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Phase 2b ORIGIN Study Open Label Extension with Atacicept in Patients with IgA Nephropathy and Persistent Proteinuria: Week 72 Interim Analysis

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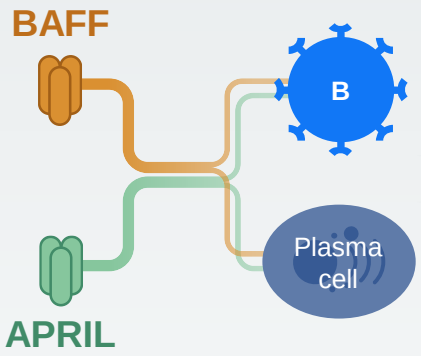
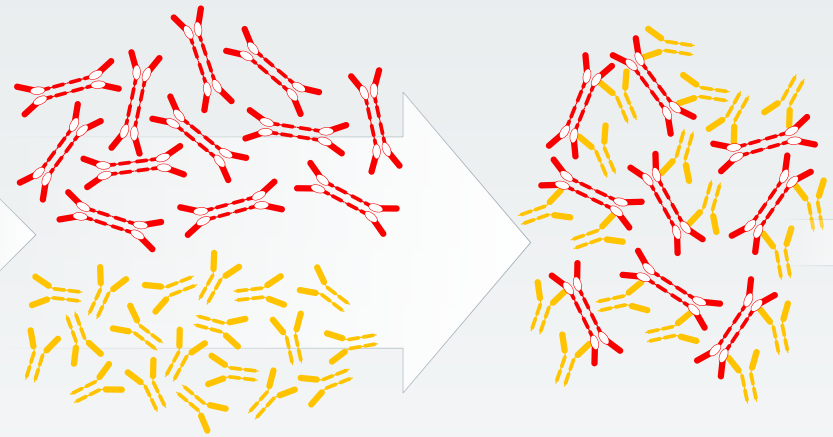
Free Communication
May 25, 2024

IgAN is a B Cell Mediated Kidney Disease

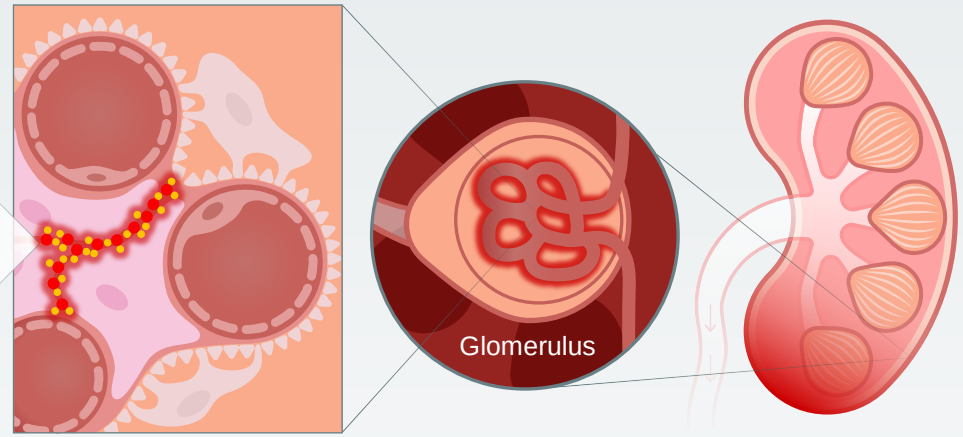
B Cell Activation



Formation of Circulating Immune Complexes



Immune Complex Deposition Leading to Glomerulonephritis and Kidney Damage

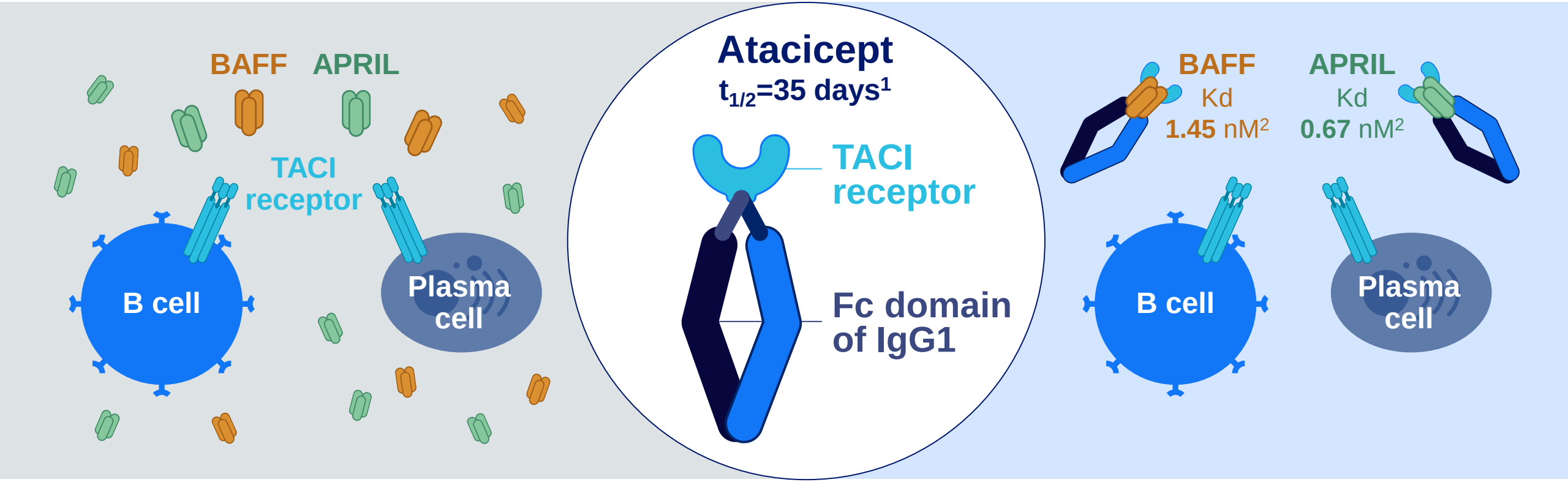


1. BAFF and APRIL are upregulated and activate B cells via the TACI receptor
2. Activated B cells produce Gd-IgA1 and autoantibodies that bind to exposed epitopes within the Gd-IgA1 hinge region…
3. …forming immune complexes…
4. …which deposit in the mesangium, resulting in glomerular inflammation (nephritis)…
5. …and progressive kidney injury with hematuria, proteinuria, and eGFR decline

APRIL = A PRoliferation-Inducing Ligand; BAFF = B-cell Activating Factor; eGFR = estimated glomerular filtration rate; Gd-IgA1 = galactose-deficient immunoglobulin A1; TACI = transmembrane activator and calcium-modulator and cyclophilin ligand interactor.

Atacicept: Dual Inhibitor of BAFF and APRIL

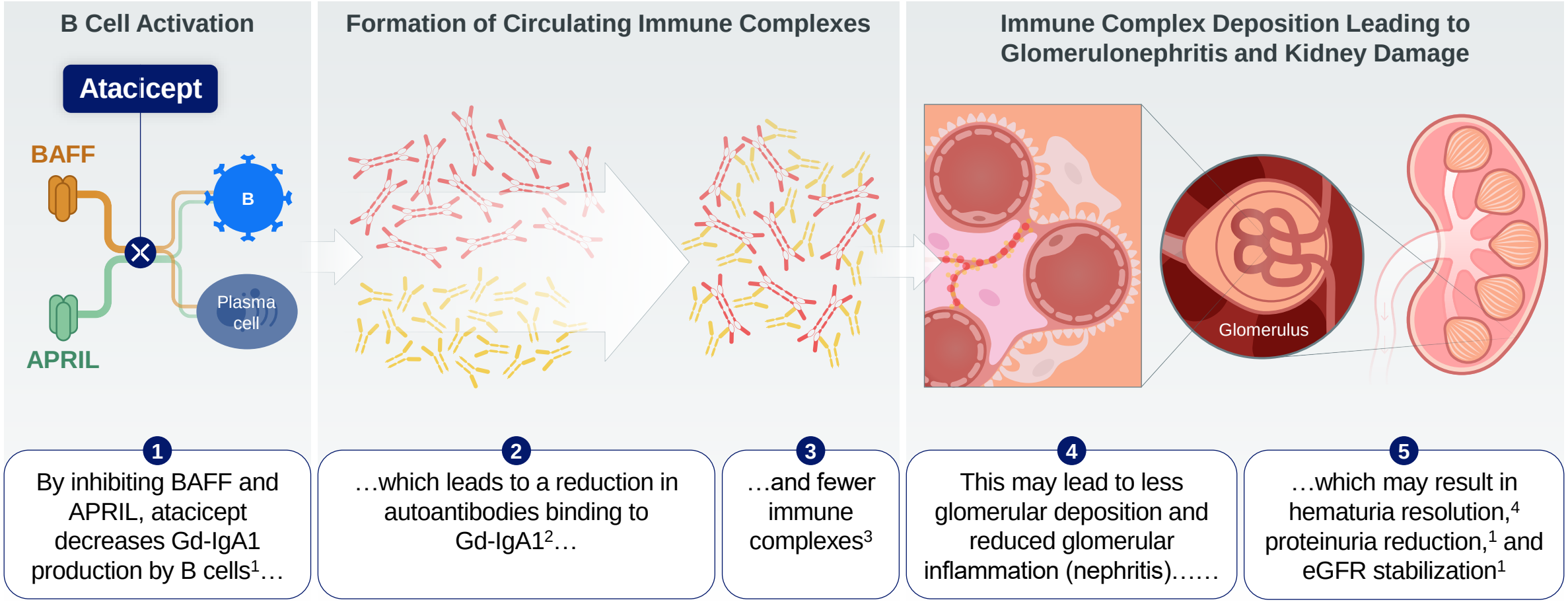
Rational Drug Design: Native TACI Receptor Fused to Fc — Fully Humanized Soluble Fusion Protein



Fc = fragment crystallizable region; IgG1 = immunoglobulin G1.

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

Atacicept Targets the Upstream Immunologic Cause of IgAN



1. By inhibiting BAFF and APRIL, atacicept decreases Gd-IgA1 production by B cells[1]…

2. …which leads to a reduction in autoantibodies binding to Gd-IgA1[2]…

3. …and fewer immune complexes[3]

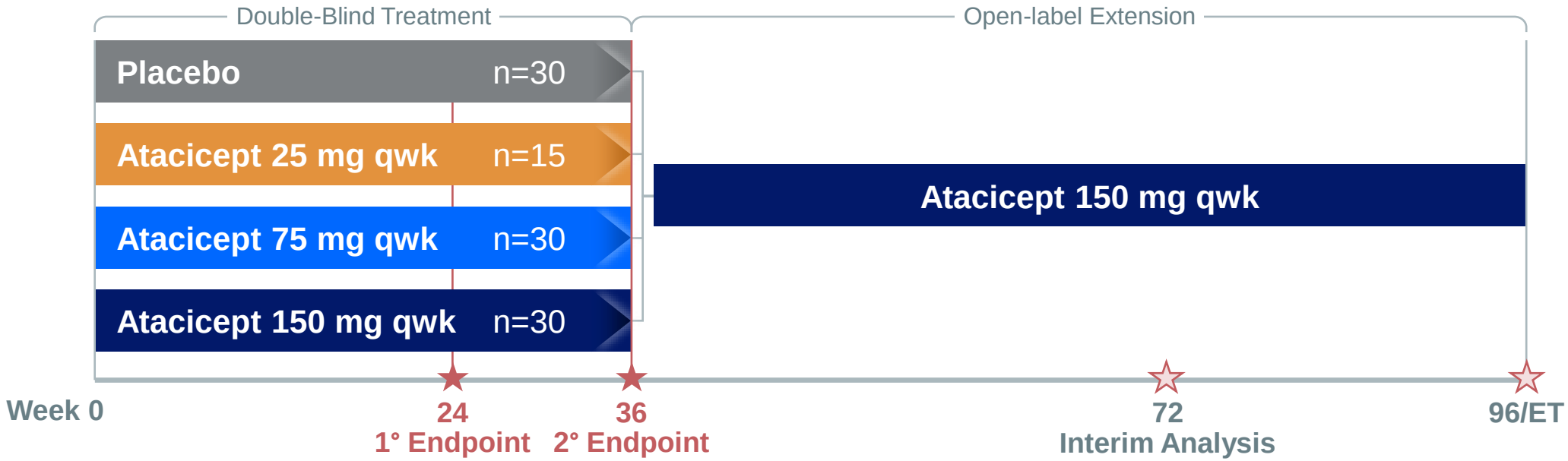
4. This may lead to less glomerular deposition and reduced glomerular inflammation (nephritis)……

5. …which may result in hematuria resolution,[4] proteinuria reduction,[1] and eGFR stabilization[1]

1. Lafayette R, et al. Kidney Int 2024;S0085-2538(24)00236-9; 2. Barratt J, et al. Nephrol Dial Transplant 2022;3 suppl 3, abstr FC051; 3. Barratt J, et al. ASN Kidney Week 2022, abstr SA-PO655;
4. Floege J, et al. Nephrol Dial Transplant 2024;39 suppl 1, abstr 123. Atacicept is an investigational therapy that has not been approved by regulatory agencies.

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 IgAN on kidney biopsy and high risk of disease progression
- Stable and optimized RAASi for ≥12 weeks
- Use of SGLT2i allowed
- UPCR-24h >0.75 g/g or UP >0.75 g per 24h
- eGFR ≥30 mL/min/1.73 m^2
- 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
- Safety

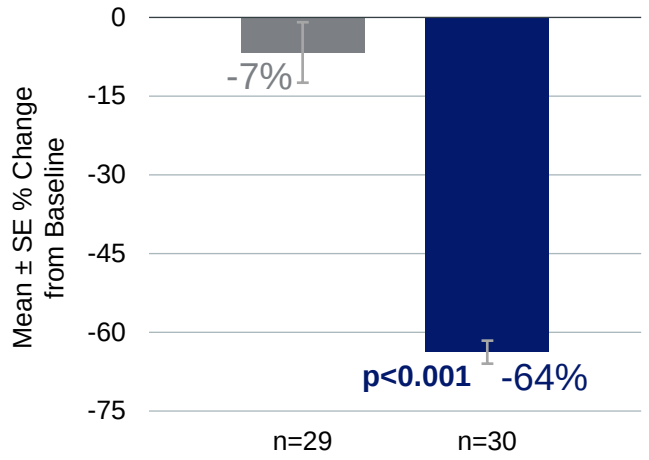
ET = end of treatment; RAASi = renin-angiotensin-aldosterone system inhibitor; SGLT2i = sodium-glucose cotransporter-2 inhibitor; UPCR = urine protein:creatinine ratio.

Demographics and Baseline Characteristics

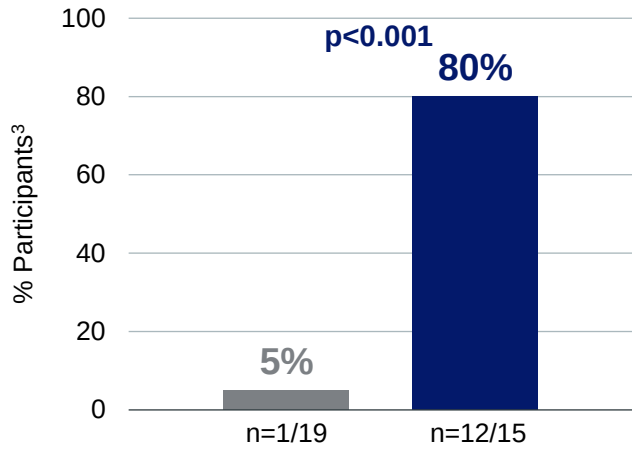
Mean ± SD or n (%)	Overall n=116	Atacicept 25 mg n=16	Atacicept 75 mg n=33	Atacicept 150 mg n=33	Placebo n=34
Age, y	39	40	41	38	39
Male sex	69 (59)	9 (56)	19 (58)	22 (67)	19 (56)
Race					
White	62 (53)	7 (44)	12 (36)	17 (52)	26 (76)
Asian	51 (44)	7 (44)	20 (61)	16 (48)	8 (24)
Other	3 (3)	2 (12)	1 (3)	0	0
eGFR, mL/min/1.73 m^2	63 ± 27.3	71 ± 28.7	64 ± 25.4	56 ± 22.7	66 ± 31.7
UPCR by 24h urine, g/g	1.6 ± 0.9	1.6 ± 0.8	1.7 ± 0.9	1.7 ± 1.0	1.6 ± 0.8
Time from biopsy, y	2.8 ± 2.8	1.7 ± 1.6	3.4 ± 2.8	3.3 ± 3.4	2.1 ± 2.4

Disease Modification Observed at Week 36

Gd-IgA1 Reduction[1]

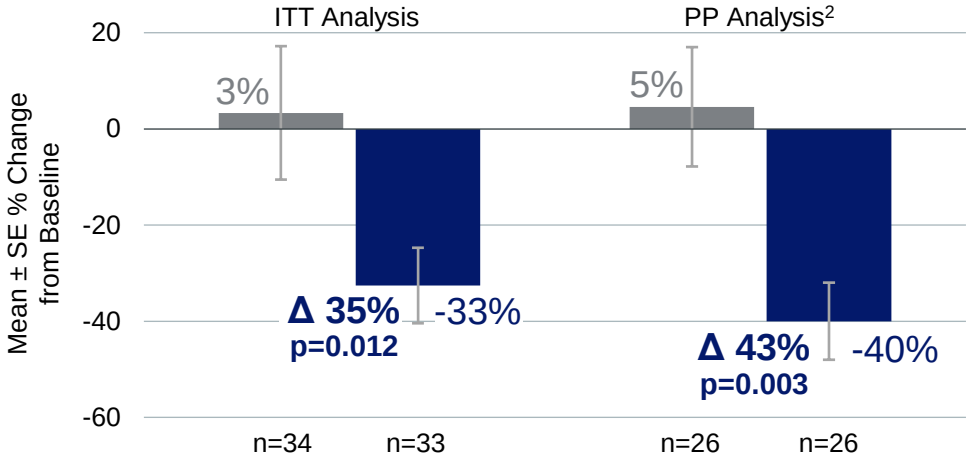


Hematuria Resolution[1]

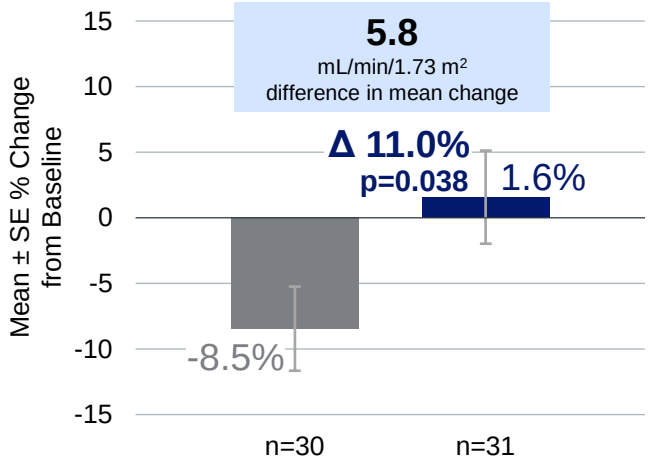


Placebo
Atacicept 150 mg

UPCR Reduction

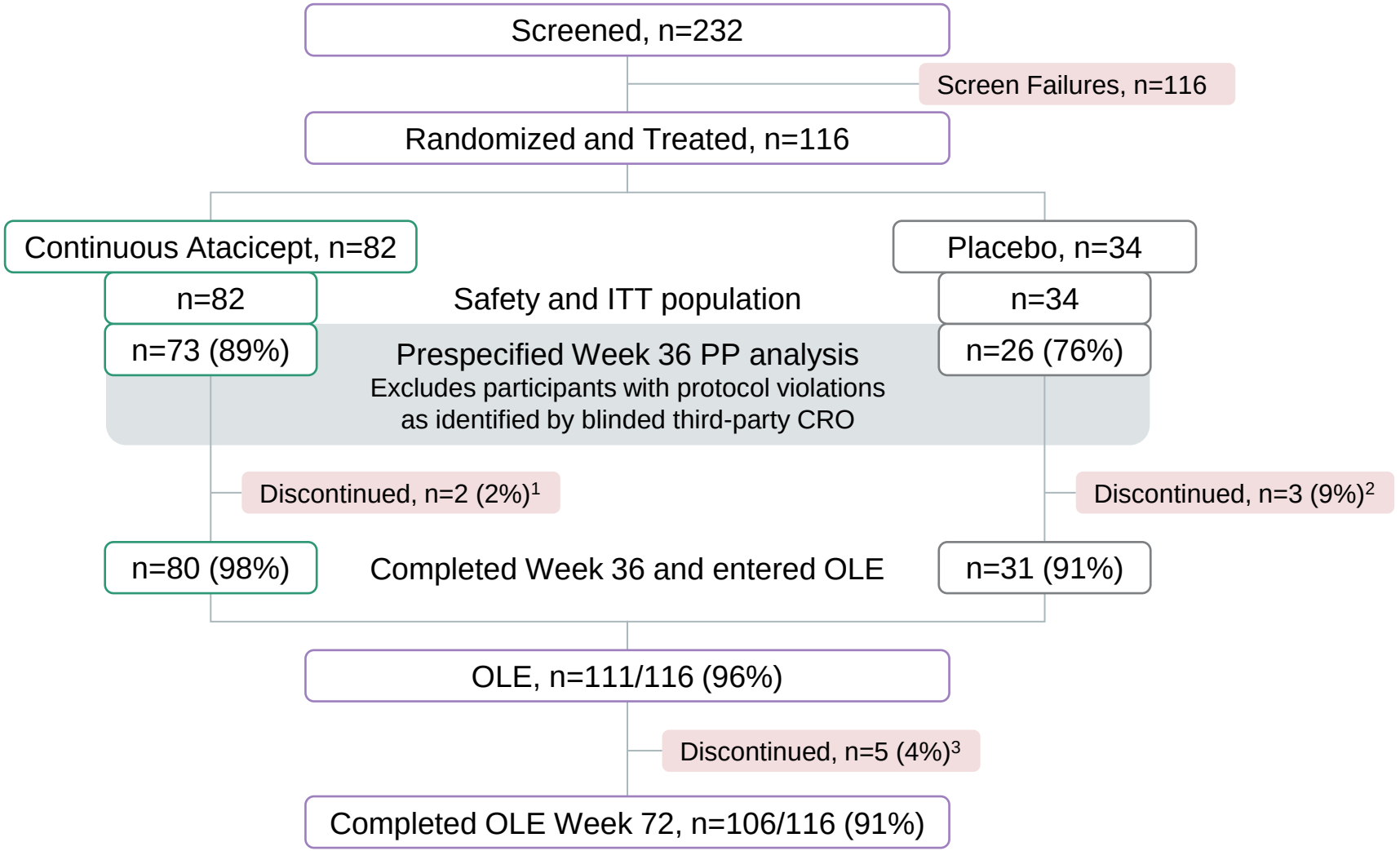


eGFR Stabilization[1]



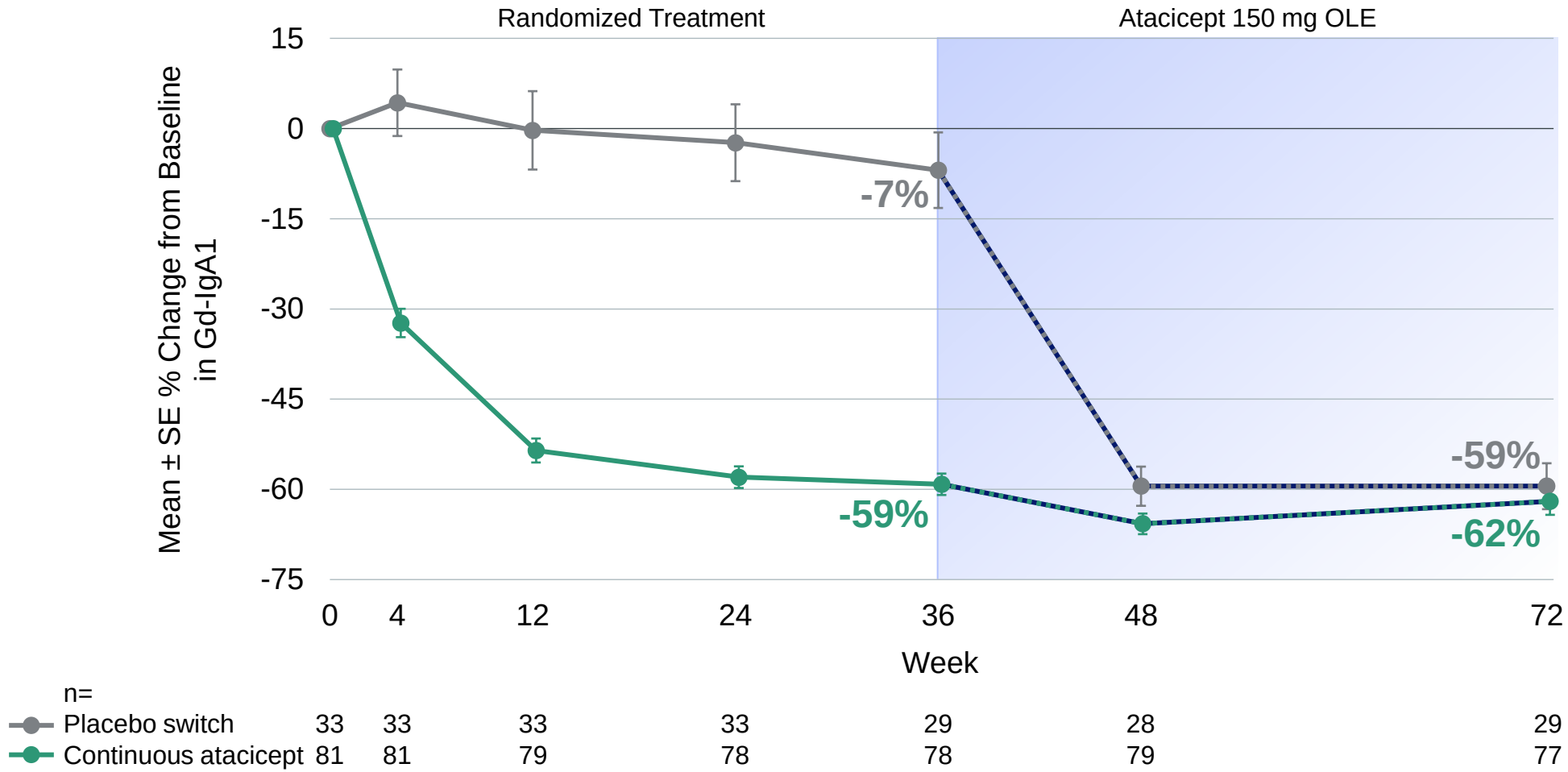
1. Intent-to-treat (ITT) analysis; 2. Prespecified Week 36 per-protocol (PP) analysis excluded participants with protocol violations through week 36 as identified by blinded third-party CRO; 3. Hematuria resolution defined as decrease to negative/trace levels in participants with baseline hematuria 1+ or higher. Lafayette R, et al. Kidney Int 2024 Mar 27:S0085-2538(24)00236-9; Floege J, et al. Nephrol Dial Transplant 2024;39 suppl 1, abstr 123.

Participant Disposition Through Week 72



OLE = open label extension. Continuous atacicept group includes all participants originally randomized to any atacicept dose in the double-blind period.
1. Discontinued to pursue elective surgery (1), discontinued due to positive hepatitis B DNA and adverse event (1).
2. Initiated prohibited medication for concomitant disease (1), discontinued due to plan to start prohibited medication for concomitant disease (1) and adverse event (1).
3. Discontinued to pursue surgery (1), discontinued due to serious adverse event of pneumonia in a heavy smoker, resolved (1), investigator decision (1), pregnancy (1), and participant withdrawal (1).

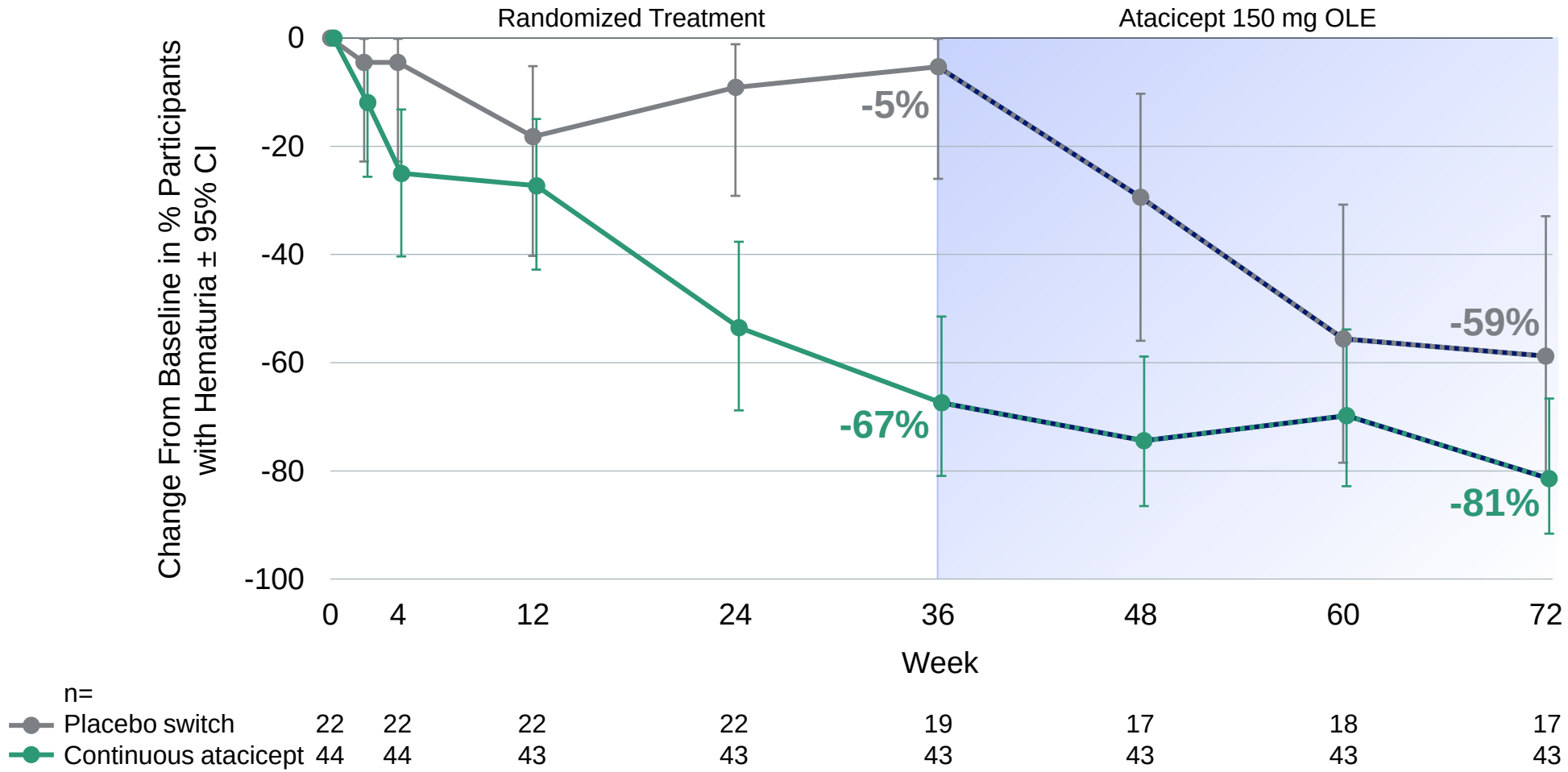
Sustained Gd-IgA1 Reduction Through Week 72



- Placebo switch to atacicept at week 36 recapitulated reductions observed in initial randomized atacicept group

Percentage changes from baseline were computed using FDA-endorsed mixed-effects modeling; continuous atacicept group includes participants originally randomized to any atacicept dose in the double-blind period; ITT analysis.

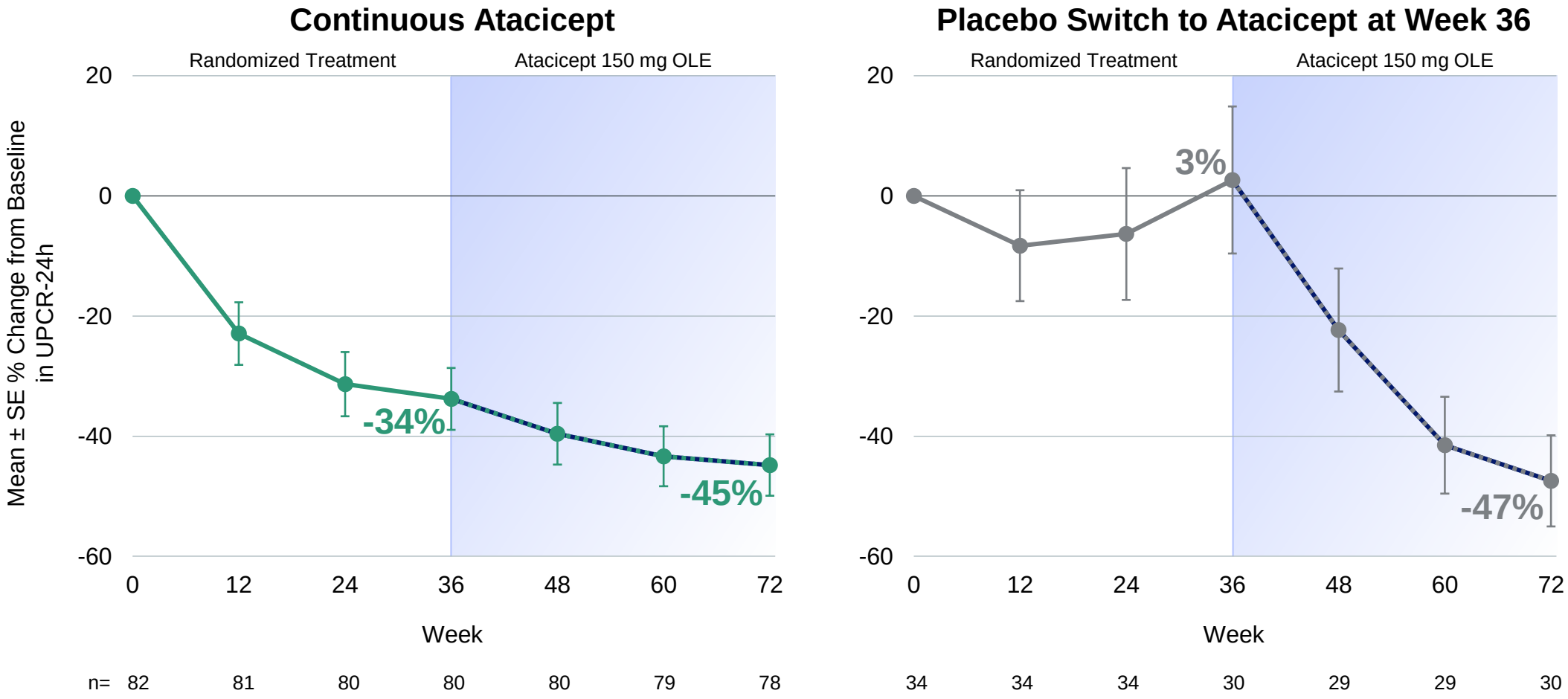
Reductions in % Participants with Hematuria Through Week 72



- Placebo switch to atacicept at week 36 recapitulated reductions observed in initial randomized atacicept group

Change from baseline in percentage of participants with hematuria at each visit out of those with baseline hematuria; microscopic hematuria was evaluated via urine dipstick at a centralized lab, and hematuria levels were graded as negative/trace, 1+, 2+, or 3+. Continuous atacicept group includes participants originally randomized to any atacicept dose in the double-blind period; ITT analysis. CI = confidence interval.

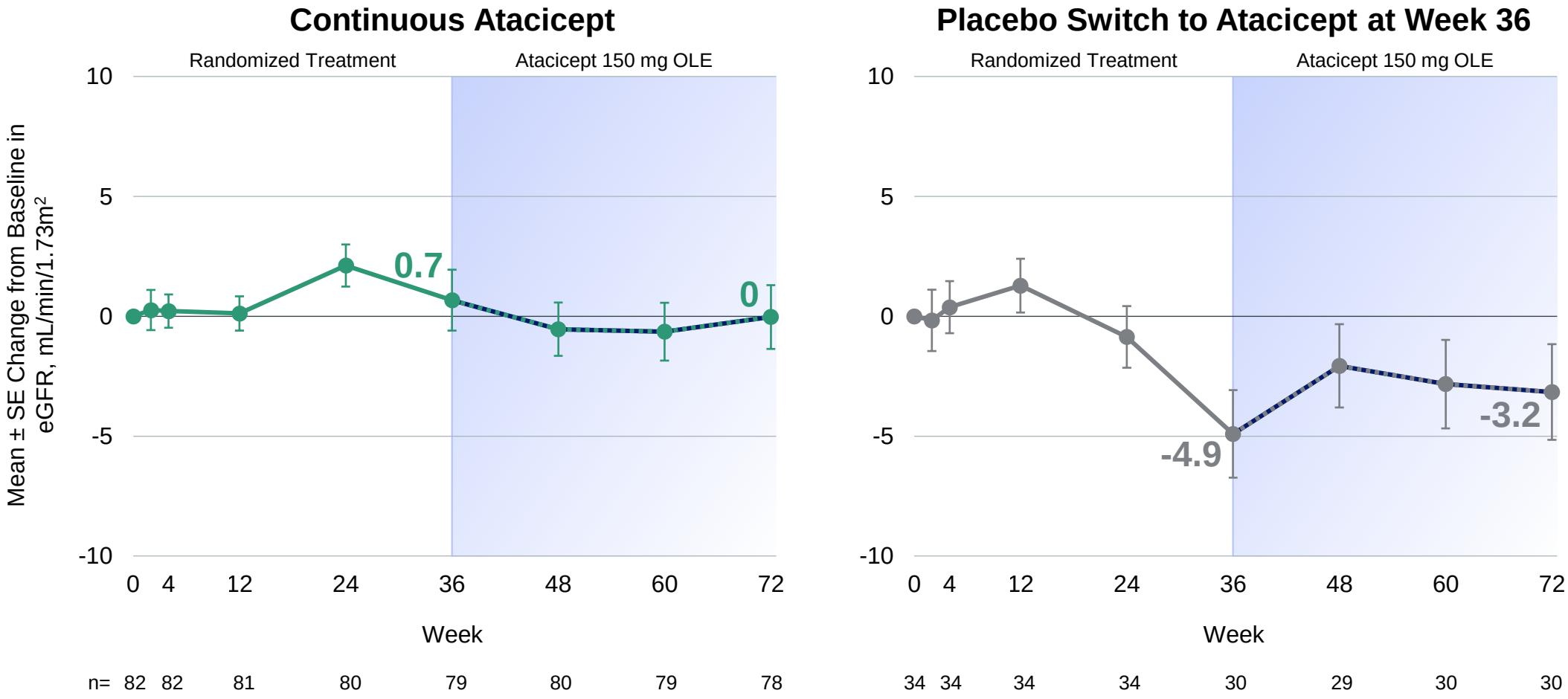
Sustained Reductions in UPCR Through 72 Weeks



- Placebo switch to atacicept at week 36 recapitulated reductions observed in initial randomized atacicept group

Percentage changes from baseline were computed using FDA-endorsed mixed-effects modeling which takes into account the effects of baseline UPCR and eGFR and implicitly imputes missing data as missing at random. Continuous atacicept group includes all participants originally randomized to any atacicept dose in the double-blind period; ITT analysis. In week 36 PP analysis, participants continuously treated with atacicept had -48% change from baseline and participants who switched from placebo to atacicept had -47% change from baseline in UPCR.

eGFR Stabilization Through Week 72



- In randomized placebo cohort, eGFR stabilized after switch to atacicept at week 36

Percentage changes from baseline were computed using FDA-endorsed mixed-effects modeling which takes into account the effects of baseline UPCR and eGFR and implicitly imputes missing data as missing at random; geometric least squares (LS) means, ratio of geometric LS means, and standard errors (SE), were transformed back into the original scale from model estimates.

Continuous atacicept group includes all participants originally randomized to any atacicept dose in the double-blind period; ITT analysis.

OLE Adverse Events Profile Consistent with Randomized Period

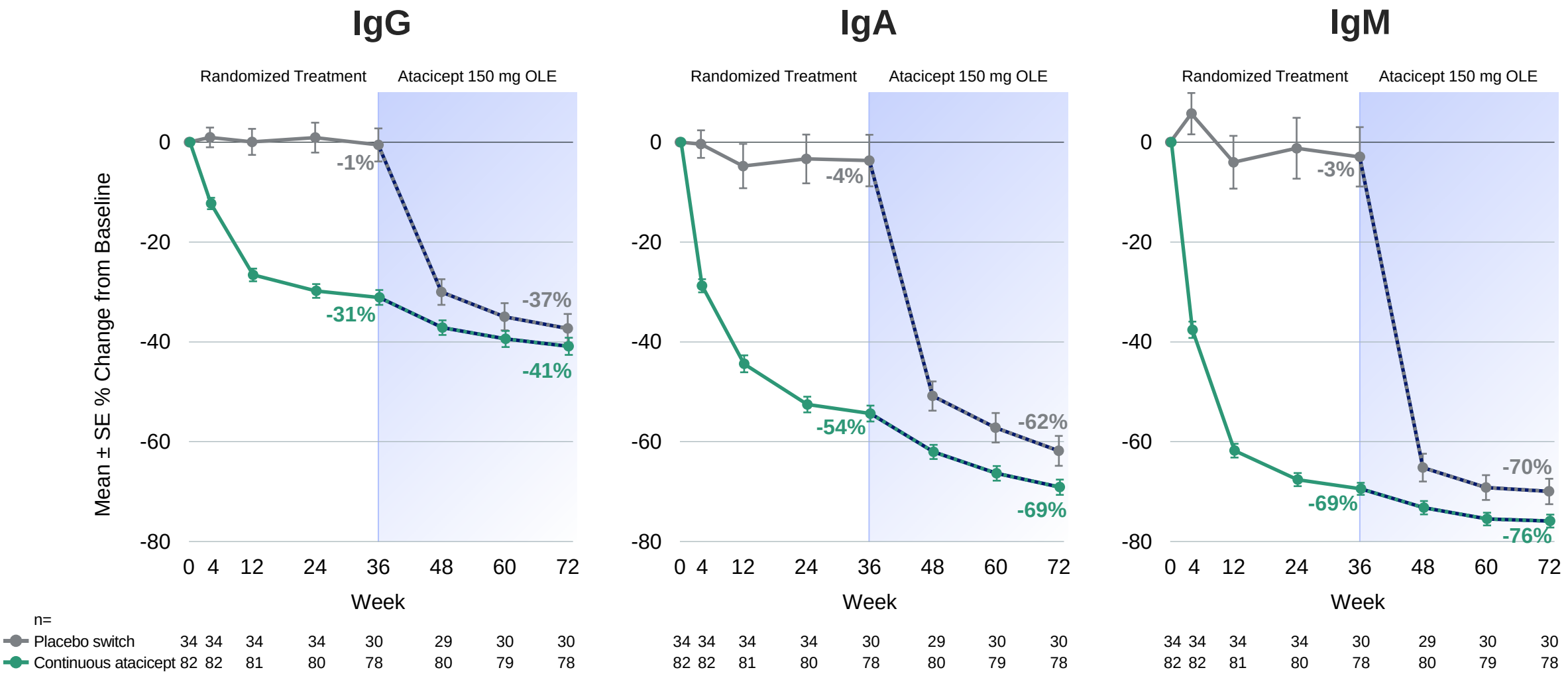
Double-Blind Data Through Week 36; OLE Data Through 12/2023[1]

	Double-blind Baseline to Week 36				Week 36 to 72	Baseline to Week 72
Participants, n (%)	Placebo n=34	Atacicept 25 mg n=16	Atacicept 75 mg n=33	Atacicept 150 mg n=33	Total OLE Atacicept 150 mg n=111	Atacicept 150 mg n=33
TEAEs	28 (82)	11 (69)	24 (73)	25 (76)	77 (69)	26 (79)
Infections and infestations	11 (32)	6 (38)	16 (48)	13 (39)	33 (30)	15 (45)
Study drug-related TEAEs[2]	14 (41)	6 (38)	17 (52)	19 (58)	51 (46)	22 (67)
Serious TEAEs	3 (9)	0	1 (3)	1 (3)	8 (7)	2 (6)
TEAEs leading to study drug discontinuation	1 (3)[3]	0	0	1 (3)[4]	1 (1)[5]	1 (3)[4]
Deaths	0	0	0	0	0	0

- Total patient exposure:
  - OLE through 12/05/23: mean 48.8 weeks, median 47.7 weeks (range 10.7 – 62.7)
  - Double-blind baseline to 12/05/23: mean 82.0 weeks, median 83.4 weeks (range 3.0 – 99.0)

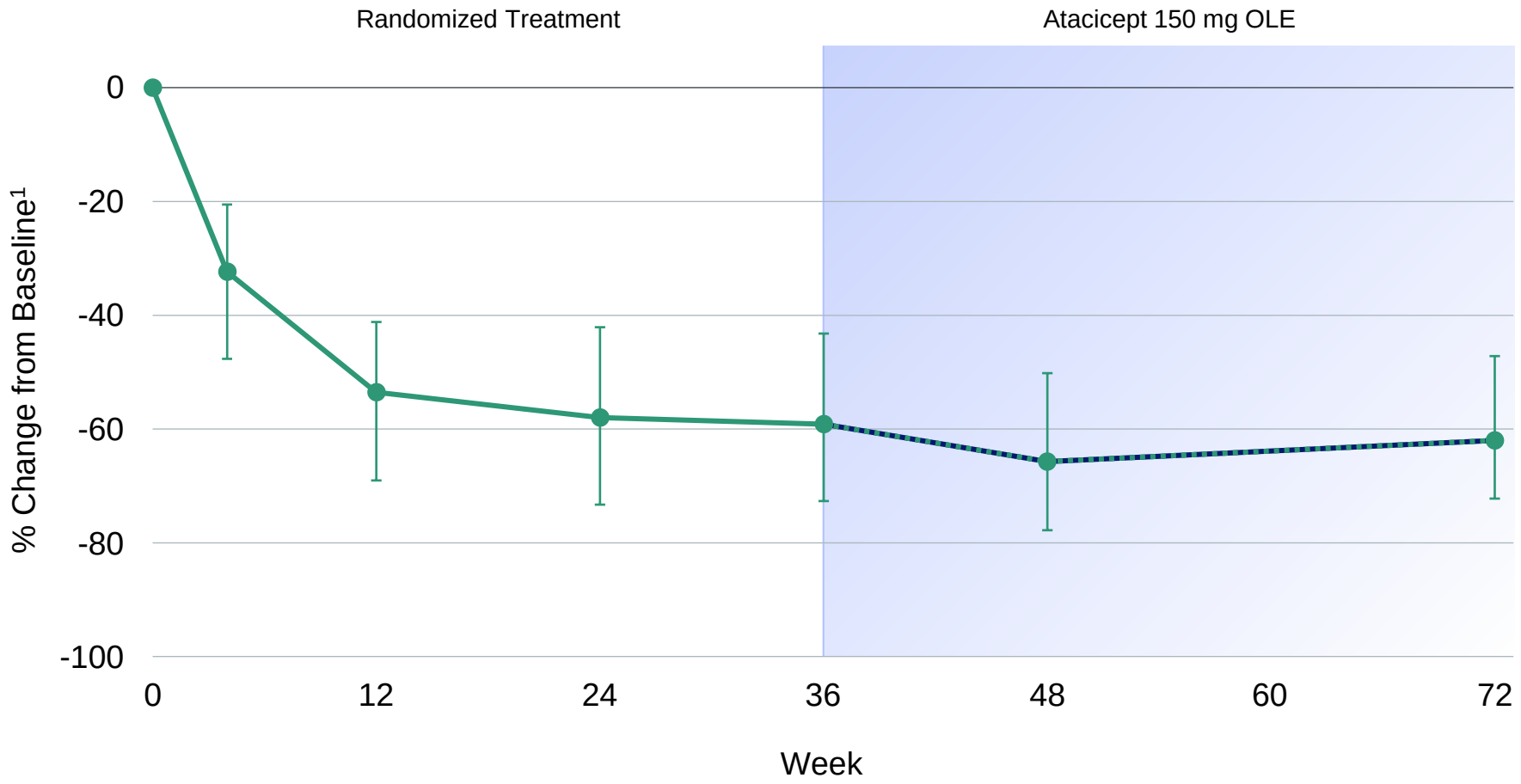
1. Week 72 cut-off includes all safety data as of 12/05/23, including visits past Week 72. AEs considered treatment-emergent during OLE period if they start anytime after first dose of open-label atacicept 150 mg through end of study.
2. Majority of study drug-related TEAEs were injection site reactions and one contributed to drug discontinuation during double-blind period.
3. Discontinued due to worsening flank pain that was not resolved; unrelated to study treatment.
4. Discontinued due to injection site reaction and positive hepatitis B DNA that resolved without treatment 3 weeks later, normal liver function throughout.
5. Discontinuation due to pneumonia in a heavy smoker, resolved.

Serum IgG, IgA, and IgM % Change Through Week 72



Percentage changes from baseline were computed using FDA-endorsed mixed-effects modeling. Continuous atacicept group includes participants originally randomized to any atacicept dose in the double-blind period; ITT analysis.

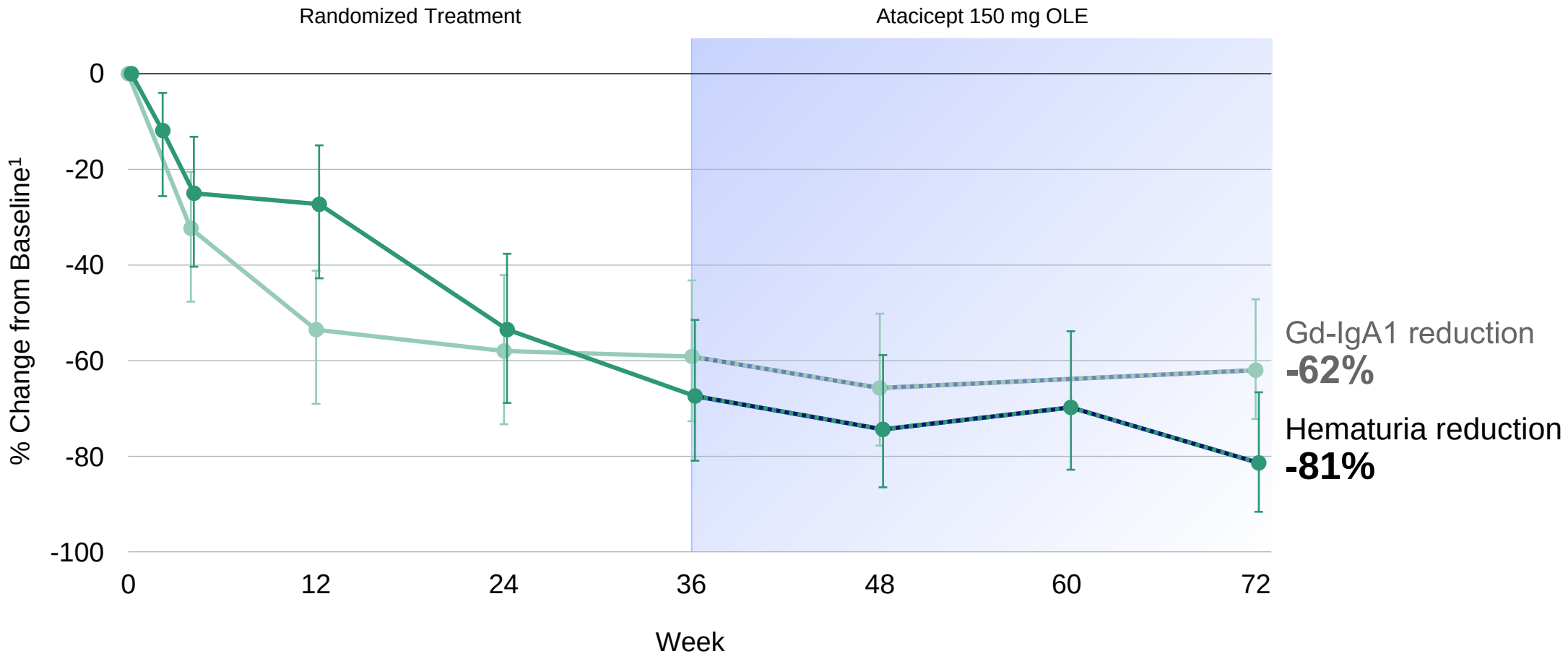
Atacicept ORIGIN Phase 2b 72 Week Results Are Consistent With a Disease Modifying IgAN Profile



Gd-IgA1 reduction
-62%

1. Gd-IgA1, UPCR, and eGFR: mean ± SE % change from baseline; hematuria: change from baseline in percentage of participants with hematuria at each visit out of those with baseline hematuria.
Data from participants originally randomized to any atacicept dose during the double-blind period in the ITT population.

Atacicept ORIGIN Phase 2b 72 Week Results Are Consistent With a Disease Modifying IgAN Profile



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Data from participants originally randomized to any atacicept dose during the double-blind period in the ITT population.

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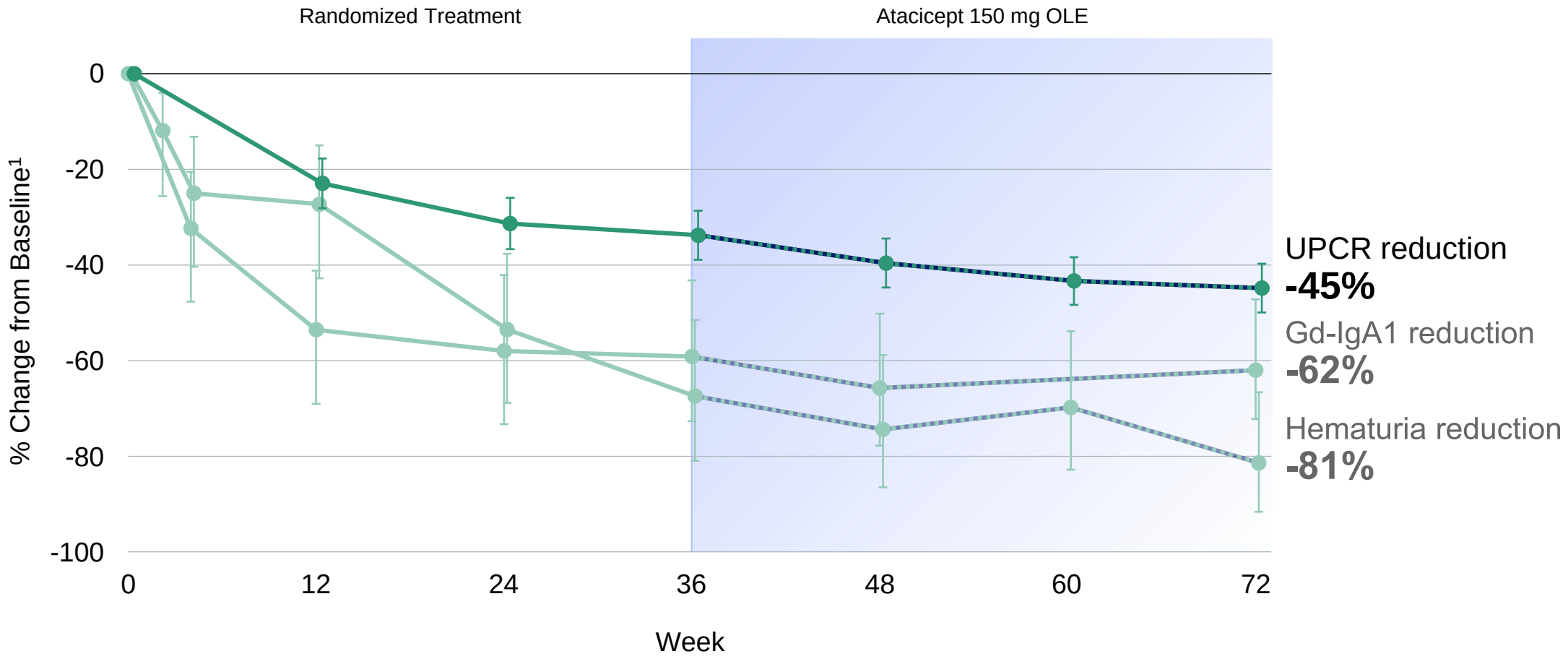

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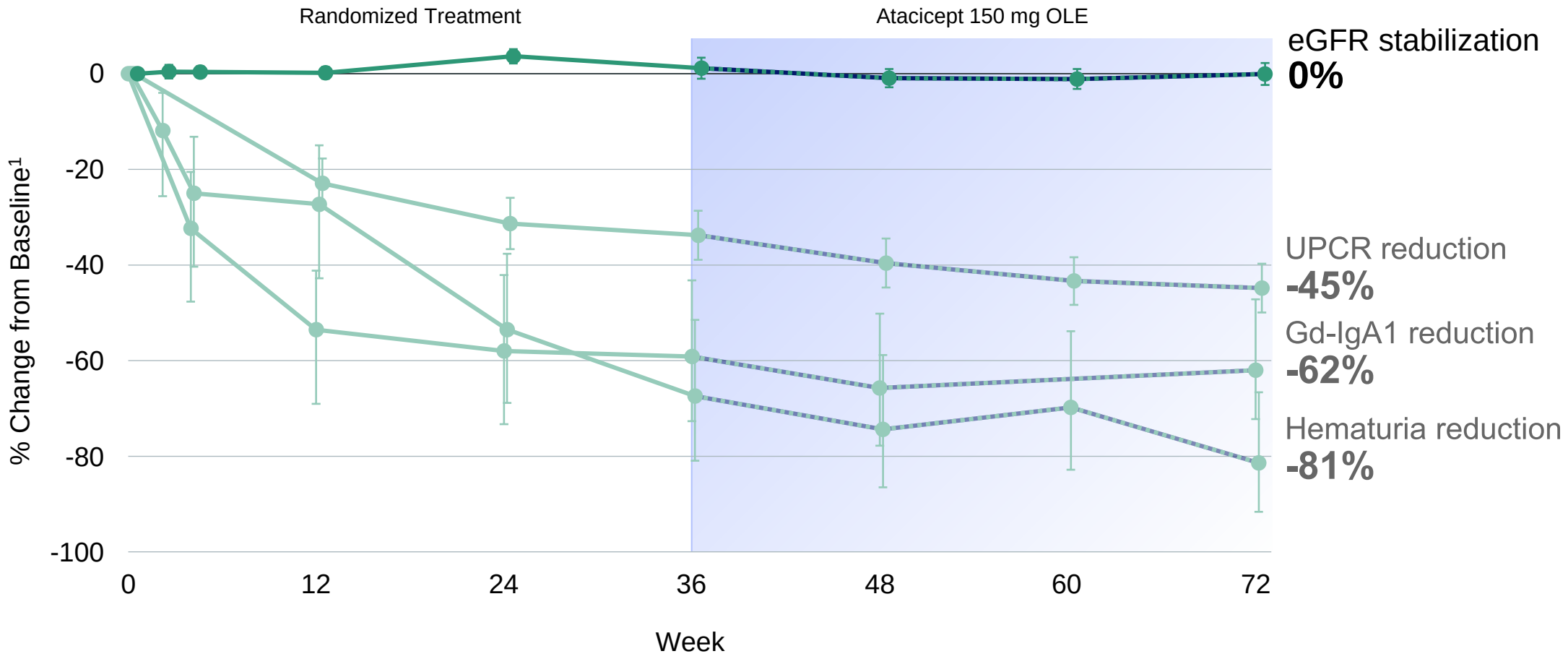
Data from participants originally randomized to any atacicept dose during the double-blind period in the ITT population.

Atacicept ORIGIN Phase 2b 72 Week Results Are Consistent With a Disease Modifying IgAN Profile



1. Gd-IgA1, UPCR, and eGFR: mean ± SE % change from baseline; hematuria: change from baseline in percentage of participants with hematuria at each visit out of those with baseline hematuria.
Data from participants originally randomized to any atacicept dose during the double-blind period in the ITT population.

Conclusions

- Participants treated with atacicept for 72 weeks demonstrated:
  - Consistent and sustained reductions in Gd-IgA1, hematuria and UPCR
  - Consistent and stable eGFR
- In aggregate, these data may provide evidence of long-term, comprehensive IgAN disease modification
- Participants switched from placebo to atacicept demonstrated similar results (Gd-IgA1, hematuria, UPCR, eGFR) to those originally randomized to atacicept during the first 36 weeks of ORIGIN 2b
- The cumulative safety profile is consistent with that observed during the randomized 36 weeks of ORIGIN 2b
- Week 72 data provide additional confidence in the ongoing ORIGIN 3 study

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