The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: OFA110867

Title: Clinical phase I/IIA study of subcutaneous administration of ofatumumab in rheumatoid arthritis subjects on stable dose methotrexate

Rationale: Ofatumumab (OFA), a fully human monoclonal antibody (MAb), targets a novel epitope on the CD20 molecule. Studies with intravenously administered ofatumumab have investigated doses up to 1000mg given twice 14 days apart leading to very rapid B cell lysis resulting in infusion reactions despite the use of IV corticosteroid (CS) premedication. The purpose of this phase I/II study was to examine the safety and tolerability, pharmacokinetics and pharmacodynamics of subcutaneously administered ofatumumab in subjects with rheumatoid arthritis on stable dose methotrexate.

Phase: I/II

Study Period: 28 weeks, which included a screening period of up to 4 weeks, 12-week 'on study' period and a 12-week safety follow-up period (to Day 169). This was followed by additional monitoring for up to 2 years to monitor for B-cell and immunoglobulin recovery, if required (extended follow-up period).

Study Design: This was a randomized, single-blind, placebo-controlled, single dose, parallel group, multi-center, dose-range finding study of subcutaneous ofatumumab in subjects with rheumatoid arthritis on stable dose methotrexate therapy. Eligible subjects were randomized into five cohorts to receive ofatumumab in the following order: cohort A1 (30mg), cohort A5 (0.3mg), cohort A4 (3.0mg), cohort A2 (100mg) and cohort A6 (60mg) or matched placebo. Dose progression beyond cohort A1 was based on B-cell depletion data and a review of available safety and tolerability data. Subjects received pre-medication with acetaminophen/paracetamol and oral antihistamine (i.e., no IV steroid pre-medication was required for subcutaneous ofatumumab administration). Subjects in the 30mg, 60mg, and 100mg cohorts were monitored in an in patient setting for four days post-dosing; subjects in the remaining cohorts were monitored in an inpatient setting for two days post-dosing.

Centres: A total of 14 centers enrolled subjects in the study: 1 in Belgium, 1 in France, 1 in Italy, 1 in Poland, 4 in Russia, 1 in Spain, 4 in Australia, and 1 in the United States.

Indication: Rheumatoid arthritis

Treatment: Single dose, subcutaneous administration: 0.3mg, 3mg, 30mg, 60mg or 100mg ofatumumab or matched placebo.

Objectives: The primary objective of the study was to characterize the safety and tolerability of ofatumumab administered as a single subcutaneous dose in subjects with rheumatoid arthritis.

Primary Outcome: Safety and tolerability as described by the incidence and severity of AEs, SAEs, clinical laboratory parameters and vital signs. Only SAEs were to be collected in the extended safety follow-up period.

Key Secondary Outcomes:

- B-cell depletion and re-population as measured by CD19+ peripheral blood B-lymphocyte
- Pharmacokinetic profile (PK)
- PK/Pharmacodynamic analysis including time to repletion and start of repletion of CD19+ B cells
- Immunogenicity

Statistical Methods: The study was designed to identify a B-cell depleting single dose of ofatumumab. The sample size was set based on feasibility and was intended to permit the development of an initial PK/PD model of CD19+ B-cell for single dose subcutaneously administered ofatumumab. No formal statistical hypothesis was tested.

Three populations were considered in the analysis:

- Safety population (all subjects randomized to treatment who received at least one dose of investigational product). This population comprised thirty five subjects.
- Modified intent-to-treat population (as all subjects randomized to treatment who received at least one dose of investigational product and who also have baseline measurement and at least one post-treatment PD measure). This population comprised thirty five subjects.
- Pharmacokinetic population (all subjects who take at least one dose of study drug and have at least one PK sample taken and analyzed). This population comprised thirty subjects (including 3 placebo subjects).

Pharmacodynamic data were analyzed through the use of summary statistics for each treatment group. (i.e. dose level) by visit. Values below assay lower limit of quantification were imputed using LLQ/2. The median depletion at

each dose level at Week 4 and/or the median depletion across weeks 2 to 4 were jointly used to inform dose selection, the use of the median ensured that at least 50% of the subjects achieved the target level of depletion at that dose level. Median depletion data at each time point were plotted over time, and individual subject data were plotted over time by treatment.

For each CD19+ depleted subject, the time to re-population of CD19+ peripheral B-lymphocyte cells to either ≥ their baseline level or ≥ lower limit of normal of 0.110GI/L, whichever was lower was listed. Similar analyses were performed for the time to start of re-population of CD19+ peripheral B-lymphocyte cells, defined as when their B cells returned to either <95% depletion from baseline or ≥ 0.01 GI/L, whichever was higher, for two consecutive samples, without further depletion subsequently.

Study Population:

	PLA	0.3mg OFA	3mg OFA	30mg OFA	60mg OFA	100mg OFA	Total (n=35)
Number of Subjects:	8	4	6	8	6	3	35
Planned, N[1]							
Randomised, N	8	4	6	8	6	3	35
Completed, n (%)	6 (75)	3 (75)	6 (100)	4 (50)	6 (100)	3 (100)	28 (80)
Total Number Subjects Withdrawn, N (%)	2 (25)	1 (25)	0	4 (50)	0	0	7 (20)
Withdrawn due to Adverse Events n (%)	1 (13)	0	0	0	0	0	1 (3)
Withdrawn due to Lack of Efficacy n (%)	0	0	0	1 (13)	0	0	1 (3)
Withdrawn for other reasons n (%)	1 (13)	1 (25)	0	3 (38)	0	0	5 (14)
Demographics							
N (ITT)	8	4	6	8	6	3	35
Females: Males	7:1	4:0	5:1	7:1	6:0	2:1	31:4
Mean Age, years (SD)	51.4 (14.68)	55.8 (15.65)	49.0 (19.88)	52.8 (12.07)	60.2 (9.47)	46.0 (7.55)	52.8 (13.72)
Race, n (%)							
White	7 (88)	4 (100)	6 (100)	7 (88)	6 (100)	3 (100)	33 (94)
American Indian or Alaska Native	1 (13)	0	0	1 (13)	0	0	2 (6)

[1]Due to the adaptive nature of the study design there was not a specific planned N for each dose level; the intention was to enrol 24-40 subjects in total

Pharmacodynamic results:

Treatment	N	Mean baseline2 (GI/L)	n day 1 pre-dose	Median day 1 pre-dose (GI/L)	n Day 29	Median % change	Min % change	Max % change
Placebo	8	0.201	8	0.14100	8	3.206	-96.95 [1]	39.94
0.3mg	4	0.178	4	0.14400	3	-48.322	-63.31	-29.57
3mg	6	0.172	6	0.15450	6	-73.147	-97.02	-2.99
30mg	8	0.213	7	0.20200	8	-98.828	-99.27	-82.96
60mg	6	0.341	5	0.31500	4	-99.024	-99.39	-97.18
100mg	3	0.234	2	0.18200	2	-98.418	-98.99	-97.84

1. The low minimum % change in CD19+ B-cells reported for the placebo group (i.e., -96.95%) was due to one placebo subject (#363) who was observed to have large unexplained fluctuations in B-cell counts over this period.
2. Baseline was the Day 1 pre-dose value or the screening value if the Day 1 pre-dose was missing

From an individual subject perspective, 17 subjects who received ofatumumab (i.e., 1/6 subjects in the 3mg group and 7/8, 6/6 and 3/3 subjects in the 30mg, 60mg and 100mg groups respectively) achieved the target CD19+ B cell depletion (i.e., ≥95% or to below LLQ) on at least one occasion during the study. Of these 17 subjects, 14 started to replete with 11 reaching the repletion criterion between 113 to 657 days. The earliest start of repletion was seen on Day 43 and latest start on Day 341.Three of the subjects who started to replete were not confirmed as having reached the repletion criterion by the end of the extended follow-up period. In addition, 3 subjects who met the depletion target were withdrawn before demonstrating start of repletion.

Pharmacokinetic results:

Following a single 0.3mg and 3mg subcutaneous administration of ofatumumab, most of the ofatumumab plasma concentration values were below the lower limit of quantitation. Due to the limited data above the lower limit of quantitation, AUC(0-t), AUC(0-∞), and t1/2 for ofatumumab could not be estimated for these dose levels. Following a

single subcutaneous administration of 30 to 100 mg, ofatumumab was slowly absorbed, with median tmax values ranging from 4.02 to 4.49 days. Ofatumumab elimination mean t1/2 values ranged from 5.84 to 7.23 days. The mean AUC(0-t), AUC(0-∞), and Cmax values for ofatumumab increased with increasing dose.

	PLA (n=8)	**0.3mg OFA (n=4)**	**3mg OFA (n=6)**	**30mg OFA (n=8)**	**60mg OFA (n=6)**	**100mg OFA (n=3)**	**Total (n=35)**
Most Frequent Adverse Events – On-Therapy (reported in 2 or more subjects receiving ofatumumab)							
Subjects with any AE(s), n (%)	5 (63)	4 (100)	5 (83)	8 (100)	4 (67)	3 (100)	24 (89)
Headache	3 (38)	1 (25)	0	5 (63)	0	2 (67)	8 (30)
Nausea	1 (13)	0	1 (17)	3 (38)	0	2 (67)	6 (22)
Upper respiratory tract infection	1 (13)	3 (75)	0	1 (13)	0	1 (33)	5 (19)
Dizziness	0	0	0	2 (25)	0	1 (33)	3 (11)
Hypertension	0	1 (25)	1 (17)	1 (13)	0	0	3 (11)
Pyrexia	0	0	1 (17)	1 (13)	1 (17)	0	3 (11)
Rheumatoid arthritis	1 (13)	0	0	3 (38)	0	0	3 (11)
Abdominal pain upper	0	1 (25)	0	1 (13)	0	0	2 (7)
Hyperhidrosis	0	1 (25)	0	1 (13)	0	0	2 (7)
Influenza-like symptoms	0	1 (25)	0	0	0	1 (33)	2 (7)
Laryngitis	0	0	1 (17)	0	0	1 (33)	2 (7)
Urinary tract infection	0	1 (25)	0	1 (13)	0	0	2 (7)
Viral infection	0	2 (50)	0	0	0	0	2 (7)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]							
Subjects with non-fatal SAEs, n (%) [related]	0	0	0	1 (13) [0]	0	0	0
Subjects with fatal SAEs, n (%) [related]	0	0	0	0	0	0	0
Atrial fibrillation	0	0	0	1 (13) [0]	0	0	0
Breast cancer	0	0	0	1 (13) [0]	0	0	0

Immunogenicity: No subject tested positive for human anti-human antibodies during the study.

Conclusion:

- After a single subcutaneous dose of 30mg, 60mg or 100mg, ofatumumab was slowly absorbed with median tmax values ranging from 4.02 to 4.49 days. Ofatumumab elimination mean t1/2 values ranged from 5.84 to 7.23 days.
- Profound CD19+ B-cell depletion was observed in all three higher dose cohorts (30mg, 60mg and 100mg), with prolonged B-cell depletion in subjects reaching the target depletion level.
- 30mg was identified as the minimal SC single dose of ofatumumab resulting in ≥95% depletion with comparable levels of depletion observed in the 60mg and 100mg cohorts.
- Overall, safety data from OFA110867 suggest that single initial doses up to 60 mg appear to be tolerated with acetaminophen/paracetamol and antihistamine pre-medications in this study population.

Within 1 year after study completion this section will either refer you to a publication or contain text interpreting the trial results.