A Translational Framework to Predict Clinical Responses to APRIL Blockade for Development of JADE101, an Anti-APRIL Monoclonal Antibody in IgAN

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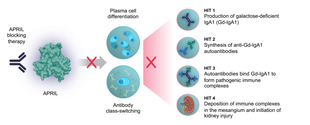
BACKGROUND

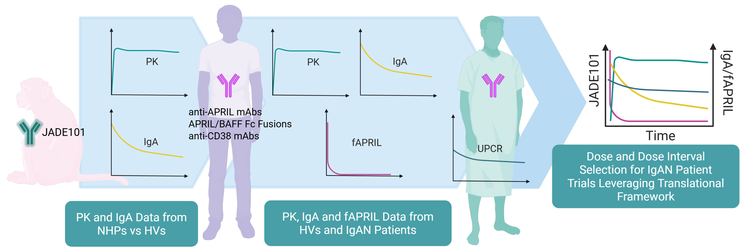
- IgA nephropathy (IgAN) is an autoimmune kidney disease characterized by mesangial deposition of immune complexes containing IgA and Gd-IgA1.
- Blocking A proliferation-inducing ligand (APRIL) is potentially disease modifying in IgAN by reducing IgA, Gd-IgA1 and proteinuria, ultimately stabilizing kidney function.
- JADE101 is a novel APRIL-neutralizing human IgG1 monoclonal antibody (mAb) designed with high affinity and extended half-life.
- Biomarker responses to APRIL inhibition were leveraged to assess preclinical to clinical translation and the consistency of pharmacokinetic (PK) and pharmacodynamic (PD) responses in healthy volunteers (HV) and IgAN patients to support development of APRIL-targeted therapies in IgAN.



Neutralizing APRIL depletes Gd-IgA1, reduces proteinuria, and **preserves eGFR**, providing a potentially **disease-modifying treatment** for IgAN without impacting B-cell development and maturation.

METHODS

- Translational PKPD models and statistical correlation were used to integrate preclinical data from the JADE101 development program with publicly available aggregate clinical trial data (mean or median) from anti-APRIL mAbs and other IgA-depleting agents (dual APRIL/BAFF inhibitors and anti-CD38 mAbs).
- Correlation coefficients (r) were used to estimate correlations between key pharmacologic properties and PKPD endpoints relevant to IgAN drug development.



CONCLUSIONS

- Anti-APRIL MOA provides biomarker rich-data expected to be predictive of clinical efficacy
- Tightly correlated biomarker responses to APRIL blockade enable preclinical and HV clinical data to inform expected clinical responses in IgAN patients.
- Depth and duration of APRIL inhibition anticipated to predict clinical activity, reflect disease-modifying potential, and define dose and dose interval for IgAN patient trials.
- PK, fAPRIL and IgA HV data can be used to define the dose and schedule designed to fully suppress APRIL throughout the dosing interval in IgAN patients.
- Complete APRIL neutralization in HVs appears to ultimately predict deep IgA and Gd-IgA1 suppression and maximal proteinuria reductions in IgAN patients.
- These associations provide a foundation for JADE101 development as a potentially disease modifying therapy in IgAN with convenient, infrequent dosing.

RESULTS

Non-human Primates vs Healthy Volunteers

***In vitro* APRIL binding affinity is predictive of *in vivo* IgA reduction in non-human primates and humans.**

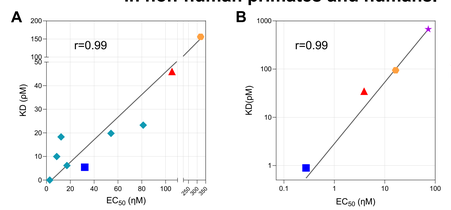


Figure 1. *In vitro* APRIL binding affinity by SPR versus *in vivo* IgA lowering potency in NHP studies (**A**) and human trials (**B**). Source: Internal data; Benchmarks manufactured based on publicly available sequences. Atacicept APRIL KD 672 pM (Vera internal data). IgA EC_{50} estimates calculated using compartmental PK models linked to indirect response models to describe IgA kinetics built using published PK and IgA concentration-time profiles for each molecule.

IgAN Patients vs Healthy Volunteers

Kinetics of anti-APRIL mAbs are consistent between healthy volunteers and IgAN patients with a direct relationship between PK and APRIL neutralization.

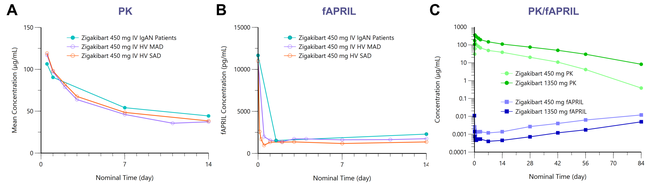


Figure 3. Comparison of PK (A) and free APRIL (fAPRIL) (B) profiles over time in healthy volunteers and participants with IgAN demonstrating no discernable kinetic differences. Overlay of PK and fAPRIL (C) demonstrating the direct relationship between an anti-APRIL mAb concentration and target neutralization. Underlying relationships are the same for other anti-APRIL mAbs, including sibeprenlimab and with higher levels of proteinuria. Similarity further supported by PK/PD modelling and simulation framework.

IgA reduction in healthy volunteers and IgAN patients is strongly associated across multiple time points and agents.

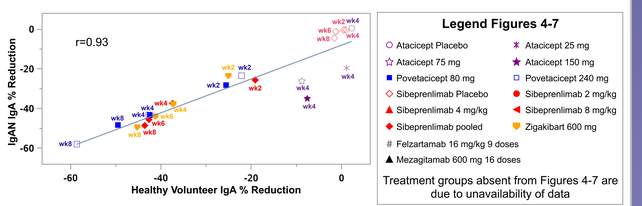
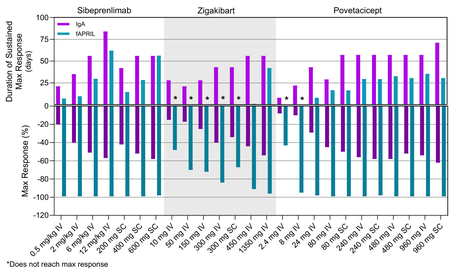


Figure 4. Trial level correlation between mean IgA reductions at Weeks 2-8 in healthy volunteers and participants with IgAN.

Healthy Volunteers



*Does not reach max response

Figure 2. Comparison of IgA reduction and fAPRIL neutralization in healthy volunteers.

IgAN Patients

Gd-IgA1 reductions are consistent with IgA reductions in IgAN patients.

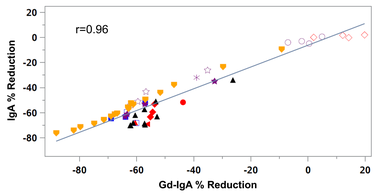


Figure 5. Trial level correlation between the mean IgA and Gd-IgA1 reduction at Weeks 1-100 in participants with IgAN.

IgA reduction at 8 weeks of treatment in IgAN patients is correlated with proteinuria reduction after 36 weeks of treatment.

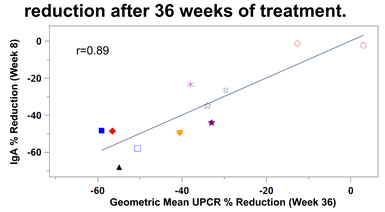


Figure 6. Trial level correlation between the mean IgA reduction and the geometric mean UPCR lowering in participants with IgAN.

The magnitude of APRIL neutralization is correlated with proteinuria reduction in IgAN patients.

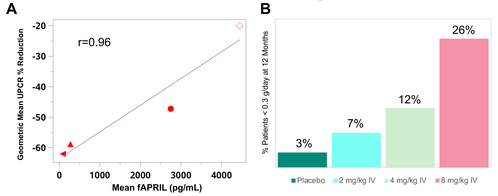


Figure 7. Trial level correlation between degree of APRIL neutralization and proteinuria reduction (A) and dose-dependence of clinical remission (B) in participants with IgAN across the Phase 2 sibeprenlimab dose range.

DATA SOURCES

Ataciept
Willen 2020 (Eur J Drug Metab Pharmacokinet) for HV IgA Figures 4 and 5 Data averaged over the Caucasian and Japanese cohorts.
Lafayette 2024 (KI Reports) IgAN IgA in Figures 4-6, Gd-IgA Figure 5, UPCR Figures 6. Week 4 and 12 IgA data averaged for Week 8 in Figure 6.

Felzartamab
Floege 2024 (ERA) for IgAN IgA Figure 6, UPCR Figure 6. IgA reductions reported as medians.

Mezagitamab
December 2024 Takeda SEC form 6-K for IgAN IgA Figures 5-6, Gd-IgA Figure 5, UPCR Figure 6.

Povetacicept
Davies 2024 (Clin Transl Sci) for HV IgA Figures 4 and 5.
Madan 2024 (ASN) for IgAN IgA Figure 5, Gd-IgA1 in Figure 5, UPCR in Figure 6. Gd-IgA used instead of IgA through Week 8 in Figures 4 and 6 due to unavailability of IgA data through Week 8 in IgAN patients.

Sibeprenlimab
Mathur 2022 (KI Reports) for HV IgA Figures 4 and 5. Data is averaged from the 2mg/kg cohort (weight=1/3) and 6 mg/kg cohort (weight=2/3).
Chan 2023 (KI Reports) for IgAN IgA Figures 4-6, Gd-IgA Figure 5. IgA data presented as pooled sibeprenlimab or placebo.
Mathur 2024 (NEJM) for IgAN IgA Figures 5-6, Gd-IgA Figure 5, UPCR Figures 6-7, Clinical remission Figure 7, fApril Figure 7. UPCR for pooled sibeprenlimab in Figure 6 was based on averaging the Week 36 UPCR % change values over the 2, 4, and 8 mg/kg dose levels.

Zigakibart
Lo 2020 (ERA-EDTA) for HV IgA Figures 4 and 5. Data is the weighted avg of the 450 mg dose (wt = 5/6) and the 1350 mg dose (wt = 1/6).
Barratt 2023 (ERA) for IgAN IgA Figures 4-6, Gd-IgA Figure 5.
Barratt 2024 (ASN abstract) for UPCR Figure 6. Week 36 UPCR result is linear interpolation between Weeks 28 and 52.

Background figure
Adapted from Mathur 2023 (J Clin Med)

Note: Data digitized from available published tables and figures to approximate actual results. These data are derived from different trials at different points in time, with differences in trial design and populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials of JADE101 and other agents have been conducted.

ACKNOWLEDGEMENTS

We thank our colleagues at Paragon Therapeutics for their contributions to the discovery of JADE101, and NHP PKPD studies.

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