1 SYNOPSIS

Name of Company: Active Biotech AB **Name of Finished Product:** ABR-215757 **Name of Active Ingredient:** N,5-diethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-N-phenyl-3-quinolinecarboxamide (INN Paquinimod)	**Individual study table referring to part of the dossier** **Volume:** **Page:**	(For national authority use only)
CTN: **09575704**		**Document Number:** 1230028

Title of Study:
An Exploratory Study to Evaluate Changes in Disease Activity and Biomarkers During Treatment With ABR-215757 (Paquinimod) in Patients With Mild Active Systemic Lupus Erythematosus (SLE)

Investigator(s):
Anders Bengtsson, MD, PhD, Department of Rheumatology, Lund University Hospital, Lund, Sweden

Iva Gunnarsson, MD, PhD, Department of Rheumatology, Karolinska University Hospital, Stockholm, Sweden

Lars Rönnblom, MD, PhD, Department of Medical Sciences, Uppsala University Hospital, Uppsala, Sweden

Søren Jacobsen, MD, DMSc, Department of Rheumatology, Rigshospitalet, Copenhagen, Denmark

Study Centre(s):
The study was conducted at three centers in Sweden (Lund, Stockholm and Uppsala) and one center in Denmark (Copenhagen)

Publication (reference):
Abstract and poster presented at the EULAR congress in London, UK 25-28 May 2011: "An Exploratory Study to Evaluate Changes in Disease Activity and Biomarkers During Treatment with ABR-215757 in Patients with Mild Active Systemic Lupus Erythematosus (SLE)", Bengtsson A.A. et al.

Studied Period (years):
First patient first visit: 05 August 2009
Last patient last visit: 10 September 2010

Phase of Development:
Phase IIa

OBJECTIVES:

The primary objective was to assess changes in disease activity and biomarkers in patients with mild active SLE during treatment with ABR-215757.

The secondary objectives were:

- To assess the safety and tolerability of ABR-215757 in patients with mild active SLE disease
- To assess the plasma levels of ABR-215757 during the study.

Name of Company: Active Biotech AB **Name of Finished Product:** ABR-215757 **Name of Active Ingredient:** N,5-diethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-N-phenyl-3-quinolinecarboxamide (INN Paquinimod)	**Individual study table referring to part of the dossier** **Volume:** **Page:**	(For national authority use only)
CTN: **09575704**		**Document Number:** 1230028

Primary endpoint:

- Changes in disease activity and biomarkers in patients with mild active SLE treated with ABR-215757.

Secondary endpoints:

- Adverse events and changes in laboratory safety parameters.
- Plasma levels of ABR-215757

METHODOLOGY:

Patients with mild active SLE were studied in an open label study with ABR-215757 as the only new treatment that was added to ongoing treatment. Patients had active disease with skin or joint symptoms or oral ulcer. Primarily, the study involved the assessment of disease activity and biomarkers (autoantibodies, complement and type I interferon) compared to baseline during and after 12 weeks of treatment. Secondary objectives of the study involved assessment of safety parameters and plasma levels of ABR-215757 during the study.

Following a screening period of one week patients were treated with ABR-215757 as the only new treatment added to ongoing SLE treatment. The first patients (n=4) were treated with ABR-215757 at 3 mg/day. The initial dose level was, however, lowered to 1.5 mg/day with an option to increase the dose to 3.0 mg/day following 28 days of treatment. A total of 9 patients were included in the 1.5 mg dose group. Patients were treated for 12 weeks with ABR-215757. During treatment there were scheduled visits on days 14, 28, 56 and 84. Follow-up visits took place 29 days and 57 days after last dose of ABR-215757. Arthritis symptoms during treatment were assessed using the 28- and the 66/68 joint indices. Skin involvement (including erythema, oral ulcers and alopecia) was monitored by the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). In order to document potential effects on other SLE disease manifestations, global disease activity was also followed using the Systemic Lupus Erythematosus disease Activity Index (SLEDAI-2K). At specified time points during the study, blood samples and biopsies were collected for analysis of established and exploratory disease markers of SLE. Safety parameters and pre-dose plasma levels of ABR-215757 were assessed throughout the study. Allowed concomitant SLE treatment included: prednisolone or equivalent at a dose of ≤15 mg/day, hydroxychloroquine, azathioprine, methotrexate and mycophenolate mofetil, all at stable doses from specified timepoints prior to the study and throughout the study.

Number of Subjects (Planned and Analyzed):

A total of 13 SLE patients were enrolled in the study, 6 patients with arthritis and 7 patients with skin symptoms or oral ulcer. Nine patients were treated with 1.5 mg ABR-215757 per day and four patients were treated with 3.0 mg ABR-215757 per day. Five patients discontinued the study prematurely. The patients were divided into 4 sub groups based on treatment dose, 1.5 or 3.0 mg per day, and main symptom at baseline, joint and mucocutaneous (skin, oral ulcer)

Name of Company: Active Biotech AB **Name of Finished Product:** ABR-215757 **Name of Active Ingredient:** N,5-diethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-N-phenyl-3-quinolinecarboxamide (INN Paquinimod)	**Individual study table referring to part of the dossier** **Volume:** **Page:**	(For national authority use only)
CTN: **09575704**		**Document Number:** 1230028

	joint 1.5 mg	joint 3.0 mg	mucocutaneous 1.5 mg	mucocutaneous 3.0 mg	Total
No. planned					max 20
No. treated	4	2	5	2	13
No. analyzed for safety	4	2	5	2	13
No. analyzed for efficacy	4	2	5	2	13
No. completed the study	4	1	3	0	8

Diagnosis and Main Criteria for Inclusion:
SLE patients aged ≥ 18 years were included in the study.

Patients had to fulfil at least 4 criteria for SLE as defined by the American College of Rheumatology (ACR) and present with active SLE disease with at least one of the following symptoms:
i) Arthritis – ≥ 2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion)
ii) Inflammatory-type skin rash
iii) Oral ulcers

Test product, Dose and Mode of Administration, Batch Number:
ABR-215757 (batch No 0146E) was given as 1.5 mg capsules. The daily dose was 1.5 or 3.0 mg. At visit days the capsules were to be taken at the clinic after all assessment had been completed.

Duration of Treatment:
Each patient was to receive daily treatment for 12 weeks.

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

Name of Company: Active Biotech AB **Name of Finished Product:** ABR-215757 **Name of Active Ingredient:** N,5-diethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-N-phenyl-3-quinolinecarboxamide (INN Paquinimod)	**Individual study table referring to part of the dossier** **Volume:** **Page:**	(For national authority use only)
CTN: **09575704**		**Document Number:**

Criteria for Evaluation:
Efficacy:

- Disease activity measurements: Systemic Lupus Erythematosus disease Activity index 2000 (SLEDAI-2K), 28-joint index, 66/68-joint index, Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)
- Biomarker measurements: Anti-double stranded DNA (anti-dsDNA) antibodies, anti-cardiolipin antibodies, Complement factors C1q, C3 and C4, type I interferon

Safety:

- Adverse events and changes in laboratory safety parameters.

Statistical Methods:
Descriptive statistics was applied.

SUMMARY - CONCLUSIONS

Pharmacokinetic Results:
The patients were well exposed to ABR-215757. Near steady state levels were reached after about 14 days of treatment. No essential dependency in the pharmacokinetics due to dose or time during up to 12 weeks of treatment with ABR-215757 was indicated.

Efficacy Results:
Improvement by 50% or more, either in the number of swollen joints (66/68 joint index) or in the CLASI total activity score, was seen in 7 out of 13 patients during treatment with ABR-215757: These decreases were seen in 4 patients out of 6 patients with arthritis and in one patient out of five patients with erythema (inflammatory-type skin rash). Two patients in the mucocutaneous group recovered completely from their symptoms, one with oral ulcer and alopecia and one patient with oral ulcer only. One patient in the joint group also suffering from alopecia at baseline recovered during treatment in regard to hair loss symptoms.

SLEDAI-2K scores did not reveal any changes in global disease activity that were not detected in the organ specific measurements (28- and 66/68-joint indices, CLASI) or in the biomarker assays, except for pyuria and the presence of urinary casts in one patient at the follow-up visit.

Name of Company: Active Biotech AB **Name of Finished Product:** ABR-215757 **Name of Active Ingredient:** N,5-diethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-N-phenyl-3-quinolinecarboxamide (INN Paquinimod)	**Individual study table referring to part of the dossier** **Volume:** **Page:**	(For national authority use only)
CTN: **09575704**		**Document Number:**

Number of patients showing improvement of symptoms during treatment

Main symptom at baseline	Total number of patients	Number of patients showing improvement*
Arthritis	6	4
Erythema	5	1
Oral ulcer	2	2
Total	**13**	**7**

*at least 50% reduction either in the number of swollen joints (66/68 joint index) or in the CLASI total activity score

Increased production of type I IFN is generally considered to be linked to both SLE disease activity and severity. Elevated type I IFN baseline levels were observed in three patients, and a decline in type I IFN activity was seen in two of these during treatment with ABR-215757. This was, however, not accompanied by reduction in SLE disease activity. It should be noted that disease improvement was generally seen in patients reported to have stable active disease and low levels of type I IFN at base line.

Other serum markers of SLE (anti-dsDNA, anti-cardiolipin or complement C1q, C3 and C4) did not change notably during treatment with ABR-215757, except for reduction in C1q seen in two patients.

Safety Results:

A total number of 98 AEs and 91 unique AEs occurred in 13 patients. All patients in the study experienced at least one AE.

The majority of the AEs were of mild intensity (74 unique AEs). A total number of 16 unique AEs of moderate intensity and one AE of severe intensity were reported.

No SAEs were reported during the study.

The most common AEs were nasopharyngitis (5), arthralgia (5), fatigue (4) and rash (4). Taking into consideration the number of patients and the duration of treatment, the frequency of AEs did not differ between dose groups (1.5 mg and 3.0 mg). The frequency of AEs was also similar in both sub-indications (joint and mucocutaneous).

Fifty % of the AEs (49/98) were considered possibly or probably related. All 13 patients experienced at least one related AE. The most common related AEs were arthralgia (4), fatigue (4) and rash (3).

Five patients discontinued the study due to adverse events. The primary AEs leading to discontinuation were arthralgia, arthritis, cutaneous lupus erythematosus, dyspnoea and rash.

Name of Company: Active Biotech AB **Name of Finished Product:** ABR-215757 **Name of Active Ingredient:** N,5-diethyl-1,2-dihydro-4-hydroxy-1-methyl-2-oxo-N-phenyl-3-quinolinecarboxamide (INN Paquinimod)	**Individual study table referring to part of the dossier** **Volume:** **Page:**	(For national authority use only)
CTN: **09575704**		**Document Number:**

The main effects of ABR-215757 on laboratory parameters were transient increases in the inflammatory markers ESR, CRP and anti-trypsin seen in 6 out of 13 patients. The highest values were generally seen when reaching approximately steady state plasma levels of ABR-215757 and declined towards the end of treatment.

With the exception of a slight elevation in mean pulse rate during treatment there were no detectable effects on vital signs. There were no chest X-ray abnormalities recorded during the study that were not present at baseline. ECG reviews showed no overall trends neither to an increase nor to a decrease of the various parameters.

CONCLUSION:

Decreased disease activity during treatment with ABR-215757 was mainly seen in patients with arthritis (4/6) or oral ulcers (2/2). In contrast, only one out of five patients with erythema (inflammatory-type skin rash) improved during treatment. The drug was well tolerated and most adverse events were mild to moderate and transient. With the exception of a transient increase in acute phase reactants seen in some patients, there were no obvious effects on laboratory parameters, vital signs or ECG parameters.

Date of the Report: 25 April, 2013