Background and Aims: ENVISION, an ongoing global P2 trial of sibeprenlimab, a mAb that neutralizes A Proliferation Inducing Ligand (APRIL) for the treatment of IgAN, previously reported an interim 43% placebo (pbo)-adjusted reduction from baseline in 24-hour uPCR at 9 months. The trial has been conducted through the ongoing COVID pandemic. To assess the effect of sibeprenlimab on COVID-risk, infection and vaccination (vac) data were recorded for all subjects. For consenting sub-study subjects (SS) (n = 72), serologic responses to SARS-CoV2 proteins were measured monthly.

Method: Serum IgG antibodies specific for SARS-CoV-2 antigens were quantified using Meso Scale Discovery (MSD) V-PLEX SARS-CoV-2 Panel 24, a validated multiplexed assay. IgG levels were reported in WHO binding antibody units (BAU)/mL. Peak Receptor Binding Domain (RBD) IgG antibody titers were evaluated for SS following primary (2-dose) mRNA vaccination. Slopes of IgG RBD decline were utilized to generate preliminary estimates of time above protective threshold. A Welch two-sample t-test was applied to the log-transformed peak RBD titer values for significance testing.

Results: Among 155 IgAN patients enrolled and followed for 16 months (with 12 monthly sibeprenlimab or pbo infusions) between August 2020 and the present, COVID infection was reported in 55 overall. Two patients were hospitalized in accordance with standard local COVID protocols; none were admitted to ICU or mechanically ventilated and there were no fatalities. All other episodes of COVID infection were considered to be of mild or moderate severity (treatment status remains blinded for AE evaluation). COVID vaccination was administered to 46 SS; including 34 recipients of mRNA vaccines only (1, 2, 3 or 4 doses). There were no identified IgAN disease flares following vaccinations. Parameters characterizing IgG RBD titer were obtained from subjects receiving a 2-dose mRNA primary vaccination with sufficient data, excluding subjects with confounding COVID infection at the time of vaccination (n = 22). All subjects achieved a peak titer of >915 BAU/mL, with similar kinetics between arms. Geometric mean peak RBD IgG antibody level (Fig. 1) following vaccination was higher in pbo recipients (5600 BAU/mL) vs Sibeprenlimab (2410 BAU/mL) (p = 0.033). RBD IgG decline post mRNA vaccination (in any patient with at least one mRNA dose without confounding subsequent vac or infection) was evaluable in 28 SS. Rates of decline were similar between groups (Fig. 2), with comparable modeled time above an arbitrary protective threshold of 300 BAU/mL (~5-6 months, data not shown). In addition, there was no evidence that sibeprenlimab impeded robust humoral immune responses to actual infection.

Conclusion: Sibeprenlimab is a promising immunomodulatory therapy for treatment of IgAN. COVID-specific vaccine and infection-induced humoral immune responses were preserved during Sibeprenlimab therapy.