Introduction: Antigen activated B cells are down-regulated by engagement of immune complexes with the inhibitory Fc receptor FcγRIIB on the B cell surface. XmAb5871, an anti-IgG4 mAb, has been engineered to enhance binding to FcγRIIB. The co- ligation of the B cell receptor-associated membrane protein CD19 and FcγRIIB by XmAb5871 results in inhibition of many activation pathways in both healthy and disease B cells and in potent suppression of B cell responses without destroying B cells.

Study Design: Phase 2 single center, open-label, multiple-dose study 15 IgG4-RD patients were enrolled to receive 5.0 mg/IgG IV infusions of XmAb5871 14 days apart for 12 doses. Dosing occurred on Days 1, 15, 29, 43, 57, 71, 85, 99, 133, 167, and 155. Final efficacy assessments occurred on Day 180, 2 weeks following the last dose.

Diagnostics:

Demographics:

- Age (Years, median [range]): 63 (43 - 77)
- Sex: Male 10 (67%), Female 5 (33%)
- Race: White 12 (80%), Asian 2 (14%), Black 1 (7%)

Disease Characteristics:

- IgG4-RD Responder Index – median [range]: 12 (2 - 30)
- IgG4 level (normal 3.9 - 86.4 mg/dl) – median [range]: 220 (25 - 2455)
- Previously treated – n (%) 10 (67%)

Activity at Baseline:

- CD19+ Plasmablasts

Number of Involved Organs at Baseline:

- Median (Range): 5 (1-10)

Exposure as of April 18, 2017:

- Median infusions (Range): 12 (5-12)

Safety:

- 31 TEAEs were reported in 13 patients. Of those, 35 events in 7 patients were considered to be drug-related, all mild or moderate in severity. The most common AEs thought to be XmAb5871-related were nausea, abdominal pain, chills, and headache, each reported in 2 subjects.

- Discontinuations: 3 patients discontinued the study early. One patient never achieved a response, a second responded but then lost response and the third responded but had an infusion-related hypersensitivity reaction after her 5th infusion that was later determined to be coincident with an anti-drug antibody response.

Mechanistic Studies:

Efficacy:

- The IgG4-RD Responder Index was measured at baseline, week 2, week 4, and then every 4 weeks thereafter.

IgG4-RD Responder Index Over Time

Conclusions:

- Of 15 patients who were enrolled, 10 have completed, 5 are ongoing.
- Of 14 patients who showed a decrease of 12 points in the IgG4-RD RI, 12 of them were within 2 weeks (i.e. after a single dose of XmAb5871).
- Of 5 patients were either corticosteroids or received them at the beginning of the study. All were able to taper off within 2 months.
- Of 3 patients discontinued early: one no response, one flare and one AE.
- Of 5 patients: had reached the end of the study with an IgG4-RD RI of 0 and no steroids between months 2-6 (definition of remission).
- Of further studies with IgG4-RD are being planned.