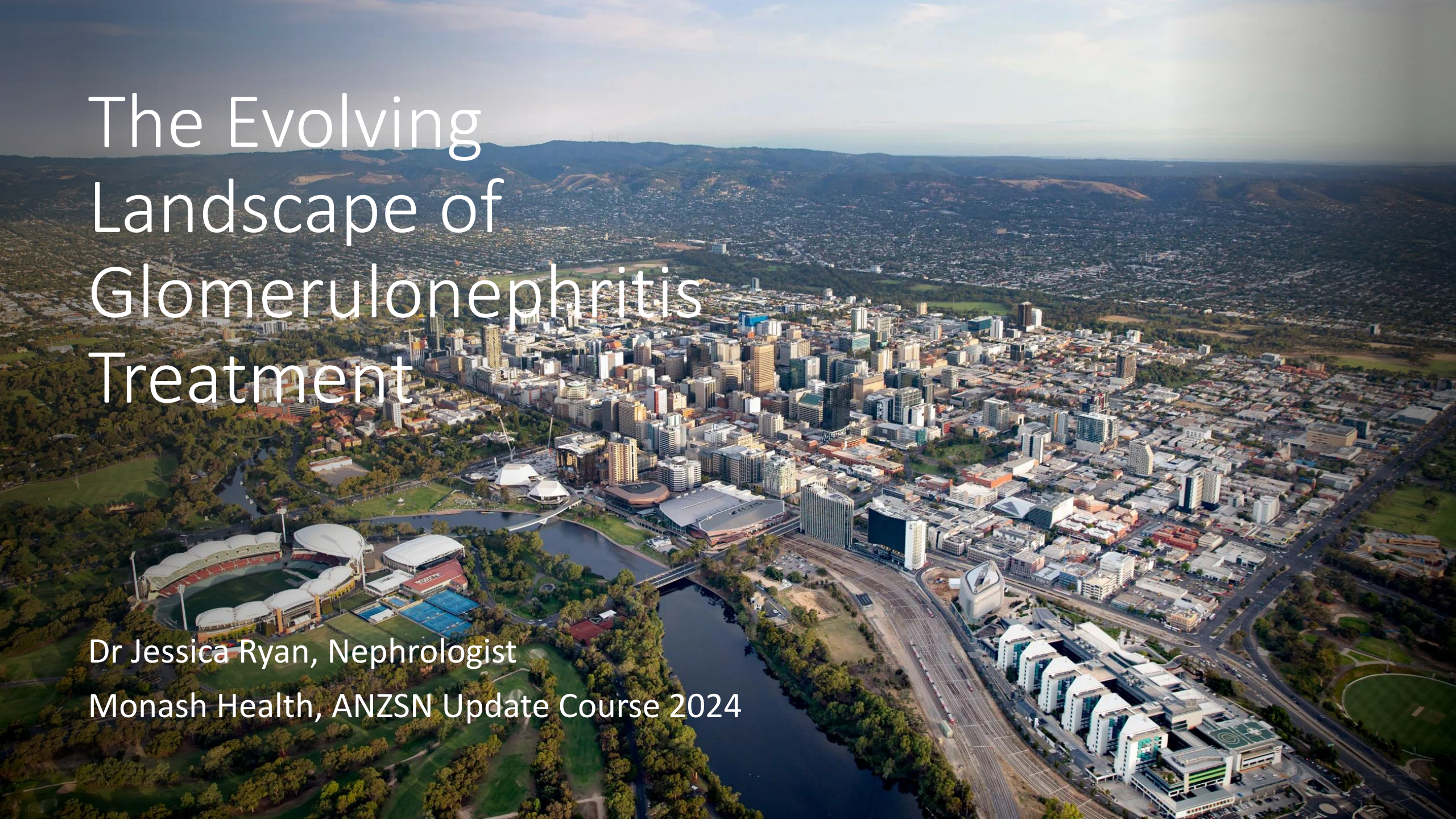
The Evolving Landscape of Glomerulonephritis Treatment



Dr Jessica Ryan, Nephrologist

Monash Health, ANZSN Update Course 2024

Disclosures

Advisory Board participation - Alexion, CSL Vifor

Educational Presentations – CSL Vifor, Astra Zeneca, Alexion, Boehringer

Research support grant – CSL Vifor

PI Industry Clinical Trials – AZ/Alexion, Calliditas Chinook, Novotech

MonashHealth

MONASH University
Medicine, Nursing and Health Sciences

ANZVASC
Australia and New Zealand Vasculitis Society

What I won’t be covering…

CART Cells
Lupus
ANCA Associated Vasculitis
SGTL2inhibitors

MonashHealth

MONASH University
Medicine, Nursing and Health Sciences

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This is not an IgAN talk but……

Talking about my generation .....

Nephrology Pipeline

FDA and EMA recognised significant proteinuria reduction as a surrogate endpoint for accelerated approval

Azathioprine (early 60s)

IV steroid for severe SLE mid 70s

Cyclophosphamide late 70s

cyclosporin 1980s

tacrolimus 1994

mycophenolate 1995

Everolimus 2010

Rituximab 2011
Eculizumab 2011
Belatacept 2011
Ravulizumab 2020
Dapagliflozin 2020
Voclosporin 2021
Budesonide 2022
Belimumab 2022
Avacopan 2022
empagliflozin 2023
Sparsentan 2023

Complement -
Pegcetacoplan
Iptacopan
Danicopan
Aro-CFB
Anti CD38 -
Mezagitamab
Felzartamab
Daratumumab
CARTCells
BAFF/APRIL-
Atacicept
Telitacicept
Sibeprenlimab
ETa receptor -
Atrasentan
Anti CD20-
Obinutuzumab
CTLA4 -
Abatacept

Diagnosis of Glomerulonephritis

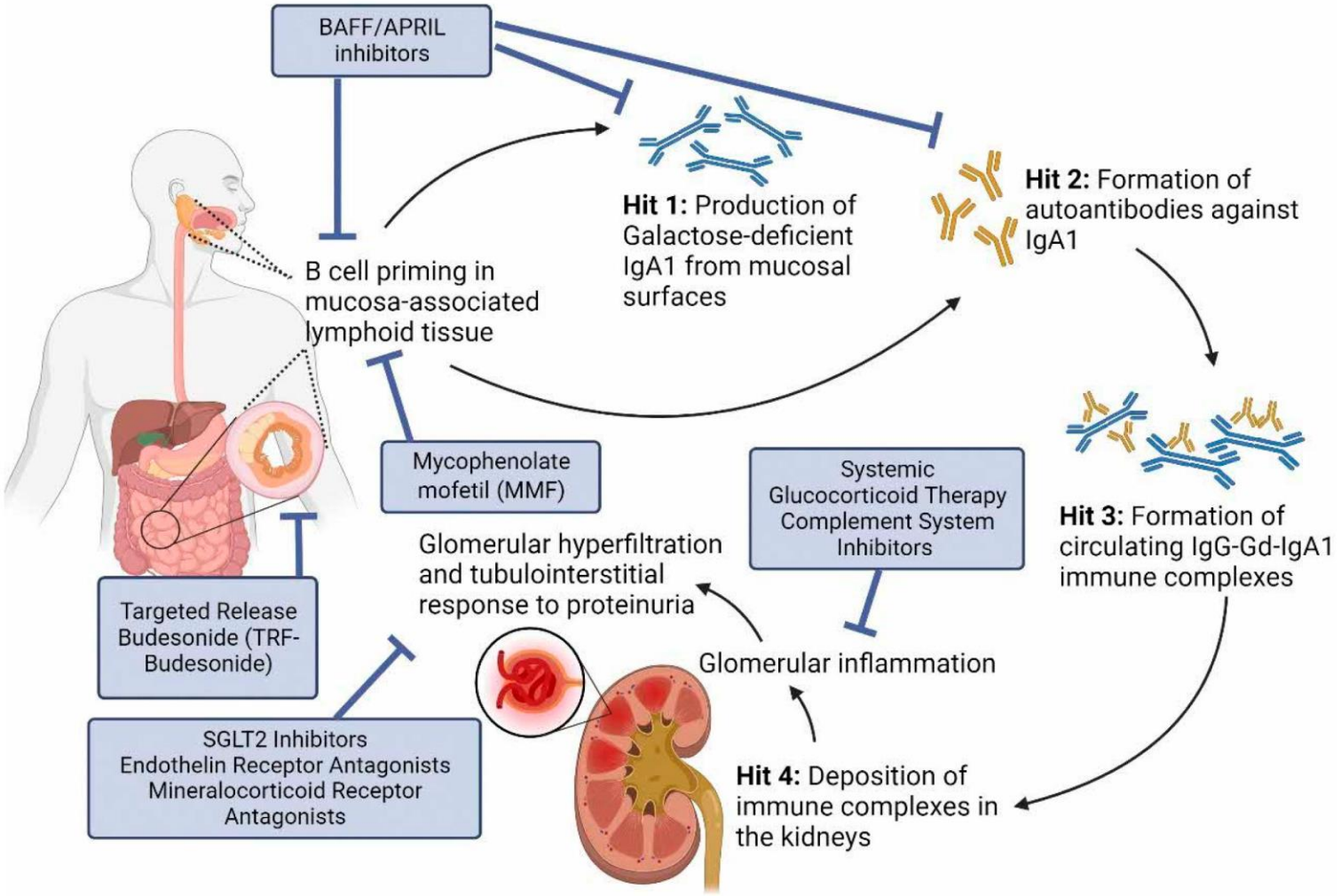
Hypertension, eGFR, urinalysis (haematuria and proteinuria), kidney biopsy

Pathogenesis of Glomerulonephritis

5 causes of GN	Simplified Pathogenesis	Therapy
Infection related GN	Innate and adaptive host defence with or without molecular mimicry	Infection Control
Autoimmune GN	Adaptive immune response to autoantigens	Transient or persistent modulation of adaptive immunity
Alloimmune GN	Adaptive response to donor antigens	Persistent modulation of adaptive immunity
Autoinflammatory GN	Inborn errors of innate immunity	Suppress complement activation
Monoclonal gammopathy-related GN	Paraprotein-releasing B cell clone or plasma cell clone	Clone-directed therapy

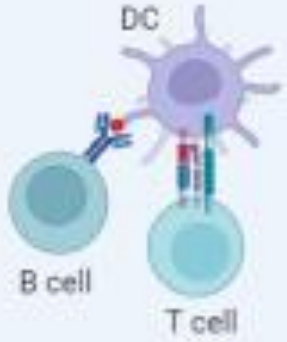
Adapted from Anders, Kitching et al, Glomerulonephritis: immunopathogenesis and immunotherapy, Nature Reviews July 2023

Pathogenesis of IgAN – the 4 HIT Hypothesis

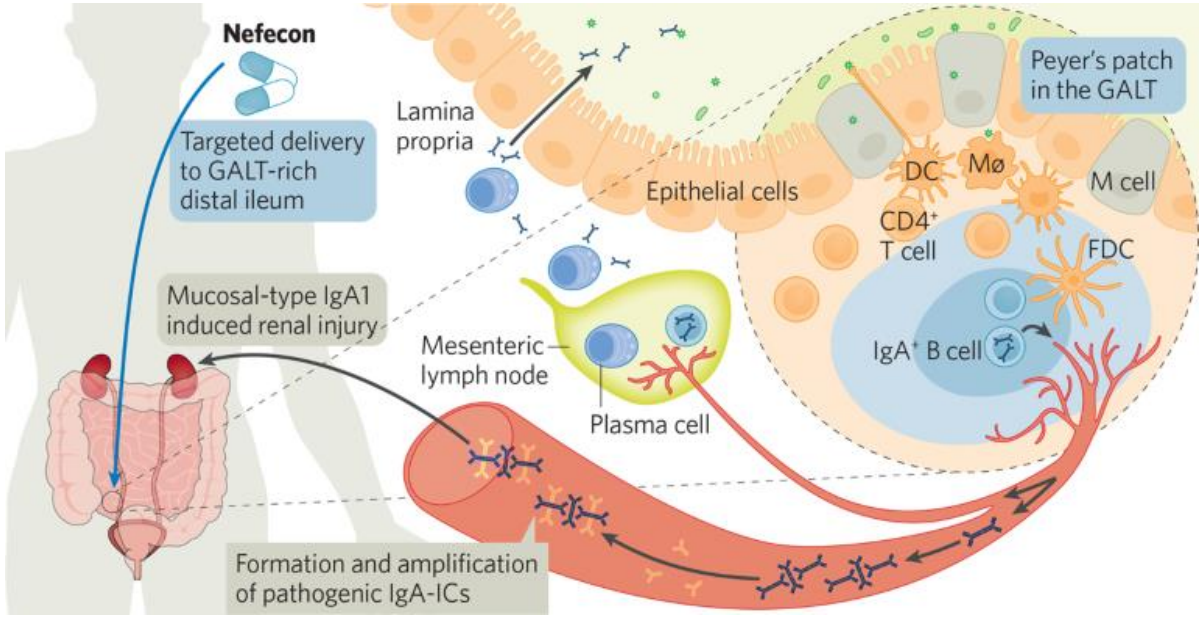


Lim et al, An Update on Current Therapeutic Options in Ig A Nephropathy, Journal of Clinical Medicine, Jan 2024

Drugs on the Horizon

Intestine	Bone Marrow	Lymphoid Tissue	Kidney
Reducing production of pathogenic antibodies	Reducing production of pathogenic antibodies	Reducing production of pathogenic antibodies	Mitigating the consequences of Nephron loss
Peyers Patch	Plasma cells	 DC B cell T cell	Halting glomerular inflammation
GALT TRF-Budesonide	**Plasma cell depletion** Mezagitamab Felzartamab	**Anti CD 20** Obinutuzumab **APRIL/BAFF** Atacicept **APRIL** Sibeprenlimab	**Complement** Iptacopan Raviluzumab **SGTL2i** Atrasentan **Endothelin A** Sparsantan **Endo A + Ang II**

Targeted Release Budesonide (Tarpeyo)



NEFIGAN – phase II randomized double-blind placebo controlled trial

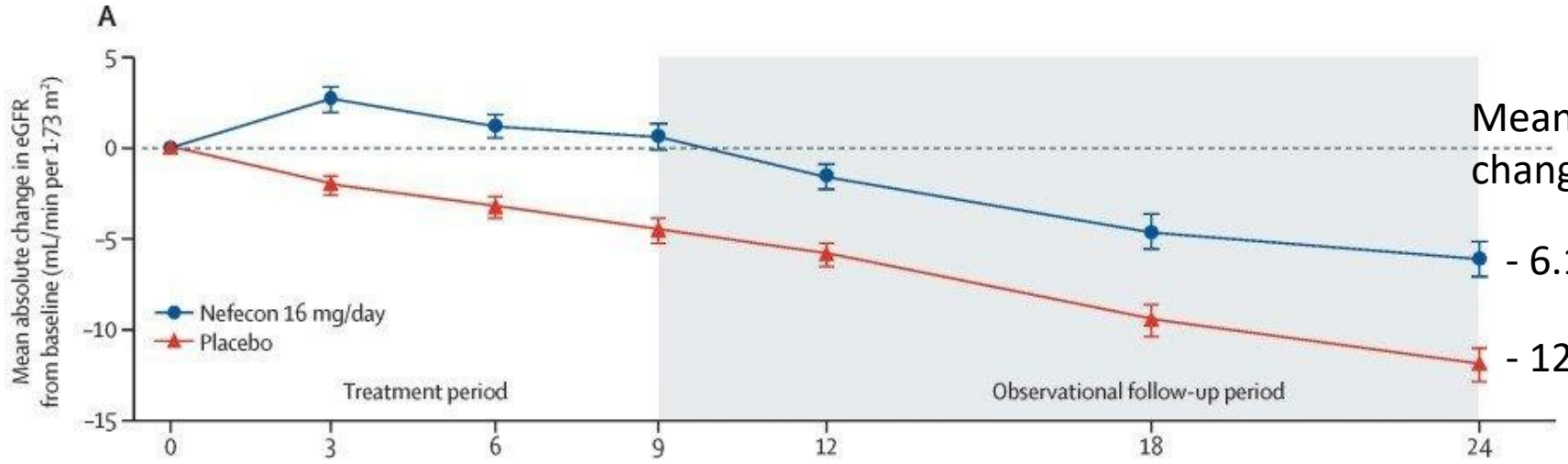
NefigArd – phase III, double blind placebo controlled trial

Primary and Secondary endpoints:

Change in proteinuria at 9 months

Change in eGFR at 9 and 12 months

NefigArd Trial Mean absolute change in eGFR from baseline to 24months (full analysis set)



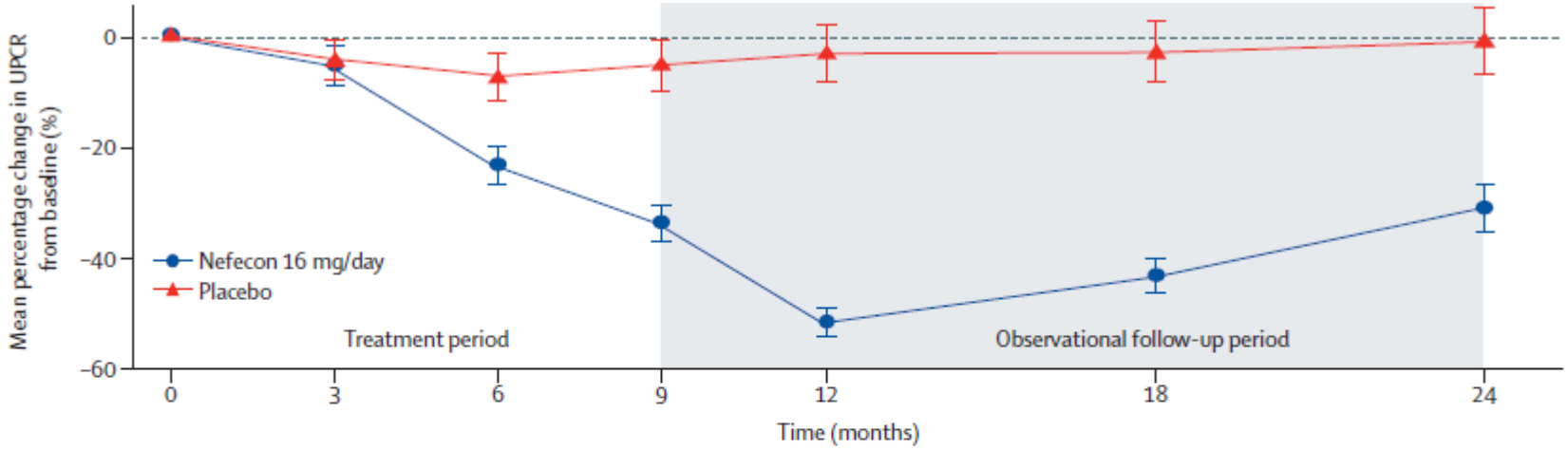
Nefecon, n	182	171	167	167	153	155	149
Placebo, n	182	178	171	164	161	150	146
Mean absolute change (95% CI) from baseline, mL/min per 1·73 m²							
Nefecon 16 mg/day		2·76 (1·62 to 3·93)	1·22 (−0·08 to 2·54)	0·66 (−0·80 to 2·15)	−1·52 (−2·96 to −0·03)	−4·59 (−6·46 to −2·66)	−6·11 (−8·04 to −4·11)
Placebo		−2·04 (−3·07 to −0·98)	−3·28 (−4·48 to −2·04)	−4·56 (−5·86 to −3·22)	−5·85 (−7·16 to −4·51)	−9·50 (−11·21 to −7·72)	−12·00 (−13·76 to −10·15)
Mean absolute difference (95% CI), mL/min per 1·73 m²							
Nefecon 16 mg/day vs placebo		4·80 (3·32 to 6·70)	4·49 (2·79 to 6·61)	5·21 (3·35 to 7·58)	4·33 (2·44 to 6·66)	4·90 (2·43 to 7·96)	5·89 (3·35 to 9·15)

Mean absolute change from baseline

- 6.11 ml/min

- 12.0 ml/min

NefigArd Trial Mean % change uPCR(g/g) from baseline to 24months (full analysis set)



Nefecon, n	182	173	169	166	157	155	145
Placebo, n	182	176	169	164	160	151	142
Mean percentage change (95% CI) from baseline, %							
Nefecon 16 mg/day		−5·2 (−11·8 to 1·9)	−23·1 (−29·5 to −16·1)	−33·6 (−39·6 to −27·0)	−51·3 (−56·2 to −45·9)	−43·1 (−49·0 to −36·6)	−30·7 (−38·9 to −21·5)
Placebo		−4·3 (−10·9 to 2·9)	−7·3 (−15·0 to 1·2)	−5·2 (−13·8 to 4·3)	−3·2 (−12·8 to 7·5)	−2·9 (−13·0 to 8·3)	−1·0 (−12·8 to 12·4)
Percentage reduction (95% CI), %							
Nefecon 16 mg/day *vs* placebo		1·0 (−9·6 to 10·5)	17·1 (6·1 to 26·7)	30·0 (19·9 to 38·8)	49·7 (41·6 to 56·6)	41·4 (31·7 to 49·8)	30·1 (16·4 to 41·5)

Does targeted-release formulation of Budesonide improve kidney function in primary IgA Nephropathy?

Part B NefIgArd trial

#NephJC

- Multicenter
- Double blinded
- Biopsy confirmed primary IgAN
- Persistent proteinuria (UPCR ≥ 0.8 g/g or ≥ 1 gram/24 hr)
- eGFR ≥ 35 to ≤ 90 ml/min/1.73 m²
- Optimized RAS inhibition

Randomization

	Time-weighted average change in eGFR from baseline		Mean absolute change in eGFR from baseline
Nefecon 16 mg od n = 182	–2·47 mL/min per 1·73 m²	p<0·0001	–6·11 mL/min per 1·73 m²
Placebo n = 182	–7·52 mL/min per 1·73 m²		–12·00 mL/min per 1·73 m²

24 months

Safety

2X Serious TEAE twice as common with Nefecon

Discontinuation due to TEAE higher with Nefecon

Common TEAE: Peripheral edema, hypertension, muscle spasm, acne & headache

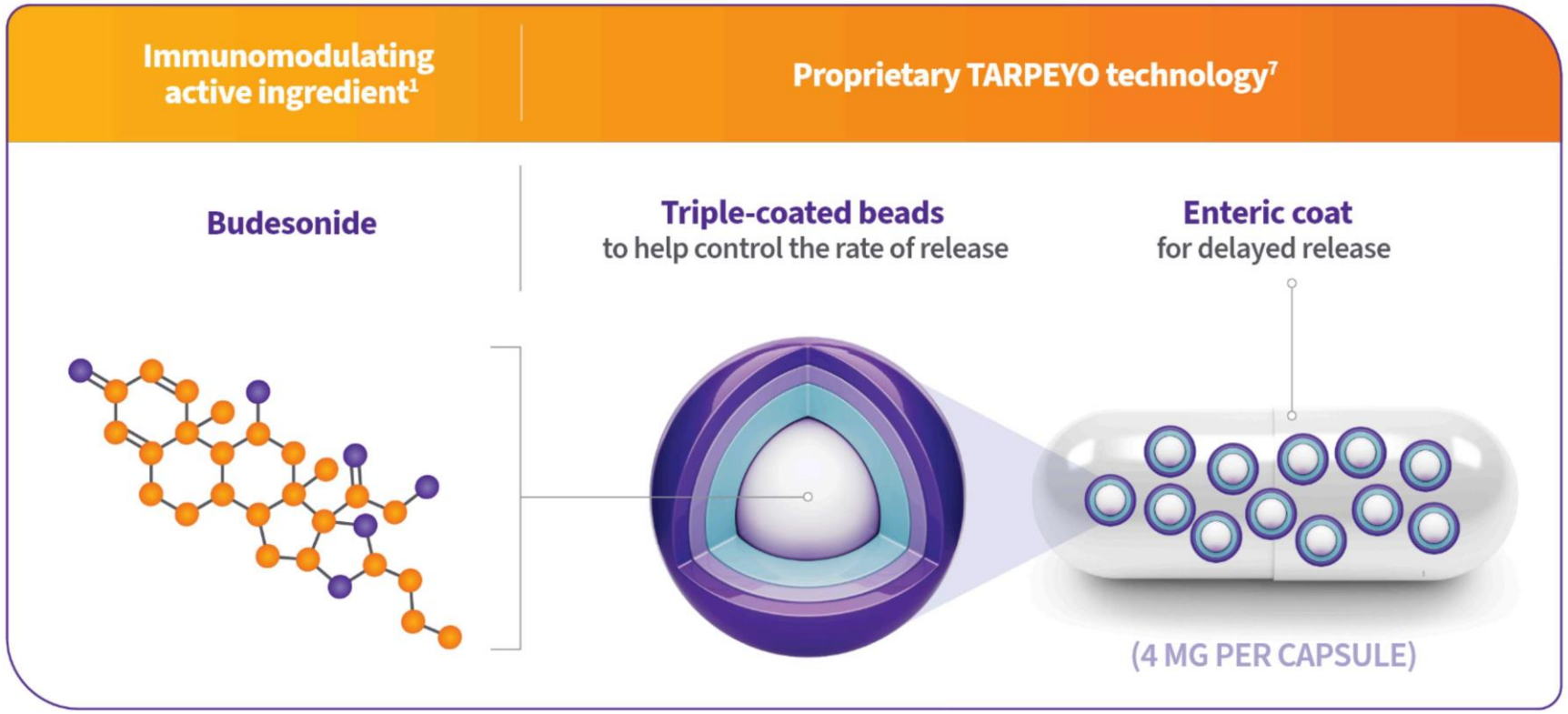
TEAE: Treatment-emergent adverse events, UPCR: Urine protein to creatinine ratio in gm/gm
eGFR: Estimated glomerular filtration rate in mL/min per 1·73 m²

Conclusion: The final NefIgArd study has verified the approved clinical benefit of Nefecon disease-specific treatment that is able to significantly reduce the rate of kidney function decline in patients with primary IgAN

Lafayette R et al. The Lancet, 2023

Visual abstract by Anant SSP MD DM
@Glomkeeper

Designed to dissolve to target Peyer's Patches



From Calliditas Therapeutics website

Table 1. Pharmaceutical Characteristics of Delayed-Release Budesonide Oral Formulations

Parameter	Nefecon	Budenofalk	Entocort	Cortiment
Enteric coating material and component	Eudragit L and S on capsule shell	Eudragit L and S on beads	Eudragit L55 on beads	Eudragit L55 and S on tablet
Nominal pH of enteric coating	Proprietary information[a]	pH 6.4 (RMS Assessment Report)	pH 5.5 (FDA)	pH 7 (FDA)
Capsule material	HPMC	Gelatin	Gelatin	N/A
Sustained-release component	Ethylcellulose-based coating on beads	Eudragit RS	Ethylcellulose	MMX (stearic acid/HPC matrix)

[a]*Nominal pH is between that of Entocort and Budenofalk (written communication, Calliditas Therapeutics).*
RMS: Regulatory Management System of the Medicines and Healthcare Products Regulatory Agency (MHRA), UK; HPMC: hydroxypropyl methylcellulose; MMX: multimatrix formulation; HPC: hydroxyproplycellulose.

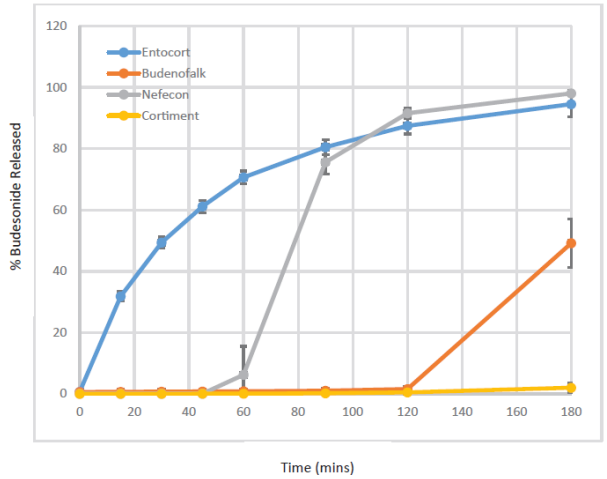


Figure 1. Dissolution profiles (mean ± SD % release) of four delayed-release budesonide oral formulations using the USP <711> method B. Only the buffer (intestinal) phase is shown; no appreciable release of budesonide was observed in the acid (gastric) phase.

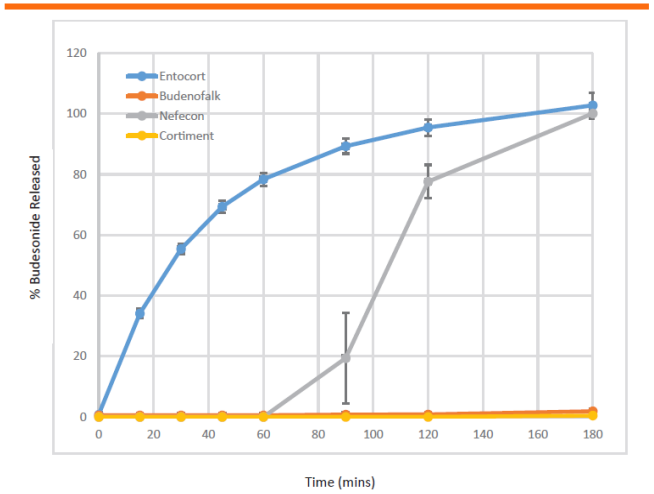


Figure 2. Dissolution profiles (mean ± SD % release) of four delayed-release budesonide oral formulations using the biorelevant method with reduced buffer phase. Only the buffer (intestinal) phase is shown; no appreciable release of budesonide was observed in the acid (gastric) phase.

Table 2. Similarity Factor (f_2) Analysis for Comparison of Dissolution Profiles

	Nefecon	Entocort EC	Budenofalk	Cortiment
f_2 value (USP)	Reference	18.1	16.0	15.8
f_2 value (biorelevant)	Reference	11.7	16.1	15.8

Dressman J, Comparative Dissolution of Budesonide from four commercially available products for oral administration: implications for interchangeability, Dissolution Technologies, Nov 2023 dx.doi.org/10.14227/DT300423P224

CONCLUSION

The dissolution data reported herein support the therapeutic goals of each product tested (Entocort EC for Crohn's disease, Budenofalk for Crohn's and UC, Cortiment for UC, and Nefecon for IgA nephropathy). Given the substantial differences in drug release patterns, widely divergent therapeutic aims, and differences in doses and dosing conditions of the four products, they cannot be regarded as either pharmaceutically or therapeutically interchangeable.

Table 1. Phar

Para			ablet
Enteric coa and co			
Nominal p co			
Capsule			
Sustain com			PC

[a]Nominal pH is
RMS: Regulato
MMX: multima

ose;

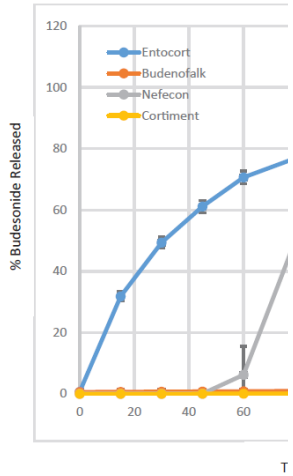


Figure 1. Dissolution profiles (m
release budesonide oral formula
Only the buffer (intestinal) phase
budesonide was observed in the

ysis for Comparison of

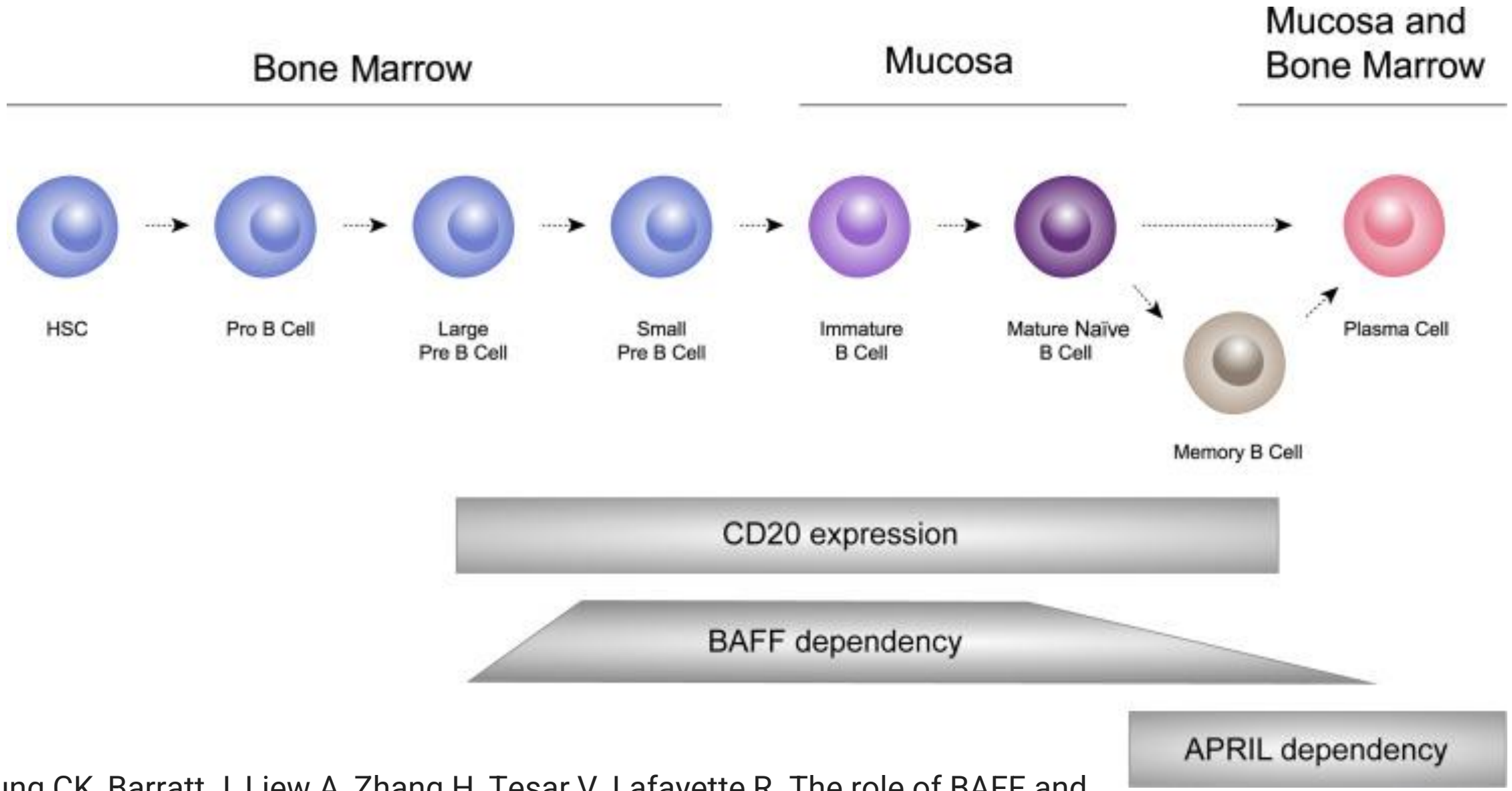
ocort EC	Budenofalk	Cortiment
8.1	16.0	15.8
1.7	16.1	15.8

ACKNOWLEDGEMENT

The author thanks RI.SE AB (Sweden) for assistance with the dissolution studies and Dr. Edmund Kostewicz (Fraunhofer ITMP) for statistical analysis.

FUNDING

This study was funded by Calliditas Therapeutics (Sweden).



Cheung CK, Barratt J, Liew A, Zhang H, Tesar V, Lafayette R. The role of BAFF and APRIL in IgA nephropathy: pathogenic mechanisms and targeted therapies. Front Nephrol. 2024 Feb

Bone Marrow

Plasma cells

Plasma cell depletion

<u>Anti CD38 monoclonal antibodies: IgAN, SLE, Membranous Nephropathy, AMR</u>

Mezagitamab Phase I IgAN and SLE (TAK-079-1006) moving into a phase II

In SLE, n=17, favourable safety profile and CD38+ cell depletion (McDonnell, Lupus and Science, 2024)

Felzartamab Phase II MN, IgAN, AMR

Felzartamab Abstract NDT ERA Phase II IgAN interim results IGNAZ study

Stable eGFR

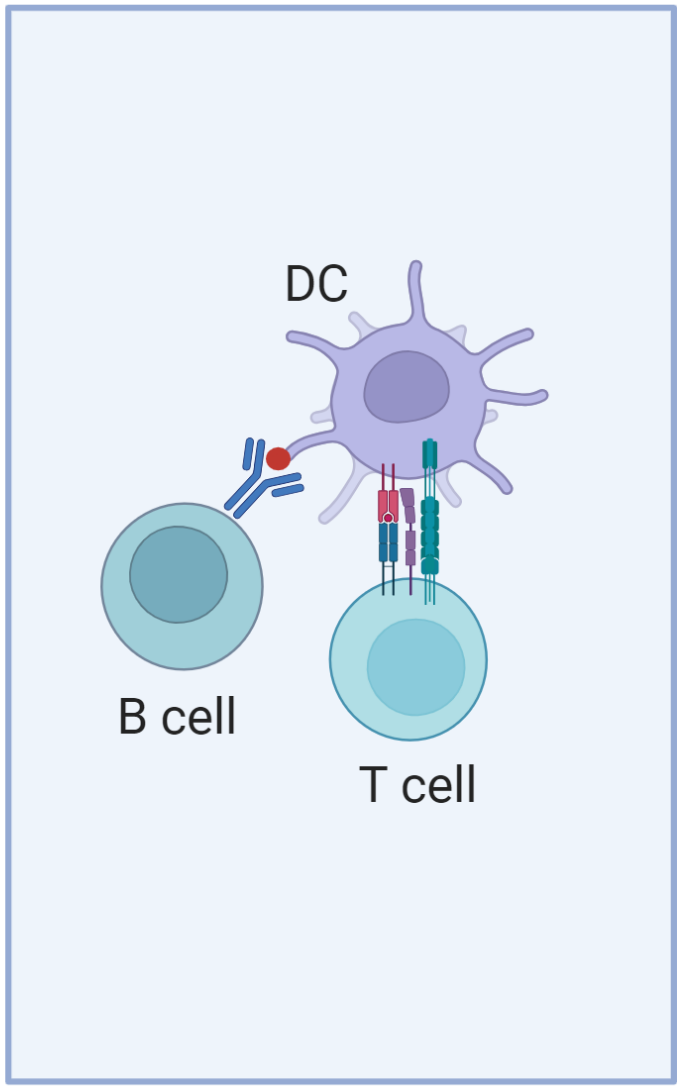
Prolonged UPCR reductions

Rapid reduction in IgA and Gd-IgA1 levels

Obinutuzumab

Type II Humanized antiCD 20 monoclonal antibody

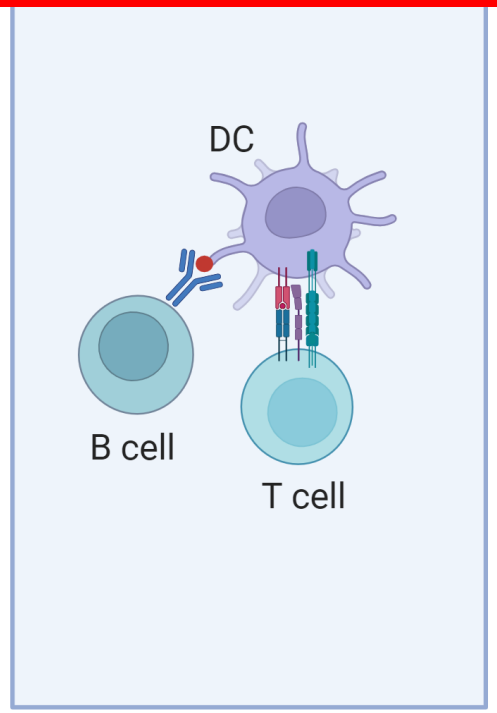
- Phase III open label vs Tacrolimus in Membranous GN NCT04629248
- Open label use in RTX resistant/dependent/ intolerant disease (NCT05050214)



Type 1 CD20 Abs eg. Rituximab	Type II CD20 Abs eg Obinutuzumab
CD20 accumulation in lipid rafts	No CD20 accumuation in lipid rafts
High CDC	Low/no CDC
ADCC	ADCC
ADCP	ADCP
Full CD20 binding capacity	Half maximal CD20 binding capacity
CD20 down regulation (FcγRIIb-mediated)	No CD20 down regulation
Weak/no homotypic cell aggregation	Homotypic cell aggregation
Direct cell death	Stronger induction of direct cell death

Adapted from Goede et al, Obinutuzumab (GA101) for the treatment of chronic lymphocytic leukemia and other B-cell non-hodgkin's lymphomas: a glycoengineered type II CD20 antibody. Oncol Res Treat. 2015;38(4):185-92. doi: 10.1159/000381524.

BAFF and APRIL play an important role in the maturation, function and survival of B cells and plasma cells



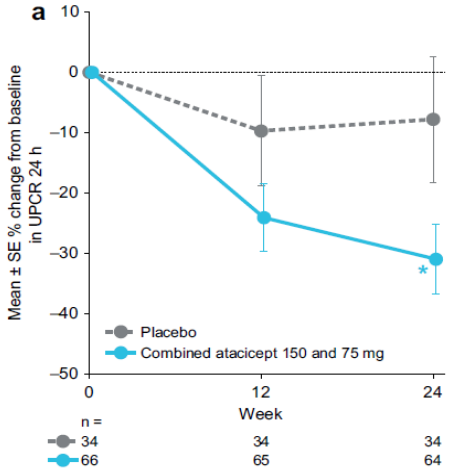
Both drugs reduce serum Gd-IgA1, at least while on therapy

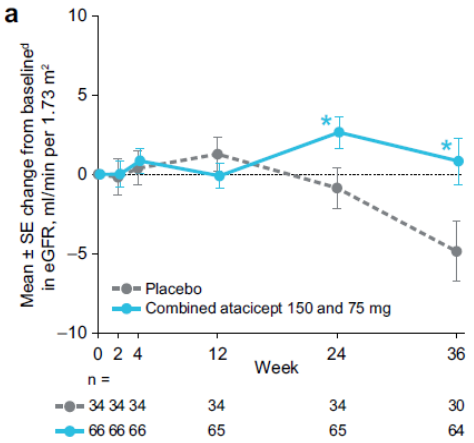
Atacicept

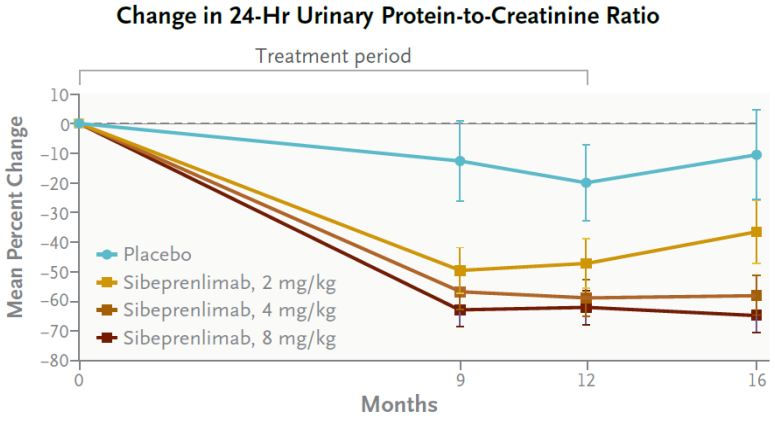
- Fusion protein that is able to bind and neutralizes both BAFF and APRIL
- Phase IIb clinical trial 116 pts randomized to atacicept 150, 75 or 25mg vs placebo
- Kidney international , published online 27 March 2024DOI: 10.1016/j.kint.2024.03.012
- Reduction in proteinuria and stabilization of eGFR
- FDA Breakthrough status May 2024

Sibeprenlimab

- Humanized IgG2 monoclonal antibody that binds to and neutralizes APRIL, a member of the TNFα superfamily
- Phase 2 trial randomized vs placebo Trial results 155 patients published NEJM DOI: 10.1056/NEJMoa2305635
- Once a month IV therapy for 12months
- FDA Breakthrough therapy Designation Feb 2024

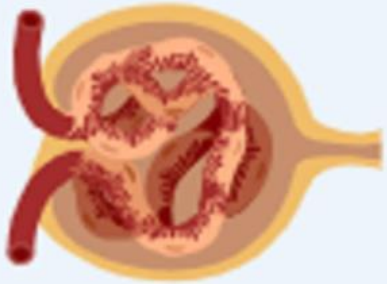






Sparsentan in IgAN

Kidney



Endothelin-1, via activation of ETaR on multiple kidney cell types, plays a key part in driving many processes associated with nephron loss in kidney disease, including vasoconstriction, cell proliferation, inflammation, apoptosis and fibrosis.

Non-immunosuppressive, dual endothelin and angiotensin receptor antagonist

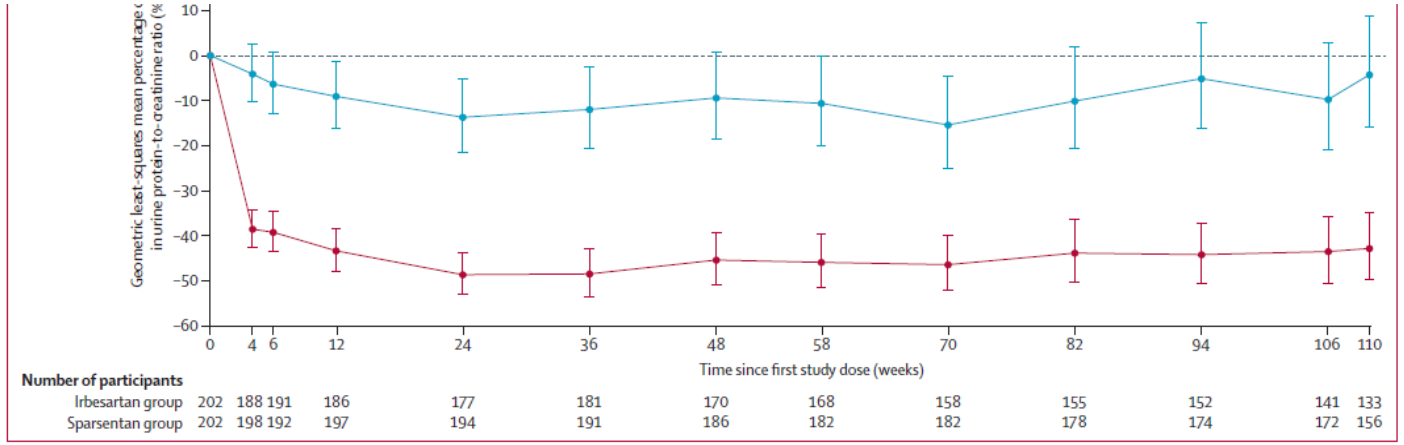
Phase 3 Protect Study Lancet Nov 2023 vs irbesartan

FDA Accelerated Approval Feb 2023 FILSPARI (drugs.com $11,258 for 30 tabs)

	Sparsentan group (n=202)	Irbesartan group (n=202)	Between-group difference (95% CI)	p value
Key secondary efficacy endpoints*				
Chronic slope from week 6 to week 110, mL/min per 1·73 m² per year	−2·7 (−3·4 to −2·1)	−3·8 (−4·6 to −3·1)	1·1 (0·1 to 2·1)	0·037
Total slope from day 1 to week 110, mL/min per 1·73 m² per year	−2·9 (−3·6 to −2·2)	−3·9 (−4·6 to −3·1)	1·0 (−0·03 to 1·94)	0·058
Other secondary efficacy endpoint*				
Absolute change from baseline to week 110, mL/min per 1·73 m²	−5·8 (−7·4 to −4·2)	−9·5 (−11·2 to −7·9)	3·7 (1·5 to 6·0)	..
Prespecified exploratory endpoint†				
Absolute change from baseline to week 114, mL/min per 1·73 m²	−6·1 (−7·7 to −4·5)	−9·0 (−10·7 to −7·2)	2·9 (0·5 to 5·3)	..

Data are least-squares mean change (95% CI) in eGFR unless otherwise stated. eGFR=estimated glomerular filtration rate. *Assessed in the full analysis set. †Assessed in patients in the full analysis set who completed the study treatment.

Table 2: **Change in eGFR**



Irbesartan

Sparsentan

SPARSENTAN in IgA Nephropathy. Does it PROTECT?

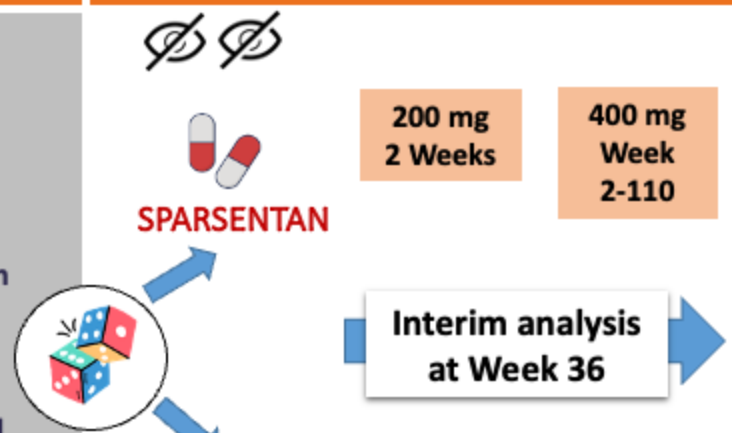
A prespecified interim analysis

#NephJC

COHORT

- 134 sites
  18 countries
- 404
  Randomized
- Biopsy-proven
  primary IgAN
- Proteinuria >1
  g/d despite
  max RAASi for
  12 weeks
- eGFR > 30
  ml/min

METHODS



RESULTS

	least sq mean % change in uPCR	Adverse Events	Edema	BP ↓	AKI
SPARSENTAN	-49.8%	88%	14%	14%	4%
IRBESARTAN	-15.1%	78%	9%	6%	1%

Least sq mean ratio
0.59 [95% CI 0.5, 0.69]

Conclusion: Once-daily treatment with sparsentan produced meaningful reduction in proteinuria compared with irbesartan in adults with IgA nephropathy. Safety of sparsentan was similar to irbesartan.

Heerspink HJ et al. The Lancet. 2023 Apr 1.

VA by Saumya Vishnoi @nephvishnoi

Sparsentan in FSGS

NEJM Nov 2023 DUPLEX Study

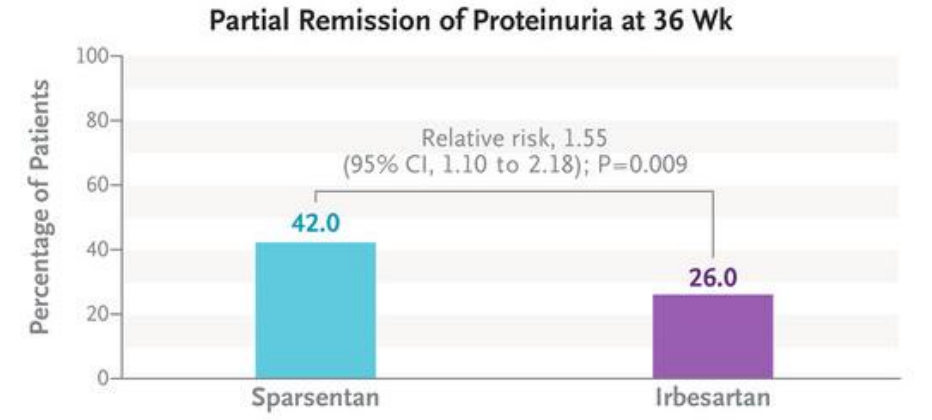
Phase III vs irbesartan (double blind, placebo controlled vs irbesartan).

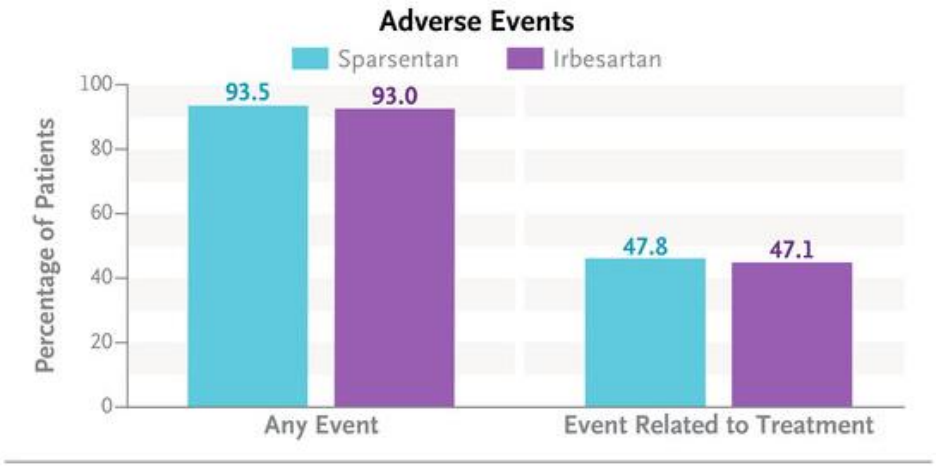
Largest interventional FSGS trial to date

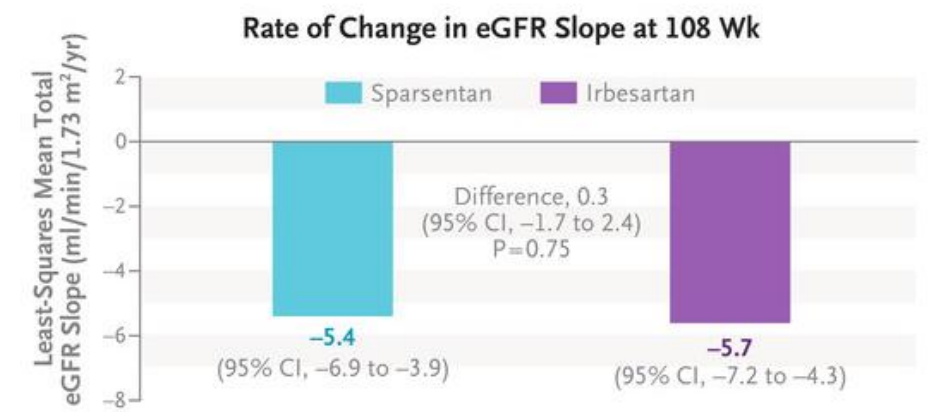
371 patients, biopsy confirmed ‘primary FSGS’ or genetic diagnosis

eGFR slope at 108 weeks did not differ significantly between those who received sparsentan and those who received irbesartan, despite a greater reduction in proteinuria at 36 weeks with sparsentan.

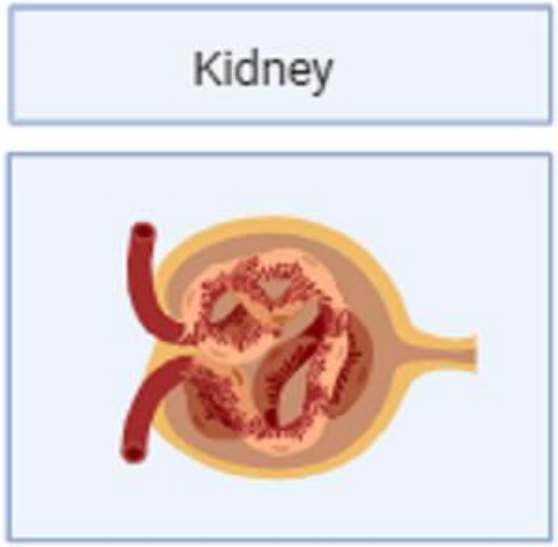
Ongoing analysis of OLE trial …..







Atrasentan

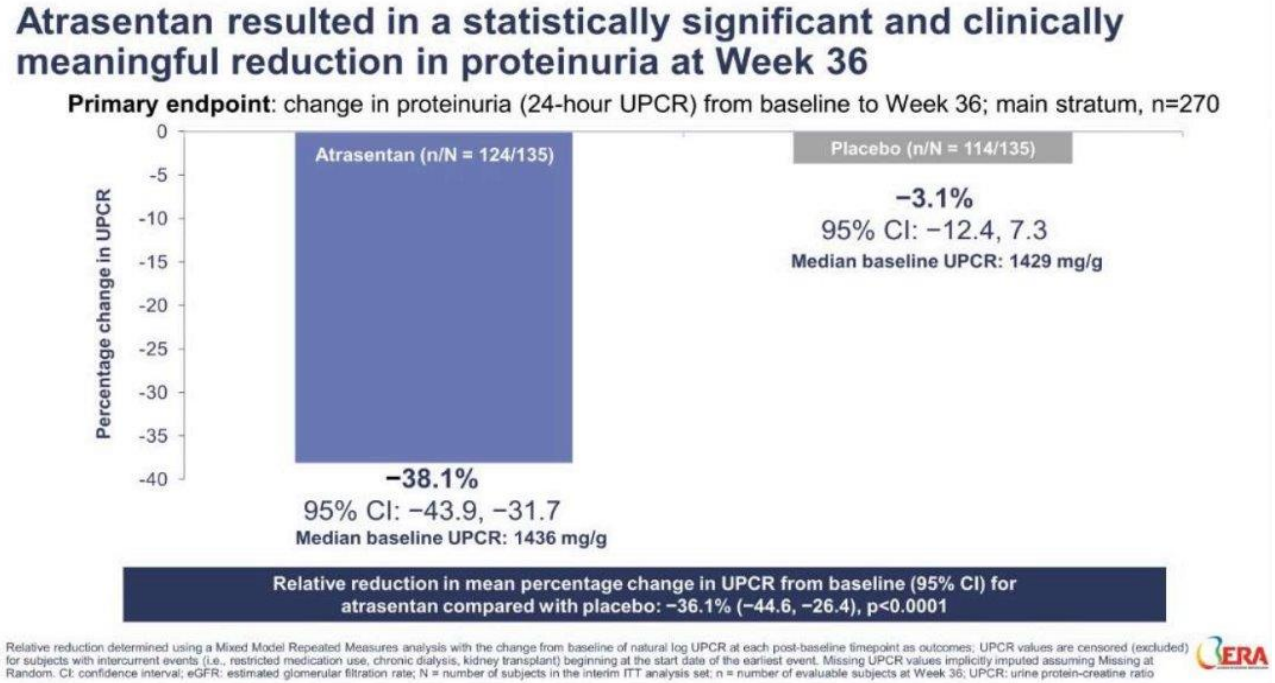


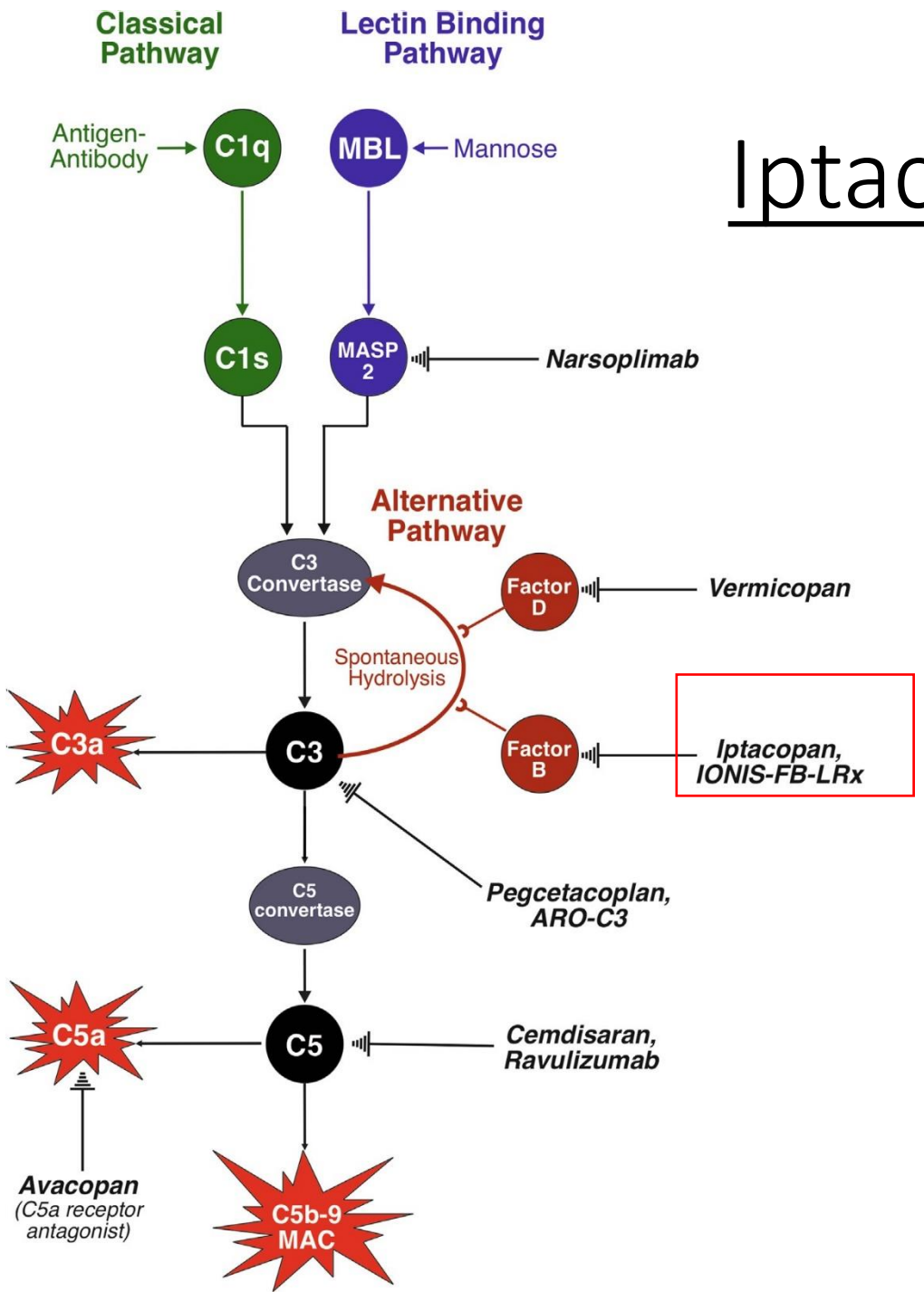
Endothelin-1, via activation of ET_aR on multiple kidney cell types, plays a key part in driving many processes associated with nephron loss in kidney disease, including vasoconstriction, cell proliferation, inflammation, apoptosis and fibrosis.

Selective endothelin A receptor antagonist (previously SONAR trial diabetic Nephropathy Lancet 2019)

Phase III, randomized trial ongoing ALIGN study IgAN

Interim results presented ERA: in addition to supportive SOC care, atrasentan achieved a 36.1% (p<0.0001) reduction in proteinuria (as measured by 24-hour urine protein to creatinine ratio [UPCR]) at 36 weeks when compared to placebo on top of supportive care.





Iptacopan (FABHALTA)

- Inhibits oral factor B of the alternative complement pathway.
- 450 adult patients SOC vs iptacopan 200mg bd for 24month treatment period.
- WCN Buenos Aires April 2024
- approximate 44% reduction in proteinuria at 9 months compared with placebo.
- the treatment effect on UPCR at 9 months was consistent across all subgroups, regardless of age, sex, race, baseline disease characteristics, and the use of sodium-glucose cotransporter-2 inhibitors
- 8th Aug 2024 FDA accelerated approval based on prespecified interim analysis of the phase 3 APPLAUSE trial in Ig A (previous phase II)

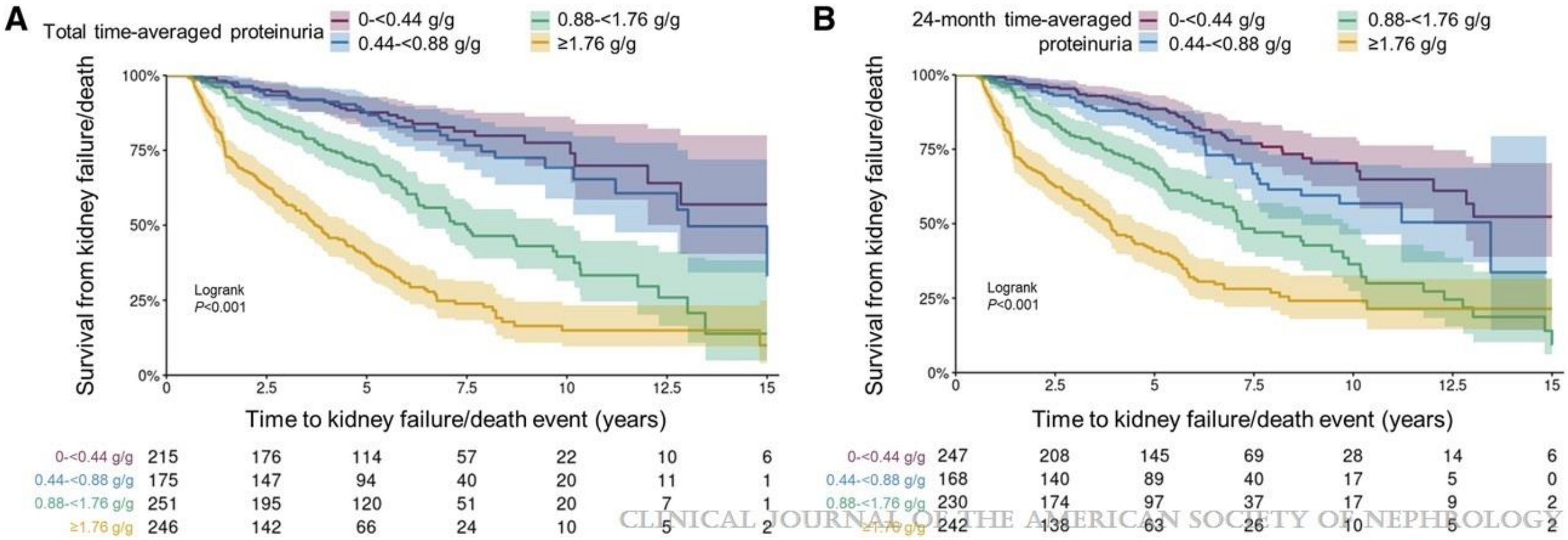
My current IgAN treatment approach in Australia in Sept 2024 …

- Renal Biopsy.
- Risk stratification and discussion with patient (IgArisk tool).
- Lifestyle measures and blood pressure control.
- Decide immunosuppression vs supportive management (Max tolerated ACE-I/ARB plus SGTL2i)

<u>If immunosuppression</u>:

1. Oral corticosteroids – low dose TESTING protocol (JAMA 2022) 6 to 9 month course (0.5mg per kg per day (max 40mg) weaning dose over 6 months plus PJP prophylaxis).
2. MMF (esp. if Chinese ethnicity) initially 1.5g per day for 12m, maintained 750mg to 1g for at least another 6 months (JAMA 2023).
3. *Enrol into a clinical trial – need to be prepared for the patient to get placebo or an unproven therapy.*

Impact of Proteinuria on long term outcomes of IgAN



CLINICAL JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Pitcher, David; Braddon, Fiona; Hendry, Bruce; Mercer, Alex; Osmaston, Kate; Saleem, Moin A.; Steenkamp, Retha; Wong, Katie; Turner, A. Neil; Wang, Kaijun; Gale, Daniel P.; Barratt, Jonathan

Clinical Journal of the American Society of Nephrology18(6):727-738, June 2023.

Challenges in treating Glomerular Disease

- Clinical trial design – how to include ‘controls’ ethically. Potential use historical controls.
- Evolving Standard of Care.
- Proteinuria and eGFR decline as surrogate endpoints.
- Develop good biomarkers of disease activity (chronicity vs activity): for example, haematuria as a marker of disease activity.
- Diversity in clinical trial recruitment: ethnicity, age, gender and renal function.
- Timing of intervention: what drug to use at what stage in which patient.
- Development of a personalized approach.