Atacicept in IgAN: Maintained Immunity From Diphtheria and Tetanus and Balanced Infections vs Placebo with a Focus on COVID-19

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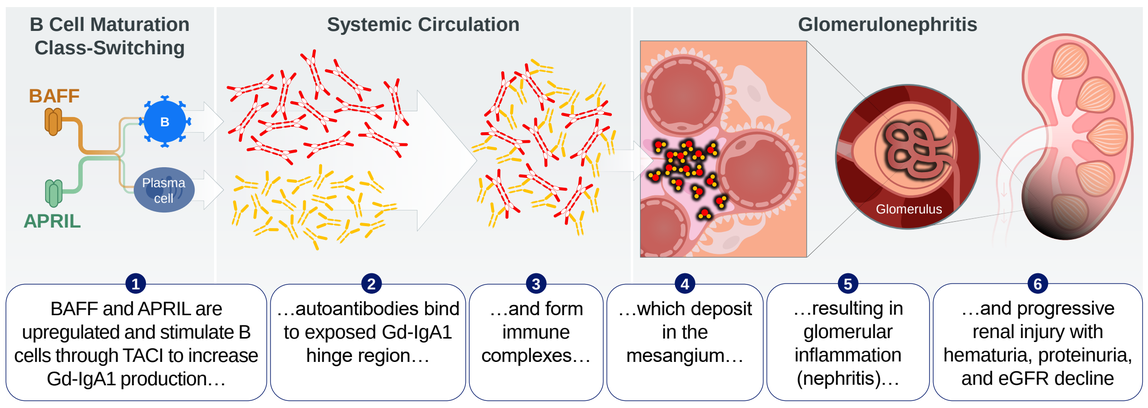
Introduction

- 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]

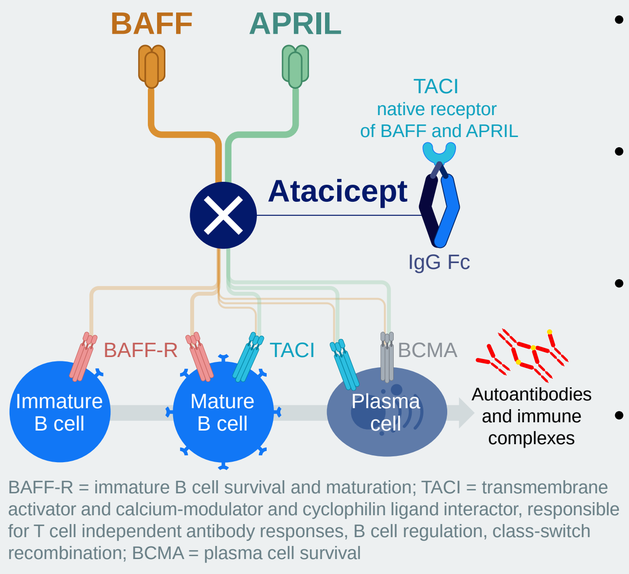
IgAN is a Disease of B-cell Origin With Renal Pathology



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

- BAFF and APRIL play an important role in the maturation, differentiation, and effector function of B cells and plasma cells, which are the source of autoantigen (Gd-IgA1) and autoantibody production leading to immune complex formation in IgAN[3-9]

Atacicept: BAFF/APRIL Dual Inhibitor With Disease Modifying Potential



BAFF-R = immature B cell survival and maturation; TACI = transmembrane activator and calcium-modulator and cyclophilin ligand interactor, responsible for T cell independent antibody responses, B cell regulation, class-switch recombination; BCMA = plasma cell survival

- Fully humanized TACI-Ig fusion protein, weekly subcutaneous self administration at home
- Low nanomolar potency vs BAFF (Kd 1.45 nM) and APRIL (Kd 0.672 nM)
- Reduces overstimulation of B cells and plasma cells[10] and autoantibody production[11]
- Dual inhibition more potent than either alone,[12] may translate to more sustained B cell modulation

Integrated Safety Analysis of Atacicept in >1000 Participants from Prior Trial Experience in Non-IgAN Indications[13]

AEs >5% in Any Arm, by Dose in the Double-Blind Placebo-Controlled Set

Participants, %	Overall n=1568	Atacicept 25 mg n=129	Atacicept 75 mg n=384	Atacicept 150 mg n=572	Placebo n=483
Discontinuation due to AE	8	11	8	8	6
Serious AE	11	12	13	11	11
Severe AE	9	8	12	10	6
Infections	46	33	47	49	44
Serious infections	4	1	6	4	4
Hypersensitivity	9	6	10	10	8
Injection site reactions	22	21	28	27	11
Cardiac arrhythmias	5	9	6	4	4
Vestibular disorders	4	4	5	5	4

AE = adverse event.

- A total of >1000 participants have received ≥1 dose of atacicept across non-IgAN indications including two large systemic lupus erythematosus studies and a long-term extension study
- Exposure-adjusted incidence rates of serious infection and serious AE were similar between atacicept and placebo
- No association between risk of infection and magnitude of pharmacodynamic effects with atacicept

Atacicept in IgAN

- The Phase 2a JANUS study showed reductions in Gd-IgA1, anti-Gd-IgA1, and immune complexes after 72 weeks of atacicept treatment[14-16]
- The Phase 2a ORIGIN study showed further Gd-IgA1 reduction as well as hematuria resolution and statistically significant proteinuria reduction and eGFR stabilization after 36 weeks of atacicept compared to placebo[17,18]
- Atacicept had comparable safety with placebo in both studies
- Based on the totality of data, the pivotal Phase 3 ORIGIN 3 study is evaluating atacicept vs placebo

Objective

- Better understanding vaccine response and immunity to diphtheria and tetanus and risk of COVID-19 infection with atacicept, may help assess atacicept's benefit risk profile, especially in an IgAN population

Methods

- In the Phase 2a JANUS study, tetanus and diphtheria titers were measured at day 1, week 48 and week 72 in addition to safety assessments
- In the Phase 2b ORIGIN study, safety data on infections including AEs of COVID-19 as reported by the investigators were analyzed by treatment arm up to week 36

Results

Protective Titers to Diphtheria and Tetanus

- No JANUS participants changed from protective to nonprotective status for diphtheria toxoid or tetanus toxoid
- Titer ≥0.1 IU/mL required to maintain immunity for both diphtheria toxoid and tetanus toxoid

Proportion of Participants Maintaining Immunity from Baseline through Week 72

	Atacicept 25 mg[a] n=6	Atacicept 75 mg[b] n=5	Placebo[c] n=5
Infections overall, n (%)	5 (83)	1 (20)	2 (40)
Vaccines, n/n (%)			
Diphtheria toxoid (DT)	5/5 (100)	5/5 (100)	4/4 (100)
Tetanus toxoid (TT)	5/5 (100)	4/4 (100)	4/4 (100)

a. One participant on atacicept 25 mg had diphtheria toxoid and tetanus toxoid titers ≥0.1 IU/mL at baseline but no post-baseline measures.
b. One participant on atacicept 75 mg had a tetanus toxoid titer ≥0.1 IU/mL at week 72 but no baseline measure.
c. One participant on placebo had diphtheria toxoid and tetanus toxoid titers <0.1 IU/mL at baseline that increased >0.1 IU/mL during treatment.

Balanced COVID-19 Infections vs Placebo

Summary of COVID-19 Infections Through Week 36

n (%)		Atacicept 25 mg n=16	Atacicept 75 mg n=33	Atacicept 150 mg n=33	Placebo n=34
Infections overall		6 (38)	16 (48)	12 (36)	11 (32)
COVID-19 infections		4 (25)	9 (27)	8 (24)	6 (18)
COVID-19 vaccine prior to infection		4 (100)	9 (100)	8 (100)	6 (100)
Severity	Mild	3 (75)	8 (89)	7 (88)	6 (100)
	Moderate	1 (25)	1 (11)	1 (13)	0
	Severe	0	0	0	0
Outcome	Recovered	4 (100)	9 (100)	7 (88)	6 (100)
	Recovering	0	0	1 (12)	0
Action taken	No dose change	2 (50)	4 (44)	5 (63)	3 (50)
	Drug interrupted	2 (50)	5 (56)	3 (38)	3 (50)
Duration of COVID-19 infection, days[a]		11.5 (8.5, 14)	8 (7, 9)	8 (6, 8)	6.5 (6, 7)

a. Duration of AE reported as median and interquartile range in days for 26 out of 27 participants who had outcome of AE as recovered/resolved.

- ORIGIN participants across atacicept and placebo arms had similar rates of overall and COVID-19 infections
- All participants with COVID-19 infection as an AE had ≥1 COVID-19 vaccine dose prior to infection
- No COVID-19 infection was serious; most were mild in severity
- Median duration of COVID-19 infection was 7.5 (IQR 7, 9) days
- There were no permanent discontinuations due to COVID-19 infections
- No COVID-19 infection was reported as study drug related

Conclusions

- As in prior experience, infections were balanced between atacicept and placebo in the Phase 2a JANUS and Phase 2b ORIGIN studies
- Atacicept treatment was associated with continued protective immunity to diphtheria and tetanus in the JANUS study
- There was no increase in incidence or severity of COVID-19 infections in the ORIGIN study
- This additional safety data provides further confidence in the ongoing ORIGIN 3 study (WCN24-AB-1414, MON-089)

SCAN FOR MORE INFO

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.** Czerkinsky C, et al. J Clin Invest 1986;77:1931-8; **4.** MacPherson AJ, et al. Mucosal Immunol 2008;1:11-22; **5.** Suzuki H, et al. J Clin Invest 2009;119:1668-77; **6.** Berthoux F et al. J Am Soc Nephrol 2012;23:1579-87; **7.** Zhao N et al. Kidney Int 2012;82:790-6; **8.** Wyatt RJ, Julian BA. N Engl J Med 2013;368:2402-14; **9.** Zhai YL, et al. 2016;95:e3099; **10.** Hiepe F, et al. Nat Rev Rheumatol 2011;3:170-8; **11.** Gordon C, et al. Arthritis Rheumatol 2017;69:122-30; **12.** Haselmayer P, et al. Eur J Immunol 2017;47:1075-85; **13.** Gordon C, et al. Rheumatol Adv Pract 2019;0:1-12; **14.** Barratt J, et al. Kidney Int Rep 2022;7:1831-41; **15.** Barratt J, et al. Nephrol Dial Transplant 2022;3 suppl 3, abstr FC051; **16.** Barratt J, et al. ASN Kidney Week 2022, abstr SA-PO655; **17.** Lafayette R, et al. ERA 2023, late breaking clinical trial oral presentation, June 17 2023; **18.** Barratt J, et al. ASN Kidney Week 2023, poster SA-PO887. **Acknowledgments:** We thank all who participated in this study and their families.

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