2 SYNOPSIS

Name of Sponsor/company: Kreussler & Co. GmbH	Individual Study Table Referring to Part of the Dossier	(For Authority Use Only)
Name of Finished Product: Aethoxysklerol®	Volume:	
Name of Active Ingredient(s): Polidocanol	Page:	

Title of the study:
Efficacy and safety of Aethoxysklerol® compared to Sodium Tetradecyl Sulfate and Isotonic Saline (placebo) for the treatment of reticular veins and spider veins including sub-group to investigate the plasma concentrations of polidocanol

Investigators:
Principal Investigator: Prof. Dr. med. Eberhard Rabe (site no. 10)
Co-investigators:
Dr. Franz-Xaver Breu (site no. 1), Dr. Ulrich Eberlein (2), Dr. Bernward Wildenhues (3), Dr. Michael Hartman (4), Dr. Rainer Jokisch (5), Prof. Michael Jünger (6), Dr. Birgit Kahle (7), Dr. Renate Murena-Schmidt (8), Dr. Felizitas Pannier-Fischer (9), Dr. Detlef Schulte-Hürmann (11), Dr. Christine Schwahn-Schreiber (12), Dr. Margrit Simon (13), Dr. Ulrike Steinbach (15), Dr. Markus Stücker (16), Dr. Ulrike Voll (17), Dr. Norbert Weindorf (18), Dr. Hans-Christian Wenzel (19), Dr. Stephan Guggenbichler (20)

Study center(s):
Site no. 1: Tegernseerstr. 101, 83700 Rottach-Egern
Site no. 2: Mohrenstr. 9a, 96450 Coburg
Site no. 3: Institut für kosmetische Medizin, Offheimer Weg 33, 65549 Limburg a.d. Lahn
Site no. 4: Zähringer Str. 14, 79108 Freiburg
Site no. 5: Rosenpark Klinik, Heidelberger Landstr. 18/20, 64297 Darmstadt
Site no. 6: Enst-Moritz-Arndt-Universität Greifswald, Klinik und Poliklinik für Hautkrankheiten, Fleischmannstr. 42-44, 17487 Greifswald
Site no. 7: Universitätshautklinik Lübeck, Ratzeburger Allee 160, 23538 Lübeck
Site no. 8: Praxis für Gefäßerkrankungen, Hansaring 102-104, 50670 Köln
Site no. 9: Statthalterhofweg 70, 50858 Köln-Junkersdorf
Site no. 10: Universitäts-Hautklinik, Bonn, Sigmund-Freud-Str. 25, 53105 Bonn
Site no. 11: Taunusstr. 37, 65183 Wiesbaden
Site no. 12: Gartenstr. 2, 21680 Stade
Site no. 13: Hauptstr. 131, 10827 Berlin
Site no. 15: Im Mühlenbach 2b, 53127 Bonn
Site no. 16: St. Maria Hilf Krankenhaus, Hiltroper Landwehr 11-13, 44805 Bochum
Site no. 17: Fürst-Wilhelm-Str. 5, 72448 Sigmaringen
Site no. 18: St. Elisabeth Krankenhaus, Josefstr. 3, 46045 Oberhausen
Site no. 19: Praxis Venenzentrum am Elsterpark, Nikolaistr. 55, 04109 Leipzig
Site no. 20: Praxis am Viktualienmarkt, Frauenstr. 17, 80469 München

Publication:
Not published yet.

Study period: 04 December 2006 (first enrolment) 10 December 2007 (last completed)	Phase of Development: Phase III

Objectives:
Primary objective:
Efficacy of Aethoxysklerol® in the treatment of C1 veins compared to placebo

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Secondary objectives:
Efficacy of Aethoxysklerol® compared to Sodium Tetradecyl Sulfate.
Safety of Aethoxysklerol®
Patient satisfaction with the treatment
Additional objective for group C:
Assessment of plasma concentrations of polidocanol

Methodology:
In this study, it was planned to evaluate at least 216 patients with C1 veins after treatment; 108 patients with C1 spider veins treated with either Aethoxysklerol® 0.5% or Sodium Tetradecyl Sulfate 1% or placebo (isotonic saline solution), 108 patients with C1 reticular veins treated with either Aethoxysklerol® 1 % or Sodium Tetradecyl Sulfate 1% or placebo as determined by randomization.
The veins in a predetermined area of one leg per patient were treated at Visit 1. A repeat injection could be given three and six weeks later if the previous injection was evaluated as unsuccessful by the investigator.
Digital photographs of the area to be treated were taken at screening (Visit 0), immediately before injection (Visit 1), at 12 weeks ± 2 week (Visit 4) and 26 weeks ± 4 weeks (Visit 5) after the last injection.
At Visit 1 the patient's veins were injected with either Aethoxysklerol® 1% (reticular veins) or Aethoxysklerol® 0.5% (spider veins) or Sotradecol® 1% or isotonic saline solution and 30 minutes later an ECG was recorded. Thirty minutes later a blood sample was taken for safety clinical laboratory parameters. The patient returned for a further 4 visits (or 6 or 7 visits, if a second or third injection was necessary).
The first follow-up treatment visit (Visit 2) was 3 weeks ± 7 days after injection at which time the patient could receive a second injection of the same allocated treatment if the first treatment was not fully successful, that was if the patient was not graded 5 on the 5-grade scale. The patient could receive a third injection of the same allocated treatment at Visit 3 if the second treatment was not fully successful, that was if the patient was not graded 5 on the 5-grade scale.
All patients returned for Visit 4 at 12 weeks ± 2 weeks after the last injection, at which time the primary endpoint was assessed and digital images were taken. Furthermore secondary endpoints, i.e. patient satisfaction, were assessed.
A final follow up visit (Visit 5) was at 26 weeks ± 4 weeks after the last injection at which time further digital images were taken. Furthermore secondary endpoints, i.e. patient satisfaction were assessed.

Extra blood samples were taken for the determination of plasma polidocanol concentrations from all patients at one specific center (Group C) at Visit 1 and at least one week after the last varicose vein injection visit.

Number of subjects:
Planned: 288 total
Group S (spider veins)
54 patients to be treated with Aethoxysklerol® 0.5%
36 patients to be treated with Sodium Tetradecyl Sulfate 1%
18 patients to be treated with Isotonic Saline

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Group R (reticulars)
54 patients to be treated with Aethoxysklerol® 1%
36 patients to be treated with Sodium Tetradecyl Sulfate 1%
18 patients to be treated with Isotonic Saline
Group C (spider veins or reticulars) for plasma polidocanol concentrations:
9 patients with spider veins to be treated with Aethoxysklerol® 0.5%
9 patients with reticular veins to be treated with Aethoxysklerol® 1%
Analyzed: 338 (safety data set)
Group S (spider veins)
82 patients treated with Aethoxysklerol® 0.5%
51 patients treated with Sodium Tetradecyl Sulfate 1%
27 patients treated with Isotonic Saline
Group R (reticulars)
76 patients treated with Aethoxysklerol® 1%
54 patients treated with Sodium Tetradecyl Sulfate 1%
26 patients treated with Isotonic Saline
Group C (spider veins or reticulars) for plasma polidocanol concentrations:
12 patients with spider veins treated with Aethoxysklerol® 0.5%
10 patients with reticular veins treated with Aethoxysklerol® 1%

Diagnosis and main criteria for inclusion:
Inclusion:
1. Male / female
2. Age between 18 and 70 years
3. C_1 veins
4. Willing and able to provide written informed consent to a participation in the study after having been informed by the investigator about the aim, course and possible risks of the study
5. Females of childbearing potential had to be: willing and able to use reliable contraceptive methods throughout the study. Reliable methods for women were hormonal contraceptives, surgical intervention (e.g. tubal ligation), intrauterine device (IUD) and sexual abstinence.

Exclusion:
1. Patients with C2-C6 venous insufficiency (which could influence the treatment success of C1 veins in this study)
2. Patients with CEAP-classifications: Es und Ec, AD, PO
3. Patients who have already undergone sclerotherapy, laser treatment and surgery during the last twelve weeks of the ipsilateral leg or during the last four weeks of the contralateral leg
4. Acute superficial or deep vein thrombosis
5. History of major superficial thrombosis
6. Patients with positive result for one of the following thrombophilia indicators: Activated Protein C resistance, increased Factor VIII activity, Antithrombin III deficiency, Protein C deficiency, Protein S deficiency, Prothrombin 20210 gene mutation, and Antiphospholipid syndrome as determined by analyzing blood samples taken on day 0
7. History or evidence of previous deep vein thrombosis

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8. Patients with all of the following risk factors of thrombosis:
   - taking hormonal contraceptives or receiving hormone replacement therapy and
   - adiposity (body mass index greater than 30) and
   - smoking
9. Patients with other factors implicating a risk of thrombosis (e.g. recent long-distance flight) as judged by investigator
10. Known coagulopathy
11. Patients with known hereditary thrombophilia
12. Major leg edema (if it could not be influenced by compression therapy)
13. Inflammatory skin disease in the area of treatment
14. Arterial occlusive disease (Fontaine Stage II or more)
15. Clinically relevant abnormalities in the 12-lead electrocardiogram (ECG).
16. Known hypersensitivity to polidocanol (macrogol lauryl ether, lauromacrogol 400) or any of the other ingredients of Aethoxysklerol®
17. Known hypersensitivity to Sodium Tetradecyl Sulfate or any of the other ingredients of Sotradecol®
18. Known pronounced allergic disposition
19. Acute severe systemic disease or poor general health
20. Severe generalized infection
21. Acute febrile states
22. Reduced mobility
23. Bronchial asthma or known strong predisposition to allergies
24. Symptoms of microangiopathy or neuropathy
25. Pregnant women
26. Lactating women
27. Antipathy against the treatment procedures, aftercare and the follow-up
28. Any participation in another clinical study within 4 weeks (30 days) prior to enrolment in this study.
29. Known history of HIV
30. Known history of hepatitis B or C.
31. History or acute state of alcoholism (5% ethanol content in the study medication) or substance abuse.
32. Regular use of disulfiram (e.g. antibuse) or similar medication.
33. Regular use of anticoagulants (except platelet aggregation inhibitors, i.e. low dose ASS)

Test product, dose and mode of administration, batch number:
Aethoxysklerol 0.5%, maximum dose per treatment session of 4.8 ml Aethoxysklerol® 0.5%, solution for injection, batch no.: 17278
Aethoxysklerol 1%, maximum dose per treatment session of 2.4 ml Aethoxysklerol® 1%, solution for injection, batch no.: 17378

Duration of treatment:
Three injections, duration of clinical phase: 26 weeks

Reference therapy, dose and mode of administration, batch number:
Sodium Tetradecyl Sulfate 1%, maximum dose per treatment session of 2.4 (reticular veins) or 4.8 ml (spider veins), solution for injection, batch no.: 050803

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Criteria for evaluation:

Efficacy:

Improvement of veins, treatment success and patient satisfaction with the treatment

Safety:

Local reactions and symptoms, adverse events, ECG, physical examination, vital signs, clinical laboratory tests

Statistical methods:

The test procedure for the primary efficacy parameter was the stratified Wilcoxon-Mann-Whitney test. For analysis of the secondary efficacy parameter the Wilcoxon-Mann-Whitney test and the exact test of Fisher were used. For analysis of safety only descriptive statistics were used. Polidocanol plasma concentration-time data were summarized with sample statistics. The systemic availability variables were summarized with descriptive statistics.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The primary statistical analysis revealed statistically significant superiority of the treatment with Aethoxysklerol® versus placebo in the assessment of the improvement of the veins according to a 5-grade scale ($p<0.0001$). The results with the per protocol data set were in line with the results of the full analysis data set and corroborated the primary analysis.

The secondary statistical analysis confirmed that Aethoxysklerol® was statistically significant superior to placebo in terms of:

1) Patient satisfaction with the treatment after 12 (± 2) weeks
2) Treatment success 12 (± 2) weeks after the last injection
3) Improvement of veins 26 weeks (± 4 weeks) after last injection
4) Patient satisfaction with the treatment after 26 (± 4) weeks
5) Treatment success 26 (± 4) weeks after the last injection

The comparison between Aethoxysklerol® and Sotradecol® in terms of the improvement of the veins 12 weeks (± 2 weeks) after the last injection (point 6. of the secondary ordered hypothesis) showed no significant differences. As an a priori ordered hypothesis testing was applied, the remaining hypotheses regarding comparison of Aethoxysklerol® and Sotradecol® could not be confirmed. The remaining endpoints were only compared descriptively and no confirmatory testing was applied.

Patient satisfaction with the treatment after 12 (± 2) weeks and after 26 (± 4) weeks (hypothesis nos. 7 and 10) showed a descriptively significant superiority of the treatment with Aethoxysklerol® as compared to Sotradecol®.

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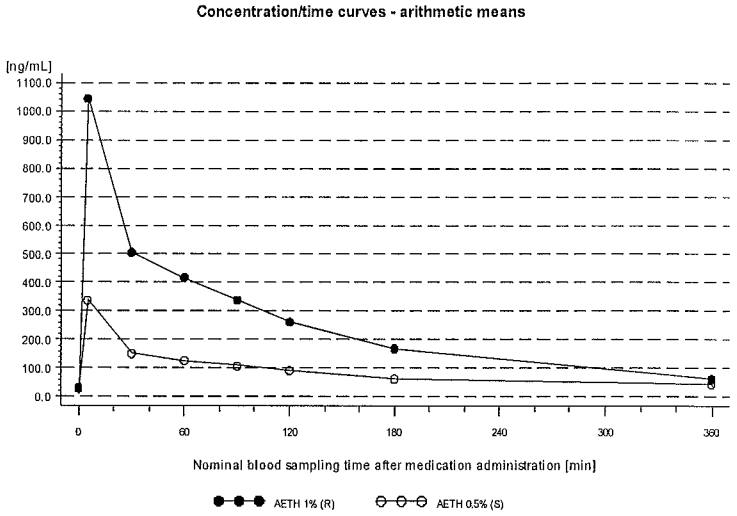
RESULTS OF THE DETERMINATION OF POLIDOCANOL CONCENTRATIONS IN PLASMA



Polidocanol in plasma – pharmacokinetic metrics

	Cmax (ng/ml)	Tmax (min)	Cmax/D (ng/ml/mg)	Lambda z (1/min)	thalf (min)	$AUC_{(0\text{-tlast})}$ (min*ng/ml)	$AUC_{(0\text{-inf})}$ (min*ng/ml)	$AUC_{(0\text{-inf})}/D$ (min*ng/ml/mg)
Group R (N=10)								
Mean	1045.7	5.3	57.8	0.00646	114.6	86878.8	98937.7	5479.7
SD	430.4	1.0	21.7	0.00201	26.5	33979.9	39752.0	1991.7
Geom. Mean	974.0	5.24	54.8	0.00623	111.3	81298.6	92329.2	5196.6
Group S (N=12)								
Mean	343.6	5.0	69.4	0.00429	258.7	31457.5	50711.4	14059.0
SD	366.4	0.3	38.2	0.00338	173.2	20828.0	25397.7	9659.4
Geom. Mean	239.3	5.0	61.2	0.00335	207.2	25432.5	42871.6	10958.1

SAFETY RESULTS:

Treatment with Aethoxysklerol® 1% and 0.5% was safe and apart from local symptoms at the injection site well tolerated.

In total, 291 from 338 patients (86.1%) experienced at least one AE in this study; in comparison a total of 286 patients (84.6%) experienced at least one drug-related AE considered to be certainly, probably or possibly related to the study medication.
Commonly observed local adverse events included irritation, discoloration and hematoma, which occurred in 39.5% - 47.7% of the patients injected with Aethoxysklerol® 1% and in 36.2% - 39.4% of the patients injected with Aethoxysklerol® 0.5%. Less frequent were pain (19.8% and 28.7%), warmth (17.4% and 13.8%) and pruritus (19.8% and 19.1%) at the injection site after administration of Aethoxysklerol® 1% and 0.5%, respectively.

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Of the related adverse events the frequencies of local symptoms, particularly of irritation, discoloration and hematoma were markedly higher in patients who were treated with Sotradecol® (63.0% - 84.3%) as compared to Aethoxysklerol® (36.2% - 47.7%). Patients who were injected with placebo generally experienced local symptoms at lower frequencies than patients in the two other treatment groups. Irritation and hematoma occurred in 18.5% - 30.8% of the patients in the placebo group.
The majority of the observed AEs were mild or moderate. Severe AEs were mainly observed in single patients who had been treated with Sotradecol. Of the two reported SAEs none was considered to be related to the study medication by the investigator.

ECG analyses and vital sign measurements did not show any clinically significant abnormal findings in any group. No clinically significant abnormalities were observed in the clinical laboratory results post treatment. Ultrasound did not reveal deep vein thrombosis in any of the treated patients. In the majority of the patients no microthromectomy needed to be performed.

CONCLUSION:
This study was conducted to demonstrate the efficacy and tolerability of Aethoxysklerol® compared to Sotradecol® and to placebo in patients with reticular veins and spider veins. A total of 338 patients were treated in this study, of these 53 patients received placebo, 180 patients received Aethoxysklerol® and 105 Sotradecol®.

The primary statistical analysis revealed statistically significant superiority of the treatment with Aethoxysklerol® versus placebo ($p < 0.0001$) in the assessment of the improvement of the veins according to a 5-grade scale.
The secondary statistical analysis confirmed that Aethoxysklerol® was statistically significantly superior to placebo ($p < 0.0001$) in terms of:

1) Patient satisfaction with the treatment after 12 (± 2) weeks
2) Assessment of the treatment success 12 (± 2) weeks after the last injection
3) The assessment of improvement of veins 26 weeks (± 4 weeks) after last injection
4) Patient satisfaction with the treatment after 26 (± 4) weeks
5) Assessment of the treatment success 26 (± 4) weeks after the last injection

For the majority of patients treated with Aethoxysklerol® (95% of the FA data set; 96% of the PP data set) or Sotradecol® (92% of the FA data set; 93% of the PP data set) a good improvement of the veins or a complete treatment success was observed at Visit 4. Similar results were seen at Visit 5.
The treatment success rates for Aethoxysklerol® were with 96% at Visit 4 and with 95% at Visit 5 significantly higher as compared to those seen for placebo. The treatment success rates for Sotradecol® were with 92% or 91% (Visit 4 or 5) slightly lower than those for Aethoxysklerol®.
The majority of patients who received treatment with Aethoxysklerol® were satisfied or even very satisfied with the treatment at Visit 4 (88%) and Visit 5 (84%). The number of patients who were satisfied or very satisfied with the treatment was significantly lower for both Sotradecol® (64% at Visit 4 and 63% at Visit 5; $p<0.0001$) and placebo (13% at Visit 4 and 11% at Visit 5; $p<0.0001$). The higher satisfaction of patients treated with Aethoxysklerol® as compared to Sotradecol® was probably due to the better safety profile of Aethoxysklerol®.