Clinical Study Report	
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A Phase IIa, Double-blind, Randomized, Placebo-controlled, Dose-finding Efficacy and Safety Study of A3309 in Patients with Dyslipidemia

Study duration (FPI-LPO) 23-Feb-2010 to 05-Jul-2010

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The clinical study was conducted, and essential study documentation archived, in compliance with company SOPs and standards, which incorporate the requirements of the EU Clinical Studies Directive 2001/20/EC and ICH Guideline for Good Clinical Practice (GCP).

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SYNOPSIS

Study Title: A phase IIa, Double Blind, Randomized, Placebo-Controlled, Dose-finding Efficacy and Safety Study of A3309 in Patients with Dyslipidemia	
Study code: A3309-005	**EudraCT No:** 2009-017878-21
Principal Investigator Ingemar Bylesjö, MD, PhD	
Study centre: Centre 1: JJ Berzelius Clinical Research Center AB, Berzelius Science Park, Linköping, Sweden.	
Publication (reference): Not applicable	
Study period: Date of first enrolment: 23-Feb-2010 Date of last subject completed: 5-Jul-2010	**Phase of development:** Phase IIa

Objectives:

Primary objectives[1]:

The primary efficacy objective of this Phase IIa study was to assess the efficacy of two dose levels of multiple doses of A3309 in patients with dyslipidemia, as determined by the change from baseline in Low Density Lipoprotein (LDL) cholesterol in comparison to placebo.

Secondary objectives[1]

The secondary efficacy objectives of this study were to assess the efficacy of two dose levels of multiple doses of A3309 in patients with dyslipidemia, as determined by the change from baseline in Total Cholesterol (TC), High Density Lipoprotein cholesterol (HDL), total triglycerides (TG) and 7α-hydroxy-4-cholesten-3-one (C4), in comparison to placebo.

Safety objectives

The safety objectives of this study included assessment of the safety and tolerability of two dose levels of multiple doses of A3309 in patients with dyslipidemia, as determined by the incidence (number [percentage]) of AEs and changes in other safety parameters including laboratory tests, vital signs, and 12-lead ECGs, in comparison to placebo.

Endpoints:

Baseline assessments were defined as the last assessment recorded before the first dose of study drug.

[1] The primary and secondary objectives were changed in Amendment 2, as described in section **Fel! Hittar inte referenskälla.**

Primary endpoint[2]**:** Change from baseline to day 28 in LDL cholesterol.

Secondary endpoint[1]**:** Changes from baseline in measurements of Total Cholesterol in plasma, TG, HDL cholesterol and C4 in serum measurements during days 14 and 28.

Safety endpoints**:** Changes from baseline in the nature, incidence and severity of AEs, clinical laboratory abnormalities and through assessment of changes over time in clinical laboratory parameters, vital signs, ECGs and physical examination findings

Methodology:

This was a Phase IIa randomized, double-blind, placebo-controlled, single-centre, dose-finding efficacy and safety study of two dose levels of A3309 in 36 patients diagnosed with dyslipidemia. The study was designed to assess the change from baseline of plasma lipids and C4 between active dose levels of A3309 and placebo.

The study consisted of 5 clinic visits at the investigative site for assessments, including one screening and one follow-up visit, for each eligible patient.

Patients were randomized in a 1:1:1 ratio to receive one of two dose levels of A3309 or placebo, orally administered.

Number of patients:

Planned number of screened patients: 72

Actual number of screened patients: 81

Planned number of included patients: 36

Actual number of included and analysed patients: 36, 12 in each treatment group

Diagnosis and main eligibility criteria:

Eligible patients needed to have dyslipidemia (for the purpose of this study defined as (TC > 5.5 mmol/L) but otherwise be healthy.

Investigational product, dosage and mode of administration, batch number:

A3309 is a stereochemically pure enantiomer with a molecular weight of 695.9 g/mol and was for the study supplied as white to off-white tablets.

Each randomized patient received a treatment kit (plastic bottles) containing 32 tablets (for 28 days of administration) of one of the following:

- A3309 2.5 mg,
- A3309 5 mg, or

[2] The primary and secondary objectives were changed in Amendment 2, as described in section **Fel! Hittar inte referenskälla.**

Matching placebo (with the same appearance as A3309 but without the active ingredient).
These tablets were taken orally with water before breakfast once daily during the treatment period.

Each treatment kit was labelled with a unique kit number; labelling did not indicate whether the medication within was one of the A3309 doses or placebo.

As all treatments were delivered in one batch, only one batch number is available: 96205-1001-01.

Duration of treatment:

The treatment period for each patient was 28 days.

Duration of patients' involvement in the study: The study lasted for approximately 8 weeks for each patient. The duration of the patients' participation in the study included 5 visits at the site, including a screening and a follow-up visit.

Statistical methods: Comparisons between the two treatment groups and placebo, regarding the primary and secondary efficacy endpoints, were made using Wilcoxon rank sum test.

Demographics, baseline characteristics and safety data were analyzed using descriptive statistics. Data are summarized by treatment group for AEs, vital signs, 12-lead ECGs, clinical laboratory tests (haematology, clinical chemistry, coagulation, urinalysis), and concomitant medication.

The sample size for this study was set to 36 patients in gross total. The patients were evenly distributed among the three treatment group giving a number per group of 12.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS

Primary efficacy endpoint[3]

The primary efficacy endpoint was the change from baseline to day 28 in LDL cholesterol. The primary comparison; the analysis of high dose (5 mg) of A3309 versus placebo, showed a statistically significant change of LDL cholesterol from baseline to day 28 between the 5 mg dose and placebo (p-value = 0.0443). The secondary comparisons, i.e. all other pair-wise comparisons between the two doses of A3309 and placebo as regards the effect on LDL cholesterol on both day 14 and 28 showed results in favour of A3309 in both treatment groups, although no statistically significant differences were detected.

Secondary efficacy endpoint[4]

[3] The primary and secondary endpoint were changed in Amendment 2, as described in section **Fel! Hittar inte referenskälla.**

[4] The primary and secondary endpoint were changed in Amendment 2, as described in section **Fel! Hittar inte referenskälla.**

The analyses of the secondary endpoints showed that there was a statistically significant change of C4 from baseline to day 28 between both the high and low dose treatment groups of A3309 and the placebo group (p-value = 0.0268 for both dose groups).

Furthermore, there was a statistically significant change in the LDL/HDL ratio from baseline to day 28 between the high dose treatment group of A3309 and placebo (p-value = 0.0040), there was also a tendency towards a reduction in the low dose treatment group, as compared to placebo, at this time-point although this effect was not statistically significant (p-value=0.0617).

Apart from these differences, there were no statistically significant differences in any of the evaluated pair-wise comparisons performed.

Despite small changes in LDL cholesterol and in the LDL/HDL ratio, the results indicate that A3309 may be an additional tool in the clinician´s armamentarium when treating patients with dyslipidemia.

SAFETY RESULTS

No deaths or SAEs occurred during the study. Of the 52 AEs reported in the study, 17 were judged to be related to the study medication. Most AEs were reported as mild and transient in nature and AEs were most prevalent in the placebo group.

There were no apparent trends in the potentially clinically significant (PCS) values and the values were equally common in all three treatment groups

Vital signs, ECG and physical examination indicated no clinically significant abnormalities.

CONCLUSION:

The results show that both doses of AA3309 were safe and well tolerated by the participating subjects. In fact, there was no increased incidence of any AEs in the active treatment groups as compared to placebo. The total number of AEs was slightly higher in the placebo group as compared to the active treatment groups although the numbers of AEs that were judged to be related to the investigational product were similar between the three treatment groups.

The primary comparison of the primary efficacy endpoint in the study was met. The results showed that the high dose of A3309 was effective in reducing the levels of LDL cholesterol after daily treatment for 28 days as compared to placebo. The results also showed that the high dose of A3309 was effective in reducing the LDL/HDL ratio at day 28 as compared to placebo. Furthermore, there was an increase in C4 at day 28 in both the high and the low doses of A3309 as compared to placebo. These results thereby indicate that A3309 could potentially be used for treating patients with dyslipidemia. However, further studies evaluating the both the safety and efficacy of long-term treatment with A3309 are needed and possibly higher doses can also be evaluated.