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CLINICAL STUDY REPORT

Document No: Final **Date of Document:** 29 February 2012

Study Number: VB-201-030

EudraCT Number: 2010-020783-38

Study Title:	A Phase II, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Assess the Effect of Multiple Doses of VB-201 on Biomarkers of Inflammation, Safety and Pharmacokinetics in Subjects with Elevated High Sensitivity C-Reactive Protein.
Development Phase:	Phase II
Product Name/Number:	VB-201
Indication Studied:	N/A
Study Design:	Double blind, randomized, dose ranging placebo controlled study.
First Subject Enrolled Date:	25 October 2010
Last Subject Completed Date:	27 October 2011
Co-ordinating Investigator:	[redacted]
Sponsor	Vascular Biogenics Ltd. 6 Jonathan Netanyahu St., OR Yehuda, 60376 Israel

The study was conducted in accordance with Good Clinical Practice (GCP), including the archiving of essential documents.

2. STUDY SYNOPSIS

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Investigator(s):

[redacted]

Study Centre(s): Multi-centre, 5 U K sites: Synexus Clinical Research Centres; Lancashire, Midlands, Scotland, Thames Valley and Wales.

Publication reference: Not Applicable

Studied period:	**Phase of development:**
First enrolment : 25 October 2010 Last subject completed : 27 October 2011	Phase II

Objectives:

Safety:

To assess and characterize the safety and tolerability of multiple doses of VB-201administered at total daily doses ranging between 5-160 mg or MTD for 4 weeks in approximately 320 subjects with elevated hsCRP.

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Efficacy:

To examine the effect of 4 weeks treatment with multiple doses of VB-201 compared to placebo on hsCRP levels.

Exploratory Bio-Markers and RNA Expression:

To examine the effect of 4 weeks treatment with different doses of VB-201 as compared with placebo on inflammatory related biomarkers and RNA expression of inflammation related genes.

PK Objective:

To assess the pharmacokinetics of VB-201 at the highest dose (80mg Q12H cohort).

Study Design:

The study design was a double blind, randomized, dose ranging, placebo controlled investigation of the effects of 4 weeks of daily oral administration of VB-201 in subjects with elevated levels of hsCRP. The study consisted of two parts. Part A: at doses of 5mg, 20mg, 40mg, 80mg, or placebo and Part B which consisted of 3 cohorts. In Part A, following eligibility screening at the baseline visit, up to 14 days later, subjects were randomized to one of the 5 dosing groups and received the assigned treatment for 28 days. Subjects were evaluated after 28 days of treatment and had a final safety evaluation via telephone 14 days after stopping treatment with study drug.

In Part B Cohort 1 (Group B1) subjects were screened for eligibility and at the baseline visit, up to 14 days later, randomized to either VB-201 120 mg Q24H or placebo. After G-I toxicity was observed, dosing in this cohort was prematurely terminated and the protocol was amended prior to the resumption of Part B dosing. Cohort 2 (Group B2) subjects then received 120mg daily, in divided doses (40mg/80mg morning and evening, 12h apart or matching placebo). In cohort 3 (Group B3) subjects received 80mg or matching placebo morning and evening, 12h apart (a total daily dose of 160mg). The 3rd cohort commenced after IDMC review of safety and tolerability data from at least 15 subjects who had participated in Group B2 and received VB-201 for at least 10 days. In Part B each subject received the assigned treatment for 4 weeks, underwent safety assessments after 14 days (Week 2) and was evaluated after 28 days of treatment (Week 4) and

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had a final safety visit, 28 days after stopping treatment.

PK sub-study design

Subjects for the PK sub-study were drawn from Group B3 (14 subjects). In order to maintain the blind of the PK sub study, the PK sub study arm included 12 subjects on VB-201 (80 mg Q12H) and 2 subjects on placebo.

On Day 0, blood samples for VB-201 assay were collected prior to dosing and 2, 4, 6, 7, 8, 9, 10, and 12 hours after dosing. On the last day of treatment subjects were given the first dose (80mg VB-201 or matching placebo) and were not given the second dose. On Day 28, blood samples for PK determination were collected prior to dosing and 2, 4, 6, 7, 8, 9, 10, and 12 hours after dosing. In addition to the samples collected on the last day of dosing, additional PK sample collections were done at 24, 48, 96, 144 and 168 hours after the final morning dose of VB-201.

Number of Subjects (planned and analysed):

Planned:

212 (Part A)

40 subjects to receive 5 mg VB-201;

40 subjects to receive 20 mg VB-201;

40 subjects to receive 40 mg VB-201;

40 subjects to receive 80 mg VB-201;

52 subjects to receive placebo;

108 (Part B)

Total = 320

Consented:

787 (642 Part A;145 Part B)

Randomised:

250 (199 Part A; 51 Part B)

Completed:

238 (192 Part A; 46 Part B)

Analysed:

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250 (199 Part A; 51 Part B)

Diagnosis and Main Criteria for Inclusion:

- Male or female subjects, ≥18 to ≤75 years of age
- Subjects who had a screening hsCRP level between 2 mg/L - 10 mg/L on 2 separate tests (3-7 days apart)
- Subjects were required to be on a stable high dose of statin for at least 3 months prior to screening including either atorvastatin ≥20 mg /day or rosuvastatin ≥10 mg /day or simvastatin ≥40mg/day

Study Product, Dose, Mode of Administration, Batch numbers:

Investigational Product: VB-201

Batch Nos.:

5mg capsules – [redacted]; 20mg capsules – [redacted]; 40mg capsules – [redacted];

40mg capsules – [redacted]

Mode of administration: Oral

Dose: 5 mg/ day, 20mg/ day, 40mg/ day, 80mg/ day, 120mg/day and 160mg/day

Duration of treatment:

28 days

Comparator Product, Dose, Mode of Administration, Batch numbers:

Comparator: Placebo

Mode of administration: Oral

Batch Nos:

Placebo capsules (size 0) – [redacted]; Placebo capsules (size 3) – [redacted]

Criteria For Evaluation:

Efficacy:

- Levels of hsCRP biomarker

Safety:

- Physical examination
- Adverse events
- Laboratory assessments (haematology, biochemistry, lipid profile, urinalysis, serum

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pregnancy test)

- ECG

Pharmacokinetics:

- VB-201 blood levels

Exploratory evaluations:

- Inflammatory biomarkers
  - Cytokines (IL-1ß, IL-6, IL-12, IL-17, IL-22, IL-23, IFN-α, IFNγ, TNFα
  - Chemokines (MCP-1, MIP-1α, MIP-1ß, IL-8)
- RNA expression
- Genetic analysis

Statistical Methods:

The primary efficacy analyses were performed on the Modified Intent to Treat (MITT) population. This population included all subjects who were randomized into the study, who received at least one dose of study medication, had a baseline efficacy evaluation and had at least one post dose efficacy evaluation. Categorical data is presented as counts and percentages. Continuous data is presented as summary statistics. All statistical comparisons are two-sided at the 5% level of significance. No adjustments to the level of significance were made for multiple comparisons.

To account for considerable intra-individual variability in hsCRP values over time, the trial was designed to capture 2 hsCRP samples 3 days apart at baseline and at week 4. The average of the 2 samples was used for analysis. Based on the generally held clinical position that a hsCRP value of 10 mg/L is a cut-off for significant inflammatory disease, values above 10 mg/L were discarded. Additionally outlier hsCRP levels were identified according to a pre-specified algorithm and discarded.

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SUMMARY – CONCLUSIONS

Efficacy Results:

Levels of hsCRP were significantly reduced from Baseline to Week 4 for the 120 mg QD cohort (p=0.026) and for all 120 mg cohorts combined (120 mg QD and 40/80 mg Q12H, p=0.005). When all 120 mg and higher cohorts (120 mg QD, 40/80 mg Q12H and 80/80 mg Q12H) were combined, a statistically significant change was also present (p=0.008). For the 120 mg QD treatment group, the change in hsCRP from Baseline to Week 4 compared to the change for placebo was also statistically significant (p=0.031).

Safety Results:

The incidence of TEAEs and drug-related TEAEs was higher than placebo in the VB-201 treatment groups dosing >20 mg/day. Most of the TEAEs were mild. Overall, the most frequent TEAEs were: nausea (10.6%), diarrhoea (5.3%), vomiting (4.8%), back pain (2.9%), rash (2.9%), upper respiratory infection (2.4%), and nasopharyngitis (2.4%).

The most frequently drug-related Treatment Emergent Adverse Events (TEAEs) were gastro-intestinal disorders (64 TEAEs in 41 subjects (19.7%)). The highest incidence of drug related TEAEs was reported in the 120mg (Q24H) group; 27 TEAEs in 12 subjects (66.7%). In this group the most frequently reported drug related TEAEs were also gastro-intestinal disorders (61.1%) and in particular nausea and vomiting (33.3% and 27.8% respectively). Three of the subjects in this group were withdrawn from the study due to the gastro-intestinal TEAEs. While these subjects' therapy assignment remained blinded, the sponsor deemed that the rate of gastro-intestinal (GI) intolerance observed would preclude further clinical development of this dosing schedule. On the basis of previous study results which showed an increase in tolerability when VB-201 was ingested with food, it was considered likely that the GI intolerance in the current study was due to local irritation of the gastric mucosa, rather than a systemic effect. In the current study all doses were ingested with food. To try to alleviate the GI intolerance observed, a modified dosing schedule for the 120mg daily dose group was implemented. This changed the dosing

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regimen from 120 mg VB-201 taken once daily to a twice daily regimen of 40mg in the morning and 80mg in the evening, 12 hours apart (40/80mg Q12H). When the 120mg dose was administered as a divided dose, the incidence of drug related TEAEs was substantially reduced, with only 4 drug related TEAEs reported in 3 subjects (25.0%). No serious or severe TEAEs occurred in this dosage group, and no subject was prematurely withdrawn due to a TEAE in this group. With the exception of VB-201, 5mg daily, this dosage regimen was the best tolerated in the current study.

In the highest dosage group, 160mg (80/80mg Q12H), there were 14 drug related TEAEs in 6 subjects (50.0%). The majority of these were again gastro-intestinal events; 9 TEAEs in 4 subjects (33.3%) and in particular nausea (6 events in 2 subjects (16.7%)).

There were no deaths during the study. There were 5 patients with a serious TEAE in this study: one in a placebo subject (TIA), 2 in the 20 mg treatment group (rectal haemorrhage and pneumonia), and 2 in the 120 mg Q24H group (TIA and humerus fracture). None of these serious TEAEs were considered related to the study medication.

There was a low incidence of abnormalities in laboratory measurements throughout the study. In addition, there appeared to be no systematic trends in any haematological, biochemical, urinalysis, or lipid profile parameters during treatment.

There were no clinically significant changes in physical examination, vital signs or 12-lead ECGs within or between treatment groups during the study.

PK analysis results

VB-201 pharmacokinetics after oral 80 mg single and multiple dose (Q12H) administration to subjects with elevated levels of hsCRP were generally consistent with previous studies of VB-201 in healthy volunteers. The mean pharmacokinetics parameters for VB-201 in subjects from this study are summarized below:

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Parameter	Day 0, Single Dose (N=12)			Day 28[d], Multiple Dose (N=12)		
	Mean	SD	CV%	Mean	SD	CV%
Cmax, ng/mL	2644.99	1322.56	50.00	11787.54	3192.58	27.08
Tmax[a], h	7.04	(6.00-10.05)	NA	6.99	(2.03-11.92)	NA
AUC_T, ng·h/mL	19000	4730	24.8	717000	300000	41.8
AUC_{12}, ng·h/mL	19600	5890	30.0	122000	38600	31.5
AUC_∞[b], ng·h/mL	165000	62800	38.0	NA	NA	NA
Rc	NA	NA	NA	6.33	1.34	21.2
CL/F, L/h	0.547	0.189	34.5	0.714	0.218	30.6
λ_z, 1/h	NA	NA	NA	0.0146	0.00275	18.8
$t_{½}$[c], h	NA	NA	NA	47.4	8.93	18.8
Rsq	NA	NA	NA	0.999	0.000750	0.0751

[a] Expressed as median and range.
[b] Calculated using corresponding subject's Day 28 λ_z value.
[c] Expressed as harmonic mean and pseudo standard deviation based on jackknife variance.
[d] Final dose and start of multiple dose PK sampling ranged from Day 26 to Day 29 of study.
NA = Not Applicable.

VB-201 plasma concentrations peaked at the same time after single and multiple doses (median Tmax were both 7 h). After multiple doses, the VB-201 plasma concentrations in the terminal, post-absorption, post-distribution phase declined in a conventional mono-exponential fashion. The mean terminal t½ (which was determined only after multiple doses because the short single dose blood collection interval precluded accurate calculation) was 47 h in this study's patients, slightly longer than the ones previously determined in healthy subjects. The Q12H multiple dose accumulation (Rc) calculated from the AUC12 ratio was 6.3-fold. This accumulation is nearly the same as one would predict (6.2-fold) from VB-201's measured 47-hour t½ and the Q12H dose administration schedule. Trough levels of VB-201 exhibited dose linearity in the dose range tested (5mg-160mg) and steady state occurred by week 2.

CONCLUSIONS: In conclusion, adequate safety of single daily doses of VB-201 up to 80 mg was observed in this study. A single daily dose of 120 mg VB-201 was, however, associated with G-I intolerance, mainly nausea and vomiting, but no laboratory abnormalities or serious G-I adverse events. When the VB-201 dosing regimen was changed to 40/80 mg Q12H with food, this substantially reduced the incidence of G-I adverse events; a higher dose of 160 mg/day (80 mg Q12H with food) for 30 days was also well-tolerated.

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A statistically significant reduction of hsCRP levels was noted with VB-201 higher doses (120 mg/day and up). This is likely to reflect anti-inflammatory and immune modulatory effects of VB-201.

VB-201 pharmacokinetics after single and multiple dose administration to subjects with elevated levels of hsCRP were generally consistent with previous VB-201 studies in healthy volunteers. Trough levels of VB-201 exhibited dose linearity in the dose range tested (5mg-160mg) and steady state occurred by Week 2.

Date of Report: 29 February 2012