2 SYNOPSIS

Name of Company: Active Biotech AB **Name of Finished Product:** - **Name of Active Ingredient:** Paquinimod (ABR-215757)	**Individual study table referring to part of the dossier** **Volume:** **Page:**	(For national authority use only)

Title of Study:
An Open-Label Study to Evaluate Biomarkers and Safety in Systemic Sclerosis Patients Treated with Paquinimod (ABR-215757)

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Study Centres:
Patients were enrolled at Site 1 in Sweden (2 patients), Site 3 in Switzerland (5 patients) and Site 4 and Site 5 in Germany (1 patient per site).

Publication (reference):
Not applicable

Studied Period (years):
First patient first visit: 30 November 2011
Last patient last visit: 15 February 2013

Phase of Development:
Phase II

OBJECTIVES:
Primary Objective:

- To study changes in disease related biomarkers in patients with progressive Systemic Sclerosis (SSc) during treatment with paquinimod.

Secondary Objectives:

- To assess the safety and tolerability of paquinimod in progressive SSc patients.
- To assess disease activity and Quality of Life (QoL) in patients with progressive SSc during treatment

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with paquinimod.

- To assess plasma levels of paquinimod during the study.

METHODOLOGY:
The study was an open-label, single arm, Phase II study. After a screening period of 14±7 days, patients were treated with 3.0 mg paquinimod daily for 8 weeks. The dose could be reduced to 1.5 mg/day depending on the tolerability of paquinimod in individual patients but none of the patients had the dose reduced during the study. During treatment, visits to the clinic were performed at Weeks 2, 4 and 8. A follow-up visit took place 4 weeks after last dose of paquinimod. The implementation of protocol amendment number 2 allowed patients to continue treatment after follow-up of the planned 8-week main study at the Investigator's discretion. However, none of the patients proceeded to the continuation phase.

At specified time points during the study, blood samples and skin biopsies were collected for analysis of biomarkers. SSc disease activity indices, including modified Rodnan Skin Score (mRSS), were followed. Safety parameters and paquinimod plasma levels were monitored throughout the study. Allowed concomitant SSc treatment included proton pump inhibitors, prostacyclin analogues and angiotensin-converting-enzyme inhibitors. Oral calcium channel antagonists, phosphodiesterase inhibitors and prednisolone (or equivalent) at a dose of ≤10 mg/day were allowed at stable doses from specified time points prior to the study and throughout the study.

Number of Patients (Planned and Analysed):
Approximately 10 patients were planned for the study. Nine patients were enrolled and completed all visits (8 weeks of treatment and follow-up). Data from all patients were included in all populations.

Diagnosis and Main Criteria for Inclusion:
To be eligible for inclusion in the study, the patient had to be at least 18 years old at the time of signing the informed consent form, have a clinical diagnosis of SSc according to American College of Rheumatology criteria, be antinuclear antibody-positive, have progressive SSc, have skin lesions on one or both forearms and have a baseline mRSS of at least 16.

Test product, Dose and Mode of Administration, Batch Number:
Paquinimod was supplied as 1.5 mg hard gelatin capsules. All patients took 2 capsules per day, which equals a daily dose of 3.0 mg. The capsules used in the study were all from batch number 0146E.

Duration of Treatment:
The patients received once daily treatment with paquinimod for 8 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Not applicable.

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Criteria for Evaluation:

Primary Endpoint

- Changes in SSc disease activity related biomarkers.

Secondary Endpoints

- Adverse Events (AEs) and changes in laboratory safety parameters.
- Disease activity.
- QoL measured by the 36-Item Short Form Health Survey (SF-36) and by the Scleroderma Health Assessment Questionnaire (SHAQ).
- Plasma levels of paquinimod.

Drug Concentration Measurements:

Blood samples to determine the plasma levels of paquinimod were collected at all visits from the baseline visit (Visit 2) until the follow-up visit.

Efficacy Assessments:

Blood samples and skin biopsies were taken for assessment of disease related biomarkers. Blood samples were taken at all visits, whereas skin biopsies (punch biopsies from lesional skin on the forearm) were taken at baseline and at Week 8.

Disease activity measurements included mRSS and digital ulcers, which were assessed at screening, baseline, Week 4, Week 8 and follow-up.

QoL was assessed using SF-36 and SHAQ at baseline, Week 8 and follow-up.

Safety Assessments:

Safety variables monitored throughout the study included:

- AEs.
- Safety laboratory evaluations.
- Vital signs.
- Physical examination.
- Electrocardiogram (ECG).

Statistical Methods:

Summary Statistics

Data were summarised by means of summary statistics. For continuous data the following summary statistics were presented; number of observations, mean value, standard deviation, minimum, first quartile, median, third quartile and maximum value. For laboratory data, biomarkers and plasma concentrations, the geometric mean and the corresponding standard error were included.

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Summary statistics were presented by visit. Individual patient data were listed.

Drug Concentration Data Analysis
Plasma concentrations were summarised by visit using summary statistics.

Efficacy Analysis
The p-values were calculated using the non-parametric two-sided Wilcoxon signed rank test at a 5% significance level.

Skin Biopsy Biomarkers
For the myofibroblast count (the histologically defined biomarker), the ratio of values at Week 8 versus baseline was derived. Summary statistics were produced for both observed values and for ratios. The myofibroblast count was expected to be log-normally distributed and observed results were therefore log-transformed. Differences from baseline were then derived, and p-values were calculated for the null hypothesis of no change from baseline at the post baseline visit. For the gene expression biomarkers (messenger Ribonucleic Acid [mRNA]), the fold change from baseline was derived by the laboratory and sent to TFS via the Sponsor. The fold change was summarised using summary statistics. The fold change was expected to be log-normally distributed and observed results were therefore log-transformed.

Based on the t-distribution, 95% Confidence Intervals (CI) were derived for changes from baseline of log-transformed data and p-values were calculated. The confidence limits were back-transformed to the original scale, to represent a CI for the ratio.

Blood Biomarkers
Summary statistics were calculated for absolute values of the serum and plasma biomarkers and for ratio between visits. A Wilcoxon rank sum test was also performed on the ratios.

Disease Activity
For mRSS, the total score and the corresponding difference from baseline in the total score were summarised by visit using summary statistics. p-values were calculated for the null hypothesis of no change from baseline at each post-baseline visit using a one-sample non-parametric Wilcoxon signed rank test. Based on the t-distribution, 95% CI was derived for both observed values and for changes from baseline. A time-adjusted Area Under the Curve (AUC) was calculated for the difference from baseline for the assessments made at Week 4, Week 8 and follow-up. This measure was presented using summary statistics with 95% CI and p-values for the Wilcoxon rank sum test.

Digital ulcers were listed by patient (location of the ulcers and start and stop dates).

Quality of Life
The results from the SF-36 and SHAQ measures were presented with summary statistics.

Safety Analysis
Safety data were in general presented with summary statistics. For safety laboratory data, vital signs and ECG results, p-values and 95% CIs were also presented.

SUMMARY - CONCLUSIONS
Drug Concentration Data Results:
The patients were well exposed to paquinimod with average trough (pre-dose) concentrations after 8 weeks paquinimod treatment of 4653±436 (mean ± standard error of the mean) nmol/L. Approximate steady state

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levels had been reached after 2 weeks of treatment.

Efficacy Results:
Myofibroblasts play an important role in the pathogenesis of fibrosis and analysis of these cells in skin biopsies demonstrated a significant (p=0.023) reduction of 8% after the 8-week paquinimod treatment compared to baseline. When analysing skin biopsies for the expression of a panel of 93 genes involved in fibrosis, a significant ($p < 0.05$) change from baseline to Week 8 was observed for 13 pro-fibrotic genes. A majority of these genes (11) was down-regulated (BCL2, CAV1, CCL11, CCR2, CTGF, ITGA3, SERPINE1, SNAI1, TGFB3, TGFBR2 and TIMP3). Up-regulation was observed for only 2 genes (Col3a1 and SIGLEC-1). Further exploratory analyses of a set of 5 type I interferon (IFN) responsive genes showed a down-regulation in a composite score in 6 of the 9 patients, indicating a decrease in type I IFN activity in the skin.

A decrease in the chemokine CCL2 serum level from baseline to Week 8 was observed in 7 of the 9 patients (p=0.07). Also, a decrease in the type I IFN activity in plasma was recorded during treatment in the one patient who had elevated activity at baseline.

As expected in this short-term clinical study, there were only minor, non-statistically significant, changes from baseline in mRSS and in time-adjusted AUC for mRSS.

A few patients developed digital ulcers during the study and a few patients had digital ulcers at baseline. About half of these digital ulcers healed during the study.

Also for the QoL assessments, only minor changes from baseline were observed in SHAQ and SF-36 scores during the study.

Safety Results:
Unique AEs reported after initiation of treatment are summarised in the following table (9 patients):

Mild AEs		Moderate AEs		Severe AEs		Total Unique AEs		
R	NR	R	NR	R	NR	R	NR	R+NR
15	15	4	2	0	1	19	18	37
R = Related, NR = Not Related								

A total of 38 AEs were reported after the paquinimod treatment had been initiated. One AE was repetitive within 1 patient, resulting in 37 unique AEs in the study. All patients reported at least 1 AE. The System Organ Class (SOC) with the highest number of AEs was Musculoskeletal and Connective Tissue Disorders. AEs reported within this SOC included arthralgia (reported by 3 patients), arthritis and myalgia (reported by 2 patients) and SSc (reported by 1 patient). AEs outside this SOC reported by more than 1 patient included headache (reported by 3 patients), diarrhoea and nasopharyngitis (reported by 2 patients each).

Of the 37 unique AEs, 19 AEs in 7 patients were assessed as possibly or probably related to study medication by the Investigators. Related AEs reported by more than 1 patient included arthralgia, myalgia, diarrhoea and headache (reported by 2 patients each).

Most of the AEs were of mild intensity. One severe AE was recorded, a case of peripheral ischaemia. This AE was also serious. The event was assessed as unlikely related to the study medication by the Investigator. No other serious AEs were reported. No AE led to dose reduction or patient withdrawal. One AE (pruritus,

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assessed as related to study medication) led to dose interruption for 7 days.

There was an increase in some of the laboratory parameters during the study, mainly transient increases in acute phase reactants (C-Reactive Protein [CRP] and erythrocyte sedimentation rate). Two patients had clinically significant CRP values, which were reported as AEs (one of which was assessed as related to study medication).

The central reader assessed one ECG reading (indicating a possible cardiac event) at follow-up as clinically significant but not related to the study medication. There were no general trends over time for the different ECG parameters during the study, including no overall QTc prolongation.

No major changes in vital signs were observed, but the majority of patients lost weight during the study.

CONCLUSION:
All patients had reached approximate steady state levels after 2 weeks of paquinimod treatment. The biomarker evaluation demonstrated a significant decrease in myofibroblast count and in a number of pro-fibrotic genes relevant in SSc, following paquinimod treatment. Paquinimod was generally well-tolerated by the patients in the study and there were no clinically important safety findings. No effects on disease activity or QoL were recorded in this short term study.

Date of the Report:
Final report, 04 September 2014