2 SYNOPSIS OF STUDY REPORT, No. (AC-052-427)

COMPANY:	(FOR NATIONAL AUTHORITY USE ONLY)
Actelion Pharmaceuticals Nederland BV	
NAME OF FINISHED PRODUCT:	
Bosentan	
NAME OF ACTIVE SUBSTANCE(S):	
Bosentan	

TITLE OF THE STUDY	Effects of bosentan in a HOMogenEous population of SSc subjects with a predefined restriction of blood flow in the hands (HOME)
STATUS OF STUDY / TYPE OF REPORT	Final study report
INDICATION	Sclerodermie patient with a history of digital ulcers
INVESTIGATORS / CENTERS AND COUNTRIES	Dr. M.C. Vonk, UMC st Radboud, the Netherlands Dr. A.J.M. Schuerwegh, LUMC, the Netherlands Dr. A.E. Voskuyl, VU, the Netherlands Dr. A. Spoorenberg, Medisch Centrum Leeuwarden, the Netherlands Dr. D. van Zeben, Fransiscus ziekenhuis, the Netherlands Dr. P.L.E. van Daele, Erasmus MC, the Netherlands Dr. Walravens Maasstadziekenhuis, the Netherlands
PUBLICATION (REFERENCE)	Knaapen H, Vonk MC et all, HOME: The effect of systemic sclerosis on the blood flow in the hands, Poster at Eular 2012 Knaapen H, Vonk MC et all, HOME: Effects of bosentan in a HOMogenEous population of SSc subjects with a predefined restriction of blood flow in the hands (HOME) preliminary results, Poster at Eular 2012 Meijs J, Schuerwegh AJM et all, Blood flow in the hands of a predefined homogeneous systemic sclerosis population: the presence of digital ulcers and the improvement with bosentan, submitted to ARD 2013

PERIOD OF TRIAL	Type Mar28 2011to Nov 28 2012	CLINICAL PHASE	Type 4
OBJECTIVES	The primary objectives were - To demonstrate the correlation of blood flow in the hands and the extent of DU disease in patients with SSc. - Evaluate the effect of bosentan on the blood flow in the hands from baseline to 12 weeks, measured by laser Doppler imaging, in SSc subjects with a history of DU disease in the past 2 years and clinically relevant reduction of blood flow at baseline. Secondary objectives were - Evaluate the effect of bosentan on the blood flow in different regions of the hands from baseline to 4 weeks and 12 weeks. -Evaluate the effect of bosentan on the hand function, pain perception and quality of life from baseline to 12 weeks, 26 weeks and 52 weeks. -Evaluate the effect of bosentan on the modified Rodnan skin score from baseline to 12 weeks, 26 weeks and 52 weeks. -Evaluate the effect of bosentan on the development of new digital ulcers and pitting scars from baseline to 12 weeks, 26 weeks and 52 weeks.		
STUDY DESIGN	Open label, non comparative study Week 0: screening. For patient fulfilling the inclusion criteria 12 weeks treatment with bosentan and follow-up visits at week 4,12,26 and 52 During visit0,4 and 12 the blood flow was measured using laser Doppler imaging (LDI) During all visits mRSS and a hand evaluation was performed		
NUMBER OF PATIENTS	51 healthy subjects were measured with LDI 56 patients were planned to be included 58 patients were screened 18 of them fulfilled the inclusion criteria 16 patients were included and obtained treatment (2 patients refused treatment) 16 patients returned for the 4 weeks follow-up		

	15 patients returned for the 12 weeks follow-up 11 patient returned for the 26 weeks follow up, only 3 complete data sets 9 patient returned for the 52 weeks follow up, only 2 complete data sets
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Inclusion criteria Male and female subjects > 18 years diagnosed with SSc; • Reduction of blood flow measured by laser Doppler imaging, of at least 50%, distally to the proximal interphalangeal joint, compared to historical healthy controls; • Women of childbearing potential must have a negative pregnancy test and use a reliable form of contraception; • A history of 1 or more DUs within 2 years prior to inclusion; • No use of bosentan in the past; • Subjects willing and able to sign informed consent. Exclusion criteria • Parenteral prostanoid treatment for DU < 3 months ago; • Chronic treatment with PDE-5 inhibitor or ERA; • History of bosentan use • Irreversible significant limitation of the hand function, e.g. amputation of more than one finger; • Other types of system- or connective tissue diseases; • Significant peripheral (macro-) vascular disease due to e.g. diabetes, hyperlipidemia, uncontrolled systemic hypertension, coagulopathy; • Any serious medical co morbidity (eg, active malignancy) such that the subjects life expectancy is < 12 months; • Known AST and/or ALT elevations higher than 3 times Upper Limit Normal (ULN); • Moderate to severe liver function disorder; • Pregnancy or breastfeeding; • Treatment with Glibenclamide, Fluconazole, Cyclosporin A, Tacrolimus or other calcineurin inhibitors; • Hypersensitivity for bosentan or one of its components; • Subjects not able to follow the protocol.
TRIAL DRUG / BATCH No.	Bosentan from commercial stock.
TRIAL DRUG DOSE / ROUTE / REGIMEN / DURATION	Bosentan 62.5 mg bid for 4 weeks orally Bosentan 125 mg bid for 8 weeks orally

CRITERIA FOR EVALUATION EFFICACY:	Correlation between blood flow in the hands, as measured by laser Doppler imaging, and extent of DU disease assessed by the mean blood flow restriction in four distinct groups of patients: patients without current DU (pitting scars allowed), patients with new DU (< 3 mo), patients with persistent DU (>3mo) and patients with significant tip-necrosis. • Change in blood flow in the hands after 12 weeks of bosentan treatment compared to the baseline, as measured by laser Doppler imaging. • Change in blood flow in different regions of the hands after 4 and 12 weeks of bosentan treatment compared to the baseline, as measured by laser Doppler imaging.
SAFETY:	Adverse observed events during the study.

STATISTICAL METHODS:

In healthy subjects and each of the four SSc patients subgroups, data were summarized descriptively by mean±SD (and if informative also as median [range]) for continuous variables and frequency for categorical variables.

Demographics were tested for significance between groups using the student's t-test. Regression analysis was used to analyze differences in blood flow across SSc subgroups at baseline. An ordinal regression analysis was performed to predict the extent of DU, with the four different stages as dependent variables, blood flow as main determinant and adjusted for sex, age and smoking status. Differences in blood flow between healthy subjects and all SSc patients at baseline were compared post hoc using analysis of covariance (ANCOVA) with subject status, sex and smoking status as fixed effects and age as a covariate in the statistical model.

The change in hand blood flow in the hands from baseline to week 12 was analyzed with a paired t-test, and any missing values were replaced by the last-value-carried-forward method. Blood flow of healthy subjects' blood flow at baseline was compared with blood flow at baseline and week 12 in SSc patients who received bosentan post hoc using ANCOVA to test significance.

All data were analyzed according to the intention-to-treat (ITT) principle. Two-sided p-values of less than 0.05 were considered to be statistically significant. Data entry was performed using Microsoft Office Access 2003. All statistical analyses were executed using SPSS 17.0 software (SPSS Inc., Chicago, USA).

PATIENT DISPOSITION:

The healthy subjects were significantly (p=0.006) younger than the SSc patients. There was no difference in age within the SSc patient subgroups. No other demographic differences were observed

EFFICACY RESULTS:

Fifty-two SSc patients and 51 healthy subjects and were included in the analysis. There was no significant difference in blood flow in the hand across the patient subgroups at baseline. Sixteen SSc patients had a reduction of blood flow of ≥50% versus healthy subjects and received bosentan. Bosentan significantly ($p<0.05$) increased the blood flow in the whole hand after 12 weeks compared with baseline.

SAFETY RESULTS:

In the 16 bosentan-treated patients treated with bosentan, two patients discontinued treatment at weeks 5 and week 8 for fever (related to bosentan) and fatigue complaints(not related to bosentan), respectively; one patient was lost to follow-up due to lung carcinoma (not related to bosentan). In one patient, the dose bosentan was maintained at 62.5 mg after week 4 because of elevated ALT/AST values (3– 5 x upper limit of normal) after up-titration (related to bosentan). Two other adverse events were reported in three patients: headache (possibly related to bosentan), inflammation of the finger tips due to intestine cancer causing vascular constriction (not related to bosentan) and one rash (not related to bosentan).

CONCLUSIONS:

No relationship was found between blood flow in the hands of SSc patients and presence of DU. After 12 weeks of bosentan treatment the blood flow had increased in the SSc patients but had not normalized to that of healthy subjects

DATE OF THE REPORT:

30 *Jul 2013*