A phase 2b, randomized, double-blind, placebo-controlled, clinical trial of atacicept for treatment of IgA nephropathy

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Richard Lafayette[1], Sean Barbour[2], Rubeen Israni[3], Xuelian Wei[4], Necmi Eren[5], Jürgen Floege[6], Vivekanand Jha[7,8,9], Sung Gyun Kim[10], Bart Maes[11], Richard K.S. Phoon[12], Harmeet Singh[13], Vladimír Tesař[14], Celia J.F. Lin[15] and Jonathan Barratt[16]

[1]Division of Nephrology, Department of Medicine, Stanford University, Stanford, California, USA; [2]Division of Nephrology, Department of Medicine, The University of British Columbia, Vancouver, Canada; [3]Clinical Development, Vera Therapeutics, Inc., Brisbane, California, USA; [4]Biostatistics, Vera Therapeutics, Inc., Brisbane, California, USA; [5]Department of Nephrology, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey; [6]Department of Nephrology and Clinical Immunology, Rheinisch Westfälische Technische Hochschule, Aachen University Hospital, Aachen, Germany; [7]The George Institute for Global Health India, New Delhi, India; [8]Faculty of Medicine, School of Public Health, Imperial College, London, UK; [9]Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, India; [10]Hallym University Sacred Heart Hospital, Anyang, Korea; [11]Department of Nephrology, AZ Delta, Roeselare, Belgium; [12]Westmead Clinical School, The University of Sydney, Sydney, Australia; [13]Western Nephrology, Arvada, Colorado, USA; [14]Department of Nephrology, First Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic; [15]Medical, Vera Therapeutics, Inc., Brisbane, California, USA; and [16]Department of Cardiovascular Sciences, College of Medicine Biological Sciences and Psychology, University of Leicester, Leicester, UK

Atacicept is a first-in-class, dual anti-B-cell Activation Factor–A Proliferation-Inducing Ligand fusion protein in clinical evaluation for treatment of IgA nephropathy. To compare efficacy and safety of atacicept versus placebo in patients with IgAN, this randomized, double-blind, placebo-controlled phase 2b clinical trial ORIGIN enrolled 116 individuals with biopsy-proven IgA nephropathy. Participants were randomized to atacicept 150, 75, or 25 mg versus placebo once weekly for up to 36 weeks. Primary and key secondary endpoints were changes in urine protein creatinine ratio based on 24-hour urine collection at weeks 24 and 36, respectively, in the combined atacicept 150 mg and 75 mg group versus placebo. The primary endpoint was met at week 24 as the mean urine protein creatinine ratio was reduced from baseline by 31% in the combined atacicept group versus 8% with placebo, resulting in a significant 25% reduction with atacicept versus placebo. At week 36, the key secondary endpoint was met as the mean urine protein creatinine ratio reduced from baseline by 34% in the combined atacicept group versus a 2% increase with placebo, resulting in a significant 35% reduction with atacicept versus placebo. The reduction in proteinuria was accompanied by stabilization in endpoint eGFR with atacicept compared to a decline with placebo at week 36, resulting in significant between-group geometric mean difference of 11%, approximating an absolute difference of 5.7 mL/min/1.73m^2. Endpoint galactose deficient IgA1 levels significantly decreased from baseline by 60% versus placebo. The safety profile of atacicept was like placebo. Thus, our results provide evidence to support a pivotal, phase 3 study of atacicept in IgA nephropathy.

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KEYWORDS: B-cell modulator; glomerular disease; IgA nephropathy

Lay Summary

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide and a significant contributor to the global burden of kidney failure, requiring dialysis or transplant. IgAN is an autoimmune disease where antibodies are produced against an aberrant, galactose-deficient IgA1 (Gd-IgA1). Current treatment of IgAN, which includes renin-angiotensin system inhibition, does not target the early steps underlying the pathology of IgAN. Atacicept is a fusion protein that is able to bind and neutralize both B-cell Activating Factor and A PRoliferation-Inducing Ligand *in vitro*. These ligands play an important role in the maturation, function, and survival of B cells and plasma cells. In the ORIGIN phase 2b study in patients with IgAN, atacicept improved kidney endpoints with a reduction of proteinuria and stabilization of estimated glomerular filtration rate while reducing serum Gd-IgA1, providing evidence that atacicept has the potential to target and improve the underlying process of IgAN.

Correspondence: *Jonathan Barratt, Department of Cardiovascular Sciences, College of Medicine Biological Sciences and Psychology, University of Leicester, University Road, Leicester LEI 7RH, UK. E-mail: jb81@leicester.ac.uk*

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IgA nephropathy (IgAN) is the most frequent biopsy-proven primary glomerular disease,[1,2] with a worldwide incidence of at least 2.5 per 100,000 people per year in adults.[3] As most patients with IgAN are diagnosed before the age of 40 years,[4–6] outcome data that typically span 10 to 15 years inherently underestimate the risk of kidney failure in this population. Outcome data showing 15% to 20% of patients with IgAN progress to end-stage kidney disease within 10 years[7] create the perception that IgAN has a low risk of progression to kidney failure. Several studies have suggested that baseline characteristics, including proteinuria and ethnicity, may be associated with increased risk of progression. In the Validation Study of the Oxford Classification of IgAN (VALIGA) study, which evaluated a broad European population with IgAN, there was a clear risk of progression related to baseline level of proteinuria even in patients with low-grade proteinuria between 0.5 and 1.0 g/d.[8] In a UK cohort with biopsy-proven IgAN and proteinuria >0.5 g/d or estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2, 50% of patients progressed to kidney failure or death within 20 years.[9] On the basis of the age and eGFR of patients at the time of diagnosis within this cohort, it was estimated that almost all patients would have developed kidney failure within their lifetime unless there was a rate of loss of eGFR <1 ml/min per year. The progression rate in some ethnicities, specifically the Asian population, may be more rapid than in Caucasians.[10,11]

A histopathologic hallmark of IgAN is accumulation of poorly *O*-galactosylated IgA1 (galactose-deficient IgA1 [Gd-IgA1]) in the glomerular mesangium, either alone or in combination with IgG and/or IgM.[12] Sampling of the serum and plasma of patients with IgAN has confirmed the presence of elevated levels of IgA-containing immune complexes containing Gd-IgA1.[13] Circulating Gd-IgA1–containing immune complexes have been shown to be target antigens for IgG antibodies with specificity for the *O*-glycans of the IgA1 hinge region.[14] Thus, IgAN appears to be an autoimmune disease with Gd-IgA1 acting as the autoantigen. The cytokines B-cell Activating Factor (BAFF) and A PRoliferation-Inducing Ligand (APRIL) are members of the tumor necrosis factor family that play an important role in the maturation, function, and survival of B cells and plasma cells, including IgA class switch recombination. Dysregulation of BAFF and APRIL signaling has been associated with elevated serum levels of Gd-IgA1, anti–Gd-IgA1 autoantibodies, immune complex formation, and recruitment of inflammatory cells to the glomeruli, all central to IgAN pathogenesis.[15,16] Furthermore, BAFF and APRIL levels are elevated in patients with IgAN and correlate with disease severity, both clinically and pathologically.[16,17]

Current treatment of IgAN, which includes renin-angiotensin system inhibition and potentially newer treatments, such as sodium-glucose cotransporter-2 inhibitors, does not target the early steps underlying the pathology of IgAN. Atacicept is a fusion protein that is able to bind and neutralize BAFF and APRIL. In the phase 2a JANUS study in patients with IgAN, atacicept reduced serum Gd-IgA1 and proteinuria compared with placebo, providing evidence that atacicept has the potential to target the underlying pathology of IgAN.[18] The objectives of the ORIGIN phase 2b study are to evaluate the efficacy and safety of atacicept in patients with IgAN and persistent proteinuria who remain at high risk of disease progression despite being on a stable prescribed regimen of renin-angiotensin-aldosterone system inhibitor. The primary and key secondary end points of the trial, proteinuria reduction at weeks 24 and 36, respectively, were chosen on the basis of the association between reduction in proteinuria at 6 to 9 months with outcomes of doubling of serum creatinine, kidney failure, and death in patients with IgAN and the regulatory precedence of accelerated or conditional marketing approval based on proteinuria reduction at 9 months.[19] Reduction of eGFR was chosen as an exploratory end point to inform the sample size of the phase 3 trial. Here, we report the results of a large global phase 2b randomized, double-blind, placebo-controlled trial of a B-cell modulatory pathway in IgAN.

METHODS

Trial design and oversight

The ORIGIN study is an ongoing, randomized, international, multicenter, double-blind, placebo-controlled, phase 2b trial (ClinicalTrials.gov: NCT04716231). The double-blind, placebo-controlled portion of the study is complete. The study was conducted on an outpatient basis and enrolled participants from 65 centers in 13 countries. Participants received blinded treatment with atacicept 150, 75, or 25 mg, or placebo, self-administered at home by s.c. injection once per week for 36 weeks. Study assessments were performed at screening, day 1 (baseline), and weeks 2, 4, 12, 24, and 36 in the double-blind period of the study. Study assessments included 24-hour urine collection (for total urine protein and urine protein-to-creatinine ratio [UPCR]) at day 1 and weeks 12, 24, and 36, and eGFR based on serum creatinine at all visits. Gd-IgA1 was evaluated at weeks 4, 12, 24, and 36 and determined by a solid phase sandwich enzyme-linked immunosorbent assay (Immuno-Biological Laboratories, Inc.) by a central laboratory at Medpace Reference Labs. At the week 36 visit following completion of all study assessments, participants were given the option to switch from double-blind treatment to open-label treatment with atacicept 150 mg for an additional 60 weeks. Study assessments during this open-label extension period will be conducted at weeks 38, 40, 48, 60, 72, 84, and 96. All participants will be assessed for safety follow-up for an additional 26 weeks after the last administration of study treatment. Further information on the assessments is available in the Supplementary Methods. After the last participant completed the week 36 visit, the study was unblinded.

The protocol was approved by the institutional review board at each participating center. All participants provided written informed consent. The trial was performed in accordance with the principles of the Declaration of Helsinki.

Vera Therapeutics led the study design, data collection, and data analysis. All authors assisted in data interpretation, writing of the report, and reviewing the manuscript.

Patient population

Eligible male or female participants (aged ≥18 years) had biopsy-proven IgAN within 10 years before screening, 24-hour urine

protein >0.75 g per day, or UPCR >0.75 g/g despite at least 12 weeks on a maximally tolerated, stable dose of renin-angiotensin-aldosterone system inhibitor, as determined by the investigator, and eGFR ≥30 ml/min per 1.73 m^2. They were required to have systolic blood pressure of ≤150 mm Hg and diastolic blood pressure of ≤90 mm Hg at screening. We excluded participants with secondary causes of IgAN (eg, liver cirrhosis and IgA vasculitis). Other exclusion criteria included evidence of rapidly progressive glomerulonephritis (loss of ≥50% of eGFR within 3 months of screening) or evidence of nephrotic syndrome within 6 months of screening (serum albumin <30 g/L in association with UPCR >3.5 mg/mg). Detailed inclusion and exclusion criteria are provided in the Supplementary Methods.

Demographics were collected at screening as reported by the participant.

Randomization and blinding

Participants were randomly assigned (2:2:1:2) to receive either atacicept 150, 75, or 25 mg, or a placebo containing the excipients used in atacicept formulation. The atacicept 25-mg dose was included in the study to provide data on safety and biomarkers; thus, the 25-mg group was not powered to inform efficacy. Participants were centrally assigned to randomized study treatment using an interactive web response system, which stratified by screening eGFR (≥30 to <45 ml/min per 1.73 m^2 and ≥45 ml/min per 1.73 m^2). This was a double-blind study. The labeling configuration of the prefilled syringes resulted in the active and placebo being identical in appearance. In case of an emergency, the investigator had the sole responsibility for determining if unmasking of a participant's treatment assignment was warranted to provide appropriate medical care. Certain laboratory results (serum IgG, IgA, and IgM) that could be indicative of treatment allocation were monitored by a central laboratory but were not reported to investigative sites or any blinded personnel. The only unblinded personnel were the independent data monitoring committee and the limited, unmasked team responsible for the conduct of the prespecified, interim analyses; members of this team were not allowed to participate in study-related activities once gaining access to unmasked information.

Outcomes

The primary outcome was the change from baseline in 24-hour UPCR at week 24 in the combined atacicept 150- and 75-mg group compared with placebo. The secondary outcome was the change in UPCR at week 36 in the combined atacicept 150- and 75-mg group as well as in individual atacicept doses versus placebo. Other prespecified end points of interest were change in UPCR at week 12, Gd-IgA1 levels, and change in eGFR at weeks 12, 24, and 36. The primary outcome was assessed in a prespecified analysis (i.e., primary end point analysis at week 24) after all participants had completed the week 24 visit or discontinued treatment early. The secondary and other prespecified outcomes were assessed in the prespecified analysis (i.e., end of the double-blind period analysis at week 36) after all participants had completed the week 36 visit or discontinued treatment early. Safety outcomes included change in serum immunoglobulin levels, treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to treatment discontinuation, and prespecified adverse events of special interest. Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 24.0). Investigators indicated the relatedness of adverse events to study medications in a binary manner (yes or no).

Statistical analysis

A sample size of 25 participants in the placebo group and a combined total of 50 participants in the atacicept 150- and 75-mg groups provides at least 80% power to test that the true relative treatment effect on proteinuria, for combined atacicept versus placebo, is at least 28% at week 24. In this sample size calculation, the SD of natural logarithm-transformed change from baseline in UPCR was assumed to be 0.55. Adjusting for a 15% dropout rate, enrollment of 30 participants was the target in each of the atacicept 150 mg, atacicept 75 mg, and placebo groups to ensure 25 participants completed week 24 in each of these groups. The sample size of 15 for the atacicept 25-mg group was chosen to provide safety and biomarker information and was not based on statistical considerations.

The primary efficacy analysis set was the full analysis set (FAS) population, including all randomized participants who received at least 1 dose of study treatment (atacicept or placebo), and all efficacy analyses were based on the randomized treatment. The safety population included all randomized participants who received at least 1 dose of study drug, and all safety analyses were based on the actual treatment received. For both analyses, the FAS population and safety population were equivalent. Prespecified sensitivity analyses for the primary and key secondary efficacy outcome were based on the per-protocol (PP) population, which included all participants in the FAS population who did not have any clinically important protocol deviations at the corresponding interim analysis. The week 24/36 PP populations were identified by a blinded third-party Contract Research Organization before each interim analysis. All statistical analyses were performed by using SAS (version 9.4 or later).

The primary analysis of proteinuria assessed UPCR data via a mixed-effects model for repeated measures (MMRM) analysis. Change from baseline in natural log-transformed UPCR was the dependent variable. Change from baseline in natural log-transformed UPCR mathematically approximates relative change in UPCR on original scale. Effects for randomized treatment, natural log-transformed baseline value, baseline eGFR category, visit (as a categorical variable), and treatment-by-visit interaction were included as independent fixed effects, and participant was included as a random effect. The primary comparison evaluated the mean difference between the combined 150- and 75-mg atacicept group versus the placebo group at week 24 using the FAS population and week 24 data cut. A separate MMRM analysis was conducted to compare change from baseline in UPCR in each individual atacicept dose group versus placebo at week 24 using the FAS population and week 24 data cut. Analyses were performed on log-transformed data, and results were back-transformed to present treatment effects on the ratio scale and displayed as percentage change from baseline. Missing data were assumed as missing at random and were implicitly imputed by MMRM. No other missing imputation procedure was performed. Both MMRM analyses were repeated to compare the combined 150- and 75-mg group versus placebo and to compare each individual atacicept dose group versus placebo at week 36 using the week 36 data cut. For the sensitivity analyses of UPCR at weeks 24 and 36, the MMRM analysis was repeated based on the corresponding PP population.

The same MMRM analysis (as described for the primary end point) was used to analyze the mean change from baseline over time for eGFR, Gd-IgA1, and IgA, IgG, and IgM levels using the FAS population and week 36 data cut. For eGFR, the results were reported as percentage change from baseline and further transformed into the absolute mean change from baseline for interpretation. Further information on the assessment of eGFR is provided in the Supplementary Methods.

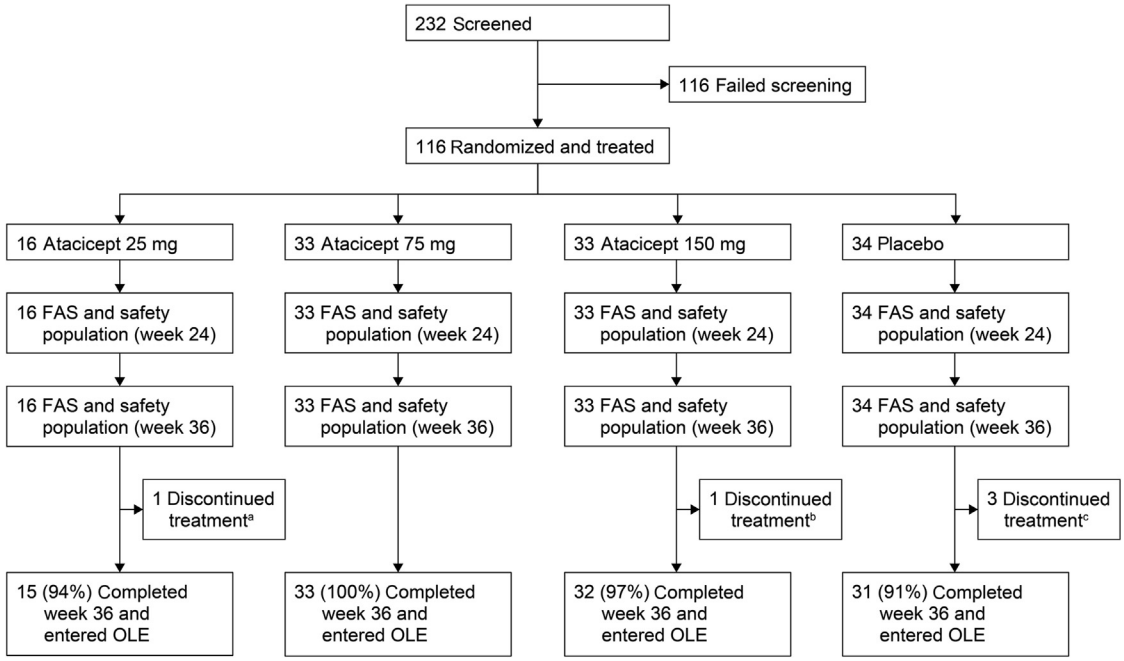


Figure 1 | Study disposition. A total of 210 participants were screened and 22 were rescreened for a total of 232 screens. [a]Discontinued to pursue elective surgery. [b]Discontinued because of positive hepatitis B DNA and adverse event (n = 1). [c]Initiated prohibited medication for concomitant disease (n = 1) and discontinued because of plan to start prohibited medication for concomitant disease (n = 1) and adverse event (n = 1). FAS, full analysis set; OLE, open-label extension.

Statistical significance for the primary end point was assessed at 2-sided 0.05 level. All other *P* values presented were 2 sided, nominal, and without adjustment of multiplicity. TEAEs were summarized by descriptive statistics, including data collected in the double-blind period at the time of the week 36 data cut.

RESULTS

Study participants

Between May 2021 and June 2022, 210 participants were screened. Of these, 116 participants were randomized and treated (82 receiving atacicept [33, 33, and 16 at 150, 75, and 25 mg, respectively]; and 34 receiving placebo; Figure 1). A total of 111 participants (80 [98%] on atacicept; 31 [91%] on placebo) completed 36 weeks of treatment in the double-blind period and continued to receive atacicept 150 mg in the open-label extension period.

In the overall study population, participants were primarily men (59%) and either White (53%) or Asian (44%), with a mean age of 39 years (Table 1). Mean eGFR at baseline was 63 ml/min per 1.73 m^2, and mean UPCR at baseline was 1.6 g/g. The inclusion criteria required eGFR ≥30 ml/min per 1.73 m^2 at screening; however, there were 4 participants who had a decrease in eGFR to <30 ml/min per 1.73 m^2 by study day 1 and, thus, are noted as having chronic kidney disease stage 4 at baseline.

Efficacy

The primary end point at week 24 was met: mean UPCR was reduced from baseline by 31% in the combined atacicept 150- and 75-mg group compared with 8% in the placebo group, resulting in a 25% reduction versus placebo at 24 weeks (95% confidence interval, 1.74%–43.01%; $P = 0.037$; Figure 2a; Supplementary Table S1). At week 24, the atacicept 150-mg group was the only individual treatment group that showed a statistically significant difference in reduction of UPCR from baseline compared with placebo, 33% compared with 7%, resulting in a 28% reduction versus placebo at 24 weeks ($P = 0.047$; Figure 2b; Supplementary Table S2). The atacicept 75-mg group showed a 28% reduction in UPCR, leading to a 22% reduction versus placebo (*P* = nonsignificant). The decline in UPCR was seen as early as 12 weeks with atacicept, most pronounced in the 150-mg group.

The key secondary end point at week 36 was met: mean UPCR was reduced from baseline by 34% in the combined atacicept 150- and 75-mg group compared with a 2% increase in the placebo group, resulting in a 35% reduction with atacicept versus placebo (95% confidence interval, 13.03%–51.53%; $P = 0.0042$). There was a greater difference in reduction of UPCR from baseline across the combined atacicept 150- and 75-mg group versus the placebo group at 36 weeks compared with 24 weeks. Mean UPCR was reduced from baseline by 33% in the atacicept 150-mg group compared with a 3% increase in the placebo group, resulting in a 35% reduction at 36 weeks with atacicept versus placebo ($P = 0.012$; Supplementary Table S2). Treatment with atacicept 75 mg resulted in a 34% reduction in UPCR, translating to a 36% reduction versus placebo ($P = 0.0085$).

Results of the FAS population analyses were supported by prespecified analyses in the PP population for the secondary

Table 1 | Demographics and baseline characteristics

Variable	Atacicept				Placebo (n = 34)	Overall (n = 116)
	25 mg (n = 16)	75 mg (n = 33)	150 mg (n = 33)	Combined 150 and 75 mg (n = 66)		
Age, yr, mean (SD)	40 (15)	41 (13)	38 (11)	40 (12)	39 (13)	39 (13)
Sex, n (%)						
Male	9 (56)	19 (58)	22 (67)	41 (62)	19 (56)	69 (59)
Female	7 (44)	14 (42)	11 (33)	25 (38)	15 (44)	47 (41)
Race, n (%)						
White	7 (44)	12 (36)	17 (52)	29 (44)	26 (76)	62 (53)
Asian	7 (44)	20 (61)	16 (48)	36 (55)	8 (24)	51 (44)
Native Hawaiian or Other Pacific Islander	0	1 (3)	0	1 (2)	0	1 (1)
Other	1 (6)	0	0	0	0	1 (1)
Not reported	1 (6)	0	0	0	0	1 (1)
Ethnicity, n (%)						
Hispanic or Latino	1 (6)	2 (6)	1 (3)	3 (5)	0	4 (3)
Non-Hispanic or Latino	15 (94)	30 (91)	32 (97)	62 (94)	34 (100)	111 (96)
Unknown	0	1 (3)	0	1 (2)	0	1 (1)
Time from biopsy to screening, yr, mean (SD)	1.7 (1.6)	3.4 (2.8)	3.3 (3.4)	3.4 (3.1)	2.1 (2.4)	2.8 (2.8)
Blood pressure, mm Hg, mean (SD)						
Systolic	127 (8)	127 (13)	127 (12)	127 (13)	127 (13)	127 (12)
Diastolic	81 (8)	80 (9)	80 (9)	80 (9)	77 (8)	79 (9)
24-h UPCR, g/g						
Mean (SD)	1.6 (0.8)	1.7 (0.9)	1.7 (1.0)	1.7 (0.9)	1.6 (0.8)	1.6 (0.9)
Median (IQR)	1.4 (1.1–1.9)	1.4 (1.2–1.9)	1.4 (1.0–2.2)	1.4 (1.1–2.2)	1.5 (0.9–2.1)	1.4 (1.0–2.1)
Urine protein excretion, g/24 h, mean (SD)	2.3 (1.0)	2.1 (1.0)	2.3 (1.2)	2.2 (1.1)	2.0 (0.9)	2.2 (1.0)
UACR, g/g, mean (SD)	1.2 (0.7)	1.3 (0.7)	1.4 (0.8)	1.3 (0.8)	1.2 (0.7)	1.3 (0.7)
eGFR,[a] ml/min per 1.73 m^2						
Mean (SD)	71 (29)	64 (25)	56 (23)	60 (24)	66 (32)	63 (27)
Median (IQR)	65 (51–90)	63 (43–79)	49 (41–63)	53 (41–72)	57 (42–87)	56 (42–76)
eGFR category, n (%)						
<30 ml/min per 1.73 m^2	0	1 (3)	1 (3)	2 (3)	2 (6)	4 (3)
≥30 to <45 ml/min per 1.73 m^2	3 (19)	8 (24)	11 (33)	19 (29)	8 (24)	30 (26)
≥45 ml/min per 1.73 m^2	13 (81)	24 (73)	21 (64)	45 (68)	24 (71)	82 (71)
Gd-IgA1, μg/L, mean (SD)	6292 (4572)	5813 (3573)	5646 (2697)	5731 (3149)	6340 (3697)	5986 (3514)
IgA, mg/dL, mean (SD)	315 (143)	313 (131)	320 (100)	317 (115)	337 (154)	323 (131)
IgG, mg/dL, mean (SD)	1018 (217)	1159 (289)	1059 (206)	1109 (254)	1153 (305)	1109 (266)
IgM, mg/dL, mean (SD)	98 (44)	121 (100)	94 (56)	107 (82)	102 (50)	105 (69)
Use of RAASi, n (%)						
ACEi only	10 (63)	6 (18)	6 (18)	12 (18)	11 (32)	33 (28)
ARB only	4 (25)	21 (64)	23 (70)	44 (67)	19 (56)	67 (58)
Dual RAASi[b]	1 (6)	3 (9)	3 (9)	6 (9)	2 (6)	9 (8)
Use of SGLT2i, n (%)	3 (19)	3 (9)	4 (12)	7 (11)	6 (18)	16 (14)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient IgA1; IQR, interquartile range; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio; UPCR, urine protein-to-creatinine ratio.

[a]eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration formula.

[b]Included participants using a stable regimen of ACEi + ARB, ACEi + mineralocorticoid receptor antagonist (MRA), or ARB + MRA.

end points (Supplementary Table S2). UPCR reduction at 24 weeks was 41% in the atacicept 150-mg group and 28% in the atacicept 75-mg group, compared with 10% in the placebo group. These resulted in a reduction of 34% ($P = 0.025$) for atacicept 150 mg and 20% ($P =$ nonsignificant) for atacicept 75 mg. At 36 weeks, compared with a 5% increase from baseline in UPCR at 36 weeks in the placebo group, a reduction of 40% was observed with atacicept 150 mg (Δ, 43%; $P = 0.0032$) and 34% with atacicept 75 mg (Δ, 37%; $P = 0.0094$; Supplementary Table S2).

Findings from the atacicept 25-mg dose group, although not powered for efficacy analyses, showed similar trends in reduction of UPCR from baseline (Supplementary Table S3).

At week 36, mean eGFR increased from baseline by 1% in the combined atacicept 150- and 75-mg group compared with an 8% reduction from baseline in the placebo group, resulting in an 11% difference ($P = 0.022$; Figure 3a and c). The adjusted geometric mean change in eGFR at week 36 was an increase of 0.8 ml/min per 1.73 m^2 in the combined atacicept 150- and 75-mg group and a decrease of 4.9 ml/min per 1.73 m^2 in the placebo group, resulting in a difference in the adjusted geometric mean change in eGFR of 5.7 ml/min per 1.73 m^2 versus placebo. This difference is consistent with the findings from the eGFR slope analyses (Supplementary Table S4). The results for the individual atacicept 150- and 75-mg groups are shown in Figure 3b and c.

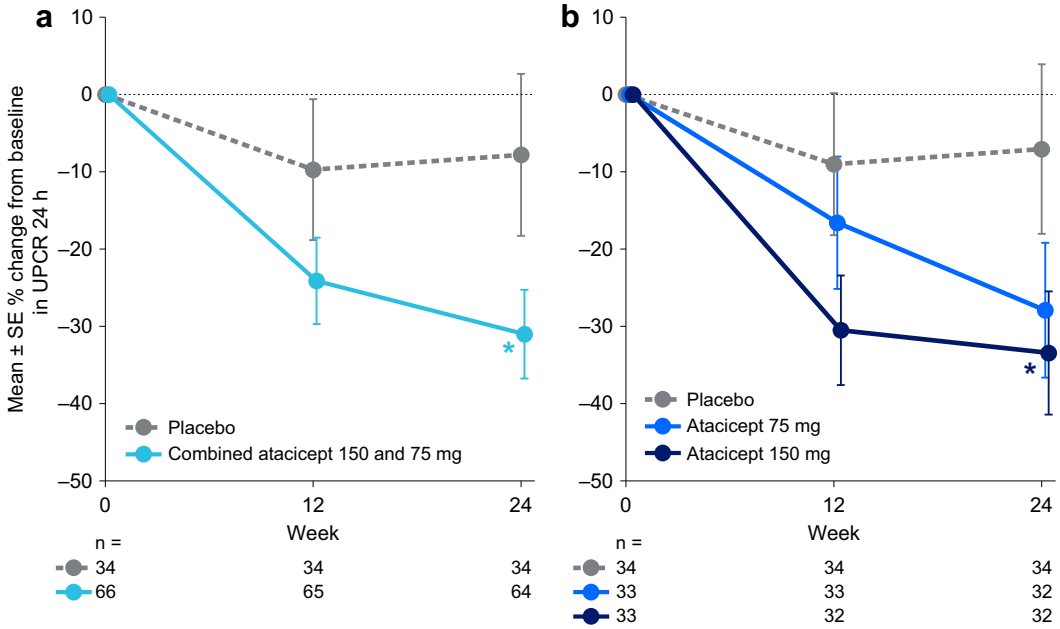


Figure 2 | Urine protein-to-creatinine ratio (UPCR) percentage change from baseline through week 24 by visit (week 24 data cut, full analysis set population). (**a**) Primary end point: combined atacicept 150- and 75-mg group versus placebo. (**b**) Individual atacicept 150- and 75-mg groups versus placebo. Changes from baseline in natural log-transformed UPCR were analyzed using mixed-effects model repeated measures (MMRM) analysis with change from baseline in log-transformed UPCR as the dependent variable; fixed effects for randomized treatment, natural log-transformed baseline value, baseline estimated glomerular filtration rate category (<45 or ≥45 ml/min per 1.73 m^2), visit, and treatment-by-visit interaction as independent variables; and participant as a random effect. The 2-sided *P* value comes directly from the model. Note: a separate MMRM analysis was used for the combined atacicept versus placebo analysis and for the 150 or 75 mg versus placebo analysis. *$P < 0.05$ versus placebo.

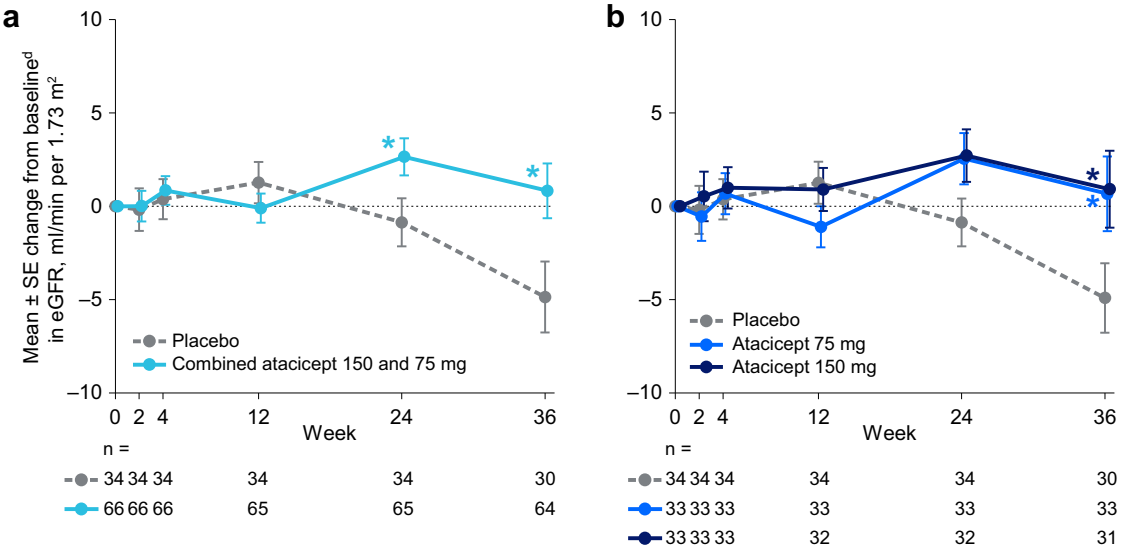
Compared with a mean 7% decrease from baseline in Gd-IgA1 with placebo at week 36, a decrease of 63% was achieved in the combined atacicept 150- and 75-mg group, resulting in a 60% decrease from baseline with atacicept versus placebo ($P < 0.0001$; Figure 4a). Similar results were observed with the individual atacicept 150-mg dose, with a mean decrease of 64% compared with 7% seen with placebo, resulting in a 61% decrease from baseline with atacicept 150 mg versus placebo ($P < 0.0001$; Figure 4b). Atacicept 75 mg also achieved a statistically significant 59% decrease from baseline compared with placebo ($P < 0.0001$; Figure 4b). Atacicept 25 mg achieved a 35% decrease from baseline compared with placebo (Supplementary Table S2).

Safety

Atacicept was well tolerated through a median (range) exposure of 36 weeks (3–38 weeks) and a mean of 35 weeks. The proportions of participants with TEAEs were generally similar between the all-atacicept and placebo groups (73% versus 79%; Table 2). TEAEs considered related to study drugs were reported for 42 participants (51%) on atacicept and 14 participants (41%) on placebo. The difference between groups in related adverse events was mainly related to injection site reactions, and most injection site reactions reported in the study were mild or moderate in severity. Overall, TEAEs were similar across the 3 atacicept dose groups, but study drug–related TEAEs, mainly composed of injection site reactions, were more frequent in the 150- and 75-mg groups compared with the 25-mg group. The incidence of serious TEAEs was low (atacicept: 2%, 2 participants; placebo: 9%, 3 participants), and none were reported to be related to study drug. Serious adverse events reported with atacicept included multiple fractures (n = 1, atacicept 75 mg) and norovirus gastroenteritis (n = 1, atacicept 150 mg). Serious adverse events reported with placebo included anaphylactic reaction due to a peanut allergy (n = 1), forearm fracture (n = 1), and flank pain and ulnar nerve paralysis (n = 1; both reported in the same participant). Two participants (n = 1, atacicept 150 mg, hepatitis B DNA increase; n = 1, placebo, pericardial effusion) had TEAEs that led to discontinuation of study drug. No deaths were reported.

TEAEs of infection were similar across the atacicept dose groups and placebo (Supplementary Table S5). The adverse event of special interest of hypersensitivity reactions was reported for 1 participant in the atacicept 150-mg group and 2 participants in the placebo group. No adverse events of special interest related to opportunistic infections, demyelinating disorders, or cardiac events were reported.

Similarly, decreases from baseline in serum IgG, IgA, and IgM were observed with atacicept through week 36, whereas levels were stable with placebo (Supplementary Figure S1). For atacicept 150 and 75 mg, mean reductions from baseline in IgG were 37% and 32%, in IgA were 63% and 54%, and in IgM were 73% and 70%, respectively. These decreases were statistically significant ($P < 0.001$) compared with changes from baseline observed with placebo (IgG: 0%; IgA: 4%; and IgM: 3%). Thus, the observed changes in Gd-IgA1 were proportionally the same



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	Baseline		Week 36					
				Mean % change			Mean absolute change, ml/min per 1.73 m²	
Treatment group	n	Mean (SD), ml/min per 1.73 m²	n	% Change (95% CI) from baseline[a]	Difference vs. placebo[b]	Nominal *P* value[c]	Absolute change (95% CI) from baseline[d]	Difference vs. placebo
Placebo	34	66.0 (31.7)	30	–8.37 (–14.7, –1.63)	—	—	–4.86 (–8.51, –0.95)	—
Combined atacicept 150 and 75 mg	66	60.1 (24.3)	64	1.44 (–3.46, 6.58)	10.7 (1.52, 20.7)	0.022	0.83 (–2.01, 3.82)	5.7
Placebo	34	66.0 (31.7)	30	–8.45 (–14.59, –1.88)	—	—	–4.9 (–8.5, –1.1)	—
Atacicept 75 mg	33	64.4 (25.4)	33	1.16 (–5.43, 8.22)	10.5 (0.32, 21.7)	0.043	0.67 (–3.2, 4.8)	5.6
Atacicept 150 mg	33	55.7 (22.7)	31	1.59 (–5.20, 8.88)	11.0 (0.61, 22.4)	0.038	0.92 (–3.2, 5.2)	5.8

Figure 3 | Estimated glomerular filtration rate (eGFR) results through week 36 (week 36 data cut, full analysis set population). (**a**) eGFR change from baseline through week 36 by visit in combined atacicept 150- and 75-mg group versus placebo. (**b**) eGFR change from baseline through week 36 by visit in individual atacicept 150- and 75-mg groups versus placebo. (**c**) eGFR results at week 36. Changes from baseline in natural log-transformed eGFR were analyzed using mixed-effects model repeated measures (MMRM) analysis with change from baseline in log-transformed eGFR as the dependent variable; fixed effects for randomized treatment, natural log-transformed baseline value, visit, and treatment-by-visit interaction as independent variables; and participants as a random effect. Note: a separate MMRM analysis was used for the combined atacicept versus placebo analysis and for the 150 or 75 mg versus placebo analysis. *$P < 0.05$ versus placebo. [a]MMRM percentage change from baseline (%) = (geometric least-squares [LS] mean ratio of week X/baseline value for each treatment − 1) × 100%. [b]Percentage change versus placebo (%) = (ratio of geometric LS mean ratios between active versus placebo − 1) × 100%. [c]The 2-sided *P* value comes directly from the model, whereas geometric LS means, ratio of geometric LS means, SEs, and 2-tailed 95% confidence intervals (CIs) are transformed back into the original scale from MMRM estimates. [d]Mean change from baseline = baseline geometric mean for total × percentage change from baseline for each treatment.

as the change in total IgA, 64% and 63% for the 150-mg group and 54% and 54% for the 75-mg group, respectively. There were no study drug discontinuations or interruptions due to hypogammaglobulinemia (serum IgG, <300 mg/L; Supplementary Figure S2). No clinically relevant differences in blood pressure measurements between treatment groups were observed (Supplementary Figure S3).

DISCUSSION

In this phase 2b, randomized, double-blind, placebo-controlled trial, the combined atacicept 150- and 75-mg group decreased UPCR by 25% (95% confidence interval, 1.74%–43.01%) at week 24 and by 35% (95% confidence interval, 13.03%–51.53%) at week 36 compared with placebo in a patient population with biopsy-proven IgAN and persistent proteinuria, despite being on a stable and maximally tolerated dose of renin-angiotensin-aldosterone system inhibitor. The reduction of 35% in proteinuria was accompanied by a stabilization in eGFR with atacicept compared with a decline in the placebo group at week 36. Gd-IgA1 levels decreased early and in sustained manner, reaching 64% and 62% from baseline at week 36 in the 150- and 75-mg groups, respectively, confirming findings from the phase 2a JANUS study in IgAN, which found a 60% reduction in Gd-IgA1 in the atacicept 75-mg group,[18] while providing efficacy data with the atacicept 150-mg dose. The phase 2a JANUS and the phase 2b ORIGIN studies provide safety data with atacicept in a patient population without concomitant immunosuppressives, unlike previous atacicept studies in systemic lupus erythematosus and lupus nephritis. The safety data in IgAN so

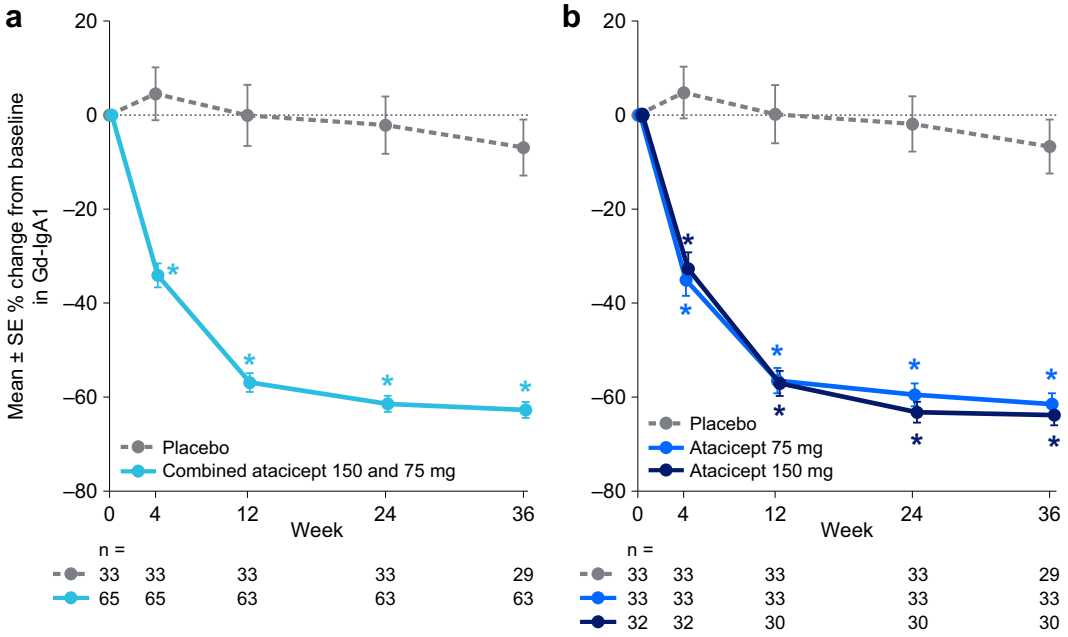

Figure 4 | Galactose-deficient IgA1 (Gd-IgA1) percentage change from baseline through week 36 by visit (week 36 data cut, full analysis set population). (**a**) Combined atacicept 150- and 75-mg group versus placebo. (**b**) Individual atacicept 150- and 75-mg groups versus placebo. *P* values, percentage changes from baseline, and treatment differences were computed using mixed-effects modeling. *$P < 0.05$ versus placebo.

far are similar to those seen in an integrated safety analysis of atacicept in all other indications.[20]

The ORIGIN phase 2b clinical trial demonstrated that treatment with atacicept, a B-cell modulator, resulted in substantial reduction in Gd-IgA1 and stabilization in kidney function in a large, multinational, randomized, double-blind, placebo-controlled clinical trial setting. A report on telitacicept, another dual inhibitor of BAFF and APRIL, supports the benefits and safety shown in ORIGIN; however, this was a smaller study (n = 44) and a China-only population with IgAN.[21]

Atacicept is different from standard therapies available for IgAN as it has the potential to target the underlying pathophysiology of IgAN. The robust reduction in Gd-IgA1 provides further evidence that atacicept targets the earlier steps in the pathogenesis of IgAN, a finding that has not been reported in IgAN clinical trials of sodium-glucose cotransporter-2 inhibitors, sparsentan, or systemic corticosteroids. This study supports a hypothesis of continuous Gd-IgA1 production even years after onset of IgAN, probably contributing to persistent proteinuria and disease progression. Preliminary results from JANUS have also shown that atacicept can decrease IgG antiglycan and immune complexes, important points of impact in IgAN pathophysiology.[22,23] The current study included a population at high risk of progression with a mean UPCR of 1.6 g/g despite being on a maximally tolerated dose of renin-angiotensin-aldosterone system inhibitor. The study was also unique compared with other recent studies in IgAN in that the study population included a subgroup of participants on sodium-glucose cotransporter-2 inhibitors at baseline. Given the increasing use of sodium-glucose cotransporter-2 inhibition for patients with chronic kidney disease, inclusion of this subgroup provides information needed to evaluate a representative patient population with IgAN. The demographics of the study population are representative of the overall population with IgAN, with a mean age of 39 years, slight male

Table 2 | Overall safety through week 36

	Atacicept					
Events	All doses (n = 82)	25 mg (n = 16)	75 mg (n = 33)	150 mg (n = 33)	Combined 150 and 75 mg (n = 66)	Placebo (n = 34)
TEAEs	60 (73)	11 (69)	24 (73)	25 (76)	49 (74)	27 (79)
Study drug–related TEAEs	42 (51)	6 (38)	17 (52)	19 (58)	36 (55)	14 (41)
Serious TEAEs	2 (2)	0	1 (3)	1 (3)	2 (3)	3 (9)
TEAEs leading to study drug discontinuation	1 (1)	0	0	1 (3)	1 (2)	1 (3)
Deaths	0	0	0	0	0	0

TEAE, treatment-emergent adverse event.
Data are given as n (%).

predominance, and race balanced between White and Asian, as seen with other IgAN studies.[18,24]

Limitations of the study include a higher proportion of White participants randomly assigned to placebo compared with atacicept. As with all other published phase 2 studies in IgAN, MEST-C (M = mesangial hypercellularity, E = endocapillary proliferation, S = segmental glomerulosclerosis, T = tubular atrophy/interstitial fibrosis, C = crescents) scores contemporaneous with biopsy at screening were not available; therefore, ascertainment of whether baseline proteinuria was more likely related to scarring rather than to active disease was not possible. The inclusion criteria for blood pressure at screening were not restrictive, which may have contributed to a study population that did not have optimal blood pressure of <120/80 mm Hg, as per Kidney Disease: Improving Global Outcomes recommendations. Last, the atacicept 25-mg dose was included in the study to provide data on safety and biomarkers; thus, the 25-mg group was not powered to inform efficacy.

The atacicept 150-mg group results appeared more robust than that of the 75-mg group based on the more rapid and greater reduction in proteinuria. Atacicept 150 mg reduced UPCR as early as week 12 and was the only individual dose that had a statistically significant decrease in UPCR compared with placebo at week 24. In addition, atacicept 150 mg showed deeper reductions in UPCR at week 24 by both FAS and PP analyses, and at week 36 by PP analysis. By the FAS analysis, the 75- and 150-mg groups had similar reductions in UPCR at week 36, which may be related to the variability of UPCR as observed in other randomized trials in IgAN.[25] Despite similar reductions in Gd-IgA1, the antiproteinuric effect of 150 mg may be due to other effects of the dose differences, or due to variability in measurements of these outcomes at these time points. Similar safety results were observed between the 75- and 150-mg groups in the current study as well as prior studies in various indications, including systemic lupus erythematosus.[20] Thus, from the totality of efficacy and safety data, atacicept 150 mg was selected for further evaluation of atacicept.

In conclusion, the ORIGIN phase 2b study demonstrates that treatment with atacicept in addition to current standard of care results in clinically and statistically significant reductions in UPCR at weeks 24 and 36. Although the study was not powered to evaluate eGFR at this early time point, the difference in eGFR between atacicept and placebo further supports the potential for atacicept to improve kidney outcomes in patients with IgAN. The efficacy and safety findings of the ORIGIN phase 2b study provide the evidence needed to support a phase 3 pivotal study (ORIGIN 3) powered to evaluate the benefit of atacicept 150 mg compared with placebo on UPCR at week 36 and the rate of change in eGFR over 2 years.

DISCLOSURE

RL reports research grants and consulting fees from Amgen, Alexion, Beigene, Calliditas Therapeutics, Chinook, Novartis, Omeros, Otsuka Roche, Travere Therapeutics, and Vera Therapeutics; as well as support for attending meetings from Calliditas Therapeutics, Novartis, and Vera Therapeutics. SB has received grants or contracts from Novartis. JF reports receiving consultancy fees from AstraZeneca, Boehringer Ingelheim, Calliditas Therapeutics, Chinook, GlaxoSmithKline, CSL Vifor, Novartis, Omeros, Stadapharm, Travere Therapeutics, and Vera Therapeutics. VJ has received grant funding from Baxter Healthcare, GSK, and Vera Therapeutics. HS reports research contracts with Vera Therapeutics, "KOL" honoraria from Travere Therapeutics, and membership to a forum of ERD networks. VT reports consulting fees from AstraZeneca, Boehringer-Ingelheim, Calliditas Therapeutics, Novartis, Omeros, Otsuka, Travere Therapeutics, and Vera Therapeutics; payment or honoraria from Calliditas, GSK, and Travere; participation on a data safety monitoring board or advisory board for Alexion, AstraZeneca, Bayer, Boehringer-Ingelheim, Novartis, Omeros, Otsuka, Travere Therapeutics, and Vera Therapeutics; and is a member of the executive committee of the International Society of Nephrology by April 2023. JB reports research grants from Argenx, Calliditas Therapeutics, Chinook Therapeutics, Galapagos, GlaxoSmithKline, Novartis, and Travere Therapeutics; and is a medical/scientific advisor for Alnylam Pharmaceuticals, Argenx, Astellas Pharma, Biocryst Pharmaceuticals, Calliditas Therapeutics, Chinook Therapeutics, Dimerix, Galapagos, Novartis, Omeros, Travere Therapeutics, UCB, Vera Therapeutics, and Visterra. RI, XW, and CJFL are employees of Vera Therapeutics and shareholders of Vera stock. All the other authors declared no competing interests.

DATA STATEMENT

Vera Therapeutics shares anonymized individual patient data on request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting no conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Vera's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data.

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AUTHOR CONTRIBUTIONS

JB contributed to the conception and design of the study. RL, JB, and RI wrote the first draft of the paper. XW provided the data analyses and directly accessed and verified the underlying data reported in the manuscript. All authors contributed to the interpretation of the data and critically revised the paper. RL, CJFL, RI, XW, and JB had full access to all the data in the study. All authors had final responsibility for the decision to submit for publication.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods. Study assessments, diagnosis and eligibility criteria, and supplementary statistical methods.

Supplementary Table S1. Treatment effect estimate for UPCR from the MMRM model by treatment and postbaseline visit (week 24 data cut, FAS population).

Supplementary Table S2. UPCR results for individual atacicept 75- and 150-mg groups and placebo at week 24 and 36 data cuts in the FAS and PP populations.
Supplementary Table S3. Efficacy results for the atacicept 25-mg group (FAS population).
Supplementary Table S4. eGFR slope results from Mixed Effect Model with Random Intercept and Random Slope (week 36 data cut, FAS population).
Supplementary Table S5. Incidence of infections through week 36 (week 36 data cut, safety population).
Supplementary Figure S1. IgG, IgA, and IgM percentage change from baseline through week 36 by visit in individual dose groups and placebo (week 36 data cut, FAS population). (**A**) IgG. (**B**) IgA. (**C**) IgM. *P* values, percentage changes from baseline, and treatment differences were computed using mixed-effects modeling. $*P < 0.05$ versus placebo.
Supplementary Figure S2. IgG absolute values (mg/dL) from baseline through week 36 by visit in individual dose groups and placebo (week 36 data cut, FAS population). Horizontal dashed line indicates 300 mg/dL, the study-defined IgG threshold for hypogammaglobulinemia.
Supplementary Figure S3. Diastolic and systolic blood pressure change from baseline at weeks 24 and 36 in individual dose groups and placebo (week 36 data cut, FAS population). (**A**) Diastolic blood pressure. (**B**) Systolic blood pressure. Boxes represent median (quartile 1, quartile 3); whiskers represent minimum and maximum; diamonds represent mean values.

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