#Oral 4-7

Longer Follow-Up of Povetacicept Shows Potential for Treatment of IgA Nephropathy (RUBY-3 Study)

Sreedhar Mandayam[1], Arvind Madan[2], Rajesh Yalavarthy[3], Dong Ki Kim[4], Frank Cortazar[5], Inwhee Park[6], Ju-Young Moon[7], Amanda Enstrom[8], Heather Thomas[8], Yih-Chieh Chen[8], Jason Sanders[8], Jiahua Li[8], Stanford Peng[8], James Tumlin[9], Sung Gyun Kim[10]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Central Florida Kidney Specialists, Orlando, FL, USA; [3]Western Nephrology, Arvada, CO, USA; [4]Seoul National University Hospital, Seoul, Republic of Korea; [5]New York Nephrology Vasculitis and Glomerular Center, Albany, NY, USA; [6]Ajou University School of Medicine, Suwon-si, Republic of Korea; [7]Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea; [8]Vertex Pharmaceuticals Incorporated, Boston, MA, USA; [9]NephroNet Clinical Trials Consortium and Emory University School of Medicine, Atlanta, GA, USA; [10]Hallym University Sacred Heart Hospital, Anyang-si, Republic of Korea

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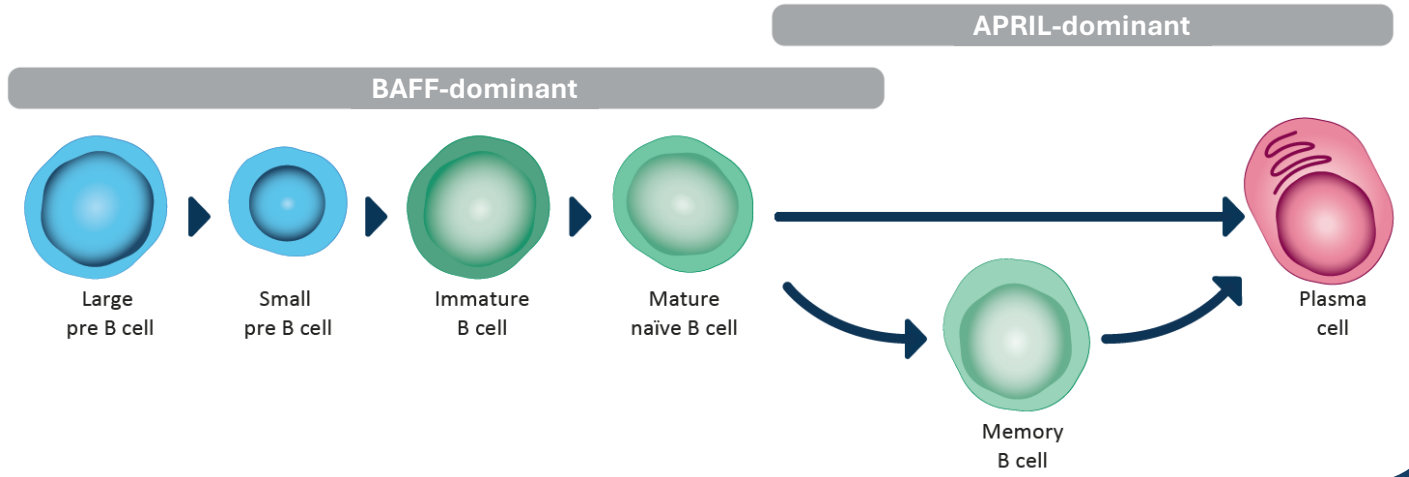
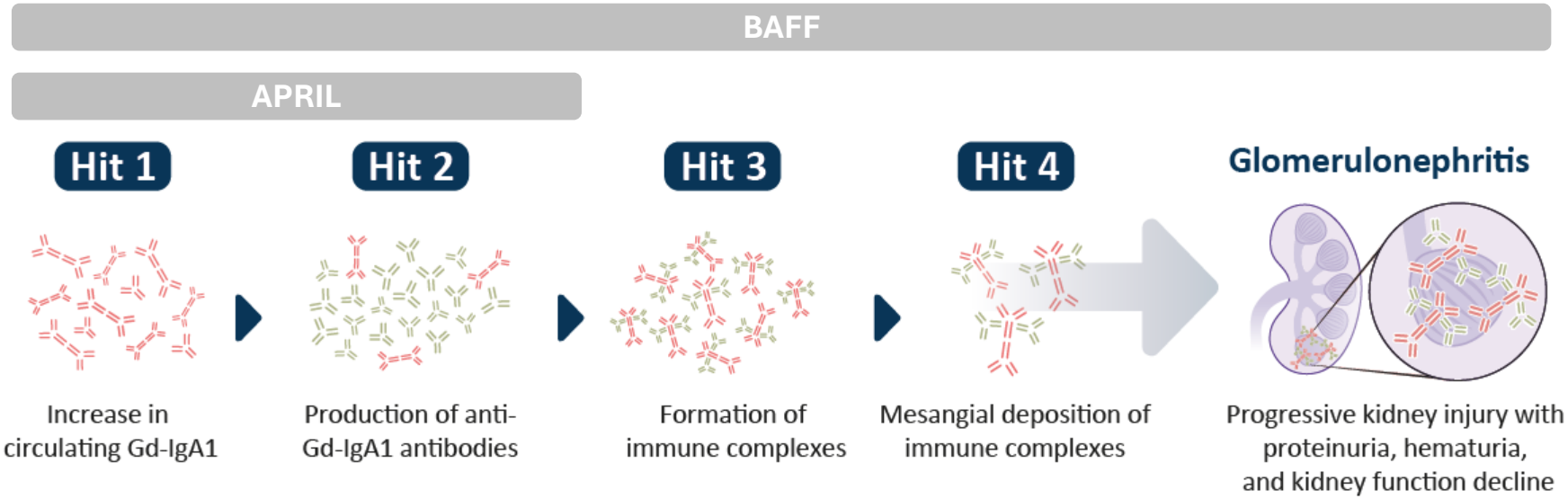
BAFF + APRIL: Central to the Pathogenesis of Autoimmune Glomerulonephritis

- **BAFF** primarily regulates earlier B cell stages; and promotes pathogenic T and innate immune cells, aberrant IgA glycosylation leading to Gd-IgA1, as well as mesangial cell proliferation and podocyte injury.
- **APRIL** primarily regulates plasma cells.



IgAN Pathogenesis

In the 4-hit hypothesis, **APRIL** primarily promotes pathogenic antibody formation (Hits 1 & 2), while **BAFF** promotes disease across the entire pathogenic spectrum.



Source: Cheung CK et al. *Front Nephrol.* 2024;1(3)1346769

Povetacicept is a Dual BAFF + APRIL Inhibitor Engineered for Superior Potency, Affinity, and Enhanced Tissue Distribution

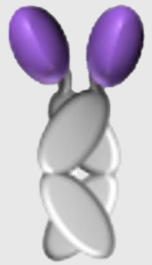
WT-TACI Fc

- Modest BAFF, weak APRIL potency
- Modest BAFF binding affinity
- Moderate tissue distribution

WT-TACI Fc	Potency IC_{50} (nM)	Binding Affinity K_d (s^{-1})
BAFF	20.8	8.63×10^{-5}
APRIL	>200	Could not be determined
BAFF + APRIL	>200	---

Directed Evolution

Povetacicept



- Superior potency against BAFF and APRIL
- Superior BAFF and APRIL binding affinity
- Enhanced biodistribution across various tissues compared to WT-TACI Fc, with higher relative distribution in the kidney

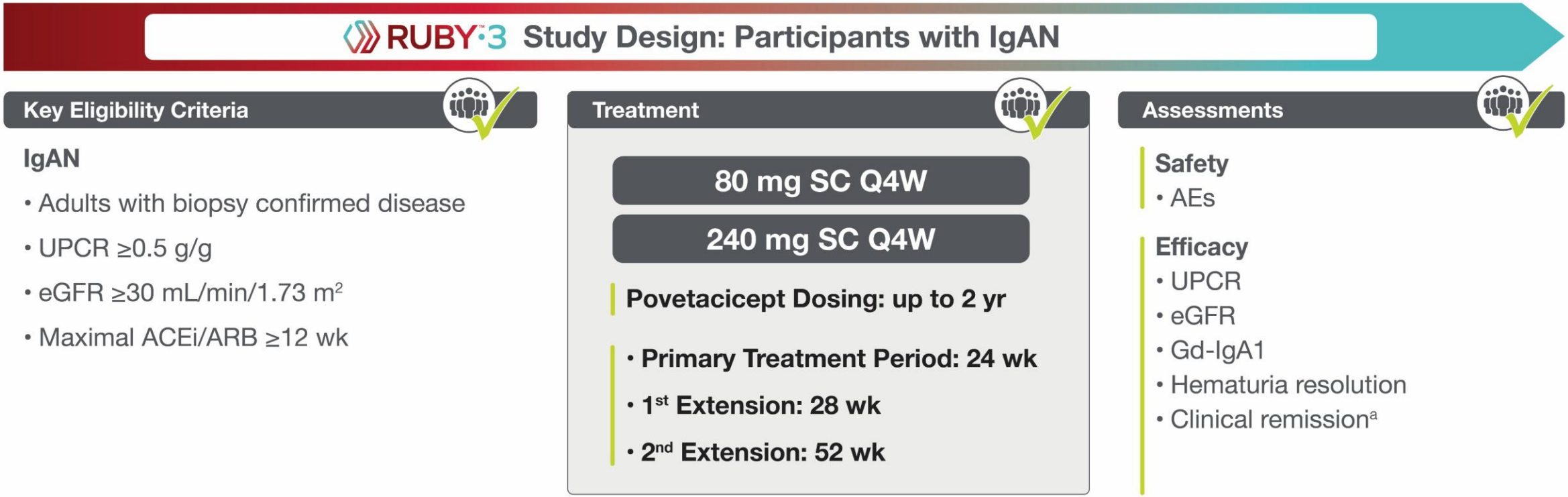
Povetacicept	Potency IC_{50} (nM)	Binding Affinity K_d (s^{-1})
BAFF	1.4	3.67×10^{-5}
APRIL	3.8	7.0×10^{-3}
BAFF + APRIL	3.1	---

Povetacicept represents a significant therapeutic advancement by **targeting the root cause** of autoimmune glomerulonephritis.

Note: Enhanced tissue distribution data on file, not shown.

Source: Evans LS et al. *Arthritis Rheumatol.* 2023;75(7)1187-1202. doi: 10.1002/art.42462

RUBY-3 Study Design



Ongoing **Phase 1/2 open-label study in adults** with IgAN receiving povetacicept

- **IgAN: 80 mg** (N=21 dosed; N=17 at Week 48) or **240 mg** (N=33 dosed; N=30 at Week 48)

Note: ClinicalTrials.gov ID: NCT05732402; date of data cut is 13 June 2025

[a] In IgAN, clinical remission is defined as UPCR <0.5 g/g, negative hematuria, and <25% reduction in eGFR versus baseline.

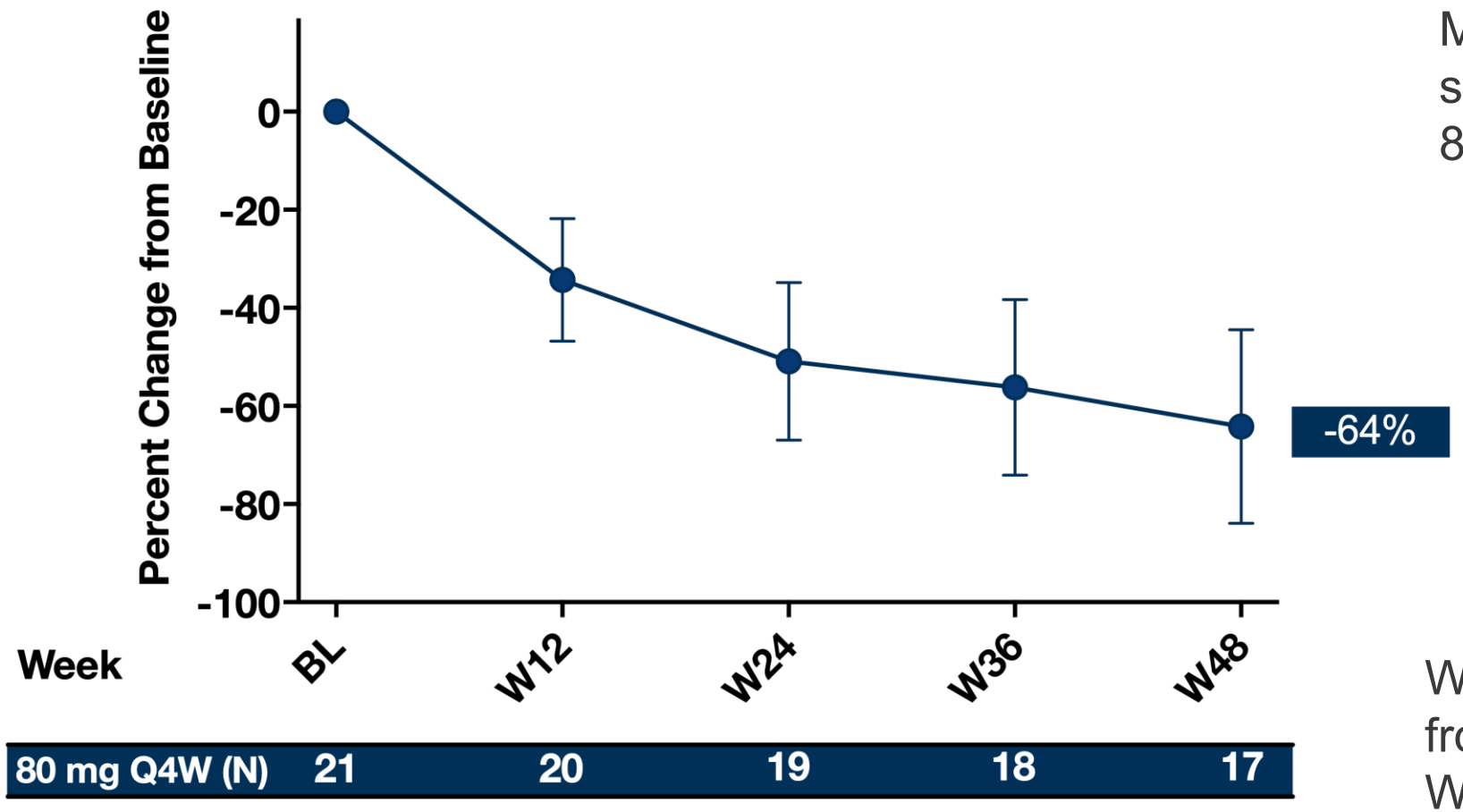
Baseline Characteristics: Participants With Moderate/Large Hematuria (>50%)

Parameter	Povetacicept 80 mg SC Q4W N = 21	Povetacicept 240 mg SC Q4W N = 33
Age; mean (SD) yr	47.6 (11.7)	45.1 (12.1)
Male; n (%)	7 (33)	18 (55)
Female; n (%)	14 (67)	15 (45)
Race (Asian/White/Other); n (%)	10 (48)/10 (48)/1 (5)	18 (55)/14 (42)/1 (3)
Time since diagnosis; median (min, max) yr	2.1 (0.2, 23.3)	4.0 (0.2, 18.7)
Time since biopsy; mean (SD) yr	2.3 (2.7)	3.0 (3.0)
ACEi/ARB use; n (%)	18 (86)	33 (100)
SGLT2i use; n (%)	6 (29)	15 (45)
Prior immunosuppression use; n (%)	4 (19)	5 (15)
Gd-IgA1; mean (SD) ng/mL	9068 (4324)	7251 (3606)
24-hr UPCR; mean (SD) g/g	1.3 (0.7)	1.2 (0.8)
eGFR; mean (SD) mL/min/1.73 m^2	76.9 (34.0)	63.5 (29.5)
Hematuria moderate or large; n (%)	11 (52)	19 (58)

Note: date of data cut is 13 June 2025

Povetacicept Reduced Proteinuria 64% at Week 48

Percent Change from Baseline to Week 48 (Mean ± SE) in 24-hour UPCR – 80 mg Q4W



Mean 24-hour UPCR decreased substantially at 48 weeks with 80 mg Q4W:

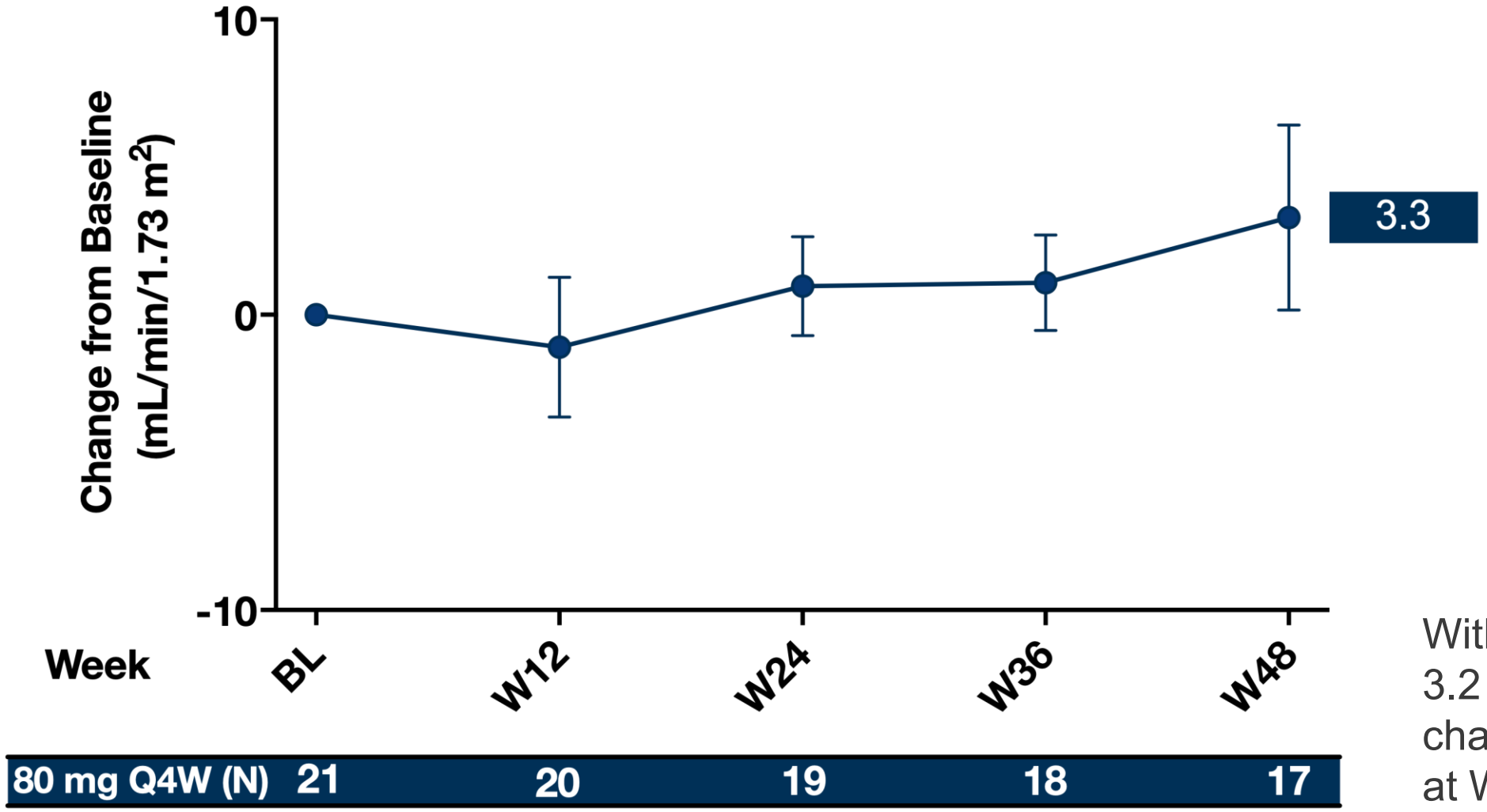
- **64% decrease** from baseline (1.3 g/g to 0.5 g/g)
- **~2/3** participants achieved UPCR <0.5 g/g

With 240 mg Q4W: 56% decrease from baseline (1.2 g/g to 0.6 g/g) at Week 48

Note: date of data cut is 13 June 2025

Povetacicept Stabilized eGFR Through Week 48

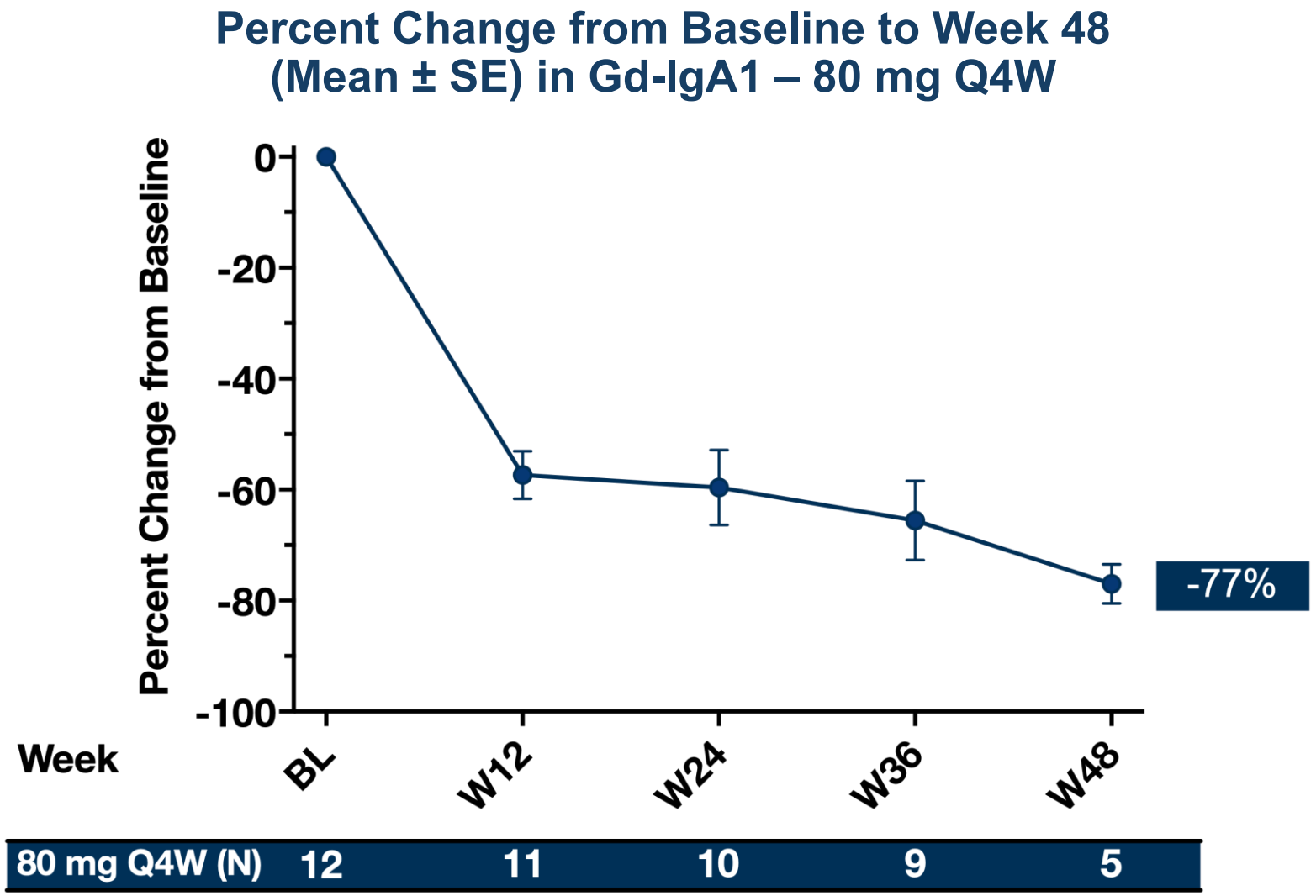
Change from Baseline to Week 48 (Mean ± SE) in eGFR – 80 mg Q4W



With 240 mg Q4W:
3.2 mL/min/1.73 m^2 change from baseline at Week 48

Note: date of data cut is 13 June 2025

Early Gd-IgA1 Reduction at Week 12 Continued at Week 48 (77%)



Mean Gd-IgA1 decreased substantially with 80 mg Q4W:

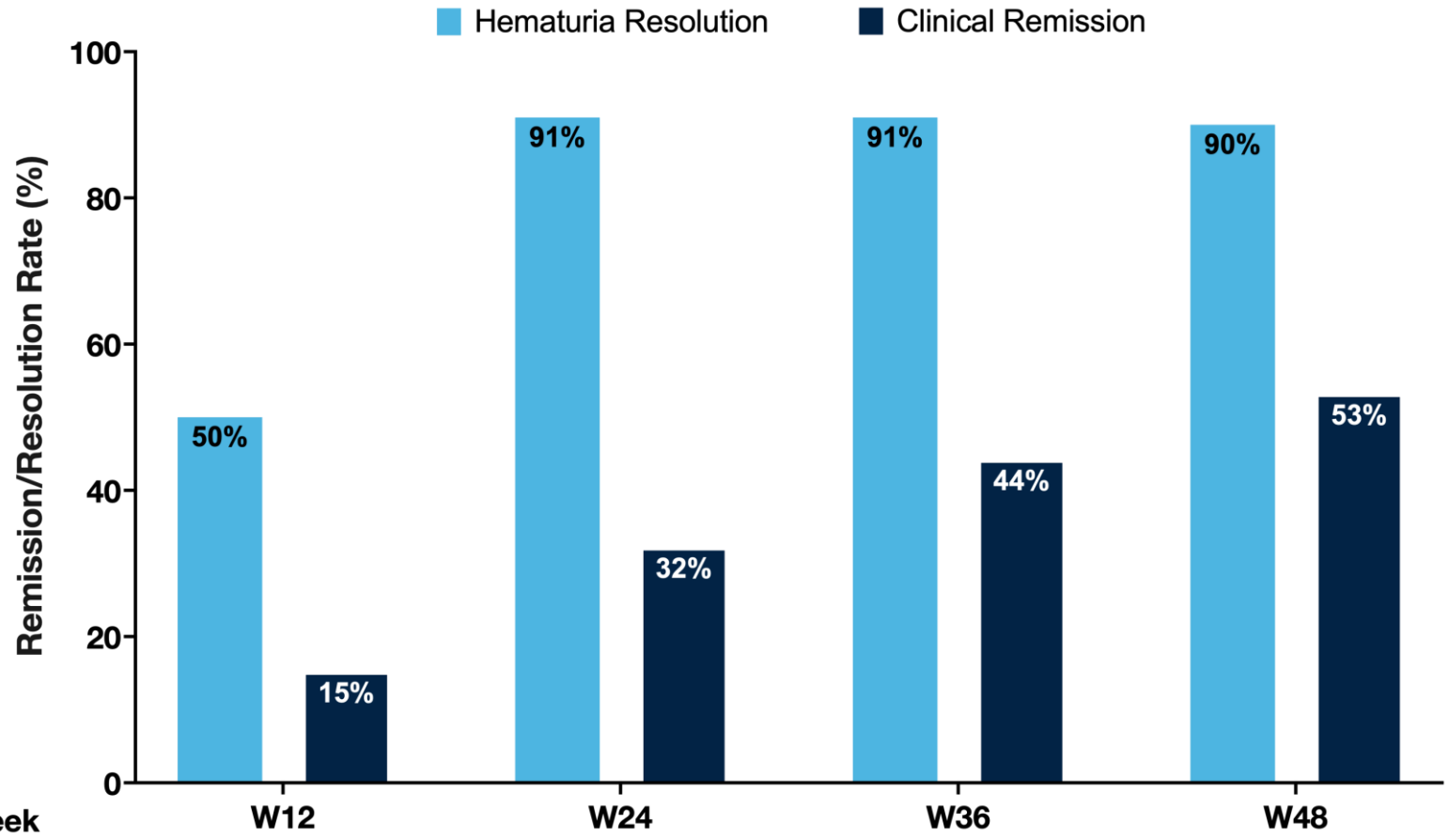
- **Declined early** by **57% at Week 12**
- Reduction **continued at Week 48 by 77%**

With 240 mg Q4W: 77% decrease from baseline at Week 48

Note: date of data cut is 13 June 2025

Substantial Proportion of Participants on Povetacicept Achieved Hematuria Resolution (90%) and Clinical Remission (53%)

Clinical Hematuria Resolution and Clinical Remission from Week 12 to Week 48 – 80 mg Q4W



Hematuria Resolution (N)	5/10	10/11	10/11	9/10
Clinical Remission (N)	3/20	6/19	8/18	9/17

Note: Clinical remission is defined as UPCR <0.5 g/g, negative hematuria, and <25% reduction in eGFR versus baseline. Hematuria resolution is defined as a decrease to negative or small levels of urine blood in subjects with baseline urine blood of moderate or large

With 240 mg Q4W:

94% achieved hematuria resolution at Week 48

34% achieved clinical remission at Week 48

Note: date of data cut is 13 June 2025

Povetacicept Was Generally Safe and Well Tolerated

Parameter	IgAN Povetacicept 80mg SC Q4W N = 21	IgAN Povetacicept 240mg SC Q4W N = 33
Any AE; n (%)	16 (76)	27 (82)
Grade 1/mild	6 (29)	7 (21)
Grade 2/moderate	9 (43)	19 (58)
Grade 3/severe	1 (5)[a]	1 (3)[b]
Grade ≥4/life-threatening, death	0	0
Related AEs; n (%)	6 (29)	10 (30)
AEs leading to discontinuation; n (%)	0	1 (3)[b]
SAE; n (%)	1 (5)[c]	1 (3)[b]
Severe hypogammaglobulinemia; n (%) **(IgAN: IgG <300 mg/dL; pMN: <150 mg/dL)**	1 (5)	4 (12)
Malignancy; n (%)	1 (5)[a]	0
Any infection; n (%)	9 (43)	21 (64)
Grade 3/severe	0	1 (3)[b]
Administration-related reaction or injection site reaction; n (%)	3 (14)	4 (12)

- Most AEs were **mild to moderate in severity**
- **No SAEs related** to povetacicept
- **No safety concerns** observed with laboratory parameters
- **No clinically meaningful trends** in ECGs or vital signs

Notes: Includes up to 104 weeks of data.
[a] Grade 3 event of carcinoma was not related to povetacicept.
[b] Grade 3 event of urinary tract infection was not related to povetacicept; participant discontinued per protocol.
[c] Grade 1 event of dermatitis was not related to povetacicept; resolved following treatment.

Note: date of data cut is 13 June 2025

Conclusions

- Povetacicept 80 mg Q4W led to early, substantial, and sustained improvements in IgAN
  - **Proteinuria declined 64%** at Week 48
  - **eGFR** was **stable** through Week 48
  - **Gd-IgA1 declined early by 57%** at Week 12 and continued at Week 48 with a **77% decline**
  - **Hematuria resolution** was **achieved** by **90%** of participants with medium/large hematuria at baseline
  - **Clinical remission** was **achieved** by **53%** of participants by Week 48.

- Povetacicept was generally **safe and well tolerated.**

- Results **support the ongoing, fully enrolled Phase 3 RAINIER study** of Povetacicept in IgAN.

Data Highlight the Potential for Povetacicept to be a Best-in-class, Transformative, Disease-modifying Treatment for IgAN

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