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INFO17-TH

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

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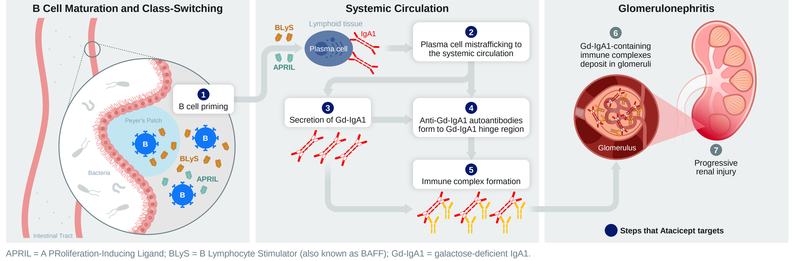
IgA Nephropathy: High Unmet Need for Effective Therapies that Halt Disease Progression

- 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.

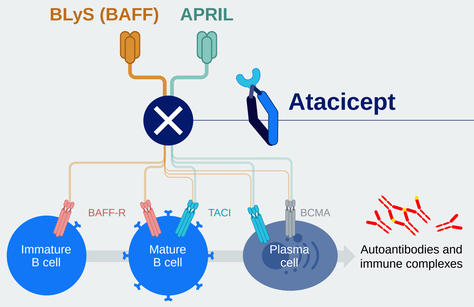
IgAN Pathophysiology and Role of BLyS (BAFF) & APRIL



APRIL = A PRoliferation-Inducing Ligand; BLyS = B Lymphocyte Stimulator (also known as BAFF); 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]
- BLyS (also known as BAFF) and APRIL play an important role in the maturation, differentiation, and effector function of B cells and plasma cells[11]
  - Both BLyS and APRIL are elevated in patients with IgAN and are each associated with clinical severity[12-14]
  - In preclinical models, overexpression of BLyS alone can lead to development of kidney IgA deposits and IgA-like nephritis in the presence of commensal flora[15]
  - BLyS can directly increase expression of factors associated with inflammation and fibrosis in mesangial cells[13]

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

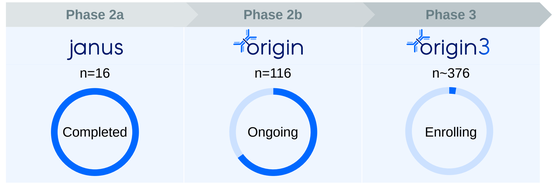


- Fully humanized TACI-Ig fusion protein, weekly subcutaneous administration
- Low nanomolar potency vs BLyS (Kd 1.45 nM) and APRIL (Kd 0.672 nM)
- Well-characterized safety profile with exposure in >1500 patients across different indications[16,17]

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

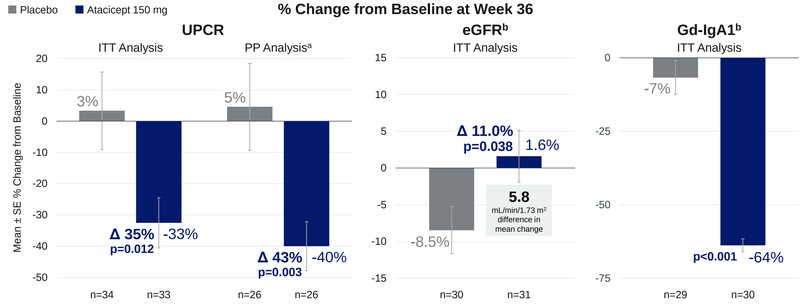
- Dual inhibition of both BLyS and APRIL may be necessary for maximal and sustained clinical efficacy
  - BLyS or APRIL alone are each capable of independently supporting plasma cell survival[18,19]
  - Dual inhibition of BLyS and APRIL decreased renal damage in an immunologic animal model more than 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 BLyS 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]

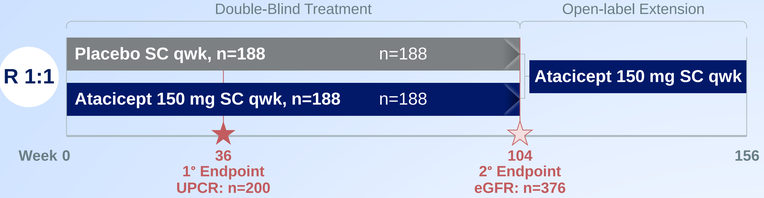


- Safety was comparable between atacicept and placebo

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/1.73m^2
- 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

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