Long-term Results From the ORIGIN Phase 2b Study of Atacicept for the Treatment of IgAN

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Disclosures

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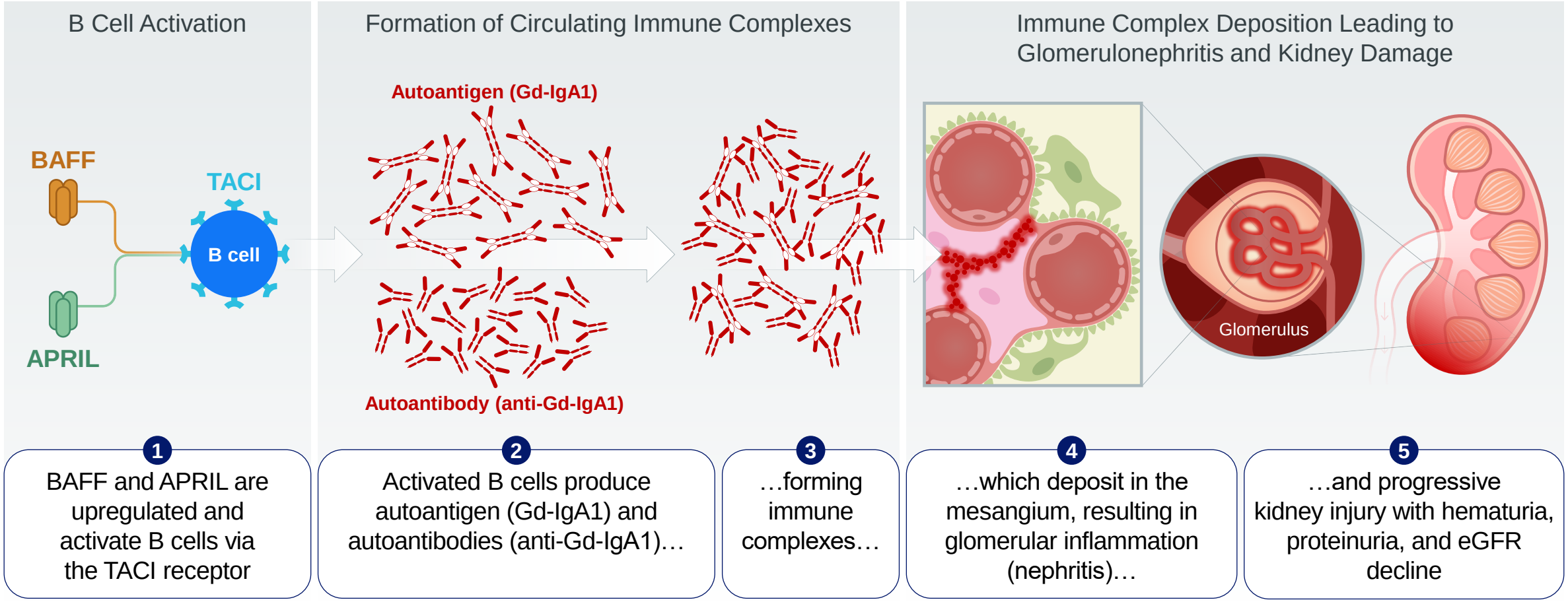
Grant Support	Argenx, Calliditas Therapeutics, Chinook Therapeutics, Galapagos, GSK, Novartis, Omeros, Travere Therapeutics, Visterra
Clinical Trials	ORIGIN (Vera Therapeutics), ADU-CL-19 & ALIGN (Chinook Therapeutics), APPLAUSE (Novartis), ARTEMIS-IGAN (Omeros), ENVISION (Visterra), NefIgARD (Calliditas Therapeutics)
Research Projects	Argenx, Calliditas Therapeutics, Chinook Therapeutics, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere Therapeutics, Visterra

IgAN is a B-cell mediated disease with kidney pathology

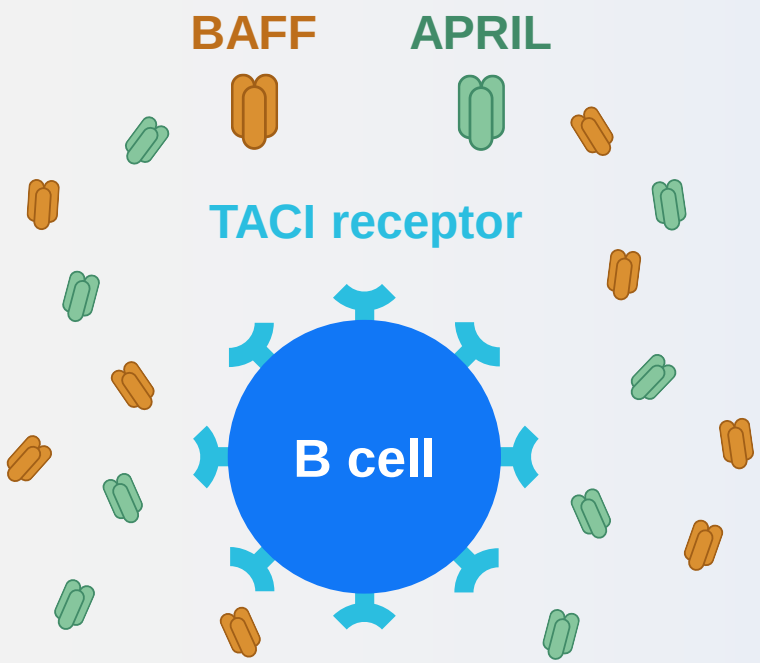


APRIL = a proliferation-inducing ligand; BAFF = B-cell activating factor; eGFR = estimated glomerular filtration rate; Gd-IgA1 = galactose-deficient immunoglobulin A1; IgAN = immunoglobulin A nephropathy; TACI = transmembrane activator and calcium-modulator and cyclophilin ligand interactor.

Cheung CK, et al. Front Nephrol. 2024;3:1346769.

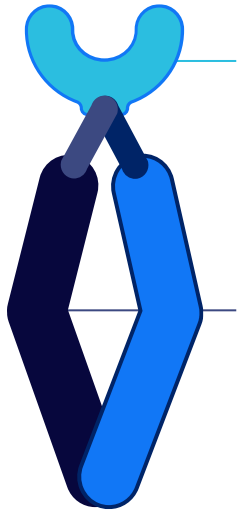
Atacicept is a dual inhibitor of BAFF and APRIL

Rational drug design: native TACI receptor fused to Fc — fully humanized soluble fusion protein



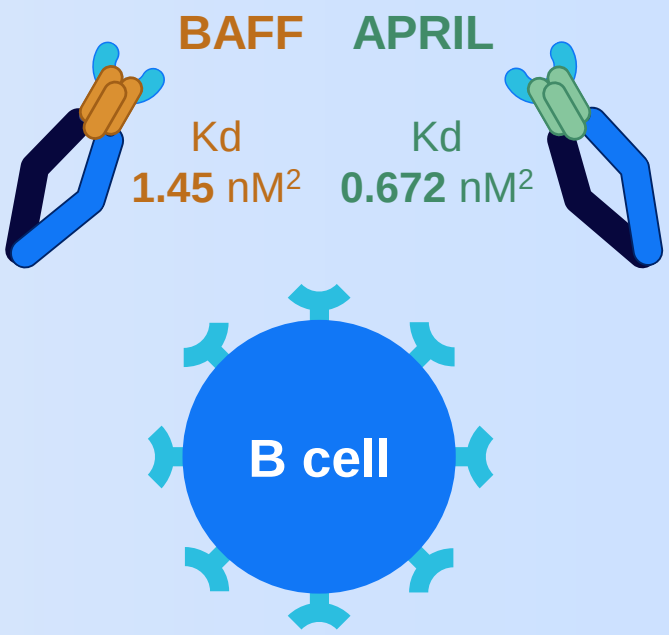
Atacicept

$t_{1/2}$=35 days[1]



TACI receptor

Fc domain of IgG1

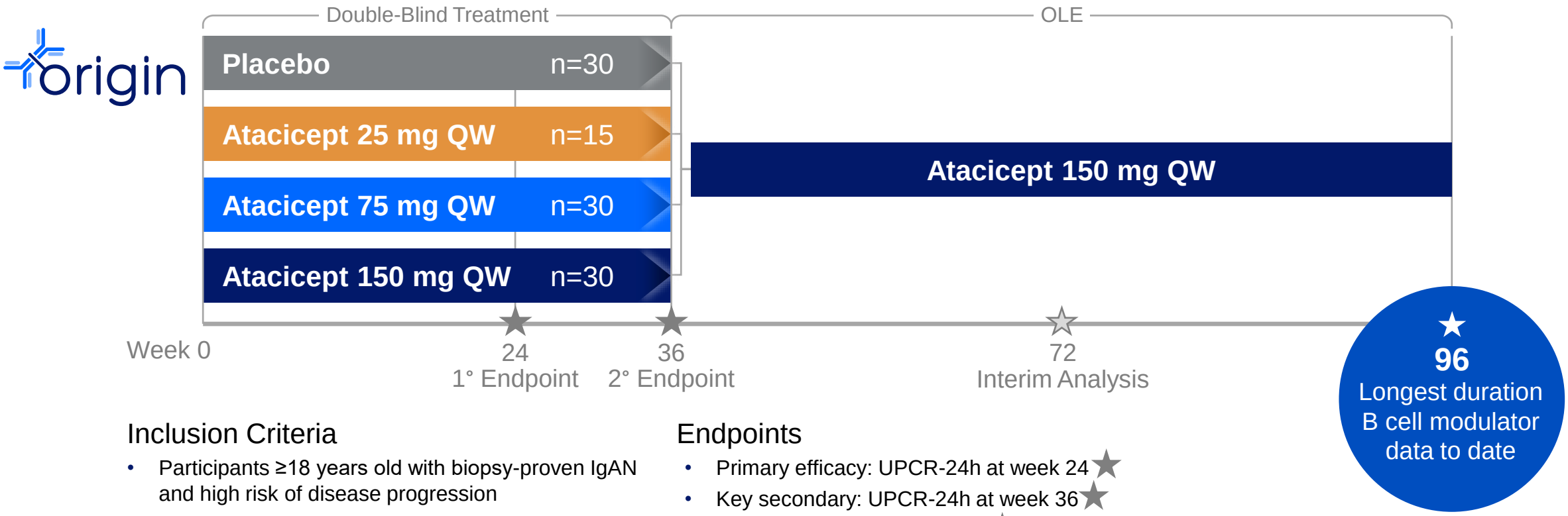


Fc = fragment crystallizable region; IgG1 = immunoglobulin G1; Kd = dissociation constant; $t_{1/2}$ = half-life.

1. Willen D, et al. Eur J Drug Metab Pharmacokinet. 2020;45(1):27-40; 2. Vera data on file.

ORIGIN Phase 2b IgAN trial: Study design and objectives

Multinational, randomized, placebo-controlled trial of atacicept self-administered at home via weekly 1-mL SC injection



Inclusion Criteria

- Participants ≥18 years old with biopsy-proven IgAN and high risk of disease progression
- UPCR-24h >0.75 g/g or UP >0.75 g per 24h
- eGFR ≥30 mL/min/1.73 m^2
- Stable and optimized RAASi for ≥12 weeks
- Use of SGLT2i allowed
- Blood pressure ≤150/90 mmHg

Endpoints

- Primary efficacy: UPCR-24h at week 24 ★
- Key secondary: UPCR-24h at week 36 ★
- eGFR change up to week 96 ☆
- Gd-IgA1 change
- Hematuria change
- Safety

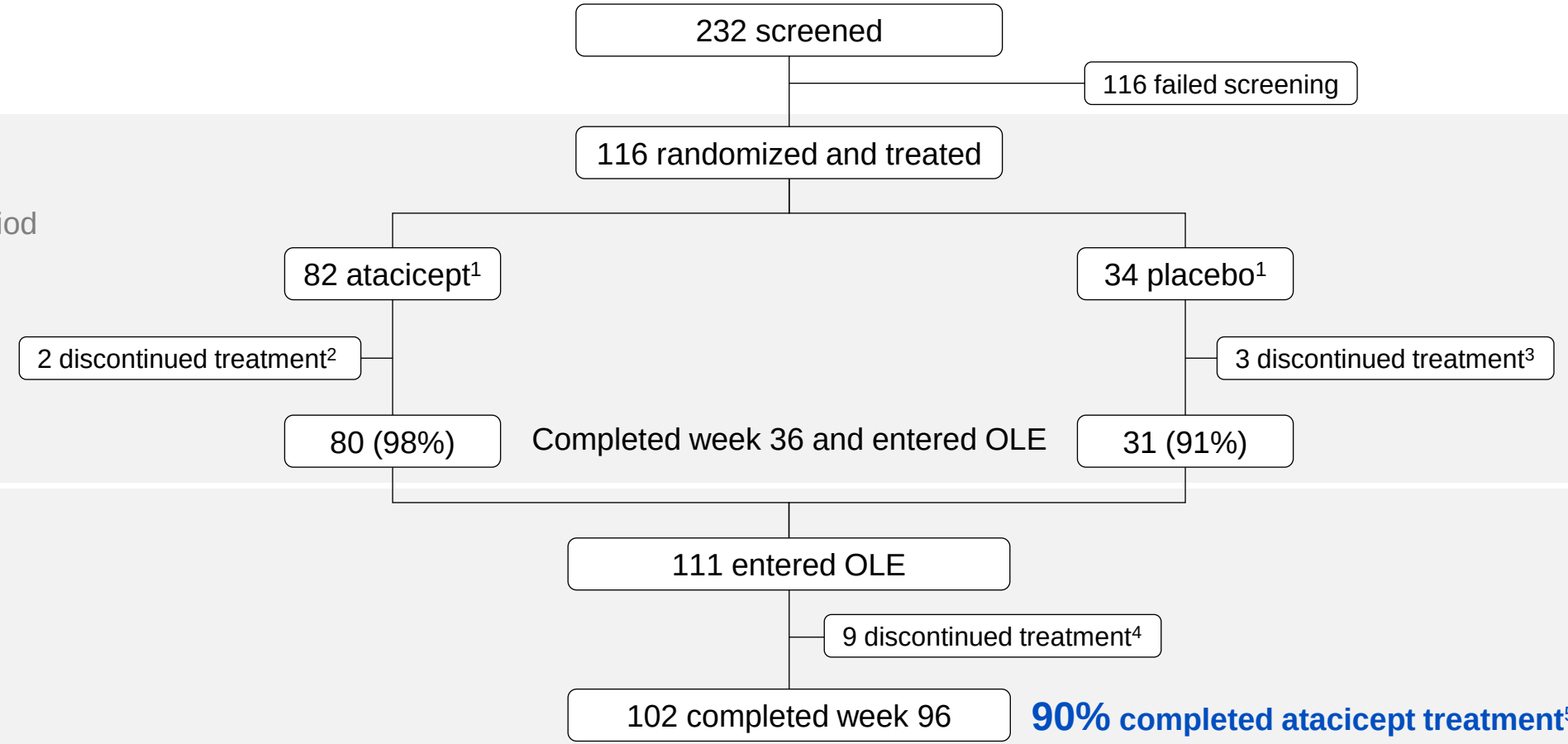
OLE = open-label extension; QW = once-weekly; RAASi = renin-angiotensin-aldosterone system inhibitors; SC = subcutaneous; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UP(CR) = urine protein (to creatinine ratio).

Demographics and baseline characteristics[1]

	Atacicept treated participants[2] n=113
Age, median (range), y	37 (18, 67)
Male sex, n (%)	67 (59)
Race, n (%)	
White	59 (52)
Asian	51 (45)
Native Hawaiian or Other Pacific Islander	1 (1)
Other/not reported	2 (2)
eGFR, mean ± SD, mL/min/1.73 m^2	62 ± 28
UPCR by 24h urine, mean ± SD, g/g	1.8 ± 1.3

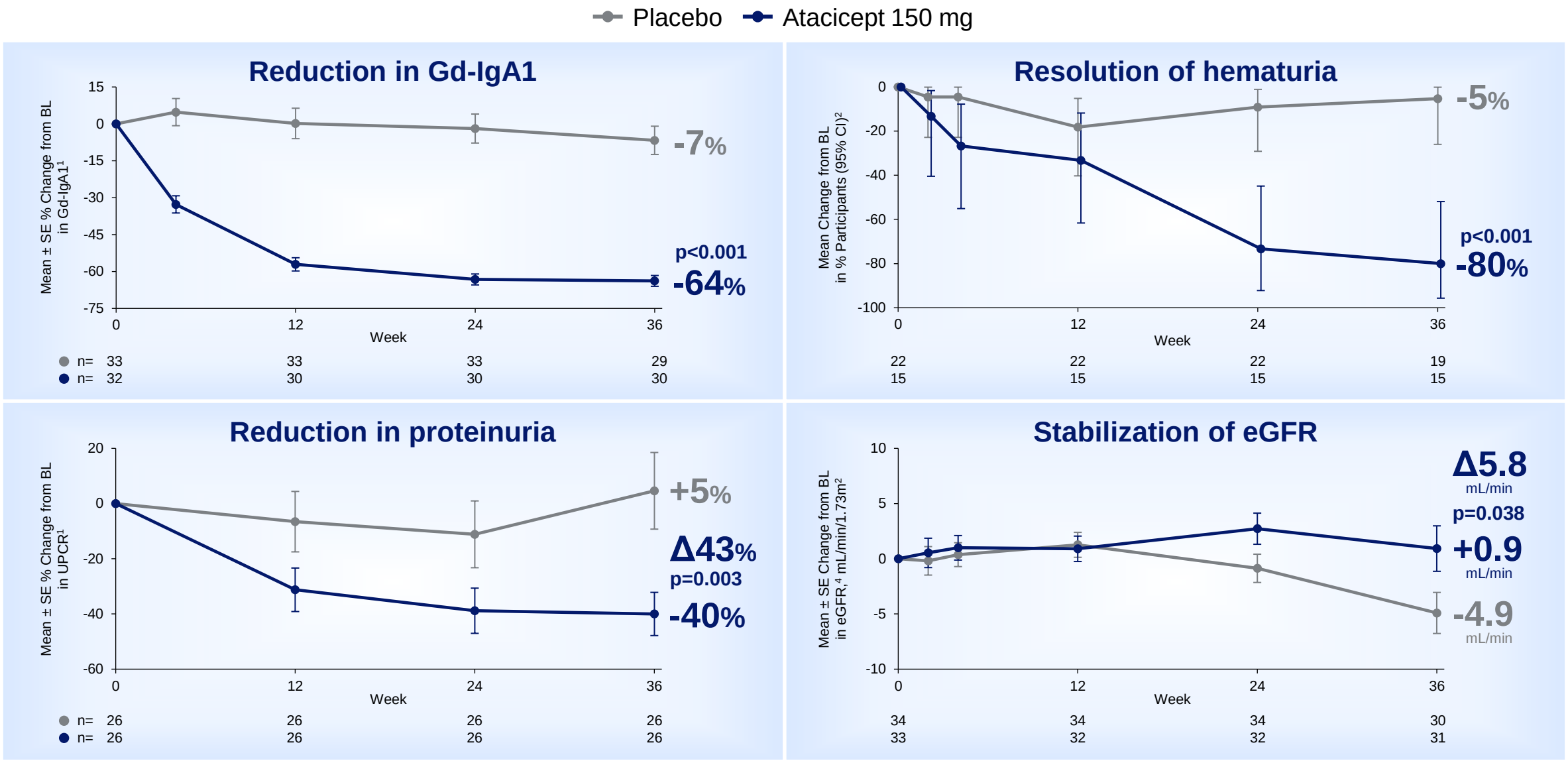
SD = standard deviation.
1. Baseline is defined as the last available measurement prior to the first dose of atacicept.
2. Atacicept group includes all participants receiving any atacicept dose at any timepoint.

Participant disposition through 96 weeks



1. Full analysis set and safety population
2. Discontinued to pursue elective surgery (n=1), and discontinued due to positive hepatitis B DNA and adverse event (n=1).
3. Initiated prohibited medication for concomitant disease (n=1), discontinued due to plan to start prohibited medication for concomitant disease (n=1) and adverse event (n=1).
4. Discontinued due to investigator decision (n=1), pregnancy (n=2), participant withdrawal (n=2), surgery (n=1), serious adverse event of pneumonia in a heavy smoker, resolved (n=1), adverse event of worsening alanine aminotransferase and aspartate aminotransferase (n=1), and medical monitor criteria (n=1).
5. 90% = 102/113 (out of the 116 randomized and treated participants, 3 discontinued placebo prior to week 36).

ORIGIN Phase 2b 36-week results consistent with disease modifying IgAN profile

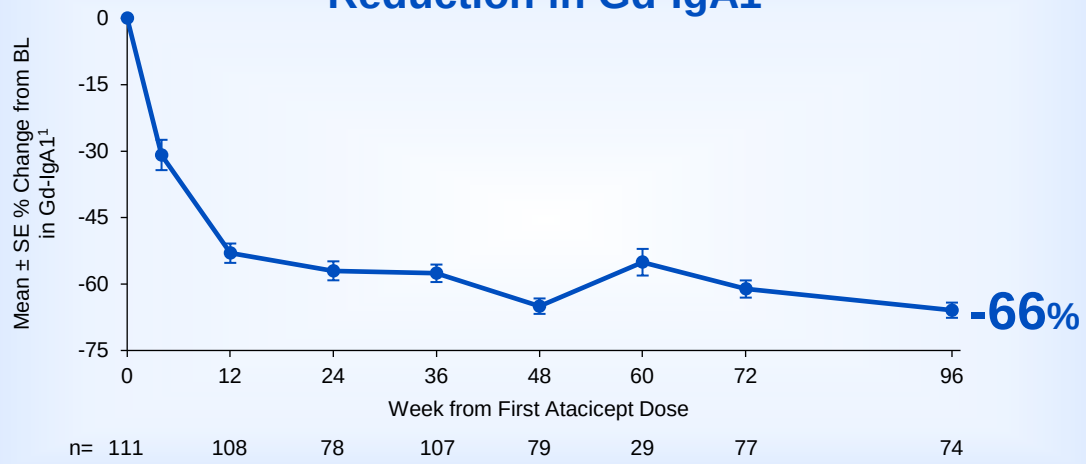


1. p-values, percentage changes from baseline, and treatment differences were computed using FDA-endorsed mixed-effects modeling; 2. Percentages represent change from baseline in number of participants with hematuria (urine dipstick blood ≥ 1+) at each visit divided by number of participants with BL hematuria shown on the lower axis; resolution defined as urine dipstick blood of trace or negative; 3. Changes from BL in eGFR were analyzed using mixed-model repeated measures (MMRM) analysis and geometric least squares (LS) means, ratio of geometric LS means, and standard errors (SE), were transformed back into the original scale from model estimates. Lafayette R, et al. Kidney Int. 2024;S0085-2538(24)00236-9.

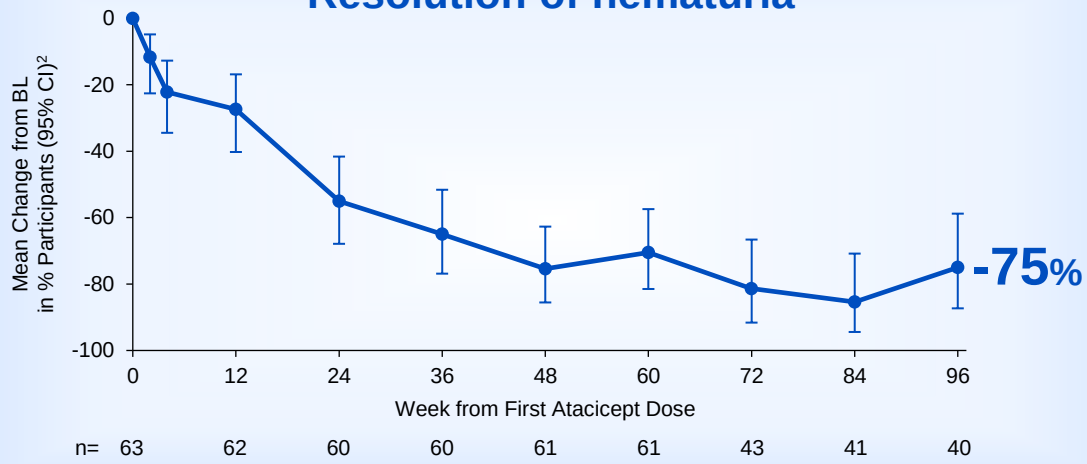
ORIGIN Phase 2b long-term results consistent with disease modifying IgAN profile

Data from first dose of atacicept through 96 weeks

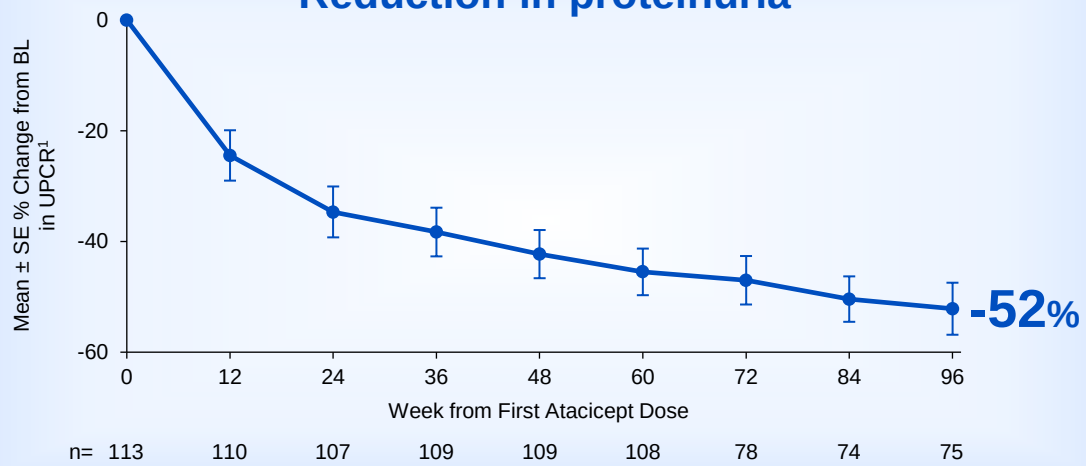
Reduction in Gd-IgA1



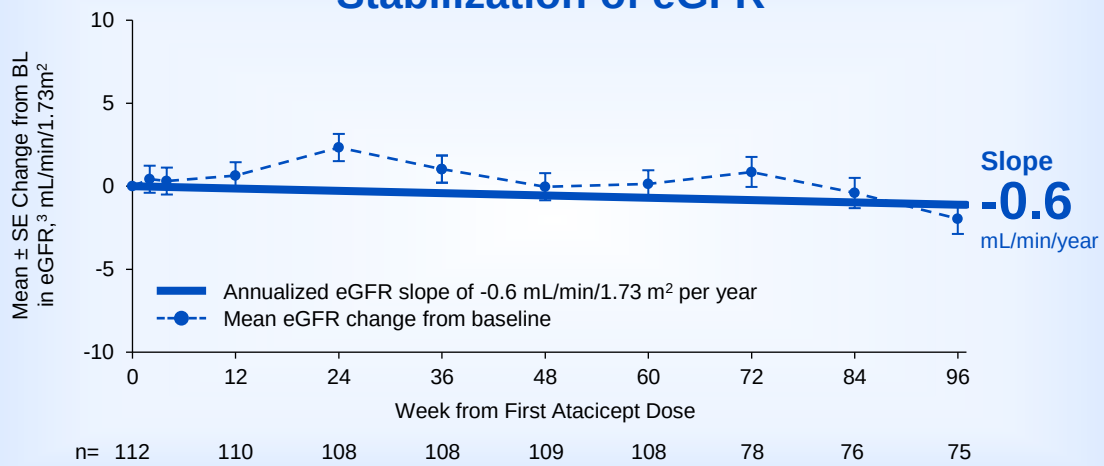
Resolution of hematuria



Reduction in proteinuria

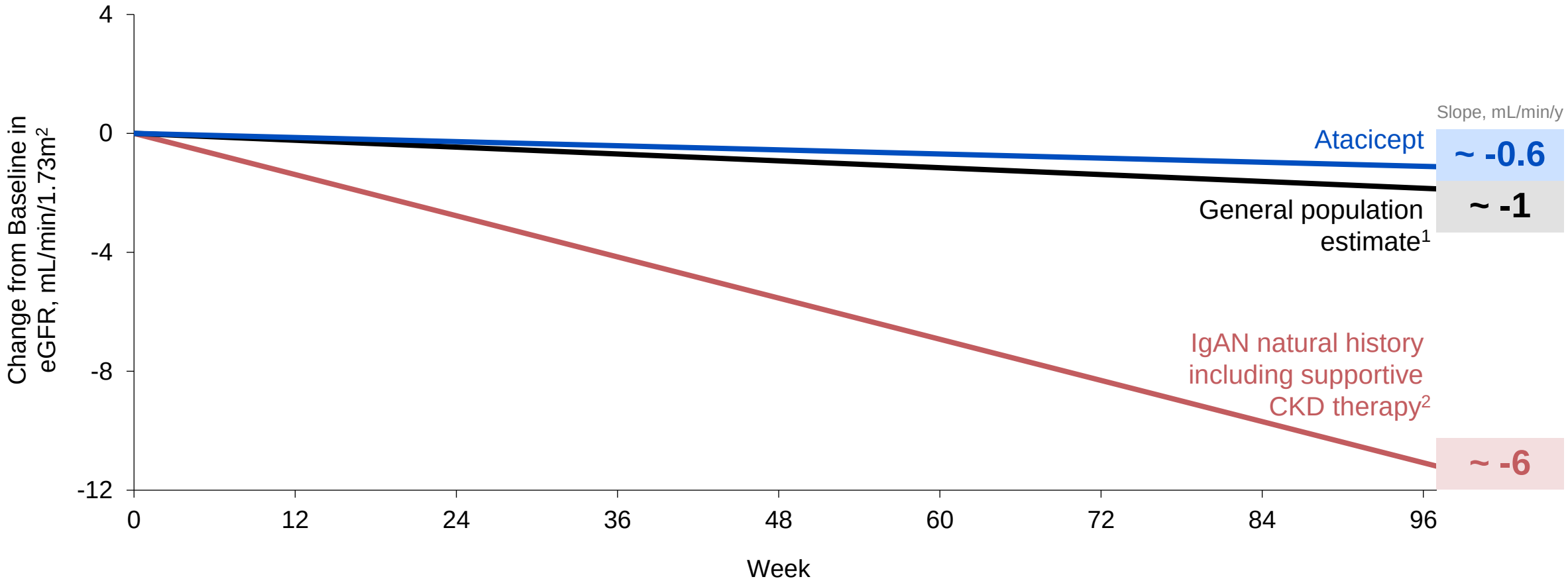


Stabilization of eGFR



Atacicept group includes all participants receiving any atacicept dose at each timepoint, with baseline (BL) defined as the last available measurement prior to the first dose of atacicept. Data from weeks 0 to 60 includes participants who switched from placebo to atacicept. 1. Percentage changes from BL computed using FDA-endorsed mixed-effects modeling; 2. Percentages represent change from baseline in number of participants with hematuria (urine dipstick blood ≥ 1+) at each visit divided by number of participants with BL hematuria shown on the lower axis; resolution defined as urine dipstick blood of trace or negative; 3. Changes from BL in eGFR were analyzed using MMRM analysis and LS estimation and SE were estimated from the model directly; eGFR slope was analyzed using mixed-effects model with random intercept and random slope and mean slope and SE were estimated from the model directly.

Atacicept treated participants have an eGFR slope profile consistent with the *general population without kidney disease*



This data is based on a cross-trial comparison and not a head-to-head clinical trial; such data may not be directly comparable due to differences in study protocols, conditions and patient populations.
Projected eGFR trajectories for general population and IgAN natural history do not represent clinical data and assume a constant eGFR slope over time. CKD = chronic kidney disease.

1. Slope estimate from Baba M, et al. PLOS ONE 2015; 2. Average historical placebo slope from 7 clinical trials3-11; 3. Lafayette R, et al. Lancet 2023; 4. Rovin BH, et al. Lancet 2023; 5. Li PK-T, et al. Am J Kidney Dis 2006; 6. Manno C, et al. Nephrol Dial Transplant 2009; 7. Lv J, et al. JAMA 2017; 8. Wheeler DC, et al. Kidney Int 2021; 9. Lv J, et al. JAMA 2022; 10. Zhang H, et al. ASN Kidney Week 2023, poster TH-PO1123; 11. Mathur M, et al. N Engl J Med 2023.

Atacicept well tolerated through 96 weeks: OLE AE profile consistent with randomized period

	Double-Blind Baseline to Week 36		Open-Label Extension Week 36 to 96[1]
Participants, n (%)	**Placebo n=34**	**All Atacicept n=82**	**Atacicept 150 mg n=111**
TEAEs	28 (82)	60 (73)	85 (77)
Infections and infestations	11 (32)	35 (43)	43 (39)
Study drug-related TEAEs[2]	14 (41)	42 (51)	52 (47)
Serious TEAEs[3]	3 (9)	2 (2)	12 (11)
TEAEs leading to study drug discontinuation[4]	1 (3)	1 (1)	2 (2)
Deaths	0	0	0

- Total participant exposure: median 96 weeks (range 3, 99); mean 91 weeks

TEAE = treatment-emergent adverse event.

1. Week 96 cut-off includes all safety data as of June 03, 2024, including visits past Week 96. AEs were considered treatment-emergent during the open-label extension period if they started after the first dose of open-label atacicept 150 mg through the end of the study. n=111 represents 80 atacicept and 31 placebo who entered the open-label extension.
2. Mostly injection site reactions.
3. Serious TEAEs during double-blind period were previously reported (Lafayette R, et al. Kidney Int. 2024;S0085-2538(24)00236-9); serious TEAEs during the OLE: excess abdominal fat and left basal bronchopneumonia (n=1), acute kidney injury (n=1), angioedema (n=1), termination of pregnancy (n=1), post cricoid ulcer (n=1), pancreatitis, passed out common bile duct stone, and acute cholecystitis (n=1), tonsillitis (n=1), pneumonia (n=1), acute coronary syndrome required hospitalization (n=1), left 5th metatarsophalangeal joint gout (n=1), mild flare of IgA nephropathy (n=1), and urethral stricture worsening (n=1).
4. Reasons for discontinuation during double-blind period were previously reported; discontinuations during the OLE were due to: pneumonia in a heavy smoker, resolved (n=1); and worsening alanine aminotransferase and aspartate aminotransferase, resolved and unrelated to study treatment (n=1).

Conclusions

- Participants treated with atacicept for 96 weeks demonstrated sustained and substantial reductions in Gd-IgA1, hematuria and UPCR with long-term stabilization of eGFR
- The cumulative favorable safety profile remains consistent with that observed during the randomized 36 weeks of ORIGIN 2b
- The conversion of an eGFR profile in patients with IgAN from one of steady, unrelenting decline to one similar to that of the general population without kidney disease through 96 weeks is a unique and compelling finding
- Collectively, these data support the potential of B-cell modulation with atacicept to modify the natural history of the disease and the potential to prevent kidney failure during the lifetime of patients with IgAN

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