Study No.: 112657 (Hx-CD20-403 Part A)

Title: A double-blind, randomized, placebo-controlled, dose escalation, multi-center phase I/II trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody in subjects with active rheumatoid arthritis who have previously failed one or more disease modifying anti-rheumatic drugs

Rationale:
This trial consisted of a double-blind, placebo controlled, dose escalation part randomized within each of three sequential dose groups (cohorts) (Part A), and a parallel group part with randomization into one of four dose groups (Part B). This report includes information and results relating to Part A. Part A was the first administration of ofatumumab to patients with RA. Consequently, the purpose of Part A of this trial was primarily to investigate the safety profile of ofatumumab in patients with active RA. Furthermore, the trial was designed to investigate pharmacokinetics (PK) and confirm the dosing range and preliminary evidence of efficacy. Overall, the evaluation of the data was used to confirm the safety and relevance of initiating Part B of the trial.

Phase: II

Study Period: 28th February 2005 (first patient screening) -4th January 2006 (last Week 24 visit)

Study Design: Double-blind, placebo controlled, dose escalation randomized within each of three sequential dose groups (cohorts). Patients received 2 infusions of ofatumumab (of either 300 mg, 700 mg, or 1000 mg) or placebo 2 weeks apart, and were followed for safety, efficacy, and PK measurements for 24 weeks. Hereafter patients were followed every 12 weeks until B-cells (CD19+ cells) had normalized.

Centres: 17 trial sites: Denmark, United Kingdom, Poland and United States

Indication: Rheumatoid arthritis

Treatment: Two intravenous infusions of ofatumumab 14 days apart (300 mg: 12 subjects; 700 mg: 10 subjects; 1000 mg: 10 subjects; placebo: 7 subjects)

Objectives:

Primary Objective

- To evaluate the safety of ofatumumab in patients with active RA

Secondary Objectives

- To evaluate the efficacy of ofatumumab in patients with active RA by measuring the degree and duration of B-cell depletion
- To determine the PK profile of ofatumumab in patients with active RA
- To determine host immune response, Human Anti Human Antibodies (HAHA), against ofatumumab

Primary Outcome: Safety (adverse events)

Secondary Outcomes (efficacy): included

- ACR20, ACR50, and ACR70 at weeks 12, 16, 20 and 24
- DAS28 at weeks 12, 16, 20 and 24
- CD19+ cells and CD20+ cells

Statistical Methods: No formal sample size calculation was performed. The planned number of patients (30) was considered adequate to evaluate safety before initiation of Part B of the trial. The full analysis population (FAS) included all subjects exposed to study drug.

Study Population:

- Males and females ≥ 18 years
- A diagnosis of rheumatoid arthritis according to the ACR criteria of at least six months duration
- Active disease at the time of screening as defined by:
  Six or more swollen joints (of 28 joints) and
  Six or more tender joints (of 28 joints) and
  Erythrocyte Sedimentation Rate (ESR) ≥ 22 mm/h (using Becton Dickinson Seditainer)
  and/or C-Reactive Protein (CRP) ≥ 10 mg/L (1 mg/dL)
- RA functional class I, II, or III
- Treatment failure to one or more DMARDs. Applicable only to patients on MTX therapy at time of screening: Treatment with a stable dose of MTX (7.5 – 25 mg/week, p.o., i.m., and/or s.c.) for at least four weeks prior to planned start of trial treatment.

	A Placebo	B 300mg	C 700mg	D 1000mg
Number of Subjects:				
Randomised, N	7	12	10	10
Reason for premature discontinuation from trial				
Deterioration of trial disease, n	3	1	1	1

Adverse event, n		1		
Demographics				
Male	0	1	1	2
Female	7	11	9	8
Median Age, years (range)	60.0 (30-88)	53.0 (37-68)	49.5 (37-58)	57.0 (33-64)
Caucasian, n	7	12	8	9
Hispanic, n	0	0	2	1
Efficacy Results: ACR20 at Week 24 (FAS population)				
	A Placebo N=7	**B 300mg N=12**	**C 700mg N=10**	**D 1000mg N=10**
ACR20 Response Rate (%)	0%	50%	70%	70%
p-value		0.044	0.010	0.010
Secondary Outcome Variable(s): ACR50 and ACR70 response rates, median change in DAS-28, EULAR response rates and B-cell depletion (week 24)				
FAS population	**A Placebo N=7**	**B 300mg N=12**	**C 700mg N=10**	**D 1000mg N=10**
ACR50 Response Rate at Week 24, (%) p value	0	25% 0.263	40% 0.103	40% 0.103
ACR70 Response Rate at Week 24, (%) p value	0	17% 0.509	20% 0.485	10% 1.000
Median change from baseline in DAS28 at Week 24, [Minimum, maximum]	-0.01 [-1.57, 1.16]	-2.15 [-4.46, 0.56]	-2.12 [-4.87, 0.00]	-2.10 [-4.26, 0.38]
EULAR Response (Good and moderate) at Week 24, (%)	29%	83%	70%	80%
Median B cell depletion (CD19+ cells) at Week 24 (%) [Minimum%, maximum%]	-1% [-27%,20%]	-83% [-100%,-49%]	-96% [-100%,-64%]	-91% [-100%,-32%]
Most Frequent Adverse Events (n)	**A Placebo N=7**	**B 300mg N=12**	**C 700mg N=10**	**D 1000mg N=10**
Number of subjects with AE's	6	12	10	9
Hypotension		5	1	1
Rash		1	3	2
Pyrexia	1	4	1	
Urticaria	1	3	1	2
Nausea	4	3	1	1
Fatigue	4	1	1	2
Dyspnea		1	1	2
Hyperhidrosis		1	2	1
Serious Adverse Events (Safety Population) n [n considered to be related to study medication] No fatal SAE's were reported	**A Placebo N=7**	**B 300mg N=12**	**C 700mg N=10**	**D 1000mg N=10**
Subjects with any SAE	0	2		1
Myocardial ischaemia				1
Anaphylactoid reaction		1 [1]		
Urticaria		1 [1]		

Conclusion:

- In patients with active RA, failing one or more DMARDs including TNF-alpha inhibitors, ofatumumab, administered as 2 i.v. infusions in doses up to 1000 mg, using a specified pre-medication and infusion regimen, was well tolerated. The maximum tolerated dose was not identified
- The B-cell depletion data and the preliminary clinical efficacy data demonstrated a clear effect of ofatumumab compared to placebo and indicated that the dose range investigated is therapeutically relevant
- Taken together, these results warranted further exploration of the optimal dose range as well as the efficacy potential, which will be examined in Part B of the trial