Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Antistax®		**EudraCT No.:** 2008-003932-40	
Name of active ingredient: Extract of Red Vine Leaves		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 20 APR 2010	**Trial No. / U No.:** 1138.11 / U10-1663-01	**Date of trial:** 06 APR 2009 – 16 NOV 2009	**Date of revision:** Not applicable

Title of trial:	A 12-week, double-blind, randomised, placebo-controlled, multicentre trial to evaluate efficacy and tolerability of Antistax® film-coated tablets, 720 mg/day orally, in male and female patients suffering from chronic venous insufficiency
Principal/Coordinating Investigator:	[redacted]
Trial sites:	20 sites in Germany
Publication (reference):	No
Clinical phase:	III
Objectives:	To assess the efficacy and tolerability of Antistax® film-coated tablets in patients with chronic venous insufficiency (CVI, CEAP Classification: Clinical Class 3 and 4a)
Methodology:	Randomised, placebo-controlled, double-blind, parallel group design according to GCP
No. of subjects:	
planned:	entered: 240
actual:	enrolled: 283 Treatment Antistax® entered: 127 treated: 126 analysed (for primary endpoint): 126 Treatment placebo entered: 123 treated: 122 analysed (for primary endpoint): 122
Diagnosis and main criteria for inclusion:	CVI, Clinical Class 3 (oedema) and 4a (mild skin changes ascribed to venous disease, e.g. pigmentation, venous eczema) according to the CEAP classification, moderate to severe varicosis and oedema
Test product:	Antistax® film-coated tablets containing 360 mg of extract of red vine leaves

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dose:	720 mg once per day (2 tablets 360 mg once per day)
mode of admin.:	Oral
batch no.:	819205
Reference therapy:	Placebo film-coated tablets
dose:	2 tablets once per day
mode of admin.:	Oral
batch no.:	08031
Duration of treatment:	12 weeks double-blind treatment phase preceded by 2 weeks run-in phase with single-blind placebo treatment
Criteria for evaluation:	
Efficacy / clinical	Primary efficacy variable: • Change from baseline in limb volume determination at day 84 (water displacement method) Secondary efficacy variables: • Change from baseline in limb volume determination at day 21 and day 42 (water displacement method) • Change from baseline in the calf circumference at day 21, 42, and 84 • Change from baseline in the subjective symptoms of CVI (tired, heavy legs, sensation of tension in the legs, pain in the legs) measured by Visual Analogue Scales (VAS) at day 21, 42, and 84 • Global assessment of efficacy by the patient at day 84 • Global assessment of efficacy by the investigator at day 84 • Questionnaire on improvement in symptoms at day 21

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Safety:	• Adverse events • Vital signs (PR, BP) • Serum chemistry laboratory parameters • Global assessment of tolerability by the patient at day 84 • Global assessment of tolerability by the investigator at day 84
Statistical methods:	Descriptive statistics; analysis of covariance for change from baseline in limb volume determination, calf circumference and subjective symptoms of CVI; log rank test for time to first improvement in symptoms; Wilcoxon test for global assessment of efficacy and tolerability; contingency table of incidence, severity and causal relationship of adverse events.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

In general, improvements were seen for all efficacy parameters evaluated after 84 days of treatment with Antistax®.

Primary endpoint

For the primary endpoint, treatment with Antistax®, at a dose level of 720 mg, led to an adjusted mean reduction in limb volume of -27.14 g of displaced water vs. -7.22 g in the placebo group, with the difference between treatment groups (-19.92 g) being statistically significant.

Secondary endpoints

Limb volumes were also measured at day 21 and day 42. Patients receiving placebo showed an impairment of leg oedema between 21 and 42 days, whereas in the Antistax® group a linear improvement of leg oedema was observed over time. The most marked and statistically significant treatment difference of the lower leg volume was observed after 84 days of treatment in favour of Antistax®. For the secondary endpoint "change from baseline in calf circumference", the adjusted mean differences to placebo were -0.04 after 21 days of treatment with Antistax® (p=0.7328), -0.13 after 42 days of treatment (p=0.3166) and -0.17 cm after 84 days of treatment (p=0.1965).

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	The absolute treatment differences increased over time for the symptoms "tired, heavy legs" and “pain in the legs”, whereas the most prominent treatment difference between Antistax® and placebo of -0.65 for “sensation of tension in the legs” was observed on day 42 (p=0.0305).On study day 84, the adjusted mean difference between Antistax® and placebo was -0.29 cm for "tired, heavy legs" (p=0.3558), -0.35 cm for "sensation of tension in the legs" (p=0.2744) and -0.66 cm for "pain in the legs" (p=0.0468). As to the time of improvement in subjective symptoms, in the Antistax® group 58.7% felt an improvement in “tired / heavy legs”, 53.9% an improvement in “tension in the legs” and 55.6% an improvement in “pain in the legs” during the first 20 days of treatment. The corresponding percentages in the placebo group were 53.3% for “tired / heavy legs”, 51.7% for “tension in the legs” and 48.3% for “pain in the legs”. The difference in improvement in subjective symptoms between Antistax® and placebo were more pronounced in the first 10 days of treatment. Concerning the global efficacy, Antistax® received better ratings than placebo by both investigators and patients. Investigators rated efficacy as good or satisfactory in 54.1% of all patients allocated to placebo and in 70.7% of all patients treated with Antistax®, whereas patients' ratings were 59.0% and 69.8%, respectively. In summary, CVI patients treated with Antistax® showed higher improvements in comparison to placebo for all efficacy parameters investigated. The difference to placebo concerning the primary endpoint “change of limb volume from baseline at day 84” was statistically significant. All findings of the present study suggest an overall beneficial effect of Antistax® on lower leg oedema and related subjective symptoms.
Safety results:	Both treatments administered during the trial (Antistax®, 720 mg, and placebo) were well tolerated. A total of 73 patients (29.4%) experienced at least one adverse event during the treatment phase of the study with the majority of the adverse events being of mild or moderate intensity. The incidence of AEs was higher in the placebo group during the study; 43 patients (35.2%) receiving placebo experienced at least one adverse event compared with 30 patients (23.8%) receiving Antistax®.

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Five patients treated with Antistax® (4.0%) and 4 patients treated with placebo (3.3%) experienced AEs judged by the investigator to be related to the study medication. Of the related AEs, all were single events except for 2 episodes of pain in the extremity in the placebo group.

During the randomised treatment period 8 patients experienced serious adverse events, 4 patients allocated to placebo (cerebrovascular accident, cardiac failure, lumbar radiculopathy, peripheral oedema with superinfection) and 4 patients allocated to Antistax® (retinal detachment, thrombophlebitis, abdominal pain, intravertebral disc protrusion). Additionally, one patient in the placebo group experienced polymyalgia rheumatica as an SAE in the post-treatment phase. No SAE was judged related to the study medication. 6 patients (5 patients receiving placebo and 1 patient receiving Antistax®) discontinued the trial prematurely because of an AE.

There were no relevant changes in blood pressure and pulse rate observed and no trend seen in the laboratory results. Tolerability was deemed good for 85% of all patients in both treatment groups.

In summary, in the present trial: treatment with Antistax® at a dosage of 720 mg was safe and well tolerated in patients with moderate to severe CVI.

Conclusions:

In summary, Antistax® was statistically significantly more effective than placebo in reducing leg oedema after 84 days of treatment and improved all assessed symptoms of CVI better than placebo. Furthermore, the excellent safety and tolerability of Antistax® in the treatment of moderate to severe CVI could be confirmed in this study. Overall, safety and efficacy data suggest a beneficial effect of Antistax® on lower leg oedema and related subjective symptoms.