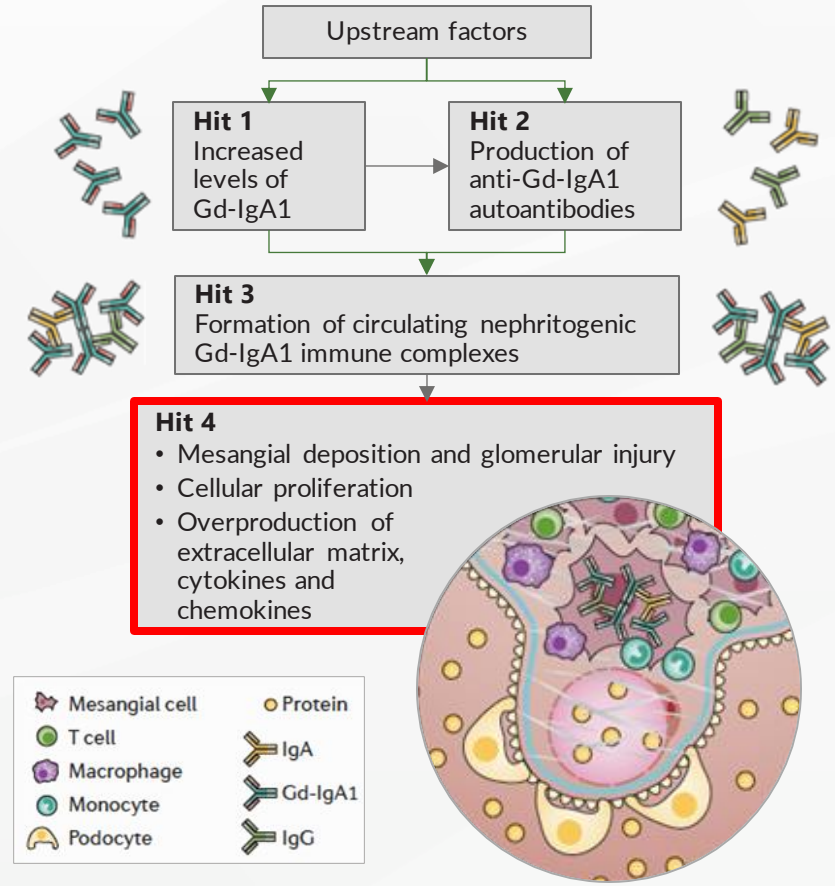
IgAN is the most common primary glomerulonephritis globally, though it is considered a rare disease

ESKD
30-45%

End-stage kidney disease (ESKD) is developed by about **30-45%** of IgAN patients over a period of 20-25 years

Limited treatment options for high-risk patients:

- RAS inhibition (ACEi/ARB) is frontline (KDIGO 1B)
- Steroids & immunosuppressive agents:
  inconsistent therapeutic benefit and accompanied by significant side effects (KDIGO 2B); Tarpeyo (budesonide) recently approved
- DAPA-CKD:
  suggests benefit of SGLT2i in non-diabetic CKD, including IgAN



Pathogenic model of IgA nephropathy

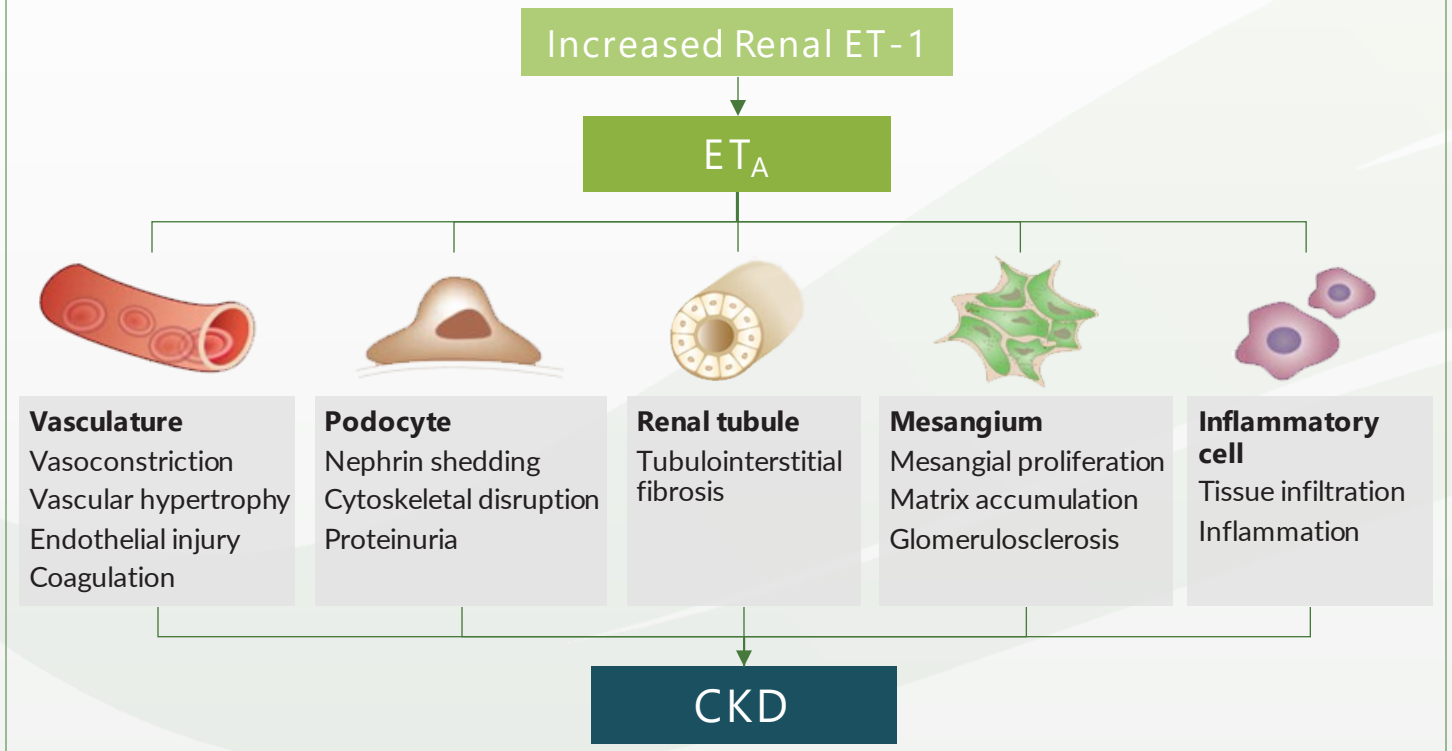
Wyatt, R. J., & Julian, B. A. (2013). IgA nephropathy. New England Journal of Medicine, 368(25), 2402-2414.
Lai, K., Tang, S., Schena, F. et al. IgA nephropathy. Nat Rev Dis Primers 2, 16001 (2016).

Endothelin System Activation in IgAN Disease Progression

ET_A activation reported to result in:

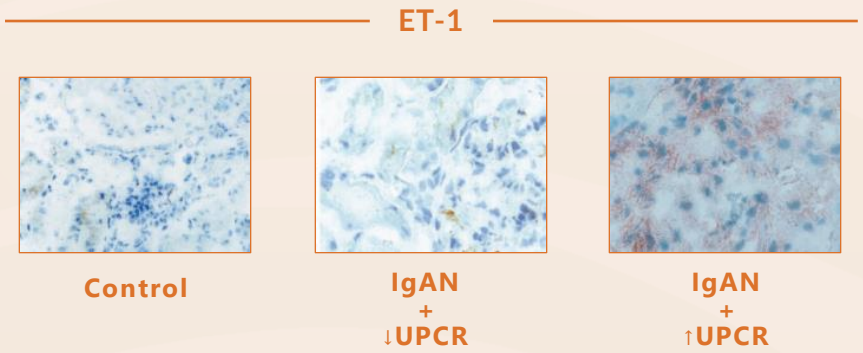
- Mesangial cell activation
- Proteinuria
- Kidney inflammation & fibrosis

… all hallmark characteristics of IgAN



Elevated kidney ET-1 expression strongly & prospectively predicted progression of IgAN, 12 months following kidney biopsy

Intense glomerular and TI ET-1 expression in IgAN patients with significant proteinuria



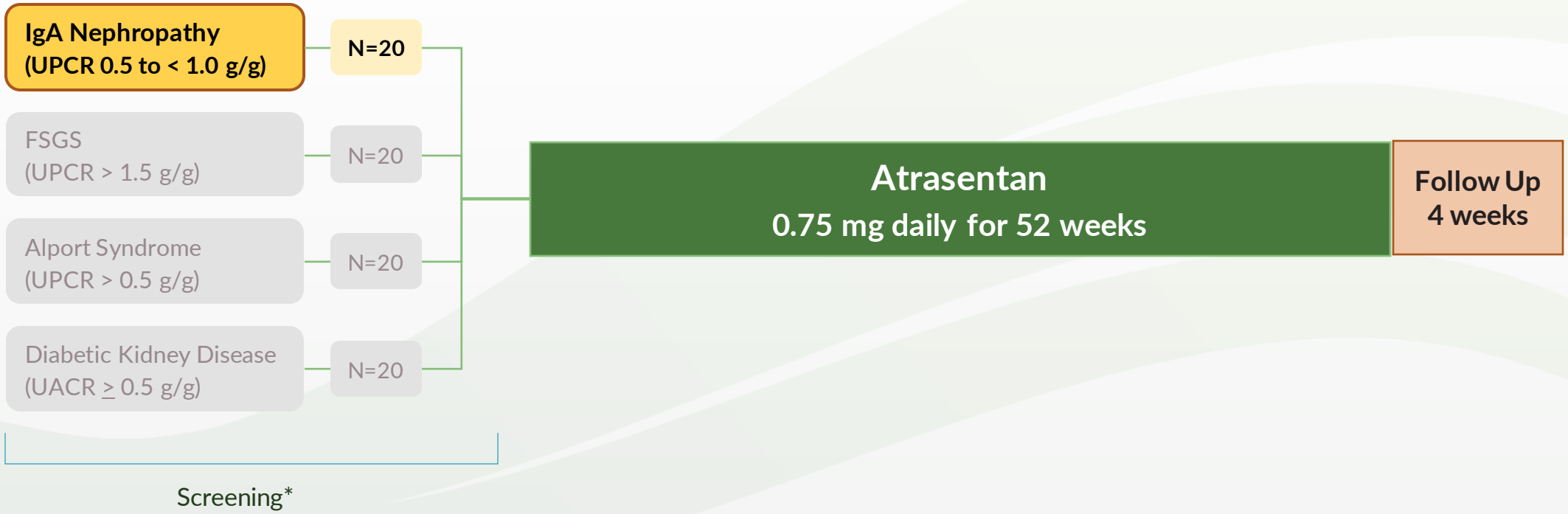
Blockade of the ET_A receptor with potent and selective **ET_A antagonist** atrasentan, represents a potential approach to treat IgAN patients at high risk of progression (**Hit 4**)

Tycova et al. Physiol. Res. 67: 93-105, 2018; Lehrke et al. J Am Soc Nephrol 2001 12: 2321–2329; Zanatta et al, Renal Failure, 2012, 34: 308–315; Kohan DE et al., Kidney Int. 2014.

AFFINITY Study Design:
Atrasentan in Patients With Proteinuric Glomerular Diseases

Study Objective

AFFINITY is a global, phase 2, open label basket study to assess the efficacy and safety of atrasentan in patients with proteinuric glomerular diseases at risk of progressive kidney function loss



* Stable RASi for all cohorts (in addition to stable SGLT2i for diabetic kidney disease)
All cohorts eGFR ≥ 30 ml/min/1.73m2, except for DKD ≥ 45 ml/min/1.73m2

AFFINITY Study Protocol; ClinicalTrials.gov Identifier: NCT04573920

Study Methods

Key Eligibility Criteria

Biopsy-proven IgAN that, in the opinion of the Investigator, is not due to secondary causes*

Receiving a maximally tolerated and optimized dose of a **RAS inhibitor** that has been stable for at least 12 weeks prior to screening

UPCR of 0.5 to < 1.0 g/g (56.5 mg/mmol to <113 mg/mmol) based on first morning void urine collected at screening

eGFR ≥ 30 mL/min/1.73 m²

Key Study Endpoints

Primary Endpoint

- **Change from baseline at week 12 in UPCR**, based on average of two 24-hour collections
- Analysis based on an MMRM model of change from baseline in UPCR

AE type, incidence, severity, seriousness and relatedness

* Biopsy could have occurred at any point in time prior to study.

AE, adverse event; MMRM, mixed-effects model repeated measures (fixed effects of visit and baseline in UPCR)

Demographics & Baseline Characteristics

Demographics (n=20)		
Age, years	*Median (Q1,Q3)*	45 (35, 58)
Women	*n (%)*	10 (50)
Race	*n (%)*	
Asian		9 (45)
White		9 (45)
Other		2 (10)
BMI (kg/m2)	*Median (Q1, Q3)*	26.2 (24.8, 29.2)

Baseline Characteristics	Median (Q1, Q3)	
Time from biopsy, years	3.9	(0.9, 11.8)
Blood pressure (mmHg)		
Systolic	128	(116, 132)
Diastolic	82	(77, 86)
Brain Natriuretic Peptide (pg/mL)	12.5	(8.8, 42.0)

Baseline Characteristics (cont)	Median (Q1, Q3)
UPCR, First morning void at screening (g/g)	0.63 (0.54, 0.70)
24-hour UPCR (g/g)	0.80 (0.73, 1.10)
24-hour urine protein excretion (g/day)	1.17 (0.85, 1.46)
Urine protein excretion (g/day) ≥ 1, n (%)	14 (70)
eGFR (mL/min/1.73 m²)*	46 (37, 74)
Concurrent RASi, n (%)	20 (100)
ACEi	8 (40)
ARB	12 (60)

* eGFR by CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

Safety and Tolerability

To date*, atrasentan has been well-tolerated in patients with IgAN (n=20)

AE Category	n (%)
Subjects with any TEAE	16 (80)
Any TEAE occurring in N>1 subjects	
COVID-19	5 (25)
Peripheral edema	2 (10)
Any Moderate TEAE	6 (30)
Any Severe TEAE	0 (0)
TEAE leading to discontinuation (headache)	1 (5)
SAE (traffic accident unrelated to study drug)	1 (5)

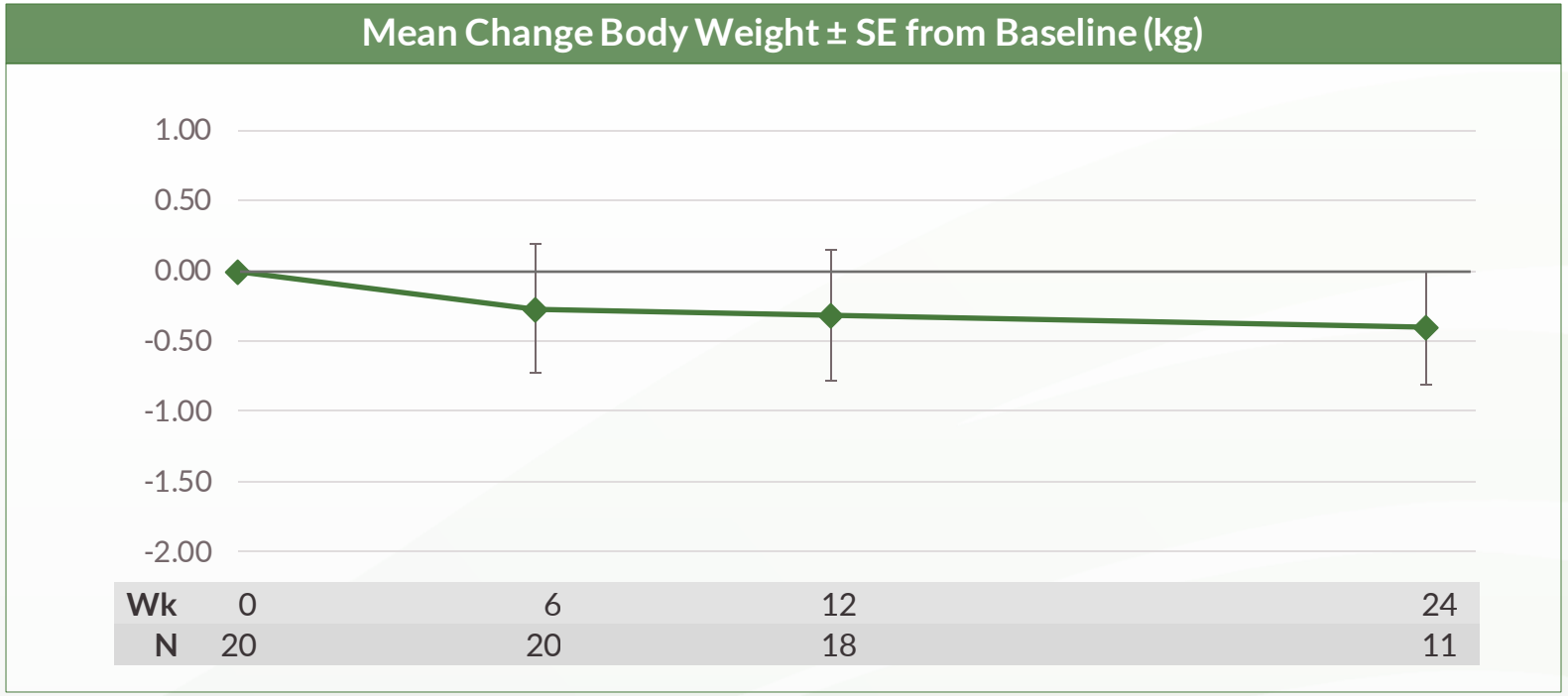
AE Category	n (%)
Treatment-related AE	5 (25)
Moderate related AE	3 (15)
Headache	1
Creatinine increase	1
Peripheral edema	1

- **No SAEs related to study drug to date**

18/20 patients remain on treatment, with time on treatment ranging from 6-52 weeks. One patient discontinued treatment and one patient has completed 52 weeks.

*Data cut-off: April 22, 2022. AE, adverse event; TEAE, treatment-emergent adverse event; SAE, serious adverse event.

No Evidence of Significant Fluid Retention



- No increase in mean body weight
- No significant elevation in BNP (median change of 2.9 pg/mL at week 12)
- No meaningful change in systolic or diastolic BP
- Minimal acute change in eGFR (0.15 mL/min/1.73 m^2 averaged across Weeks 2 and 6)

Atrasentan Provides Clinically Meaningful Proteinuria Reduction in Patients with IgAN Receiving Optimized SOC

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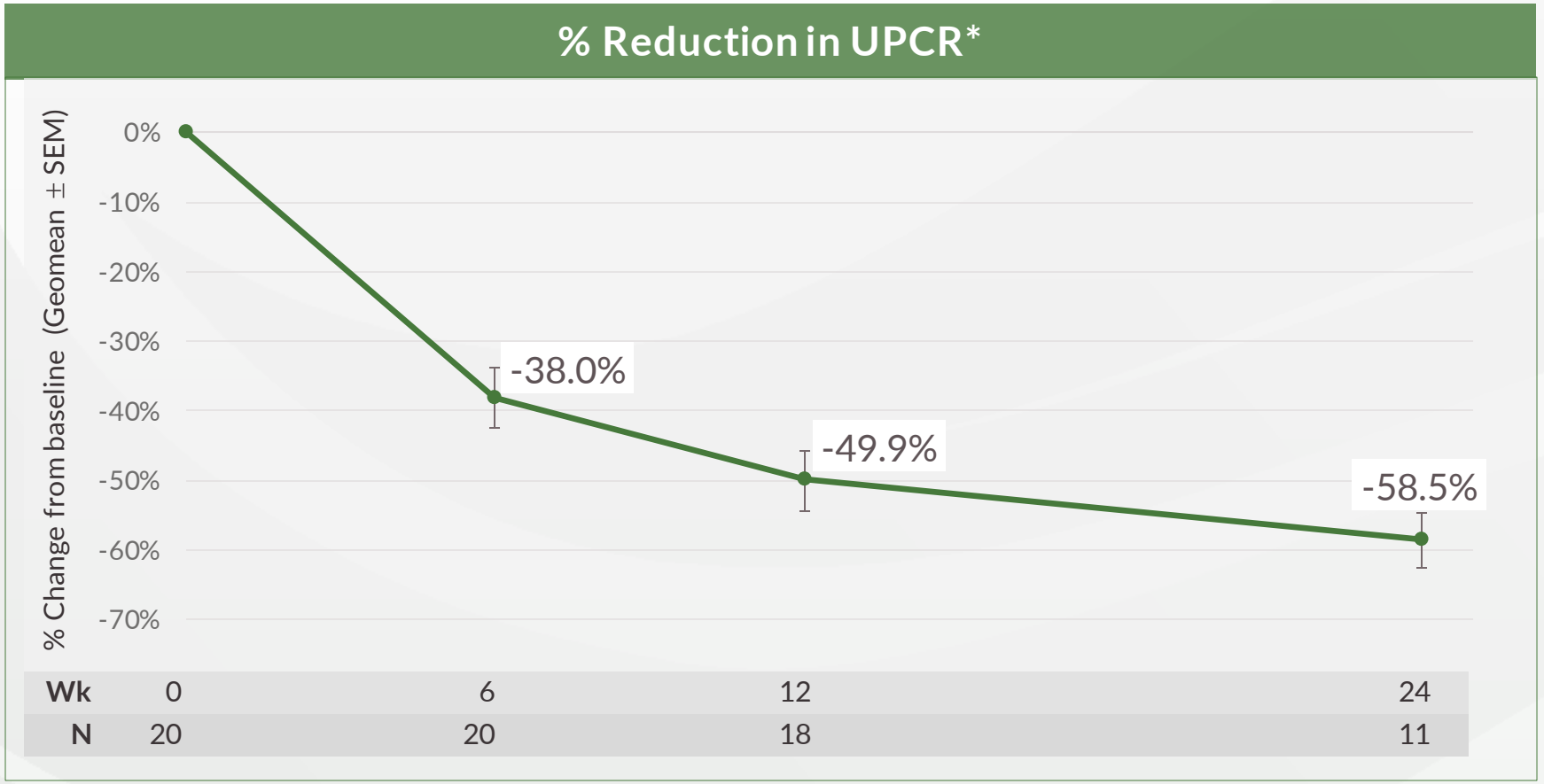

Median baseline 24-h urine protein excretion: 1.17 g/day (Q1,Q3: 0.85, 1.46 g/day)

*Results plotted are based on the least squares mean +/- SE of change from baseline on natural log scale from the MMRM back-transformed to a percent reduction from baseline scale

CHINOOK THERAPEUTICS

Atrasentan Provides Clinically Meaningful Proteinuria Reduction in Patients with IgAN Receiving Optimized SOC

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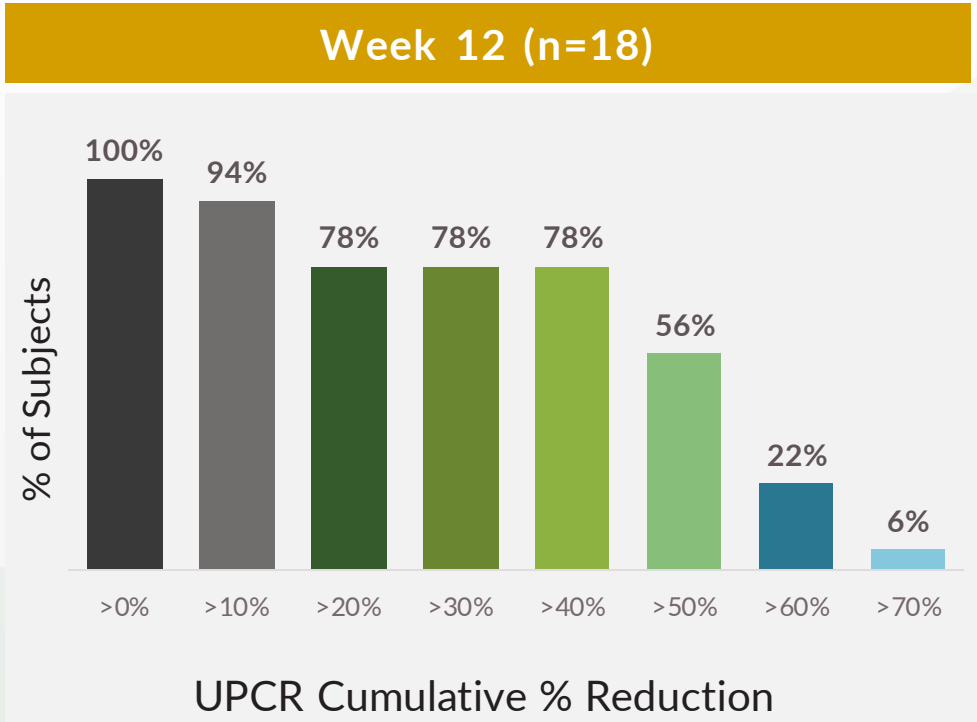
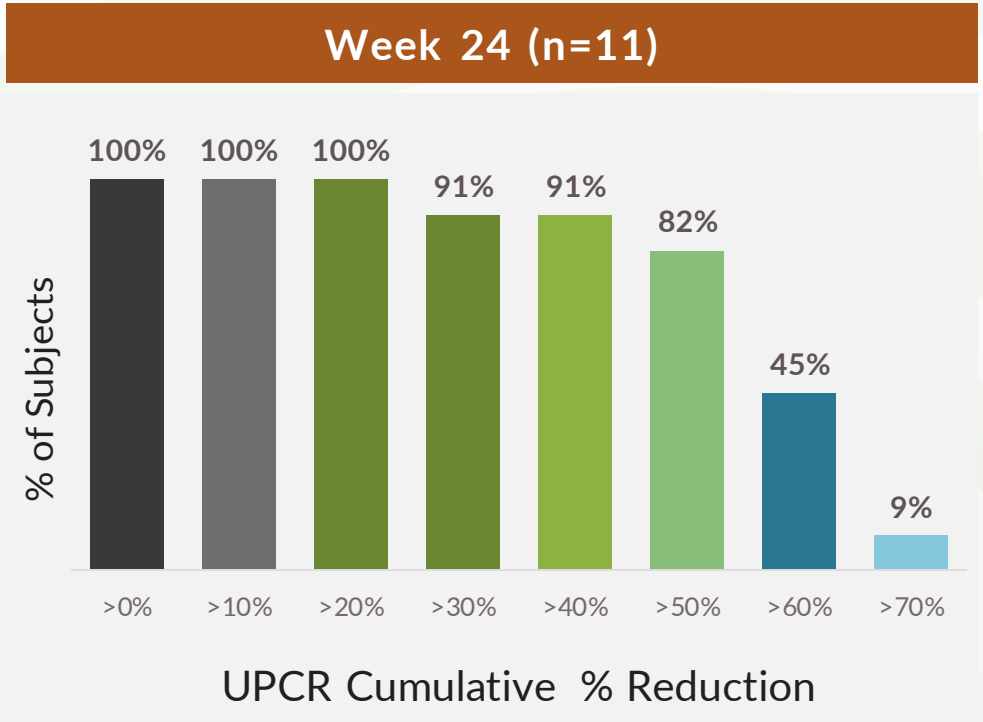
- **91%** of patients achieved >40% reduction in proteinuria at Week 24





CHINOOK THERAPEUTICS

Treatment with Atrasentan Provides Clinically Meaningful Proteinuria Reduction and is Well-tolerated in Patients with IgAN

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Interim AFFINITY IgAN data:

- In this Phase II study with 20 patients, 70% of patients had baseline total urine protein >1g/day despite optimized SOC treatment, representing an IgAN population at high risk for progression
- Treatment with atrasentan resulted in clinically meaningful reductions in proteinuria at weeks 6, 12 and 24
- There were no meaningful changes in blood pressure and acute eGFR, suggesting proteinuria reductions were not primarily due to hemodynamic effects of atrasentan
- Generally well-tolerated with no treatment-related SAEs
- There was no increase in BNP and mean bodyweight, suggesting minimal fluid retention

This interim analysis demonstrates that atrasentan provides proteinuria reductions in patients with IgAN who remain at risk for progression with residual proteinuria despite optimized standard-of-care treatment.

ALIGN phase 3 trial of atrasentan in patients with IgAN is currently enrolling (NCT04573478)
Inclusion:

- eGFR ≥ 30 mL/min/1.73 m^2
- Total urine protein ≥ 1 g/day based on 24-hour urine collection at screening

CHINOOK THERAPEUTICS