Top-line Results of a Phase 2, Double-blind, Randomized, Placebo-Controlled Study of a Reversible B Cell Inhibitor, XmAb®5871, in Systemic Lupus Erythematosus (SLE)

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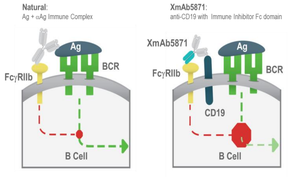
Introduction:

Antigen activated B cells are down-regulated by engagement of immune complexes with the inhibitory Fcγ receptor FcγRIIb on the B cell surface. XmAb5871, an anti-CD19 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.



Objectives:

Primary Objective:

To determine the ability of XmAb5871 to maintain SLE disease activity improvement achieved by a brief course of disease-suppressing IM steroid therapy in SLE patients.

Secondary Objectives:

To evaluate time to loss of SLE disease activity improvement achieved by a brief course of disease-suppressing IM steroid therapy in SLE patients.

To evaluate the safety and tolerability of every other week IV administration of XmAb5871 in patients with SLE.

To evaluate the pharmacokinetics (PK) and immunogenicity of every other week IV administration of XmAb5871 in patients with SLE

Exploratory Objectives:

To characterize PD effects on absolute B cell count, autoantibodies, complement and cytokine levels over time.

Patient Population:

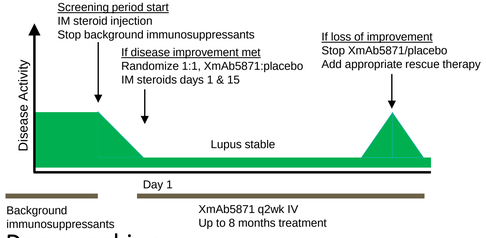
Male and female patients ages 18 to 65 inclusive with active SLE at screening. Patients had to stop all immunosuppressant agents by randomization, but were allowed to remain on hydroxychloroquine and prednisone equivalent of 10 mg or less per day. Patients could not have organ threatening disease.

Study Design:

Phase 2 randomized, double-blind, placebo-controlled study of approximately 100 patients with active SLE

Patients had to have moderate to severe non-organ threatening SLE activity defined as either a SELENA SLEDAI of ≥6 (≥4 points of which must come from non-serological finding) OR ≥ 1 BILAG B OR ≥ 1 BILAG A score.

104 SLE patients were enrolled to receive 5.0 mg/kg IV infusions of XmAb5871 14 days apart for 16 doses. Patients remained in study for up to 225 days with dosing given until LOI was apparent or through Day 211 (2 weeks prior to Day 225).



Demographics:

		XmAb5871 (N=52)	Placebo (N=52)
Age	**Years, median (range)**	**45.5 (23 - 65)**	**43.5 (20-64)**
Sex	**Female**	**50 (96.2%)**	**49 (94.2%)**
Race	**White**	**19 (36.5%)**	**25 (48.1%)**
	Black	**26 (50.0%)**	**25 (48.1%)**
	Asian	**2 (3.8%)**	**1 (1.9%)**
	American Indian or Alaska Native	**2 (3.8%)**	**1 (1.9%)**
	Other	**3 (5.8%)**	**0**
Screening SLE Activity	**Baseline BILAG, median (range)**	**17 (8, 28)**	**16 (9, 32)**
	Baseline SLEDAI, median (range)	**8 (4, 16)**	**10 (2, 18)**

Disposition:

	XmAb5871 (N=52)	Placebo (N=52)
Completed the Study to Day 225	**28 (53.8%)**	**17 (32.7%)**
Reasons for Early Discontinuation:		
Loss of Improvement	**14 (58.3%)**	**25 (71.4%)**
Adverse Event *	**7 (29.2%)**	
Withdrawal	**3 (8.6%)**	**10 (21.1%)**

* Includes 6 XmAb-treated patients that had infusion-related events on the first dose and withdrew from the study due to intolerance to medication.

Safety:

TEAEs:

531 TEAEs were reported in 85 patients. Of those, 149 events in 41 patients were considered to be drug-related (26% in the placebo arm). The vast majority of TEAEs were mild or moderate in severity. The most common AEs seen in >5% of patients are shown below:

XmAb5871-04 TEAEs in > 5% of Patients

TEAE (MedDRA)	XmAb5871 (N=52)		Placebo (N=52)	
	All TEAE, n (%)	Related TEAE n(%)	All TEAE, n (%)	Related TEAE, n(%)
Nausea	**20 (38.5)**	**14 (26.9)**	**9 (17.3)**	**5 (9.6)**
Headache	**12 (23.1)**	**6 (11.5)**	**1 (1.9)**	**--**
Muscle spasms	**5 (9.6)**	**3 (5.8)**	**6 (11.5)**	**1 (1.9)**
Back pain	**8 (15.4)**	**5 (9.6)**	**2 (3.8)**	**--**
Upper respiratory tract infection	**4 (7.7)**	**--**	**6 (11.5)**	**--**
Vomiting	**9 (17.3)**	**9 (17.3)**	**1 (1.9)**	**--**
Dizziness	**8 (15.4)**	**3 (5.8)**	**1 (1.9)**	**--**
Cough	**4 (7.7)**	**2 (3.8)**	**4 (7.7)**	**1 (1.9)**
Diarrhoea	**4 (7.7)**	**1 (1.9)**	**4 (7.7)**	**1 (1.9)**
Urinary tract infection	**5 (9.6)**	**--**	**3 (5.8)**	**--**
Flushing	**7 (13.5)**	**4 (7.7)**	**0 (0.0)**	**--**
Nasopharyngitis	**4 (7.7)**	**--**	**3 (5.8)**	**--**
Pain in extremity	**6 (11.5)**	**--**	**1 (1.9)**	**--**
Abdominal pain	**5 (9.6)**	**2 (3.8)**	**1 (1.9)**	**--**
Abdominal pain upper	**3 (5.8)**	**3 (5.8)**	**2 (3.8)**	**1 (1.9)**

SAEs:

13 SAEs were reported in 11 subjects in the study:

- **XmAb5871:**
  Fever, SLE flare (lung), Atrial fibrillation, Worsening hypertension, Iron deficiency anemia, Pneumonia (36 days after last dose [10 half-lives]), Infusion related reaction, Vertigo
- **Placebo:**
  Anemia SLE flare, SLE flare (enteritis), angioedema, migraine headache

- All SAEs were considered Not or Unlikely Related except the infusion related reaction.
- There were no deaths and no opportunistic infections.

Analysis:

Analysis Populations	
Efficacy Evaluable	**All subjects who completed Day 225, had LOI, or discontinued due to a drug-related adverse event Excludes 12 treated subjects who discontinued early with no LOI and no toxicity (2 XmAb, 10 placebo)**
Intent to Treat	**All subjects that received a partial dose of XmAb5871 or placebo**
Day 169 Efficacy	**Original 6-month endpoint**

Primary Endpoint:

The primary endpoint was Loss of Improvement at Day 225 in the Efficacy Evaluable Population was not statistically significant (p = 0.18). However, the first secondary endpoint of time to loss of improvement was significant (p = 0.025).

		XmAb5871 (N=50)	Placebo (N=42)
Response Rate (No loss of improvement through Day 225)	**n (%)**	**21 (42.0)**	**12 (28.6)**
95% Confidence Interval		**(28.2, 56.8)**	**(15.7, 44.6)**
Non-Responder	**n (%)**	**29 (58.0)**	**30 (71.4)**
Loss of improvement at any visit	**n (%)**	**23 (46.0)**	**30 (71.4)**
Early discontinuation for toxicity (assigned non-responder status)	**n (%)**	**6 (12.0)**	**0**

Secondary Endpoints:

Time to Loss of Improvement Thru Day 225 Planned Visit – Efficacy Evaluable

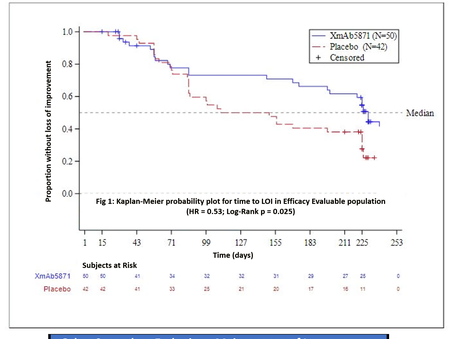


Fig 1: Kaplan-Meier probability plot for time to LOI in Efficacy Evaluable population (HR = 0.53; Log-Rank p = 0.025)

Time to Loss of Improvement Thru Day 225 Planned Visit – Intent to Treat

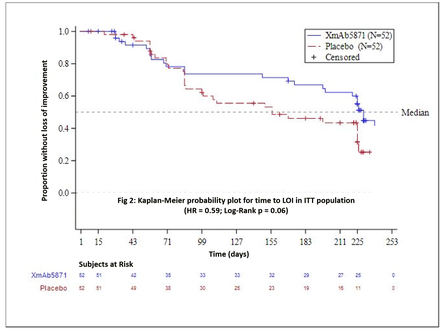


Fig 2: Kaplan-Meier probability plot for time to LOI in ITT population (HR = 0.59; Log-Rank p = 0.06)

Other Secondary Endpoints: Maintenance of Improvement			
	Efficacy Evaluable Population		
	XmAb5871	**Placebo**	**p value**
% Response at Day 169	**58**	**40.5**	**0.11**
	Intent to Treat Population		
	XmAb5871	**Placebo**	**p value**
% Response at Day 225	**40.4**	**23.1**	**0.06**
% Response at Day 169	**57.7**	**34.6**	**0.02**

Median Time on Treatment and Number of Infusions Received			
		XmAb5871 (N=52)	**Placebo (N=52)**
Time on Treatment	**Months, median (range)**	**6.9 (0.0 – 7.4)**	**3.6 (0 – 7.0)**
Number of Infusions	**Median (range)**	**15 (1 – 16)**	**8.5 (1 – 16)**

Conclusions:

- Positive trend in primary endpoint, proportion of efficacy-evaluable patients who did not experience loss of improvement (LOI) by Day 225, but did not meet statistical significance (XmAb5871 42% vs. placebo 28.6%, p = 0.18)
- Median time to LOI (a secondary endpoint) was extended by 76% for patients treated with XmAb5871 (median 230 days vs. 131 days for patients on placebo, hazard ratio = 0.53, p = 0.0252)
- XmAb5871-treated patients remained without increase in disease activity and on study longer than the placebo patients.
- Risk of increased SLE disease activity was reduced by 47% for patients treated with XmAb5871 (median 230 days vs. 131 days for patients on placebo, hazard ratio = 0.53, p = 0.0252)
- XmAb5871 well-tolerated and safety profile consistent with previous studies, except for discontinuations from infusion reactions. In order to avoid the infusion reactions, a subcutaneous formulation will be used in future studies. Bioavailability studies with the SC drug showed no infusion reactions or GI-related infusion reactions in a healthy population of 40 subjects.