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

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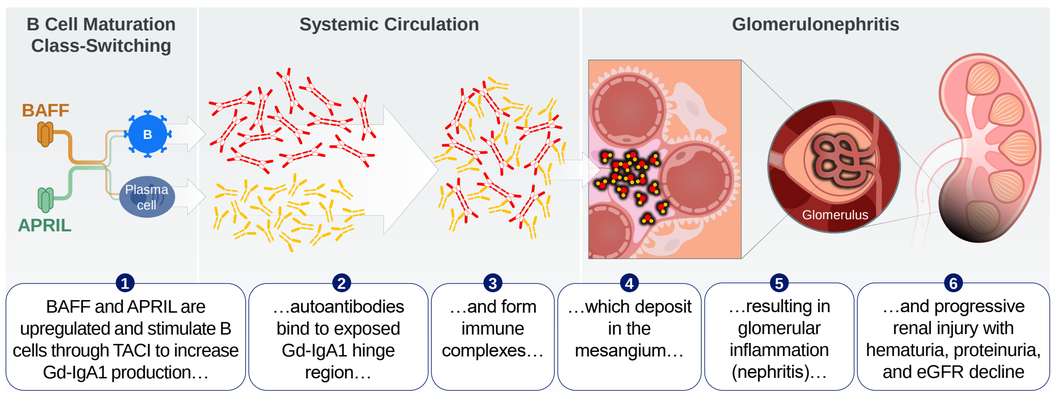
IgAN: High Unmet Need for Effective Therapies that Halt Disease Progression

- IgAN is a serious, immune-mediated, progressive disease with an average age at diagnosis of 35 years old[1]
- Despite current standard of care with RASi and CKD supportive care,[4] renal function declines steadily
- Up to 50% of IgAN patients progress to ESRD, requiring dialysis or renal transplant[2]; in a UK cohort with progressive disease, most progressed to renal failure within 10–15 years[3]
- 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]

CKD = chronic kidney disease; ESRD = end-stage renal disease; IgAN = IgA nephropathy; RASi = renin-angiotensin system inhibitor.

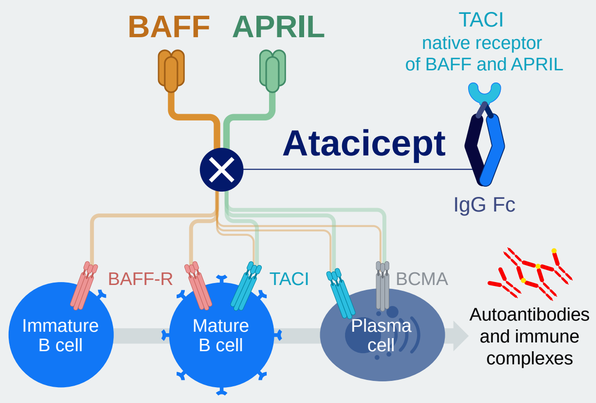
IgAN is a B-cell Disease With Renal Pathology



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

- Elevated serum levels of Gd-IgA1 are recognized as an autoantigen by anti-Gd-IgA1 autoantibodies, forming immune complexes that lead to renal damage in IgAN[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 renal 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]

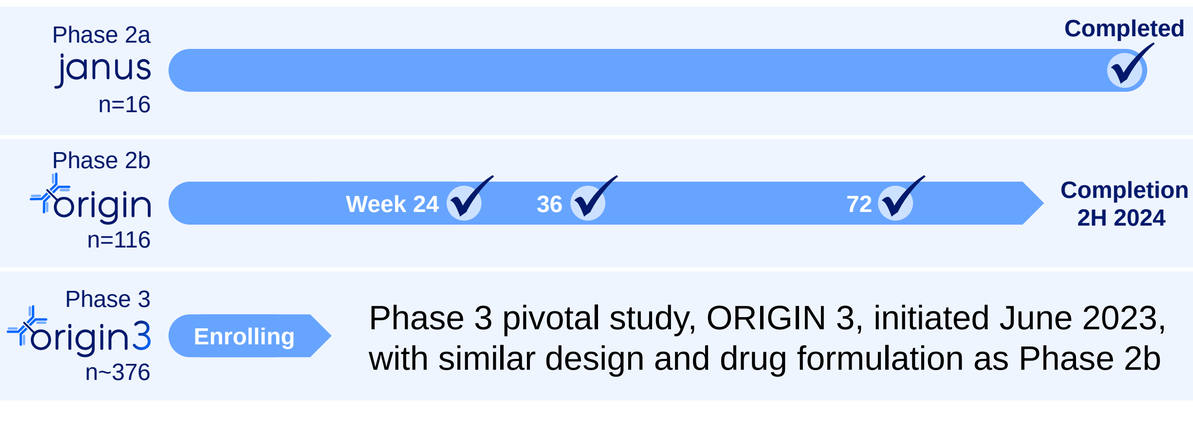
Atacicept: Dual BAFF & APRIL Inhibitor With Disease-Modifying Potential



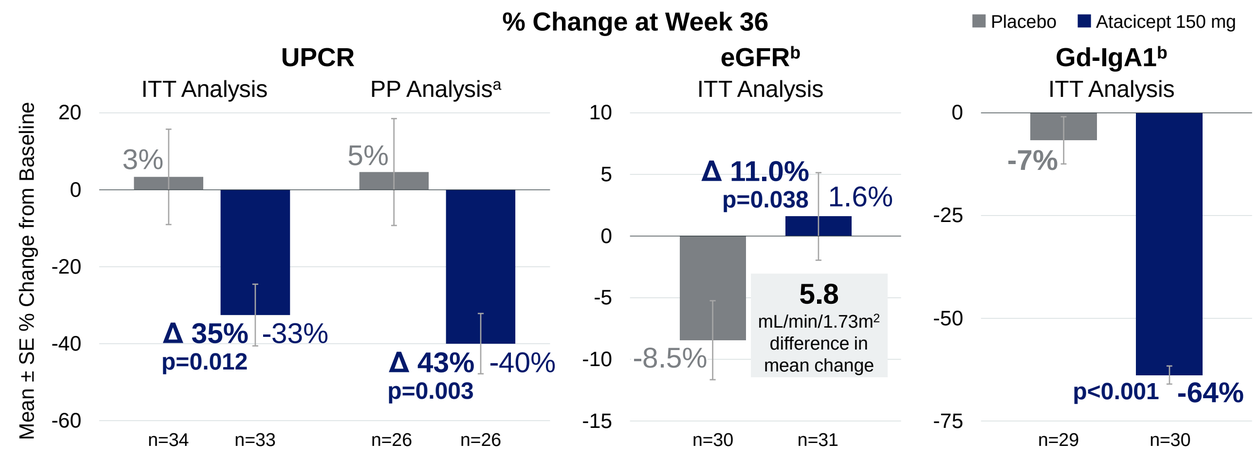
BAFF-R: immature B cell survival and maturation; TACI: T cell independent antibody responses, B cell regulation, class-switch recombination; BCMA: plasma cell survival.

- 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)
- Well-characterized safety profile in >1500 patients across indications[16,17]
- 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



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



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.

- Safety was comparable between atacicept and placebo

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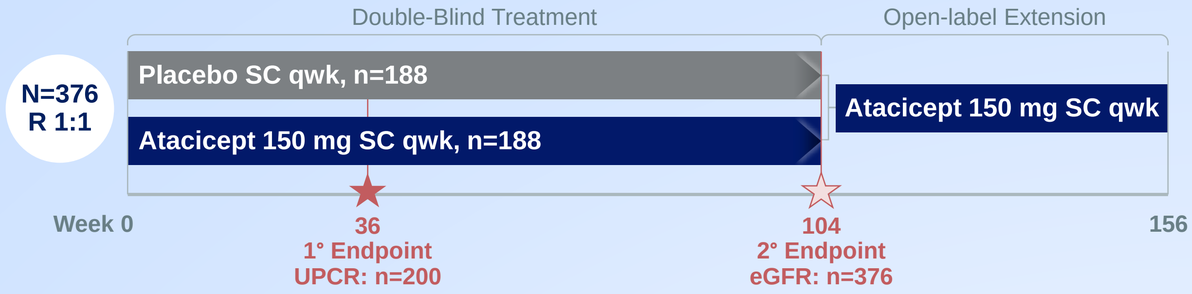
- Global, randomized, double-blind, placebo-controlled Phase 3 trial evaluating efficacy and safety of atacicept 150 mg for treatment of IgAN



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

- Participants 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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