

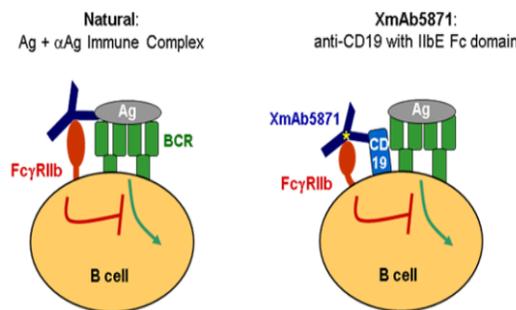
A Phase 1b/2a Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of XmaB[®]5871 in Patients with Rheumatoid Arthritis

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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 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 B cell down-regulation in a manner analogous to immune complexes.



Objectives:

Primary Objective: To determine the safety and tolerability profile of multiple dose, every 14-day, IV administration of XmaB5871.

Secondary Objectives: To characterize the PK and immunogenicity of multiple dose, IV-administered XmaB5871.

To evaluate the effect of XmaB5871 on RA disease response as measured by changes in DAS28-CRP at Week 13 (Part B).

Exploratory Objectives: To characterize PD, effects on biomarkers of disease/inflammation, and effects on RA disease activity by DAS28-CRP, EULAR and ACR criteria in all dose groups over time.

Patient Population:

Patients with active RA on stable non-biologic DMARD therapy. Active RA at screening was defined as:

Part A: ≥ 4 SJC (out of 28) AND ≥ 4 TJC (out of 28) AND at least 1 of the following: ESR ≥ 28 mm/hr, OR hsCRP ≥ 10 mg/L, OR Morning stiffness ≥ 45 minutes.

For Part B: ≥ 5 SJC (out of 28) AND ≥ 5 TJC (out of 28), AND Positive RF OR ACPA, AND hsCRP ≥ 10 mg/L (reduced to hsCRP ≥ 6 mg/L by amendment)

Study Design:

Phase 1b multiple center, randomized, placebo-controlled, double-blinded, multiple ascending dose clinical study (Part A) followed by Phase 2a cohort extension (Part B) at the top dose examined in Part A.

RA patients were randomized (3:1) to receive ascending IV infusions of XmaB5871 (0.3, 1.0, 3.0 and 10.0 mg/kg) or placebo 14 days apart for 6 doses (Part A), followed by an expansion cohort at 10.0 mg/kg or placebo (randomized 2:1) 14 days apart for 6 doses (Part B).

Dosing occurred on Days 1, 15, 29, 43, 57 and 71. Efficacy assessments occurred on Day 85, 2 weeks following the last dose.

Results:

Pharmacokinetics (PK):

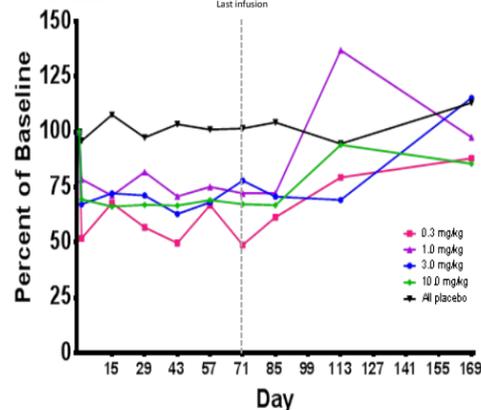
- C_{max} and AUC increased in an approximately proportional manner with dose increment with little accumulation.
- T_{1/2} averaged 3.5 ± 1.0 days.

Pharmacodynamics (PD):

Complete CD19 receptor occupancy was demonstrated from Day 2 through the end of dosing for the 1.0, 3.0, and 10.0 mg/kg cohorts, with recovery to baseline levels occurring with clearance of drug.

Peripheral B cell count decreased after dosing in all cohorts, with a mean reduction at nadir of approximately 30-40 % of baseline values. The nadir did not increase with increasing dose.

Mean % of Baseline Absolute B Cell Count by Cohort



Safety:

Multiple dose XmaB5871 was safe and generally well tolerated. The most common AEs in the XmaB5871 group were vomiting, headache and nausea. Nine subjects (23%), all receiving 10.0 mg/kg, had their XmaB5871 IV infusion temporarily suspended as a result of gastrointestinal-related symptoms (nausea, vomiting or diarrhea). In all cases the patients were able to continue the infusion after a short interruption (5-31 minutes) and symptoms did not typically recur on continuation of the infusion or during subsequent infusions. Two subjects experienced infusion-related reactions with hypotension (both at 10 mg/kg) and were discontinued. The nature and severity of these infusion reactions were consistent with those reported for other monoclonal antibody therapies.

SAEs: 2 SAEs occurred in 2 XmaB5871 treated patients, both in the 10 mg/kg group; 1 Infusion-related reaction with hypotension occurring during the 2nd infusion and 1 deep venous thrombosis with onset 22 days (> 6 half-lives) after the last infusion.

Immunogenicity: 7 patients (7/40, 17.5%), all in the 10.0 mg/kg XmaB5871 group, and 1 placebo patient (1/16, 6%) had at least one sample positive for ADA. The majority were of low titer; only 2 of the 7 patients had positive ADA samples that remained positive after a >2-fold dilution. One of these 2 patients experienced apparent hypersensitivity reactions during the 2nd and 3rd infusions associated with the development of ADA at the time of 2nd infusion with increasing ADA titer thereafter. There was no strong correlation between ADA response and drug exposure for any patient in this study.

Summary of XmaB5871 TEAEs in ≥ 2 Patients (Ranked by Frequency in Total XmaB5871 Subjects)											
TEAE (MedDRA preferred term)	Number (% of Subjects)										
	Part A						Part B		All		
	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	10.0 mg/kg	Total A XmaB	Pbo A	10.0 mg/kg	Pbo B	All 10.0 mg/kg	All XmaB 5871	All Pbo
Vomiting	1 (33.3%)	0	1 (16.7%)	1 (14.3%)	3 (13.6%)	0	4 (22.2%)	0	5 (20%)	7 (17.5%)	0
Headache	0	1 (16.7%)	1 (16.7%)	1 (14.3%)	3 (13.6%)	1 (14.3%)	4 (22.2%)	0	5 (20%)	7 (17.5%)	1 (6.3%)
Nausea	0	1 (16.7%)	1 (16.7%)	2 (28.6%)	4 (18.2%)	0	2 (11.1%)	1 (11.1%)	4 (16%)	6 (15%)	1 (6.3%)
Pyrexia	0	1 (16.7%)	2 (33.3%)	0	3 (13.6%)	0	1 (5.6%)	0	1 (2.5%)	4 (10%)	0
Arthralgia	0	1 (16.7%)	2 (33.3%)	0	3 (13.6%)	0	1 (5.6%)	0	1 (2.5%)	4 (10%)	0
Diarrhea	0	0	0	0	0	0	3 (16.7%)	0	3 (7.5%)	3 (7.5%)	0
Viral upper respiratory infection	0	0	0	2 (28.6%)	2 (9.1%)	1 (14.3%)	1 (5.6%)	0	3 (7.5%)	3 (7.5%)	1 (6.3%)
Infusion related reaction	0	0	0	1 (14.3%)	1 (4.5%)	0	1 (5.6%)	0	2 (5%)	2 (5.0%)	0
Vessel puncture site bruise	0	0	0	1 (14.3%)	1 (4.5%)	0	1 (5.6%)	1 (11.1%)	2 (5%)	2 (5.0%)	1 (6.3%)
Bronchitis	0	1 (16.7%)	1 (16.7%)	0	2 (9.1%)	0	0	0	0	2 (5.0%)	0
Tracheitis	0	0	1 (16.7%)	1 (14.3%)	2 (9.1%)	0	0	0	1 (2.5%)	2 (5.0%)	0
Blood pressure increased	0	0	0	0	0	0	2 (11.1%)	0	2 (5%)	2 (5.0%)	0
Body temperature increased	0	0	1 (16.7%)	1 (14.3%)	2 (9.1%)	0	0	0	1 (2.5%)	2 (5.0%)	0
Anxiety	0	0	1 (16.7%)	0	1 (4.5%)	0	1 (5.6%)	0	1 (2.5%)	2 (5.0%)	0
Hypertension	0	0	0	1 (14.3%)	1 (4.5%)	0	1 (5.6%)	0	2 (5%)	2 (5.0%)	0
Pain in extremity	0	0	0	1 (14.3%)	1 (4.5%)	2 (28.6%)	0	0	1 (2.5%)	1 (2.5%)	2 (12.5%)
Rheumatoid arthritis	0	1 (16.7%)	0	0	1 (4.5%)	1 (14.3%)	0	1 (11.1%)	0	1 (2.5%)	2 (12.5%)
Influenza like illness	0	0	0	0	0	1 (14.3%)	0	1 (11.1%)	0	0	2 (12.5%)

Other: There was no apparent treatment effect on RA-related autoantibodies (RF and ACPA), T cell count, NK cell count or serum levels of immunoglobulins (IgE, IgG, IgG₁₋₄ and IgM).

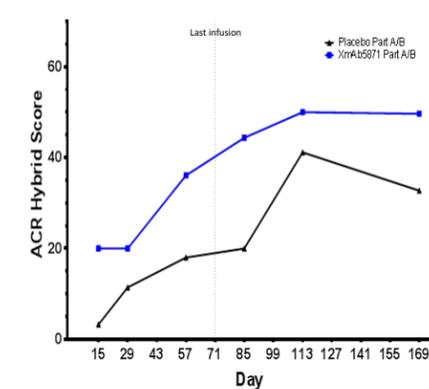
Efficacy:

15 XmaB5871-treated and 8 placebo-treated patients in Part B of the study completed all 6 infusions and the disease activity assessment at Day 85. More subjects treated with XmaB5871 (10 mg/kg) achieved DAS28-CRP low disease or remission at Day 85 than did the placebo-treated subjects. Similar trends in DAS28-CRP (and ACR assessments) were seen in the combined treatment groups. Responses were generally maintained in the post-treatment period.

ACR, DAS28-CRP, and EULAR Responses at Day 85

	Part A					Part B		All			
	0.3 mg/kg XmaB5871	1.0 mg/kg XmaB5871	3.0 mg/kg XmaB5871	10.0 mg/kg XmaB5871	All Part A XmaB5871	Part A Placebo	10.0 mg/kg XmaB5871	Part B Placebo	All 10.0 mg/kg XmaB5871	All Placebo	All A/B XmaB5871
Day 85	N=3	N=6	N=6	N=6	N=21	N=7	N=15	N=8	N=21	N=15	N=36
ACR20	3 (100.0%)	3 (50.0%)	4 (66.7%)	5 (83.3%)	15 (71.4%)	2 (28.6%)	13 (86.7%)	5 (62.5%)	18 (85.7%)	7 (46.7%)	28 (77.8%)
ACR50	1 (33.3%)	0 (0.0%)	2 (33.3%)	3 (50.0%)	6 (28.6%)	1 (14.3%)	6 (40.0%)	1 (12.5%)	9 (42.9%)	2 (13.3%)	12 (33.3%)
ACR70	1 (33.3%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	2 (9.5%)	0 (0.0%)	3 (20.0%)	0 (0.0%)	3 (14.3%)	0 (0.0%)	5 (13.9%)
ACR Hybrid Score Mean (SD)	46.5 (20.4)	31.5 (14.2)	37.8 (34.3)	40.2 (18.2)	37.9 (22.2)	20.2 (24.3)	48.1 (27.1)	24.2 (35.5)	45.8 (24.7)	22.3 (29.8)	42.2 (24.5)
ACR Hybrid Score Median	35.9	29.7	50.0	41.1	39.4	10.1	50.0	27.6	50.0	20.0	44.4
DAS28-CRP Disease Activity											
High	0 (0.0%)	1 (16.7%)	1 (16.7%)	0 (0.0%)	2 (9.5%)	1 (14.3%)	2 (13.3%)	2 (25.5%)	2 (9.5%)	3 (20.0%)	4 (11.1%)
Moderate	2 (66.7%)	3 (50.0%)	2 (33.3%)	2 (33.3%)	9 (42.9%)	5 (71.4%)	8 (53.3%)	6 (75.0%)	10 (47.6%)	11 (73.3%)	17 (47.2%)
Low	0 (0.0%)	1 (16.7%)	1 (16.7%)	2 (33.3%)	4 (19.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	4 (19.0%)	0 (0.0%)	6 (16.7%)
Remission	1 (33.3%)	1 (16.7%)	2 (33.3%)	2 (33.3%)	6 (28.6%)	1 (14.3%)	3 (20.0%)	0 (0.0%)	5 (23.8%)	1 (6.7%)	9 (25.0%)
EULAR Response											
No	0 (0.0%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	3 (14.3%)	5 (71.4%)	2 (13.3%)	2 (25.0%)	3 (14.3%)	7 (46.7%)	5 (13.9%)
Moderate	2 (66.7%)	4 (66.7%)	2 (33.3%)	1 (16.7%)	9 (42.9%)	1 (14.3%)	8 (53.3%)	6 (75.0%)	9 (42.9%)	7 (46.7%)	17 (47.2%)
Good	1 (33.3%)	1 (16.7%)	3 (50.0%)	4 (66.7%)	9 (42.9%)	1 (14.3%)	5 (33.3%)	0 (0.0%)	9 (42.9%)	1 (6.7%)	14 (38.9%)

Median ACR Hybrid Score Over Time



Conclusions:

XmaB5871, when administered as an IV infusion every 2 weeks over a period of 12 weeks, was found to be safe and generally well tolerated. Although the trial was not designed to observe a significant difference in efficacy results between XmaB5871- and placebo-treated patients, sufficient efficacy trends were seen to warrant continued clinical development of XmaB5871 in autoimmune diseases.

A Phase 1b/2a Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of XmAb®5871 in Patients with Rheumatoid Arthritis (RA)

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Background: XmAb®5871 is a humanized Fc engineered monoclonal antibody that binds to the B cell restricted surface antigen CD19 and has enhanced Fc binding to the inhibitory Fcγ receptor IIb (FcγRIIb). Co-ligation of CD19 and FcγRIIb by XmAb5871 has been demonstrated to reversibly down-regulate B cell activity. XmAb5871 is being developed for the treatment of B cell mediated autoimmune disorders.

Objectives: The primary objective was to determine the safety, tolerability, PK, PD and immunogenicity profile of XmAb5871 in patients with active RA on stable non-biologic DMARD therapy. A secondary objective (Phase 2a) was to evaluate the effect of XmAb5871 on RA disease response at Day 85 as measured by changes in DAS28-CRP.

Methods: This Phase 1b/2a multi-center, randomized, placebo-controlled, double-blinded, clinical study was conducted in patients with active RA despite DMARD therapy. Patients received 6 IV administrations of XmAb5871 or placebo (Pbo) on an every 14 day schedule. In the Phase 1b, 30 RA patients were randomized to Pbo or XmAb5871 in 4 consecutive dose cohorts of 0.3, 1, 3, or 10 mg/kg. After completion of the Phase 1b, 27 patients with active disease were enrolled in the Phase 2a to receive either 10 mg/kg XmAb5871 or Pbo in a 2:1 ratio.

Results: A total of 57 patients were enrolled; 40 patients received at least 1 dose of XmAb5871. Complete CD19 receptor occupancy was seen at doses of 1, 3, and 10mg/kg from 1st dose through the completion of dosing. Peripheral B cell count decreased after dosing in all cohorts, with a mean reduction at nadir of ~50%. The reduction was seen after the 1st dose and did not increase with subsequent doses. XmAb5871 was generally well tolerated, with 2 SAEs in the XmAb5871 group (infusion-related reaction, venous thrombosis). The most common treatment-related adverse events in the XmAb5871 group were nausea, vomiting or diarrhea that occurred during the 1st infusion in 25% of patients. Two subjects experienced infusion reactions with hypotension (both at 10 mg/kg) and were discontinued. The nature and severity of these infusion reactions were consistent with those reported for other monoclonal antibody therapies. In Phase 2a, there were 15 XmAb5871 treated and 8 Pbo treated patients evaluable for disease activity assessment at Day 85. More subjects treated with XmAb5871 (10 mg/kg) achieved DAS28-CRP low disease or remission at Day 85 than did the Pbo treated subjects (5/15 vs 0/8; 33% vs 0%). In addition, 40% (6/15) of the XmAb5871-treated patients achieved an ACR50 and 20% (3/15) achieved an ACR70 vs 12.5% (1/8) and 0% respectively of the Pbo-treated subjects. The mean ACR hybrid score achieved by XmAb5871- treated patients in Part A and B was 42.2, whereas the Pbo patients had a mean of 22.3 at Day 85.

Day 85	ACR Score			DAS28 CRP				
	Group	ACR20	ACR50	ACR70	High	Moderate	Low	Remission
Part A	Placebo	29%	14%	0%	14%	72%	0%	14%
Part A	XmAb5871	71%	29%	10%	10%	43%	19%	29%
Part B	Placebo	63%	13%	0%	25%	75%	0%	0%
Part B	XmAb5871	87%	40%	20%	13%	53%	13%	20%
All	Placebo	47%	13%	0%	20%	73%	0%	7%
All	XmAb5871	78%	33%	14%	11%	47%	17%	25%

Conclusions: The results of this study show that further investigation of XmAb5871 in B cell mediated autoimmune disease is warranted.

Supported by: Xencor Inc., Monrovia, CA, USA

