Report Synopsis of Study:	**MICA**	
EudraCT-Nr.:	**2011-002539-24**	
Vorlage-Nr.:	**4037945**	
1) **Name of Sponsor/Company:** Klinikum der Ludwig-Maximilians Universität München	4) **Individual Study Table Referring to Part of the Dossier:** not applicable[1] Volume: not applicable Page: not applicable	*(For National Authority Use only)*
2) **Name of Finished Product:** Mipomersen		
3) **Name of Active Substance:** Mipomersen sodium		

5) **Title of Study[2]:**

Effect of Mipomersen on LDL-Cholesterol levels in Patients with Severe LDL-Hypercholesterolemia and Atherosclerosis Treated by Regular LDL-Apheresis

6) **Principal Investigator(s):** Prof. Dr. med. Klaus Parhofer

7) **Study centre(s):** Ludwig-Maximilians Universität München
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8) **Publication (reference):**

9) **Studied period (years)[3]:** 2 years 9 months Date of first enrolment: 03.08.2012 Date of last completed: 15.05.2015	10) **Phase of development:** Phase II

11) **Objectives:**

Primary Objectives:

The primary objectives of this study are to prove the concept for efficacy of mipomersen in patients with severe LDL-hypercholesterolemia and atherosclerosis treated by regular LDL-apheresis and to explore the consequent benefits for patients in therapy management.

The goal of the first phase is to demonstrate that 6 months of mipomersen treatment reduces LDL-cholesterol in patients on regular LDL-apheresis and with similar side effects as reported in patients not treated by concomitant apheresis therapy and to estimate the extent of reduction. The goal of the second phase is to evaluate the clinical significance of the reduction in terms of possible adaptions in apheresis therapy, i.e. to evaluate in how many patients apheresis duration can be shortened, intervals between two consecutive apheresis treatments can be stretched or apheresis can be discontinued.

Secondary Objectives:

- Evaluation of the safety and tolerability of mipomersen in patients on regular apheresis
- Evaluation of mipomersen in patients on regular apheresis on other lipid parameters

[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

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- Evaluation of pharmacokinetic characteristics of mipomersen in patients on regular apheresis therapy

12) **Methodology:**

This is a phase I-II study. The study will be performed as a mono-center, randomized, controlled study to evaluate the efficacy and safety of 38 weeks of treatment with mipomersen vs. a control in patients with severe LDL-hypercholesterolemia and atherosclerosis treated by regular LDL-apheresis.

The study will consist of 2 phases. In the first phase (26 weeks), patients will be treated with mipomersen and unchanged weekly apheresis to evaluate safety and efficacy of mipomersen given on top of regular apheresis. In the second phase (12 weeks) (Phase II study), mipomersen will be continued and apheresis conditions will be adjusted according to clinical necessity (change in apheresis duration, change in between-apheresis intervals, and discontinuation of apheresis) to evaluate whether treatment with mipomersen leads to a change of clinical intensity of apheresis therapy.

13) **Number of patients (planned and analyzed):** 17 / 18

14) **Diagnosis and main criteria for inclusion:**

Patients must meet all of the following inclusion criteria to be eligible for enrolment into the trial:

1. The patient is a male or female, age >/= 18 years.
2. The patient fulfils German criteria for regular LDL-apheresis:
   - Established atherosclerosis
   - LDL-cholesterol >/=130 mg/dl despite maximal possible drug therapy.
3. Regular (weekly) LDL-apheresis >/= 3 months; no change in apheresis system for 6 weeks.
4. The patient has fasting pre-apheresis LDL-C >/= 130 mg/dL at screening.
5. The patient is receiving a stable, maximally tolerated, lipid-lowering regimen, and is expected to remain on this regimen through the end of treatment, including both:
   - A maximally tolerated statin treatment greater than zero, unless the patient has a documented history of statin intolerance, stable for at least 12 weeks prior to screening.
   - A stable low-fat diet (e.g. NCEP-ATP III therapeutic lowering cholesterol or equivalent).
   - Note: Patients may receive another class of lipid-lowering therapy (e.g. cholesterol absorption inhibitors, bile- acid sequestrants, fibrates, niacin, fish oil), as long as it (drug and dose) has been stable for at least 6 weeks prior to screening
6. The patient has a body mass index (BMI) </= 40 kg/m2 with weight stable (± 4 kg) for > 6 weeks prior to screening.
7. The patient satisfies one of the following criteria:
   - Females: Non-pregnant and non-lactating; either surgically sterile, post-menopausal (e.g. one year without menstrual periods), or patient or partner compliant with an acceptable and highly effective contraceptive regimen (a regimen which results in a failure rate of less than 1% per year) for 4 weeks prior to screening, and willing to remain compliant during and for 24 weeks after the last investigational product dose.
   - Males: Either surgically sterile or patient or partner is willing to utilize an acceptable and highly effective contraceptive method during and for 24 weeks after the last investigational product dose.
8. Patients with the ability to follow study instructions and likely to attend and complete all required visits.
9. Written informed consent of the patient

15) **Test product, dose and mode of administration, batch number:**

Mipomersen sodium, Dose: 200 mg/week, Mode of application: Subcutaneous (sc) Injection

16) **Duration of treatment:**

38 weeks

17) **Reference therapy, dose and mode of administration, batch number:**

Not applicable. There will be a control group with unchanged weekly apheresis therapy

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18) **Criteria for evaluation:**

Efficacy:

Mean pre-apheresis LDL-cholesterol was 185±45 mg/dl in our study cohort. With regular apheresis being continued mipomersen reduced pre-apheresis LDL-cholesterol significantly by 22.6±17.0% (p=0.002) to absolute values of 143.7±36.5 mg/dl. There was no significant change in the control group (+1.6±9.3%, Table; Figure). Similarly apoB was reduced by 24.5 ± 16% (p=0.03). Post-apheresis changes were 17.8±19.7% (p=0.04) and 17.3±14.5% (p=0.008), respectively. Significant reductions in pre apheresis total cholesterol (20.5± 17%, p=0.02) and non-HDL-cholesterol (23.6± 20.4%, p=0.02) were observed throughout treatment, consistent with the mean reductions in LDL-cholesterol and apoB. Mipomersen also decreased pre-apheresis lipoprotein(a) concentration from a baseline of 67.3±66.5 mg/dl by 13.5±15.4% compared with a 0.6%±19% decrease in the control group though without reaching statistical significance (p=0.19). There were no significant changes in triglycerides, HDL-cholesterol and the other parameters. Of the 7 patients on mipomersen continuing to phase 2 of the study none could reduce the frequency of apheresis.

Table: Lipid parameters (expressed in mean ± standard deviation (SD) in mg/dl) before and under 12-24 weeks of treatment with mipomersen. Difference between parameters is expressed in mean percent ± SD. The p-value for significance relates to the comparison between mipomersen and control group.

	mipomersen			control			
pre-apheresis	baseline	on treatment	% change ± SD	baseline	on treatment	% change ± SD	p
total chol	285.1 ± 55.1	205.0 ± 44.0	-20.6 ± 16.0	219.2 ± 19.1	222.4 ± 29.5	-1.2 ± 6.0	0.02
LDL-chol	184.9 ± 45.1	143.7 ± 36.5	-22.6 ± 17.0	141.3 ± 19.4	144.6 ± 30.6	-1.6 ± 9.3	0.002
Lp(a)	67.3 ± 66.5	70.2 ± 72.9	-13.3 ± 14.6	88.0 ± 85.6	95.5± 100.9	-0.6 ± 19.2	0.19
triglycerides	152.3 ± 77.1	108.5 ± 48.0	-25.5 ± 14.8	203.4 ± 106.0	198.9 ± 105.0	-3.2 ± 37.0	0.32
HDL-chol	46.3 ± 8.8	44.7 ± 8.6	-3.6 ± 10.4	50.5 ± 8.2	48.6 ± 9.1	-3.6 ± 10.4	0.96
non-HDL-chol	211.8 ± 57.9	160.3 ± 46.2	-24.1 ± 19.5	168.6 ± 16.0	173.8 ± 24.5	-2.9 ± 8.4	0.02
VLDL-chol	26.3 ± 13.4	23.6 ± 5.5	-7.3 ± 26.7	24.1 ± 8.6	27.9 ± 9.0	-17.9 ± 16.7	0.11
Apo-B	141.7 ± 27.7	111.2 ± 28.9	-24.5 ± 16.1	119.4 ± 7.6	115.4 ± 14.1	-3.6 ± 6.8	0.03

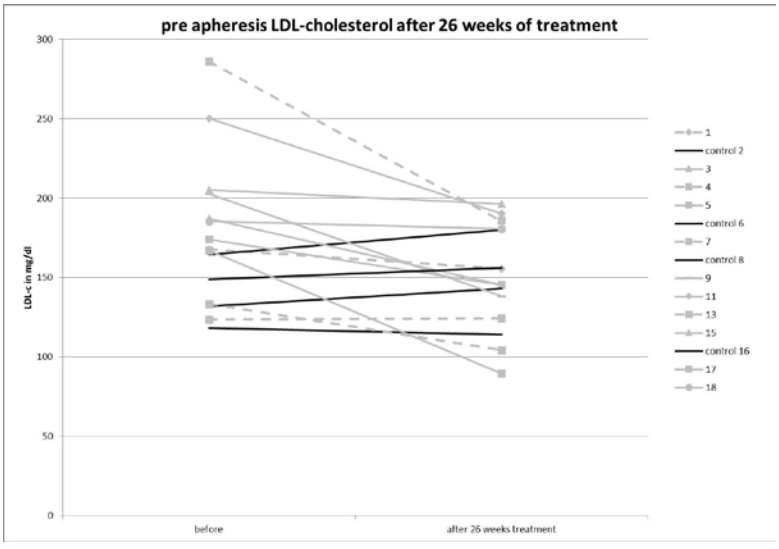

Figure: Reduction of pre apheresis LDL-cholesterol after 12-26 weeks of treatment with mipomersen (data are expressed in mean ± SD).

Safety:

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Of the 11 patients randomized to mipomersen 3 patients discontinued the drug early due to side effects (2 for injection site reactions and 1 for flu-like symptoms) and were replaced. Further 4 patients discontinued mipomersen during treatment weeks 12 – 26 again for side effects (1 due to elevations of liver enzymes, the other 3 due to injection site reactions (ISR) and flu-like symptoms (FLS)) and were not replaced. None of control patients interrupted the study.

19) **Statistical methods:**

The sample size calculation was based on the assumption that a similar LDL-cholesterol reduction (20%) as described in patients not on apheresis can be observed. A sample size of 17 was calculated (randomized with allocation ratio of 12:5 for mipomersen : control) to reach a power of 80%. Due to recruitment problems only 15 patients (11:4) were recruited (with additional 3 that were replaced early in the study). The percent change of LDL-cholesterol from baseline to week 26 was compared between the treatment groups using the Welch t-test. The type I error level is α=0.05 for two-sided testing%. All parameters were analyzed by a paired comparison. The primary endpoint was the percent change of LDL-cholesterol from baseline to the end of the 26 week treatment period (in patients terminating mipomersen between weeks 12 and 26 the last treatment periods were used to calculate the primary endpoint). To test for statistical significance a non-parametrical Wilcoxon test was used. To measure linear relationships Pearsons Correlation coefficient was applied. These tests were performed using the SPSS, Inc. software (SPSS, Inc., Chicago, IL). The critical P value for significance was set at 0.05.

20) **Summary – Conclusions:**

Efficacy results:

Mipomersen decreases preapheresis LDL-cholesterol significantly ($p<0.002$) by 24.2% compared to control. Mipomersen did not reduce the frequency of apheresis.

Safety results:

Of 14 patients exposed to mipomersen 7 discontinued the drug: 3 within 12 weeks (they were replaced) and 4 later in the study. Elevations of liver enzymes, injection site reactions (ISR) and flu-like symptoms (FLS) were the most common side effects.

Conclusion:

In summary, mipomersen is effective in lowering LDL-cholesterol significantly in patients on regular lipoprotein apheresis. However adverse events such as ISRs and FLSs do occur frequently and restrict clinical use. With newer highly effective treatment options available(PCSK9 inhibitors), which are characterized by a much lower rate of side effects mipomersen should be used reluctantly in subjects on regular lipoprotein apheresis. Based on our results it may be considered in subjects not qualifying for PCSK9 inhibition.

21) **Date of the report:** May 13th, 2016