[Kreussler Studies]

SUMMARY OF
PIVOTAL STUDIES ON
SCLEROTHERAPY OF VARICOSE VEINS

randomized

FDA

controlled

GCP

prospective

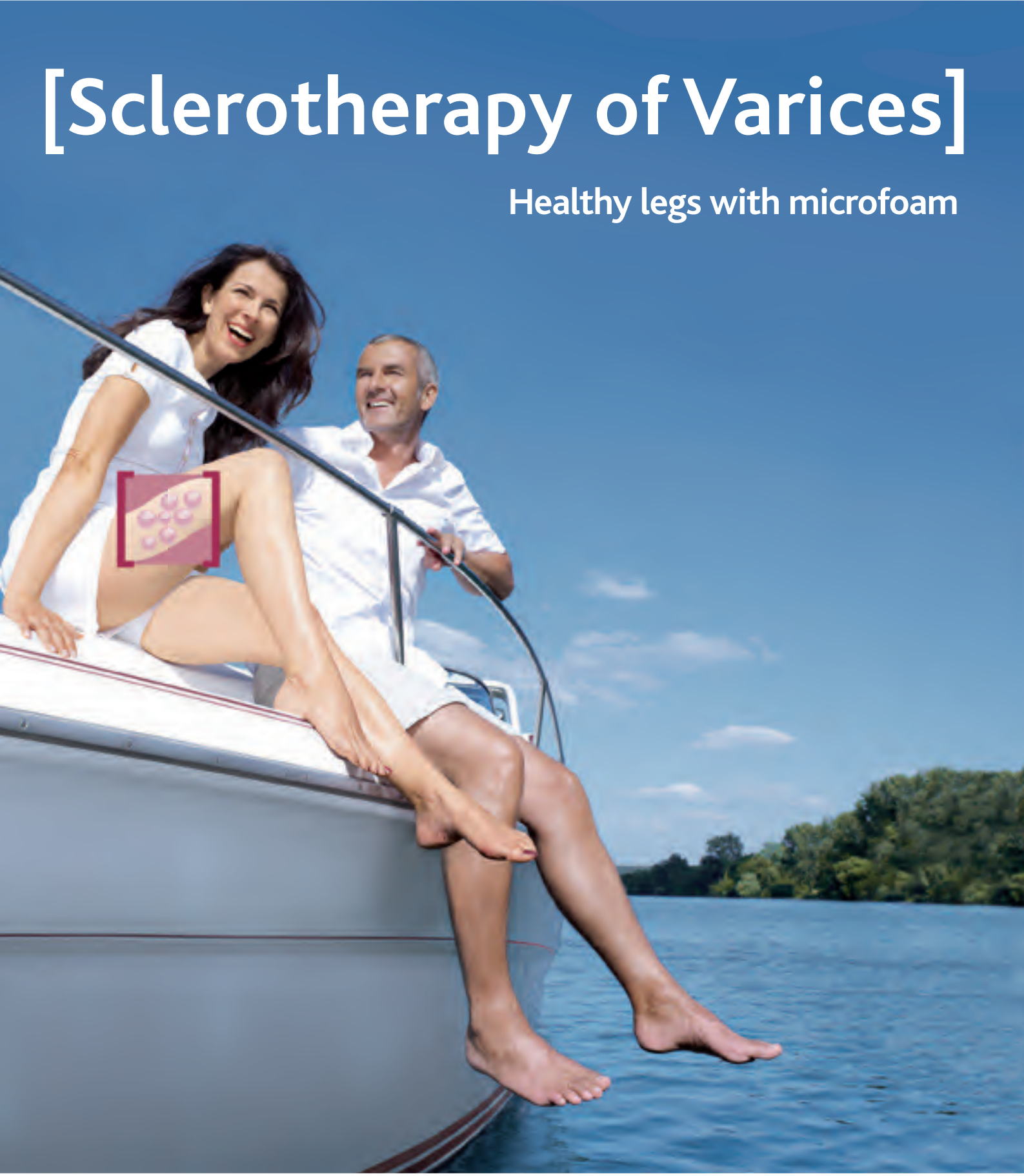
blinded

multicenter

kreussler PHARMA

[Sclerotherapy of Varices]

Healthy legs with microfoam



kreussler PHARMA

Aethoxysklerol® worldwide No1 of sclerosing agents

Chemische Fabrik Kreussler & Co. GmbH • P.O. Box 12 04 54 • D-65082 Wiesbaden

The ESAF Study
Efficacy and Safety of Great Saphenous Vein Sclerotherapy Using Standardized Aethoxysklerol® Foam

The ESAF study was the first Good Clinical Practice (GCP) compliant, randomized, prospective, controlled multicenter clinical trial in Germany to evaluate the efficacy and safety of foam sclerotherapy of the great saphenous vein (GSV) compared with liquid sclerotherapy.

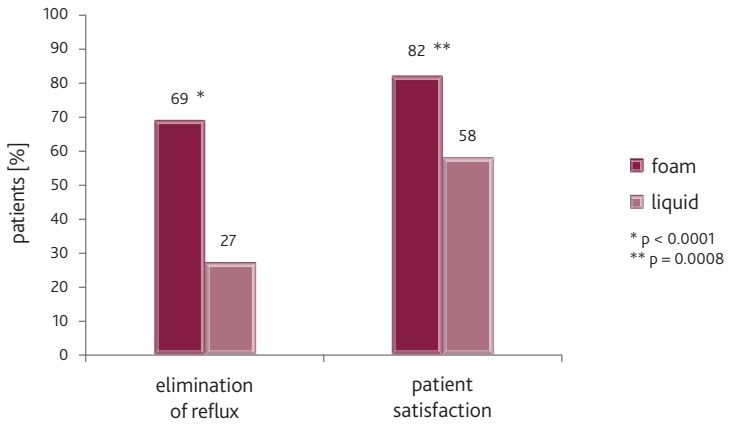
Treatment method

106 patients were treated in 11 study centers with polidocanol 3% (POL, German trade name Aethoxysklerol®) either as foam or liquid under standardized treatment conditions. Eligible patients had an incompetent GSV with a reflux of > 1 s and a diameter of less than 12 mm, measured 3 cm below the sapheno-femoral junction (SFJ).
Standardized microfoam was prepared with the EasyFoam® Kit. Foam or liquid Aethoxysklerol® was injected into the GSV under ultrasound guidance at least 10 cm below the SFJ. Only one injection with a maximum dose of 5 ml foam or 4 ml liquid was allowed per session. Further treatment was possible 2 and 4 weeks following the first.

Efficacy and safety criteria

The primary efficacy criterion was the elimination of reflux (from > 1 s to < 0.5 s) measured 3 cm below the SFJ at 3 months after the last injection. The most important secondary criteria were patient satisfaction and safety of the treatment.

Results: The ESAF study proves the efficacy and safety of foam sclerotherapy



The ESAF study clearly shows that reflux was eliminated effectively with POL foam in significantly more patients (69%) in comparison with liquid sclerosant (27%). In addition, significantly more patients were satisfied (voted "improved") with foam (82%) compared to liquid (58%) sclerotherapy. The number of incidents was comparable in both treatment groups and included mainly mild transitory reactions close to the injection site. No serious adverse drug reactions were observed.

Conclusion

- **Successful treatment of the GSV was significantly higher with Aethoxysklerol® foam (69%) compared with its liquid form (27%)** Five out of 11 study centers even had a success rate of 100% with foam. In those centers, higher mean volumes had been injected into GSVs with a smaller mean diameter. In this study only one injection of the GSV was allowed per session. Superior results can be reached in daily practice if GSVs, tributaries and accessory veins are treated in one session.
- **Treatment success was achieved with small volumes of foam in an average of only 1.3 sessions**
- **Patient satisfaction was significantly higher after foam sclerotherapy**
- **Sclerotherapy with foam is as safe as liquid sclerotherapy**

In summary, foam sclerotherapy with Aethoxysklerol® is a highly effective and safe method for the treatment of incompetent great saphenous veins.

The EASI Study
Efficacy and Safety of Aethoxysklerol®, Sotradecol® and Isotonic Saline for the Sclerotherapy of Telangiectasias and Reticular Varicose Veins

The EASI study compared the efficacy and safety of polidocanol (POL, German trade name Aethoxysklerol®) with sodium tetradecyl sulphate (STS, Sotradecol®) and isotonic saline (placebo) for the treatment of telangiectasias and reticular varicose veins with sclerotherapy. The FDA-approved, double-blind, randomized, prospective, controlled multicenter trial was designed to obtain marketing authorization in the USA for POL under the trade name Asclera™.

Treatment method

160 patients with telangiectasias and 156 patients with reticular varicose veins were included in 19 German practices and hospitals. They received placebo or treatment with POL or STS according to the regulations of the German and US marketing authorizations, respectively.

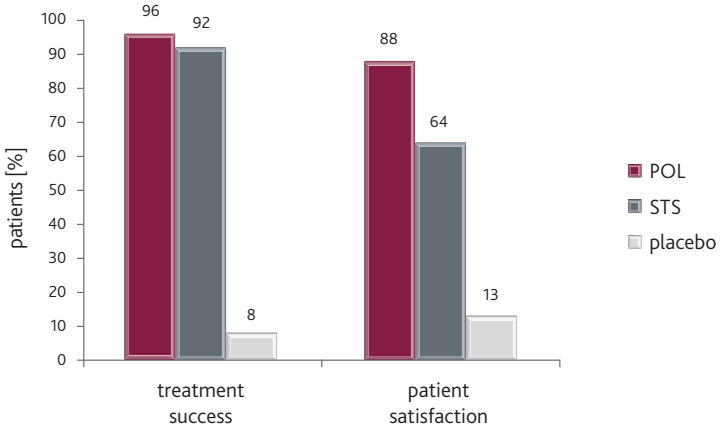
Type of varicose vein	POL	STS	Saline (placebo)	Max. dose per session
Telangiectasias	0,5% (n = 82)	1% (n = 51)	0,9% (n = 27)	4,8 ml
Reticular varicose veins	1% (n = 76)	1% (n = 54)	0,9% (n = 26)	2,4 ml

The concentration of STS used during this study was requested by the FDA. In daily practice, however, it may be common to dilute the drug.
Three treatment sessions per patient were allowed depending on the treatment success.

Efficacy and safety criteria

Three and 6 months after the last injection, the efficacy and safety as well as patient satisfaction were evaluated. The primary efficacy criterion was the improvement of the veins assessed by means of photographs taken with a newly established digital imaging system. The treated area was rated by the investigator and blinded medical experts according to a 5-grade scale. Treatment success was defined as grade 4 (good improvement) or 5 (complete treatment success).

Results: The EASI study clearly shows the high efficacy of Aethoxysklerol®



The mean score of improvement 3 months after the last treatment was significantly higher ($p < 0.0001$) with POL (4.52) and STS (4.47) than with placebo (2.19).
The treatment was successful in a slightly higher percentage of patients with POL (96%) than with STS (92%).
The mean percentage of patients who were "satisfied" or "very satisfied" with their treatment after 3 months was significantly higher ($p < 0.0001$) with POL (88%) than with STS (64%) or placebo (13%).
Results after 3 and 6 months were comparable.
Treatment with POL was safe and, apart from transitory symptoms at the injection site, well tolerated.

Conclusion

- **The treatment success rate of Aethoxysklerol® 0.5% and 1% in the treatment of small varicose veins was 96%, which was a little, but not significantly, higher than that of STS (92%)**
- **Aethoxysklerol® showed fewer side effects and was better accepted by patients than STS**

In summary, the EASI study demonstrates that Aethoxysklerol® is highly effective in the treatment of telangiectasias and reticular varicose veins while showing an excellent safety profile.

The ESA-China Study
Efficacy and Safety of Aethoxysklerol® for Sclerotherapy of Varicose Veins in Chinese Patients

The Good Clinical Practice (GCP) compliant, double-blind, randomized, prospective, controlled multicenter ESA study was designed to show that sclerotherapy with polidocanol (POL, German trade name Aethoxysklerol®) is an efficacious and safe treatment for varicose veins in the Han Chinese population and to obtain marketing authorization for POL in China.

Treatment method

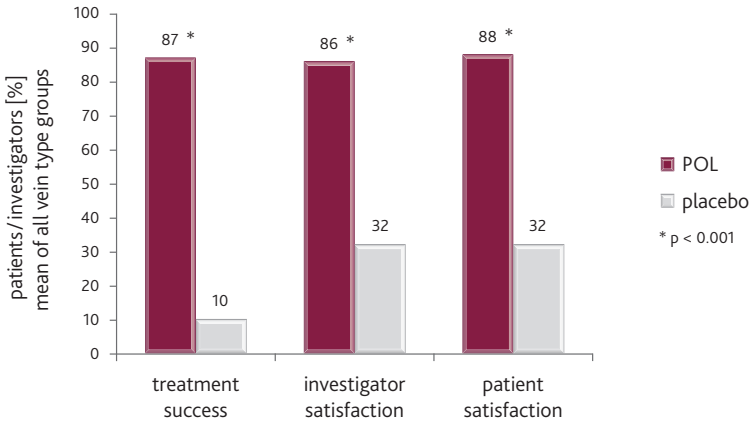
In this study 214 patients received treatment with liquid Aethoxysklerol® and 71 patients received placebo. A maximum of 3 treatment sessions were possible depending on the treatment success.

Group	Type of varicose vein	Treatment
Group A	Telangiectasias of < 1 mm	POL 0.5% (n = 72) or placebo
Group B	Reticular veins and/or small-sized varicose veins of 1-5 mm	POL 1% (n = 70) or placebo
Group C	Medium-sized and/or large non-saphenous subcutaneous varicose veins of > 5 mm and with reflux of > 0.5 s	POL 3% (n = 72) or placebo

Efficacy and safety criteria

The primary efficacy criterion was the outcome of the treatment at 3 months after the last sclerotherapy session. In group A and B, efficacy of treatment was assessed by means of photographs taken with the digital imaging system established in the EASI study. The treated area was rated by the investigator according to a 5-grade scale. Treatment success was defined as grade 4 (good improvement) or 5 (complete treatment success). For group C, efficacy was evaluated by duplex examination and treatment success was defined as occlusion of the vein and/or absence of reflux > 0.5 s. Secondary efficacy variables were investigator and patient satisfaction as well as safety of POL.

Results: The ESA-China study confirms the excellent efficacy of Aethoxysklerol® in Chinese patients



Three months after the last treatment, the success rate was significantly higher with POL than with placebo throughout all vein type groups (mean of group A: 87%, group B: 86% and group C: 89%). Additionally, both the percentages of investigators and patients who voted "satisfied" or "very satisfied" with the treatment outcome were significantly higher with POL (86% and 88%, respectively) than with placebo.

The study clearly showed that sclerotherapy with Aethoxysklerol® was safe and well tolerated in Chinese patients apart from mild transitory reactions at the injection site.

Conclusion

- **The treatment success rate in small, medium-sized and large non-saphenous varicose veins was significantly higher with 0.5%, 1% and 3% Aethoxysklerol® (87%) than with placebo (10%)**
- **Liquid sclerotherapy remains a reliable treatment option for medium-sized and large varicose veins (89% treatment success)**
- **Investigator and patient satisfaction was very high (86% and 88%) after sclerotherapy with POL**
- **Aethoxysklerol® was well tolerated in Chinese patients**

In summary, the multicenter ESA study confirms in the Han Chinese ethnic group the findings from previous studies: Aethoxysklerol® is highly effective and safe in the treatment of varicose vein patients.

The French Registry
The Immediate and Medium-Term Safety of 12,173 Sclerotherapy Sessions

The objective of this prospective multicenter registry was to assess the safety of liquid and foam sclerotherapy in the treatment of varicose veins.

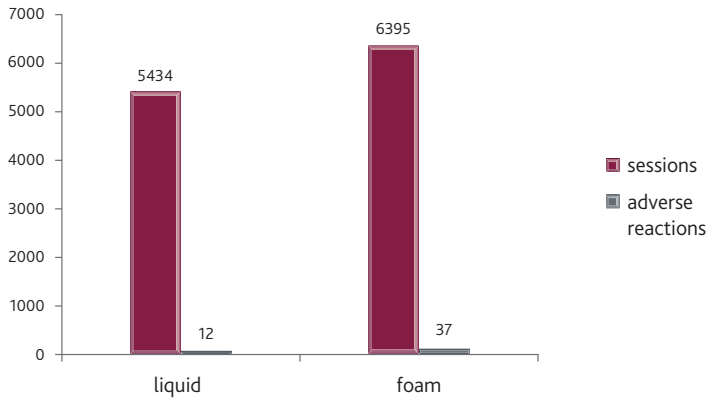
Treatment method

In this registry 22 phlebologists were included, 20 French, 1 Italian and 1 Spanish. To evaluate the daily practice in phlebology, no specifications were given regarding the sclerosing technique or agent. The sclerosant mostly used was polidocanol followed by sodium tetradecyl sulphate. No data on the efficacy of the treatment were collected.
All adverse reactions had to be reported consecutively during the 4-week registry period and at an additional 1 month follow-up. Pigmentation and matting were not separately assessed.

Results: All types of varicose veins can be safely treated with sclerotherapy

During the observation period 12,173 sclerotherapy sessions were carried out in 22 phlebology clinics. All types of varicose veins were treated, from telangiectasias and reticular varicose veins (5,924 sessions) to saphenous varicose veins (2,395 sessions). Liquid sclerosant was used in 5,434 sessions, foam in 6,395 and both foam and liquid were used in 344 sessions. In the treatment of telangiectasias and reticular varicose veins, liquid sclerotherapy was more common (3,631 versus 2,293 foam sessions), whereas foam was applied significantly more in the treatment of great and small saphenous varicose veins (2,025 versus 370 liquid sessions). Ultrasound guidance was used in 35% of the sessions.

Safety: The French Registry confirms the safety of liquid and foam sclerotherapy



Overall, adverse reactions were reported in 49 cases (0.40%) after 12,173 sessions of sclerotherapy. In the liquid group, 12 (0.22%) reactions were observed and in the foam group, 37 (0.58%).

Immediate safety of sclerotherapy

Visual disturbances were the most frequent immediate adverse reactions with 16 cases (0.25%) in the group treated with foam and 4 cases (0.07%) in the liquid group. Interestingly, 70% of the visual disturbances occurred after treatment of reticular veins and telangiectasias. Other reported cases were vasovagal fainting in 0.08%, coughing in 0.03%, paresthesia in 0.02% as well as nausea and metallic taste in 0.01% of patients. All incidents were mild and spontaneously regressed without any sequelae.

Medium-term safety of sclerotherapy

Medium-term complications were rare and solely observed after foam sclerotherapy. One femoral vein thrombosis (0.008%) was reported and one distal muscular vein thrombosis (0.008%), both of which could be treated without sequelae. In addition, 4 cases (0.03%) of benign extensions of the sclerosing process to muscular or perforating veins were observed and 3 cases of intense superficial thrombophlebitis. No other adverse reactions were observed.

Conclusion

- **The risk of complications after treatment with sclerotherapy is very low (0.40%)**
- **All incidents observed after sclerotherapy were transitory and resolved spontaneously**
- **No other than the above-mentioned adverse reactions were observed in this registry**

In summary, those results clearly demonstrate that sclerotherapy with liquid and foam is a very safe treatment for all types of varicose veins.

The French Polidocanol Registry
The Long-Term Safety of Sclerotherapy with Polidocanol

In the first French registry 12,173 sclerotherapy sessions performed by 22 physicians were analyzed for medium-term safety. The sclerosant mostly used was polidocanol (POL, French trade name: Aetoxisclérol®). To determine the long-term safety of POL, this follow-up registry over a period of 4 years was conducted with patients of the first registry who had been treated with POL. The FDA encouraged this registry and the results accounted for the approval of POL in the USA.

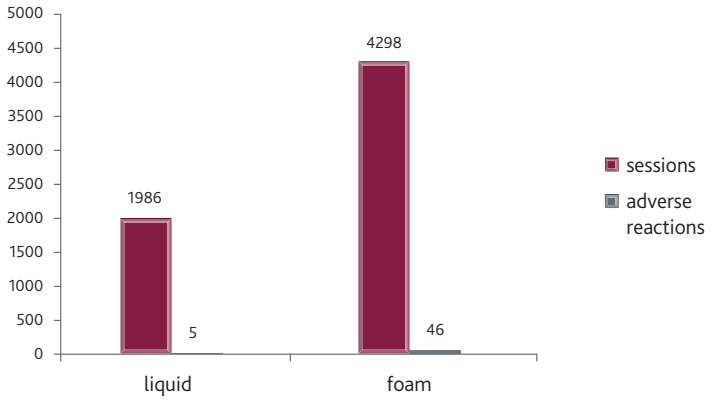
Treatment method

Twelve physicians of the first French registry participated in this long-term safety evaluation. Patients with at least one POL injection during the first registry and potential additional injections with POL during the observation period of this registry were included. Consequently, the number of adverse reactions differs slightly between the two registries. Patients were interviewed over telephone or face-to-face for immediate and delayed adverse reactions of each injection. The mean follow-up time was 27 months, 50% were followed-up for 32-44 months, thus covering a total of 3,357 patient years.

Results: All types of varicose veins can be safely treated with sclerotherapy

During the observation period 1,605 patients were treated with POL in 6,284 sessions. Most of the sessions were performed with Aetoxisclérol® foam (4,298 versus 1,986 with liquid). Telangiectasias and reticular varicose veins were the most frequently treated veins, followed by saphenous varicose veins, tributaries and recurrent varicose veins. Different vein types were treated in one session.

Safety: The French Polidocanol Registry confirms the long-term safety of polidocanol



Overall, immediate, medium-term and long-term adverse reactions were reported in 51 cases (0.81%) after 6,284 sessions of sclerotherapy. The onset of adverse reactions occurred mostly at the day of treatment or within the first 4 weeks after sclerotherapy. In the liquid group, 5 (0.25%) reactions were observed and in the foam group, 46 (1.07%).

The incidents observed after sclerotherapy with liquid POL included 2 cases of inflammation, 1 case of cramp, 1 case of pigmentation and 1 of visual disturbance.

After foam sclerotherapy were observed 13 cases of visual disturbances (0.30%), 8 muscular vein thromboses (0.19%), 7 cases of headaches or migraines (0.16%), 6 cases of vasovagal fainting (0.14%) and 3 cases of nausea and vomiting (0.07%). One deep vein thrombosis (0.02%) occurred after foam sclerotherapy in a patient with thrombophilia after anticoagulant treatment had been discontinued. Additionally, 2 cases of inflammation and 1 case of allergic reaction, 1 of shortness of breath, 1 of chest tightness, 1 of paresthesia, 1 extension of the sclerosis to a perforating vein and 1 case of superficial phlebitis were reported. No other incidents were observed.

Conclusion

- **The overall risk of complications after sclerotherapy with POL is very low (0.81%)**
- **Liquid sclerotherapy with POL has an even lower incidence of adverse reactions (0.25%)**
- **Visual disturbances occurred very rarely after liquid and foam sclerotherapy altogether, but seem to be slightly more frequent with foam (0.30%); they all spontaneously regressed without any sequelae**
- **No other than the above-mentioned adverse reactions were observed**

In summary, those results clearly demonstrate the very good safety profile of polidocanol in the short and long term for the treatment of all types of varicose veins.

If you have any questions, please contact:
Chemische Fabrik Kreussler & Co. GmbH
P.O. Box 12 04 54 · D-65082 Wiesbaden
Tel.: +49 (0)611 9271-0
Fax: +49 (0)611 9271-111

Rabe et al. Efficacy and Safety of Great Saphenous Vein Sclerotherapy Using Standardised Polidocanol Foam (ESAF): A Randomised Controlled Multicentre Clinical Trial. Eur J Vasc Endovasc Surg 2008;35(2):238-45 [Page 3]

Rabe et al. Sclerotherapy of telangiectases and reticular veins: a double-blind, randomized, comparative clinical trial of polidocanol, sodium tetradecyl sulphate and isotonic saline (EASI study). Phlebology 2010;25(3):124-31 [Page 4]

Zhang et al. Efficacy and safety of Aethoxysklerol® (polidocanol) 0.5%, 1% and 3% in comparison with placebo solution for the treatment of varicose veins of the lower extremities in Chinese patients (ESA-China Study). Phlebology 2012;27(4):184-190 [Page 5]

Guex et al. Immediate and Midterm Complications of Sclerotherapy: Report of a Prospective Multicenter Registry of 12,173 Sclerotherapy Sessions. Dermatol Surg 2005;31(2):123-8 [Page 6]

Guex et al. The French Polidocanol Study on Long-Term Side Effects: A Survey Covering 3,357 Patient Years. Dermatol Surg 2010;36 Suppl 2:993-1003 [Page 7]

The International Nonproprietary Name (INN) of the active ingredient Polidocanol is Lauromacrogol 400.

[Micro-Sclerotherapy]

Therapy with potential

For beautiful healthy legs

kreussler PHARMA

Aethoxysklerol® worldwide No1 of sclerosing agents