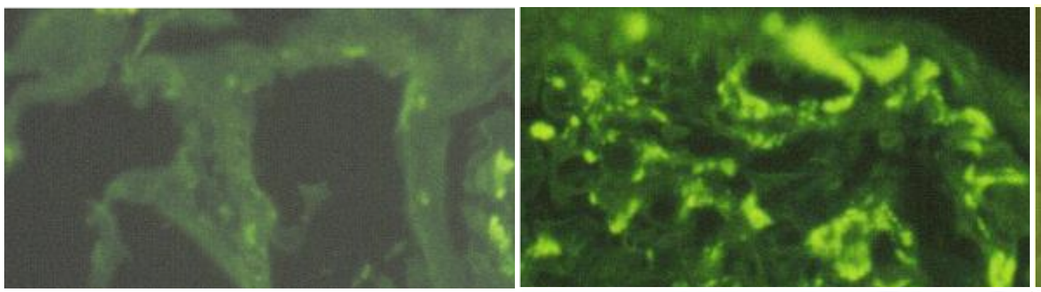
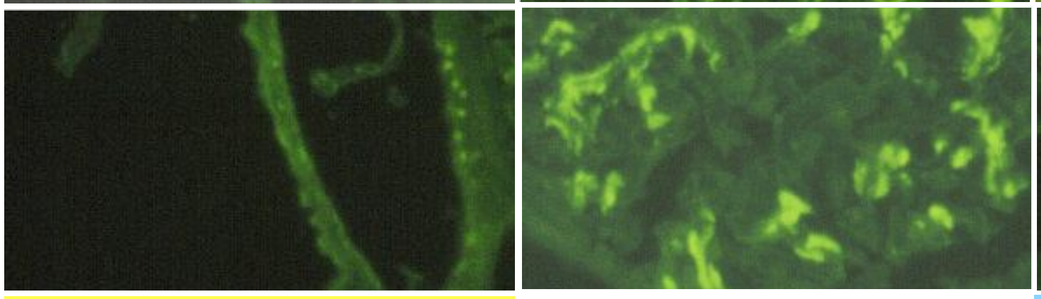
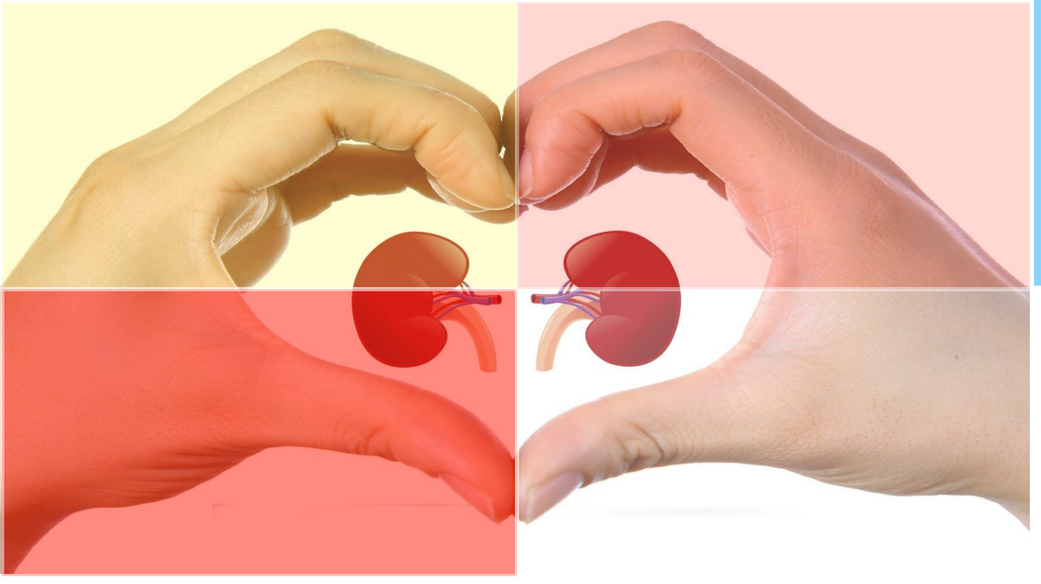




New treatment options for IgA-nefropathy

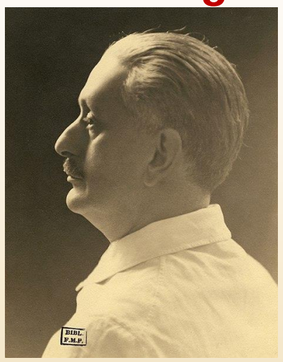
Raphaël Duivenvoorden, MD PhD
Internist-nephrologist
Radboudumc



Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	n.v.t
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	n.v.t

Jean Berger



1968

1994

Machio et al. NDT
ACEi vs placebo, N=39

2003

Praga et al. JASN
ACEi vs placebo, N=44

2006

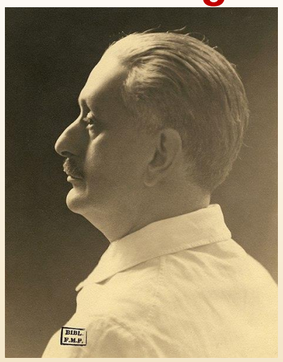
HKVIN study. AJKD
ARB vs placebo, N=109

2007

IgACE study. JASN
ARB vs placebo, N=66

2022 ?

Jean Berger



1968

Pozzi et al. JASN
Steroids vs Supportive care, N=86

2004

Manno et al. NDT
ACEi vs Steroid, N=97

2009

STOP IgA study. NEJM
Immunosuppression vs Supportive care, N=162

2015

TESTING study. JAMA
Steroid vs Supportive care, N=262

2017

2022 ?

2003

Praga et al. JASN
ACEi vs placebo, N=44

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IgACE study. JASN
ARB vs placebo, N=66

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HKVIN study. AJKD
ARB vs placebo, N=109

“High impact clinical trials ASN 2021” – TESTING study

2021

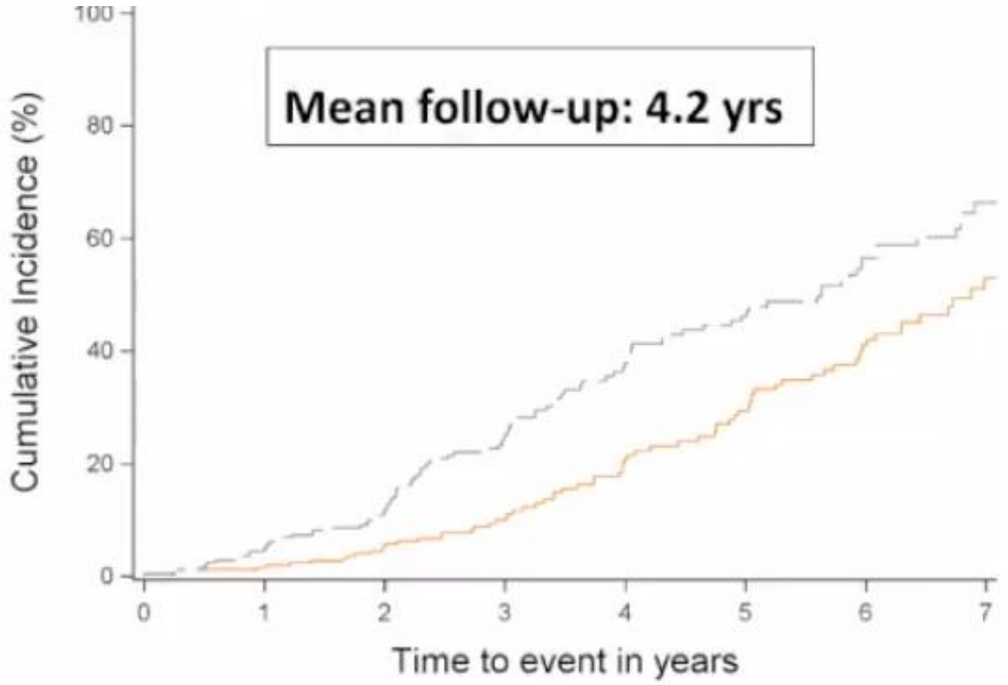
TESTING: Therapeutic Evaluation of STeroids in IgA Nephropathy Global Study

Vlado Perkovic on behalf of the TESTING study group:

High Impact Clinical Trials
ASN Kidney Week 2021

- Compound: Methylprednisolone, oral
- Dose: 0.6-0.8 mg/kg or 0.4 mg/kg per day
- 6-9 months of treatment, 4.2 years follow-up
- 503 patients divided in 2 groups
- eGFR: 61.5 (SD 23.6) ml/min/1.73m2
- Proteinuria: 2.42 (SD 1.98) g / dag
- ACE/ARB: all on max tolerated dose

Effect on composite endpoint (40% eGFR reduction, kidney failure, kidney death)



47% reduction

(HR 0.53, 95%CI 0.39-0.72, P<0.0001)

“High impact clinical trials ASN 2021” – TESTING study

2021

TESTING: Therapeutic Evaluation of STeroids in IgA Nephropathy Global Study

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ASN Kidney Week 2021

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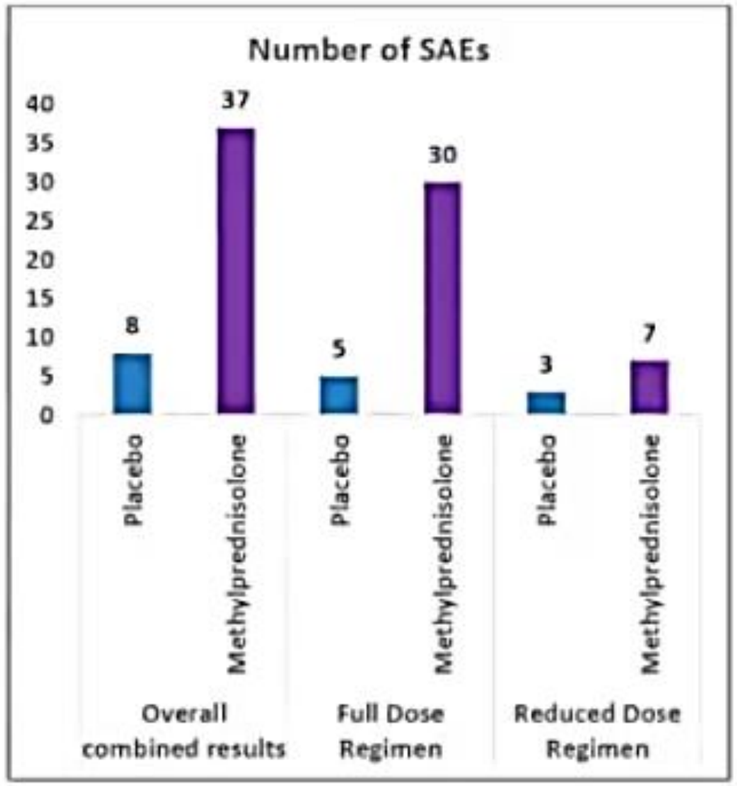
Serious Adverse Event rate



Full dose (N=136): NNT benefit 8.5 vs harm 8.1

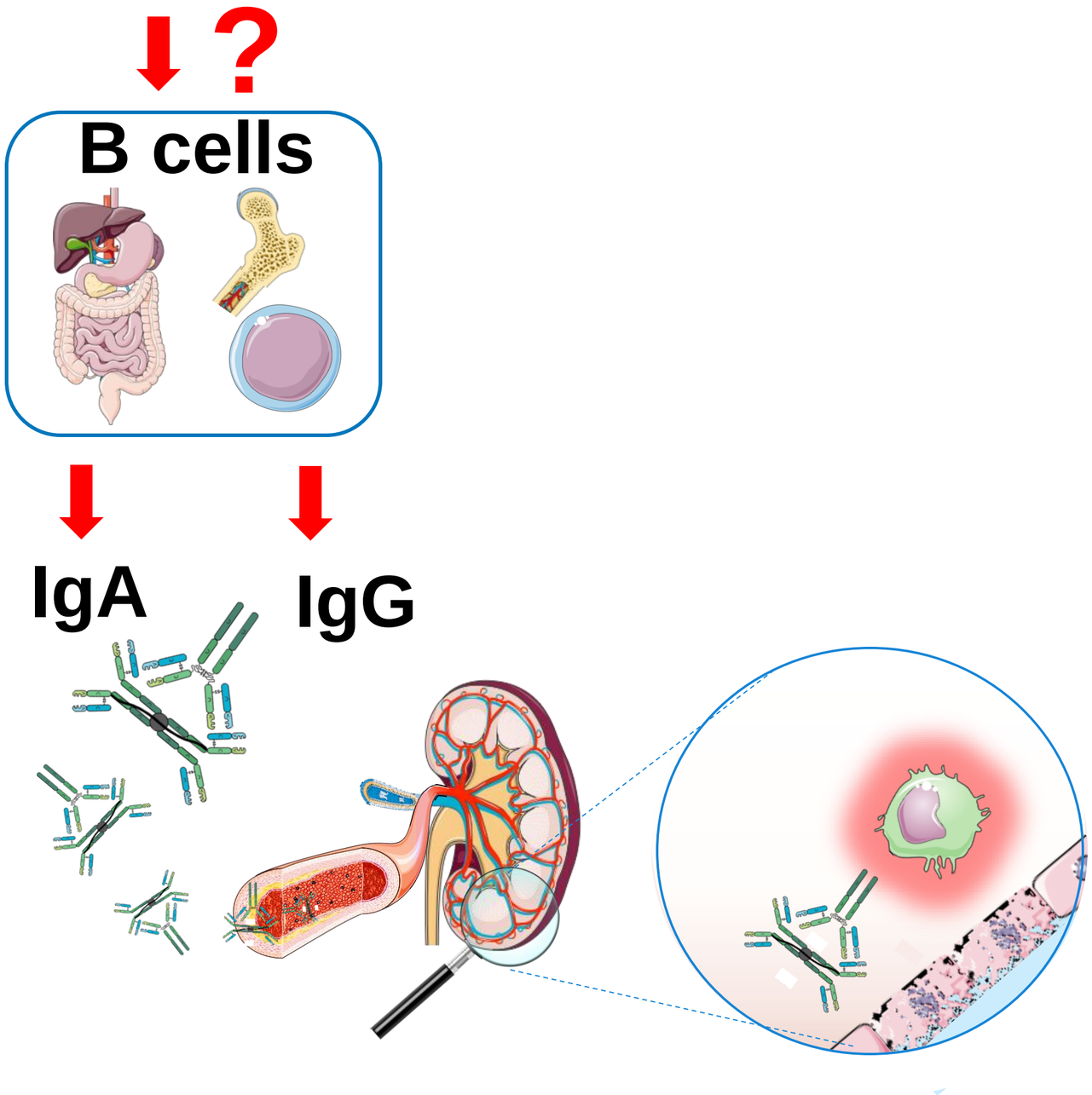
Reduced dose (N=121): NNT benefit 6 vs harm 41

What’s new?

Potential new therapies for IgA nefropathy

Compound	Target	Mechanism of action
Atacicept	B cells	BLyS and APRIL inhibitor
Telitacicept	B cells	BLyS and APRIL inhibitor
BION-1301	B cells	APRIL inhibitor
VIS649	B cells	APRIL inhibitor
Felzartamab	B cells	Anti CD38
Blisibimod	B cells	BAFF inhibitor
Fostamatinib	B cells	SYK inhibitor
Narsoplimab	Complement	MASP-2 inhibitor
Iptacopan	Complement	Factor B inhibitor
ONIS-FB-LRx	Complement	Factor B inhibitor
Ravulizumab	Complement	C5 inhibitor
Avacopan	Complement	C5aR inhibitor
Cemdisiran	Complement	C5 inhibitor
Pegcetacoplan	Complement	C3 inhibitor
Nefecon	GALT	Corticosteroid release in ileum
Atrasentan	Glomerulair capillary pressure lowering	Endothelin A receptor inhibitor
Sparsentan	Glomerulair capillary pressure lowering	Angiotensin II type 1 (AT1) receptor and ETA receptor inhibitor
Dapagliflozine	Glomerulair capillary pressure lowering	SGLT2 inhibitor

Mechanism of action of potential new therapies for IgA nephropathy



Mechanism of action of potential new therapies for IgA nephropathy

GALT

Nefecon

B cells

Atacicept

Telitacicept

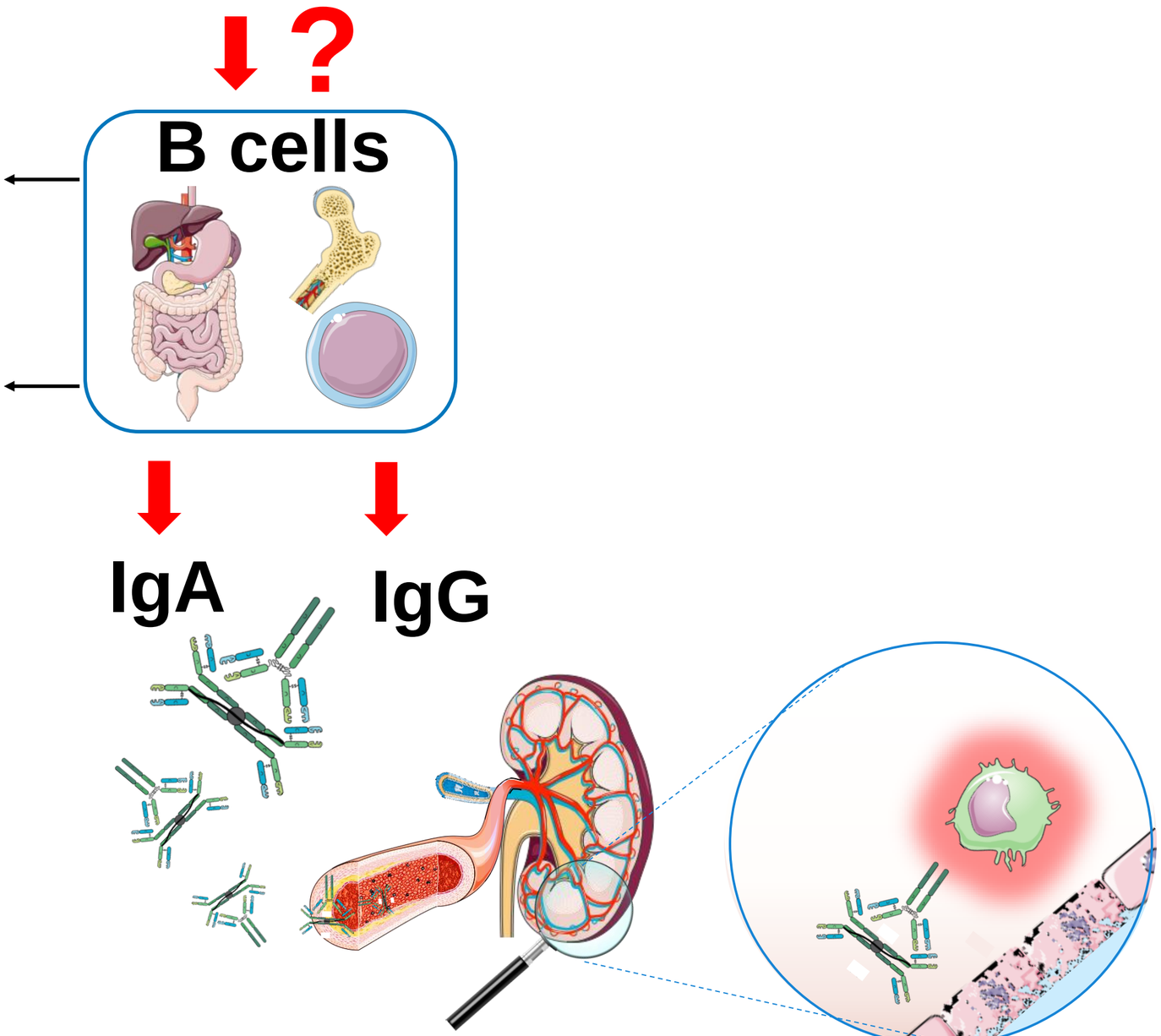
BION-1301

VIS649

Felzartamab

Blisibimod

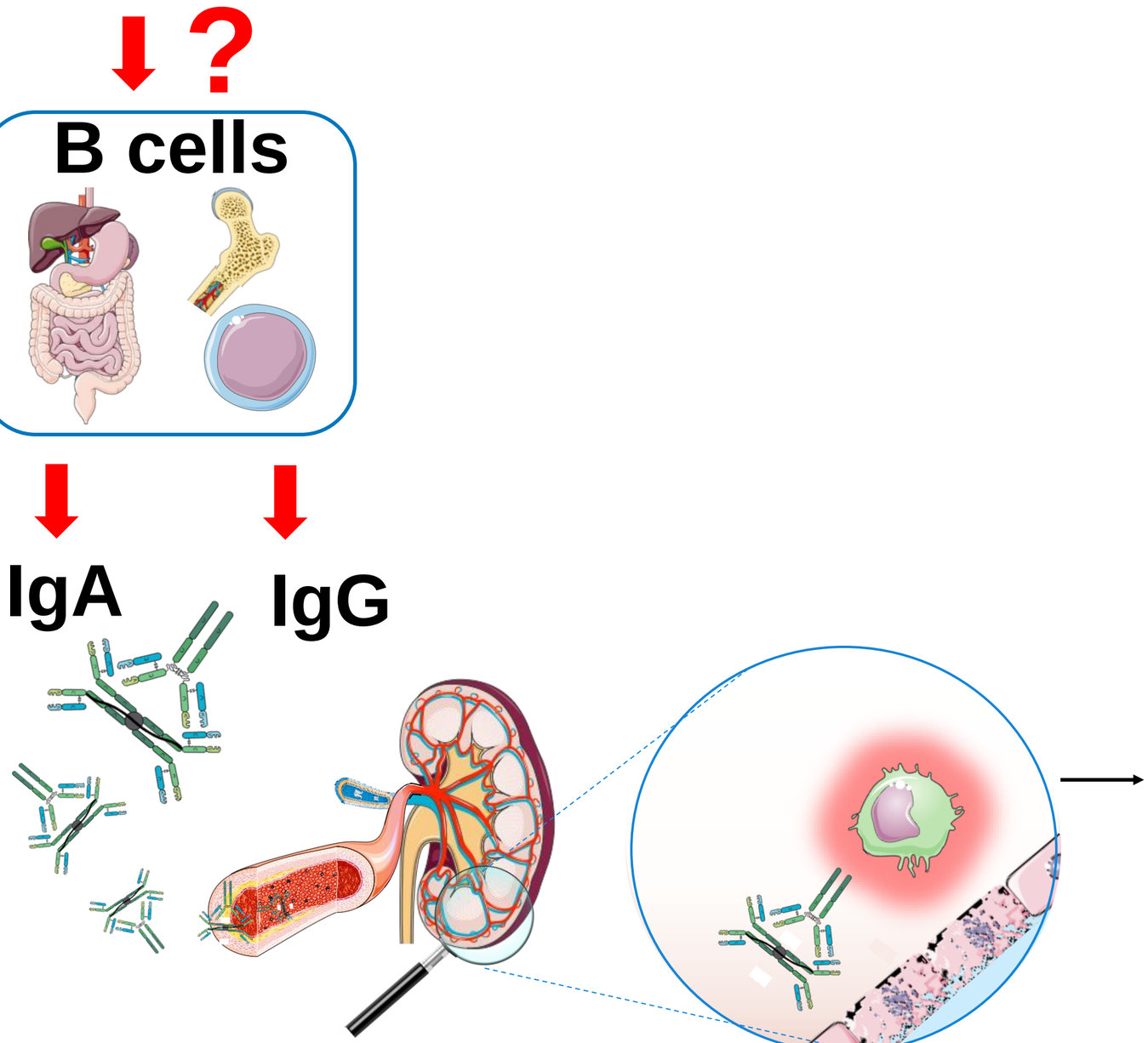
Fostamatinib



Mechanism of action of potential new therapies for IgA nephropathy

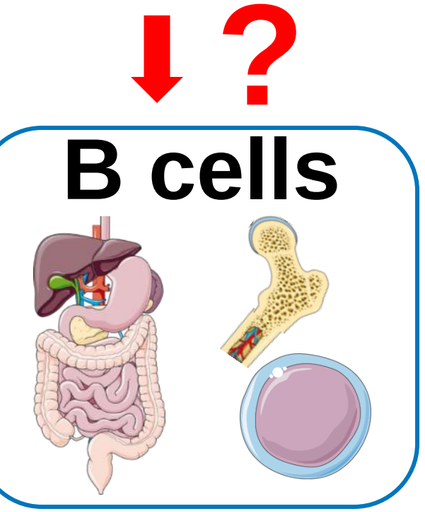
GALT
Nefecon

B cells
Atacicept
Telitacicept
BION-1301
VIS649
Felzartamab
Blisibimod
Fostamatinib



Complement
Narsoplimab
Iptacopan
ONIS-FB-LRx
Ravulizumab
Avacopan
Cemdisiran
Pegcetacoplan

Mechanism of action of potential new therapies for IgA nephropathy



GALT

Nefecon

B cells

Atacicept

Telitacicept

BION-1301

VIS649

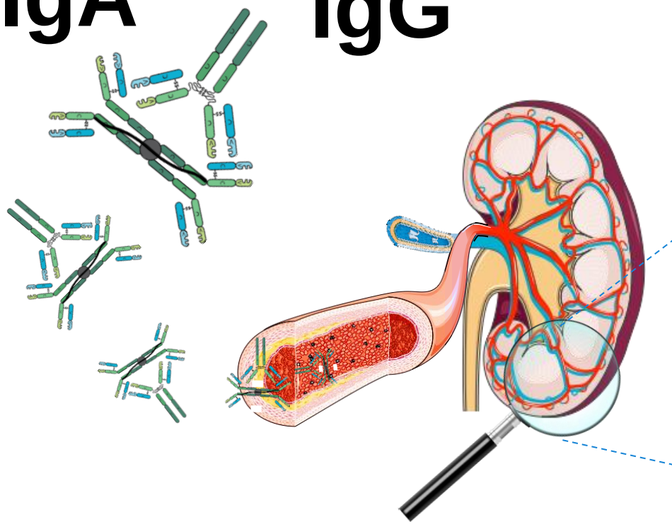
Felzartamab

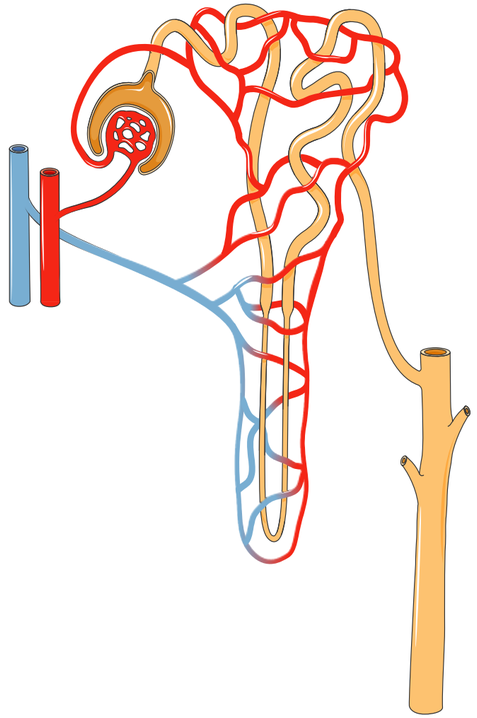
Blisibimod

Fostamatinib

IgA

IgG



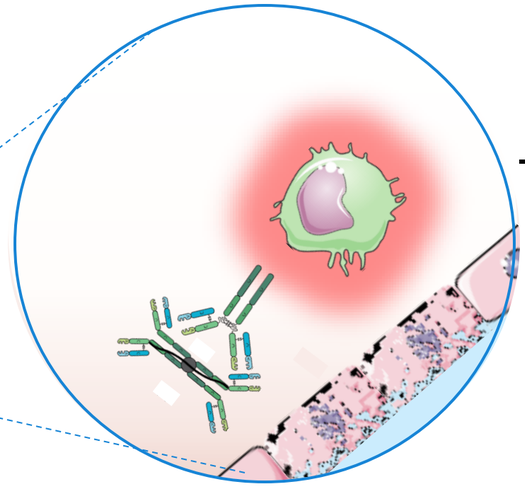


Glomerular capillary pressure lowering

Atrasentan

Sparsentan

Dapagliflozine



Complement

Narsoplimab

Iptacopan

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Avacopan

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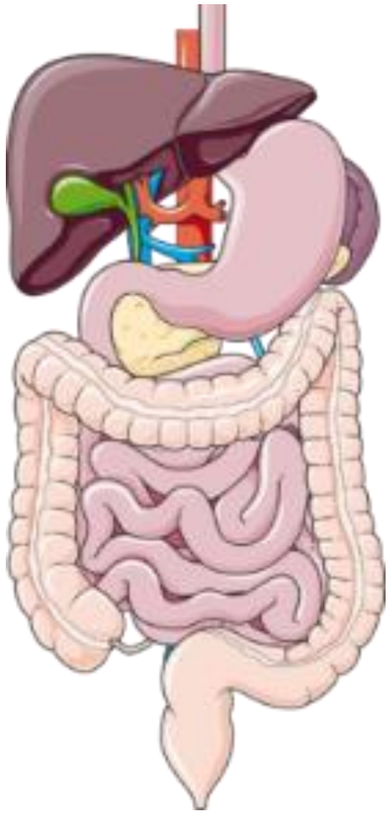
Pegcetacoplan



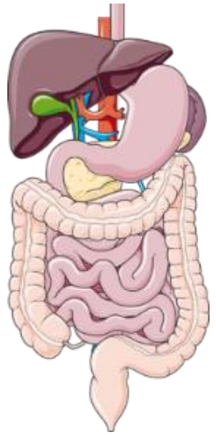
Targeting GALT

Targeting GALT

2017

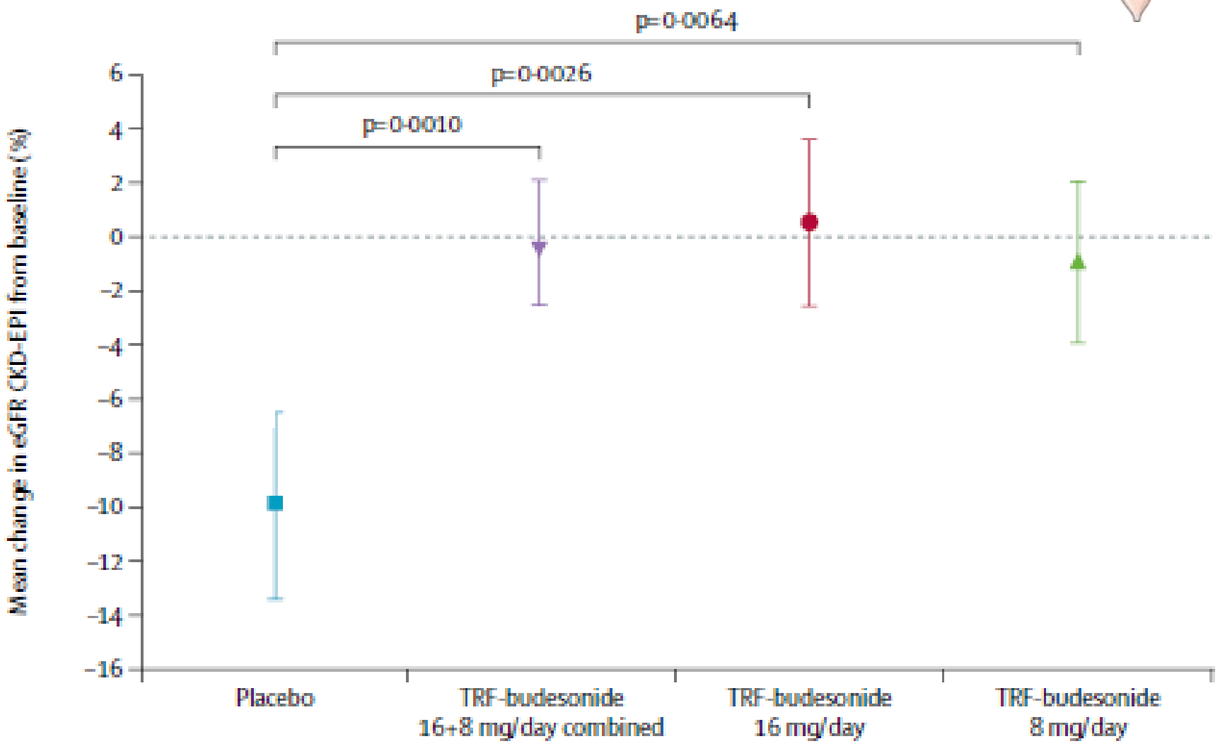
Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

Bengt C Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Johan W de Fijter, Jürgen Floege, Gerd Hetzel, Alan G Jardine, Francesco Locatelli, Bart D Maes, Alex Mercer, Fernanda Ortiz, Manuel Praga, Søren S Sørensen, Vladimir Tesar, Lucia Del Vecchio, for the NEFIGAN Trial Investigators



- Compound: Nefecon, oral
- Mechanism: Steroid release in ileum
- 153 patients divided in 3 groups
- 9 months of treatment
- eGFR: ~ 75-80 ml/min
- Proteinuria: ~ 1g / dag
- ACE/ARB: ~ 60%

Effect on renal function



Targeting GALT

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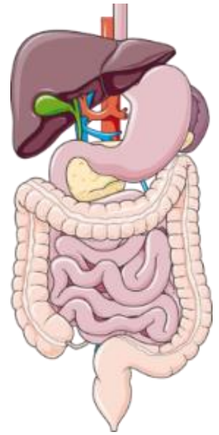

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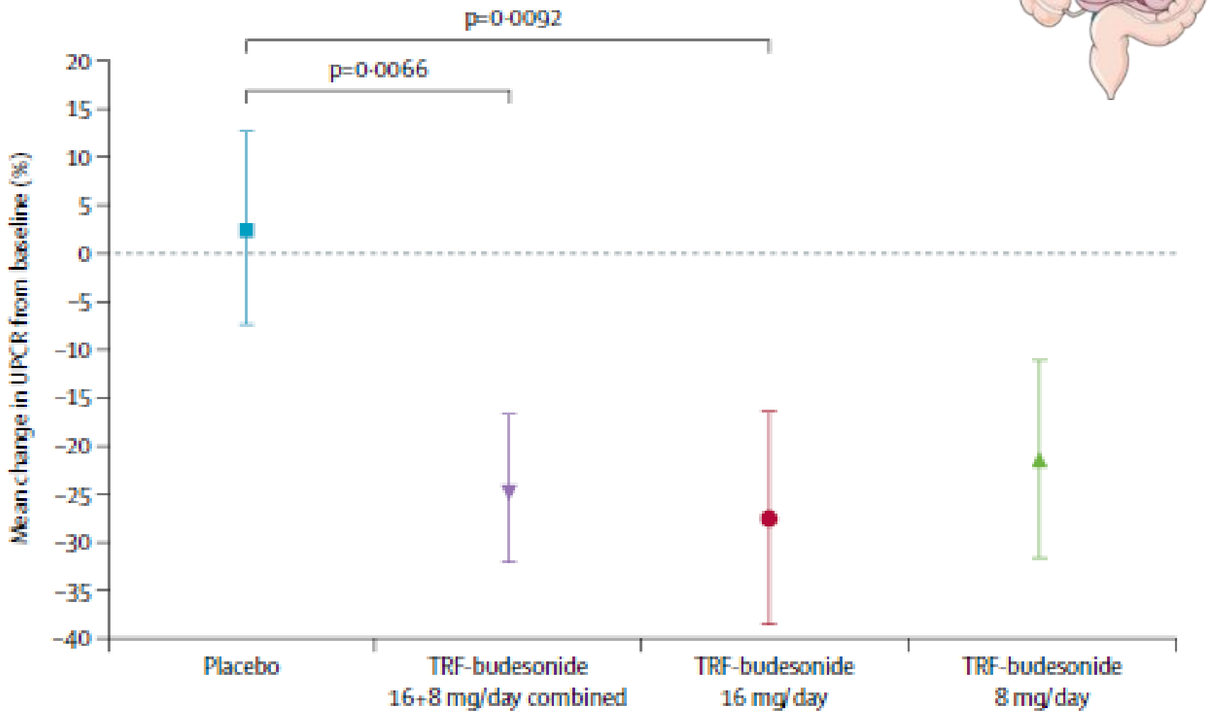
Effect on proteinuria



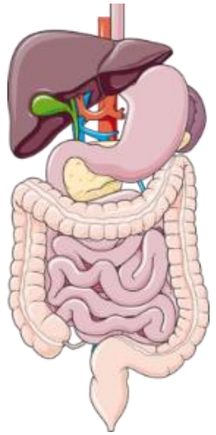
Targeting GALT

2021

POS-830

NEFECON FOR THE TREATMENT OF IgA NEPHROPATHY IN PATIENTS AT RISK OF PROGRESSING TO END-STAGE RENAL DISEASE: THE NEFIGARD PHASE 3 TRIAL RESULTS

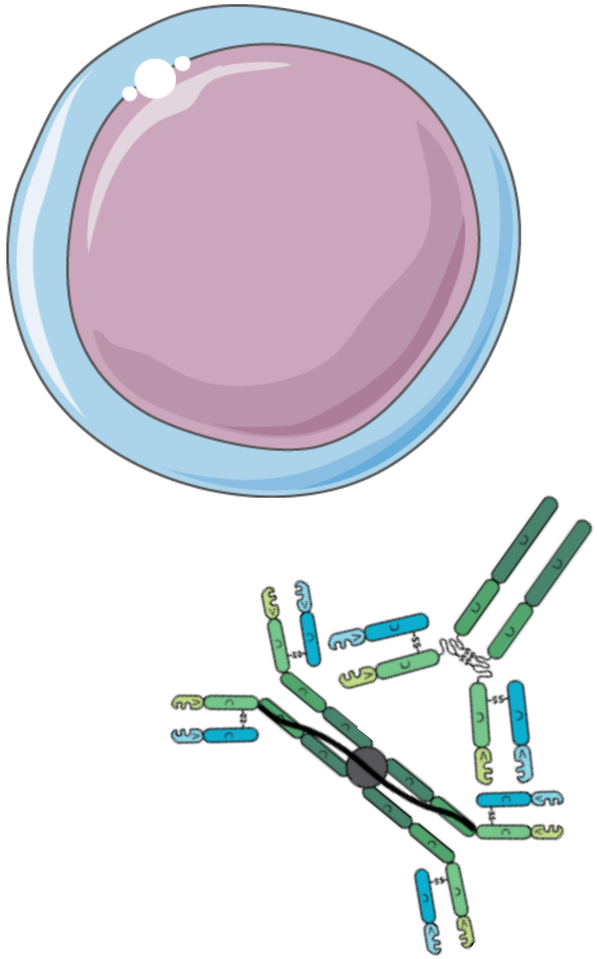
BARRATT, J*[1], Stone, A[2], Kristensen, J[3]



- Compound: Nefecon 16mg/day, oral
- Mechanism: Steroid release in ileum
- 199 patients divided in 2 groups
- 9 months treatment
- eGFR: 35-90 ml/min
- Proteinuria: >1g / dag
- ACE/ARB: 100%

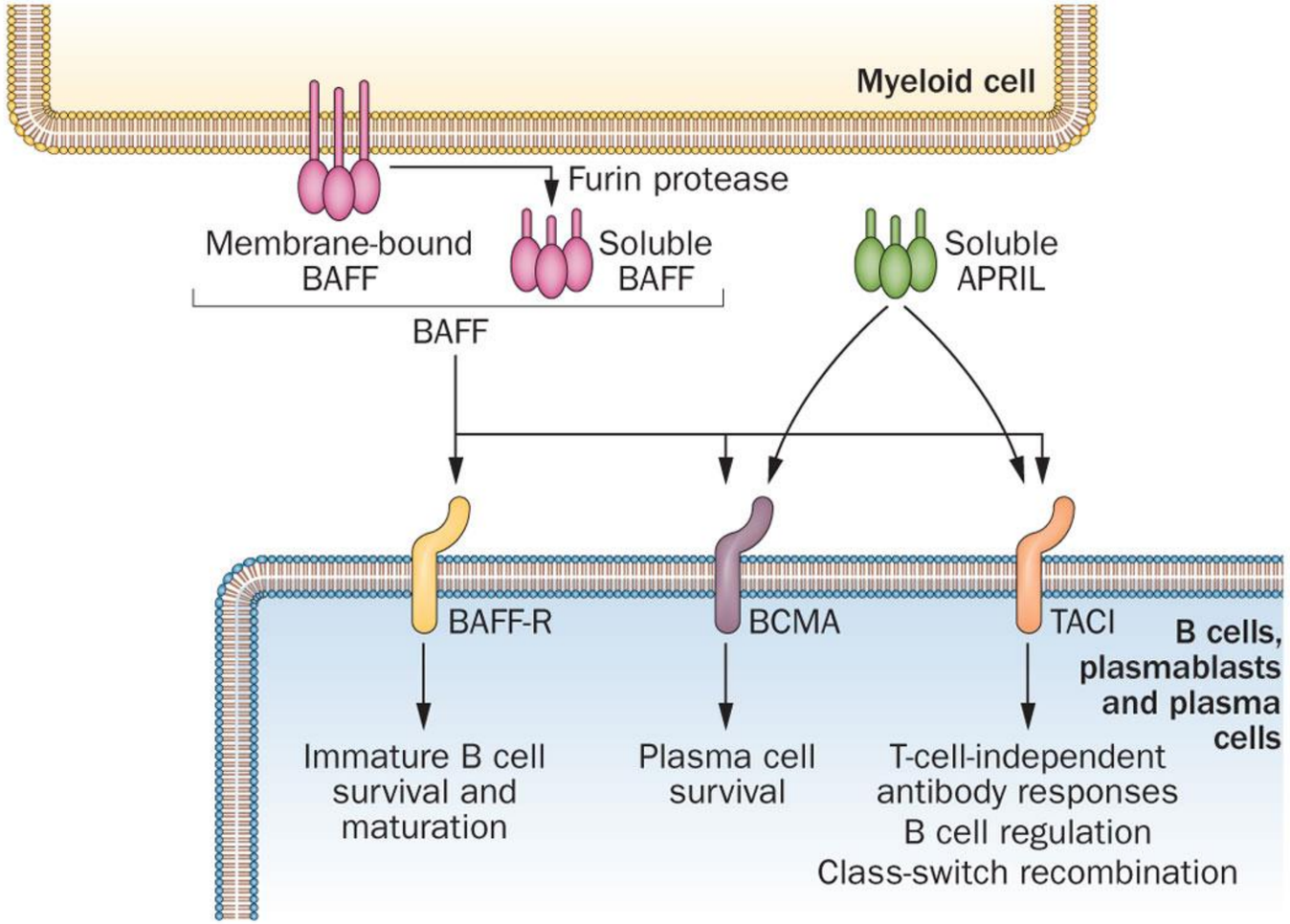
Preliminary results

- Proteinuria decreased by 27% in Nefecon vs placebo (p=0.0005).
- 3.87 ml/min (7%) less eGFR decline in de Nefcon vs placebo (p=0.0029).



Targeting B cells

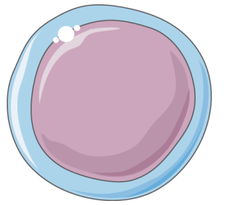
Targeting B cells



Nat. Rev. Rheumatol. **doi:10.1038/nrrheum.2014.33**

2020

Targeting B cells



ABSTRACT: PO1843

Results of a Phase 1 Trial to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BION-1301 in Healthy Volunteers

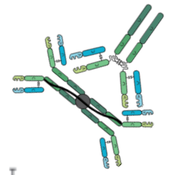
Session Information

» Glomerular Diseases: Clinical, Outcomes, and Trials - 1

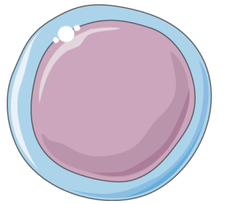
October 22, 2020 | Location: On-Demand

Abstract Time: 10:00 AM - 12:00 PM

- Compound: BION-1301, i.v.
- Mechanism: B cells
- 63 patiënts divided over 4 groups
- 2,5 - 4 months treatment
- Healthy volunteers



Targeting B cells



2021

FC040 **INTERIM RESULTS OF PHASE 1 AND 2 TRIALS TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND CLINICAL ACTIVITY OF BION-1301 IN PATIENTS WITH IGA NEPHROPATHY**

Jonathan Barratt[1], Billy Hour[2], Cailin Sibley[3], Angelique Mittan[3], Suzanne Roy[3], Colleen Stromatt[3], Aaron Endsley[4], Jeannette Lo[3], Alan Glicklich[3]

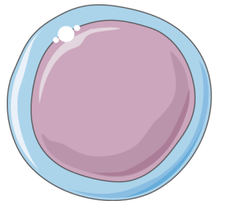
[1]University of Leicester, Leicester, United Kingdom, [2]Amicis Research Center, United States of America, [3]Chinook Therapeutics, Inc. and [4]Certara, Inc

- Compound: BION-1301, i.v.
- Mechanism: B cells
- 20 patients divided over 2 groups
- 3 months treatment
- eGFR 35-90 ml/min
- Proteinuria >0,5 g / dag
- ACE/ARB: 100%

Preliminary results

RESULTS: In Part 3 of Phase 1 and the Phase 2 OLE trial to date, BION-1301 has been well tolerated in IgAN patients receiving a 450mg dose every two weeks for 12+ weeks with no SAEs observed. Consistent with PD responses previously reported in HVs, durable reductions in serum levels of fAPRIL and immunoglobulins were also observed in IgAN patients. Clinically meaningful reductions in proteinuria were observed as early as 12 weeks and were associated with the reduction in IgA. Additional data from patients receiving long-term treatment will be updated.

Targeting B cells



2021

Nephrology Dialysis Transplantation

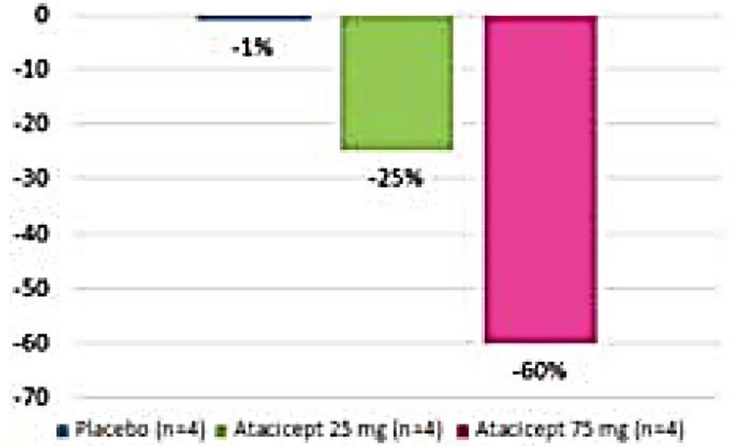
MO039

THE 24-WEEK INTERIM ANALYSIS RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY OF ATACICEPT IN PATIENTS WITH IGA NEPHROPATHY AND PERSISTENT PROTEINURIA

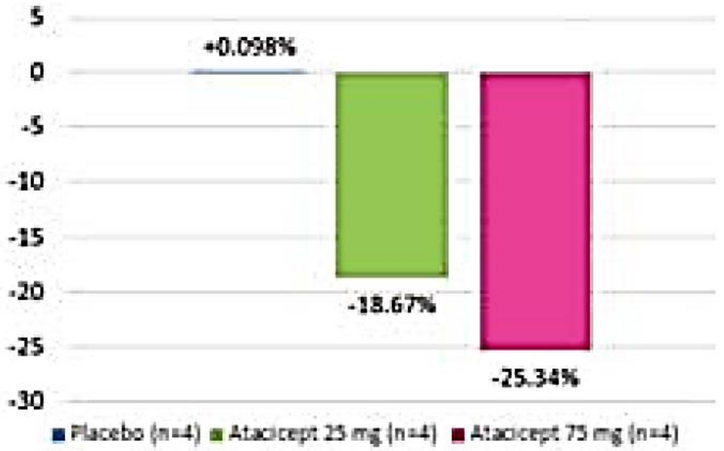
Jonathan Barratt[1], James A. Tumlin[2], Yusuke Suzuki[3], Amy Kao[4], Aida Aydemir[5], Yulia Zima[5], Gerald Appel[6]

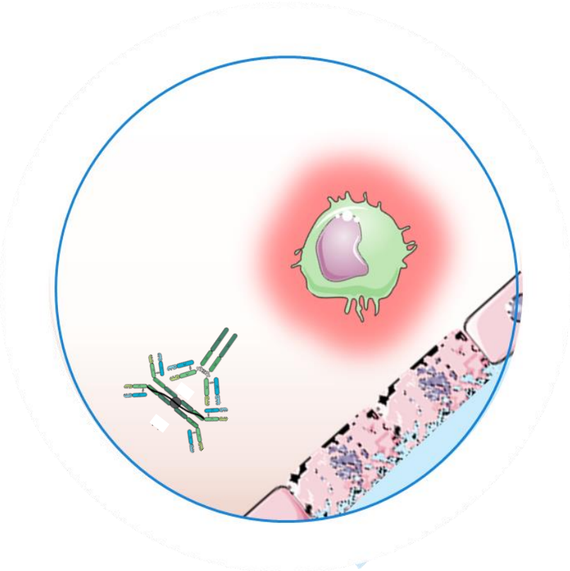
- Compound: atacicept, s.c.
- Werking: B cells
- 16 patients divided over 3 groups
- 24 weeks of treatment
- eGFR: ?
- Eiwit in urine: >1,0 g / dag
- ACE/ARB: 100%

Effect on Gd-IgA1



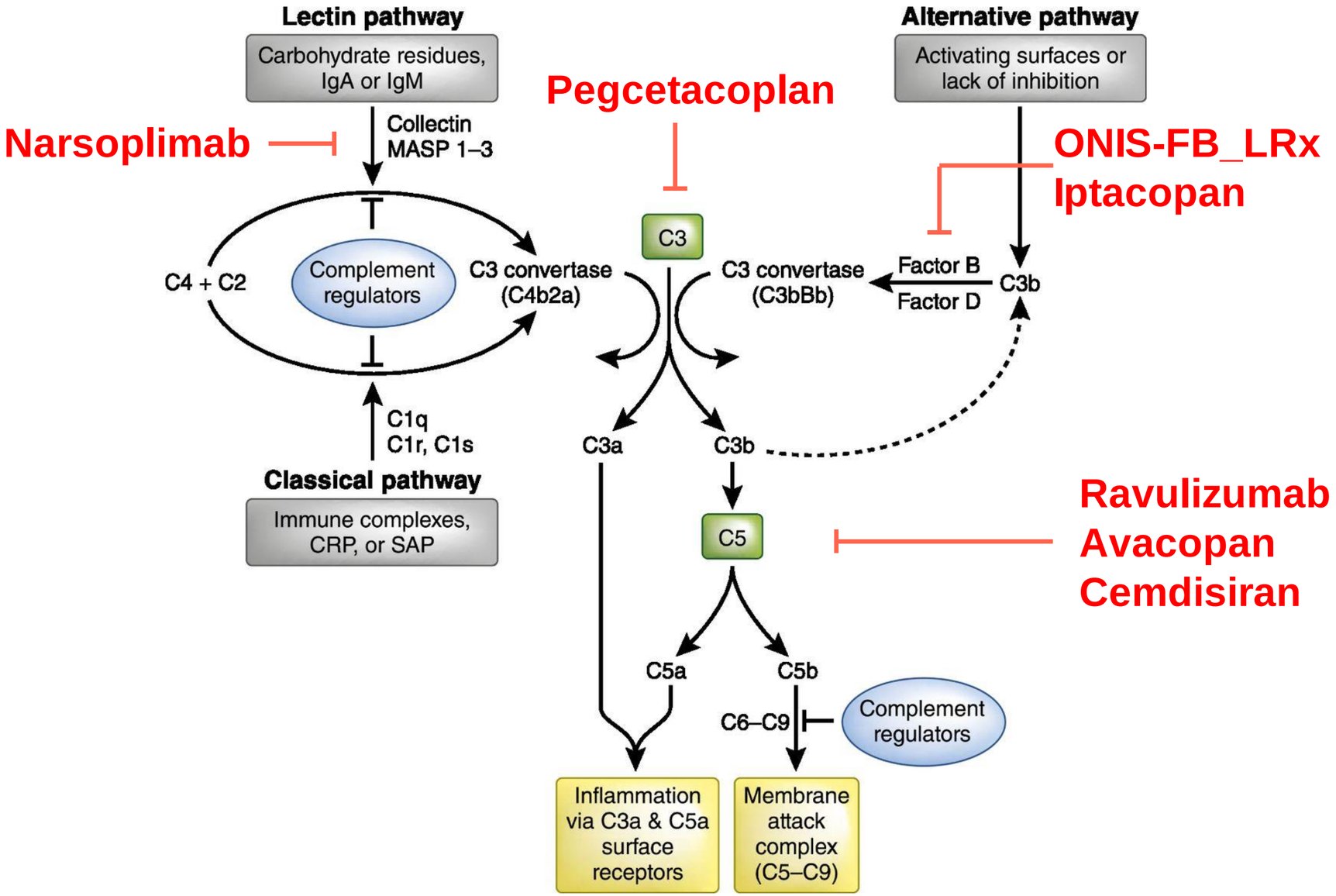
Effect on proteinuria





Targeting complement

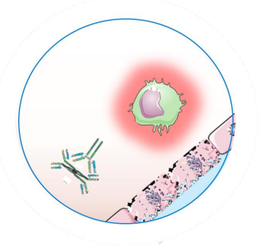
Targeting Complement



JASN 2017, 28 (9) 2571-2578

2017

Targeting Complement



TO012
C5A RECEPTOR INHIBITOR AVACOPAN IN IGA NEPHROPATHY STUDY FREE

Annette Bruchfeld, Patrick Nachman, Samir Parikh, Richard Lafayette, Antonia Potarca, Janet Diehl, Lisa Lohr, Shichang Miao, Thomas Schall, Pirow Bekker

Nephrology Dialysis Transplantation, Volume 32, Issue suppl_3, May 2017, Page iii82, https://doi.org/10.1093/ndt/gfx129.TO012
Published: 26 May 2017

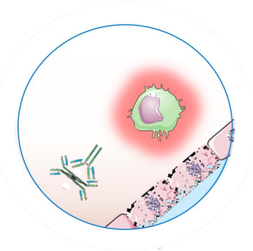
- Compound: Avacopan
- Mechanism: C5a receptor antagonist
- 7 patients
- 12 weeks treatment, 12 weeks follow-up
- eGFR: 66 (18) ml/min
- Proteinuria: UPCR: 1801 (1181-3392) mg/g
- ACE/ARB: 100%

Results:

- Proteinuria improved in 6 patients (on average -80 mg/g/week)
- 3 patients achieved a UPCR <1 g/g
- 2 of these 3 patients returned to baseline levels at the end of the 12-week follow-up
- eGFR was did not change

2020

Targeting Complement



KI REPORTS
KIReports.org
CLINICAL RESEARCH

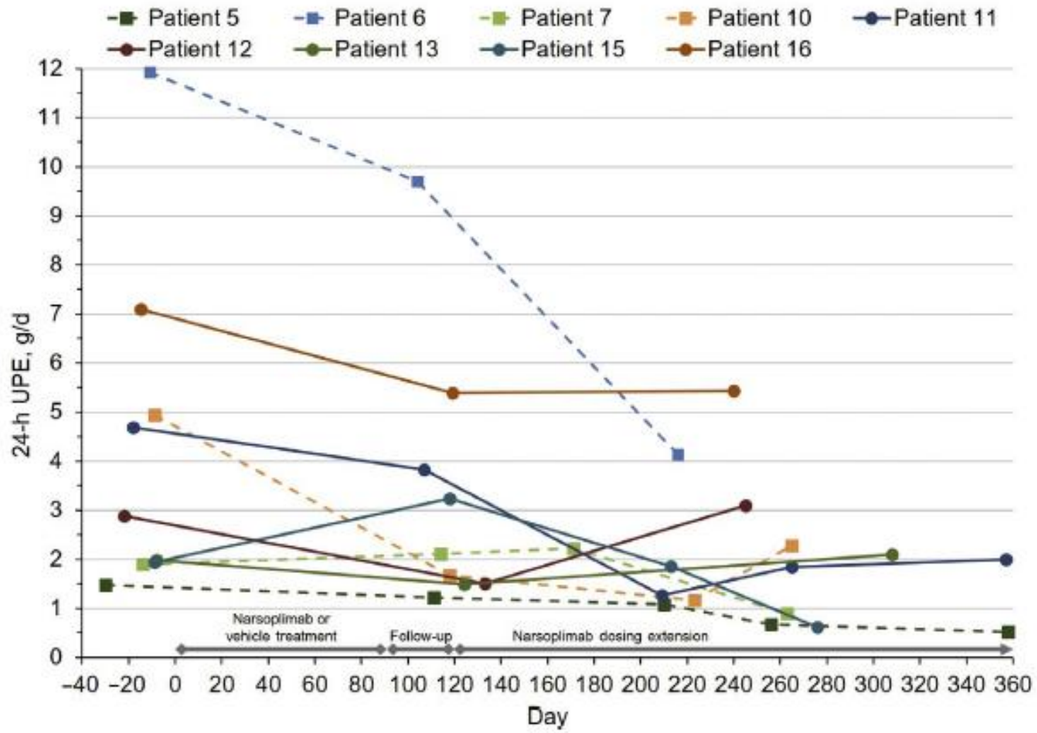
Safety, Tolerability and Efficacy of Narsoplimab, a Novel MASP-2 Inhibitor for the Treatment of IgA Nephropathy

Richard A. Lafayette[1], Brad H. Rovin[2], Heather N. Reich[3], James A. Tumlin[4], Jürgen Floege[5] and Jonathan Barratt[6]

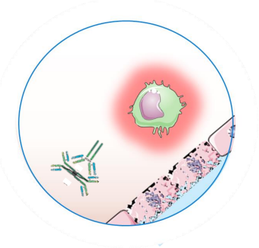
[1]Division of Nephrology, Department of Medicine, Stanford University, Stanford, California, USA; [2]Division of Nephrology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; [3]Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [4]NephroNet Clinical Research Consortium, Atlanta, Georgia, USA; [5]Department of Nephrology and Clinical Immunology, RWTH Aachen University Hospital, Aachen, Germany; and [6]Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK

- Compound: Narsoplimab
- Mechanism: MASP-2 inhibitor
- 9 patients divided over 2 groups
- 3 months treatment
- eGFR ~ 37 ml/min
- Eiwit in urine: > 1 g / dag
- ACE/ARB: 100%

61% reduction in proteinuria



Targeting Complement



Final 12-week Endpoint Analyses of a Phase 2 Dose-Ranging Study to Investigate the Efficacy and Safety of Iptacopan in Primary IgA Nephropathy

Professor Jonathan Barratt

on behalf of the Iptacopan IgAN Program Steering Committee

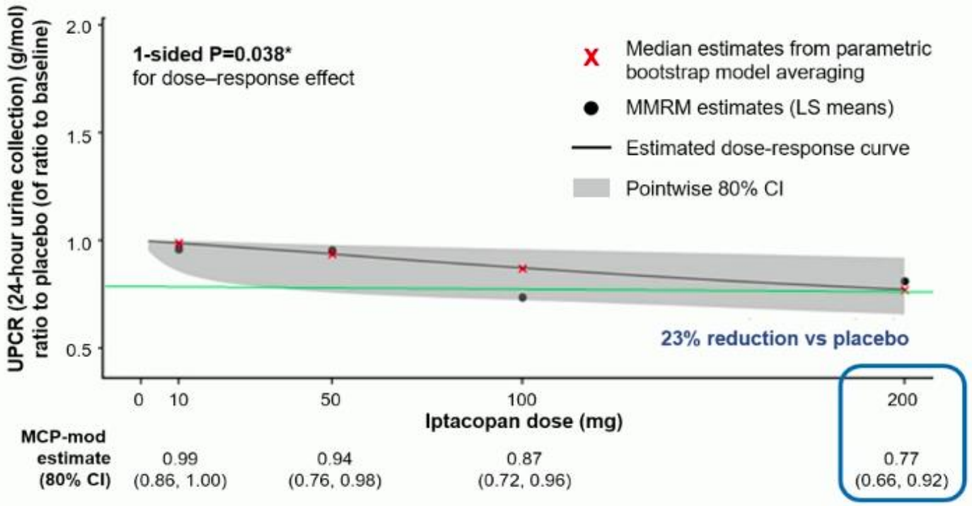
University of Leicester & John Walls Renal Unit, Leicester, UK

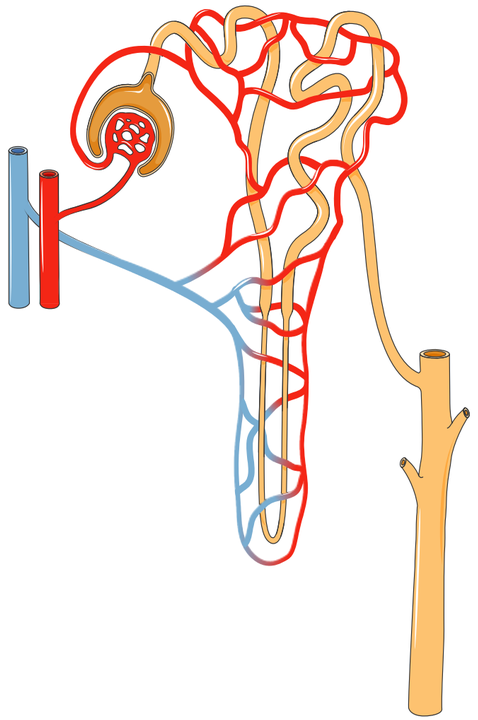
58th ERA-EDTA Congress, Berlin, June 5–8, 2021

2021

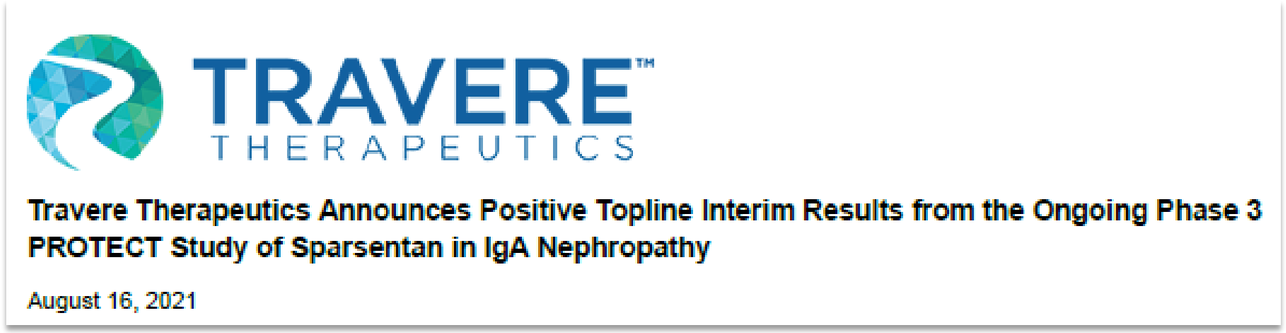
23% reduction in proteinuria

- Compound: Iptacopan
- Mechanism: Factor B inhibitor
- 87 patients divided over 5 groups
- 12 weeks treatment
- eGFR: >30 ml/min
- Proteinuria: >1 g / dag
- ACE/ARB: 100%





Glomerular capillary pressure lowering

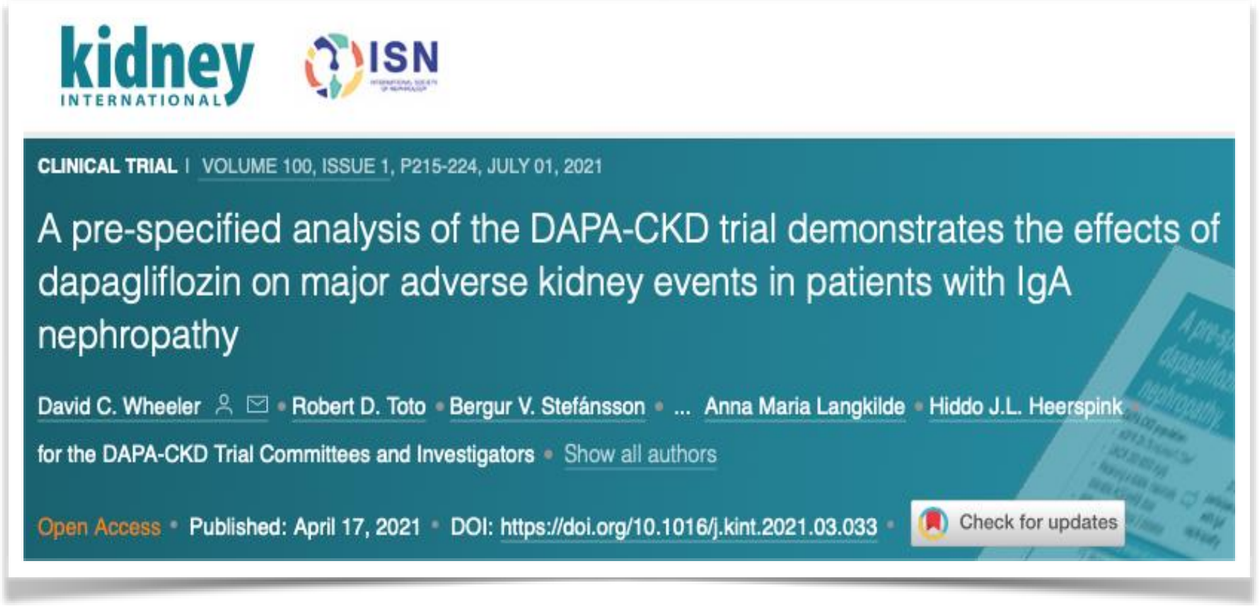


- Phase 3 clinical trial
- N = 404
- Sparsentan vs irbesartan
- Duration: 114 wks
- Proteinuria of ≥1 g/day
- eGFR ≥30 mL/min/1.73 m2
- On ACEi/ARB

Press release august 2021
unblinded interim analysis

Mean reduction in proteinuria from baseline at Week 36 in first 280 patients:

Sparsentan 49.8 % vs Irbesartan 15.1% ($p<0.0001$)



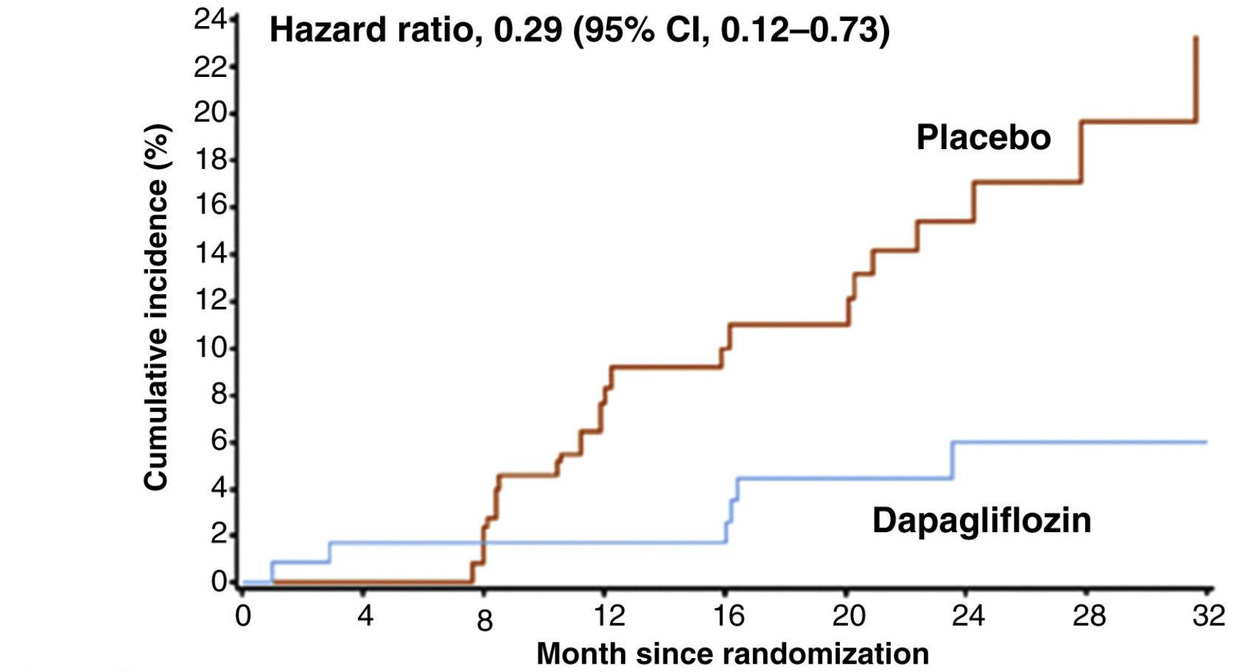
- 270 investigator reported IgAN
- 254 biopsy proven IgAN
- 137 dapagliflozin / 130 placebo
- Median follow-up 2.1 years
- 14% DM2

Baseline characteristics

Age	51 years
Female	33%
SBP	127 mmHg
eGFR	44 ml/min/1.73m2
UACR	900 mg/g
ACEi or ARB	100%

Kidney Int 2021;100:215-24

Composite primary outcome

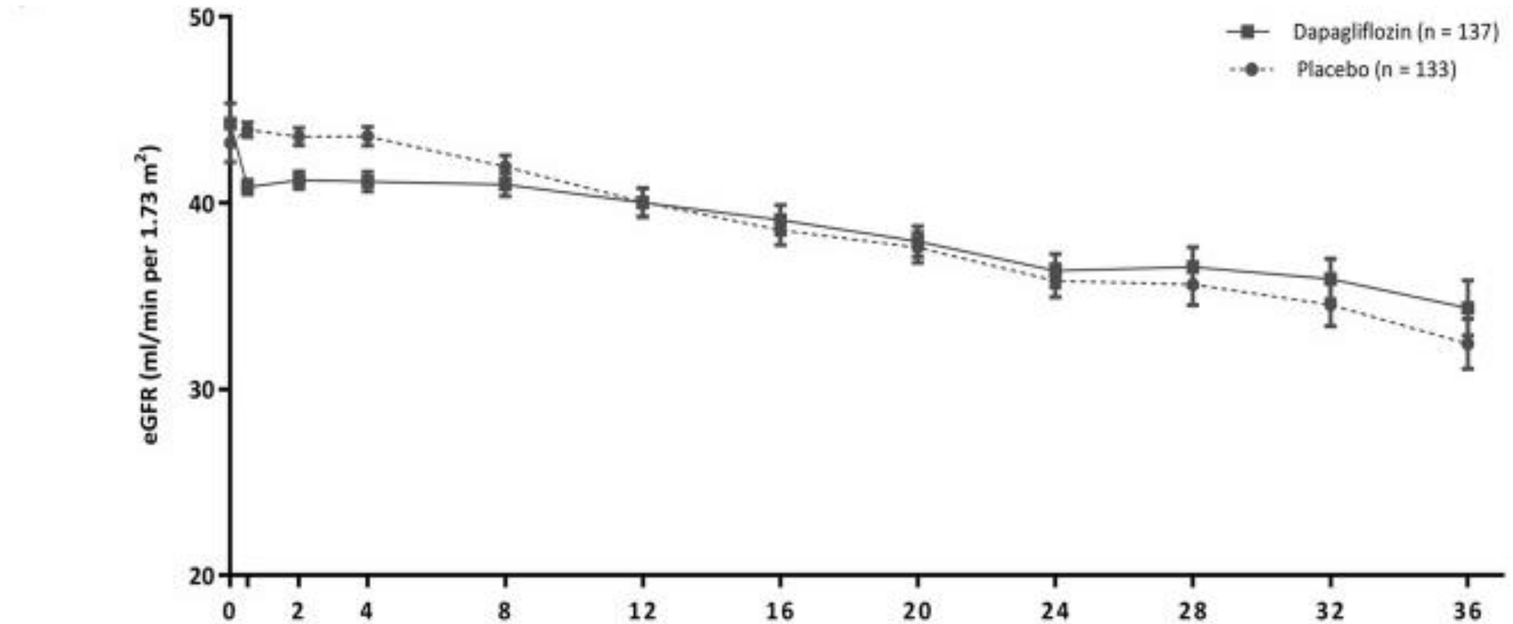


No. at Risk									
Dapagliflozin	137	107	106	105	104	93	61	43	17
Placebo	133	113	108	101	96	92	51	32	19

- **ARR of 11%**

Kidney Int 2021;100:215-24

Change from baseline eGFR



Participants per time point											
Dapagliflozin	137	130	121	111	95	99	98	95	77	53	34	10
Placebo	133	129	124	118	105	100	98	93	80	45	28	19

-3.5

versus

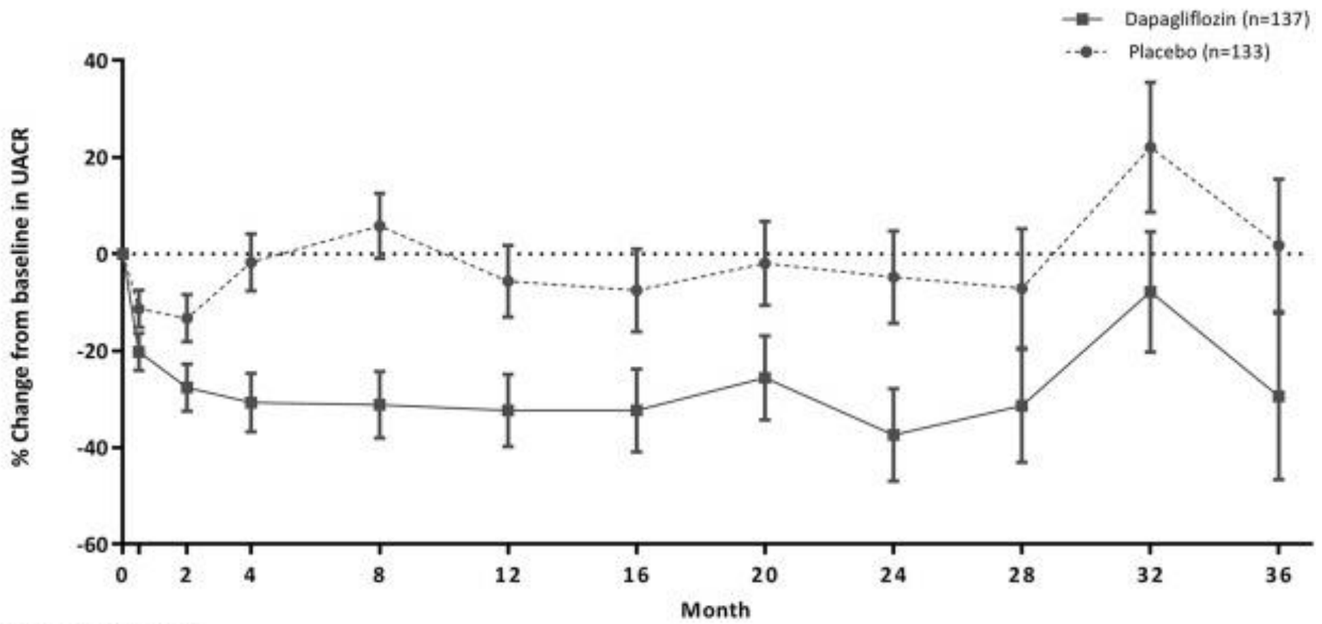
-4.7

ml/min/1.73m2

per year

Kidney Int 2021;100:215-24

Change in proteinuria



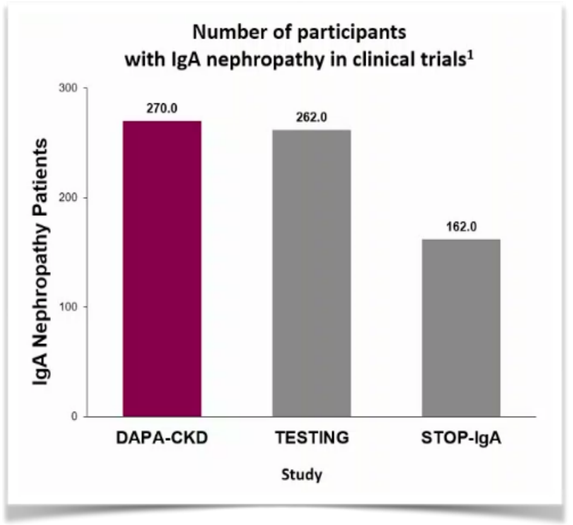
Participants per time point												
Dapagliflozin	137	130	121	111	95	99	98	95	77	53	34	10
Placebo	133	129	124	118	105	100	98	93	80	45	28	19

25% reduction in UACR

Kidney Int 2021;100:215-24

Conclusion

- Dapagliflozin reduces risk of eGFR decline >50%, ESRD, renal or cardiovascular death in IgAN patients.
- RR 71%, ARR of 11% over 2.1 years period
- No prior trial of any therapeutic agent in IgA nephropathy has demonstrated an effect of this magnitude
- Safety was excellent
- Limitation is that it is not clear whether RASi dosage had been proactively maximized.



Kidney Int 2021;100:215-24

Conclusion

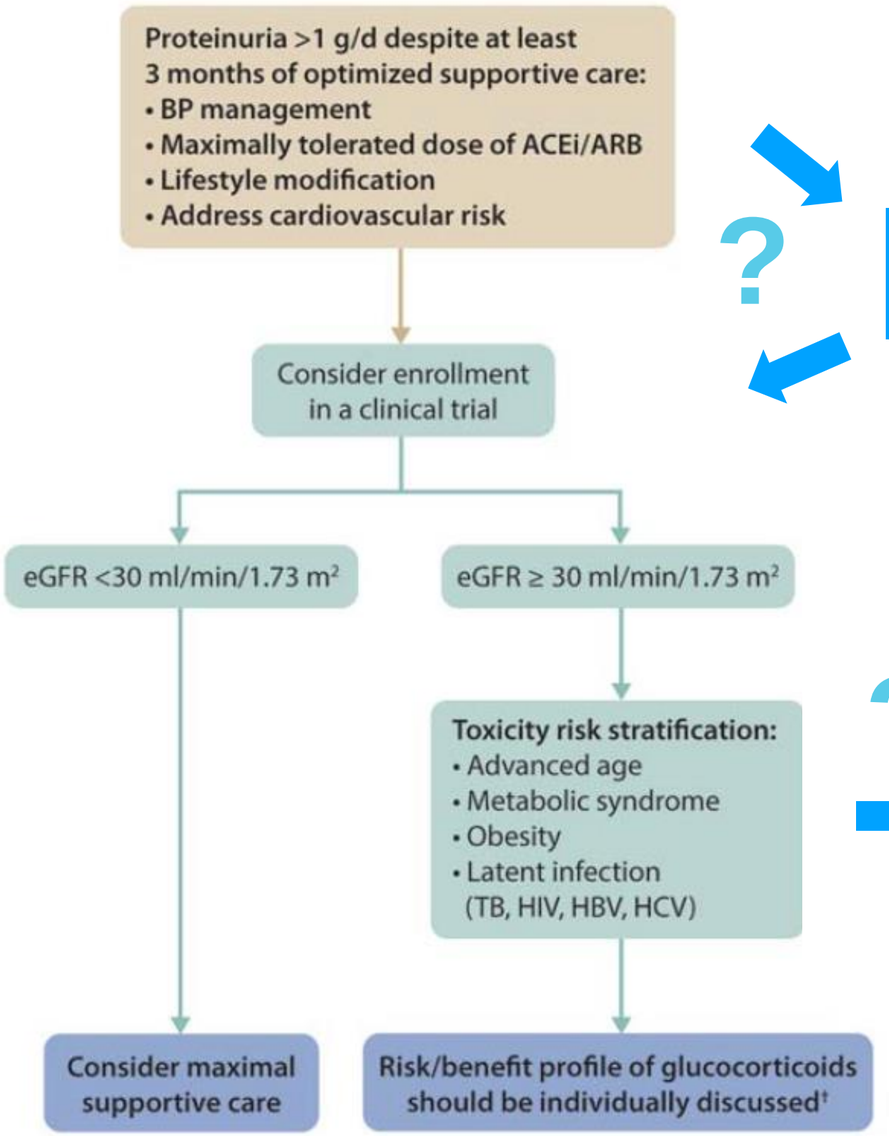
Supportive care:

- Additional glomerular capillairy pressure lowering with SGLT2 or AT1/ETA inhibitor seems beneficial -> Study results need to be awaited.

Immune targeting therapies in patients with eGFR > 30 and protenuria > 1g/day:

- Latest results from TESTING indicate efficacy of corticosteroids, but patient selection and dosage is important to balance benefit vs harm.
- Enteral corticosteroids seems beneficial and may bring a better balance in benefit vs harm -> Phase 3 study results need to be awaited.
- Substantial activity in drug development for IgA nefropathy, targets include B-cells and complement -> Phase 2 and 3 studies are being set up / ongoing.

KDIGO 2021



?

- **AT1/ETA receptor blocker**
- **SGLT2 inhibitor**

?

- **Enteral corticosteroids**
- **B cell directed therapy**
- **Complement inhibitor**

Future challenge:

How to identify which patient benefits from which treatment (biomarker, biopsy, clinical characteristics, adverse events profile, etc..)?