SYNOPSIS

Name of Sponsor/Company: Xencor, Inc. **Name of Finished Product:** XmAb®5871 **Name of Active Ingredient:** XmAb®5871	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLINDED, ASCENDING MULTIPLE-DOSE STUDY OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF XmAb®5871 IN PATIENTS WITH RHEUMATOID ARTHRITIS		
Principal Investigator: N/A **Investigators:** Petr Sramek, MD**,** Janos Bartalos, MD; Bernadette Rojkovich, MD, Gabriella Sulyok, MD; Éva Balázs, MD; Maria Jaraczewska-Baumann, MD; Mariusz Korkosz, MD; Stefan Daniluk, MD; Dr. Anna Zubrzycka-Sienkiewicz; Jana Zimanova, MD		
Study center(s): Pharmaceutical Research Associates CZ; PRA Magyarország Kft. Fázis I-es Klinikai Farmakológiai Vizsgálóhely; Budai Irgalmasrendi Kórház Kht.; Drug Research Center (DRC); Csongrád Megyei, Dr. Bugyi István Kórház; NZOZ Centrum Medyczne HCP; Rheumatology Unit, Dept. of Internal Medicine, University Hospital, Krakow; NZOZ Centrum Osteoporozy I Chorob; Linea Corporis chirurgia plastyczna Sp. z o.o.; Summit Clinical Research, s.r.o.		
Publications (reference): None at time of writing this report		
Studied period (years): Date first patient screened: 19 December 2012 Date last patient follow-up: 30 September 2014		**Phase of development:** 2a

Objectives:

Primary:

- To determine the safety and tolerability profile of multiple dose, every 14-days, intravenous (iv) administration of XmAb5871 in patients with rheumatoid arthritis (RA)

Secondary:

- To characterize the pharmacokinetics (PK) and immunogenicity of multiple dose, intravenously administered XmAb5871 in patients with RA
- To evaluate the effect of XmAb5871 on RA disease response as measured by changes in Disease Activity Score 28 using C-reactive protein (DAS28-CRP) at Week 13 (Part B)

Methodology: The Phase 2a clinical study was conducted in 2 parts: Part A was a multiple ascending dose portion followed by Part B, an expansion cohort, to further investigate one of the doses previously studied in Part A (10 mg/kg).

Number of patients (planned and analyzed): 56 patients were dosed in the complete study: 29 patients in Part A (22 XmAb5871, 7 placebo) and 27 patients in Part B (18 XmAb5871, 9 placebo). 51 patients completed the study (36 XmAb5871, 15 placebo).
Diagnosis and main criteria for inclusion: 18–70 years of age, inclusive (up to 65 years in the Czech Republic); diagnosis of RA present for at least 6 months as defined by 1987 American College of Rheumatology (ACR) RA classification criteria with active disease on stable non-biologic disease modifying anti-rheumatic drug (DMARD) therapy; Global functional class I, II, or III according to the ACR 1991 revised criteria.
Test product, dose and mode of administration, batch number: In Part A, XmAb5871 was administered as an iv infusion over 2 hours, every 14 days, for up to 6 administrations at one of 4 doses (0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg and 10 mg/kg). In Part B, the Dose Escalation Safety Committee (DESC), following a full review of data from Part A, determined that the dose to use in Cohort 5 would be 10 mg/kg.
Duration of treatment: 85 days
Reference therapy, dose and mode of administration, batch number: N/A
Criteria for evaluation: PK variables derived from plasma XmAb5871 concentrations; Efficacy parameters (Changes in DAS28-CRP, EULAR response, ACR20/50/70 and ACR hybrid responses from baseline to Week 13). **Safety:** Adverse events**;** Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature)**;** Electrocardiogram (12-lead ECG)**;** Immunogenicity (anti-XmAb5871 antibody – anti-drug antibodies, ADA)**;** Physical examination (including height and weight)**;** Clinical laboratory (clinical chemistry, hematology, coagulation, and urinalysis).

SUMMARY – CONCLUSIONS

SAFETY RESULTS:

Across both Part A and Part B of the study, related treatment-emergent adverse events (TEAEs) with the highest frequency, which were reported in more than 10% of all patients who received any dose of XmAb5871, were vomiting (17.5%), nausea (15.0%), and headache (10%).

Summary of All Study XmAb5871-02 Treatment-related TEAEs in ≥ 2 Patients (Ranked by Frequency in Total XmAb5871-treated Patients)

	Number (%) of Subjects										
	Part A						Part B		All		
TEAE (MedDRA preferred term)	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg	10.0 mg/kg	Total A	Placebo A	10.0 mg/kg	Placebo B	All 10.0 mg/kg	All XmAb5871	All placebo
	N = 3	N = 6	N = 6	N = 7	N = 22	N = 7	N = 18	N = 9	N = 25	N = 40	N = 16
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
Nausea	0	1 (16.7%)	1 (16.7%)	1 (14.3%)	3 (13.6%)	0	2 (11.1%)	0	3 (12%)	5 (12.5%)	0
Headache	0	1 (16.7%)	1 (16.7%)	0	2 (9.1%)	0	2 (11.1%)	0	2 (8%)	4 (10.0%)	0
Diarrhoea	0	0	0	0	0	0	3 (16.7%)	0	3 (12%)	3 (7.5%)	0
Pyrexia	0	1 (16.7%)	1 (16.7%)	0	2 (9.1%)	0	1 (5.6%)	0	1 (4%)	3 (7.5%)	0
Infusion related reaction	0	0	0	1 (14.3%)	1 (4.5%)	0	1 (5.6%)	0	2 (8%)	2 (5.0%)	0
Bronchitis	0	1 (16.7%)	1 (16.7%)	0	2 (9.1%)	0	0	0	0	2 (5.0%)	0
Body temperature increased	0	0	1 (16.7%)	1 (14.3%)	2 (9.1%)	0	0	0	1 (4%)	2 (5.0%)	0
Influenza-like illness	0	0	0	0	0	1(14.3%)	0	1(11.1%)	0	0	2 (12.5%)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Treatment-related TEAEs: includes those TEAEs judged by the Investigator to have a possible, likely, or definite relationship to treatment.

PK RESULTS:

Across all dose levels, last dose clearance averaged 15.16 ± 3.68 mL/day/kg. Last dose volume of distribution averaged 49.27 ± 14.17 mL/kg. Accumulation with a dosing interval of every 2 weeks was low (8% to 22% increase in AUC from first to last dose). Last dose half-life averaged 3.51 ± 1.06 days.

IMMUNOGENICITY RESULTS:

Anti-drug antibody (ADA) positive samples were found in seven (17.5%) XmAb5871 treated subjects, all in the 10.0 mg/kg group, and in 1 placebo treated subject. There was no definitive association with the presence of ADA and adverse events except in one patient who experienced symptoms of hypersensitivity reaction. There was no strong correlation between ADA response and drug exposure.

EFFICACY RESULTS:

DAS28-CRP and EULAR Responses at Day 85

	DAS28-CRP Diesease Activity				EULAR Response		
	High	Moderate	Low	Remission	No	Moderate	Good
All 10.0 mg/kg N=21	2 (9.5%)	10 (47.6%)	4 (19.0%)	5 (23.8%)	3 (14.3%)	9 (42.9%)	9 (42.9%)
All XmAb 5871 N=36	4 (11.1%)	17 (47.2%)	6 (16.7%)	9 (25.0%)	5 (13.9%)	17 (47.2%)	14 (38.9%)
All Placebo N=15	3 (20.0%)	11 (73.3%)	0	1 (6.7%)	7 (46.7%)	7 (46.7%)	1 (6.7%)

ACR Responses at Day 85

	ACR 20	ACR 50	ACR 70
All 10.0 mg/kg N=21	18 (85.7%)	9 (42.9%)	3 (14.3%)
All XmAb 5871 N=36	28 (77.8%)	12 (33.3%)	5 (13.9%)
All Placebo N=15	7 (46.7%)	2 (13.3%)	0

Patients who received XmAb5871 compared to those who received placebo, on Day 85, showed:

- Higher rates of ACR20, ACR50 and ACR70 response versus the placebo group
- More patients with DAS28-CRP Disease Activity scores of low disease activity and remission (41.7% XmAb5871-treated versus 6.7% placebo-treated in Parts A and B and 42.8% versus 6.7% in the 10 mg/kg cohort)
- A higher rate of "good" European League Against Rheumatism (EULAR) response

CONCLUSION:

XmAb5871 was safe and generally well tolerated by patients with RA within the studied dose range.

Generally, the efficacy parameters evaluated in this clinical trial showed a trend of improvement of RA in patients who received XmAb5871 when compared to placebo.

Date of the report: October 4, 2016