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SA-PO887

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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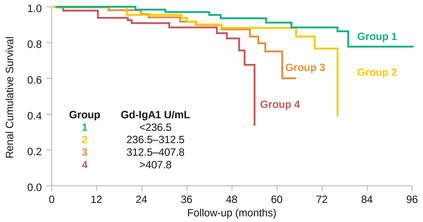
Introduction

- IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide, with up to 50% of patients progressing to ESRD or death within 20 years[1,2]
- Hematuria is an important indicator of IgAN activity representing active inflammation of glomeruli (glomerulonephritis), and resolution is associated with improved renal outcomes[3,4]
- IgAN is characterized by elevated serum levels of galactose-deficient IgA1 (Gd-IgA1), anti-Gd-IgA1 autoantibodies, and immune complexes that lead to kidney damage[5-7]
- High Gd-IgA1 levels are associated with greater risk of renal function deterioration, ESRD, and death[8]

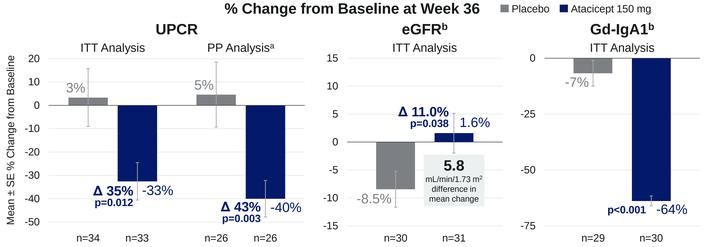


- Reduction of Gd-IgA1 has been correlated with remission of hematuria[9]
- Gd-IgA1 production is driven by the role of the B Lymphocyte Stimulator (BLyS, also known as BAFF) and A PRoliferation-Inducing Ligand (APRIL) signaling pathway in the maturation, differentiation, and effector function of B cells and plasma cells[10,11]

Atacicept: Dual Inhibitor of BLyS (BAFF) and APRIL

- Atacicept is a dual anti-BLyS/APRIL fusion protein in clinical development for IgAN treatment; by targeting upstream processes, atacicept has disease-modifying potential for treating IgAN
- The Phase 2b ORIGIN study is a randomized, double-blind, placebo-controlled clinical trial evaluating atacicept in IgAN that met its primary endpoint
- A pivotal Phase 3 trial is evaluating the effect of atacicept 150 mg vs placebo on proteinuria and renal function preservation in IgAN (Barratt J, et al. poster INFO17-TH)

- The week 36 results of the Phase 2b ORIGIN study were recently reported, including a similar safety profile between atacicept and placebo through 36 weeks and promising efficacy:[12]



p-values, percentage changes from baseline, and treatment differences were computed 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.

Objectives

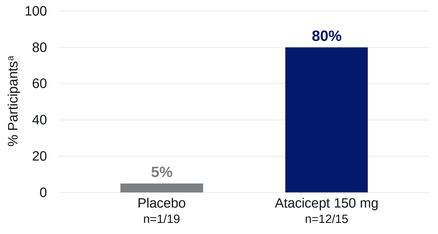
- To evaluate changes in hematuria level and serum Gd-IgA1 quartiles over 36 weeks with atacicept 150 mg, the dose being evaluated in a pivotal Phase 3 study, vs placebo
- To evaluate the association between changes in Gd-IgA1 and changes in hematuria level at week 36

Methods

- Microscopic hematuria was evaluated on urine dipstick; participants with hematuria 1+ or higher at baseline were evaluated for improvement at week 36
- At baseline, 4, 12, 24, and 36 weeks, serum Gd-IgA1 values were assessed 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
- The relationship between percentage change from baseline in Gd-IgA1 and hematuria level at week 36 was evaluated using Spearman's correlation method

Results

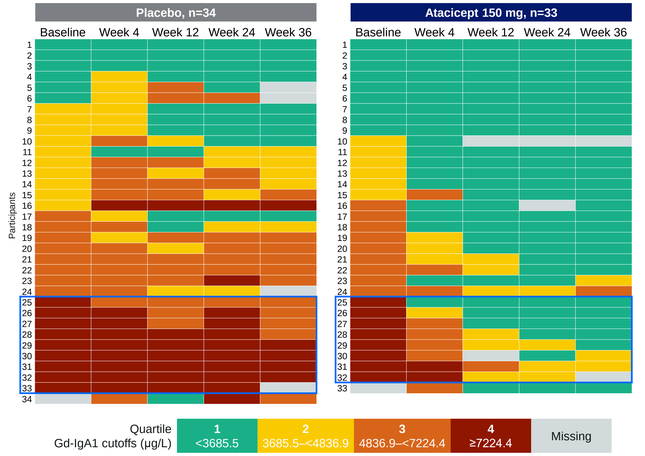
Hematuria Improvement at Week 36



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

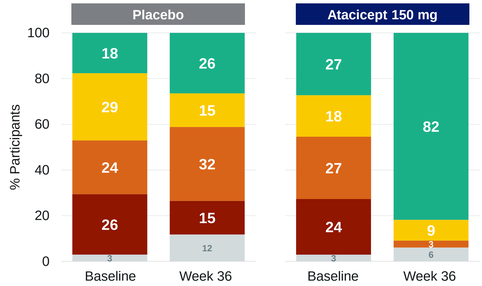
a. Percentages calculated using number of participants with hematuria 1+ or higher at baseline as denominator. Hematuria grades: negative/trace = ≤0.03 mg/dL; 1+ = 0.06–0.1 mg/dL; 2+ = 0.2–0.5 mg/dL; 3+ = 1.0–1.1 mg/dL.

Lower Gd-IgA1 Quartiles through Week 36



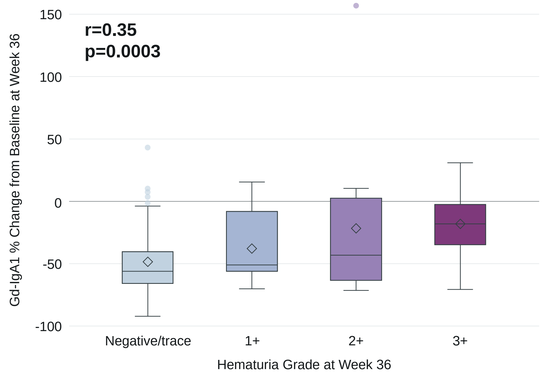
- In the placebo group, all 9 participants with the highest baseline Gd-IgA1 quartile, 4, remained in quartile 3 or 4 at the last nonmissing visits
- In the atacicept 150 mg group, all 8 participants with the highest baseline quartile had reductions to quartile 1 or 2 at the last nonmissing visits

Shifts to Lower Gd-IgA1 Quartiles 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, while most participants on placebo transiently increased or decreased by 1 quartile

Gd-IgA1 Correlated with Hematuria at Week 36



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
- Gd-IgA1 reduction was correlated with lower hematuria at week 36 (r=0.35, p=0.0003)
- 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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