Atacicept Reduces Hematuria and Serum Gd-IgA1, Both Associated with Long-term Renal Outcomes in IgAN: 36 Week Results from the Phase 2b ORIGIN Study

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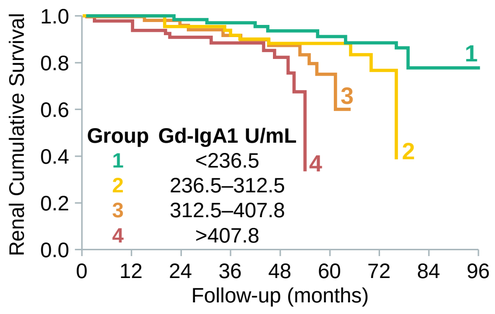
Introduction

- IgA nephropathy (IgAN) is the most common primary glomerulonephritis and a significant contributor to ESRD worldwide[1,2]
- Hematuria is an indicator of IgAN activity representing active glomerulonephritis and resolution is associated with improved renal outcomes[3,4]

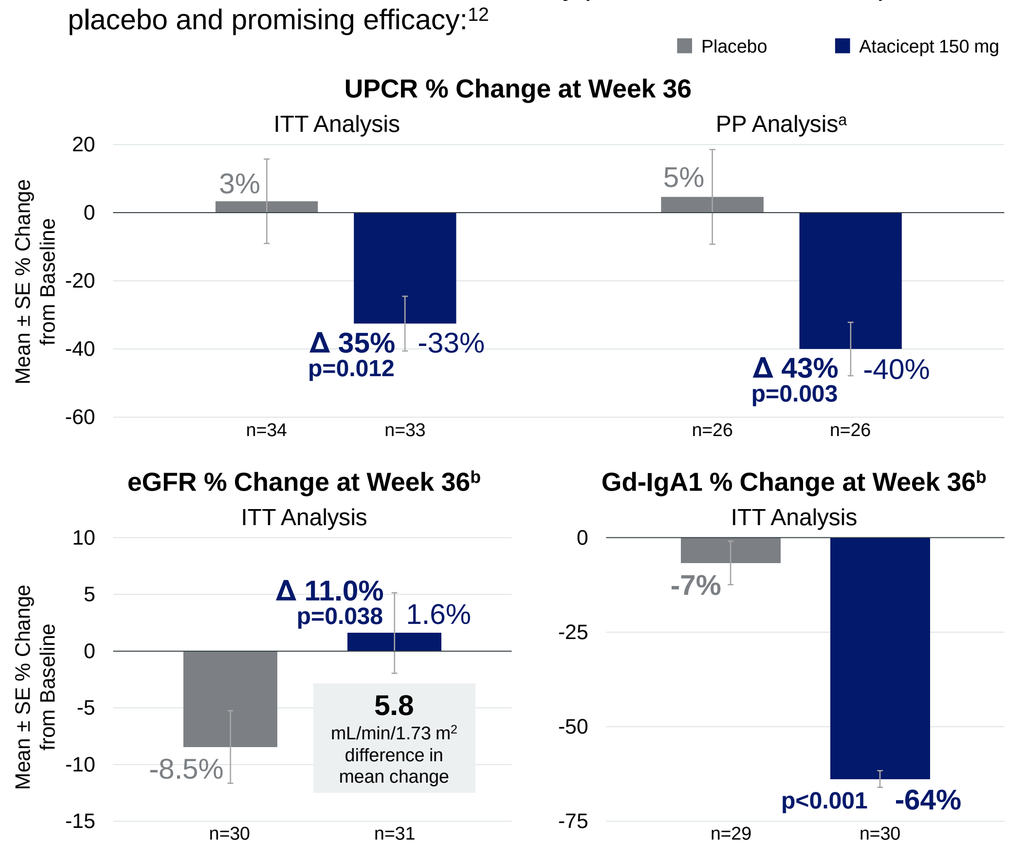


- Elevated serum levels of Gd-IgA1 are recognized as an autoantigen by anti-Gd-IgA1 autoantibodies, forming immune complexes that lead to renal damage in IgAN[5-7]
- High Gd-IgA1 levels are associated with greater risk of renal function deterioration, ESRD, and death[8]
- Gd-IgA1 reduction has been correlated with hematuria remission[9]
- Gd-IgA1 and anti-Gd-IgA1 production by B cells and plasma cells is driven by the BAFF and APRIL signaling pathway[10,11]

APRIL = A PRoliferation-Inducing Ligand; BAFF = B-cell Activating Factor; ESRD = end-stage renal disease; Gd-IgA1 = galactose-deficient immunoglobulin A1.

Atacicept: Dual BAFF/APRIL Inhibitor

- Atacicept is a fully humanized fusion protein composed of TACI, a native receptor for BAFF and APRIL, and the Fc portion of IgG, in clinical development for weekly subcutaneous self-administration at home
- The Phase 2b ORIGIN study, a randomized, double-blind, placebo-controlled clinical trial evaluating atacicept in IgAN, met its primary endpoint
  - Week 36 results showed a similar safety profile between atacicept and placebo and promising efficacy:[12]



p-values, % changes from baseline, and treatment differences were analyzed using FDA-endorsed mixed-effects modeling which takes into account effects of baseline UPCR and eGFR. a. Per-protocol (PP) analysis identified and excluded protocol violations at week 36 data cut prior to unblinding; b. n numbers show participants with available data at week 36; data for all 34 and 33 participants receiving placebo and atacicept 150 mg, respectively, were included in model.
Fc = fragment crystalline; TACI = transmembrane activator and calcium-modulator and cyclophilin ligand interactor.

- A pivotal Phase 3 trial is evaluating the effect of atacicept 150 mg vs placebo on proteinuria and renal function preservation in IgAN (WCN24-AB-1414)

Objectives

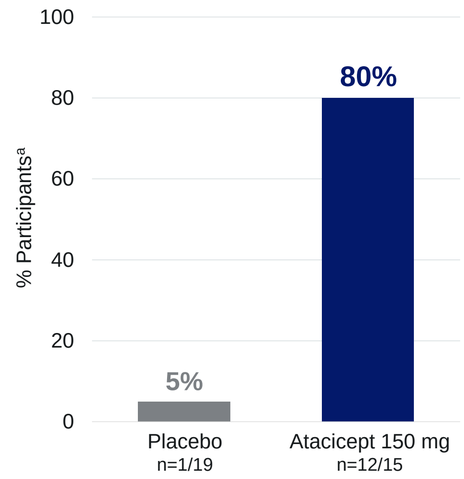
- To evaluate changes in hematuria grade and serum Gd-IgA1 quartiles over 36 weeks with atacicept 150 mg vs placebo
- To evaluate the association between changes in Gd-IgA1 and hematuria grade at week 36

Methods

- Microscopic hematuria
  - Evaluated on urine dipstick; participants with hematuria 1+ or higher at baseline were evaluated for improvement at week 36
- Serum Gd-IgA1
  - Assessed at baseline, 4, 12, 24, and 36 weeks using a solid phase sandwich enzyme-immunosorbent assay (ELISA) kit (Immuno-Biological Laboratories, Inc., Minneapolis, MN) by a central laboratory at Medpace (Cincinnati, OH) and classified into intra-study quartiles using cutoffs derived from baseline Gd-IgA1 values from the ORIGIN population
- Relationship between Gd-IgA1 % change from baseline and hematuria grade at week 36
  - Evaluated using Spearman's correlation method

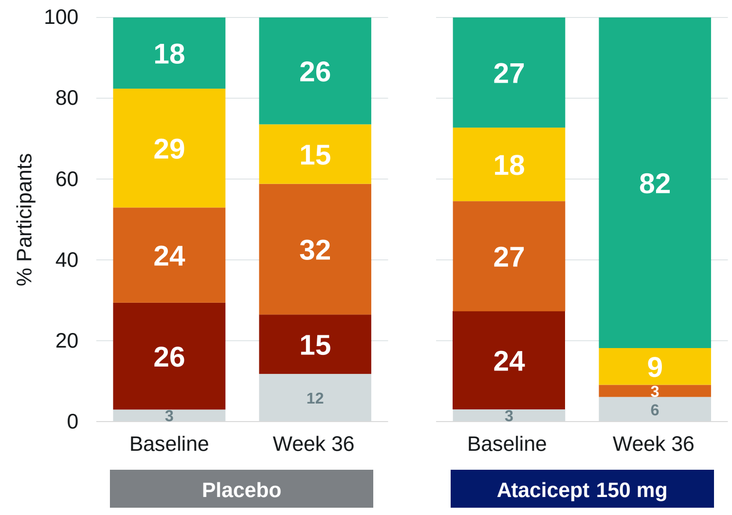
Results

Hematuria Improvement and Lower Gd-IgA1 Quartiles at Week 36



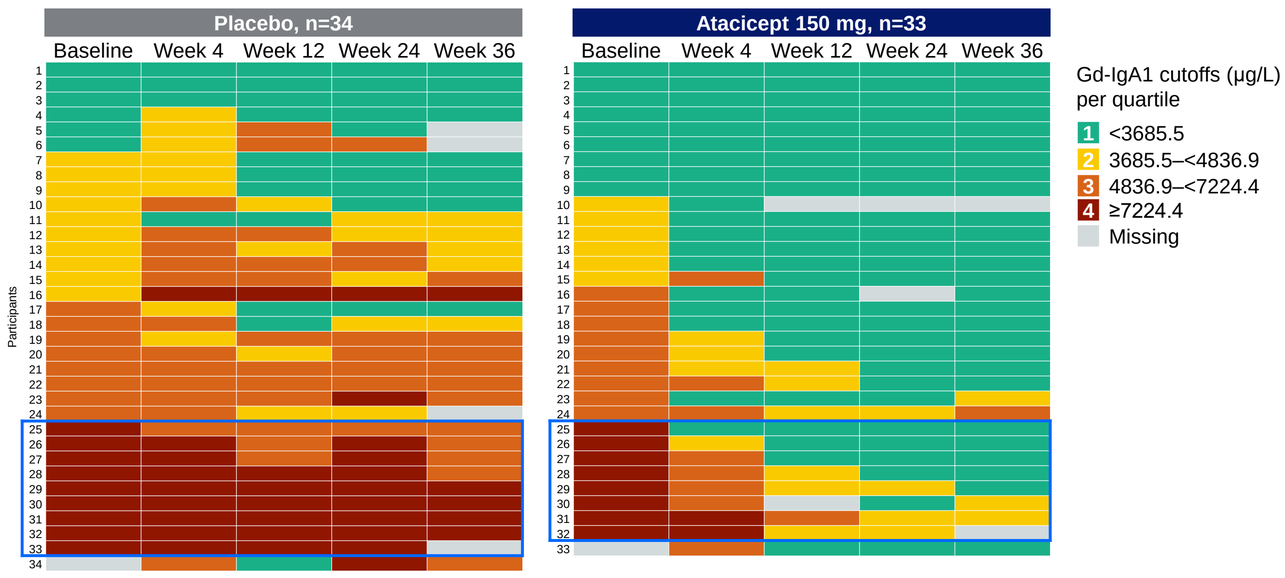
a. Percentages calculated using number of participants with hematuria 1+ or higher at baseline as denominator. Hematuria grades: negative/trace = ≤0.03 mg/dL; 1+ = 0.06–0.1 mg/dL; 2+ = 0.2–0.5 mg/dL; 3+ = 1.0–1.1 mg/dL.

- More participants with hematuria 1+ or higher at baseline improved to negative or trace on atacicept than placebo at week 36



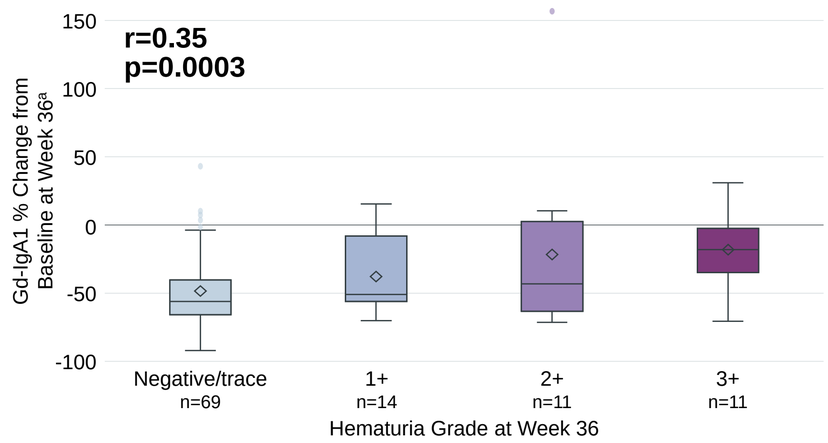
- Atacicept 150 mg led to steady Gd-IgA1 reductions to the lowest quartile, 1, at 36 weeks in 27/33 (82%) participants
- Most participants on placebo transiently increased or decreased by 1 quartile

Lower Gd-IgA1 Quartiles Through Week 36



- In the placebo group, all 9 participants with the highest baseline Gd-IgA1 quartile, 4, remained in quartile 3 or 4 at the last nonmissing visits
- In the atacicept 150 mg group, all 8 participants with the highest baseline quartile had reductions to quartile 1 or 2 at the last nonmissing visits

Greater Gd-IgA1 Reduction Was Associated With Lower Grades of Hematuria at Week 36



a. Boxes show median (interquartile range); whiskers show quartile 1 – (1.5 x interquartile range) and quartile 3 + (1.5 x interquartile range); diamonds show mean; circles show outliers; b. Hematuria grades: negative/trace = ≤0.03 mg/dL; 1+ = 0.06–0.1 mg/dL; 2+ = 0.2–0.5 mg/dL; 3+ = 1.0–1.1 mg/dL.

Conclusions

- In addition to clinically and statistically significant effects on renal function, atacicept 150 mg achieved an improvement in hematuria and a durable and significant Gd-IgA1 reduction over 36 weeks
- Hematuria improved to negative or trace in most participants receiving atacicept 150 mg (80% vs 5% placebo)
- Regardless of baseline serum Gd-IgA1 quartile, the vast majority of participants receiving atacicept 150 mg for 36 weeks achieved Gd-IgA1 reductions to the lowest quartiles, which has been associated with improved renal clinical outcomes
- Greater Gd-IgA1 reduction was associated with lower grades of hematuria at week 36
- These results provide further evidence supporting atacicept as a potential disease-modifying treatment for IgAN

References: 1. Lai KN, et al. Nat Rev Dis Primers 2016;2:16001; **2.** Pitcher D, et al. Clin J Am Soc Nephrol 2023;18:727-38; **3.** Sevillano AM, et al. J Am Soc Nephrol 2017;28:3089-99; **4.** Yu G, et al. Am J Kidney Dis 2020;76:90-9; **5.** Wyatt RJ, Julian BA. N Engl J Med 2013;368:2402-14; **6.** Suzuki H, et al. J Clin Invest 2009;119:1668-77; **7.** Berthoux F et al. J Am Soc Nephrol 2012;23:1579-87; **8.** Zhao N et al. Kidney Int 2012;82:790-6; **9.** Suzuki Y, et al. Clin Exp Nephrol 2014;18:770-7; **10.** MacPherson AJ, et al. Mucosal Immunol 2008;1:11-22; **11.** Zhai YL, et al. Medicine (Baltimore) 2016;95:e3099; **12.** Lafayette R, et al. ERA 2023, late breaking clinical trial oral presentation, June 17, 2023.

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SCAN FOR MORE INFO

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