SCAN FOR MORE INFO

INFO17-TH

ORIGIN 3: Pivotal Phase 3 Study Evaluating Effect of Atacicept vs Placebo on Proteinuria and Renal Function Preservation in IgAN

Jonathan Barratt[1], Bart D. Maes[2], Rubeen K. Israni[3], Xuelian Wei[3], Jürgen Floege[4], Vivekanand Jha[5], Vladimir Tesar[6], Hong Zhang[7], Sean Barbour[8], Hitoshi Suzuki[9], Hernan Trimarchi[10], Celia J.F. Lin[3], Richard A. Lafayette[11]

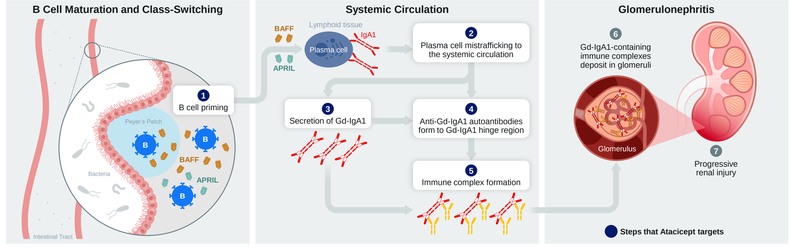
[1]University of Leicester, Leicester, UK; [2]AZ Delta vzw, Roeselare, West-Vlaanderen, Belgium; [3]Vera Therapeutics, Inc., Brisbane, CA, US; [4]Rheinisch-Westfälische Technische Hochschule Aachen, Aachen, Nordrhein-Westfalen, Germany; [5]The George Institute for Global Health India, New Delhi, Delhi, India; [6]Univerzita Karlova, Praha, Czechia; [7]Peking University First Hospital, Beijing, Beijing, China; [8]The University of British Columbia, Vancouver, BC, Canada; [9]Juntendo University Faculty of Medicine, Tokyo, Japan; [10]Hospital Británico de Buenos Aires, Argentina; [11]Stanford University, Stanford, CA, US; on behalf of the ORIGIN 3 Study Team

IgA Nephropathy: High Unmet Need for Effective Therapies that Halt Disease Progression

- IgAN is a serious, immune-mediated, progressive disease with an average age at diagnosis of 30 years old[1]
- Up to 50% of IgAN patients progress to ESRD, requiring dialysis or kidney transplant[2]; in a UK cohort with progressive disease, most progressed to kidney failure within 10–15 years[3]
- Current standard of care includes RASi and supportive care[4]
- There is a high unmet medical need for new safe and effective disease-modifying treatments for IgAN that target the source of disease[5,6]

RASi = renin-angiotensin system inhibitor; IgAN = IgA nephropathy.

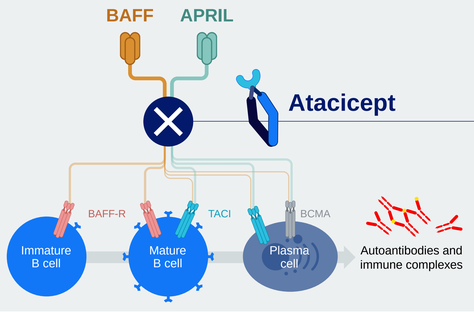
IgAN Pathophysiology and Role of BAFF & APRIL



APRIL = A PRoliferation-Inducing Ligand; BAFF = B-cell Activating Factor; Gd-IgA1 = galactose-deficient IgA1.

- IgAN is characterized by elevated serum levels of Gd-IgA1, anti-Gd-IgA1 autoantibodies, and immune complexes that lead to kidney damage[7-10]
- BAFF and APRIL play an important role in the maturation, differentiation, and effector function of B cells and plasma cells[11]
  - Both BAFF and APRIL are elevated in patients with IgAN and are each associated with clinical severity[12-14]
  - In preclinical models, overexpression of BAFF alone can lead to development of kidney IgA deposits and IgA-like nephritis in the presence of commensal flora[15]
  - BAFF can directly increase expression of factors associated with inflammation and fibrosis in mesangial cells[13]

Atacicept: Dual BAFF/APRIL Inhibitor With Disease-Modifying Potential

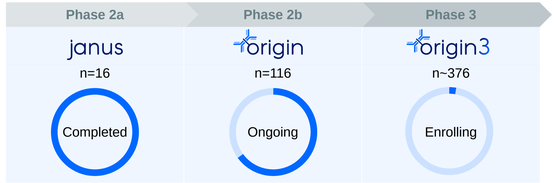


- Fully humanized TACI-Ig fusion protein, weekly subcutaneous administration
- Low nanomolar potency vs BAFF (Kd 1.45 nM) and APRIL (Kd 0.672 nM)
- Well-characterized safety profile with exposure in >1500 patients across different indications[16,17]

BAFF-R: immature B cell survival and maturation
TACI: T cell independent antibody responses, B cell regulation, class-switch recombination
BCMA: plasma cell survival.

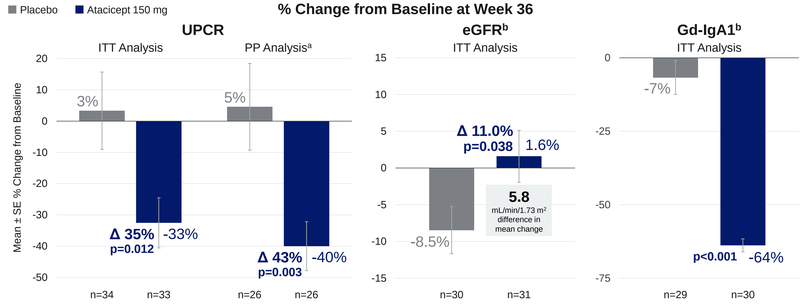
- Dual inhibition of both BAFF and APRIL may be necessary for maximal and sustained clinical efficacy
  - BAFF or APRIL alone are each capable of independently supporting plasma cell survival[18,19]
  - Dual inhibition of BAFF and APRIL decreased renal damage in an immunologic animal model more than individual inhibition of either pathway alone[18]
  - Inhibiting both biologic targets may avoid compensatory increase in parallel signal[20,21]
  - Inhibiting APRIL alone may lead to upregulation of BAFF signaling with potential consequences on efficacy[22]

Atacicept Clinical Development Program in IgAN



- Two Phase 2 studies, JANUS and ORIGIN, evaluated safety and efficacy of atacicept vs placebo in IgAN
- Phase 3 pivotal study, ORIGIN 3, initiated Jun 2023

Phase 2b ORIGIN Results: Atacicept 150 mg SC qwk vs Placebo[23]

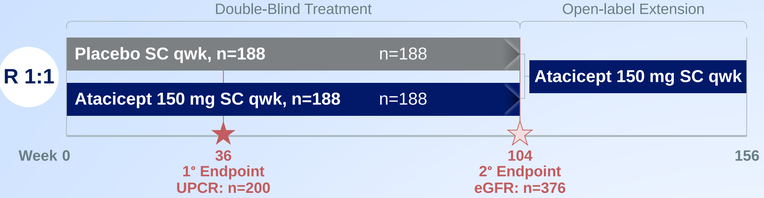


- Safety was comparable between atacicept and placebo

p-values, percentage changes from baseline, and treatment differences were computed using FDA-endorsed mixed-effects modeling which accounts for effects of baseline urine protein:creatinine ratio (UPCR) and eGFR.
a. 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.

origin3

- Global, randomized, double-blind, placebo-controlled Phase 3 trial evaluating efficacy and safety of atacicept 150 mg for treatment of IgAN
- ~376 participants will be enrolled



Inclusion Criteria

- ≥18 years old with IgAN on renal biopsy
- Stable RASi at maximum-labeled or tolerated dose for ≥12 weeks
- UPCR-24h ≥1.0 g/g or UP ≥1.0 g per 24h
- eGFR ≥30 mL/min/1.73m²
- Blood pressure ≤150/90 mmHg

Exclusion Criteria

- IgAN secondary to another condition
- Nephrotic syndrome within 6 months of screening
- ≥50% loss of eGFR within 3 months of screening

Other Study Characteristics

- Patients on stable SGLT2i dose for ≥12 weeks allowed in study

Endpoints

- Primary efficacy: % change in UPCR-24h at week 36 analyzed using a mixed-effects model with repeated measurement
  - >90% power at week 36
- Key secondary: annualized eGFR slope up to week 104
  - 90% power for eGFR Δ 4 mL/min at week 104
- Safety

NCT04716231. SGLT2i = sodium-glucose cotransporter-2 inhibitor.

Participate in origin3

Learn more at theORIGINiganstudy.com
or contact us at clinicaltrials@veratx.com

References: **1.** Jarrick S, et al. J Am Soc Nephrol 2019;30:866-76; **2.** Kwon CS, et al. J Health Econ Outcomes Res 2021;8:36-45; **3.** Pitcher D, et al. Clin J Am Soc Nephrol 2023;18:727-38; **4.** KDIGO 2021; **5.** Maixnerova D, et al. J Clin Med 2022;11:2810; **6.** Huang X, Xu G. Front Pharmacol 2021;12:715253; **7.** Wyatt RJ, Julian BA. N Engl J Med 2013;368:2402-14; **8.** Czerkinsky C, et al. J Clin Invest 1986;77:1931-8; **9.** Suzuki H, et al. J Clin Invest 2009;119:1668-77; **10.** MacPherson AJ, et al. Mucosal Immunol 2008;1:11-22; **11.** Schneider P. Curr Opin Immunol 2006;17:282-9; **12.** Xin G, et al. J Nephrol 2013;26:683-90; **13.** Cao Y, et al. Mol Med Rep 2020;21:795-805; **14.** Zhai Y, et al. Medicine (Baltimore) 2016;95:e3099; **15.** McCarthy D, et al. J Clin Invest 2011;121:3991-4002; **16.** Gordon C, et al. Rheumatol Adv Pract 2019;0:1-12; **17.** Vera data on file; **18.** Haselmayer P, et al. Eur J Immunol 2017;47:1075-85; **19.** Benson M, et al. J Immunol 2008;180:3655-9; **20.** Yeh T, et al. J Allergy Clin Immunol 2020;146:1109-20.e4; **21.** Tsiantoulas et al. Nature 2021;597:92-6; **22.** Vallerskog T, et al. Arthritis Res Ther 2006;8:R167; **23.** Lafayette R, et al. ERA 2023, late breaking clinical trial presentation June 17, 2023.

Acknowledgments: We thank all the patients who participate in this study and their families.

8000 Marina Boulevard, Suite 120, Brisbane, CA 94005. (650) 770-0077. medinfo@veratx.com.

vera therapeutics

KIDNEY WEEK 2023
November 1-5 | Philadelphia, PA