1 Title Page

Trial Title	A Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral VB-201 in Patients with Moderate to Severe Plaque Psoriasis
Protocol No.	VB-201-079
EudraCT No	2012-002763-10
Name of test drug/product	VB-201
Comparator	Not applicable
Indication	Moderate to Severe Plaque Psoriasis
Design	Randomized, double-blind, 16-week, placebo-controlled trial followed by a 16-week placebo-controlled dose-ranging phase, followed by 8-week VB-201 treatment phase for all subjects.
Development phase	Phase 2
Sponsor	Vascular Biogenics Ltd. 6 Jonathan Netanyahu St., Or Yehuda 60376 Israel Phone: 972-3-6346450 Fax: 972-3-6346449
Coordinating investigator	There was no global coordinating investigator. Coordinating investigator for Germany: Prof. Dr. Ulrich Coordinating investigator for Spain: Dr. Luis Puig Sanz Coordinating investigator for Poland: Dr. Jolanta Węglowska There was no coordinating investigator for Israel
Author of report	Noa Lowenton-Spier, Vascular, Biogenics Ltd
First subject visit	20-Nov-2012
Last subject visit	26-Nov-2014
Version and date of report	Final version 08-Mar-2016
This trial was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.	

2 Synopsis

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Name of Finished Product: VB-201		
Name of Active Ingredient:		

Title of trial:
A Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral VB-201 in Patients with Moderate to Severe Plaque Psoriasis

Investigator(s) and trial centers:
A total of 29 Investigators participated in this trial.

Germany

- Prof. Dr. Thomas Dirschka, Centroderm GmbH, Wuppertal
- Prof. Dr. Ulrich Mrowietz, Psoriasis Zentrum Universitäts Hautklinik Kiel
- Dr. Johannes Niesmann, Bochum
- Dr. Sandra Philipp, Psoriaris Studienzentrum, Klinik für Dermatologie, Charité CCM, Berlin
- Dr. Peter Radny, Derma-Study-Center, Friedrichshafen
- Dr. Michael Sebastian, Hautarztpraxis Mahlow
- Dr. Georg Popp, licca clinical research institute, Augsburg
- Dr. Athanasios Tsianakas, Universitätsklinikum , Klinik und Poliklinik für Hautkrankheiten, Münster
- Dr. Ridwan Weber, Schweinfurt
- Dr. Peter Weisenseel, SciDerm Clinics, Hamburg
- Prof. Dr. Thomas Werfel, Medizinische Hochschule, Klinik für Dermatologie und Venerologie-OE, Hannover
- Dr. Dagmar Wilsmann-Theis, Rheinische-Friedrich-Wilhelms Universität, Klinik und Poliklinik für Dermatologie, Studienzentrum, Bonn
- Dr. Martin Miehe, Hautarztzentrum Tegel, Berlin
- Dr. Ralph von Kiedrowski, CMS³ - Company for Medical Study & Service Selters UG, Selters
- Prof. Dr. Michael Sticherling, Studienambulanz der Hautklinik Universitätsklinikum, Erlangen
- Dr. Henning Franz, Wolfenbüttel
- Dr. Ullrich Krüger, Goslar
- Prof. Dr. Knut Schäkel, Universität-Hautklinik, Heidelberg

Spain

- Dr. Caridad Morales Munera, Hospital de Sant Pau i de la Santa Creu DermatologyDepartment, Barcelona
- Dr. José Luis López Estebaranz, Hospital Fundación Alcorcón Dermatology Department, Madrid
- Dr. Servando Marrón, Hospital de Alcañiz Dermatology Department, Alcañiz
- Dr. Pablo de la Cueva, Hospital Universitario Infanta Leonor Dermatology Department, Madrid
- Dr. Carlos Ferrándiz, Hospital Universitario Germans Trials i Pujol Dermatology Department, Badalona

Israel

- Prof. Avner Shemer, Lev Yasmin Clinic, Netanya

Poland

- Węgłowska Jolanta, MD, Prywatna Praktyka Lekarska Jolanta Węglowska, Wrocław
- Witkowska Dagmara, MD Centrum Medyczne ADAMER, Wrocław
- Turek-Urasińska Katarzyna, MD, PhD, Spółka Cywilna Andrzej Królicki, Tomasz Kochanowski, Laser Clinic, Szczecin
- Bzdulska-Doskocz Beata, MD "ALERGO-MED" Specjalistyczna Przychodnia Lekarska Sp. z.o.o,Tarnów
- Pszonak Agnieszka, MD MedicaProFamilia, Warszawa

Name of Sponsor/Company: Vascular Biogenics Ltd. Name of Finished Product: VB-201 Name of Active Ingredient:	Volume: Page:	(For National Authority Use Only)

Publication (reference):
Not applicable

Studied period (years): First subject visit: 20-Nov-2012 Last subject visit: 26-Nov2014	**Phase of development:** Phase 2

Objectives:
- Efficacy

To examine the effect of treatment with two different doses of VB-201 compared to placebo for 16 weeks and 24 weeks on measures of disease activity in subjects with psoriasis
- Safety

To examine the safety and tolerability of up to 24 weeks' treatment with VB-201 vs. placebo in subjects with psoriasis.

Methodology:
Stage 1: The initial 16 weeks of this study was a double-blind, parallel-group, placebo-controlled randomized study with oral administration of VB-201 at doses of 80 mg/day or 160 mg/day (80 mg BID) or placebo.
Subjects were screened for eligibility and then, up to 28 days later, at the baseline visit, randomized to one of three treatment groups (1:2:2): VB-201 80 mg/day, VB-201 160 mg (80 mg BID) or placebo, respectively.
Stage 2: At week 16, VB-201 subjects continued to receive blinded treatment with the same dose assigned in the initial phase; placebo subjects crossed over to VB 201 160 mg (80 mg BID) for an additional 8 weeks.
Each subject had a final safety visit 4 weeks after stopping treatment with study drug.

Number of subjects (planned and analyzed):	Planned to be randomized: 186 screened: 235	randomized: 194 completed: 138	analyzed efficacy: 186 analyzed safety: 194

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Diagnosis and main criteria for inclusion:

1. Subjects who meet all of the following criteria were considered for enrollment into this study:
1. Fully understood all elements of and signed and dated the written Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved informed consent before initiation of protocol-specified procedures
2. Male or female subjects, ≥18 to ≤75 years of age, who with a diagnosis of chronic plaque psoriasis for at least 6 months prior to screening
3. Plaque psoriasis covering between 10% to 30 % of body surface area (BSA)
4. PASI severity moderate to severe, scoring at least 10 but no higher than 20
5. For a female subject; either:

- subject was of non-childbearing potential, defined as: menopause with amenorrhea >2 years, hysterectomy, or bilateral oophorectomy

or

- agreed to continue to use adequate contraception (double-barrier contraception, specifically, a condom and occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository or sexual abstinence or vasectomized partner) throughout the study and for at least one month following termination and had a negative pregnancy test at screening and before the first dose of study drug

Males had to use at least one method of contraception (e.g., condom) throughout the study

6. In the opinion of the investigator, the subject would have been compliant and would have a high probability of completing the study and all required procedures

Test product, dose and mode of administration, batch number:

Daily oral administration of:

- VB-201 80 mg/day
- VB-201 160 mg

In order to maintain the study blind, all subjects were administered study medication in the morning (2 capsules) and in the evening (2 capsules). Subjects randomized to the VB-201 80 mg/day received 80 mg in the morning and placebo in the evening.

Morning (AM) and Evening (PM) doses of study medication were to be taken with food 12 ± 2 hours apart.

Batch numbers: VB-201 80 mg: 3065G12A, 3065G12B, 3205B13A, 3205B13B, 3351A14A, 3351A14B

Duration of treatment:

Subjects participated in the study for up to 32 weeks: with up to 4 weeks for screening and establishment of baseline followed by 16 weeks (Stage 1) of blinded treatment [VB-201 at 80 mg/day or 160 mg, or placebo], 8 additional weeks (Stage 2) of double-blind treatment with VB-201 at a dose of either 80 mg/day or 160 mg and a follow-up visit 4 weeks after their last dose of study medication.

Reference therapy, dose and mode of administration, batch number:

Placebo, 2 capsules in the morning and 2 in the evening.

Morning (AM) and Evening (PM) doses of study medication were to be taken with food 12 ± 2 hours apart.

Batch numbers: 3064G12A, 3064G12B, 3350A14A, 3350A14B

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Criteria for evaluation:
Efficacy:

- Stage 1

Primary Efficacy Endpoint:
The proportion of subjects in the VB-201 160 mg treatment group who achieved at least 50% improvement from the baseline PASI score at Week 16 (PASI50) compared to the proportion of PASI50 responders in the placebo group.

Secondary Endpoints:

- Proportion of subjects in each of the VB-201 treatment groups and in the combined (both dose groups) VB-201 treatment groups who achieved at least 75% improvement from the baseline PASI score (PASI75) at Week 16 compared to the proportion of PASI75 responders in the placebo group
- Mean change in the PASI score from baseline to Week 16 in each of the two VB-201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to the mean change in the placebo group
- Change in affected Body Surface Area (BSA) from baseline to Week 16 in each of the VB-201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to placebo
- Change in PGA scores from baseline to Week 16 in each of the VB-201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to the placebo group, to include analyses of: (a) proportion with PGA score of 0-1, and (b) proportion with PGA score of 4-5
- Change in Patient Psoriasis Global Assessment scores from baseline to Week 16 in each of the VB-201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to the placebo group
- The proportion of subjects in the VB-201 80 mg/day treatment group who achieved at least 50% improvement from the baseline PASI score at Week 16 (PASI 50) compared to the proportion of PASI 50 responders in the placebo group

Tertiary Endpoints:

- Change in itching VAS (only in subjects having itching at baseline rated at ≥10 mm on a 100 mm VAS scale) from baseline to week 16 in each of the VB 201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to placebo
- Change in pain VAS (only in subjects with pain at baseline rated at ≥10 mm on a 100 mm VAS scale) from baseline to week 16 in each of the VB 201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to placebo
- Change in the product of PGA x BSA from baseline to Week 16 in each of the VB 201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to placebo
- Change in the DLQI scores from baseline to Week 16 in each of the VB 201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to placebo

- Stage 2

Primary Efficacy Endpoint:
The proportion of subjects in the VB-201 160 mg treatment group who achieved at least 50% improvement from the baseline PASI score at Week 24 (PASI50) compared to the proportion of PASI50 responders in the placebo group.

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Secondary Endpoints:

- Proportion of subjects in each of the VB-201 treatment groups and in the combined (both dose groups) VB-201 treatment groups who achieved at least 75% improvement from the baseline PASI score (PASI75) at Week 24 compared to the proportion of PASI75 responders in the placebo group
- Mean change in the PASI score from baseline to Week 24 in each of the two VB-201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to the mean change in the placebo group
- Change in affected Body Surface Area (BSA) from baseline to Week 24 in each of the VB-201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to placebo
- Change in PGA scores from baseline to Week 24 in each of the VB-201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to the placebo group, to include analyses of: (a) proportion with PGA score of 0-1, and (b) proportion with PGA score of 4-5
- Change in Patient Psoriasis Global Assessment scores from baseline to Week 24 in each of the VB-201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to the placebo group

Tertiary Endpoints:

- Change in itching VAS (only in subjects having itching at baseline rated at ≥10 mm on a 100 mm VAS scale) from baseline to week 24 in each of the VB 201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to placebo
- Change in pain VAS (only in subjects with pain at baseline rated at ≥10 mm on a 100 mm VAS scale) from baseline to week 24 in each of the VB 201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to placebo
- Change in the product of PGA x BSA from baseline to Week 24 in each of the VB 201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to placebo
- Change in the DLQI scores from baseline to Week 24 in each of the VB 201 treatment groups and in the combined (both dose groups) VB-201 treatment groups compared to placebo.

Note: For week 24 placebo group efficacy responses, modeling of the trajectory of response for the placebo group during weeks 0-16 was to be used to determine the placebo week 24 values for all endpoints.

Statistical methods:

The primary efficacy analysis was completed in the Modified Intent-To-Treat (MITT) population. This population included all subjects randomized who received at least one dose of study medication and had at least one efficacy evaluation (i.e. PASI score) after study treatment was begun.

Efficacy analysis was also completed on the Per-Protocol population; these were exploratory and were defined in the Statistical Analysis Plan (SAP).

Categorical data were presented as counts and percentages. Continuous data were presented as summary statistics. All statistical comparisons were two-sided at the 5% level of significance. No adjustments to the level of significance were made for multiple comparisons.

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Summary - Conclusions:

Efficacy results:
A total of 186 subjects participated in this trial. Of those, 123 were male. The mean age ranged from 43.0 ± 12.38 for the placebo to 46.1 ± 12.34 for the VB-201 80 mg group. At baseline, all treatment groups presented with similar demographic and characteristics.

Results for primary, secondary and tertiary efficacy variables for Stage 1 did not show any statistically significant difference in favor of VB-201 at any dose.
During Stage 2, a statistically significant difference (p=0.0004) for the PASI50 responder rate after 24 weeks compared to Week 16 for those subjects who crossed-over was observed; there was no other statistically significant difference for the primary efficacy variable of Stage 2. Furthermore, a statistically significant difference (p=0.0009) for the PASI75 responder rate for one subject who crossed-over from placebo to VB-201 160 mg was observed. No other statistically significant difference for any of the secondary efficacy endpoints of Stage 2 was observed.
Statistically significant differences for tertiary efficacy endpoints could be observed for BSA x PGA (p=0.0496) and PGA thickness (p=0.0105) in those subjects who crossed-over after 16 weeks of treatment with placebo to the VB-201 160 mg. No other statistically significant differences were observed.

Safety results:
In total, 61 (77.2%) subjects in the VB-201 160 mg arm, 26 (76.5%) subjects in the VB-201 80 mg arm, 23 (32.9%) subjects after switch to VB-201 160 mg after week 16 and 54 (66.7%) subjects in the placebo arm had at least one adverse event (AE) reported during the study.

Table 1: Summary of All Adverse Events. Safety population

	VB-201 160 mg (n=79)	VB-201 80 mg (n=34)	VB-201 160 mg Cross over (n=70)	Placebo (n=81)
Number of subjects with AEs	61 (77.2%)	26 (76.5%)	23 (32.9%)	54 (66.7%)
Number of subjects with drug-related AEs	31 (39.2%)	13 (38.2%)	7 (10.0%)	20 (24.7%)
Number of subjects with AEs of at least moderate severity	34 (43.0%)	12 (35.3%)	14 (20.0%)	26 (32.1%)
Number of subjects with drug-related AEs of at least moderate severity	12 (15.2%)	4 (11.8%)	5 (7.1%)	6 (7.4%)
Number of subjects with at least one serious AE	1 (1.3%)	1 (2.9%)	0 (0.0%)	2 (2.5%)
Number of subjets with drug-related serious AEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Of those subjects who had AEs reported, 12 subjects in the VB-201 160 mg arm, 4 subjects in the VB-201 80 mg arm, 6 subjects in the placebo arm and 5 subjects who switched to VB-160 mg after week 16 had drug-related AEs of at least moderate severity. One serious adverse event was reported in the VB-201 160 mg arm, 1 in the VB-201 80 mg arm and 2 in the placebo arm. No serious adverse event was reported after switch to VB-201 160 mg after week 16. No drug-related serious adverse events were reported in any treatment arm and at any time.

Conclusion:
The primary analysis of the primary endpoint PASI50 responder rate at week 16 and at week 24 did not show a statistically significantly superiority of VB-201 at any dose over the placebo during stage 1, the number of subjects with AEs was higher in the VB-201 160 mg arm compared to the. VB-201 80 mg arm and the placebo arm. None was drug-related.

Date of report: 08-Mar-2016