Clinical trial results:
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

Summary

EudraCT number	2012-003057-29
Trial protocol	CZ SK HU
Global end of trial date	30 September 2014

Results information

Result version number	v1 (current)
This version publication date	12 November 2016
First version publication date	12 November 2016
Summary attachment (see zip file)	XmAb5871-02 Study Synopsis (XmAb5871-02_EudraCT_final_synopsis_04Oct2016.pdf)

Trial information

Trial identification

Sponsor protocol code	XmAb5871-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Xencor, Inc.
Sponsor organisation address	111 West Lemon Avenue, Monrovia, United States, CA 91016
Public contact	Chief Medical Officer, Xencor Inc, 1 8584803890, pfoster@xencor.com
Scientific contact	Chief Medical Officer, Xencor Inc, 1 8584803890, pfoster@xencor.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2014
Global end of trial reached?	Yes
Global end of trial date	30 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

In Part A, a sentinel dosing strategy was used for the first dose of Cohort 1. The first 2 patients in Cohort 1 were randomized such that 1 patient received XmAb5871 and 1 patient received placebo. This sentinel pair were dosed first and were observed for 48 – 72 hours before study drug was administered to the remainder of the cohort. For all remaining cohorts, no more than 3 patients were infused on any given day.

Dose escalation to the next cohort occurred after review by the Dose Escalation Safety Committee (DESC) of safety data up to at least Day15 for all patients in a cohort. Progression to the next higher dose only occurred if the previous dose level was deemed to be safe and well tolerated by the DESC.

Background therapy:

Currently taking methotrexate (MTX) consecutively for ≥ 12 weeks and on a stable dose of oral or subcutaneous MTX at 7.5-25 mg weekly for ≥ 4 weeks at randomisation visit. A lower MTX dose was accepted if it was the highest tolerated dose; however, toxicity documentation by the Investigator was required.

All patients were to take folic acid to minimize toxicity, according to local guidelines.

Evidence for comparator:

Not applicable - comparator was standard of care for the disease plus placebo.

Actual start date of recruitment	19 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Hungary: 22
Worldwide total number of subjects	57
EEA total number of subjects	57

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	46
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled from 3 countries: Poland, Czech Republic and Hungary. Screening of patients in to Part A lasted from 19 Dec 2012 to 16 Jul 2013. Screening of patients in to Part B began on 02 Sept 2013 and ended on 07 Apr 2014. The last patient was randomised in to the study 15 Apr 2014.

Pre-assignment

Screening details:

Subjects dropping-out or withdrawing, for any reason, without completing all screening evaluations successfully, were considered as "screening failures". Such subjects did not receive a subject number, and no data were collected in the eCRFs. The Investigator kept a screening log of all subjects screened.

Period 1

Period 1 title	Part A (Cohorts 1-4)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

30 patients in Part A (23 XmAb5871, 7 placebo)

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A (Active)

Arm description:

Patients treated with active treatment

Arm type	Experimental
Investigational medicinal product name	XmAb5871
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

XmAb5871 at one of 4 doses (0.3, 1.0, 3.0, 10.0 mg/kg) was administered as an iv infusion over 2 hours every 14 days for 6 doses. XmAb5871 drug product was a liquid
product supplied in single-use glass vials.

Arm title	Part A (Placebo)

Arm description:

Patients treated with placebo treatment

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo of equal volume to match XmAb5871 was administered by iv infusion over 2 hours. The placebo solution was a vehicle control (10 mM sodium phosphate, 150 mM sodium chloride with 0.01% (w/v) polysorbate 20, pH 7.2)

Number of subjects in period 1[1]	Part A (Active)	Part A (Placebo)
Started	22	7
Completed	21	7
Not completed	1	0
Adverse event, non-fatal	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The patient enrollment in to Part A does not correspond with enrollment in to Part B. Part B was an expansion Cohort and included the enrollment of a different group of patients, in accordance with the protocol.

Period 2

Period 2 title	Part B (Cohort 5)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

27 patients in Part B (18 XmAb5871, 9 placebo)

Arms

Are arms mutually exclusive?	Yes
Arm title	Part B (Placebo)

Arm description:

Patients treated with placebo treatment

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo of equal volume to match XmAb5871 was administered by iv infusion over 2 hours. The placebo solution was a vehicle control (10 mM sodium phosphate, 150 mM sodium chloride with 0.01% (w/v) polysorbate 20, pH 7.2)

Arm title	Part B (Active)

Arm description:

Patients treated with active treatment

Arm type	Experimental
Investigational medicinal product name	XmAb5871
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

XmAb5871 administered to an expansion cohort (Cohort 5), to further investigate one of the doses previously studied in Part A (10 mg/kg), administered as an iv infusion over 2 hours every 14 days for 6 doses. XmAb5871 drug product was a liquid product supplied in single-use glass vials.

Number of subjects in period 2[2]	Part B (Placebo)	Part B (Active)
Started	9	18
Completed	8	15
Not completed	1	3
Consent withdrawn by subject	1	1
Adverse event, non-fatal	-	2

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The patient enrollment in to Part A does not correspond with enrollment in to Part B. Part B was an expansion Cohort and included the enrollment of a different group of patients, in accordance with the protocol.

Baseline characteristics

Reporting groups	
Reporting group title	Part A (Active)
Reporting group description:	
Patients treated with active treatment	
Reporting group title	Part A (Placebo)
Reporting group description:	
Patients treated with placebo treatment	

Reporting group values	Part A (Active)	Part A (Placebo)	Total
Number of subjects	22	7	29
Age categorical			
Patient Age was collected at patient enrollment			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Patient Age at enroollment			
Units: years			
median	59	61	
full range (min-max)	45 to 65	48 to 69	-
Gender categorical			
Units: Subjects			
Female	19	6	25
Male	3	1	4

Subject analysis sets	
Subject analysis set title	Pharmacokinetic Coh 2
Subject analysis set type	Safety analysis
Subject analysis set description:	
PK data for patients in Cohort 2 receiving 1.0 mg/kg XmAb5871	
Subject analysis set title	Pharmacokinetic Coh 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
PK data for patients in Cohort 1 receiving 0.3 mg/kg XmAb5871	
Subject analysis set title	Pharmacokinetic Coh 3
Subject analysis set type	Safety analysis

Subject analysis set description:

PK data for patients in Cohort 3 receiving 3.0 mg/kg XmAb5871

Subject analysis set title	Pharmacokinetic Coh 4 and 5
Subject analysis set type	Safety analysis

Subject analysis set description:

PK data for patients in Cohorts 4 and 5 receiving 10.0 mg/kg XmAb5871

Subject analysis set title	Pharmacokinetic Coh 4
Subject analysis set type	Safety analysis

Subject analysis set description:

PK data for patients in Cohort 4 receiving 10.0 mg/kg XmAb5871

Subject analysis set title	Pharmacokinetic Coh 5
Subject analysis set type	Safety analysis

Subject analysis set description:

PK data for patients in Cohort 5 receiving 10.0 mg/kg XmAb5871

Reporting group values	Pharmacokinetic Coh 2	Pharmacokinetic Coh 1	Pharmacokinetic Coh 3
Number of subjects	6	3	6
Age categorical			
Patient Age was collected at patient enrollment			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Patient Age at enroollment			
Units: years			
median	59	58	60.5
full range (min-max)	53 to 65	52 to 63	52 to 64
Gender categorical			
Units: Subjects			
Female	5	3	5
Male	1	0	1

Reporting group values	Pharmacokinetic Coh 4 and 5	Pharmacokinetic Coh 4	Pharmacokinetic Coh 5
Number of subjects	25	7	18
Age categorical			
Patient Age was collected at patient enrollment			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			

Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Patient Age at enroollment			
Units: years median full range (min-max)	 60 25 to 69	 59 45 to 63	 60.5 25 to 69
Gender categorical Units: Subjects			
Female Male	21 4	6 1	15 3

End points

End points reporting groups

Reporting group title	Part A (Active)
Reporting group description:	
Patients treated with active treatment	
Reporting group title	Part A (Placebo)
Reporting group description:	
Patients treated with placebo treatment	
Reporting group title	Part B (Placebo)
Reporting group description:	
Patients treated with placebo treatment	
Reporting group title	Part B (Active)
Reporting group description:	
Patients treated with active treatment	
Subject analysis set title	Pharmacokinetic Coh 2
Subject analysis set type	Safety analysis
Subject analysis set description:	
PK data for patients in Cohort 2 receiving 1.0 mg/kg XmAb5871	
Subject analysis set title	Pharmacokinetic Coh 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
PK data for patients in Cohort 1 receiving 0.3 mg/kg XmAb5871	
Subject analysis set title	Pharmacokinetic Coh 3
Subject analysis set type	Safety analysis
Subject analysis set description:	
PK data for patients in Cohort 3 receiving 3.0 mg/kg XmAb5871	
Subject analysis set title	Pharmacokinetic Coh 4 and 5
Subject analysis set type	Safety analysis
Subject analysis set description:	
PK data for patients in Cohorts 4 and 5 receiving 10.0 mg/kg XmAb5871	
Subject analysis set title	Pharmacokinetic Coh 4
Subject analysis set type	Safety analysis
Subject analysis set description:	
PK data for patients in Cohort 4 receiving 10.0 mg/kg XmAb5871	
Subject analysis set title	Pharmacokinetic Coh 5
Subject analysis set type	Safety analysis
Subject analysis set description:	
PK data for patients in Cohort 5 receiving 10.0 mg/kg XmAb5871	

Primary: Safety and Tolerability

End point title	Safety and Tolerability[1]
End point description:	
Safety and tolerability assessments consisted of AEs, vital signs, electrocardiogram (ECG), clinical laboratory, immunogenicity and physical examination. Assessments were performed according to the time points defined in the schedules of assessments. Data presented is number of patients with Treatment Emergent AEs (TEAEs) and number of patients confirmed as positive for anti-XmAb5871 antibodies (ADA).	
End point type	Primary
End point timeframe:	
From Randomisation (Day -1) to Day 169	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: For this explorative study, no prospective calculations of statistical power were made. The sample size was selected to provide information on safety, tolerability, PK, efficacy and PD following single and multiple doses of XmAb5871.
Descriptive statistics were provided for selected demographic, safety, PK, PD, and biomarker data by cohort. Descriptive statistics on continuous data includes means, medians, SDs and ranges, while categorical data may be summarized using frequency counts and %s.

End point values	Pharmacokinetic Coh 2	Pharmacokinetic Coh 1	Pharmacokinetic Coh 3	Pharmacokinetic Coh 4 and 5
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	3	6	25
Units: Number of patients				
Number of patients with TEAE	3	3	5	19
Patients with +ve anti-XmAb5871 (ADA)	0	0	0	7

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (Plasma Concn)

End point title	Pharmacokinetics (Plasma Concn)

End point description:

To characterize the PK of multiple-dose, intravenously administered XmAb5871 in patients with RA. All figures presented are averages across the Cohorts

End point type	Secondary

End point timeframe:

After final dose

End point values	Pharmacokinetic Coh 2	Pharmacokinetic Coh 1	Pharmacokinetic Coh 3	Pharmacokinetic Coh 4 and 5
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	3	6	25
Units: Plasma XmAb5871 concentrations				
number (not applicable)				
Trough concentrations on Day 85 (ng/mL)	382	89.3	1639	4297

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy

End point title	Efficacy

End point description:	
Efficacy assessments were measured according to the time points defined in the Protocol	
End point type	Secondary
End point timeframe:	
From Day 1 to Day 169	

End point values	Part A (Active)	Part A (Placebo)	Part B (Placebo)	Part B (Active)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	7	8	15
Units: Efficacy Measurements				
median (full range (min-max))				
ACR Hybrid Score on Day 85	39.4 (-23.1 to 70.9)	10.1 (1.4 to 59.7)	27.6 (-52.4 to 61)	50 (-14.3 to 86.9)
DAS28-CRP Score on Day 85	3.2 (1.8 to 5.9)	4.6 (2.1 to 5.7)	4.2 (3.4 to 6.1)	4.1 (1.7 to 5.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy (EULAR)

End point title	Efficacy (EULAR)
End point description:	
Number of patients achieving a specific EULAR score (No, Moderate or Good) at Day 85	
End point type	Secondary
End point timeframe:	
Day 85	

End point values	Part A (Active)	Part A (Placebo)	Part B (Placebo)	Part B (Active)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	7	8	15
Units: Number of patients				
No	3	5	2	2
Moderate	9	1	6	8
Good	9	1	0	5

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy (ACR Score)

End point title	Efficacy (ACR Score)
End point description:	
Number of patients achieving an ACR score of ACR20, ACR50 or ACR70.	
End point type	Secondary
End point timeframe:	
Day 85	

End point values	Part A (Active)	Part A (Placebo)	Part B (Placebo)	Part B (Active)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	7	8	15
Units: Number of patients				
ACR20	15	2	5	13
ACR50	6	1	1	6
ACR70	2	0	0	3

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (Cmax after final dose)

End point title	Pharmacokinetics (Cmax after final dose)
End point description:	
Cmax - Maximal observed serum concentration.	
End point type	Secondary
End point timeframe:	
After final dose	

End point values	Pharmacokinetic Coh 2	Pharmacokinetic Coh 1	Pharmacokinetic Coh 3	Pharmacokinetic Coh 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	3	6	7
Units: ng/mL				
number (not applicable)				
Cmax after final dose	21287	4943	59913	257015

End point values	Pharmacokinetic Coh 5			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: ng/mL				
number (not applicable)				

Cmax after final dose	272832			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (Clearance after final dose)

End point title	Pharmacokinetics (Clearance after final dose)

End point description:

To characterize the PK of multiple-dose, intravenously administered XmAb5871 in patients with RA. All figures presented are averages across the Cohort. Clearance of drug from the body, CL = Dose/AUCinf

End point type	Secondary

End point timeframe:

After final dose

End point values	Pharmacokinetic Coh 2	Pharmacokinetic Coh 1	Pharmacokinetic Coh 3	Pharmacokinetic Coh 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	3	6	7
Units: mL/day/kg				
number (not applicable)				
Clearance after final dose	15.27	15.82	16.95	16.29

End point values	Pharmacokinetic Coh 5			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: mL/day/kg				
number (not applicable)				
Clearance after final dose	13.83			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (Half-life)

End point title	Pharmacokinetics (Half-life)

End point description:

To characterize the PK of multiple-dose, intravenously administered XmAb5871 in patients with RA. All figures presented are averages across the Cohort. Terminal half-life computed over the terminal portion of the concentration versus time profile. Computed as Half-life = ln(2)/Lambda, where Lambda is the

slope of the regression line through the terminal portion of the plot of natural log of concentration vs. time

End point type	Secondary

End point timeframe:

After final dose

End point values	Pharmacokinetic Coh 2	Pharmacokinetic Coh 1	Pharmacokinetic Coh 3	Pharmacokinetic Coh 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	3	6	7
Units: Hours				
number (not applicable)				
Half-life	62.39	65.8	79.09	98.4

End point values	Pharmacokinetic Coh 5			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: Hours				
number (not applicable)				
Half-life	93.3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded at each clinic visit from signing of the Informed Consent Form until completion of the End of Study visit.

Adverse event reporting additional description:

At every patient visit, patients were asked non-leading questions to determine the occurrence of AEs. In addition, all AEs reported spontaneously during the course of the clinical study were recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Part A (Active)

Reporting group description:

Patients receiving active treatment (XmAb5871) during Part A (0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg or 10 mg/kg)

Reporting group title	Part A (Placebo)

Reporting group description:

Patients receiving placebo treatment (placebo) during Part A.

Reporting group title	Part B (Active)

Reporting group description:

Patients receiving active treatment (XmAb5871) during Part B (10 mg/kg)

Reporting group title	Part B (Placebo)

Reporting group description:

Patients receiving placebo treatment (placebo) during Part B.

Serious adverse events	Part A (Active)	Part A (Placebo)	Part B (Active)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	0 / 7 (0.00%)	1 / 18 (5.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Venous thrombosis	Additional description: 1 patient receiving XmAb5871 10 mg/kg had a phlebothrombosis of the right lower limb of moderate intensity, considered to be possibly related to the study drug. SAE occurred 22 days after the final infusion. Sponsor classified relationship unlikely.		
subjects affected / exposed	0 / 22 (0.00%)	0 / 7 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Post herpetic neuralgia	Additional description: 1 patient receiving placebo had post-herpetic neuralgia of moderate intensity, considered to be possibly related to the study drug, 2 days after final infusion.		

subjects affected / exposed	0 / 22 (0.00%)	0 / 7 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Infusion related reaction	Additional description: 1 patient receiving XmAb5871 10 mg/kg had an infusion-related reaction with hypotension of severe intensity, considered to be definitely related to the study drug. The patient was permanently withdrawn from study drug; patient fully recovered.		
subjects affected / exposed	1 / 22 (4.55%)	0 / 7 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Herpes zoster	Additional description: 1 patient receiving placebo had an abdominal herpes zoster of moderate intensity, considered to be possibly related to the study drug, 2 days after final infusion.		
subjects affected / exposed	0 / 22 (0.00%)	0 / 7 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection bacterial	Additional description: 1 patient receiving placebo had a bacterial respiratory tract infection of mild intensity, considered not to be related to the study drug.		
subjects affected / exposed	0 / 22 (0.00%)	0 / 7 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B (Placebo)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Venous thrombosis	Additional description: 1 patient receiving XmAb5871 10 mg/kg had a phlebothrombosis of the right lower limb of moderate intensity, considered to be possibly related to the study drug. SAE occurred 22 days after the final infusion. Sponsor classified relationship unlikely.		
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Post herpetic neuralgia	Additional description: 1 patient receiving placebo had post-herpetic neuralgia of moderate intensity, considered to be possibly related to the study drug, 2 days after final infusion.		

subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Infusion related reaction	Additional description: 1 patient receiving XmAb5871 10 mg/kg had an infusion-related reaction with hypotension of severe intensity, considered to be definitely related to the study drug. The patient was permanently withdrawn from study drug; patient fully recovered.		
subjects affected / exposed	0 / 9 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Herpes zoster	Additional description: 1 patient receiving placebo had an abdominal herpes zoster of moderate intensity, considered to be possibly related to the study drug, 2 days after final infusion.		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection bacterial	Additional description: 1 patient receiving placebo had a bacterial respiratory tract infection of mild intensity, considered not to be related to the study drug.		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3.5 %

Non-serious adverse events	Part A (Active)	Part A (Placebo)	Part B (Active)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 22 (77.27%)	4 / 7 (57.14%)	13 / 18 (72.22%)
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 7 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Body temperature increased			
subjects affected / exposed	2 / 22 (9.09%)	0 / 7 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 22 (4.55%)	0 / 7 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 22 (13.64%)	1 / 7 (14.29%)	4 / 18 (22.22%)
occurrences (all)	3	1	4
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 22 (13.64%)	0 / 7 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Infusion related reaction			
subjects affected / exposed	1 / 22 (4.55%)	0 / 7 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Vessel puncture site bruise			
subjects affected / exposed	1 / 22 (4.55%)	0 / 7 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Influenza like illness			
subjects affected / exposed	0 / 22 (0.00%)	1 / 7 (14.29%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 22 (13.64%)	0 / 7 (0.00%)	4 / 18 (22.22%)
occurrences (all)	3	0	4
Nausea			
subjects affected / exposed	3 / 22 (13.64%)	0 / 7 (0.00%)	2 / 18 (11.11%)
occurrences (all)	4	0	2
Diarrhoea			
subjects affected / exposed	0 / 22 (0.00%)	0 / 7 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 22 (4.55%)	0 / 7 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	3 / 22 (13.64%)	0 / 7 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Pain in extremity			
subjects affected / exposed	1 / 22 (4.55%)	2 / 7 (28.57%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Rheumatoid arthritis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 7 (14.29%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 22 (9.09%)	1 / 7 (14.29%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Bronchitis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 7 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Tracheitis			
subjects affected / exposed	2 / 22 (9.09%)	0 / 7 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Part B (Placebo)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 9 (77.78%)		
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Body temperature increased			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Infusion related reaction			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Vessel puncture site bruise			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)		
occurrences (all)	0		
Rheumatoid arthritis			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Infections and infestations Viral upper respiratory tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Tracheitis subjects affected / exposed occurrences (all)	 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2012	Amendment 1 applied to the Czech Republic only. The CSP was amended on 29 October 2012, primarily to comply with the recommendations received from Competent Authority Statni Ustav Pro Kontrolu Leciv (State Institute for Drug Control) in Czech Republic. However, Amendment 1 was not formally approved because the Sponsor withdrew submission on 07 November 2012. The changes implemented in Amendment 1 were as follows: 1. The upper limit of the age of the participating subjects in Part A of the clinical study was reduced from 70 to 65 years 2. The subjects were to follow-up for 72 hours post end of infusion for first dosing and 24 hours for the subsequent dosings; as a result, all outpatient visits up to the last dosing were changed from outpatient into inpatient visits 3. The subjects with known residential exposure to an individual with tuberculosis prior to or during screening (if not treated with appropriate chemoprophylaxis) or positive Quantiferon test at screening were excluded
15 January 2013	The Clinical Study Protocol was amended primarily to enhance subjects' safety, to increase scientific validity, to improve feasibility of the clinical study, and to correct mistakes and inconsistencies detected in Protocol Version 1.0 dated 31 July 2012. Amendment 2, dated 15 January 2013, applied for Hungary, Poland, Romania and the Slovak Republic only. A separate protocol amendment was prepared for the Czech Republic in compliance with recommendations received from the Czech Competent Authority. The major changes implemented in the present Amendment 2 were as follows: 1. Exclusion of subjects with positive Quantiferon test at screening. 2. Assessment of some additional safety laboratory parameters. 3. Adding of time point for vital signs assessment at 15 minutes after end of infusion; clarification of time points for vital signs assessment on dosing days and on non dosing days. 4. Prolongation of fasting period for the subjects before dosing, and waiving of obligation to fast before blood sampling except screening and Day –1. 5. Change of time points for blood sampling for PK on non-dosing days. 6. Collecting an additional blood sample for Biomarker Development. 7. Clarification of consequences following occurrence of significant safety events with respect to interruption of dose escalation. 8. Correction of criteria given for ACR classification of functional capacity.

19 January 2013	Amendment 3 applied to the Czech Republic only. The CSP was amended on 19 January 2013, primarily to enhance subjects' safety, to increase scientific validity, to improve feasibility of the clinical study, and to correct mistakes and inconsistencies detected in Clinical Study Protocol Version 2.0, dated 29 October 2012. A part of the changes that were addressed in this amendment were already implemented in Amendment 1. The major changes implemented in Amendment 3, dated 19 January 2013 were as follows: 1. Assessment of some additional safety laboratory parameters. 2. Adding of time point for vital signs assessment at 15 minutes after end of infusion; clarification of time points for vital signs assessment on dosing days and on non dosing days. 3. Prolongation of fasting period for the subjects before dosing, and waiving of obligation to fast before blood sampling except screening and Day –1. 4. Change of time points for blood sampling for PK on non-dosing days. 5. Collection of an additional blood sample for Biomarker Development. 6. Clarification of consequences following occurrence of significant safety events with respect to interruption of dose escalation. 7. Correction of criteria given for ACR classification of functional capacity. A separate amendment was prepared for Hungary, Romania, Poland and the Slovak Republic (Amendment 2, dated 15 January 2013) implementing the same changes as listed in Amendment 3.
26 August 2013	Amendment 4, dated 26 Aug 2013, applied to the Czech Republic only. It was prepared to define the dose of the study drug XmAb5871 for the expansion cohort (Cohort 5) as recommended by the DESC. During the DESC meeting on 16 August 2013 the safety data of Cohort 4 through at least Day 15 were discussed and all available cumulative safety data from the previous cohorts were reviewed to assess the presence of any cumulative toxicity. The maximum dose of 10.0 mg/kg was considered safe and well tolerated to be used in the expansion cohort. The updated safety information for XmAb5871 was implemented in the protocol. The number of countries was updated as the clinical study was withdrawn in Romania.
23 October 2013	Amendment 5 dated 23 October 2013 was prepared in order to modify the Inclusion Criterion No 6/b. The required hsCRP value was reduced from greater than or equal to 10.0 mg/L to 6 mg/L, in order allow inclusion of a greater proportion of rheumatoid arthritis patients with active disease on stable non-biologic DMARD therapy in Part B of this clinical study. Separate amendments were prepared for the Czech Republic (Amendment 5 dated 23 October 2013) and for Hungary, Poland and the Slovak Republic (Amendment 6 dated 23 October 2013) implementing the same changes.
23 October 2013	Amendment 6 dated 23 October 2013 was prepared in order to modify the Inclusion Criterion No 6/b. The required hsCRP value was reduced from greater than or equal to 10.0 mg/L to 6 mg/L, in order allow inclusion of a greater proportion of rheumatoid arthritis patients with active disease on stable non-biologic DMARD therapy in Part B of this clinical study. Separate amendments were prepared for the Czech Republic (Amendment 5 dated 23 October 2013) and for Hungary, Poland and the Slovak Republic (Amendment 6 dated 23 October 2013) implementing the same changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported