Nonclinical Safety Profile of JADE101, a Half-Life Extended Fully Human Monoclonal Antibody Targeting APRIL for the Treatment of IgAN

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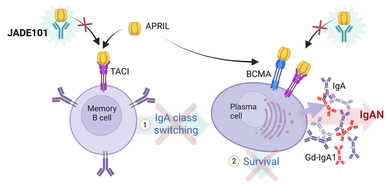
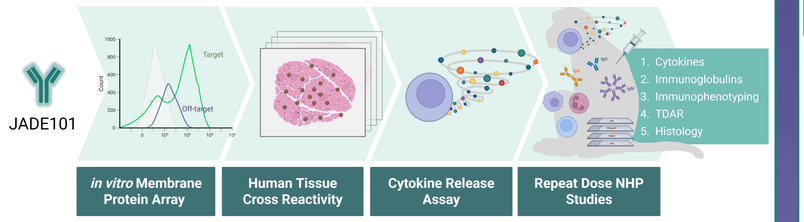
BACKGROUND

IgA nephropathy (IgAN) is a chronic autoimmune kidney disease characterized by mesangial deposition of immune complexes containing IgA and Gd-IgA1. A proliferation-inducing ligand (APRIL), a TNF superfamily cytokine, is critical in driving production of Gd-IgA1 through IgA class switching. Blocking APRIL reduces Gd-IgA1 levels resulting in reduced proteinuria and preservation of kidney function in IgAN patients. Evaluation of anti-APRIL therapies has consistently shown a favorable safety profile in healthy volunteers and IgAN patients. JADE101 is a fully human anti-APRIL IgG1 monoclonal antibody (mAb) engineered for high affinity, to limit effector function, and to extend half-life. Studies were conducted to characterize the nonclinical safety profile of JADE101.



METHODS

Nonclinical safety studies conducted with JADE101 included an in vitro membrane protein array, a human tissue cross reactivity assay, an in vitro cytokine release assay with human whole blood, and repeat-dose studies in non-human primates (NHP). In vivo studies included evaluation of cytokines, B cell activating factor (BAFF), immunoglobulins (Ig), immunophenotyping, T cell-dependent antibody response (TDAR), and histology.



RESULTS

JADE101 showed no cell membrane binding in a panel of human tissues

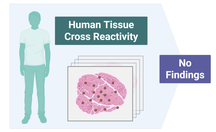


Figure 8. Specific binding of biotinylated JADE101 was assessed by immuno-histochemistry in a panel of 37 frozen human tissues.

JADE101 showed no histological changes in NHP tissues

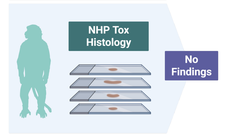


Figure 9. NHPs were dosed with JADE101 SC at 0, 40, 80, or 174 mg/kg/dose Q2W (Days 1, 15, 29). Tissues were collected at the end of the dosing phase for histological evaluations.

RESULTS

No off-target binding of JADE101 against panel of human proteins

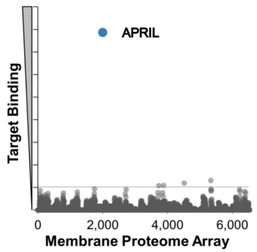


Figure 1. Human membrane proteins (>6000) were expressed in individual wells of HEK-293T cells arrayed in 384-well plates. Potential JADE101 binding to the targets was assessed by flow cytometry.

JADE101 does not elicit cytokine release *in vitro*

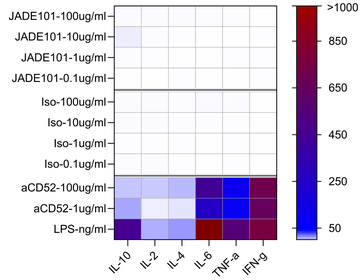


Figure 2. Heat map depicts average fold change from PBS-treated human whole blood samples after 24hr incubation (average for 10 donors) at each stimulation condition.

JADE101 administration in NHPs does not elicit cytokine release

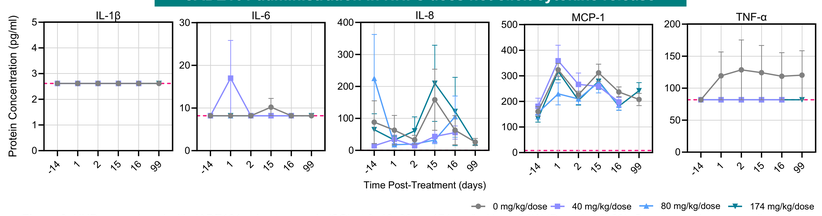


Figure 3. NHPs were dosed with JADE101 subcutaneously (SC) at 0, 40, 80, or 174 mg/kg/dose Q2W (Days 1, 15, 29). Serum samples were collected and analyzed for cytokine levels. Pink-dotted line represents LLOQ. Data shown as mean ± SEM. Data from males and females combined.

JADE101 administration in NHPs does not induce BAFF

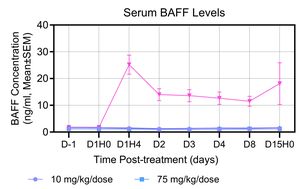


Figure 4. NHPs were dosed with JADE101 intravenously (IV) at 10 mg/kg single dose or SC at 75 or 150 mg/kg Q2W (Days 1, 15, 29) or with 10 mg/kg of a positive control B cell depleter. Serum samples were collected and analyzed for BAFF levels. Data shown as mean ± SEM.

JADE101 administration in NHPs reduced serum immunoglobulins consistent with MOA

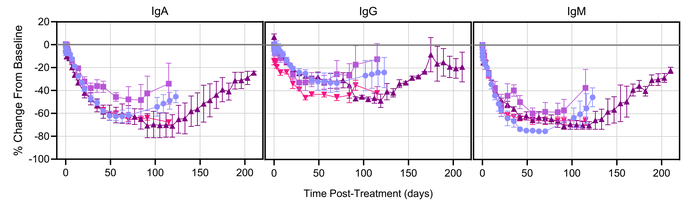


Figure 5. NHPs were dosed with a single dose of JADE101 IV at 4 or 30 mg/kg or SC at 10 or 100 mg/kg. Serum samples were collected and analyzed for immunoglobulins (IgA, IgG, and IgM). NHPs at 10 and 100 mg/kg SC were sampled out to 115 days post-dose, NHPs at 4 mg/kg IV were sampled out to 123 days post-dose, and NHPs at 30 mg/kg IV were sampled out to 210 days post-dose. IgA and IgM reductions ranged from 54.7–67.6% (IgA) and 61.5–75.4% (IgM) from baseline. IgG reductions ranged from 34.6–47.7% from baseline. IgA, IgG, and IgM levels returned predictably towards baseline following JADE101 clearance. Data shown as mean ± SEM.

JADE101 administration in NHPs does not impact immune cell populations

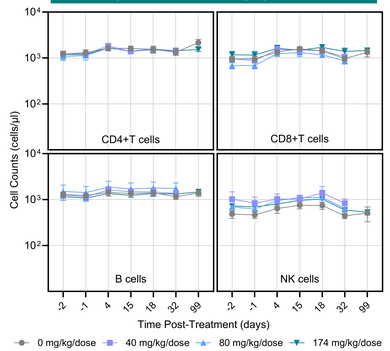


Figure 6. NHPs were dosed with JADE101 SC at 0, 40, 80, or 174 mg/kg/dose Q2W (Days 1, 15, 29). Immune cells were characterized by flow cytometry pre-study and on Days 4, 15, 18, 32, and 99 (control and high dose only). Data shown as mean ± SEM. Data from males and females combined.

Robust vaccination responses to KLH immunization retained in JADE101-treated NHPs with kinetics comparable to control

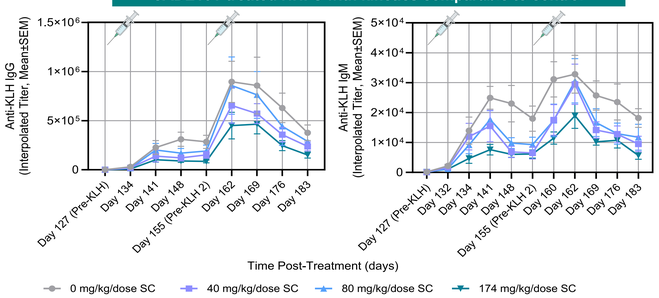


Figure 7. NHPs were dosed with JADE101 SC at 0, 40, 80, or 174 mg/kg/dose Q2W for 26 weeks. KLH was administered on Days 127 and 155. Anti-KLH IgG and IgM antibodies were quantitated using an ELISA assay at several timepoints following KLH administration. Data shown as mean ± SEM. Data from males and females combined.

CONCLUSIONS

- JADE101 demonstrated low potential for off-target binding and cytokine release in vitro and no specific cell membrane binding in human tissues
- Consistent with an anti-APRIL MOA, JADE101 resulted in marked reductions of IgA and IgM, and modest reductions in IgG in NHPs (IgG sparing), all of which returned towards baseline following JADE101 clearance
- Despite reductions in immunoglobulins, JADE101-treated NHPs mounted robust humoral responses to KLH antigen with kinetics comparable to control (consistent with robust vaccination responses with anti-APRILs in HVs[1])
- JADE101 was well tolerated in NHPs at high doses, with no histological effects or effects on immune cells, soluble BAFF levels, or cytokines
- Other anti-APRIL mAbs (Sibeprenlimab[1,2,3,4] and Zigakibart[5,6]) have consistently shown an excellent safety profile in global clinical trials including no effect on circulating immune cell populations and no clinically meaningful immunosuppression

Therefore, by potently blocking APRIL-mediated signaling, JADE101 has the potential to provide disease-modifying treatment to IgAN patients with low risk of toxicity and no impact on circulating immune cells

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