Synopsis

Title of the clinical trial:

VELVET (Veltuzumab various doses exploratory trial), a randomized, double blind, placebo controlled, multicentre, multinational phase II dose range finding trial in subjects with moderate to severe rheumatoid arthritis insufficiently controlled with either methotrexate alone or methotrexate plus anti-tumour necrosis factor biological treatment, comparing 3 different subcutaneous dosages of anti-CD20 monoclonal antibody veltuzumab to placebo as an add-on therapy to methotrexate.

Short Title / Acronym: VELVET (Veltuzumab various doses exploratory trial)

Investigators and Trial Sites:

Approximately 75 sites were to be initiated for this trial in the following regions (countries): Europe (Czech Republic, Germany, Hungary, Italy, Poland, Spain, and United Kingdom), Canada, United States of America (USA) and Latin America (Argentina and Mexico).

A total of 32 sites were actually initiated in the following regions (countries): Europe (Czech Republic, Germany, Hungary, Poland and Spain), Canada, USA and Latin America (Mexico). However, trial medication was administered in the following regions (countries) only: Europe (Czech Republic and Germany), Canada and Latin America (Mexico).

Coordinating investigator:

PPD

Publication (reference):

Not applicable.

Studied period:

02 Aug 2011 (first subject first visit)

01 Oct 2012 (last subject last visit)

Phase of Development:

Phase II, therapeutic, dose-range finding exploratory trial

Objectives:

- To investigate the efficacy, safety and tolerability at Week 24 of 3 different subcutaneous (SC) dose levels of the humanized anti-CD20 antibody veltuzumab as an add-on treatment to methotrexate (MTX) compared to MTX alone in subjects with moderate to severe rheumatoid arthritis (RA).
- To evaluate the durability of the clinical response and safety of veltuzumab over 48 weeks.
- To identify the dosage(s) of veltuzumab with the most favourable benefit-risk profile to be further evaluated in the subsequent phase II/III clinical program in subjects with moderate to severe RA.

Methodology:

This was a multi-centre, placebo-controlled, double-blind, randomized, 4-arm parallel group trial, comparing 3 different dose levels (80 mg, 160 mg and 320 mg) of veltuzumab to placebo, administered weekly (Days 1, 8, 15 and 22) by SC injection to subjects with moderate to severe RA (cumulative veltuzumab doses 320 mg, 640 mg, and 1280 mg, respectively). All subjects were on continued stable co-medication with MTX (15 to 25 mg per week).

The trial consisted of a screening phase with two visits (1 visit 4 to 12 weeks prior to first administration of trial medication [Screening Visit 1] and a second randomisation visit 2 weeks prior to first administration of trial medication [Screening Visit 2]), a 4-week treatment phase (Week 1 to 4 [Visit 3 to 6]), a core phase from Week 4 to Week 24 (Visit 7 to 16) and a follow-up phase from Week 24 to Week 48 (Visit 17 to 19). Subjects who had not reached the threshold of B-cell repletion (defined as 40 B-cells/μL or at least 70% of their individual baseline [Visit 3, Day 1] B-cell count), as well as subjects whose immunoglobulin (Ig) levels were below the following values: IgM 0.20 g/L and/or IgG 5.0 g/L by the end of the trial (Week 48), were to be followed up further outside of the protocol.

This trial was globally put on a voluntary temporary halt (10 Nov 2011) due to potential quality issues with the trial medication vialling process, which was communicated to the health authorities. At the time of temporary halt, only 11 subjects had received trial medication. Subsequently, the sponsor decided to terminate the trial early on 01 Oct 2012 following the last per protocol visit of the treated subjects.

Pharmacokinetics (PK) assessments were to be performed for a subset of 15 subjects per treatment group at selected sites.

In the same subset of subjects, an exploratory biomarker panel for the evaluation of B-cell sub-populations (e.g. immature, mature naive, memory B-cells and plasmablasts) was to be evaluated. However, as the trial ended prematurely, only 1 subject was recruited in the sub-study. This subject had received trial medication at Visit 3 and Visit 4 only i.e. the subject did not receive full treatment. Therefore, to avoid further burden for the subject, given that no interpretation of data is possible from 1 single subject on partial treatment, it was decided to stop collection of samples for the exploratory biomarkers starting at Visit 13. No analysis of PK or exploratory biomarker panel data was performed. However, B-cell counts, defined as CD19+ lymphocytes, were determined at baseline, before first administration, and for the duration of the trial up to termination.

No. of subjects (total and for each treatment) planned and analysed:

It was planned that 360 subjects were to be screened to allow 300 eligible subjects (75 subjects per arm) to be randomized. This trial was terminated early when 74 subjects had been screened, 25 had been randomized and 11 had received at least 1 administration of trial medication.

Analysis Populations – All Subject Enrolled Set

	MTX+ Placebo N=7	MTX+ V80 mg N=5	MTX+ V160 mg N=6	MTX+ V320 mg N=7	Total MTX + V N=18
	n (%)	n (%)	n (%)	n (%)	n (%)
All subjects enrolled set	7 (100)	5 (100)	6 (100)	7 (100)	74
Safety analysis set	3 (42.9)	2 (40.0)	3 (50.0)	3 (42.9)	8 (44.4)

Diagnosis and main criteria for inclusion:

- Ability and willingness to provide written informed consent and to comply with the requirements of the protocol.
- Outpatient, male or female, at least 18 years of age at Screening (Visit 1).
- Active disease defined as:
  - Diagnosis of RA using the American College of Rheumatology (ACR) criteria for the classification of RA for at least 6 months prior to trial entry (Screening, Visit 1).
  - Swollen joint count (SJC) ≥ 6 and tender joint count (TJC) ≥ 6 referred to as the 66/68 – joint count system.
  - High sensitivity C-reactive protein (CRP) ≥ 15 mg/L and/or an erythrocyte sedimentation rate ≥ 28 mm/hour.
  - Positive rheumatoid factor (RF) ≥ 14 IU/mL and/or anti-cyclic citrullinated protein ≥ 20 U.

- An inadequate response to previous or current treatment with either MTX alone or MTX plus anti-tumour necrosis factor alpha (anti-TNFα) biological treatment. Subjects were not to have received more than 2 different anti-TNFα therapies.

Investigational Medicinal Product, dose and mode of administration, batch no:

Veltuzumab 80 mg, 160 mg or 320 mg was administered as once weekly SC injections on Days 1, 8, 15 and 22. The batch number was 305-03-001 (veltuzumab 75 mg/mL)

Reference product, dose, mode of administration, batch no:

Placebo was administered as once weekly SC injections on Days 1, 8, 15 and 22. The batch number was 305-02-001.

Non-Investigational Medicinal Product:

In addition to trial medication administration, subjects were on a stable dose of weekly MTX (between 15 mg and 25 mg/week) and a stable dose of adequate folic acid (at least 5 mg per week). MTX and folic acid were purchased locally by the site.

Duration of treatment:

Subjects were to undergo treatment for 4 weeks, followed by a core phase of 20 weeks and a follow-up phase of 24 weeks. As the trial was terminated early, only 11 subjects received at least 1 dose of trial medication; of these, 4 subjects received all 4 doses thus completing the treatment phase, 2 subjects received 3 doses, 3 subjects received 2 doses and 2 subjects received 1 dose. Of the 11 subjects who were treated; 8 completed the core phase and follow-up phase according to the protocol, while the remaining 3 subjects withdrew during the core phase.

Criteria for evaluation:

Efficacy

The primary efficacy variable was the ACR20 response rate at Week 24. Responders were defined as those subjects whose improvement from baseline to endpoint fulfilled the following criteria:

≥ 20% reduction in the TJC (66/68)

≥ 20% reduction in the SJC (66/68)

≥ 20% reduction in at least 3 of the following additional measures:

- Subject's assessment of pain (visual analog scale [VAS] form)
- Subject's global assessment of disease activity (VAS)
- Physician's global assessment of disease activity (VAS)
- Degree of disability (Health assessment questionnaire-disability index [HAQ-DI])
- Level of acute-phase reactant (CRP).

Secondary efficacy variables were as follows:

- ACR50 and ACR70 response rates, which were defined the same as ACR20 above except they required a reduction of 50% and 70%, respectively in the specified criteria.
- The hybrid ACR score, which combined the ACR20, ACR50, and ACR70 response rates with a subject's mean percentage improvement in core set measures.
- The proportion of subjects achieving a major clinical response, defined as having a continuous ACR70 for at least 24 weeks until Week 48. The proportion of subjects having a continuous ACR70 for at least 24 weeks even if the ACR70 response ended before Week 48 was also assessed.
- Disease activity scores for 28 joint-counts and the CRP level (DAS28-CRP).
- European League Against Rheumatism (EULAR) response. To be classified as responders, subjects had to have a significant change in DAS28-CRP and a low current disease activity.
- HAQ-DI scores.
- Short Form 36 (SF-36) quality of life questionnaire scores.
- Functional assessment of chronic illness therapy-fatigue (sub-scale) (FACIT-F) scores.
- Subject's assessment of pain, physician's global assessment of disease activity and subject's assessment of disease activity VAS scores.
- RA flares, defined as a return or increase of disease activity beyond baseline DAS28-CRP (type I) or an increase in DAS28-CRP by ≥ 1.2 when compared to the lowest DAS28-CRP previously attained in the trial (type II).
- RF and anti-cyclic citrullinated protein values.

Safety

Safety assessments were performed throughout the trial via the monitoring of adverse events (AEs), physical examinations, vital signs, laboratory results (haematology, serum biochemistry, and urinalysis) and electrocardiograms.

Pharmacokinetic

Pharmacokinetic (PK) assessments were to be performed for a subset of 15 subjects per treatment group at selected sites. At the time of early termination only 1 subject had PK assessments conducted. Therefore, no analysis of PK data was performed in this trial.

Exploratory Biomarkers (B-cells Sub-Population)

Exploratory Biomarker assessments were to be performed for a subset of 15 subjects per treatment group at selected sites. At the time of early termination, only 1 subject had been recruited in the sub-study. This subject had received trial medication at Visit 3 and Visit 4 only i.e. the subject did not receive full treatment. Therefore, to avoid further burden for the subject, given that no interpretation of data is possible from 1 single subject on partial treatment, it was decided to stop collection of samples for the exploratory biomarkers starting at Visit 13. Laboratory data from samples collected at Visits 3, 4, 6, 10 and 13 were reported from the specialized academic laboratory to ICON Clinical Research Ltd. No further assessment was conducted; therefore, no analysis of exploratory biomarker data was performed in this trial.

Statistical methods:

This trial was prematurely terminated with only a small number of subjects being exposed to the trial medication. While this did not alter the trial objectives, this abbreviated clinical trial report will only report descriptively on safety and efficacy of the exposed subjects.
The data were presented by summaries and listings only, no inferential statistics or additional analyses were performed. All summary tables were presented by treatment and visit for the whole trial period. Along with each treatment arm an additional arm containing the 3 pooled Veltuzumab doses was presented.

For all continuous variables, n (sample size), mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum were presented descriptively by time and treatment for both absolute values and changes from baseline. The number and percentage of subjects by treatment group was presented for categorical variables.
A missing count was presented if there were 1 or more missing values. For all discrete variables, frequency tables including absolute and relative frequencies by time and treatment were generated.

The All Subject Enrolled Set included all subjects enrolled in the trial. A subject who had been given a subject identification number and provided informed consent was considered to have been enrolled in the trial. This set was used for all listings.

The Safety Analysis Set consisted of all randomized subjects who received at least 1 dose of trial medication. The Safety Analysis Set was used for summaries of demographic and baseline characteristics and all safety, efficacy and tolerability related variables. Subjects were assigned to and analysed by the treatment they actually received.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

No notable differences were observed across the treatment groups with regard to demographic and other baseline characteristics. The median age of subjects was 59 years for subjects assigned to veltuzumab and 58 years for subjects assigned to placebo. Most subjects were female (6 subjects, 75.0%) and White (5 subjects, 62.5%). The mean BMI was similar for subjects assigned to veltuzumab (28.18 kg/m^2) as those assigned to placebo (25.10 kg/m^2). All subjects were taking disease-modifying anti-rheumatic drugs (DMARDs).

Trial results

This trial was globally put on a voluntary temporary halt (10 Nov 2011) due to potential quality issues with the trial medication vialling process, which was communicated to the health authorities. At the time of temporary halt, only 11 subjects had received trial medication; 3 had received placebo, 2 had received veltuzumab 80 mg, 3 had received veltuzumab 160 mg and 3 had received to veltuzumab 320 mg, all in combination with weekly MTX (between 15 mg and 25 mg/week) and a stable dose of adequate folic acid (at least 5 mg per week) in accordance with the protocol.

Only 4 subjects had received all 4 doses of trial medication at the time of the temporary halt; 3 were assigned to veltuzumab (veltuzumab 160 mg: 1 subject; veltuzumab 320 mg: 2 subjects) and 1 was assigned to placebo. Subsequently, the sponsor decided to terminate the trial early on 01 Oct 2012 following the last per protocol visit of the treated subjects. No efficacy conclusions according to the protocol could be drawn. No clinical safety signal and no increased clinical safety risk were observed that precludes continued clinical investigation of veltuzumab.

Complete efficacy assessments could only be performed for the 4 subjects who received all 4 doses of trial medication. The remaining 7 subjects had efficacy assessments performed for the visits at which they received trial medication only.

No subject had an ACR20 response to treatment at Week 24; however, an ACR20 response to treatment was observed at other time-points for 2 subjects in the placebo group (1 subject at Week 4 and 1 subject at Week 32, 40 and 48); 1 subject in the veltuzumab 160 mg at Week 4; and 1 subject in the veltuzumab 320 mg group at Week 3 and Week 8. Three of these subjects had received all 4 injections of trial medication, while the fourth (i.e. subject from the placebo group who had an ACR20 response at Week 4) received only 2 injections of trial medication. No subject had an ACR50 or ACR70 response to treatment at any time-point.

ACR hybrid responses, mainly improvements, were observed across all treatment groups; improvements of up to 49.99% (n=1) were observed in the placebo group compared with 19.99% in the veltuzumab 80 mg group (n=2), 28.61% in the veltuzumab 160 mg group (n=1) and 17.21% in the veltuzumab 320 mg group (n=2). A moderate EULAR response to treatment was also observed exclusively in the placebo group for 2 subjects at Week 4 and 1 subject at Week 48.

Four subjects experienced an RA flare during this trial; 1 subject in the placebo group, 1 subject in the veltuzumab 80 mg group, and 2 subjects in the veltuzumab 320 mg group.

B-cell counts (CD19+ lymphocytes) were depleted from baseline at all timepoints for the evaluable subjects in the veltuzumab group (n=6) and increased from baseline at most timepoints for subjects in the placebo group (n=3). In the veltuzumab group, the greatest average change from baseline in B-cell counts during treatment was an average decrease of approximately 96% (range: 95% to 98%), which was observed at Week 3. The B-cell counts started to replenish after Week 3 and were approximately 12% and 15% relative to baseline at Week 24 and Week 48, respectively. In the placebo group, the greatest average change from baseline in B-cell counts during the study was an average increase of approximately 60%, which was observed at Week 40. B-cell counts in the placebo group were approximately 110% relative to baseline at Week 24 and Week 48.

Other efficacy and quality of life data, such as VAS, HAQ-DI, SF-36, FACIT-F data, were highly variable and generally unremarkable.

No deaths or serious adverse events occurred during this trial. TEAEs, all of which were of mild intensity, occurred in 7 of the 8 subjects (87.5%) assigned to veltuzumab and 2 of the 3 subjects (66.7%) assigned to placebo. Individual TEAEs occurred in no more than 1 subject in any treatment group.

One subject from the veltuzumab 320 mg group experienced treatment-related TEAEs of headache, 11.5 hours after the first injection of veltuzumab; and pyrexia (fever) and pyrexia (fever chills), 12 hours and 50 minutes, after the first injection of veltuzumab, on the first day of treatment; both events resolved the following day without intervention.

Three subjects had TEAEs of urinary tract infection during the trial; 1 subject from the veltuzumab 80 mg group, 1 subject from the veltuzumab 320 mg group and 1 subject from the placebo group; these events resolved without intervention and were assessed by the Investigator as unrelated to the trial medication.

Conclusions:

Administration of SC veltuzumab 80 mg, 160 mg and 320 mg as an add-on treatment to MTX in the 8 subjects described, raised no important safety findings and no increased risk that precludes continued clinical investigation of veltuzumab. B-cells were depleted by an average of approximately 96% relative to baseline at Week 3 during treatment with veltuzumab and were replenished to approximately 12% and 15% relative to baseline at Week 24 and Week 48, respectively. No conclusions could be drawn with regard to the efficacy of veltuzumab 80 mg, 160 mg and 320 mg based on the protocol due to the low number of subjects treated in this early termination trial.