CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-201s000

MEDICAL REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 17, 2009

From: Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products /CDER

To: File

Subject: Polidocanol NDA #21201: Safety Review of Anaphylaxis Cases

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Materials Reviewed:

1. Polidocanol proposed labeling
2. ODS Postmarketing Safety Review, Adverse Events associated with Sclerosing Agents, Marilyn Pitts, October 22, 2004
3. Sponsor reply to inquiry concerning Exitus, Anaphylactic reaction, cardiac arrest, December 2 and 8, 2009 (including line listings and CIOMS forms)
4. Khin U, Clinical Review, dated November 16, 2009
5. Guex J, et al. Immediate and Midterm Complications of Sclerotherapy: Report of a Prospective Multicenter Registry of 12, 173 Sclerotherapy sessions. Am Soc Derm Surgery 2005; 31: 123-8.
6. Sotradecol (sodium tetradecyl sulfate) approved label
7. Clinical Pharmacology review, Peter Hinderling, November 24, 2009.

Polidocanol 0.5 and 1% (Asclera) injection has a proposed indication for sclerotherapy of uncomplicated spider veins, (b) (4), very small varicose veins (≤1 mm in diameter), and uncomplicated reticular veins (small varicose veins (b) (4) 1 to 3 mm in diameter) in the lower extremity. The proposed dose is 0.1 to 0.3 ml per injection; multiple injections may be needed. The label recommends a maximum volume of (b) (4) ml for spider veins and (b) (4) ml for reticular veins and a total maximum volume (for any sclerotherapy session, which could involve treating multiple veins) of 10 ml.

Post-marketing cases of anaphylactic reactions, some with fatal outcomes, have been reported in association with polidocanol use in other countries. The purpose of this review is to provide an

analysis of the available safety data for polidocanol with regard to cases of anaphylaxis, cardiac arrest, and death and make recommendations regarding label language describing this event and possible post-market risk mitigation and surveillance strategies.

NDA 21-201 trials

The pivotal trial in the NDA (EASI trial), included 338 patients (180 exposed to polidocanol 0.5 and 1%; 105 exposed to sodium tetradecyl sulfate; 53 exposed to placebo) treated for spider and reticular veins. The *mean±SD volume* injected in patients with reticular veins was 1.5± 0.5 ml of 1% polidocanol, and that in patients with spider veins was 1.1 ± 0.8 ml of 0.5% polidocanol. No cases of anaphylaxis or death were reported. One patient receiving polidocanol experienced severe urticaria which required hospitalization and IV corticosteroid and antihistamine administration.

An additional 251 patients were exposed to polidocanol 0.5 and 1% in 4 other trials exploring the intended indication (OHIO, MICA, ASK-94-002, and ASK-96-001-from Table 4 in the Clinical Review). Higher concentrations of polidocanol were studied in three additional trials with a total exposure to polidocanol of 80 subjects. According to the clinical review no cases of death or anaphylaxis were reported. There were 3 cases of hypersensitivity reactions (hives, sneezing, tongue and lip numbness) associated with higher concentrations (3%) and volumes (4 to 8 ml) than those in the proposed labeling for polidocanol.

Registries

The French Polidocanol Registry (5) provided information about adverse reactions reported in association with sclerosing agents when used for multiple types of varicose veins. Data from 12, 173 sessions were included. Each sclerotherapy session was reported consecutively; the same patient could have been treated several times. Unique numbers of patients were not reported in the publication. Three types of sclerosing agents were reported as "commonly used" in France at the time of the registry (polidocanol, sodium tetradecyl sulfate, and chromated glycerin) but the usage data for each agent was not provided. No cases of anaphylaxis or death were reported.

As part of the current NDA, the sponsor sent surveys to a subset of patients enrolled in the French Registry who had received polidocanol 0.5 to 1%. In these 1605 patients, two "inflammatory reactions" were reported according to the clinical review. No cases of anaphylaxis were reported.

CIOMS reports of Anaphylaxis

The sponsor submits 29 reports of anaphylactic reaction (or similar—urticaria, angioedema) with *no fatal outcome*. Two cases are excluded from this analysis because alternate factors could be identified that could explain the event (history of "spontaneous" angioedema, erroneous diluent used).

Indication: "Leg Varices" (n=24)

Nine cases with serious outcomes (hospitalization, ED visit) report the use of polidocanol doses within those recommended by the proposed labeling (Appendix 1). The total drug volume

administered ranged from 0.25 ml to 10 ml. The cases (n=3) with the most severe clinical course (loss of blood pressure, cardiac arrest, etc.) involved doses of 4 to 10 ml (given over 3 injections) of the 2% product. Cases that reported smaller doses (≤2 ml) of a 0.5 or 1% product included events such as angioedema, difficulty breathing, chest tightness which required emergency treatment (often with steroids or epinephrine). In all cases, the patient recovered.

Seven additional serious cases did not report dose and involved adverse events such as anaphylactic shock, anaphylactic reactions, hypotension, loss of consciousness, bronchial spasm and drop in blood pressure. All patients reportedly recovered.

Eight cases reported non-serious outcomes (urticaria, hives, asthma, angioedema).

Indication: Other venous anomalies (n=3)

One serious case of anaphylactic shock was reported with a dose of 20 ml of polidocanol for esophageal varices. Another serious case of anaphylactoid reaction (shock ,dyspnea, urticaria) was reported with the use of 2ml polidocanol for hemorrhoids. The remaining case (for hemorrhoids 0.1 to 0.2 ml) reported non-serious urticaria

CIOMS reports of Cardiac Arrest

The sponsor submits 6 cases of cardiac arrest without fatal outcomes; all cases were considered serious. Three cases involved pediatric patients; age reported was 14 years (leg varices), 8 months and 14 months (both esophageal varices). The remaining two cases involved polidocanol in foam form (7 ml to 30 ml). One additional case is included was included in the anaphylaxis series above.

CIOMS reports with Fatal Outcomes

The sponsor submits 19 cases reporting fatal outcomes. Four cases were excluded from the analysis. In one case, the death from cancer occurred two years after drug administration; in another the patient died from a pulmonary embolism two weeks after treatment. Another reported the use of polidocanol for hemorrhoids in a pregnant woman who ultimately gave birth to a child with anencephaly. Death from spinal meningitis was reported in a patient receiving a spinal injection of polidocanol for facet joint syndrome.

Indication: "Leg Varices" (n=3)

Three cases reported fatal outcomes in association with polidocanol use for leg varices.

- In the first case, involving two 0.5 ml injections of 0.5% polidocanol, the patient experienced loss of consciousness and cardiac arrest after arising from the table immediately after receiving the second dose. Autopsy revealed arrhythmogenic right ventricle.

- The second case involves the use of polidocanol 1% (volume unreported) for 5 injections. During the 5th injection, the patient lost consciousness, experienced "shock" and was not resuscitated.

- The third case describes anaphylactic shock and respiratory arrest 5 minutes after a 1ml injection of polidocanol 2%.

Indication: Other venous anomalies (n=11)

Eleven cases reported fatal outcomes in patients receiving polidocanol therapy for treatment of esophageal varices or GI bleeding. In general, these cases reported large volumes of polidocanol administration (12 to 40 ml). In six cases, death occurred on the same day as the administration of the drug. In many cases, patient comorbidities (i.e., organ failure, cancer, hepatic disease) was likely a major contributor to the fatal outcome. However, in one case, anaphylactic shock and ARDS was reported as the adverse event.

Indication: Unreported (n=1)

One fatal case did not report the indication or dose of polidocanol; the cause of death (same day as drug administration) was listed as cardiac failure.

Experience with Sotradecol

Sotradecol (sodium tetradecyl sulfate) is the only other approved sclerosing agent for the treatment of small varicose veins. Sodium tetradecyl sulfate was originally approved in 1946; marketing was suspended in 2002 because the sponsor was (b) (4) (b) (4). In 2004, Sotradecol was approved by the Office of Generic Drugs. The approved dose is 0.5 to 2 ml (preferably 1 ml maximum) for each injection with the maximum single treatment not exceeding 10ml.

The label of Sotradecol contains information in the Warnings section about the risk of anaphylaxis. The following bolded statement appears:

Emergency resuscitation equipment should be immediately available. Allergic reactions, including fatal anaphylaxis, have been reported. As a precaution against anaphylactic shock, it is recommended that 0.5 ml of Sotradecol be injected into a varicosity, followed by observation of the patient for several hours before administration of a second or larger dose. The possibility of an anaphylactic reaction should be kept in mind and the physician should be prepared to treat it appropriately.

In addition, a description of 4 cases of anaphlaxis with fatal outcomes are included in the Adverse Reactions section. One case reported a history of asthma which is a contraindication to Sotradecol use. These cases are further described in a review by the Office of Drug Safety in 2004 (2)

A search of AERS for more recent reports (from 2004 to the time of this review) revealed one probable case (ISR 5320833) of serious allergic reaction. Anaphylactic shock, loss of consciousness, and drop in oxygen saturation occurred immediately following an injection

patient who received 2ml of 0.1% Sotradecol for the treatment of reticular veins; she reportedly recovered.

Conclusion:

The post-marketing cases are strongly suggestive of an association between polidocanol therapy and allergic and anaphylaxis adverse events. The fatal cases of interest are not well documented and, in one case, confounded by heart disease. However, given the temporal relationship between drug administration and death, it appears that the drug may have had a contributory effect.

Although it is difficult to draw a specific conclusion about the relationship between drug dose and the incidence of the events based on post-marketing reports, it does appear that some of the most worrisome cases (cardiac arrest, loss of blood pressure) probably involve administration of volumes of polidocanol of > 2 to 3 ml. This volume is entirely within the range recommended in the currently proposed labeling. Ostensibly, higher doses would lead to a greater chance of systemic exposure, which would lead to the conclusion that limiting the volume of drug administered to the absolute minimum necessary is wise. However, when dealing with anaphylactic reactions, it seems that even one molecule of the offending agent could provoke the reaction. It is apparent from the Clinical Pharmacology review that with the proposed dosing, polidocanol achieves measureable plasma levels.

Given the apparent problems with higher (than the maximum labeled dose) volumes of polidocanol as well as the concerning cases involving use in some off label indications (esophageal varices), these practices should be avoided.

The fact that the development program for the proposed indication contains no reports of anaphylaxis not particularly reassuring given the small numbers of patients exposed to polidocanol. Although the subset of the French Registry offers a larger denominator of patients, one can only be 95% certain that it may not occur any more frequently than 1/535 (if one employs the rule of 3). Reports of hypersensitivy (urticaria, inflammation) are found in both the trials and registry data. It is impossible to estimate incidence of these events based on post-marketing reports because of the uncertainties of the rate of reporting, although given the worldwide use of polidocanol (reported to be (b) (4) exposures by the sponsor), it appears that they are rare.

In any case, the threshold for accepting a certain (serious) risk when the drug is given for an utterly cosmetic reason is quite high, even if the rate of risk is very rare. It is understood that prescribers and patients may accept these risks in the quest to eradicate spider and reticular veins (as evidenced by the availability of another sclerosing agent, Sotradecol which possesses a similar adverse event profile). However, it is possible to offer strategies to increase the likelihood of safe use of polidocanol.

Recommendations:

Labeling:

A Warning should appear in the label as follows:

Cases of severe allergic reactions have been reported in association with polidocanol use, some have included anaphylaxis, cardiac arrest, and death. These reactions may be more likely with larger volumes (> 3 ml), therefore the dose of polidocanol should be limited to the minimum necessary to treat the vein. Use in veins larger than 3mm should be avoided.. The physician should be prepared to treat anaphylaxis appropriately and should have emergency resuscitation equipment readily available.

Patients who demonstrate any sign of hypersensitivity to polidocanol (wheezing, sneezing, generalized urticaria) should not receive the drug again.

This warning should appear bolded in the label. A boxed warning could be considered, but as there are no clear criteria for boxing safety information, this warrants further discussion with the review team. One advantage to including a boxed warning would be its prominence on advertising and marketing materials (to both prescribers and patients).

The Sotradecol label contains information about the administration of a test dose followed by a period of observation to guard against serious anaphylaxis. The usefulness of this practice for polidocanol is questionable given the recommended (0.1 to 0.3 ml) doses.

Other Risk Management:

According to Section 505-1 of FDAAA, the reason for requiring a Risk Evaluation and Mitigation Strategy (REMS) is to "ensure that the benefit of the drug outweighs the risks associated with the drug". The regulations offer criteria to consider when making such a determination. These include: size of the population to be treated, the seriousness of the disease to be treated, benefit to treatment, and the seriousness of the event. Interestingly, the frequency of occurrence of the adverse event is not included.

A REMS should be required as part of the approval that would include a Communication Plan to physicians describing the risk associated with polidocanol and directing prescribers to limit the volume administered, have emergency equipment available, and to not readminister in patients displaying signs of hypersensitivity.

The Communication Plan should be distributed for a finite period of time after approval (2 to 3 years), should be distributed periodically (every 6 months) and should be sent to all prescribers that the sponsor plans to market to /detail.

A Medication Guide (MG) could be considered for this product as one of the requirements for a MG ("the drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product") applies in this case. However, practically, this drug will be dispensed by the physician administering the drug and discussions of risk/benefit would take place prior to administering the drug, in the office or practice setting. This drug is not administered chronically and hypersensitivity reactions appear within minutes of the injections,

so the need for a MG becomes obsolete after the patient receives the dose. Input on the utility of a Medication Guide should be obtained from the Division of Risk Management.

Elements to assure safe use (restricted distribution) is not necessary as this product is intended to be administered by physicians in their practice settings.

Post-Marketing Surveillance

The sponsor should be required to submit an analysis of all serious hypersensitivity events on an annual basis for review by the Agency. All serious hypersensitivity reactions should be reported as 15-day reports.

Appendix 1

Asclera 0.5 to 1%

Proposed indication: uncomplicated spider veins, (b) (4), varicose veins < 1mm, reticular veins (varicose veins (b) (4) 1 to 3 mm) in the lower extremity).

Proposed dose: 0.1 to 0.3 ml per injection, multiple injections may be needed, maximum volume (b) (4) ml for spider veins, max volume (b) (4) mg for reticular, max volume 10 ml for any session.

Summary of "Anaphylactic Reaction" Cases reporting ≤10 ml dose/session:

Case #	Reported Indication	Dose information	Outcome	Time course	Clinical Course	Treatment
Ae20290	Leg varices	10 ml given over 3 injections (2%)	Hospitalized, recovered	Immediately after last injection	Anaphylactic reaction, no blood pressure, loss of consciousness	Fluids, respiratory support, O2, epi, steroids
Ae20190	Leg varices (perforating veins)	4 ml in one injection (2%)	Hospitalized, recovered	5 minutes after injection	Severely SOB, Cardiac arrest	NR
Ae20390	Leg varices	4 ml (2%)	Hospitalized, recovered	Few minutes	Severe dyspnea, loss of blood pressure, ECG evidence of ischemia	Steroids, epi,
Ae051596	Leg varices	0.8 ml (1%)	NR	Lasted for 1.5 hour after injection	Quincke Oedema	Steroids, H1 blocker
Ae10202	Leg varices	0.25 ml (1%)	Hospitalized, recovered	Immediately	Quincke Oedema, vasovagal	NR

					reaction, pharyngeal inconvenience	
Ae018D04	Leg varices (collateral varicosity)	1.5 ml (1%)	Emergency, recovered	NR	Difficulty breathing, chest tightness, malaise	Steroids
Ae001dk06	Spider veins	Not given (1%)	Emergency, recovered	After treatment	Quinckes Oedema, severe swelling of lips, throat, and eyes	Steroid, epi
Ae008J07	Leg Varices	0.5 ml x 7 (0.5%)	Emergency, recovered	Immediate	Discomfort, “insignificant” drop in BP	Fluids
Ae12F06	Small varices and telangiectasias	2 ml of 0.5%	Hospitalized, recovered	NR	Quincke’s edema, giant urticaria, laryngeal spasm	NR

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1%/ (b) (4)

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/s/

MARY R SOUTHWORTH
12/17/2009

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 18, 2009

TO: Michael Monteleone, Regulatory Project Manager
Khin U, Medical Officer
Division of Cardiovascular and Renal Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA 21-201

APPLICANT: Chemische Fabrik Kreussler & Co., GmbH.

DRUG: Aethoxysklerol® (Polidocanol)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Aethoxysklerol® (polidocanol) for the treatment of reticular veins and spider veins.

CONSULTATION REQUEST DATE: 08/21/2009

DIVISION ACTION GOAL DATE: 01/10/2010

PDUFA DATE: 01/10/2010

I. BACKGROUND:

Chemische Fabrik Kreussler & Co., GmbH., seeks approval of Aethoxysklerol® (polidocanol) for the treatment of reticular veins and spider veins. The applicant presents data from a new pivotal study, EASI, entitled, "Efficacy and safety of Aethoxysklerol® compared to Sodium tetra-decyl sulfate and Isotonic saline (placebo) for the treatment of reticular veins and spider veins."

The applicant previously submitted data to the agency under NDA 21-201 in 2003 for consideration by the agency to grant marketing approval of polidocanol for the treatment of varicose veins of the lower extremities. Previous FDA GCP inspections of a different pivotal study, entitled, "Double Blind Prospective Randomized Comparative Multicenter Trial between Aethoxysklerol (polidocanol) and Sotredecol (sodium tetradecyl sulfate) in the Management of Varicose Veins of the Lower Extremities," conducted in support of the initial NDA 21-201 submission revealed problems with data integrity at two of three sites inspected at that time. Two sites resulted in OAI classifications; that of Dr. John Pfeifer in Troy, Michigan, and Dr. Mitchel Goldman in La Jolla, California. The original NDA 21-201 received a Not Approvable letter on August 2, 2004, in part, due to the GCP inspectional findings at 2 of the 3 clinical investigator sites inspected; there was insufficient documentation to assure data quality and integrity.

A new pivotal study, EASI, was targeted for inspection. Assessment of the new data indicates that the efficacy and safety results were not significantly different at any center, and no single site was found to significantly influence study results. However, based on the above history with this applicant and drug, the conduct of GCP inspections of centers that enrolled the largest number of patients to verify data integrity and protocol adherence was considered warranted. Therefore, routine audits were requested to assess data integrity and human subject protection for the clinical trial identified above, which was submitted in support of this application.

Two clinical sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811); that of Dr. Margrit Simon, Site number 13, and that of Dr. Markus Stücker, Site number 16. These sites were selected by the product review division because they represent high enrolling sites.

In addition, the NDA applicant and EASI study sponsor, Chemische Fabrik Kreussler & Co., GmbH, and a CRO, (b) (4), were inspected in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810).

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI#1: Dr. med. Margrit Simon (Center # 13) Hauptstr. 131, 10827 Berlin, GERMANY	Protocol EASI/32 subjects	October 26-29, 2009	Pending Interim classification: VAI
CI#2: PD Dr. med. Markus Stücker (Center #16) St. Maria Hilf Krankenhaus, 44805 Bochum, GERMANY	Protocol EASI/29 subjects	October 19-22, 2009	Pending Interim classification: VAI
Sponsor: **Chemische Fabrik Kreussler & Co., GmbH.** Dr. Stephan Travers Rheingaustrasse 87-93 D-65203 Wiesbaden Germany	Protocol EASI/338 total patient population	November 2-5, 2009 *Overlapped with CRO inspection. Actual Sponsor inspection took place at CRO location.*	Pending Interim classification: NAI
CRO: (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)	Protocol EASI/338 total patient population	November 2-5, 2009 *Overlapped with Sponsor inspection.*	Pending Interim classification: VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. CI#1: Dr. med. Margrit Simon

(Site Number 13)
Hauptstr. 131, 10827 Berlin,
GERMANY

a. What was inspected: The site screened 41 subjects, 32 of those were randomized and treated. All 32 subjects completed the study through visit 5. The study records of 41 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to eCRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary: Generally, the investigator's execution of Protocol EASI was found to be adequate. The primary efficacy endpoint data were verifiable. However, there were some data discrepancies between what was recorded on some of the source documents and what was recorded on the eCRF. For most subjects it appeared that the site filled out the eCRF for inclusion/exclusion criteria as "negative" for thrombophilia indicators based on blood taken at day 0 but did not yet have those actual results. There were also examples of times listed for study events for subjects that did not appear accurate; being off by 10-15 minutes. This observation resulted in the appearance that study subjects had multiple events occurring at exactly the same time point or out of proper sequence by a few minutes, and that some subjects received study treatments prior to randomization. In addition, changes found in source documents did not always reveal what was originally written and often did not contain any attribution indicating who made changes and dates of the same. The Form FDA 483, Inspectional Observations, was shared and discussed with the review division Medical Officer, Dr. Khin U, on November 9, 2009. Khin U discussed the possibility that the inspectional observations with respect to protocol deviations and record keeping discrepancies, did not appear to be clinically significant because it did not appear to be a systematic violation that would corrupt data interpretation for efficacy and safety endpoints across all study centers.

Consistent with the routine clinical investigator compliance program assessments, the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. A Form FDA 483 was issued citing 4 Observations. The review division may wish to consider each violation, outlined in the Form FDA 483 (4 violations), and provided below, as it pertains to individual study subjects, and the review division may wish to sensor subject-specific data as appropriate.

1. Protocol exclusion criteria number 6 specified that patients with a positive result for one of the listed thrombophilia indicators, as determined by analyzing blood samples taken on day 0 were to be excluded, but review of subject source documents and eCRFs found:

a. With only a few exceptions, the entry on the eCRF concerning the results of the day 0 sample was checked "no" on the same day the sample was collected, in some cases within less than 30 minutes after the sample was collected.

b. Some subjects were randomized and treated prior to receipt of valid thrombophilia sample results, such as 1301 (randomized and treated the same day the resample was collected) and with the second study drug treatment also done prior to receipt of results, and 1302 (randomized and treated the day before the resample was collected).

2. Times listed for study events are not in all cases accurate, and in some cases appear to have been changed to make it appear that protocol timeframes were followed. For example:

a. The eCRF for subject 1317 shows that Visit 1 photos were taken at 12:24 and 12:26, that randomization occurred at 12:31 with verification at 12:32, and that the subject received injections of study medication at 12:25 to 12:29, which is prior to randomization and at the same time one of the photos was taken. Source documents showed that the original entries for injection times were 12:45 to 12:49, with the ECG done at 12:57. It appears that the injection times were altered so that the ECG would appear to have occurred at least 15 minutes after the injection.

b. The eCRF for subject 1318 shows that visit 1 injection times were changed, with the original entries being less than 15 minutes prior to the ECG.

c. Records for subject 1320 show that visit 1 photos were taken at 13:25 and 13:26, with study drug injections given at 13:25 to 13:30.

d. Records for subject 1325 show that visit 1 photos were taken at 18:04 and 18:06, randomization and verification occurred at 18:01 and study drug injections began at 18:00.

3. Several subjects appear to have received their first dose of study drug prior to randomization:

a. Subject 1331 – randomization/verification occurred at 10:25/10:26 per eCRF entries, and study drug injections occurred at 10:20 to 10:21 per worksheet and eCRF.

b. Subject 1338 – randomization/verification occurred at 19:04/19:05 per eCRF entries, and study drug injections occurred at 18:55 to 18:56 per worksheet and eCRF.

c. Subject 1339 – randomization/verification occurred at 16:02/16:03 per eCRF entries, and study drug injections occurred at 15:50 to 15:51.

4. Source documents do not contain any initials or signatures to show who made entries, and changes to entries were sometimes made in an inappropriate manner, by completely obliterating the original entry, or by writing over the original entry, with changes rarely being initialed or dated to show when and by whom they were done.

The FDA field investigator, Barbara Frazier, provided additional insight (in an email dated November 10, 2009) by providing an informal summary of the explanation given to her verbally by the clinical investigator, Dr. Simon, during the inspection. Barbara Frazier stated that the investigator did not offer any excuses. Dr. Simon's explanation for the time recording issues was that they used watches or wall clocks to write down the time of study events in the worksheet (such as, start and stop time of injections, time of post injection vital signs, assessments etc). Dr. Simon said that she remembered there was at least one time during the study when she realized that her watch was wrong by 10 or 15 minutes. Dr. Simon said that they never treated subjects prior to randomization and that either the site must not have written the times down accurately, or there was a 5 to 10 minute difference between the computer time and the watches/wall clocks used by the study site personnel.

c. **Assessment of data integrity**: Based on discussions between the DSI reviewer and the Review Division MO, and consideration of the verbal explanations from Dr. Simon to the FDA field investigator the findings are unlikely to significantly impact data integrity. The data for Dr. Simon's site, associated with study EASI submitted to the Agency in support of NDA 21-201, appear reliable based on available information. The general observations and actions on inspection are based on preliminary communications with the FDA field investigator.

2. **CI#2: Dr. med. Markus Stücker**
(Site Number 16)
St. Maria Hilf Krankenhaus, 44805
Bochum, GERMANY

a. **What was inspected**: The site screened 37 subjects, 29 of those were randomized and treated. All 29 subjects completed the study through visit 5. The study records of 37 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary: Generally, the investigator's execution of Protocol EASI was found to be adequate. The primary efficacy endpoint data were verifiable. However, there were some data discrepancies between what was recorded on some of the source documents and what was recorded on the eCRF. For 3 subjects treated for reticular veins, it appeared that they received more than the protocol specified 8 injections at their initial treatment. According to the FDA field investigator, the source documents for these subjects had illegible original entries, which were then changed to reflect that 8 injections were given. However, the eCRFs for these subjects showed an audit trail of data entered; original entries ranged from 10 to 12 injections, and then entries were updated to read 8 injections. The other major observation made at this site was that the date and time of occurrence of Adverse Events (AE) was not accurately recorded in subject eCRFs. The site recorded AE date and time of occurrence when the subject actually came to the clinic for an appointment instead of when the subject stated the AE began.

The Form FDA 483, Inspectional Observations, was shared and discussed with the review division Medical Officer, Dr. Khin U, on November 9, 2009. Khin U suggested that the observations did not appear to be clinically significant because again it did not appear to be a systematic violation that would corrupt data interpretation for efficacy and safety endpoints across all study centers.

Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. A Form FDA 483 was issued citing 2 observations. The review division may wish to consider each violation, outlined in the Form FDA 483 (2 violations), and provided below, as it pertained to individual study subjects, and the review division may wish to sensor subject-specific data as appropriate.

1. The protocol specified that no more than 8 injections could be given at each treatment for reticular veins, but review of subject records found that 3 subjects (1615, 1619, 1636) treated for reticular veins appeared to have been given more than 8 injections at their initial treatment. Source data for these subjects had been changed to read "8", with the original entries made completely illegible. The eCRF entries for the 3 subjects showed that the original entry for subject 1615 was 10, the original entry for subject 1619 was 12, and the original entry for subject 1636 was 10.

2. Start date and time entered for AEs was the date and time of the first clinic appointment after the AE began, and not the actual date/time reported by the subject. For example, several subjects reported hematomas beginning the day of or the day after a treatment, but the start date entered in the eCRF was the appointment date, which was 7 or more days later.

Also, subjects with hyperpigmentation showed start dates of 80 to 90 days after treatment, although subjects indicated start dates of approximately 10 days.

The FDA field investigator, Barbara Frazier, provided additional insight (in an email dated November 10, 2009) by providing an informal summary of the explanation given to her verbally by the site clinical sub-investigator who actually did the treatments, assessments, and most of the eCRF entries for Dr. Stücker. The sub-investigator stated that [she] would never change data and that what probably happened was that she had written an entry on the wrong line, and had to correct it. The FDA field investigator informed her that by obliterating the original entry on the worksheet, it became impossible for FDA to assess whether it was or was not a simple entry error, and that the eCRF showed that she had changed the number of injections after immediate auto-queries by the eCRF as she was entering the data. The FDA field investigator stated that other than this data entry issue, for those 3 subjects noted above, that no other similar issues were identified.

c. **Assessment of data integrity:** Based on discussions between the DSI reviewer and the Review Division MO, and consideration of the verbal explanations from the site sub-investigator to the FDA field investigator, the 483 findings are unlikely to significantly impact data integrity. The data for Dr. Stücker's site, associated with study EASI submitted to the Agency in support of NDA 21-201, appear reliable based on available information. The general observations and actions on inspection are based on preliminary communications with the FDA field investigator.

3. **Sponsor:**
Chemische Fabrik Kreussler & Co., GmbH.
Dr. Stephan Travers
Rheingaustrasse 87-93
D-65203 Wiesbaden
Germany

And

CRO: (Location of the combined Sponsor and CRO inspection)
(b) (4)

a. What was inspected:

The sponsor and CRO were inspected in a combined audit that took place at the CRO location in Munich. The Sponsor/Monitor/CRO data validation compliance program, CP 7348.810 was completed. Specifically, the inspection covered adherence to protocol EASI, assessment of clinical monitoring reports, and study records and procedures.

The EIRs were not available at the time this CIS was written. The EIRs for the CRO and Sponsor inspections are currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary:

Records and procedures were clear, complete and well organized. There was nothing to indicate under-reporting of AEs/SAEs. The two expert reviewers (in France and Australia) of the photographs from study visits 1, 4, and 5 made their assessments on paper CRFs. Those CRFs were available and were reviewed against the data listings submitted to the NDA and provided in the background materials for study sites 13 and 16. No discrepancies were noted.

Review of monitoring reports found no major issues. However, a study nurse at site 11 apparently did not understand exactly how randomization was supposed to occur. Assigned drug was mixed up between two subjects, 1106 and 1117, and it appeared that these subjects were treated only once. There was a monitoring visit to site 11 within a week or two after this occurred, and the problems (and actions taken) were listed in the monitoring report.

A Form FDA 483 was issued to the CRO citing one inspectional observation. Specifically,

Protocol exclusion criteria number 6 specified that patients with a positive result for one of the listed thrombophilia indicators, as determined by analyzing blood samples taken on day 0, were to be excluded. However, the design of subject source documents and eCRFs was such that 7 of the 19 study sites completed the entire eCRF page on the day of Visit 0, including "acceptable results" for the sample taken for thrombophilia indicators even though the thrombophilia indicator results could not have been available at the time the eCRF was completed. The 7 sites were 2, 3, 5, 7, 13, 15 and 18. For site 5, this observation applies only to the first 9 subjects; the site corrected the issue for subjects 510-525.

According to the FDA field investigator, Barbara Frazier, the CRO plans to make a written response to the Form FDA 483. She stated that the response will likely include written assurance that no subjects were entered into study EASI who did not meet inclusion/exclusion criteria.

c. **Assessment of data integrity**: Based on preliminary review of the inspectional observations for the Sponsor and CRO, and discussions between the DSI reviewer and the Review Division MO, the findings are unlikely to significantly impact data integrity for study EASI submitted to the Agency in support of NDA 21-201. The general observations and actions on inspection are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on preliminary review of inspectional findings, the study data collected by Dr. Simon and Dr. Stücker appear reliable. The inspection of the sponsor and CRO found that records and procedures were clear, complete and well organized, that reporting of AEs/SAEs appeared adequate, and a review of monitoring reports found no major issues.

The 2 CI sites and the CRO were issued Form FDA 483s, Inspectional Observations. Site 13, that of Dr. Simon, had protocol compliance and record keeping deviations. Briefly, this site recorded in the CRF for day 0 that subjects met inclusion criteria regarding blood test results for thrombophilia indicators on the same day the sample was taken, and times recorded for study events such as randomization, treatment injections, ECGs, and treatment site photographs appeared out of proper order, and study records did not contain adequate attribution for entries and changes to the same.

Site 16, that of Dr. Stücker, had protocol compliance and record keeping deviations. Briefly, 3 subjects may have been given more than the protocol-specified limit of 8 injections for reticular veins, at their initial treatment. Subjects 1615, 1619 and 1636 appeared to have received 10, 12, and 10 injections, respectively, based on data entry into the eCRF. However, the source records for these 3 subjects revealed changes made to them to read only 8 injections had been given. It is unclear if this was a protocol deviation, a record keeping discrepancy, or both. This site also recorded the date of AE occurrence as the date of the first clinical appointment after the AE began instead of the date of the actual occurrence as reported by the subject on several occasions. As a result, reported hematomas that began on the day of or day after a treatment were recorded as occurring 7 days or more after the actual occurrence. Also, hyperpigmentation that began approximately 10 days after a treatment was recorded as starting 80 to 90 days after treatment.

Finally, the CRO was cited because the CRF was confusing for day 0. The design was such that the day 0 CRF requested a result for lab results regarding specimens taken on day 0 that could not have been completed on the same day. A number of study sites filled

out the day 0 CRF for thrombophilia indicators with the actual result even though the result was not available until days after day 0. This resulted in the appearance that the day 0 CRF was completed without the thrombophilia indicator test results available.
A copy of each Form FDA 483 was provided to the review division medical officer, Dr. U, on November 9, 2009. Khin U and DSI reviewer Lauren Iacono-Connors discussed the inspectional observations with respect to protocol deviations and record keeping discrepancies, and felt that they did not appear to be clinically significant because they did not appear to represent systematic violations that would corrupt data interpretation for efficacy and safety endpoints across all study centers. The review division may, however, wish to consider each violation pertaining to protocol adherence and record keeping, outlined in each the Form FDA 483s, and described in detail above, and sensor subject-specific data from study analyses as appropriate. The final reports (EIRs) for these inspections have not been completed to date.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigator and copies of the Form FDA 483, inspectional observations, issued. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1% (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAUREN C IACONO-CONNORS
11/18/2009

TEJASHRI S PUROHIT-SHETH
11/18/2009

COMBINED CLINICAL & STATISTICAL REVIEW

Application Type	NDA
Application Number(s)	21-201
Priority or Standard	Priority
Submit Date(s)	21-Jul-2008; 10-Jul-2009
Received Date(s)	23-Jul-2008; 10-Jul-2009
PDUFA Goal Date	10-Jan-2010
Division / Office	DCaRP/ODE I/OND
Reviewer Name(s)	Khin Maung U, M.D. John Lawrence, Ph.D.
Review Completion Date	16-Nov-2009
Established Name	Polidocanol
(Proposed) Trade Name	ASCLERA™
Therapeutic Class	Sclerosant
Applicant	Chemische Fabrik Kreussler & Co., GmbH
Formulation(s)	0.5% & 1.0% solution for injection
Dosing Regimen	Group S: ASCLERA™ 0.5% (0.1 to 0.3 ml per injection [redacted])
	Group R: ASCLERA™ 1 % (0.3 ml per injection [redacted])
Indication(s)	Sclerotherapy of C_1 veins:
	Group S: (<1 mm diameter; spider veins, [redacted], very small varicose veins)
	Group R: (b)(4) 1–3 mm diameter; reticular varices and small varicose veins)
Intended Population(s)	Patients with C_1 varicose veins

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1 Recommendations/Risk Benefit Assessment

Background/Introduction

ASCLERA™ (active ingredient = polidocanol) is a sclerosing agent proposed in this NDA 21-201 for the indication of treatment of small varicose veins {C_1, spider veins (<1 mm diameter) and reticular veins ((b) (4) 1 to 3 mm diameter)} of the lower extremities.

The action of polidocanol is chemical (not pharmacological). As a non-ionic surfactant, the hydrophobic pole of the drug molecule attaches to the lipid membrane of venous endothelial cells and disrupts the osmotic barrier. The resulting cell destruction creates a highly thrombogenic exposed endothelial surface to which platelets attach followed by thrombus formation, obliterating the vein lumen which is later replaced by fibrous tissue.

NDA 21-201 has a long history with FDA. The sponsor had submitted the MICA (Michigan and California) and OHIO trials as pivotal trials to the Division of Dermatology and Dental Drug Products, first on 10/01/1999, and re-submitted – with 21 amendments – on 11/10/2003.

On 08/02/2004, the Office of Drug Evaluation III issued a non-approvable letter because

(i) the efficacy of polidocanol was not demonstrated as superior or non-inferior to the reference drug Sotradecol®,
(ii) there was little or no assessment of risk of deep vein thrombosis (DVT) following injection with polidocanol,
(iii) FDA GCP inspections revealed problems with data integrity or data quality at two (Michigan and California) of three sites inspected,
(iv) controls were inadequate to prevent micro-organisms surviving the sterilization procedures, and
(v) pivotal pharmacokinetic results were not reliable to meet *in vivo* bioavailability requirements under 21 CFR 320.

NDA 21-201 and related IND 35,139 were transferred to the Division of Cardiovascular and Renal Products in May, 2005. After FDA evaluation of a special protocol assessment, the sponsor submitted the current NDA on 07/21/2008 addressing the issues stated in the non-approvable letter. The submission consists of:

(1) the EASI (**E**fficacy and safety of **A**ethoxysklerol™ compared to **S**odium tetra-decyl sulfate and **I**sotonic saline (placebo) for the treatment of reticular and spider veins) trial as the pivotal trial to support efficacy and provide safety data related to DVT evaluated by ultrasound, and
(2) data from a prospective survey of a sample of 1,605 patients (taken from the French Registry of >3,000 patients who had received 12,173 sclerotherapy treatments in 2003-2005). This sample of patients who were surveyed had undergone 6,444 sclerotherapy sessions, including 2,041 sessions with liquid polidocanol. The survey provided long term safety data, including safety information related to DVT.

Preliminary review of data to determine acceptability for filing revealed that all of the

equipment used to manufacture ASCLERA™ had been relocated to a newly constructed facility. The CMC review team considered that this required revalidation of the manufacturing processes, including the sterilization procedure which was one of the issues for non-approvable by FDA in 2004. The review clock was stopped, and then restarted after the sponsor submitted a complete response on 07/10/2009.

The pivotal **EASI** trial is a placebo-and comparator-controlled, double-blind, multicenter trial. It was conducted at 19 centers in Germany, and randomized 338 patients with C_1 varicose veins (reticular veins and spider veins) to polidocanol (180 patients), Sotradecol® (105 patients) and placebo (53 patients), including 22 patients (called Group C) treated open-label at one center to determine pharmacokinetic data. Patients with spider veins were treated with polidocanol liquid 0.5% and those with reticular veins were treated with polidocanol liquid 1%. Sotradecol® could not be blinded; a non-blinded member of the study personnel not involved in study assessments prepared the syringe for injection and handed it to the blinded investigator.

The primary efficacy endpoint in the EASI trial was improvement of the treated veins on a 5-grade scale on standardized digital photographic images at 12 (± 2) weeks after the last injection evaluated by each investigator and two independent blinded medical experts (comparison of change from pre-treatment baseline between polidocanol and isotonic saline). Assuming that the effect of polidocanol 0.5% in spider veins is equal to that of polidocanol 1% in reticular veins, a pooled, stratified analysis of patients was done using stratified Wilcoxon-Mann-Whitney test.

The OHIO trial was a randomized, double-blind, active-controlled trial with valid data for efficacy evaluation in the earlier submission to FDA. While the results of the OHIO trial do not contribute to the regulatory decision, they suggest that the efficacy of polidocanol and Sotradecol® in patients in the United States appeared to be generally comparable with that observed in patients in Europe (the EASI trial).

Safety data in the current submission is based on: (i) 338 patients in the pivotal EASI trial, (ii) 685 patients in seven clinical studies which had been submitted earlier to FDA in 2003, and (iii) The French Polidocanol Registry of 1,605 patients who were surveyed using standardized questionnaires. The data were recorded on case report forms to evaluate long-term AEs following the 6,444 sclerotherapy sessions these patients underwent in 2003-2004, including 2,041 sessions treated with liquid polidocanol. A simple pooling of data was not done due to differences in evaluation of the safety data.

1.1 Recommendation on Regulatory Action

Based on review of the clinical data submitted in this NDA, the recommended regulatory action is **approvable** (§21 CFR 314.110) pending the sponsor's response to comply with the changes suggested in (1) Indications and Usage, (2) Dose Considerations, (3) Contraindications and (4) Warnings and Precautions sections of the proposed labeling (Section 9.2 Labeling Recommendations) of this review.

1.2 Risk Benefit Assessment

The primary efficacy analysis of EASI trial revealed statistically significant superiority of polidocanol over placebo for the mean *change* from pre-treatment baseline in digital photograph scores (5-grade scale) at 12 (± 2) weeks for the full analysis data set (4.52 ± 0.65 for polidocanol vs. 2.19 ± 0.68 for placebo; p<0.0001) as well as the per-protocol data set (4.55 ± 0.63 for polidocanol vs 2.09 ± 0.41 for placebo; p<0.0001).

The same is true also for the active comparator Sotradecol® compared to placebo suggesting adequate *assay sensitivity* of the EASI trial.

This statistically significant improvement in photographic scores from baseline at 12 (±2) weeks from baseline was maintained at 26 weeks (6 months) suggesting that patients obtained sustained cosmetic benefit.

Patients' subjective perception of their satisfaction with treatment (on a scale of 1 to 5) showed that a significant (p<0.0001) proportion of patients treated with polidocanol were "satisfied" or "very satisfied" at 12 weeks (88%) and 26 weeks (84%), compared to patients treated with Sotradecol (64% at 12 weeks and 63% at 26 weeks) or placebo (13% at 12 weeks and 11% at 26 weeks).

The success rate (by objective photographic evaluations) and the subjective patient satisfaction rates were significantly correlated (p=0.0381 to p<0.0001).

From the safety perspective, there were no deaths in any of the clinical studies. In the EASI trial, serious adverse events reported consisted of 2 patients: one patient was hospitalized for exacerbation of existing fibromyalgia, and one patient experienced severe urticaria requiring hospitalization and parenteral treatment with corticosteroids and antihistamines. Withdrawals due to AE consisted of one patient who was diagnosed with borrelia infection and another with intermittent tachycardia 7 days after treatment.

In the seven earlier clinical studies, significant AEs were reported on 5 patients treated with 4 to 8 ml polidocanol 3%, and 2 patients treated with Sotradecol®. These included ecchymoses and hyperpigmentation (4 AEs), local pain, inflammation, swelling and itching (1 AE), superficial vein thrombosis and Neovascularization (2 AEs) and possible allergic reaction manifested as tongue or lip feeling numb, or hives or sneezing (3 AEs).

In the French Polidocanol Registry, 68 AEs were reported by 54 patients during 58 sclerotherapy sessions, of which 51 AEs reported by 37 patients during 41 sessions were associated with polidocanol. Of these, 46 AEs were associated with polidocanol *foam*, and 5 AEs were associated with polidocanol *liquid* (p=0.0033). The five AEs associated with polidocanol liquid were one visual disturbance, one cramp and two inflammatory reactions observed soon after administration, and one hyperpigmentation observed as a delayed AE.

DVT was one AE of specific primary concern for this drug product which was not sought for in the seven earlier clinical studies, and was a reason for non-approval in 2004.

In the EASI trial, DVT was evaluated by ultrasound evaluations at screening visit

(baseline), Visit 1a (one week ± 3 days after injection of polidocanol) and at Visit 4 (12 weeks ± 2 weeks after injection of polidocanol). No DVTs were found following treatment with polidocanol or Sotradecol® or placebo.

In the French Polidocanol Registry, 14 DVTs were associated with *foam* sclerosants, of which 8 were noticed in relation to polidocanol foam. Two DVTs were associated with *liquid* sclerosants, both with other liquid sclerosants. No DVTs were reported in any patient who had been treated with polidocanol liquid.

Common AEs observed in the EASI trial and in the seven earlier clinical studies were local AEs such as hematoma, ecchymoses, hyperpigmentation, neovascularization and blister, and local sensations such as itching, pain, warmth and burning. Systemic AEs were very rarely reported, which included taste perversion, paresthesia and cramps. Microthrombectomy to prevent pigmentation was necessary less frequently with polidocanol at Visit 1a and Visit 2 compared to Sotradecol® in the EASI trial.

There were no clinically important laboratory abnormalities or changes in vital signs in the EASI trial, the seven earlier clinical studies or the French Polidocanol Registry. In the EASI trial, there were no marked changes in the QTc_F duration between screening and Visit 1, and no differences in the QTc_F between treatment groups.

The sustained cosmetic benefit obtained by treatment of C_1 spider and reticular veins using polidocanol liquid appears to exceed the risk of local AEs which are minor and transient in nature. The absence of DVTs in patients treated with polidocanol liquid further alleviates safety concerns. The efficacy and safety profile of polidocanol liquid appears to be similar to that of Sotradecol®, another liquid sclerosant which was approved for the treatment of varicose veins in 2004 by FDA Office of Generic Drugs.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

In accordance with §21 CFR 314.81 (b)(1)(ii), the postmarket reporting requirement for "… *information concerning any bacterial contamination, or significant chemical, physical or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application*," the sponsor submitted a signed commitment to (1) conduct stability studies, (2) add one commercial batch yearly on a rotating principle, (3) provide annual reports of post-approval stability testing, (4) report information concerning bacterial contamination, significant chemical, physical or other deterioration in the drug product or failure to meet established product specifications, and, (5) in the event of a batch of drug product failing to meet specifications during the course of stability testing, to withdraw this batch from the market.

2 Introduction and Regulatory Background

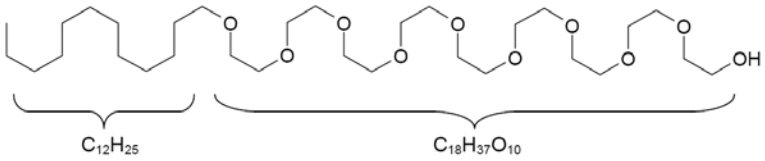
Polidocanol, the active ingredient of ASCLERA™, is a sclerosing agent used in the treatment of varicose veins (sclerotherapy). It is simpler than surgery to perform, has lower morbidity and is less expensive.

2.1 Product Information

Name of Drug: ASCLERA™ 1% and ASCLERA™ 0.5%

Active Ingredient: Polidocanol (0.5% & 1.0%) (INN: lauromacrogol 400), a detergent.

Structural formula:



$=C_{30}H_{62}O_{10}$

Molecular formula: $C_{12}H_{25}(OCH_2\text{-}CH_2\text{-})_nOH$ where *n* has an average value of 9.
Nominally, $C_{30}H_{62}\ O_{10}$.

Mean Molecular Weight: Approximately 600.

2.2 Tables of Currently Available Treatments for Proposed Indications

Sotradecol® (active ingredient Sodium Tetradecyl Sulfate) was approved in 2004 by FDA (Table 1) for sclerotherapy of leg varices, including spider veins and reticular veins.

Table 1 Table of currently available treatment for the proposed indication

Application #	Drug	Approving Office	Approval date	Indication
ANDA 40-541	Sodium tetradecyl sulphate	Office of Generic Drugs	12-Nov-2004	Treatment of varicose veins

The Office of Generic Drugs performed an "expedited review" of an "abbreviated new drug application (ANDA)" of Sotradecol®; the application was granted expedited review because of "*a nationwide shortage of this medically necessary drug product*." The approval was based on the finding of bioequivalence of Bioniche Pharma USA's product Sotradecol® injection 1% and 3% to an earlier preparation of Sotradecol® injection 1% and 3% manufactured by Elkin Sinn (a Division of A.H. Robbins Co., Inc.) which had been withdrawn. In this NDA for POLIDOCANOL®, Sotradecol® is used as a positive control in the pivotal and supportive trials.

2.3 Availability of Proposed Active Ingredient in the United States

ASCLERA™ is not currently marketed in the United States. ASCLERA™ will be manufactured by [redacted] (b) (4), one of two manufacturers in the CMC section of the NDA.

2.4 Important Safety Issues With Consideration to Related Drugs

There is a large amount of experiential data (published and unpublished) from widespread and off-label use of sclerosants to treat varicose veins in Europe, Australia, New Zealand and Latin America.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The major points in the long history of this Drug Product with FDA are as follows:

- The initial **IND 35,138** was first submitted to Division of Medical of Imaging, Surgical and Dental Drug products on **02-Jul-1990**, then was transferred to the Division Dermatology (Jan-1994), re-transferred to the Division of Medical Imaging, Surgical and Dental Drug Products (1994), and re-transferred again to the Division of Dermatology and Dental Drug Products (DDDDP) (01-Apr-1996), with several changes in the review team.
- After Pre-NDA meetings with FDA on 12-Jan-1998 and 23-Sep-1998, the sponsor conducted the MICA (Michigan and California) and OHIO trials. On 01-Oct-1999, the sponsor submitted data from the MICA and OHIO trials together with data from two Japanese PK studies and an Australian study, and filed NDA 21-201 in DDDDP.
- On 29-Nov-1999, DDDDP suggested to the sponsor to withdraw the NDA because the PK studies lacked validated methods, to use radio-labelled polidocanol to determine the pharmacokinetics of the drug, and to develop an assay method to determine systemic levels of polidocanol. The NDA was withdrawn on 01-Dec-1999.
- There were more Pre-NDA meetings on 10-Oct-2001 and 21-Oct-2001 to discuss issues related to Chemistry, Pharmacokinetics and Clinical aspects of the trials.
- The NDA was re-filed on 10-Nov-2003, with subsequent NDA Amendments filed to address the issues related to Pharm-Tox (Amendments #1 dated 17-Nov-2003 and #3 dated 05-Dec-2003), Chemistry (Amendment #2 dated 24-Nov-2003) and Pharmacokinetics (Amendment #4 dated 09-Dec-2003). At the filing meeting, more review issues were found (requiring the sponsor to file Amendments #9 through 21).
- On 02-Aug-2004, NDA 21-201 for ASCLERA™ (polidocanol) was issued a "not approvable" letter by the Office of Drug Evaluation III, because
  (i) the efficacy of polidocanol was not demonstrated as superior or non-inferior to the reference drug Sotradecol®,
  (ii) there was little or no assessment of risk of deep vein thrombosis (DVT),

(iii) FDA GCP inspections revealed problems with data integrity at two of three sites inspected (MICA trial in Michigan and California); FDA inspection found the third site in Ohio (the OHIO trial) to have valid data, but it enrolled only 75 patients treated with the study drug, which was not adequate to evaluate safety issues,

(iv) controls were inadequate to prevent micro-organisms surviving the sterilization procedures, and

(v) the pivotal PK results did not meet *in vivo* bioavailability requirements under § 21 CFR 320.

- In Nov-2004, the Office of Generic Drugs approved sodium tetradecyl sulphate for treatment of varicose veins. The sponsor contended that this OGD approval had no regard for the safety concerns raised by DDDDP in the not approvable letter for polidocanol.
- This NDA 21-201 and related IND 35,139 were transferred from DDDDP to DCaRP in May, 2005.
- In the 18-May-2005 initial meeting between the sponsor and DCaRP, the Division suggested that the sponsor plan a clinical trial to resolve outstanding issues, principally to *submit documentation* to FDA in a prospective clinical trial at statistical probability level (p-value) way below 0.05 for efficacy, and to show (i) long-term safety data, including data related to DVT, in an adequate sample of patients (e.g., ICH guidelines require 1,500 patients to be studied for safety), (ii) durability of treatment effect (i.e., no re-canalization of the varicose vein after sclerosant treatment), and (iii) dose-response. The Division also encouraged the sponsor to determine if the product can be used for an additional clinical benefit besides cosmetics (e. g., decrease in pain).
- On 12-Aug-2005, Chemische Fabrik Kreussler & Co., GmbH submitted a tentative protoco (b) (4)

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- Following telephone conferences, the sponsor submitted a request for a SPA on 06-Mar-2006, in which they would incorporate the Division's advice to focus on safety, including DVT-screening. This resulted in the EASI (**E**fficacy and safety of **A**ethoxysklerol® (polidocanol) compared to **S**odium tetra-decyl sulfate and **I**sotonic saline (placebo) for the treatment of reticular veins and spider veins) trial submitted as the pivotal trial to demonstrate efficacy of polidocanol for this NDA.
- Regarding safety, the sponsor maintained that in >28 countries in Europe, Asia, Australia and South America where polidocanol had been used, no serious adverse safety reports had been recorded, and that an open-label Australian study comprising 34,878 limbs treated with polidocanol showed a small AE rate of 0.6% (707 AEs) including only 5 (0.1%) cases of DVT. However, the Division contended that these clinical studies did not screen for DVTs. The sponsor could not obtain the safety data from the Australian study for FDA to review.
- In support of the NDA, the sponsor committed to submit the safety data from the "French Registry" of 12,173 sclerotherapy treatments[1] including 5,434 sessions with liquid sclerosants (75% using polidocanol which allegedly demonstrated the safety of liquid sclerotherapy. The sponsor committed also to prospectively contact at least 700 patients treated with liquid polidocanol 0.5% and 1% to obtain data related to long term adverse events (from the time of the procedure to the time of the survey), using case report forms (CRFs) to transfer data from this prospective survey of patients in the French registry, and then perform their own safety analysis.

2.6 Other Relevant Background Information

Polidocanol was registered in Germany in 1966 as a sclerosing agent under the name Aethoxysklerol® (and re-approved in 2004). It is currently licensed for the treatment of varicose veins in 13 countries including Argentina, Austria, Belgium, Denmark, Finland, France, Germany, Italy, Luxembourg, the Netherlands, Spain, Sweden and Switzerland (but not in the United States), and is currently available in more than 50 countries.

Sotradecol® (active ingredient Sodium Tetradecyl Sulfate) was approved in 2004 by FDA (Table 1) for sclerotherapy of leg varices, including spider veins and reticular veins (Please see Section 2.2). In this NDA, Sotradecol® was used as a comparator.

Another sponsor has submitted an IND for polidocanol ***foam*** (Varisolve®) for the treatment of (b) (4)

Although frequently used off-label in the US for sclerotherapy of varicose veins, polidocanol in any form (liquid or foam) is not registered in the US.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sponsor submitted documentation (audit certificates) that all clinical trial sites that participated in the EASI were audited for data integrity. The CRO (b) (4) (b) (4) for the EASI study audited for integrity of the Trial Master File, and audited and certified the data integrity by performing quality control check for paper-based data entry.

To ensure data integrity, the Division suggested to the sponsor that a copy of the randomization code for all study centers be submitted to the Division ***before*** the EASI trial started. The sponsor submitted the randomization code to FDA which was maintained unopened until after the NDA was submitted to FDA for review. Because the nature of data collection was electronic, this action ensured the integrity of the randomization code had any electronic glitch occurred.

3.2 Compliance with Good Clinical Practices

One of the conditions based on which a previous NDA 21-201 for polidocanol was issued a "non approval" letter in 2004 was that "FDA GCP inspections revealed problems with data integrity or data quality at two of three sites inspected."

In November 2003, the sponsor submitted two previous trials which were carried out at three sites. At two of the three sites {MICA study in Southfield, **MI**chigan (John Pfeifer, M.D.) and La Jolla, **CA**lifornia (Mitchel Goldman, M.D.)}, FDA GCP inspections (assignment date 11-Mar-2004) revealed serious problems with data integrity. FDA inspection at the third site in Cincinnati, Ohio (the OHIO study, Joann Lohr, M.D.) found valid data, but this site enrolled only 75 patients treated with the study drug which was considered inadequate to evaluate safety issues.

Previous FDA GMP inspections also found that controls were inadequate to prevent micro-organisms surviving the sterilization procedures, and that pivotal PK results did not meet *in vivo* bioavailability requirements under 21 CFR 320.

The new pivotal efficacy data for this application comes from the EASI trial – a prospective, randomized, double-blind, placebo- and comparator-controlled, multicenter, clinical trial performed on 338 patients at 19 centers in Germany.

Long-term safety evaluation is made from data on 1,605 patients who had undergone 6,444 sessions of sclerotherapy, including 2,041 treatment sessions with liquid polidocanol, recorded in the French Polidocanol Registry 2008 (FPR 2008).

Based on (i) the above historical situation and (ii) the EASI trial, in which the efficacy and safety results were not significantly different at any center, a consult was made to DSI to request GCP inspections to verify data integrity of the following two centers that

enrolled the largest number of patients:

Table 2 Sites in the EASI trial which enrolled the largest number of patients

Center #	Clinical Investigator	Address in Germany	Number enrolled
13	Dr. med. Margrit Simon	Hauptstr. 131, 10827 Berlin	32
16	PD Dr. med. M. Stücker	St. Maria Hilf Krankenhaus, 44805 Bochum	29

As of the filing date today (16-Nov-2009) of this review, I have not received a clinical inspection summary from DSI. From my initial communications with DSI and with the FDA field investigator who conducted the GCP inspections in Germany, and my review of the Forms FDA 483s issued to the above two clinical investigators and copies of the exhibits provided to me by the FDA field investigator, my findings and inferences are as follows:

(A) there were protocol violations in the form of

(i) incorrect times of injections (e.g., injections were recorded before randomization times),

(ii) the protocol-specified number of injections per visit was exceeded for some patients, and

(iii) thrombophilia test results were not available for some patients before the injections, as required by the protocol.

(B) there were some record keeping deficiencies in that AEs such as hematoma or hyperpigmentation were reported not at the time of its occurrence but when the patient came for the next visit.

These do not appear to be serious 483 observations. The clinical investigators' verbal explanations of the incorrect times (that the computer clock and the wall clock showed different times by some minutes) appear plausible. The sponsor provided information that the protocol-specified maximum number of injections were exceeded in a few patients (please see section 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations) which could be attributed to injections of varicose veins outside the area of record for the study protocol.

I do not think that there are data integrity issues in a "systematic" manner. Even using the worst case scenario for these two sites and discarding their data from efficacy analyses, the efficacy outcome is not effected because polidocanol still wins over placebo with a very high level of statistical significance ($P<0.0001$).

3.3 Financial Disclosures

The sponsor submitted certification that all of the 19 clinical investigators who participated in the EASI study had no disclosable financial interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

An additional modern facility, called (b) (4), was constructed adjacent to the original (b) (4) facility. All of the equipment that had been used to manufacture ASCLERA were relocated and revalidated/requalified. This new facility is being inspected for GMP. The inspection findings are not yet available.

4.2 Clinical Microbiology

One of the conditions for which a previous NDA 21-201 for polidocanol was issued a "non approval" letter in 2004 was that "controls are inadequate to prevent micro-organisms surviving the sterilization procedures."

The sterility validation information on the polidocanol manufacturing process originally submitted in the NDA in July 2008 was not current due to transition from (b) (4) (b) (4) (old) facility) to the newly constructed (b) (4). The sponsor submitted that all of the sterilization processes – including performance requalification data summary from the relocated sterilizers (i.e., (b) (4) (b) (4)) showing successful sterilization and depyrogenation of containers, closures, filling equipment and components which come in direct contact with the product – and the associated equipment were re-qualified after installation at the new facility.

The review by the CMC microbiology team is not yet available at the time of filing this review.

4.3 Preclinical Pharmacology/Toxicology

There are no new pharm-tox issues. The pharm-tox review refers to the submission of 2003.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The action of polidocanol is chemical in nature and not pharmacological. Polidocanol is a non-ionic surfactant. The hydrophobic pole of the molecule attaches to the lipid cell membrane and disrupts the osmotic barrier of cells causing cell destruction. When injected intravenously, polidocanol at concentrations ranging from 0.5% to 3% induces endothelial damage with denudation of the vein lining. The absence of endothelial cells

results in failure of nitric oxide production, with loss of smooth muscle relaxation; venospasm then ensues. The exposed surface is highly thrombogenic; platelets aggregate at the site of damage and attach to the venous wall. Eventually, a dense network of platelets, cellular debris, and fibrin occludes the vessel. The vein is obliterated and is replaced later with connective fibrous tissue.

Polidocanol will attach to all cell membranes including red cells, and also to plasma proteins. When mixed with blood, polidocanol is rapidly deactivated by protein binding.

4.4.2 Pharmacodynamics

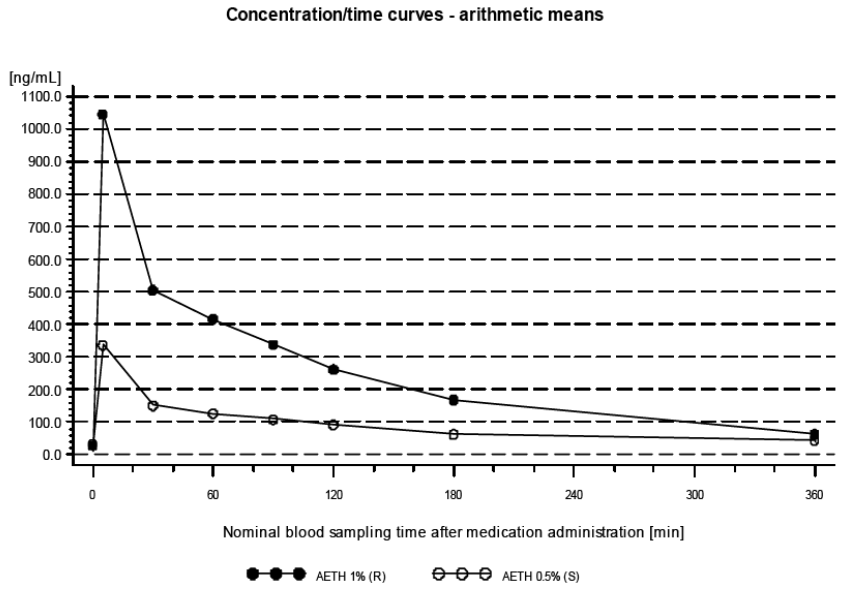
Not applicable.

4.4.3 Pharmacokinetics

One of the conditions for which a previous NDA 21-201 for polidocanol was issued a "non approval" letter in 2004 was that "pivotal pharmacokinetic results are not reliable to meet *in vivo* bioavailability requirements under 21 CFR 320."

In the EASI trial, 22 patients in Group C had extra blood samples taken at Visit 1 to assess plasma concentrations of polidocanol. At 5 minutes after injection in all patients, the maximum polidocanol plasma levels were detected (Figure 1), depending on the injected volume and concentration of Polidocanol. From 30 minutes to 3 hours after administration the values declined and returned to their initial values or were slightly above their initial values at 6 hours after application. At 6 hours after administration, the plasma concentration of polidocanol was <100 ng/ml in 20 of 22 cases (the other two values being 103.5 and 126.8 ng/ml).

Figure 1 Polidocanol concentrations in plasma



Dose proportionality for polidocanol 0.5% and 1% was not observed. The dose adjusted $AUC_{(0\text{-inf})}$ for polidocanol 0.5% was nearly three times higher compared to polidocanol 1%, and $t_{½}$ was approximately twofold higher. The mean values of the dose-adjusted C_{max} for polidocanol 0.5% and 1% were approximately similar (Table 3).

Table 3 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

Further pharmacokinetic information is being reviewed in detail by the clinical pharmacology reviewer; the Clin-Pharm review is not available at the time of filing this review.

5 Sources of Clinical Data

Tables of Studies/Clinical Trials

Table 4 shows a list of polidocanol trials submitted by the sponsor. Five trials are relevant to efficacy evaluation: EASI, OHIO, MICA, ASK-94-002 and ASK 96-001. Three other trials, ASK-97-01-00, AET-AS25/4 and AET-P2/1/US studied polidocanol at doses other than 0.5% and 1.0% intended for this indication. The French Registry Study is a survey type study to provide long-term safety data on patients after sclerotherapy with liquid polidocanol from the French Polidocanol Registry 2008 (FPR 2008).

Table 4 Number of patients involved in clinical trials of polidocanol

Study	Polidocanol*			Sotradecol®				Placebo (Saline)†			Total studied	Comments
	0.5% (S)	1% (R)	Total	0.25% (S)**	0.5% (R)**	1%† (S+R)	Total	(S)	(R)	Total		
Controlled, randomized, single-blind trials												
EASI	94	86	180	-	-	105	105	27	26	53	338	Pivotal trial
OHIO	25	25	50	25	25	-	50	-	-	-	150#	Also studied 3% polidocanol and 1.5% Sotradecol®
Total	119	111	230	25	25	105	155	27	26	53	438	Number studied for analysis of blinded studies
Open-label, concentration-controlled trials in Japan												
ASK-94-002§	18/20	44/50	62/70	-	-	-	-	-	-	-	161α	αAlso studied 2% and 3% polidocanol
ASK-96-001§	50/51	29/29	79/80	-	-	-	-	-	-	-	100β	βAlso studied 0.25% polidocanol
Total	68/71	73/79	141/150	-	-	-	-	-	-	-	141	Number studied in open-label trials
All clinical trials of polidocanol												
Grand Total	187	184	371	76	79	-	155	27	26	53	579	Number studied in **all** controlled trials
Trials not useful for efficacy analyses												
MICAΔ	29	31	60	33	32	-	65				179	*54 patients received 3% polidocanol and 1.5% sotradecol®*
ASK-97-01-00‡	-	-	-	-	-	-	-	-	-	-	*30*	***Only** studied **3.0%** polidocanol*
AET-AS25/4‡	-	-	-	-	-	-	-	-	-	-	*40*	***Only** studied **0.25%** polidocanol*
AET-P2/1/US	-	-	-	-	-	-	-	-	-	-	*10*	***Only** studied **2.0%** polidocanol*
French Registry	-	-	-	-	-	-	-	-	-	-	-	*Post-treatment survey for safety data only*

(S)= spider veins; (R)= reticular veins; *Patients enrolled in EASI, OHIO, ASK-94-002 and ASK-96-001;**Patients enrolled in EASI and OHIO; †Patients enrolled in EASI only; #includes 50 patients at other doses; §Open-label, drug concentration-controlled trials in Japan; αincludes 89 patients at other doses; βincludes 20 patients at other doses; ΔFDA GCP inspections revealed major data integrity issues, data not acceptable; ‡Open-label, uncontrolled, using doses other than 0.5% & 1.0%.

5.2 Review Strategy

For efficacy review of the EASI trial

One of the conditions for which a previous NDA 21-201 for polidocanol was issued a "non approval" letter in 2004 was that "the efficacy of polidocanol was not demonstrated as superior or non-inferior to the reference drug Sotradecol®."

For efficacy review, only the EASI trial and the OHIO trial have valid data to review. The EASI trial is the only study in the sponsor's submission which contains data alleged by the sponsor to show that polidocanol beats placebo. I will focus my efficacy review on the primary and secondary efficacy analyses in the pivotal EASI trial, and use descriptive efficacy analyses from the OHIO trial as supportive data.

From a clinical reviewer's perspective, I plan to determine if the EASI study demonstrates a "very high success rate (i.e., $p < 0.001$ or $p < 0.0001$)" for the primary efficacy endpoint which is a fairly objective endpoint of improvement in digital images (i.e., pre- versus post-treatment digital photograph evaluations by the investigator and two blinded experts, with rigorous control of the techniques and analyses).

For the EASI trial to be persuasive, I plan to determine if the results are positive for ***both*** (i) the improvement in digital images, and (ii) the subjective endpoint of patients' satisfaction with treatment.

I would consider the results more persuasive if the EASI trial data show statistical correlation between the primary efficacy endpoint (improvement in digital images) and the secondary endpoint of patients' satisfaction with treatment.

For safety review

One of the conditions for which a previous NDA 21-201 for polidocanol was issued a "non approval" letter in 2004 was that "there was little or no assessment of risk of deep vein thrombosis following injection with polidocanol."

To demonstrate safety related to deep vein thrombosis (DVT) which is known to occur largely during the first week after injection of sclerosant, I will focus my review of the EASI trial on the evaluation of ultrasound evaluations for DVT which were performed at Visit 1a (one week ± 3 days) and at Visit 4 (12 weeks ± 2 weeks) after evaluation of the primary efficacy endpoint). Safety data related to history of patients reporting leg pain, swelling, hospitalization and treatment for DVT will also be sought for; however, many DVTs are asymptomatic and, therefore, historical or symptom data in the EASI trial may under-report the incidence of DVT following treatment with polidocanol.

The Division suggested to the sponsor that >1,000 (ICH requires 1,500) patients need to be studied in clinical trials and followed for 1 year for safety. Since the EASI-Study enrolled a total of 338 patients of which only 155 patients were treated with polidocanol, we advised the sponsor to obtain more safety data by prospectively collecting post-treatment data from a substantial sub-sample of patients who had received polidocanol in the French registry, which had on record 12,173 sclerotherapy sessions for approximately 3,000 patients. The sponsor developed a standardized questionnaire to

collect data related to short and long-term sequale such as DVT and re-canalization (from the time of the sclerotherapy procedure to the time of the survey), and created CRFs to transfer this data for statistical analysis. This French Polidocanol Registry study provided long-term safety evaluation on patients after sclerotherapy with liquid polidocanol for Safety Review of this NDA (*please see section* 7.1.1 Studies/Clinical Trials Used to Evaluate Safety).

5.3 Discussion of Individual Studies/Clinical Trials

The **EASI trial** was a prospective randomized, placebo- and comparator-controlled, *double-blind*, comparative, multicenter study of 338 patients with C_1 varicose veins (reticular veins and spider veins) to determine the efficacy and safety of 0.5% and 1% polidocanol solution compared to Sotradecol® (sodium tetradecyl sulfate) and isotonic saline (placebo), conducted at 19 centers in Germany. Sotradecol® could not be blinded; to keep the investigator blinded, a non-blinded dedicated member of the study personnel not involved in study assessments prepared the syringe for injection and handed it over ready for use to the blinded investigator. The non-blinded member signed a form ensuring that he/she did not inform the investigator about the treatment.

The EASI trial is the main pivotal trial in NDA 21-201. The EASI trial had a sub-group (called Group C) at one center where patients had extra blood samples drawn at Visit 1 and at one week after the last varicose vein injection visit to determine the plasma polidocanol concentrations. This pharmacokinetic study in Group C was performed under open-label conditions.

Details of the EASI trial protocol are presented in Section 9.4.2 EASI trial.

Review of the primary efficacy endpoint and secondary efficacy endpoints in the EASI trial are presented in section:
6.1.4 Analysis of Primary Endpoint(s) and section
6.1.5 Analysis of Secondary Endpoints(s).

The **OHIO** trial was a single-center, randomized, double-blind, active-controlled trial conducted in the US to compare the efficacy of polidocanol to Sotradecol® in the treatment of varicose veins of diameter:

- ≤1 mm (50 patients randomized to receive polidocanol 0.5% or Sotradecol® 0.25%),
- >1 – 3 mm (50 patients randomized to receive polidocanol 1% or Sotradecol® 0.5%), and
- 3 – 6 mm (50 patients randomized to receive polidocanol 3% or Sotradecol® 1.5%).

Review of the efficacy data from the OHIO trial is presented in sections:
6.1.4 Analysis of Primary Endpoint(s) and
6.1.5 Analysis of Secondary Endpoints(s).

The **MICA** trial was also a randomized, double-blind, active-controlled trial to compare the efficacy of polidocanol to Sotradecol® in the treatment of varicose veins of diameter

≤1 mm, >1 – 3 mm, or 3 – 6 mm, conducted at two centers in the US, one in Southfield, Michigan and the other in La Jolla, California. FDA GCP inspections at both sites revealed major data integrity issues, and data were not acceptable; therefore, data from the MICA trial will not be reviewed.

There was ***no*** placebo group in either the OHIO or the MICA trial. At that point in time, there was no concept of performing a "non-inferiority" trial. Sotradecol® had not been approved by FDA at that time, and had not been studied against placebo; therefore, Sotradecol® cannot be used as a "historical control" to perform a non-inferiority analysis.

ASK-94-002 and **ASK 96-001** studies (Table 4) were open-label studies conducted in Japan; these studies had no placebo or active-comparator. Two other trials, **ASK-97-01-00** and **AET-AS25/4**, studied doses of polidocanol other than 0.5% and 1.0% intended for this indication.

The **French Polidocanol Registry** study was a survey type study to provide long-term safety evaluation on patients after sclerotherapy with liquid polidocanol from the French Polidocanol Registry 2008. Data from this provided the main information for Safety Review (*please see section* 5.2 Review Strategy *and section* 7.1.1 Studies/Clinical Trials Used to Evaluate Safety).

6 Review of Efficacy

Efficacy Summary

Efficacy data for the primary endpoint is derived from a single pivotal, placebo-and comparator-controlled, double-blind, multicenter, **EASI** trial conducted at 19 centers in Germany. The EASI trial randomized 338 patients with C_1 varicose veins (reticular veins and spider veins) to polidocanol (180 patients), Sotradecol® (105 patients) and placebo (53 patients). Patients with spider veins were treated with polidocanol 0.5% and those with reticular veins were treated with polidocanol 1%. Sotradecol® could not be blinded; a non-blinded member of the study personnel not involved in study assessments prepared the syringe for injection and handed it to the blinded investigator.

The 338 patients enrolled in the EASI trial included a subgroup of 22 patients (called Group C) treated open-label at one center (10 patients received polidocanol 1% and 12 received polidocanol 0.5%) to determine pharmacokinetic data.

The primary efficacy endpoint in the EASI trial was improvement of the treated veins on a 5-grade scale on standardized digital photographic images at 12 (± 2) weeks after the last injection evaluated by each investigator and two independent blinded medical experts (comparison of change from pre-treatment baseline between polidocanol and isotonic saline).

Of the 316 patients (not including the 22 patients in Group C), 313 patients (155 treated with polidocanol, 105 with Sotradecol®, and 53 with placebo) had valid assessments of digital images at 12 (± 2) weeks (full analysis (FA) data set). 47 patients in the FA data set were excluded due to protocol deviations; leaving 266 patients (135 treated with polidocanol, 84 with Sotradecol®, and 47 with placebo) which comprise the per protocol (PP) data set. Assuming that the effect of polidocanol 0.5% in spider veins is equal to that of polidocanol 1% in reticular veins, a pooled, stratified analysis of patients was done using stratified Wilcoxon-Mann-Whitney test on both the FA data set and the PP data set.

The primary efficacy analysis of the FA data set revealed statistically significant superiority of polidocanol over placebo for the mean *change* from pre-treatment baseline in digital photograph scores (5-grade scale) evaluated by the investigator and two independent medical experts at 12 (± 2) weeks (4.52 ± 0.65 for polidocanol vs. 2.19 ± 0.68 for placebo; $p<0.0001$). The same is true also for Sotradecol® (4.47 ± 0.74) vs. placebo (2.19 ± 0.68), suggesting adequate *assay sensitivity* of the EASI trial.

Similarly, for the PP data set, the primary efficacy analysis revealed statistically significant superiority of polidocanol over placebo for the mean *change* from pre-treatment baseline in digital photograph scores (5-grade scale) at 12 (± 2) weeks (4.55 ± 0.63 for polidocanol ™ vs. 2.09 ± 0.41 for placebo; $p<0.0001$). For the PP data set, too, the same is true for Sotradecol® (4.45 ± 0.75) vs placebo (2.09 ± 0.41), suggesting adequate *assay sensitivity* of the EASI trial.

This statistically significant superiority of polidocanol over placebo for the mean *change* in digital photograph scores at 12 (± 2) weeks from baseline was maintained at 26 weeks (6 months) providing objective documentation of sustained cosmetic benefit.

Patients' subjective perception of their satisfaction with treatment (on a scale of 1 to 5) also showed that a significantly ($p<0.0001$) larger proportion of patients treated with polidocanol were "satisfied" or "very satisfied" at 12 weeks (88%) and 26 weeks (84%), compared to patients treated with Sotradecol® (64% at 12 weeks and 63% at 26 weeks) or placebo (13% at 12 weeks and 11% at 26 weeks).

In addition, the Spearman's correlation coefficients of improvement in digital photographs with patients' satisfaction score were statistically significant.

The highly significant ($p<0.0001$) success rate found by objective photographic evaluations and the highly significant ($p<0.0001$) patient satisfaction rates which are significantly ($p=0.0381$ to $p<0.0001$) correlated are persuasive of the efficacy of polidocanol in the treatment of C_1 varicose veins (reticular and spider veins).

Many of the patients required more than one treatment session. Of 86 patients with reticular veins treated with 1% polidocanol, 38 (44.2%) patients had one treatment session, 30 (34.9%) patients had two treatment sessions, and 18 (20.9%) patients had three treatment sessions. Of 94 patients with spider veins who were injected with 0.5% polidocanol, 17 (18.1%) patients had one treatment session, 33 (35.1%) patients had two treatment sessions, and 44 (46.8%) patients had three treatment sessions.

At each treatment session, patients needed multiple injections: the *number of injections* of polidocanol 1% administered to patients with reticular veins ranged from 5.1 to 6.5, and that of polidocanol 0.5% administered to patients with spider veins ranged from 7.9 to 10.0 injections. The *mean±SD volume* injected in patients with reticular veins was 1.5 ± 0.5 ml of 1% polidocanol, and that in patients with spider veins was 1.1 ± 0.8 ml of 0.5% polidocanol.

The OHIO trial, a randomized, double-blind, active-controlled trial with valid data for efficacy evaluation in the earlier submission to FDA, did not have a placebo group. The results of the OHIO trial do not contribute to the regulatory decision to recommend approval which is based solely on the efficacy findings of the EASI trial. The OHIO trial does provide information that the efficacy (and safety) profile of polidocanol and Sotradecol® in patients in the United States appeared to be generally comparable with that observed in patients in Europe (the EASI trial).

6.1.1 Methods

As mentioned earlier in section 5.2 Review Strategy, I will focus my efficacy review on the primary and secondary efficacy analyses in the pivotal EASI trial, and use the descriptive analyses of efficacy data in the OHIO trial as supportive information.

Review of efficacy variables: In the pivotal EASI trial**,** the primary efficacy endpoint was improvement of treated veins on digital images at **12 (± 2) weeks** after the last injection

(comparison between polidocanol and isotonic saline) as evaluated by each investigator and two independent blinded medical experts using the following 5-grade scale, where

- 1 is “worse than before”
- 2 is “same as before”
- 3 is “moderate improvement”
- 4 is “good improvement”
- 5 is “complete treatment success”

The success rate was derived from the 5-grade-scale where

- **“***treatment success***”** was grade 4 or 5, and
- **“***treatment failure***”** was grade 1, 2 or 3 on the 5-point scale.

Statistical methods: The primary statistical hypothesis for efficacy was to show that polidocanol was superior to placebo. A pooled, stratified analysis of Groups S and R was done assuming that the effect of polidocanol 0.5% in spider veins is equal to the effect of polidocanol 1% in reticular veins.

Since the primary efficacy variable was the *change* in digital images of veins on a 5-grade scale at 12 weeks (± 2 weeks) after the last injection from pre-treatment digital images (comparison between polidocanol and placebo) no baseline-adjustment was necessary.

Only if the result of primary efficacy analysis was statistically significant were the following secondary endpoints tested at the same significance level in an ordered manner. The testing procedure stops once a non-significant result was found, and the remaining endpoints are to be compared descriptively only. The following ordered secondary endpoints were tested:

Comparison between polidocanol and placebo **12** (± 2) weeks after the last injection:

1) Patient satisfaction with the treatment.
2) Assessment of the treatment success.

Comparison between polidocanol and placebo **26** (± 4) weeks after the last injection:

3) The assessment of improvement of veins in digital photographs according to a 5-grade scale (the same statistical test were used as for the primary efficacy parameter)
4) Patient satisfaction with the treatment.
5) Assessment of the treatment success.

Comparison between polidocanol and Sotradecol® **12** (± 2) weeks after the last injection:

6) The assessment of improvement of veins in digital photographs according to a 5-grade scale
7) Patient satisfaction with the treatment.
8) Assessment of the treatment success.

Comparison between polidocanol and Sotradecol® **26** (± 4) weeks after the last

injection:

9) The assessment of improvement of veins in digital photographs according to a 5-grade scale
10) Patient satisfaction with the treatment.
11) Assessment of the treatment success.

The test procedure for the primary efficacy parameter was the stratified Wilcoxon-Mann-Whitney test. For analysis of the secondary efficacy parameters the Wilcoxon-Mann-Whitney test and the exact test of Fisher were used.

Group C patients were not included and they were not considered for efficacy analyses.

Statistical data sets: The data were analyzed using the following data sets (Table 5).

Table 5 Number of patients is statistical data sets

Data set	Polidocanol	Sotradecol®	Placebo	Total
Safety data set	180	105	53	338*
Full analysis (FA) data set	155	105	53	313
Per Protocol (PP) data set	135	84	47	266

*22 patients were in Group C for determination of plasma polidocanol concentrations

Safety data set: This is the subset of patients who were randomized and received study medication regardless of any protocol violations. Group C patients (for determination of plasma polidocanol concentrations) are included here.

Full analysis (FA) data set: This is the subset of patients who were randomized and received study medication, and had valid assessment of digital photographs at 12 weeks. Patients with relevant protocol deviations were included into this dataset. Group C patients were not included here and not considered for the efficacy analysis.

Per Protocol (PP) data set: This is the subset of patients who were randomized and received study medication, had valid assessment of digital photographs at 12 weeks, and adhered to all protocol conditions.

6.1.2 Demographics

The demographics of the EASI trial (safety data set) are summarized in Table 6.

All treatment groups had similar demographic characteristics, with a mean age of the study participants of 43.7 ± 11.6 years (mean ± SD).

The majority of patients were female Caucasians.

Patients were on average 168 ± 6.7 cm tall and weighed 67 ± 11 kg, with a relatively normal mean body mass index of 23.7 ±3.6 kg/m².

The majority (65%) of patients had never smoked; 12% were ex-smokers and 23% were smokers.

Table 6 Demographic data (safety data set) of patients in EASI trial

	Aethoxysklerol® (N=180)	Sotradecol® (N=105)	Placebo (N=53)	Total (N=338)	p-value
Gender					
male	8 (4%)	3 (3%)	0 (0%)	11 (3%)	0.336
female	172 (96%)	102 (97%)	53 (100%)	327 (97%)	
Age on signing informed consent [years]					
Mean	44.0	43.2	43.9	43.7	0.981
SD	11.6	10.7	13.2	11.6	
Min	19	19	19	19	
Max	69	70	66	70	
18 - 25 yrs	11 (6%)	7 (7%)	6 (11%)	24 (7%)	0.773
26 - 40 yrs	58 (32%)	31 (30%)	12 (23%)	101 (30%)	
41 - 65 yrs	105 (58%)	64 (61%)	33 (62%)	202 (60%)	
>65 years	6 (3%)	3 (3%)	2 (4%)	11 (3%)	
Height [cm]					
Mean	168.0	166.9	167.3	167.5	0.491
SD	6.6	6.9	6.8	6.7	
Min	150	151	146	146	
Max	189	189	180	189	
Weight [kg]					
Mean	66.96	66.11	66.51	66.63	0.882
SD	10.48	11.08	13.18	11.10	
Min	49.0	48.0	46.0	46.0	
Max	104.0	93.0	113.0	113.0	

51% of the patients were included for a sclerotherapy of their spider veins and 49% for sclerotherapy of their reticular veins.

In 46% of the patients the right leg was treated and for 54% the left leg.

The most frequent treatment area was the back of knee (31%), followed by the outer upper part of the lower leg (10%) and the back of the upper part of the lower leg (10%).

The demographic data of patients in the supportive OHIO trial is summarized in Table 7.

There was only one male patient, so the information for gender is not shown.

While patients randomized to polidocanol were significantly older than patients randomized to Sotradecol® in (i) ≤1 mm vein-size group (46.0 years *vs.* 38.4 years, p=0.014) and (ii) >3-6 mm vein-size group (44.4 years *vs.* 37.7 years, p=0.023), this difference in was not clinically significant. There were no statistically significant differences between treatment groups in weight or height.

Table 7 Demographic data of patients in OHIO trial

Variable	Vein size ≤1 mm		p-value+	Vein size >1-3 mm		p-value	Vein size >3-6 mm		p-value
	A* N=21	B* N=25		A N=23	B N=23		A N=25	B N=25	
AGE (years)									
Mean	38.4	46.0	**0.014**#	40.3	39.3	0.7215	37.7	44.4	**0.023**#
STD	10.9	9.5		10.9	7.7		10.2	9.9	
Min	22	21		24	26		22	24	
Max	58	64		62	57		58	65	
HEIGHT (inches)									
Mean	65.2	64.9	0.630	65.2	65.5	0.6109	66.0	66.1	0.930
STD	1.9	2.3		2.0	2.7		2.2	2.6	
Min	62	60.5		61	60.8		61.5	63	
Max	70	69.3		69	71		70.3	73.5	
WEIGHT (pounds)									
Mean	141.5	148.4	0.323	152.0	155.3	0.7574	154.2	155.9	0.831
STD	21.3	24.5		42.8	27.0		29.8	27.2	
Min	115.5	93		109	118.8		113	112	
Max	197	214		275	215		235	210	

*A: Sotradecol®; B: polidocanol; +Two-sample t-test of treatment with Sotradecol® (A) and polidocanol (B); #p values in bold are significant at 0.05 level.

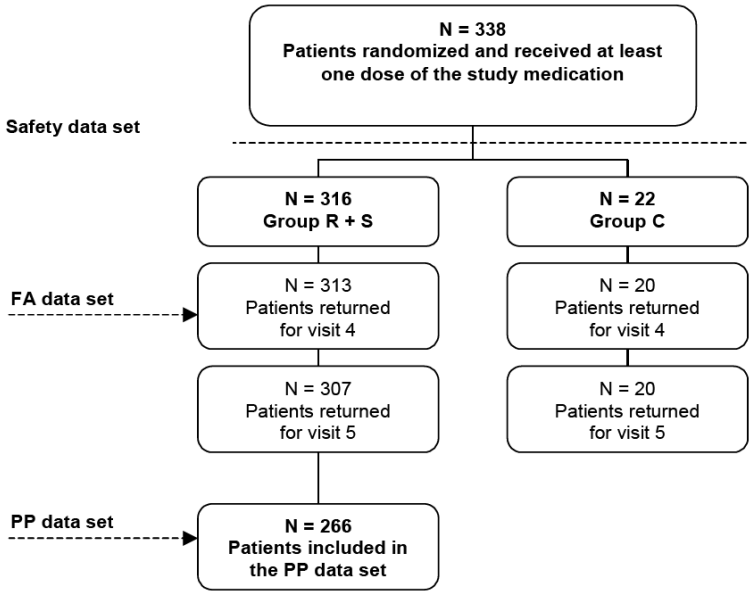
6.1.3 Subject Disposition

A total of 338 patients were enrolled in the EASI trial (Figure 2) and received at least one dose of the study medication ("safety data set"). At the beginning of the study a larger number of patients with spider veins as compared to those with reticular veins were enrolled. Due to this initial imbalance in strata, patients with reticular veins were actively sought to participate in the study, resulting in a higher total number of patients.

Of these 338 patients (Figure 2), 22 patients were included in Group C (for determination of plasma polidocanol concentrations). Group C patients were not included in the FA or PP data sets and were not considered for the efficacy analysis.

The remaining 316 patients were included in Groups R and S. 313 of these patients had valid assessments of digital photographs at 12 weeks (= "full analysis data set). For the "per protocol data set" 47 patients of the FA data set were excluded due to protocol deviations so that the PP data set comprised 266 patients.

Figure 2 Disposition of patients in EASI trial



Thirteen patients discontinued the study prematurely, 4 patients in Group C and 9 patients in Groups R and S. The most frequent reasons for study termination were that the patients were lost to follow up (N=5 patients), non-compliance with the study protocol (N=4) and adverse events (N=2).

The study was conducted in 19 study centers in Germany. The number of patients recruited per center ranged between 3 and 32. The first patient was enrolled on 04 December 2006 and the last patient completed the study on 10 December 2007.

The mean duration of the study period was 201 ± 29 days (mean ± SD; range: 31 – 314 days, safety data set). The mean time between:

- the screening visit and Visit 1 was 11 ± 3.8 days (mean ± SD),
- Visit 1 and Visit 2 was 21.2 ± 4.3 days,
- Visit 1 and Visit 3 was 21.1 ± 5.0 days,
- between the last injection (at visit 1, 2 or 3) and Visit 4 was 85.0 ± 13.5 days, and
- between the last injection (at visit 1, 2 or 3) and Visit 5 180.1 ± 21.5 days.

The duration of the study period and the time between visits was similar for all treatment groups.

The disposition of patients in the OHIO trial is summarized in Table 8. 73/75 (97.3%) patients in the polidocanol group, completed the study per protocol, while in the Sotradecol® group, 69/75 (92.0%) patients completed the study per protocol. Two (2.7%) patients in each group were lost to follow-up. Four (5.3%) patients in the Sotradecol® group received study drug that was diluted with an incorrect saline concentration.

Table 8 Disposition of patients in OHIO trial

		Polidocanol	Sotradecol®
Spider veins (≤1 mm)			
Number of patients		25	25
Completed the study: n (%)	**Yes**	25 (100%)	21 (84%)
	No	0	4 (16%)
Reticular veins (1 - 3 mm)			
Number of patients		25	25
Completed the study: n (%)	**Yes**	23 (92%)	23 (92%)
	No	2 (8%)	2 (8%)
Varicose veins (>3 – 6 mm)			
Number of patients		25	25
Completed the study: n (%)	**Yes**	25 (100%)	25 (100%)
	No	0	0

6.1.4 Analysis of Primary Endpoint(s)

EASI trial

The primary efficacy analysis revealed statistically significant ($p<0.0001$) superiority of polidocanol over placebo (isotonic saline) in the improvement of veins evaluated by the change in mean values (5-grade scale) of the digital photographs at Visit 4 from pre-treatment mean values of the digital photographs at Visit1 (Table 9). The results with the per protocol data set were consistent with the results of the full analysis data set.

Table 9 Improvement of veins in digital photographs after 12 weeks (Visit 4)

Full Analysis data set			
Grade	**Polidocanol (N=155)**	**Sotradecol®** (N=105)	**Placebo** (N=53)
Mean ± SD (N)	4.52* ± 0.65 (154)	4.47*± 0.74 (104)	2.19 ± 0.68 (53)
1	0	1 (1.0%)	0
2	3 (1.9%)	1 (1.0%)	49 (92.5%)
3	4 (2.6%)	6 (5.7%)	0 (0.0%)
4	56 (36.1%)	36 (34.3%)	2 (3.8%)
4.5**	1 (0.6%)	0	0
5	90 (58.1%)	60 (57.1%)	2 (3.8%)
Missing	1 (0.6%)	1 (1.0%)	0
Per Protocol data set			
Grade	**Polidocanol (N=135)**	**Sotradecol®** (N=84)	**Placebo** (N=47)
Mean ± SD (N)	4.55* ± 0.63 (135)	4.45*± 0.75 (84)	2.09 ± 0.41 (47)
1	0	1 (1.2%)	0
2	2 (1.5%)	1 (1.2%)	45 (95.7%)
3	4 (3.0%)	4 (4.8%)	0
4	47 (34.8%)	31 (36.9%)	2 (4.3%)
5	82 (60.7%)	47 (56.0%)	0

*p <0.0001 compared to placebo (Wilcoxon-Mann-Whitney test); **For patient 437 the evaluation of one of the medical experts was not available and therefore the median of the evaluation of the investigator and one of the medical experts was 4.5.

The same is true also for Sotradecol® compared to placebo, which can be considered as suggesting adequate assay sensitivity of the EASI trial.

For the majority of patients treated with polidocanol 94.8% of the FA data set; 95.5% of the PP data set) or Sotradecol® (91.4% of the FA data set; 92.9% of the PP data set) good improvement of the veins (grade 4) or complete treatment success (grade 5) was observed at Visit 4, whereas, for 92.5% (FA data set) or 95.7% (PP data set) of patients treated with placebo no change (grade 2) was reported (Table 9).

Reviewer's comments: The primary efficacy endpoint is susceptible to bias because the results are technique-dependent, and the interpretation involves subjective elements. Particularly, the digital photographic techniques must be adequately standardized (for equipment, position, lighting) and the examinations and readings made in a standardized blinded manner by independent third parties. My examination of several pre- and post-treatment digital photographs submitted on CDs shows that the digital photographs were well-standardized and well-produced.

As for disagreements in the evaluations of digital images that result twice with a difference of >2 points between the investigator and one/more of the experts, we had suggested that these evaluations should NOT be deleted, but assigned the worst case scenario, i.e., if the patient is assigned one of the polidocanol doses, the evaluation should be adjudicated a "failure," and if the patient is assigned sodium tetradecyl sulphate or normal saline, the evaluation should be adjudicated a "success." The sponsor decided to delete these evaluations. However, this happened with only one patient. I do not think that it would have any effect on the statistical evaluation of the primary endpoint for either the Full Analysis data set or the Per Protocol data set.

The OHIO trial

The primary efficacy variable in the OHIO trial was the disappearance of varicosities, which was determined by a blinded panel of 3 vascular surgeons, who made their determinations on the basis of coded photographs.

Table 10 summarizes the results of the primary efficacy variable for the 3 vein sizes. The upper panel of Table 10 presents categorical results for complete disappearance (i.e., veins for which the panel of vascular surgeons gave a score of 5 ("complete disappearance") were classified as "yes" on this variable; all other received a classification of "no"). (Reviewer's *comment: This grading scale is different from that used for the EASI trial*.)

The lower panel of Table 10 is a summary of the disappearance of varicosities scores based upon the 5-point scale, including a difference score based on the least square means.

Table 10 Disappearance of varicosities *4 weeks* after treatment in OHIO trial

	Polidocanol	Sotradecol®	Least square difference
Spider veins (≤1 mm)			
Number of patients	25	21	
Disappeared (n,%): Yes	4 (16.0%)	5 (23.8%)	
No	21 (84.0%)	16 (76.2%)	
Disappearance* score: Mean (SD)	3.96 (0.83)	4.30 (0.50)	-0.344 (0.21)
Min ~ Max	1.33 ~ 5	3.33 ~ 5	
p value# (Confidence interval)	0.104 (-0.072 – 0.760)		
Reticular veins (1 - 3 mm)			
Number of patients	23	23	
Disappeared (n,%): Yes	6 (26.1%)	3 (13.0%)	
No	17 (73.9%)	20 (87.0%)	
Disappearance* score: Mean (SD)	4.28 (0.89)	4.00 (0.83)	0.275 (0.21)
Min ~ Max	1.67 ~ 5	1.50 ~ 5	
p value# (Confidence interval)	0.191 (-0.690 – 0.139)		
Varicose veins (>3 – 6 mm)			
Number of patients	25	25	
Disappeared (n,%): Yes	[redacted]	[redacted]	
No	[redacted]	[redacted]	
Disappearance* score: Mean (SD)	[redacted]	[redacted]	[redacted]
Min ~ Max	[redacted]	[redacted]	
p value# (Confidence interval)	[redacted]		

*Disappearance (1-5 scale): 1=worse than before, 2=same as before, 3=the minority disappeared, 4=the majority disappeared, 5=complete disappearance of varicosities; #Treatment with POLIDOCANOL® compared with Sotradecol® using 2-way ANOVA.

*Reviewer's comment: While both drugs caused the disappearance of relatively similar number of the varicosities that were treated, no conclusion can be made with regard to any statistically significant difference or therapeutic equivalence between the 2 drugs for any vein size (or for all vein sizes combined) for this variable. It appears that the sponsor realized from the OHIO trial that using a composite score of 4 and 5 to determine "improvement" would be more likely to produce a positive result; they used this information in the EASI trial (*Table 9*).*

6.1.5 Analysis of Secondary Endpoints(s)

I will review the protocol-specified secondary endpoints in the order that they were defined *a priori* in the statistical analysis plan, but will show the Visit 4 (Week 12) and Visit 5 (Week 26) results together where appropriate.

Patient satisfaction and estimation of drug: At Visits 4 and 5 the patients received the digital images of the treatment area taken at Visit 1 and were asked to rate their satisfaction with the current treatment using a verbal rating scale, where 1 was "very unsatisfied" and 5 was "very satisfied". The patients were also asked for their estimation what drug (one of the liquid sclerosants or placebo) they thought they have received.

Table 11 shows that the majority of patients who were treated with polidocanol were "satisfied" or "very satisfied" with the treatment at Visit 4 (88%) and Visit 5 (84%), which was significantly ($p<0.0001$) higher than the number of patients who were satisfied or very satisfied with the treatment for Sotradecol® (64% at Visit 4 and 63% at Visit 5; $p<0.0001$) or placebo (13% at Visit 4 and 11% at Visit 5; $p<0.0001$).

Table 11 Patient satisfaction after 12 wk (Visit 4) and 26 wk (Visit 5) - FA data set

	Polidocanol (N=155)	**Sotradecol®** (N=105)	**Placebo** (N=53)
Patient satisfaction with treatment after 12 weeks (Visit 4)			
Very unsatisfied	2 (1.3%)	12 (11.4%)	35 (66.0%)
Somewhat unsatisfied	5 (3.2%)	14 (13.3%)	9 (17.0%)
Slightly satisfied	12 (7.8%)	12 (11.4%)	2 (3.8%)
Satisfied	62 (40.3%)	43 (41.0%)	4 (7.5%)
Very satisfied	73 (47.4%)	24 (22.9%)	3 (5.7%)
Missing	1 (0.6%)	0	0
Patient satisfaction with treatment after 26 weeks (Visit 5)			
Very unsatisfied	7 (4.5%)	19 (18.1%)	36 (67.9%)
Somewhat unsatisfied	6 (3.9%)	9 (8.6%)	11 (20.8%)
Slightly satisfied	12 (7.7%)	11 (10.5%)	0
Satisfied	58 (37.4%)	37 (35.2%)	3 (5.7%)
Very satisfied	72 (46.5%)	29 (27.6%)	3 (5.7%)

Table 12 Patient estimation of drug at 12 wk (Visit 4) and 26 wk (Visit 5) - FA data set

	Polidocanol (N=155)	**Sotradecol®** (N=105)	**Placebo** (N=53)
Patient estimation of treatment after 12 weeks (Visit 4)			
Sclerosant	147 (95.5%)	100 (95.2%)	9 (17.0%)
Placebo	7 (4.5%)	5 (4.8%)	44 (83.0%)
Missing	1 (0.6%)	0	0
Patient estimation of treatment after 26 weeks (Visit 5)			
Sclerosant	146 (94.2%)	100 (95.2%)	6 (11.3%)
Placebo	9 (5.8%)	5 (4.8%)	47 (88.7%)

At Visits 4 and 5 approximately 95% of the patients, who received treatment with polidocanol or Sotradecol®, stated that they thought they have received the active treatment, and 83% (Visit 4) or 89% (Visit 5) of the patients treated with placebo were right with their estimation that they have received placebo (Table 12).

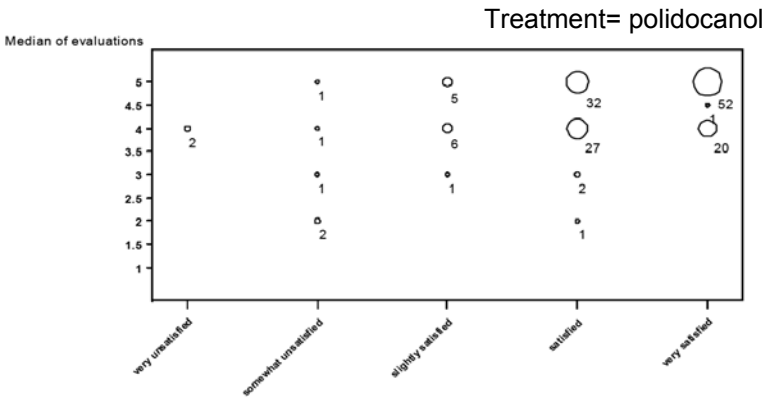
Correlation of improvement of veins and patient satisfaction: Table 13 shows the Spearman correlation coefficients and their significance between the patient satisfaction scores and the improvement of the veins according to the 5-grade scale as assessed by the investigator and two independent blinded medical experts. These correlation coefficients and p-values indicate that the improvement of the veins correlated moderately and positively with the patient satisfaction for polidocanol and placebo at Visit 4 and for all treatments at Visit 5.

Table 13 Correlation coefficients of improvement of veins with patient satisfaction at wk 12 (Visit 4) and wk 26 (Visit 5)

Treatment	Spearman Correlation Coefficient	p value
At 12 weeks (Visit 4)		
Polidocanol	0.31434	**<0.0001**
Placebo	0.47078	**0.0004**
Sotradecol®	0.10592	0.2846
Total	0.50456	**<0.0001**
At 26 weeks (Visit 5)		
Polidocanol	0.32794	**<0.0001**
Placebo	0.28573	**0.0381**
Sotradecol®	0.22554	**0.0207**
Total	0.51716	**<0.0001**

Source: Section 14.4.2.14.1

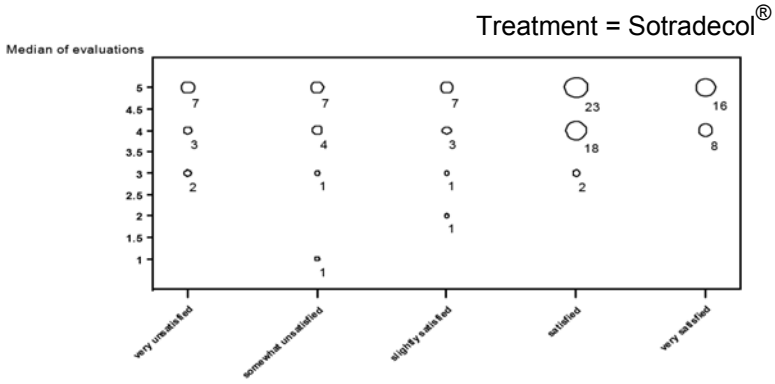
Figure 3 Correlation of improvement of veins with patient satisfaction at Week 12 (Visit 4) for polidocanol - FA data set by treatment



(Source: Section 14.4.2.14.1)

The correlation of the two variables for polidocanol was much more pronounced (Figure 3) than their correlation for Sotradecol® (Figure 4).

Figure 4 Correlation of improvement of veins with patient satisfaction at week 12 (Visit 4) for Sotradecol®, FA data set by treatment



(Source: Section 14.4.2.14.1)

Reviewer's comments: As stated earlier, to be persuasive the results must be positive for BOTH (i) improvement in digital images (pre-versus post-treatment) evaluated by the investigator and blinded experts, with rigorous control of the techniques and analyses, and (ii) a subjective finding of patient satisfaction with treatment. The EASI studied showed that the results for both of these endpoints are positive.

The correlation between the improvement of the veins and the patient satisfaction is not pronounced, because the categories of the 5-grade scale for the assessment by the investigator and the categories of the verbal rating scale for the assessment of the patient satisfaction do not match exactly, i.e. a patient with 'complete treatment success' may be 'satisfied' or 'very satisfied' with the treatment. However, also other factors, e.g. subjective rating by the patient, could have an influence on the variables.

The evaluation of the investigator and the medical experts was based on objective criteria (i.e., photographic evaluations), whereas the patients' rating of their satisfaction with the treatment was subjective and could also include their experience of adverse events or local symptoms, etc. Therefore, the results of the correlation analyses appear to suggest that patients treated with polidocanol were more satisfied with their treatment compared to Sotradecol® because of a better safety profile of polidocanol.

However, the comparison between polidocanol and Sotradecol® in terms of the improvement of the veins 12 weeks (± 2 weeks) after the last injection showed no significant differences. As the a priori ordered hypothesis testing was applied, the remaining comparisons of polidocanol and Sotradecol® could only be made descriptively and no confirmatory testing could be applied. Thus, patient satisfaction with the treatment after 12 (± 2) weeks and after 26 (± 4) weeks, which showed a descriptively significant superiority of the treatment with polidocanol as compared to Sotradecol® (Table 11) could not be considered a statistically significant finding.

Treatment success: The treatment success rates were derived from the assessment of the 5-grade-scale where grades 4 or 5 on the 5-point scale were defined as treatment success and grades 1, 2 or 3 were defined as treatment failure. The treatment success rates (number of patients with treatment success) for polidocanol were 96% at Visit 4 and 95% at Visit 5 (Table 14), being significantly higher compared to those seen for placebo (p value < 0.0001).

Table 14 Treatment success rates at 12 wk (Visit 4) and 26 wk (Visit 5) – FA data set

Treatment success?*	**Polidocanol** (N=155)	**Sotradecol®** (N=105)	**Placebo** (N=53)
At 12 weeks (Visit 4)			
Yes	147 (94.8%)**	97 (92.4%)**	4 (7.5%)
No	7 (4.5%)	8 (7.6%)	49 (92.5%)
Missing	1 (0.6%)	0	0
At 26 weeks (Visit 5)			
Yes	147 (94.8%)**	96 (91.4%)**	3 (5.7%)
No	8 (5.2%)	9 (8.6%)	50 (94.3%)

*Treatment success: Yes= Grade 4 to 5, No= Grade 1 to 3; derived from median of evaluation; **p<0.0001 compared to placebo.

The treatment success rates for Sotradecol® were 92% and 91% (Visits 4 and 5, respectively, Table 14), which were slightly lower than those for polidocanol, but significantly higher compared to placebo (p value < 0.0001). The comparison between polidocanol and Sotradecol®, however, revealed no statistically significant differences in treatment success.

Digital photographic assessment of improvement of veins after 26 weeks (Visit 5): The findings of digital photographic assessment of improvement of veins 26 weeks after treatment are shown in Table 15.

Table 15 Improvement of veins in digital photographs at 26 wk (Visit 5)

Full Analysis data set			
Grade	**Polidocanol** (N=155)	**Sotradecol®** (N=105)	**Placebo** (N=53)
Mean ± SD (N)	4.54* ± 0.67 (155)	4.45*± 0.77 (105)	2.19 ± 0.68 (53)
1	0	1 (1.0%)	0
2	4 (2.6%)	2 (1.9%)	48 (90.6%)
3	4 (2.6%)	6 (5.7%)	2 (3.8%)
4	51 (32.9%)	36 (34.3%)	0
4.5	2 (1.3%)	0	0
5	94 (60.6%)	60 (57.1%)	3 (5.7%)
Per Protocol data set			
Grade	**Polidocanol** (N=135)	**Sotradecol®** (N=84)	**Placebo** (N=47)
Mean ± SD (N)	4.55* ± 0.69 (135)	4.51*± 0.77 (84)	2.11 ± 0.48 (47)
1	0	1 (1.2%)	0
2	4 (3.0%)	2 (2.4%)	44 (93.6%)
3	3 (2.2%)	2 (2.4%)	2 (4.3%)
4	42 (31.1%)	27 (32.1%)	0
4.5**	1 (0.7%)	0	0
5	85 (63.0%)	52 (61.9%)	1 (2.1%)

*p <0.0001 compared to placebo (Wilcoxon-Mann-Whitney test); **For patient 437 the evaluation of one of the medical experts was not available and therefore the median of the evaluation of the investigator and one of the medical experts was 4.5.

The mean values for patients treated with polidocanol were 4.45 ± 0.67 (FA) and 4.55 ± 0.69 (PP), and, for patients treated with Sotradecol®, 4.45 ± 0.77 (FA) and 4.51 ± 0.77 (PP) at 26 weeks (Visit 5). The improvement of veins in patients treated with polidocanol or Sotradecol® was significantly higher than those treated placebo which had mean values of 2.19 ± 0.68 (FA) and 2.11 ± 0.48 (PP) (p value < 0.0001). No significant differences between polidocanol and Sotradecol® were observed at Visit 4 or Visit 5.

Reviewer's comments: The secondary statistical analysis supported the notion that polidocanol was significantly 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, and

5) Treatment success 26 (± 4) weeks after the last injection

While no statistical measure to account for multiple comparisons was pre-specified in the statistical analysis plan, the statistical analysis plan did state that the above secondary endpoints were to be performed only if the results of the primary efficacy analysis was statistically significant, and then the secondary endpoint results were to be tested in an ordered manner and to be stopped once a non-significant result was found. The secondary analyses continued to show statistically significant differences at p<0.001 compared to placebo; thus, I do not think there is a need to use statistical procedures to adjust for multiple comparisons.

Secondary endpoints in OHIO trial: Secondary variables were (i) overall clinical improvement and (ii) overall patient satisfaction.

The overall clinical improvement was determined by a panel of 3 vascular surgeons who evaluated the treatment area by comparing photographs taken prior to treatment with those taken 16 weeks after the final treatment, and assigning scores ranging from 0 to 10 (where 0= no improvement or worse than before, and 10= perfect cosmetic result). The grouping of these scores were: 0 – 2 = poor, 2 – 4 = fair, 4 – 6 = moderate, 6 – 8 = good and 8 – 10 = excellent. There were overlapping of scores for groups.

Each evaluator graded the photographs by comparing and evaluating the following 3 variables: (i) vein disappearance, (ii) hyperpigmentation, and (iii) neovascularization (called matting in CRF). Although hyperpigmentation and neovascularization were independently analyzed as adverse events, they were taken into consideration when judging the overall clinical improvement of the treated area. The average of the clinical improvement scores from the 3 evaluators was the basis for the analyses of this secondary efficacy variable. The overall clinical improvement for patients in the two treatment groups is summarized in Table 16.

Table 16 Clinical improvement in OHIO trial

		Polidocanol	Sotradecol®
Spider veins (≤1 mm)			
Number of patients		25	21
Clinical improvement* score:	**Mean (SD)**	6.70 (2.10)	6.89 (2.18)
	Min ~ Max	0.83 ~ 9.67	0.83 ~ 9.83
Reticular veins (1 - 3 mm)			
Number of patients		23	23
Clinical improvement* score:	**Mean (SD)**	7.00 (2.44)	5.55 (1.94)
	Min ~ Max	0.67 ~ 9.67	1.33 ~ 8.83
Varicose veins (>3 – 6 mm)			
Number of patients		25	25
Clinical improvement* score:	**Mean (SD)**		
	Min ~ Max	(b) (4)	(b) (4)

*Clinical improvement (0-10 scale): 0=no improvement or worse than before, to 10=perfect cosmetic result; categorically, 0-2: poor, 2-4: fair, 4-6: moderate, 6-8: good, 8-10: excellent.

Reviewer's comment: Using an ANOVA model containing treatment, vein-size and treatment-by-vein size interaction, the analyses found that neither the effect of treatment nor effect of vein size was significant. It is possible that there were too few

patients enrolled in each treatment group to be able to show any statistically significant differences.

The overall patient satisfaction was based on a 4-point scale where 1 = unsatisfied, 2 = moderately satisfied, 3 = satisfied, and 4 = very satisfied. At the final visit, the patients completed a CRF, which included their degree of overall satisfaction with the treatment.

Table 17 Patient satisfaction in OHIO trial

	Polidocanol	Sotradecol®
Spider veins (≤1 mm)		
Number of patients	25	21
Unsatisfied: n (%)	3 (12.00)	3 (14.29)
Moderately satisfied: n (%)	6 (24.00)	4 (19.05)
Satisfied: n (%)	4 (16.00)	5 (23.81)
Very satisfied: n (%)	12 (48.00)	9 (42.86)
Reticular veins (1 - 3 mm)		
Number of patients	23	23
Unsatisfied: n (%)	0	3 (13.04)
Moderately satisfied: n (%)	2 (8.70)	5 (21.74)
Satisfied: n (%)	4 (17.39)	8 (34.78)
Very satisfied: n (%)	17 (73.91)	7 (30.43)
Varicose veins (>3 – 6 mm)		
Number of patients	25	25
Unsatisfied: n (%)	[redacted]	(
Moderately satisfied: n (%)	[redacted]	b
Satisfied: n (%)	[redacted]	[redacted]
Very satisfied: n (%)	[redacted]	[redacted]

*CMH (Cochran-Mantel-Haenszel) test after controlling for vein size.

There were no significant differences in the categorical distribution of patient satisfaction between polidocanol and Sotradecol for any vein size (Table 17).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dose of polidocanol used in the EASI study was based on the approved dose for polidocanol licensed in Germany (as Aethoxysklerol®) [redacted]. The concentration of polidocanol was dependent on the diameter of the C_1 vein to be treated: i.e.,

- C_1 spider veins (diameter <1 mm) were injected with 0.5% polidocanol (0.1 to 0.3 ml per injection up to 16 injections per treatment day); The maximum dose allowed per treatment session was 4.8 ml (24 mg) of polidocanol 0.5%.
- C_1 reticular veins (diameter 1 ~ 3 mm) were injected with 1% polidocanol (0.3 ml per injection up to 8 injections (24 mg) per treatment day).

To maintain blinding, the maximum dose allowed for Sotradecol® 1% was also 2.4 ml in the R group and 4.8 ml in the S group for the maximum of 8 or 16 injections per

treatment session, respectively. This was below the licensed maximum dose stated in the package leaflet for Sotradecol® which allowed 1% or 3% Sotradecol® to be used at a maximal volume of 10 ml per treatment session.

Table 18 shows the information related to dosing of the study drugs used in EASI trial.

Table 18 Protocol-specified doses of liquid sclerosant in EASI trial

	Polidocanol					Sotradecol®				
	Conc	**Vol per inj**	**# inj per session**	**Max vol**	**Max dose**	**Conc**	**Vol per inj**	**# inj per session**	**Max vol**	**Max dose**
Spider veins	0.5%	0.1 ~ 0.3 ml	16 (max)	4.8 ml	24 mg	1%	0.1 ~ 0.3 ml	16 (max)	4.8 ml	48 mg
Reticular veins	1%	0.3 ml	8 (max)	2.4 ml	24 mg	1%	0.3 ml	8 (max)	2.4 ml	24 mg

In Table 19, I present the pre-specified doses (from Table 18) and actual dose of polidocanol (administered at Visit 1). The doses administered in the EASI trial were within the protocol-specified limits.

Table 19 Protocol-specified dose and actual dose of sclerosants used in EASI trial

Polidocanol						
		Conc	**Vol per inj**	**# inj per session**	**Max vol**	**Max dose**
Spider veins:	Pre-specified dose	0.5%	0.1~0.3 ml	16 (max)	4.8 ml	24 mg
	Actual dose given*			7.9 ~ 10.0	1.1 ± 0.8	5.5 mg
Reticular veins:	Pre-specified dose	1%	0.3 ml	8 (max)	2.4 ml	24 mg
	Actual dose given*			5.1 ~ 6.5	1.5 ± 0.5	15 mg
Sotradecol®						
		Conc	**Vol per inj**	**# inj per session**	**Max vol**	**Max dose**
Spider veins:	Pre-specified dose	1%	0.1~0.3 ml	16 (max)	4.8 ml	48 mg
	Actual dose given*			7.2 ~ 9.8	1.2 ± 0.9	12 mg
Reticular veins:	Pre-specified dose	1%	0.3 ml	8 (max)	2.4 ml	24 mg
	Actual dose given*			4.9 ~ 6.0	1.4 ± 0.5	14 mg

*dose at Visit 1

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The statistically and clinically significant improvement found at 12±2 weeks by objective digital photographic assessment (Table 9) and treatment success rates (Table 14), and the subjective improvement of patient satisfaction (Table 11) all appear to persist up to their evaluation again at 26 weeks (Table 15, Table 14, and Table 11), suggesting persistence of efficacy up to 6 months following treatment.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

Polidocanol is injected in small volumes at low total doses for a local cosmetic effect, and does not reach significant levels in the systemic circulation. Thus, I focused my safety review on local reactions and on the issue of deep vein thrombosis (DVT) which was one of the reasons for non-approval of the earlier Nov-2003 submission.

Safety data in the current submission is based on: (i) 338 patients in the pivotal EASI trial, (ii) 685 patients in seven clinical studies which had been submitted before to FDA in 2003, and (iii) the French Polidocanol Registry of 1,605 patients (a sample taken from 3000 patients in the French Registry treated in 12,173 sclerotherapy sessions in 2003-2004) who were surveyed prospectively by questionnaires for long-term AEs following the 6,444 sclerotherapy sessions they underwent in 2003-2004, including 2,041 sessions treated with liquid polidocanol. A simple pooling of data was not done due to differences in evaluation of the safety data.

There were no deaths in any of the clinical studies

In the EASI trial, Serious Adverse Events (SAEs) were reported by 2 patients: one was hospitalized for exacerbation of existing fibromyalgia, and one patient experienced severe urticaria requiring hospitalization and parenteral treatment with corticosteroids and antihistamines. Withdrawals due to AEs were reported by one patient who was diagnosed with borrelia infection and another with intermittent tachycardia 7 days after sclerotherapy treatment.

In the seven earlier clinical studies, significant AEs were reported on 5 patients treated with 4 to 8 ml of polidocanol 3% (higher than the concentration requested in this application) and 2 patients treated with Sotradecol®. These included ecchymoses and hyperpigmentation (4 AEs), local pain, inflammation, swelling and itching (1 AE), superficial vein thrombosis and neovascularization (2 AEs) and possible allergic reaction manifested as tongue or lip feeling numb, or hives or sneezing (3 AEs).

In the French Polidocanol Registry, 54 patients reported 68 AEs during 58 sessions, of which 51 AEs in 37 patients in 41 sessions were associated with polidocanol. Of these, 46 AEs were associated with polidocanol foam, and 5 AEs were associated with polidocanol liquid (p=0.0033). The five AEs associated with polidocanol liquid were one visual disturbance, one cramp and two inflammatory reactions observed soon after administration, and one hyperpigmentation observed as a delayed AE.

Deep vein thrombosis (DVT) was an AE of specific primary concern for this drug product. DVT was not sought for in the seven earlier clinical studies, which was one of the reasons for non-approval of the submission in 2004. In the EASI trial, DVT was evaluated by ultrasound evaluations at screening visit (baseline), Visit 1a (one week ± 3 days after injection of polidocanol) and at Visit 4 (12 weeks ± 2 weeks after injection of polidocanol). No DVTs were found following treatment with polidocanol or Sotradecol®

or placebo in the EASI trial. In the French Polidocanol Registry, 14 DVTs were associated with *foam* sclerosants, of which 8 were noticed in relation to polidocanol foam. Two DVTs were associated with liquid sclerosants, both with other liquid sclerosants. No DVT was reported in any patient who had been treated with polidocanol liquid.

Common AEs observed in the EASI trial are local AEs which included hematoma, hyperpigmentation and neovascularization, and local sensations or symptoms which included itching, pain, warmth and burning. Microthrombectomy to prevent pigmentation was necessary less frequently with polidocanol at Visit 1a and Visit 2 compared to Sotradecol®.

In the seven earlier clinical studies, too, the common AEs were local reactions such as inflammation, swelling, redness, skin necrosis, itching, induration, incrustation, blister, dermatitis, ecchymoses, hyperpigmentation and neovascularization. Systemic AEs were rarely recorded, which included taste perversion, paresthesia and cramps. While superficial vein thrombosis, an intended result of sclerotherapy, was also reported.

There were no clinically important laboratory abnormalities or changes in vital signs in the EASI trial, the seven earlier clinical studies or the French Polidocanol Registry.

In lieu of a thorough QT study, patients in EASI trial had ECGs done at screening and at 30±15 minutes after treatment at Visit 1. The QT intervals were measured, and QTc_B and QTc_F values calculated. There were no QTc_F values >480 ms observed, no differences in the QTc_F between treatment groups, and no marked changes in the QTc_F duration between screening and Visit 1. The range of change in QTc_F is from -1 ms to 2.7 ms.

The FDA ODS (Office of Drug Safety) investigation comparing the safety data for polidocanol in the WHO Vigisearch database and in published and unpublished literature versus AERS reports for the OGD-(Office of Generic Drugs)-approved liquid sclerosant Sotradecol® shows no signal that liquid polidocanol is more unsafe than Sotradecol® (both are detergents with similar mechanism of action).

There is also a large body of experiential data (published and unpublished) from widespread use of sclerosants (liquid and foam) to treat varicose veins in Europe, Australia, New Zealand and Latin America, where AEs associated with sclerotherapy have been very rare.

We conclude that there are no unexpected safety signals, and that the safety profile of polidocanol liquid as a sclerosant appears to be as safe as Sotradecol®, another liquid sclerosant approved for treatment of varicose veins by the FDA Office of Generics in 2004.

7.1 Methods

Exposure to liquid polidocanol in a total population of **338** patients in the pivotal EASI trial is ***not*** adequate to characterize the safety information for an appropriate evaluation of the benefits (mainly cosmetic) *versus* the risks (DVT, anaphylaxis).

The sponsor alluded to safety data from seven other small studies they had submitted previously to this NDA. However, five of them contained patients treated with doses of polidocanol different than that sought in this NDA. Only two (MICA and OHIO) trials were randomized, controlled, blinded trials; however, one (MICA) trial was found by FDA GCP inspections to have major data integrity issues, including whether or not polidocanol was administered to patients and how much was administered.

In 2005, there was a report that the French Society of Phlebology (Société Francaise de Phlébologie) had initiated a prospective multicenter registry (the French Registry)[1] aimed at describing the incidence of adverse events after a reporting period of 8 weeks. The French Registry consisted of 12,173 sclerotherapy treatments {including 5,434 sessions with liquid sclerosants (75% using polidocanol), and 344 sessions using both liquid and foam}, in approximately 3000 patients, and evaluated the side effects of both liquid and foam sclerosants, given blind or under ultrasound guidance, and for both small varicose veins (telangiectases or spider and reticular veins) and large varicose veins. The study was limited to the outpatient practice of 22 physicians during a single 8-week period. There is no accounting of the number of patients treated or of those lost to follow-up. Thus, no standardized inferences can be drawn from the data or extrapolated to the population of patients whose spider or reticular varicose veins are treated with liquid polidocanol.

The Division suggested that the sponsor obtain long-term safety data from this registry. The sponsor committed to prospectively collect data from this French registry by contacting at least 700 patients treated with polidocanol 0.5% and 1% to determine long term adverse events (from the time of the procedure to the time of the survey). The sponsor then created CRFs to transfer data from this prospective survey of patients in the registry, and performed their own safety analysis which was submitted in this NDA.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As discussed above, safety review of this application is based on data in (Table 20):

(i) the pivotal EASI trial (338 patients),
(ii) the seven earlier clinical studies which have been previously submitted to FDA (685 patients), and
(iii) a subsample of patients in the French Polidocanol Registry who responded to the questionnaires.

Table 20 List of clinical studies for safety evaluation

Study	Polidocanol *			Sotradecol				Placebo (Saline)†			Total patients studied	Comments
	0.5% (S)	1% (R)	Total	0.25% (S)**	0.5% (R)**	1%† (S+R)	Total	(S)	(R)	Total		
Pivotal, controlled, randomized, blinded trial												
EASI	94	86	180	-	-	105	105	27	26	53	338	Pivotal trial
Controlled, randomized, blinded trials												
OHIO	25	25	50	25	25	-	50	-	-	-	150#	Also 25 pts each recd 3% polidocanol or 1.5% sotradecol
MICA$^{\Delta}$	29	31	60	33	32	-	65				179	54 patients received 3% polidocanol and 1.5% sotradecol
Open-label studies in Japan												
ASK-94-002§	18/20	44/50	62/70	-	-	-	-	-	-	-	161$^{\alpha}$	$^{\alpha}$Also studied 2% and 3% polidocanol
ASK-96-001§	50/51	29/29	79/80	-	-	-	-	-	-	-	100$^{\beta}$	$^{\beta}$Also studied 0.25% polidocanol
Open-label studies that studied other doses												
ASK-97-01-00‡	-	-	-	-	-	-	-	-	-	-	*6*	***Only** studied **3.0%** polidocanol*
AET-AS25/4‡	-	-	-	-	-	-	-	-	-	-	*79*	***Only** studied **0.25%** polidocanol*
AET-P2/1/US	-	-	-	-	-	-	-	-	-	-	*10*	***Only** studied **2.0%** polidocanol*
The French Polidocanol Registry												
French Registry	-	-	-	-	-	-	-	-	-	-	1605	Post-treatment survey for safety data only

(S)= spider veins; (R)= reticular veins; *Patients enrolled in EASI, OHIO, ASK-94-002 and ASK-96-001;**Patients enrolled in EASI and OHIO; †Patients enrolled in EASI only; #includes 50 patients at other doses; §Open-label, drug concentration-controlled trials in Japan; αincludes 89 patients at other doses; βincludes 20 patients at other doses; ΔFDA GCP inspections revealed major data integrity issues, data not acceptable; ‡Open-label, uncontrolled, using doses other than 0.5% & 1.0%.

7.1.2 Categorization of Adverse Events

Polidocanol is injected in small volumes and low total doses to achieve a local cosmetic effect, is administered usually in one session in the majority of patients, and does not reach any significant levels in the systemic circulation. Thus, for safety evaluation, I focused my review of data on local reactions and AEs related to them, and the important issues of superficial and deep vein thrombosis.

<u>EASI trial:</u>

The safety variables were evaluated as the occurrence of local and general adverse events, including

(a) pain during and 2 min after injection at Visit 1 (and Visits 2 and 2a if applicable) rated according to the following 5-grade scale: (1) Extremely severe, (2) Severe, (3) Moderate, (4) Mild, and (5) None,

(b) the Investigator's assessments at Visits 1, 2, (2a and 2b if applicable), 3 and 4 for presence or absence of Hyperpigmentation, Hematoma, Neovascularization and Other findings,

(c) subjective sensations at Visits 1, 2, (2a and 2b if applicable), 3 and 4, such as

Itching, Pain, Warmth, Burning, and Others, rated according to the following 5-point scale: (1) Extremely severe, (2) Severe, (3) Moderate, (4) Mild, and (5) None

(d) basic safety variables in routine clinical chemistry and haematology tests, urinalysis, Thrombophilia testing, Vital signs, ECG, and

(e) occurrence of DVT (by duplex ultrasound examination at Visits 0, 2, 2a, 2b, and 3).

The seven earlier clinical studies which have been previously submitted to FDA:

Immediate local and systemic reactions were evaluated as follows: Immediately after injection of liquid sclerosant, immediate systemic reactions that were looked for included dizziness, visual disturbances, nausea, vomiting, dyspnea, cardiac manifestations, hypotension, fainting, asthma, skin reactions (urticaria, pruritus) and anaphylactic shock, their severity being reported on a 4-point scale. The immediate local reactions looked for included pain, inflammation, swelling and local allergy (on a 4-point scale).

Delayed reactions were recorded one week after treatment and at each follow-up visit. The reactions recorded included superficial vein thrombosis, ecchymosis, skin necrosis, hyperpigmentation and neovascularization. Deep vein thrombosis (DVT) was not sought for, which was one of the reasons for non-approval of the initial NDA in 2005.

The French Polidocanol Registry:

In the French Polidocanol Registry, the sponsor performed a questionnaire survey of 1605 patients who had received polidocanol at least once during 6444 sessions within a four-year period, covering 3,357 patient-years. The details of data retrieval from the registry, transfer to case report forms (CRFs) and the AEs which were evaluated are described in section 9.4.3 The French Polidocanol Registry survey.

The AEs which were asked explicitly in the questionnaires (and listed on CRFs) include

- local reactions such as deep vein thrombosis, muscle vein thrombosis, paresthesia, cutaneous necrosis, and
- systemic reactions such as allergic reaction, anaphylactic shock, vaso-vagal fainting, visual disturbances, and headache or nausea or vomiting (on treatment day).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of data across studies was done because

(i) The EASI trial and the seven earlier clinical studies used different doses of polidocanol in different concentrations,

(ii) The EASI trial was the only placebo-controlled trial, and

(iii) The French Polidocanol Registry survey consisted of patients who had received different forms (liquid and foam) of polidocanol in different doses in 2003-2004.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure to polidocanol in the EASI trial:
In the EASI trial, many patients had more than one treatment session (Table 21):

- Of 86 patients with reticular veins treated with polidocanol 1% and 54 patients with reticular veins treated with Sotradecol®, 38 (44.2%) patients and 26 (48.1%) patients, respectively, received one treatment session, 30 (34.9%) patients and 17 (31.5%) patients had two treatment sessions, and 18 (20.9%) patients and 11 (20.4%) patients had three treatment sessions.
- Of 94 patients with spider veins who were injected with polidocanol 0.5% and 51 patients with spider veins who were injected with Sotradecol, 17 (18.1%) patients and 30 (58.8%) patients, respectively, received one treatment, 33 (35.1%) patients and 12 (23.5%) patients had two treatment sessions, and 44 (46.8%) patients and 9 (17.6%) patients had three treatment sessions.
- All 53 patients who received placebo were treated three times, except one patient in the reticular vein group (one treatment visit) and 1 patient in the spider vein group (two treatment visits).

Table 21 Number of patients who had 1, 2 or 3 treatment sessions, mean total volume (ml) and amount (mg) of study medication injected (safety data set)

		Visit 1		Visit 2		Visit 3	
Treatment		(N=338)		(N=231)		(N=134)	
		ml	mg	ml	mg	ml	mg
Aethoxysklerol® 1% (R)	Mean	1.5	15 mg	0.9	9 mg	0.8	8 mg
	SD	0.5		0.5		0.5	
	N	86		48		18	
Sotradecol® (R)	Mean	1.4	14 mg	0.5	5 mg	0.6	6 mg
	SD	0.5		0.4		0.4	
	N	54		28		11	
Placebo (R)	Mean	1.5		1.5		1.4	
	SD	0.6		0.6		0.4	
	N	26		25		25	
Aethoxysklerol® 0.5% (S)	Mean	1.1	5.5 mg	1.0	5 mg	0.8	4 mg
	SD	0.8		0.6		0.7	
	N	94		77		44	
Sotradecol® (S)	Mean	1.2	12 mg	0.5	5 mg	0.4	4 mg
	SD	0.9		0.3		0.2	
	N	51		21		9	
Placebo (S)	Mean	1.6		1.3		1.1	
	SD	1.0		0.8		0.5	
	N	27		27		26	

Source: Sponsor's table 12.

Patients with reticular veins received a *mean volume* of 1.5 ± 0.5 ml (mean ± SD) polidocanol 1% or 1.4 ± 0.5 ml Sotradecol® at Visit 1 (Table 21). The *mean volume* injected in patients with spider veins was with 1.1 ± 0.8 ml polidocanol 0.5% or 1.2 ± 0.9 ml Sotradecol® (Table 21).

In patients with reticular veins the *number of injections* administered in the polidocanol 1% group per visit ranged from 5.1 to 6.5, in the Sotradecol® group from 4.9 to 6.0 and in the placebo group from 5.4 to 6.1. Patients with spider veins on average received more injections per visit (polidocanol 0.5%: 7.9-10.0 injections, Sotradecol: 7.2-9.8, placebo: 7.9-10.7).

The protocol-specified maximum number of 8 injections per visit for patients with reticular veins was exceeded at Visit 1 in a few patients who received polidocanol 1% (max. 13 injections) and at Visit 2 in patients who received placebo (max. 9 injections).

In some patients with spider veins, the protocol-specified maximum number of 16 injections per visit was exceeded in the polidocanol 0.5% group at Visit 2 (max. 19 injections) and in the Sotradecol® group at Visit 1 (max. 25 injections).

Exposure to polidocanol in the seven earlier clinical studies:

Of 685 patients enrolled in the seven earlier clinical studies (Table 20), 501 patients had been administered one dose of liquid polidocanol (Table 22); of these 501 patients, 260 patients had received one administration of liquid polidocanol at the doses of 0.5% or 1% for the indication sought in this NDA.

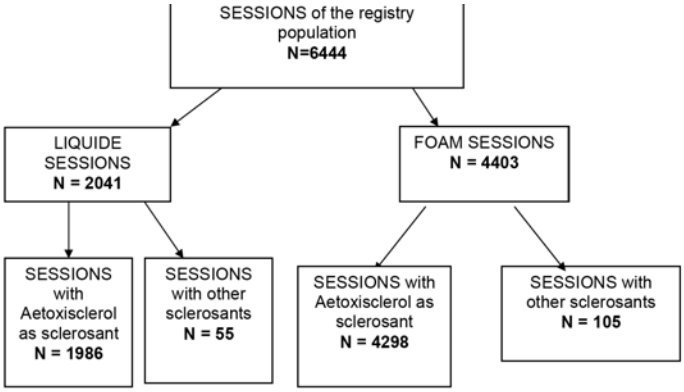
Table 22 Exposure to polidocanol in 7 earlier clinical studies

Concentration	OHIO	ASK-94-002	ASK-96-001	ASK-97-01-00	AET-AS25/4	AET-P2/1/US	MICA	Total
0.5%	**25**	**20**	**51**				**29**	**125**
1.0%	**25**	**50**	**29**				**31**	**135**
2.0%		89				10		99
3.0%	25			30			27	82
0.25%			20		40			60
Total	75	159	100	30	40	10	87	501

Exposure to polidocanol in The French Polidocanol Registry:

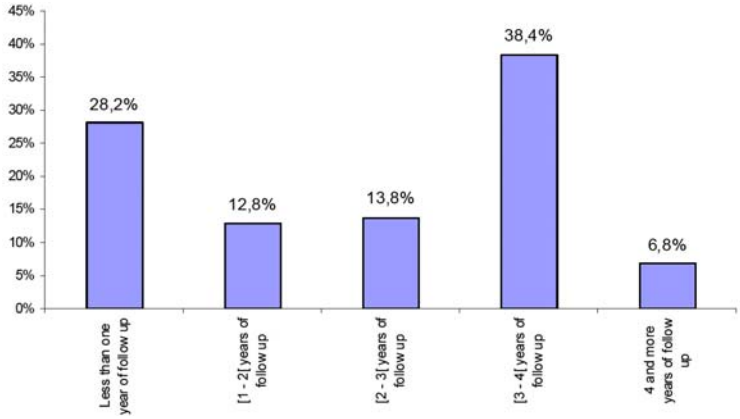
A total of 1,605 patients who had received at least one polidocanol injection in 6,444 sclerotherapy sessions (Figure 5) were surveyed for AEs they had experienced during the survey period of about 4 years – from April 2004 to April 2008 – covering 3,357 patient-years. polidocanol was used in 6,284 sessions, and other sclerosants such as Scleremo®, or Thrombovar® were administered either alone or in combination with polidocanol in 160 sessions.

Figure 5 Flow chart of patients surveyed in the French Polidocanol Registry



In the majority of sessions (N=4,403), the foam formulation of sclerosants was used (Figure 5). Liquid sclerosants were used less frequently (N=2,041). In some patients who received polidocanol, a few sessions have been performed exclusively with other sclerosants, for which polidocanol could be ruled out as causing the AEs. No AEs were reported after a treatment session during which different sclerosants were administered.

Figure 6 Duration of follow-up per patient (in years)



71.8% of the patients were followed up at least 12 months, and 59.0 % of the patients were followed up for 24 months (Figure 6). During this observation time, most adverse events were observed to occur on the treatment day or immediately afterwards.

The majority of patients who received at least one polidocanol injection were treated for C_1 varicose veins (70.72%, with 32.53% reticular veins and 38.19% spider veins (Table 23), which are the veins of interest for this application). Other types of varicose veins treated in this French Polidocanol Registry survey were: great saphenous vein trunk or junction (14.76%), main tributaries of the great saphenous vein (11.28%), and small varices or non-saphenous veins (9.76%).

Table 23 French Registry – Number of sessions by type of varicose vein (n=6444)

Type of vein	Yes	
	N	%
Reticulars	2096	32.53
Spider veins	2461	38.19
Great saphenous vein trunk or junction	951	14.76
Small saphenous vein trunk or junction	291	4.52
Main tributaries	727	11.28
Small varices or nonsaphenous	629	9.76
Perforating veins	157	2.44
Postsurgical recurrences	668	10.37

Liquid sclerosants were used most frequently for patients with C_1 varicose veins (96.9%, with 37.2% reticular veins and 59.7% spider veins, Table 24).

Table 24 French Polidocanol Registry – Number of sessions by type of varicose vein treated with liquid sclerosants (n=2,041)

Type of vein	Yes	
	N	%
Reticulars	759	37.19
Spider veins	1218	59.68
Great saphenous vein trunk or junction	53	2.60
Small saphenous vein trunk or junction	6	0.29
Main tributaries	76	3.72
Small varices or nonsaphenous	368	18.03
Perforating veins	16	0.78
Postsurgical recurrences	9	0.44

The concentration and volume of liquid polidocanol used in the treatment sessions in the French Polidocanol Registry are shown in Table 25.

Table 25 Volume (ml) of liquid polidocanol used in treatment sessions in the French Registry

Type of vein	n	MD	Mean	Standard Deviation	Median	Minimum	Maximum
Reticulars	759	0	2.10	0.67	2.00	0.80	7.50
Spider veins	1217	1	2.14	0.55	2.00	1.00	7.50
Great saphenous vein trunk or junction	53	0	2.12	0.56	2.00	1.00	4.00
Small saphenous vein trunk or junction	6	0	2.25	0.61	2.50	1.00	2.50
Main tributaries	76	0	2.72	2.68	2.50	1.00	25.00
Small varices or nonsaphenous	368	0	2.56	0.92	2.00	1.00	5.00
Perforating veins	16	0	1.47	0.59	1.00	1.00	2.50
Postsurgical recurrences	9	0	1.89	0.33	2.00	1.00	2.00

7.2.2 Explorations for Dose Response

No explorations for dose response were performed.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in the EASI trial, in any of the seven earlier clinical studies or in the French Polidocanol Registry survey.

7.3.2 Nonfatal Serious Adverse Events

In the EASI trial, 2 SAEs were reported. Both patients had received treatment with polidocanol 0.5%.

Patient #191 was treated in two sessions with polidocanol 0.5%, and was hospitalized for an episode of fibromyalgia (a condition which the patient was found to have had prior to the injections).

Patient #199 was treated once with polidocanol 0.5%, following which the patient reported severe urticaria requiring hospitalization and parenteral treatment with corticosteroids and antihistamines.

In the seven earlier clinical studies, and in the French Polidocanol Registry survey, no SAEs were reported.

7.3.3 Dropouts and/or Discontinuations

In the EASI trial, 2 patients withdrew from the trial due to adverse events:

- Patient #77 was diagnosed with severe borrelia infection 96 days after the third treatment session with placebo. The infection persisted till after the end of the trial.
- Patient #607 reported intermittent tachycardia 7 days after the first treatment with polidocanol 0.5%; patient recovered without sequale.

(Note: There were 11 other patients (reference: sponsor's subject data listing 16.2.1.1) who were lost to follow-up (patients did not come for Visit 4 or Visit 5 or had moved to another city) for whom no information regarding delayed AEs is available.)

No dropouts and/or premature discontinuations due to AEs were reported in the seven earlier clinical studies.

7.3.4 Significant Adverse Events

In the EASI trial, 2 patients had significant AEs which resulted in withdrawal of these patients from the trial (see above).

In the seven earlier clinical studies, 7 patients (5 in polidocanol group and 2 in Sotradecol® group) experienced significant AEs as follows (note: these occurred with

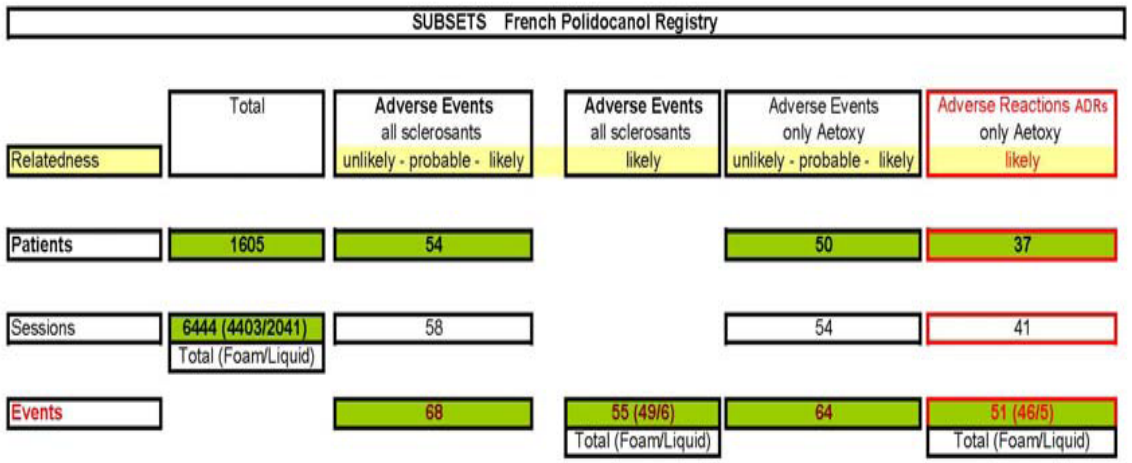
injections of 4 to 8 ml of polidocanol 3.0%, which is not the dose and concentration sought for approval in this application) :

- Patient # 1303: After injection of 4 ml polidocanol 3.0%, the patient experienced ecchymoses (1 cm^2), and superficial vein thrombosis (10 cm) reported 1 week after treatment, and discoloration due to an intravascular hematoma noted at 6 weeks.
- Patient # 1305: After injection of 8 ml Sotradecol® 1.5%, the patient experienced local pain, inflammation, itching and swelling immediately after injection which lasted about 2 minutes. She also reported ecchymoses (7 cm^2) 1 week after treatment and hyperpigmentation at 1 month. These resolved at the final evaluation visit.
- Patient # 1307: After injection of 7 ml Sotradecol® 1.5%, the patient experienced ecchymoses (15 cm^2) noted 1 week after treatment, which persisted (2 cm^2) till 4 weeks after treatment, with hyperpigmentation remaining at the final visit.
- Patient # 1308: After injection of 5 ml polidocanol 3.0%, the patient experienced pain, inflammation, swelling and severe hives immediately after injection, lasting about 2 minutes. The patient reported her tongue felt numb at approximately 5 minutes after treatment which lasted about 2 minutes. Superficial vein thrombosis (3 cm) and neovascularization were noted 1 week after treatment, which disappeared by the final visit, with residual hyperpigmentation.
- Patient # 1312: After injection of 8 ml polidocanol 3.0%, the patient experienced pain, inflammation, swelling and hives immediately after injection, and her tongue felt numb which lasted about 5 minutes. Superficial vein thrombosis (4 cm) was noted at 2 weeks after treatment, which remained (2 cm) up to the 4^{th} week but disappeared by the final visit, leaving residual hyperpigmentation noted at 8 weeks after treatment and at the final visit.
- Patient #1323: After injection of 6 ml polidocanol 3.0%, the patient experienced superficial vein thrombosis (2 cm) and ecchymoses, noted 1 week after treatment, and hyperpigmentation 4 weeks after treatment, which disappeared by the final visit.
- Patient # 1324: After injection of 7 ml polidocanol 3.0%, the patient experienced numbness in her tongue and lips which recovered within 15 minutes, and a sneezing attack which lasted 5 minutes. Hyperpigmentation was noted at 4 weeks and at the final visit.

Significant AEs reported in French Polidocanol Registry survey: Of 54 patients who reported 68 AEs during 58 sessions (Figure 7), 51 events in 37 patients during 41 sclerotherapy sessions were reported in association with injection of polidocanol (polidocanol) used in foam (46 events) or liquid (5 events) form.

Of these 5 AEs seen after administration of polidocanol liquid, 2 were observed immediately {visual disturbance (1), cramp (1)}, 2 inflammatory reactions were observed soon after administration, and hyperpigmentation was observed as a delayed AE.

Figure 7 Adverse Events in French Polidocanol Registry



7.3.5 Submission Specific Primary Safety Concerns

Unlike other cardiovascular and renal drugs which have to be taken daily for a long time, the safety concerns for polidocanol liquid – which is injected in small volumes for a local cosmetic effect without reaching any significant levels in the circulation – are (i) allergic or anaphylactic reactions, (ii) local reactions (inflammation, skin necrosis, superficial vein thrombosis, ecchymoses, pigmentation), and (iii) deep vein thrombosis.

Allergic reactions including urticaria, numbness in tongue and/or lips, and local reactions reported in the EASI trial, the seven earlier clinical studies and the French Polidocanol Registry survey are reviewed in sections 7.3.2, 7.3.3 and 7.3.4 (above).

Deep vein thrombosis (DVT) was an AE of specific primary concern for this drug product. DVT was not sought for in the seven earlier clinical studies previously submitted to FDA, which was one of the reasons for non-approval of the submission in 2004.

DVTs are known to occur largely during the first week after injection of sclerosant, and many DVTs are asymptomatic so that historical or symptom data may under-report this AE following treatment with polidocanol liquid.

In the EASI trial, DVT was evaluated prospectively by ultrasound evaluations at screening visit (baseline), Visit 1a (one week ± 3 days after injection of polidocanol) and at Visit 4 (12 weeks ± 2 weeks after injection of polidocanol).

No case of DVT was found by ultrasound evaluation in the EASI trial following treatment with polidocanol or Sotradecol® or placebo (Table 26).

Table 26 Ultrasound findings to evaluate DVT in EASI trial

Patients with reticular veins				
Ultrasound finding		**Polidocanol 1%** (n=86)	**Sotradecol®** (N=54)	**Placebo** (N=26)
DVT at screening	No	86 (100%)	54 (100%)	26 (100%)
	Yes	0	0	0
DVT at Visit 1a	No	86 (100%)	54 (100%)	26 (100%)
	Yes	0	0	0
DVT at Visit 4	No	86 (100%)	54 (100%)	26 (100%)
	Yes	0	0	0
Patients with spider veins				
		Polidocanol 0.5% (n=94)	**Sotradecol®** (N=51)	**Placebo** (N=27)
DVT at screening	No	94 (100%)	51 (100%)	27 (100%)
	Yes	0	0	0
DVT at Visit 1a	No	93 (100%)*	51 (100%)	27 (100%)
	Yes	0	0	0
DVT at Visit 4	No	88 (100%)**	51 (100%)	27 (100%)
	Yes	0	0	0

In the French Polidocanol Registry, 14 DVTs (Table 31) were associated with *foam* sclerosants, of which 8 were noticed in relation to polidocanol *foam*. Two DVTs were associated with liquid sclerosants, both with other liquid sclerosants. No DVT was reported in any patient who had been treated with polidocanol liquid.

For one DVT reported medium-term after administration of polidocanol ***foam***, the physician's notes stated that the patient suffered from Thrombophilia (heterozygote Factor V Leiden). The patient's medical history revealed prior DVT with an onset long before sclerotherapy with polidocanol was performed. Even though anticoagulants were prescribed, the patient had stopped taking the medication; sclerotherapy was performed during this period when the patient was not taking anticoagulants. It is likely that the DVT detected was the previously diagnosed DVT which had persisted due to termination of anticoagulant therapy.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the EASI trial, the numbers of patients who experienced local reactions following treatment with liquid sclerosants are shown in Table 27, and those who experienced local sensations are shown in Table 28.

Table 27 Number of patients with local reactions (safety data set)

Patients with reticular veins			
Local Reaction	**Polidocanol** 1% (n=86)	**Sotradecol®** (N=54)	**Placebo** (N=26)
Hyperpigmentation: Absent	52 (60.5%)	19 (35.2%)	23 (88.5%)
Present	34 (39.5%)	35 (64.8%)	3 (11.5%)
Hematoma: Absent	44 (51.2%)	20 (37.0%)	21 (80.8%)
Present	42 (48.8%)	34 (63.0%)	5 (19.2%)
Neovascularization: Absent	79 (91.9%)	47 (87.0%)	25 (96.2%)
Present	7 (8.1%)	7 (13.0%)	1 (3.8%)
Other: Absent	82 (95.3%)	49 (90.7%)	25 (96.2%)
Present	4 (4.7%)	5 (9.3%)	1 (3.8%)
Patients with spider veins			
Local Reaction	**Polidocanol** 0.5% (n=94)	**Sotradecol®** (N=51)	**Placebo** (N=27)
Hyperpigmentation: Absent	59 (62.8%)	9 (17.6%)	27 (100.0%)
Present	35 (37.2%)	42 (82.4%)	0
Hematoma: Absent	60 (63.8%)	16 (31.4%)	22 (81.5%)
Present	34 (36.2%)	35 (68.6%)	5 (18.5%)
Neovascularization: Absent	86 (91.5%)	38 (74.5%)	26 (96.3%)
Present	8 (8.5%)	13 (25.5%)	1 (3.7%)
Other: Absent	81 (86.2%)	28 (54.9%)	27 (100.0%)
Present	13 (13.8%)	23 (45.1%)	0

Table 28 Number of subjects who experienced local sensations (safety data set)

Patients with reticular veins			
Local Sensations	**Polidocanol** 1% (n=86)	**Sotradecol®** (N=54)	**Placebo** (N=26)
Itching: Absent	69 (80.2%)	41 (75.9%)	26 (100.0%)
Present	17 (19.8%)	13 (24.1%)	0
Pain: Absent	69 (80.2%)	42 (77.8%)	23 (88.5%)
Present	17 (19.8%)	12 (22.2%)	3 (11.5%)
Warmth: Absent	71 (82.6%)	45 (83.3%)	24 (92.3%)
Present	15 (17.4%)	9 (16.7%)	2 (7.7%)
Burning: Absent	50 (58.1%)	13 (24.1%)	18 (69.2%)
Present	36 (41.9%)	41 (75.9%)	8 (30.8%)
Other: Absent	83 (96.5%)	48 (88.9%)	25 (96.2%)
Present	3 (3.5%)	6 (11.1%)	1 (3.8%)
Patients with spider veins			
Local Sensations	**Polidocanol 0.5%** (n=94)	**Sotradecol®** (N=51)	**Placebo** (N=27)
Itching: Absent	76 (80.9%)	36 (70.6%)	25 (92.6%)
Present	18 (19.1%)	15 (29.4%)	2 (7.4%)
Pain: Absent	67 (71.3%)	32 (62.7%)	26 (96.3%)
Present	27 (28.7%)	19 (37.3%)	1 (3.7%)
Warmth: Absent	81 (86.2%)	38 (74.5%)	26 (96.3%)
Present	13 (13.8%)	13 (25.5%)	1 (3.7%)
Burning: Absent	57 (60.6%)	14 (27.5%)	19 (70.4%)
Present	37 (39.4%)	37 (72.5%)	8 (29.6%)
Other: Absent	85 (90.4%)	44 (86.3%)	25 (92.6%)
Present	9 (9.6%)	7 (13.7%)	2 (7.4%)

The number of patients who required microthrombectomy (to prevent pigmentation) is shown in Table 29.

Table 29 Microthrombectomy in EASI trial

Patients with reticular veins			
Visit	**Polidocanol** 1% (n=86)	**Sotradecol®** (N=54)	**Placebo** (N=26)
Visit 1a*	20 (23.3%)	17 (31.5%)	1 (3.8%)
Visit 2*	24 (27.9%)	20 (37.0%)	0
Visit 2a*	11 (22.9%)	8 (28.6%)	1 (3.8%)
Visit 3*	7 (14.9%)	3 (10.7%)	1 (3.8%)
Visit 3a*	1 (5.6%)	1 (9.1%)	0
Patients with spider veins			
Visit	**Polidocanol** 0.5% (n=94)	**Sotradecol®** (N=51)	**Placebo** (N=27)
Visit 1a*	25 (26.9%)	19 (37.3%)	0
Visit 2*	11 (12.0%)	19 (37.3%)	0
Visit 2a*	13 (17.1%)	3 (14.3%)	1 (3.7%)
Visit 3*	6 (8.0%)	1 (4.8%)	1 (3.7%)
Visit 3a*	5 (1.4%)	2 (22.2%)	0

*percent of those who returned; Ref: sponsor's summary data table 14.7.8, pages 367–371 of EASI study report

For the seven earlier clinical studies, only information previously submitted in the Integrated Summary of Safety and related data were available. The safety information was not pooled for the seven studies, but presented in three groups:

(i) safety data related to controlled, randomized, blinded (OHIO and MICA) trials,

(ii) safety data related to open-label study-drug concentration-controlled studies (ASK 94-002/21/JPN and ASK 96-001/21/JPN), and

(iii) safety data related to open-label, uncontrolled studies (AET-AS25/4, AET/P2/1/US, and ASK-97-01-00).

The ISS submitted previously in 2003 had been reviewed by FDA. There were no SAEs or deaths, and no patients withdrew because of AEs. The following is a summary of common AEs in the data presented in ISS:

- In the controlled randomized blinded (OHIO and MICA) trials (consisting of 150 and 179 patients, respectively), the most common AEs were local reactions. Most patients reported no pain following injection with either polidocanol or Sotradecol®. Fewer patients who were injected with polidocanol than Sotradecol®, respectively, experienced inflammation (21.7% vs. 34.5%, p=0.046), swelling (10.1% vs. 21.8 %, p=0.005), ecchymoses (53.8% vs 66.9%, p=0.022), skin necrosis (1.3% vs 4.9%), hyperpigmentation (60.5% vs 69.6%, p=0.071) and neovascularization (8.2% vs. 8.4%). Superficial vein thrombosis, an intended result of sclerotherapy, was found in 51.3% of patients injected with polidocanol vs. 51.8% of those injected with Sotradecol®. Systemic AEs were rarely recorded for polidocanol or Sotradecol® consisting of taste perversion (1.3% vs 0.6%) and paresthesia (2.5% vs 1.2%). In the Sotradecol® group, 1.2% each experienced edema and dizziness, and 0.6% each experienced dry mouth and nervousness.

- In the open-label study-drug concentration-controlled studies (consisting of 261 patients treated in Japan), the most common AEs were superficial vein thrombosis (70 patients, 29.2%) and hyperpigmentation (66 patients, 27.5%), followed by ecchymoses (6 patients, 2.5%), induration (5 patients, 2.1%), phlebitis (2 patients, 0.8%), and itching, dermatitis, redness, incrustation (1 patient, 0.4%, each).
- In the open-label, uncontrolled studies (consisting of 95 patients), 9 patients reported moderate pain (4 reporting persistent pain), 2 reported inflammation, and 1 reported a local allergic reaction during the immediate 2 hours following polidocanol injection. Delayed local reactions included thrombophlebitis in 9 patients, superficial vein thrombosis in 7 patients, hyperpigmentation in 6 patients, and ecchymosis in 2 patients. No patients experienced skin necrosis. One patient reported mild cramps during the second week after treatment, and one patient reported a 1 cm^2 blister in the area where compression had been applied, which healed without sequale. One patient experienced languor and mild chest pain immediately after treatment.

The French Polidocanol Registry: In the total registry population of 1,605 patients, 54 patients experienced a total of 68 adverse events during 58 sclerotherapy sessions with liquid and/or foam agents (Figure 7).

Of these 54 patients, 37 patients (during total of 41 sclerotherapy sessions) experienced 51 AEs that were associated with an injection of polidocanol. Of these, 46 AEs were associated with an injection of polidocanol *foam*, and 5 AEs were associated with an injection of polidocanol *liquid*.

Liquid sclerosants were associated with a significantly (p=0.0033) lower incidence of AEs (0.39%) compared to foam sclerosants (1.14%) (Table 30).

Table 30 AEs in relation to foam or liquid sclerosant treatment in the French Polidocanol Registry

AEs	Foam sclerosant (n=4403)	Liquid sclerosant (n=2041)	Total patients (n=6444)
Present: n (%)	50 (1.14%)	8 (0.39%)	58 (0.9%)

Chi^2 = 8.6457; p=0.0033

AEs associated with liquid sclerosants (Table 31): Of 8 AEs associated with injection of *liquid* sclerosants, 5 AEs were observed after injection with polidocanol *liquid* which included: one cramp, two inflammatory reactions, one hyperpigmentation and one visual disturbance. Two DVT events and one AE of edema were associated with other liquid sclerosants.

AEs associated with foam sclerosants (Table 31): The most common adverse reactions observed after injection with polidocanol *foam* were 13 visual disturbances (out of a total of 15 associated with liquid sclerosants). Only one such event was seen after treatment with polidocanol *liquid* (above).

Also 8 AEs of DVT (out of a total of 14 DVTs associated with liquid sclerosants) were noticed in relation with polidocanol *foam* only. Other common AEs noted with foam sclerosants included headache and syncope (7 AEs each).

Table 31 Number of patients with AEs associated with injection of liquid vs foam sclerosants in The French Polidocanol Registry

Adverse events	Foam			Liquid		
	N	%	Percentage in relation to the total number of foam sessions (n=4403)	N	%	Percentage in relation to the total number of liquid sessions (n=2041)
Allergic reaction	1	1.67	0.0227			
Breast Cancer	2	3.33	0.0454			
Cramps				1	12.50	0.0490
Skin Necrosis	1	1.67	0.0227			
Thrombosis Venous Superficial	1	1.69	0.0227			
Dyspnoea	2	3.33	0.0454			
Headache	7	11.67	0.1590			
Inflammatory Reaction	2	3.33	0.0454	2	25.00	0.0980
Deep Vein Thrombosis	14	23.73	0.3180	2	25.00	0.0980
Nausea and vomiting	4	6.67	0.0908			
Oedema lower limb				1	12.50	0.0490
Pain in calf	1	1.67	0.0227			
Paresthesias	1	1.67	0.0227			
Pigmentation disorder				1	12.50	0.0490
Syncope Vasovagal	7	11.67	0.1590			
Thrombosed varicose vein	2	3.33	0.0454			
Visual disturbances	15	25.00	0.3407	1	12.50	0.0490
Total	60	100.00	1.3627	8	100.00	0.3920

7.4.2 Laboratory Findings

In the EASI trial, there were no changes on the clinical laboratory test results effected by the different sclerosant treatments, and no obvious pattern or trend over time was observed for the laboratory parameters.

There were deviations from the reference range for all laboratory tests including those at screening; these deviations were judged by the investigators to be not clinically significant. In some patients, results of the thrombophilia testing which deviated from the reference range could not be evaluated by the investigator.

“Not evaluable” results were documented in 20 patients for antithrombin III, protein C and protein S activity, and less frequently for factor VIII activity, partial thromboplastin time and prothrombin time. “Not evaluable” laboratory values of hematocrit, GLDH and urine erythrocytes and ketone each were documented in ≤ 5 patients.

One patient (Patient 389) had “not evaluable” laboratory values deviating from the reference range measured at Visit 1 for albumin, alkaline phosphatase, creatinine, GOT (AST), Gamma-GT and Urea.

Clinically significant laboratory abnormalities were recorded for the following patients at screening:

- Patient 105: β2 glycoprotein antibody and cardiolipin antibody were above normal range at screening.
- Patient 186: leukocytes above the reference range were measured, which returned to within reference range at Visits 1 and 4.
- Patient 404: protein S activity was below normal range and outside the exclusion range.

In the seven earlier clinical studies, there was no evidence of any systematic change in any of the laboratory parameters following treatment with polidocanol.

The French Polidocanol Registry survey did not involve any laboratory tests.

7.4.3 Vital Signs

In the EASI trial and in the seven other clinical studies, no clinically significant abnormalities or changes following treatment were observed for pulse, systolic and diastolic blood pressure or body temperature measured at each visit.

The French Polidocanol Registry survey did not involve evaluation of vital signs.

7.4.4 Electrocardiograms (ECGs)

In lieu of a thorough QT study, the sponsor presented ECG data on patients in the EASI trial. ECGs were recorded at screening, and at 30±15 min after treatment at Visit 1. QT intervals were measured by the cardiologist of the ECG provider, and corrected for heart rate using Bazett's correction (QTc_B) and Friedericia's correction (QTc_F).

Mean absolute QTc_F values at screening and at Visit 1 for each treatment group are listed in Table 32.

There were no absolute QTc_F values > 480 ms observed in this study. QTc_F values > 450 ms were recorded in one patient in the Sotradecol® (R) group at screening and in three patients and one patient in the polidocanol 0.5% and placebo (S) group, respectively, at Visit 1.

A change in QTc_F from baseline of ≥ 30 ms was observed in one patient each in the groups polidocanol 1%, Sotradecol® (R) and polidocanol 0.5%.

A change in QTc_F from baseline > 60 ms was observed in one patient who had been treated with polidocanol 0.5% at Visit 1.

The mean change from baseline at Visit 1 ranged from –1.0 to 1.3 ms in patients with reticular veins and from 0.4 to 2.7 ms in patients with spider veins (Table 32).

No marked changes in the mean QTc_F duration were observed between screening and Visit 1. There were no evident differences between the treatment groups.

Table 32 Absolute QTc values (Friedericia's correction) and change from baseline (safety data set)

Treatment		Screening (N=338)	Visit 1 (N=338)	
		Absolute QTcF - duration [ms]	Absolute QTcF - duration [ms]	Baseline-adjusted QTcF - duration [ms]
AETH 1% (R)	Mean	410.3	409.7	-1.0
	SD	15.1	16.5	12.3
	Min	374	378	-29
	Max	439	449	31
	N	83	86	83
Sotradecol (R)	Mean	408.3	407.3	-0.4
	SD	18.6	17.4	12.0
	Min	371	377	-20
	Max	469	449	36
	N	52	54	52
Placebo (R)	Mean	408.3	409.3	1.3
	SD	15.8	15.4	12.1
	Min	372	375	-20
	Max	441	440	19
	N	24	26	24
AETH 0.5% (S)	Mean	410.5	412.2	2.0
	SD	16.4	18.2	13.7
	Min	361	377	-32
	Max	449	467	62
	N	88	94	88
Sotradecol (S)	Mean	401.4	404.2	2.7
	SD	16.8	15.4	12.0
	Min	358	373	-36
	Max	432	441	23
	N	49	51	49
Placebo (S)	Mean	411.0	412.0	0.4
	SD	16.2	16.3	12.0
	Min	376	386	-20
	Max	442	452	26
	N	25	27	25

If >1 ECG was evaluated, the last ECG was taken for analysis.

7.5 Other Safety Explorations

Not applicable.

7.6 Additional Safety Evaluations

Not applicable.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

There is no post-marketing experience for the drug product submitted for approval in this application. However, there is a large body of experiential data (published and unpublished) from widespread use of sclerosants (liquid and foam) to treat varicose veins in Europe, Australia, New Zealand and Latin America. In these data, adverse events and/or technical complications of the procedure have been very rare.

The FDA ODS (Office of Drug Safety) investigation comparing the safety data for polidocanol in the WHO Vigisearch database and in published and unpublished literature versus AERS reports for the OGD-(Office of Generic Drugs)-approved liquid sclerosant Sotradecol® shows no signal that liquid polidocanol is more unsafe than Sotradecol® (both detergents with similar mechanism of action).

DVT and other complications associated with microbubbles in the systemic circulation (e.g., visual symptoms, neurological symptoms, etc.) are reported only with use of *foam* sclerosants, not with liquid polidocanol used in this application.

9 Appendices

9.1 Literature Review/References

A relatively recent published prospective multicenter registry of 12,173 sclerotherapy treatments[1] in France including 5,434 sessions with liquid sclerosants (75% using polidocanol) showed the relative safety of liquid sclerotherapy with polidocanol. The sponsor committed to submit safety data from the "French Registry" for at least 700 patients treated with polidocanol 0.5% and polidocanol 1.0%.

In a prospective, randomized multicenter trial[2] of 3% polidocanol *foam* (45 patients) vs. 3% *solution* of polidocanol (43 patients) to determine the rates of elimination of reflux in the Greater Saphenous Vein (GSV) and of recanalization, follow-up evaluations after 3 weeks showed 84% elimination of reflux in the GSV with polidocanol *foam* vs. 40% with polidocanol *solution* ($P<0.01$). At 6 months, 2 patients in the polidocanol *foam* group had re-canalized, vs. 6 in the polidocanol *solution* group, with no additional recanalization in either group at one year, and no differences in AEs.

The recently completed ESAChina trial[3] enrolled 288 Han Chinese patients with C_1 (spider and reticular) or C_2 veins at 3 centers in China during December 2007 and February 2009. Patients were randomized (3:1) to treatment with polidocanol 0.5% (spider vein), 1.0% (reticular vein) and 3% (C_2 vein) vs. placebo. 90.2 to 91.8% of patients treated with polidocanol were positive responders, compared to 5.3 to 14.3% treated with placebo. Patient satisfaction rates were 86.9 to 91.8% in polidocanol-treated patients vs 27.3 to 38.1% in placebo-treated patients. There were no SAEs. AEs consisted of mild to moderate local tenderness, pain, pigmentation and nausea.

9.2 Labeling Recommendations

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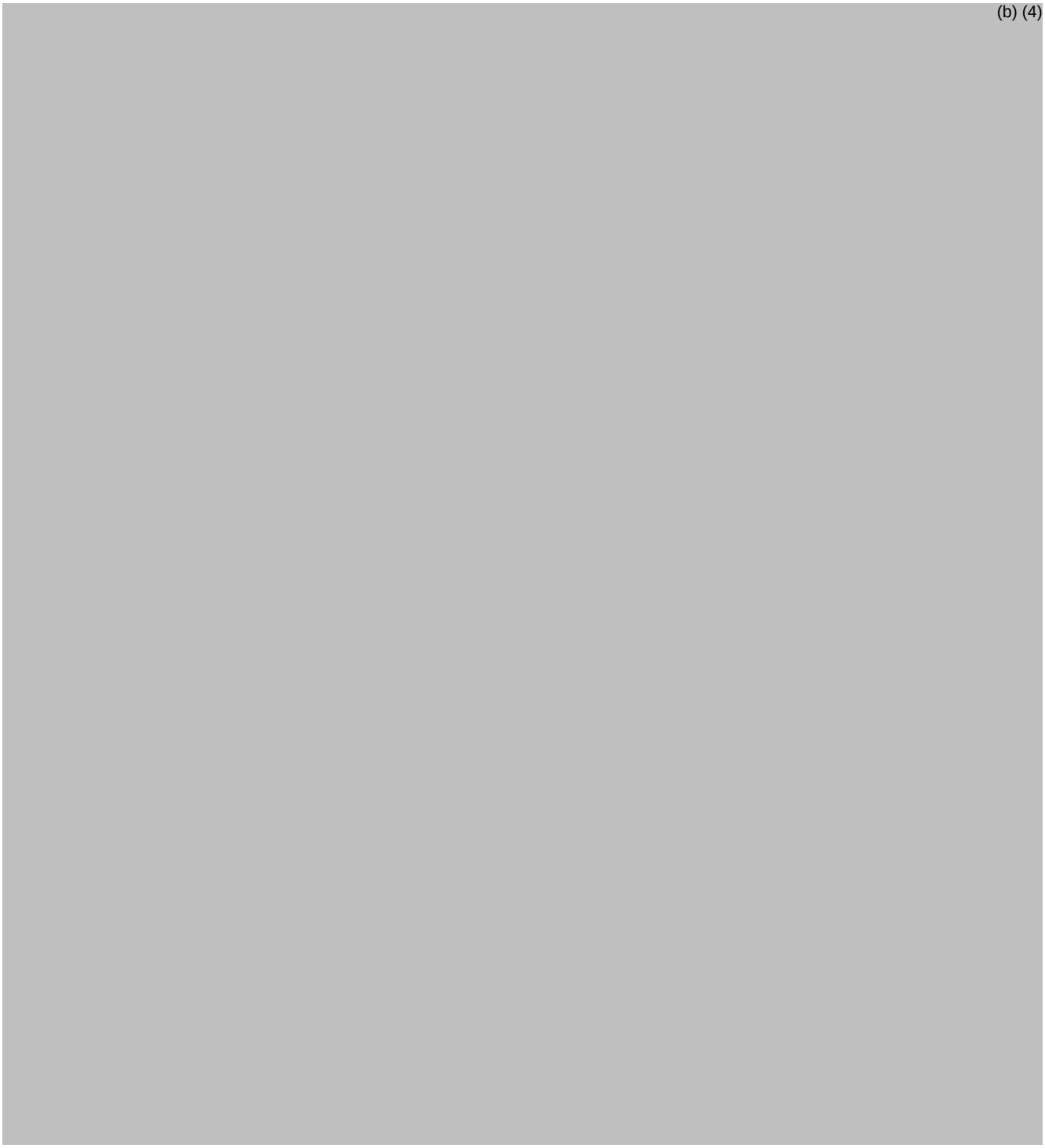
(b) (4)



9.3 Advisory Committee Meeting

Not applicable.

9.4 Detailed description of individual studies

9.4.1 Clinical classification of varicose veins

CEAP- Classification[4] of chronic venous disorders according to Eklöf et al., 2004
C_0: No visible or palpable signs of venous disease.
C_1: Telangiectases (spider veins) or reticular veins.
C_2: Varicose veins; distinguished from reticular veins by a diameter of 3 mm or more.
C_3: Edema.
C_4: Changes in skin and subcutaneous tissue secondary to CVD, now divided into 2 subclasses to better define the differing severity of venous disease:
C_{4a}: Pigmentation or eczema.
C_{4b}: Lipodermatosclerosis or atrophie blanche.
C_5: Healed venous ulcer.
C_6: Active venous ulcer.
S: Symptomatic (ache, pain, tightness, skin irritation, heaviness, muscle cramps)
A: Asymptomatic

Etiological classification

Ec: congenital	Ep: primary
Es: secondary (post thrombotic)	En: no venous cause identified

Anatomic classification

As: superficial veins	Ap: perforator veins
Ad: deep veins	An: no venous location identified

Pathophysiologic classification

Pr: reflux	Po: obstruction
Pr,o: reflux and obstruction	Pn: no venous pathophysiology identifiable

Example: For the patient who has painful swelling of leg, varicose veins, and acute ulceration with duplex scan showing reflux of great saphenous vein above and below the knee, incompetent calf perforator veins, and axial reflux in femoral and popliteal veins, the classification is: **C**6,s**, E**p**, A**s,p,d**, P**r

Reticular veins
- Dilated bluish subdermal veins, usually 1 mm to less than 3 mm in diameter. Usually tortuous.
- Excludes normal visible veins in persons with thin, transparent skin.
- Synonyms include blue veins, subdermal varices, and venulectasies.
- In this study the term “reticular veins” or “reticulars” was used.

Telangiectases
Confluence of dilated intradermal venules less than 1 mm in caliber. Synonyms include spider veins, hyphen webs and thread veins. In this study the term “spider veins” or “spiders” is used.

9.4.2 EASI trial

Note: Only portions of the protocol and study report which have not been discussed in the earlier efficacy and safety review sections of this review are presented below.

Objectives of the EASI trial

Primary objective:

- Efficacy of polidocanol in the treatment of C_1 veins compared to placebo

Secondary objectives:

- Efficacy of polidocanol compared to Sodium Tetradecyl Sulfate.
- Safety of polidocanol
- Patient satisfaction with the treatment

Experimental Design: A prospective randomized, placebo and comparator controlled, double blind, comparative, multicenter study (to be performed at approx 20 centers in Germany.

It was planned that at least 216 patients with C_1 veins will be evaluated:

- 108 patients with C_1 spider veins treated with polidocanol 0.5% or Sodium Tetradecyl Sulfate 1% or placebo (isotonic saline solution);
- 108 patients with C_1 reticular veins treated with polidocanol 1 % or Sodium Tetradecyl Sulfate 1% or placebo.

At each of the 20 participating centers, there were at least 3 patients treated with polidocanol, 2 patients with Sodium Tetradecyl Sulfate 1% and 1 patient with isotonic saline (placebo).

Dose: The dose in this study was based on the approved dose for polidocanol that is licensed in Germany. The concentration of polidocanol was dependent on the diameter of the C_1 vein (reticulars, which are between 1 mm and 3 mm in diameter were be injected with polidocanol 1%, and spiders with a diameter <1 mm were injected with 0.5% polidocanol. The maximum dose of polidocanol 1% per treatment session was 2.4 ml in the R group; and that of polidocanol 0.5% was 4.8 ml in the S group. The exact amount injected was decided by the treating physician.

Inclusion criteria

1) Subjects were males or females, 18-70 years old
2) C_1 veins
3) Willing and able to provide written informed consent
4) For females of childbearing potential: willing and able to use reliable contraceptive methods throughout the study

Exclusion criteria There were 33 exclusion criteria:

1. Patients with C_2-C_6 venous insufficiency
2. Patients with CEAP-classifications: E_s and $E_{c,}$ $A_{D,}$ P_O
3. Patients who had already undergone sclerotherapy, laser treatment and surgery of C_2-C_6 veins during the last 12 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
8. Patients with ***all*** of the following risk factors of thrombosis:
   - taking hormonal contraceptives or receiving hormone replacement therapy,
   - adiposity (body mass index > 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 ASCLERA™
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., antabuse) or similar medication.
33. Regular use of anticoagulants (except platelet aggregation inhibitors, i.e., low dose ASS)

Endpoints The **primary efficacy variable** was improvement of treated veins on digital images, on a 5-grade scale, evaluated **12 weeks** (± 2 weeks) after the last injection. Comparison between polidocanol and placebo (isotonic saline).

Secondary efficacy variables are listed earlier in this review in section 6.1.1 Methods.

The patients rated their satisfaction with the current treatment at Visit 4 and 5 using the following verbal rating scale; the assessment was to be made by allocation to one of the five categories:

very unsatisfied	somewhat unsatisfied
slightly satisfied	satisfied
very satisfied	

Digital images of the treatment area were taken at Visit 1 before injection. The images taken at Visit 3 and Visit 4 were compared to the images documenting the status at Visit 1 and were evaluated by each investigator and two independent blinded medical experts.

The treatment area was rated according to a 5-grade scale, where

1 is “worse than before”	2 is “same as before”
3 is “moderate improvement”	4 is “good improvement”
5 is “complete treatment success”	

The success rate was derived from the 5-grade-scale where treatment success was grade 4 or 5, and treatment failure was grade 1, 2 or 3 on the 5-point scale.

If there was a difference of more than 2 points in the score between the investigator and/or one of the two medical experts the digital images were reassessed a second time by all of them. If there was still a difference of more than 2 points this evaluation was deleted.

To assess the reliability of assessment between the three assessors (investigator and 2 blinded observers), intra-individual differences between the assessments on the 5-grade scale were calculated and compared in total and within each treatment group. The correlation coefficients of the 5-grade score between different assessors were calculated.

If there was no evidence that the assessments differ or include any bias between assessors, the median rating of the three assessors (investigator, two independent blinded medical experts) was used as the endpoint for the statistical analysis. Since this was a measurement of change in the clinical assessment of veins, no baseline adjustment was necessary.

Further secondary analysis were done with the individual ratings of each of the assessors.

Safety Variable

The safety variables are the occurrence of local and general adverse events, including

(a) Pain during and 2 min after injection at Visit 1 (and 2 and 2a if applicable),

(b) the Investigator's assessments at Visits 1, 2, (2a and 2b if applicable), 3 and 4 for presence or absence of Hyperpigmentation, Hematoma, Neovascularization and Other findings,

(c) Subjective sensations at Visits 1, 2, (2a and 2b if applicable), 3 and 4, such as Itching, Pain, Warmth, Burning, and Others,

(d) Basic safety variables in routine clinical chemistry and haematology tests, urinalysis, Thrombophilia testing, Vital signs, ECG, and

(e) occurrence of DVT (by duplex ultrasound examination at Visits 0, 2, 2a, 2b, and 3).

(a) Pain during treatment session at Visit 1 (and 2 and 3 if applicable)
The patient was asked whether he/she had experienced pain {rated according to the following 5 grade scale: (1) Extremely severe, (2) Severe, (3) Moderate, (4) Mild, and (5) None}:
during injection (irrespective of its degree), and 2 minutes after the injection

(b) Investigator's assessments at Visits 1, 1a, 2, (2a, 3 and 3a if applicable), 4 and 5
At each visit the investigator assessed the treated area for the presence or absence of each of the following signs:

Hyperpigmentation	Hematoma
Neovascularization	Other

(c) Subjective sensations at Visits 1, 1a, 2, (2a and 3, 3a if applicable), 4 and 5
The patient was asked whether he/she had experienced {rated according to the following 5 point scale: (1) Extremely severe, (2) Severe, (3) Moderate, (4) Mild, and (5) None} the following sensations in the area of treatment immediately after and one hour after the injections at Visit 1 (and if applicable Visit 2 and Visit 3) and since the last assessment at Visit 1a, 2a, 3a, 4 and 5:

Itching	Pain
Warmth	Burning
Other	

(d) Basic safety variables
(1) Blood and urine samples were collected for routine clinical laboratory tests (below).
(2) Clinical chemistry: Sodium, potassium, calcium, SGOT, SGPT, gamma-GT, alkaline phosphatase, LDH, GLDH, total bilirubin, total protein, albumin, glucose, urea, creatinine, C-reactive protein, partial thromboplastin time (PTT), prothrombin time INR
(3) Hematology: Hemoglobin, hematocrit, erythrocytes, total leucocytes, platelets
(4) Urinalysis: pH, blood, protein, glucose, ketones, nitrite
(5) Thrombophilia testing: Blood samples were collected at Visit 0 for the following tests:
Protein C resistance, Increased Factor VIII activity, Antithrombin III deficiency, Protein C deficiency, Protein S deficiency, Prothrombin 20210 gene mutation, and Antiphospholipid syndrome. The results of the thrombophilia testing must be available before the first treatment at Visit 1.
(6) Vital signs
(7) ECG taken at screening and at 30±15 min after the first treatment with study drug at Visit1 (PR, QRS and QT_c intervals)

(e) Occurrence of DVT (by duplex ultrasound examination): The number of patients who develop DVT were counted and summarized in a frequency table by treatment group and visit.

Statistical analysis

The primary efficacy variable was the assessment of the treatment of the veins, according to a 5-grade scale, made 12 weeks (± 2 weeks) after the last injection (comparison between polidocanol and placebo). Since this rating scale is a measurement of the change in the clinical assessment of veins, no baseline-adjustment was necessary.

The Wilcoxon-Mann-Whitney test was used to detect a shift in the location of the treatment groups. A stratified version of this test was used to include and adjust for the factor center.

The secondary efficacy variables are defined as follows:

- The patient satisfaction after 12 and 26 weeks was compared between treatment groups by means of the Wilcoxon-Mann-Whitney test.
- The assessment of improvement of veins according to a 5-grade scale made 26 weeks (± 4 weeks) after last injection; the same statistical test was performed as for the primary efficacy parameter (comparison between polidocanol and placebo)
- The assessment of improvement of veins according to a 5-grade scale was correlated with the patient satisfaction scores.
- The success rate was derived from the 5-grade-scale as follows:

Treatment success: Grade 4 or 5 on the 5-point scale

Treatment failure: Grade 1, 2 or 3 on the 5-point scale

The success rate was calculated at 12 and 26 weeks after last injection for each treatment group separately (comparison between polidocanol and Sotradecol® at 12 weeks and 26 weeks comparison between polidocanol and placebo at 12 and 26 weeks). The exact test of Fisher was used to compare the success rates between the treatment groups. A test for homogeneity of odds-ratios across all centers (equal odds-ratio across all centers) was performed in addition.

Sample size:

The significance level was set to **1% *for sample size calculation***. Based on previous data for the same indication, drug (0.5% and 1% polidocanol), and efficacy parameter, an average score of 4 in the active group was observed. A pooled standard deviation of 1.2 units between active group and placebo was calculated. A two group t-test with a **1% two-sided significance level** would have **90%** power to detect a difference in means of 1.29, assuming that the common standard deviation was 1.2, when the sample sizes were **54** in the polidocanol group (0.5 or 1%) and **18** in the placebo group. The sample size of **36** for Sotradecol® was determined on the assumption that Sotradecol® has an equal effect.

The total sample size was calculated as **108** patients in each group:

Group S (spider veins)
54 patients treated with polidocanol 0.5%
36 patients treated with Sotradecol® 1%
18 patients treated with Isotonic Saline

Group R (reticulars)
54 patients treated with polidocanol 1%
36 patients treated with Sotradecol® 1%
18 patients treated with Isotonic Saline

Assuming a drop-out rate of 20%, **270** patients were planned to be enrolled to obtain **216** evaluable patients (i.e. patients included into the Full analysis subset).

Group C (spider veins or reticulars) for plasma polidocanol concentrations: The study also planned to enroll:
9 patients with spider veins to be treated with polidocanol 0.5%

9 patients with reticular veins to be treated with polidocanol 1%

However, the level of statistical significance to be used for analysis was **"two-sided with a significance level of 5%**." A pooled stratified analysis between Group S and Group R was to be done, followed by a separate analysis in each stratum. A similar statistical analysis plan was used for comparison of polidocanol vs Sotradecol® and polidocanol vs placebo.

Actual enrolled and analyzed: 338 (safety data set)

Group S (spider veins)
82 patients treated with polidocanol 0.5%
51 patients treated with Sotradecol® 1%
27 patients treated with Isotonic Saline

Group R (reticulars)
76 patients treated with polidocanol 1%
54 patients treated with Sotradecol® 1%
26 patients treated with Isotonic Saline

Group C (spider veins or reticulars) for plasma polidocanol concentrations:
12 patients with spider veins treated with polidocanol 0.5%
10 patients with reticular veins treated with polidocanol 1%

Procedure

Formulation: Study drug was dispensed in glass ampoules (filled with 2 ml of product) packed in sterile condition for surgical use. A treatment unit comprised 1 to 3 ampoules of polidocanol 1% or 0.5%.

Controls: Sotradecol® 1% (2 ml per ampoule) was the positive control. Physiological (0.9%) saline (154 mmol/l sodium and 154 mmol/l chloride) was the negative control.

Dose administration: The assigned study drug was injected into C_1 veins selected for evaluation. The investigator wrote the description of the exact location of the treatment area (e.g., --- cm below a prominent scar or birthmark or approx. 4 inches below the knee, etc.), and marked on a diagram of the leg the area treated.

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.

Blinding: To maintain blinding, dedicated unblinded study personnel not involved in the assessment of study subjects prepared the syringe for injection by aspirating the solution from the appropriate ampoule and handing it over to the blinded investigator.

Compliance: The study drug was given by intravenous injection by the investigator.

Pre-study screening: At Visit 0, between 1 and 7 days before treatment, the patients were screened and the varicose veins assessed. A standardized ultrasound examination was performed to exclude DVT. A thorough blood testing for thrombophilia was performed, including Protein C resistance, Increased Factor VIII activity, Antithrombin III deficiency, Protein C deficiency, Protein S deficiency, Prothrombin 20210 gene mutation, and Antiphospholipid syndrome.

Study procedures: The study procedures are outlined in the study flow chart (Figure 8), below.

The thrombophilia test results must be reviewed before the first treatment at Visit 1.

The veins selected for injection must be clearly visible C_1 veins (spider veins or reticular veins) and the treatment area was approximately 12x12 cm (4.7 x 4.7 inches). For study purposes, areas dominated by one of the C1 vein types, i.e. reticulars or spiders, were chosen. Only the selected veins in the treatment area were injected and evaluated.

Figure 8 Study flow chart

	Visit 0 (Screening)	Visit 1 [1] (1-14 days after screening)	Visit 1a 1 week (± 3 days) after Visit 1	Visit 2 3 weeks (± 7 days) after Visit 1	Visit 2a 1 week (± 3 days) after Visit 2	Visit 3 3 week (± 7 days) after Visit 2	Visit 3a 1 week (± 3 days) after Visit 3	Visit 4 12 weeks (± 2 weeks) after last injection	Visit 5 26 weeks (± 4 weeks) after last injection
					Only performed if 2nd injection is given	Only performed if 2nd injection is given	Only performed if 3rd injection is given		
Informed consent	x								
Documentation of area to be treated	x								
Inclusion and exclusion criteria	x	x							
Personal data and medical history	x								
Physical examination	x								
Vital signs	x	x[2]	x	x[2]	x	x[2]	x	x	x
Pregnancy test if applicable	x	x		x[3]		x[3]			
Clinical laboratory tests	x	x[4]						x	
ECG	x	x[4]							
Ultrasound to exclude DVT	x		x					x	
Thrombophilia testing	x								
Digital image of area to be treated	x	x (before injection)						x	x
Treatment (injection of study medication)		x		x[5]		x[5]			
Micro-thrombectomy			x[6]	x[6]	x[6]	x[6]	x[6]		
Compression stocking [7]		x		x[5]		x[5]			
Blood sampling for concentrations of polidocanol [8]		x						x[11]	
Assessment of change in health and general adverse events		x	x	x	x	x	x	x	x
Evaluation of treatment success by investigator [9]				x		x		x	x
Assessment of treatment area by investigator and patient		x	x	x	x	x	x	x	x
Current medication	x	x	x	x	x	x	x	x	x
Patient satisfaction [10]								x	x
Patient estimation of drug (placebo or active)								x	x
Appointment for next visit	x	x	x	x	x	x	x	x	
Study closure									x

[1]before visit 1 the results of the laboratory tests and thrombophilia testing must be available; [2]Before and 30 (± 15) min after treatment; [3]only necessary if second or third injection was given; [4]30 minutes (± 15) after treatment; [5]If according to the investigator there was not complete improvement after the first or second treatment session, (i.e. grade 5 was not achieved) and therefore a second or third treatment was necessary; [6]If deemed necessary; [7]Compression stocking had to be worn for 2 weeks during the day from immediately after the injection but not on the day before the next visit or the day of the visit; [8]Only for group C: before first injection and 5 min, 30 min, 1h, 1.5h, 2h, 3h and 6h after first injection for plasma concentrations of polidocanol; [9]before treatment in order to evaluate if further treatment was necessary; [10]Patients received the baseline picture (digital image) in order to assess their satisfaction with the treatment; [11]At least one week after the last varicose vein injection, Group C only for PK sample and Questioning about which medications, cosmetics creams, oils, shampoos etc. used during the 7 days prior to the baseline PK sampling and in the 7 days before the additional PK sampling

Digital photographs of the treatment area 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, using identical digital camera systems and a standardized procedure of taking digital images.

At Visit 1 the patient's veins were injected with polidocanol 1% (reticular veins) or polidocanol 0.5% (spider veins) or Sotradecol® 1% or isotonic saline solution following a detailed standardized guideline for sclerotherapy. The veins were injected with the patient lying in the supine position. Thirty minutes later an ECG was recorded. Thirty (±15) min later a blood sample was taken for safety clinical laboratory parameters.

After injection the patient wore a compression stocking for two weeks to close the vein lumen and facilitate the development of fibrous tissue formation. The patient was encouraged to walk for at least 15-20 minutes after treatment. The compression stocking was removed on the day before the next visit so that the compression skin marks vanish before the visit.

The patient could receive a second and a third injection of the same assigned treatment if the first treatment was not fully successful.

The patient returned for a further 3 visits (or 4 or 5 visits, if a second or third injection is 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.

Patients receiving a second injection returned for the follow up Visit 2a, at 3 weeks ± 7 days after Visit 2. Patients receiving a third injection returned for the follow up Visit 2b at 1 week ± 3 days after Visit 2a.

At Visit 2, Visit 2a and Visit 2b microthrombectomy was performed if necessary. Microthrombectomy – the expression of small coagula possibly appearing after the treatment – was necessary to prevent hyperpigmentation.

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. Also 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. Also 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.

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

Digital photographs of the treatment area, using identical digital camera systems and a standardized procedure, were taken immediately before injection (Visit 1), at 12±2 weeks (Visit 3, the protocol-specified primary efficacy endpoint evaluation), and at 26±4 weeks (Visit 4, the protocol-specified secondary endpoint evaluation).

The improvement of the veins according to the 5-grade scale was assessed by the investigator and two independent blinded medical experts, and the median of these values was used to calculate the mean values. For one patient (437) the evaluation of one of the medical experts was not available and therefore the median was calculated from the evaluation of the investigator and the second medical expert.

If there was a difference of more than 2 points in the score between the investigator and/or one of the two medical experts the digital images had to be reassessed a second time by all of them. A difference of more than 2 points in the treatment success as assessed by the investigator and the two medical experts

after re-evaluation was observed for patient 415. Therefore, this evaluation was classified as not evaluable; a worst case-approach was applied and the evaluation was classified as treatment success as this patient was assigned to the active comparator Sotradecol®.

To assess the reliability of assessment of digital photographs between the three assessors (investigator and 2 blinded observers), intra-individual differences between the assessments on the 5-grade scale were calculated and compared in total and within each treatment group. The correlation coefficients of the 5-grade score between different assessors were calculated. In addition, intra-class correlation coefficients were calculated.

If there was no evidence that the assessments differed or included any bias between assessors, the grading was used and aggregated as follows:

For statistical analysis, the median rating of the three assessors (investigator, two independent blinded medical experts) was used as endpoint for the statistical analysis. Further secondary analysis was done with individual ratings of each of the assessors.

9.4.3 The French Polidocanol Registry survey

The French Polidocanol Registry: In the French Polidocanol Registry, the sponsor performed a questionnaire survey of 1,605 patients who had received polidocanol at least once during 6444 sessions were surveyed within a four years period, covering 3,357 patient-years.

All physicians taking part in the French Registry were contacted and asked to participate in the follow up registry. 12 of the 22 physicians agreed. They were asked to retrieve data from those patients of the French Registry that have been at least treated once with polidocanol.

Data were retrieved either by entries from the patient files or by direct contact during follow up visits. Patients who were not treated and recorded during the survey time of the French Registry or did not receive polidocanol during that time were not included.

Each patient was given a dedicated number, and the patient's sclerotherapy treatment session was documented.

The investigators noted the agent that was used, its concentration, the volume applied and the date when the session took place, whether liquid and foam was administered, and in cases where foam sclerosants were applied the exact ratio between liquid and air was provided. Also the usage of ultrasound guidance was asked.

In every session the caliber of the varicose veins that were treated was specified.

Adverse events were asked explicitly and the following adverse reactions occurring most commonly with sclerotherapy were provided in a list on the CRF:

- muscular vein thrombosis
- allergic reaction
- anaphylactic shock
- paresthesias
- cutaneous necrosis
- vaso-vagal fainting
- visual disturbances
- headache (on treatment day)
- nausea and vomiting (on treatment day)
- deep vein thrombosis

Physicians could also add any adverse events that were not mentioned on the list on a free text field.

In case a deep vein thrombosis was reported further specification was inquired: i.e. description of the leg (left leg, right leg), the personal history of DVT and whether investigations for thrombophilia were done.

For each adverse event that occurred during the survey time the date of the presumed treatment session that might have caused the adverse event was indicated and the physicians notified the period of onset after treatment (immediate (on treatment day), medium (next day ≤ 1 month), delayed (> 1 month ≤ 2 years). In a description, more details or possible other reasons of the adverse event could be given.

For every adverse event the physician stated the relationship (excluded, unlikely, likely) of sclerotherapy regarding the onset of the adverse event.

In April 2008, the data log point was defined and thus indicated the end of the registry.

CRFs were collected and data were entered into an SAS database. Double data entry was performed for all data. After data reconciliation the data base was locked. Data were evaluated and compiled in a statistical report. Data were analyzed with SAS software (SAS Institute Inc. Cary, NC, USA) in the Department of Epidemiology and Biostatistics of the (b) (4).

Only 5 adverse reactions were due to an injection with polidocanol liquid: one visual disturbance and one cramp were observed immediate-term, two inflammatory reactions were observed mediate term after administration and one pigmentation was observed delayed term.

REFERENCES

[1] Guex J-J, Allaert FA, Gillet J-L, Chleir F. Immediate and midterm complications of sclerotherapy: Report of a prospective multicenter registry of 12,173 sclerotherapy sessions. *Dermatol Surg* 2005; 31: 123-8.

[2] Hamel-desnos C, Desnos P, Wollmann J-C, Ouvry P, Mako S, Allaert F-A. Evaluation of the efficacy of polidocanol in the form of foam compared with liquid form in sclerotherapy of the greater saphenous vein: initial results. *Dermatol Surg* 2003; 29: 1170-1175.

[3] Jiwei Z, Schliephake DE, Malouf GM, Otto J, Zaiping J, and Yong-quan G. Polidocanol/lauromacrogol 400 vs. placebo for sclerotherapy of C_1 and C_2 non-saphenous trunk varicose veins: a double-blind, randomized, controlled, multi-center clinical trial (ESAChina Study). Presented at *World Congress of the International Union of Phlebology (UIP) in September 2009* in Monaco. (Source: Sponsor's abstract of the trial and the set of slides presented at the UIP conference.)

[4] Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, Meissner MH, Moneta GL, Myers K, Padberg FT, Perrin M, Ruckley CV, Smith PC and Wakefield TW for the American Venous Forum International Ad Hoc Committee for Revision of the CEAP Classification, Helsingborg, Sweden. *J Vasc Surg* 2004; 40: 1248-52.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KHIN M U

11/16/2009

The sustained cosmetic benefit obtained appears to exceed the risk of local AEs which are minor and transient, and absence of deep vein thrombosis. The efficacy and safety profile of polidocanol liquid appears to be similar to that of Sotradecol, another liquid sclerosant which was approved for treatment of varicose veins by FDA Office of Generic Drugs in 2004. Based on review of the clinical data, the recommendation is approvable, pending the sponsor's response to comply with the suggested changes to labeling.

DSI CONSULT: Request for Clinical Inspections

Date: August 21, 2009

To: Leslie Ball, M.D., Director, Division of Scientific Investigations
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Dr. Norman Stockbridge, M.D., Ph.D. Division Director
Division of Cardiovascular and Renal Products

Dr. Khin U, M.D., Medical Officer and Review Team Leader
Division of Cardiovascular and Renal Products

From: Michael Monteleone, M.S., Regulatory Project Manager, DCaRP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-21-201
Applicant/ Applicant contact information (to include phone/email):

Chemische Fabrik Kreussler & Co., GmbH.
Attention: Stephan Travers, M.D.
Rheingaustrasse 87-93
D-65203 Wiesbaden
Germany

US Agent:
Howard Smith, INC Research
675 Peter Jefferson Parkway
Suite 120
Charlottesville, VA 22911

804-556-6357
hsmith@incresearch.com

Drug Proprietary Name: N/A
NME or Original BLA (Yes/No): NME
Review Priority (Standard or Priority): Class 2 Re-Submission, 6 month clock

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): N/A

PDUFA:
Action Goal Date: January 10, 2010
Inspection Summary Goal Date: November 26, 2009

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Dr. med. Margrit Simon, (Center # 13) Hauptstr. 131, 10827 Berlin, GERMANY	EASI (HCR: 1085/KRS)	32	Treatment of C1 varicose veins
PD Dr. med. M. Stücker, (Center #16) St. Maria Hilf Krankenhaus, 44805 Bochum, GERMANY	EASI (HCR: 1085/KRS)	29	Treatment of C1 varicose veins

III. Site Selection/Rationale

In the history of this application, previous FDA GCP inspections (assignment date 11-Mar-2004) revealed problems with data integrity at two of three sites inspected {MICA study in Michigan (John Pfeifer, M.D.) and California (Mitchel Goldman, M.D.)}; FDA inspection found the third site in Ohio (the OHIO study, Joann Lohr, M.D.) to have valid data, but it enrolled only 75 patients treated with the study drug. Dr. Roy Blay in DSI was the reviewer for these inspections and EIRs.

The new pivotal data for this Application comes from a 338-patient prospective, randomized, double-blind, placebo- and comparator-controlled, multicenter, EASI (Efficacy and safety of Aethoxysklerol® compared to Sodium tetra-decyl sulfate and Isotonic saline (placebo) for the treatment of reticular veins and spider veins) trial performed at 19 centers in Germany.

While the efficacy and safety results were not significantly different or driving the results at any center, based on the above history, a consideration was made to conduct GCP inspections of centers that enrolled the largest number of patients to verify data integrity and protocol adherence.

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
__X__ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Michael Monteleone, RPM at 301-796-1952 *or* Dr. Khin U, Medical Officer at 301-796-1156.

Concurrence: (as needed)

____K. U_____ Medical Team Leader

__N. Stockbridge__ Division Director (for foreign inspection requests or requests for 5 or more sites only)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21201	ORIG 1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1% (b) (4)
NDA 21201	ORIG 1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1% (b) (4)
NDA 21201	ORIG 1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1% (b) (4)
NDA 21201	ORIG 1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1% (b) (4)

/s/

MICHAEL V MONTELEONE
08/21/2009

KHIN M U
08/21/2009

NORMAN L STOCKBRIDGE
08/21/2009

DSI CONSULT: Request for Clinical Inspections

Date: August 6, 2008
To: Leslie K. Ball, M.D., Director, DSI, HFD-45
Constance Lewin, Chief, GCP Branch 1, HFD-46
Sharon K. Gershon, Pharm.D., GCPB 1, HFD-46

Through: Norman Stockbridge, M.D., Ph.D., Director, DCaRP

From: Alisea Crowley, Ph.D., Regulatory Health Project Manager, DCaRP

Subject: **Request for Clinical Inspections**
NDA 21-201
Chemische Fabrik Kreussler & Co., GmbH
Aethoxysklerol® (Polidocanol)

Protocol/Site Identification:

This NDA Amendment provides for the following indication: the use of Aethoxysklerol® (0.5% and 1.0% solution for injection) as a sclerosant in the treatment of patients with C_1 varicose veins. The pivotal data for this Application comes from a 338-patient prospective, randomized, double-blind, placebo- and comparator-controlled, multicenter, EASI (**E**fficacy and safety of **A**ethoxysklerol® compared to **S**odium tetra-decyl sulfate and **I**sotonic saline (placebo) for the treatment of reticular veins and spider veins) study performed at 19 centers in Germany. Long-term safety evaluation is made on patients after sclerotherapy with polidocanol from the French Polidocanol Registry 2008 (FPR 2008).

The following protocols/sites essential for approval have been identified for GCP inspection.

Indication	Protocol #	Site (Name and Address)	Number of Subjects
Treatment of C_1 varicose veins	EASI (HCR: 1085/KRS)	Dr. med. Margrit Simon, (Center # 13) Hauptstr. 131, 10827 Berlin, GERMANY	32
Treatment of C_1 varicose veins	EASI (HCR: 1085/KRS)	PD Dr. med. M. Stücker, (Center #16) St. Maria Hilf Krankenhaus, 44805 Bochum, GERMANY	29
Treatment of C_1 varicose veins	The French Polidocanol Registry 2008 (FPR 2008)	Dr. Lausecker, (Center #12) 7 Bis Rue de L'Hopital, 67600, Selestat, FRANCE	25

Note: In the history of this application, previous FDA GCP inspections (assignment date 11-Mar-2004) revealed problems with data integrity at two of three sites inspected {MICA study in Michigan (John Pfeifer, M.D.) and California (Mitchel Goldman, M.D.)}; FDA inspection found the third site in Ohio (the OHIO study, Joann Lohr, M.D.) to have valid data, but it enrolled only 75 patients treated with the study drug which was not adequate to evaluate safety issues. Dr. Roy Blay in DSI was the reviewer for these inspections and EIRs.

Based on the above history, while the efficacy and safety results were not significantly different or driving the results at any center, a consideration was made to conduct GCP inspections of centers that enrolled the largest number of patients to verify data integrity.

International Inspections:

We have requested inspections because (please check appropriate statements):

____ There are insufficient domestic data

__X__ Only foreign data are submitted to support an application

____ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

_____ Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **January 21, 2009**. We intend to issue an action letter on this application by (action goal date) **December 26, 2008**.

Should you require any additional information, please contact Alisea Sermon.

Concurrence: (if necessary)

Khin Maung U, M.D., Acting Team Leader / Medical Reviewer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Alisea R. Crowley
8/6/2008 02:17:12 PM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER REVIEW

Request for Special Protocol Assessment (SPA)

IND #:	35,139 (Sponsor's Serial # 078)	**RELATED NDA:**	**21-201** (#035)
IND Volumes:	A 26.1	Document ID#:	N-000-C
SPONSOR:	Chemische Fabrik Kreussler & Co., GmbH	DRUG NAME:	Aethoxysklerol®
DATE SUBMITTED:	*12-Jun-2006*	DATE RECEIVED:	*14-Jun-2006*
DATE ASSIGNED:	*16-Jun-2006*	DATE COMPLETED:	*30-Jun-2006*
MEDICAL OFFICER:	Khin Maung U, MD		

SUBMISSION **Amended Protocol – EASI Study:** ***Efficacy and safety of Aethoxysklerol® compared to sodium tetra-decyl sulfate and isotonic saline (placebo) for the treatment of reticular veins and spider veins***

Indication Sclerotherapy of C_1 veins: Group S: spider veins (spiders) and Group R: reticular veins (reticulars)

1. BACKGROUND HISTORY

The sponsor submitted a request for SPA on 06-Mar-2006, incorporating the Division's advice to focus on safety, including DVT-screening, in a protocol titled the **EASI Study**. It is a prospective randomized, placebo- and comparator-controlled, double-blind, comparative, multicenter study of 216 evaluable patients with C_1 varicose veins to determine the efficacy and safety of 0.5% and 1% Aethoxysklerol® solution at approximately 20 centers in Germany. This will be the main pivotal study (in conjunction with the OHIO study) in NDA 21-201 which the sponsor plans to submit. The study aims to provide long-term safety characteristics of Aethoxysklerol®, particularly the incidences of DVT and recanalization of treated veins at 3 and 6 months after the injection of Aethoxysklerol®.

In the SPA, The sponsor committed to submit also the safety data from the "French Registry[1]". The sponsor will contact at least 700 patients treated with Aethoxysklerol® 0.5% and 1% to determine prospectively the long term adverse events (from the time of the procedure to the time of the survey), and create CRFs to transfer data for a safety analysis.

Review of the SPA completed on 14-Apr-2006 identified several issues related to efficacy, safety, the endpoints, the statistical plan and electronic data processing. By letter dated 20-Apr-2006, the Division provided comments on the SPA and answers to the sponsor's questions.

Following a phone contact with me on 17-May-2006, the sponsor submitted an amended EASI-protocol incorporating the changes suggested by FDA, and a list of questions. Please refer to my review of the SPA (filed in DFS dated 14-Apr-2006) for detailed description and comments on the original EASI-study protocol. In this review, I will comment on appropriateness and adequacy of the modifications made to the amended protocol (8th draft).

2. CLINICAL BACKGROUND

2.1	**Literature Review**	A relatively recent published prospective multicenter registry of 12,173 sclerotherapy treatments[1] in France including 5,434 sessions with liquid sclerosants (75% using Aethoxysklerol®) showed the relative safety of liquid sclerotherapy with Aethoxysklerol®. The sponsor committed to submit safety data from the "French Registry" for at least 700 patients treated with Aethoxysklerol® 0.5% and Aethoxysklerol® 1.0%.
2.2	**Other relevant NDAs and INDs**	NDA 21-201 for Aethoxysklerol® by the same sponsor. (b) (4) (Varisolve) – foam sclerosing agent from another sponsor.

3. PROPOSED CLINICAL TRIAL – Amended EASI-study protocol

5.1	**Monitors and their Qualifications**	No change.
5.2	**Principal Investigator**	No change.

[1] Guex J-J, Allaert FA, Gillet J-L, Chleir F. Immediate and midterm complications of sclerotherapy: Report of a prospective multicenter registry of 12,173 sclerotherapy sessions. *Dermatol Surg* 2005; 31: 123-8.

5.3	**Institutional Review Board**	Not specified in submitted protocol.
5.4	**Title:**	**Amended Protocol – EASI Study:** ***Efficacy and safety of Aethoxysklerol® compared to Sodium tetradecyl sulfate and Isotonic saline (placebo) for the treatment of reticular veins and spider veins***
5.5	**Objectives of the study**	No change: Primary objective: • Efficacy of Aethoxysklerol® in the treatment of C_1 veins compared to placebo No change: Secondary objectives: • Efficacy of Aethoxysklerol® compared to Sodium Tetradecyl Sulfate. • Safety of Aethoxysklerol® • Patient satisfaction with the treatment
5.6	**Experimental Design**	No change: Briefly a prospective randomized, placebo and comparator controlled, double blind, comparative, multicenter study (to be performed at approx 20 centers in Germany). At least 216 patients with C_1 veins will be evaluated; • 108 patients with C_1 ***spider*** veins will be treated with Aethoxysklerol® 0.5% or Sodium Tetradecyl Sulfate 1% or placebo (isotonic saline solution); • 108 patients with C_1 ***reticular*** veins will be treated with Aethoxysklerol® 1 % or Sodium Tetradecyl Sulfate 1% or placebo. Each center will enroll at least 3 patients treated with Aethoxysklerol®, 2 patients with Sodium Tetradecyl Sulfate 1% and 1 patient with isotonic saline (placebo).
5.7	**Patient population**	No change.
5.8	**Procedure**	
	5.8.1 Formulation	No change.
	5.8.2 Controls	No change.
	5.8.3 Dose administration	No change.
	5.8.4 Blinding and Randomization	No change for Blinding. ***Protocol Change***: A sealed copy of the randomization code will be sent to DCaRP.
	5.8.5 Informed Consent	Not submitted with the protocol.
	5.8.6 Compliance	The study drug is given by intravenous injection by the investigator.
	5.8.7 Pre-study screening	***Protocol Change***: At Visit 0, between 1 and 14 days before treatment, the patients will be screened and the varicose veins will be assessed. A standardized ultrasound examination will be performed to exclude DVT. A thorough blood testing for thrombophilia will be performed, including Protein C resistance, Increased Factor VIII activity, Antithrombin III deficiency, Protein C deficiency, Protein S deficiency, Prothrombin 20210 gene mutation, and Antiphospholipid syndrome.
	5.8.8 Study procedures	***Protocol Change***: The sponsor stated that a new Visit 1a was added at 1 week ±3 days after the first injection to detect any ongoing DVT one week (±3 days) after injection. Ultrasound for DVT at Visit 0 (baseline) and Visit 4 (12 weeks after last injection) remain unchanged. Ultrasound for detection of (baseline) DVT was deleted from the 2nd and 3rd treatment visits. The first follow-up visit (Visit 2) is 3 weeks ± 7 days after injection at which time the patient may receive a second injection of the same allocated treatment if the first treatment was not fully successful, i.e., if the patient was not graded 5 on the 5-grade scale. The patient may receive a third injection of the same allocated treatment at Visit 3, if the second treatment was not fully successful, i.e., if the patient was not graded 5 on the 5-grade scale. At Visit 1a, 2, 2a, 3 and 3a microthrombectomy will be performed if necessary to prevent hyperpigmentation.

All patients will return for Visit 4 at 12 weeks ± 2 weeks after the last injection. The primary endpoint will be assessed and digital images will be taken. ***Protocol Change***: Also, the secondary endpoint of patient satisfaction will be assessed at Visit 4.

A final follow up visit (Visit 5) is at 26 weeks ± 4 weeks after the last injection at which time further digital images will be taken. ***Protocol Change***: Also, the secondary endpoint of patient satisfaction will be assessed at Visit 5.

The study procedures are outline in the amended study flow chart, below.

STUDY FLOW CHART

	Visit 0 (Screening)	Visit 1[8] (1-14 days after screening)	Visit 1a 1 week (± 3 days) after Visit 1	Visit 2 3 weeks (± 7 days) after Visit 1	Visit 2a 1 week (± 3 days) after Visit 2	Visit 3 3 week (± 7 days) after Visit 2	Visit 3a[1] 1 week (± 3 days) after Visit 2a	Visit 4 12 weeks (± 2 weeks) after last injection	Visit 5 26 weeks (± 4 weeks) after last injection
Informed consent	x								
Phlebological assessment and documentation of area to be treated	x								
Inclusion and exclusion criteria	x	x							
Review of exclusion criteria			x	x	x	x	x	x	x
Personal data and medical history	x								
Physical examination	x								
Vital signs	x	x[2]	x	x[2]	x	x[2]	x	x	x
Pregnancy test if applicable	x	x		x		x			
Clinical laboratory tests	x	x[3]						x	
ECG	x	x[4]							
Ultrasound to exclude DVT	x		x					x	
Thrombophilia testing	x								
Digital image of area to be treated		x (before injection)						x	x
Treatment (injection of study medication)		x		x[5]		x[5]			
Microthrombectomy			x[6]	x[6]	x[6]	x[6]	x[6]		
Compression stocking[7]		x		x[5]		x[5]			
Assessment of change in health and general adverse events		x	x	x	x	x	x	x	x
Evaluation of treatment success by investigator				x		x		x	x
Assessment of treatment area by investigator		x	x	x	x	x	x	x	x
Current medication	x	x	x	x	x	x	x	x	x
Patient satisfaction								x	x
Patient estimation of drug (placebo or active)								x	x
Appointment for next visit	x	x	x	x	x	x	x	x	
Study closure									x

[1]Only if complete treatment success (grade 5) is not achieved; [2]Before and 30 (± 15) min after treatment; [3]30 (± 15) min after treatment; [4]30 minutes (±15) after treatment; [5]If according to the investigator there is not complete improvement after the first or second treatment session, (i.e. grade 5 is not achieved) and a second or third treatment is necessary; [6]If deemed necessary; [7]Compression stocking will be worn for 2 weeks during the day from immediately after the injection but not on the day before the next visit or the day of the visit; [8]before visit 1 the results of the laboratory tests and thrombophilia testing must be available; [9]before treatment, to evaluate if further treatment is necessary.

5.8.9 Pharmacokinetic procedures

The sponsor continues to request a waiver to perform PK studies because analytical tests have not yet been completed to determine if a method can be developed sensitive enough to detect the expected plasma concentrations of polidocanol administered at relatively low doses (0.2 ~ 0.4 mg/kg BW).

On 03-Mar-2006, the sponsor submitted PK data of Aethoxysklerol 3% in ASK-00-01-00. The Clin-Pharm Reviewer, Dr. Robert O Kumi, states in his review that per 21 CFR Part 320.21, NDA applications should include "evidence measuring the *in vivo*

bioavailability of the drug product that is the subject of the application or information to permit FDA to waive the submission of evidence measuring *in vivo* bioavailability". The assay used in Study ASK 00-01-00 was able to detect drug following doses up to 2.0 mg/kg, and therefore, for the proposed study that employs lower doses (0.3 and 0.4 mg/kg), drug levels should still be detectable, at least at early time points, even at these lower doses based on the reported assay sensitivity. The sponsor should show a documented effort to develop an assay with lower sensitivity than the existing assay; if such an assay cannot be developed, the existing assay is acceptable.

5.8.10 Pharmacodynamic — See efficacy variables, below.

5.8.11 Endpoints

Primary efficacy variable

- No change: Improvement of treated veins on digital images, on a 5-grade scale, evaluated **12 weeks** (± 2 weeks) after the last injection. Comparison between Aethoxysklerol® and placebo (isotonic saline).

Protocol Change: *If there is a difference of more than 2 points in the score between the investigator and/or one of the two medical experts the digital images will be reassessed a second time by all of them. If there is still a difference of more than 2 points this evaluation will be classified as not evaluable. A worst-case approach will be applied, i.e., if the patient was assigned to the Aethoxysklerol group, the evaluation would be classified as treatment failure, and if the patient is assigned to the sodium tetradecyl sulfate or placebo group, the evaluation would be classified as success.*

Secondary efficacy variables

Protocol changes: Six new secondary efficacy variables are added as follows. They are now listed in the hierarchical order in which statistical testing will be done, and the testing procedure stopped once a non-significant result is found.

1 Patient satisfaction with the treatment **12** (± 2) weeks after the last injection. Comparison between Aethoxysklerol® and placebo.

2 Physician assessment of treatment success **12** (± 2) weeks after the last injection. Comparison between Aethoxysklerol® and placebo.

3 Assessment of improvement of veins on a 5-grade scale evaluated **26 weeks** (± 4 weeks) after last injection; the same statistical test will be performed as for the primary efficacy parameter. Comparison between Aethoxysklerol® and placebo (isotonic saline).

4 Patient satisfaction with the treatment after **26 weeks** (± 4 weeks). Comparison between Aethoxysklerol® and placebo (isotonic saline).

5 Physician assessment of treatment success **26** (± 4) weeks after the last injection. Comparison between Aethoxysklerol® and placebo

6 Assessment of improvement of veins on a 5-grade scale evaluated **12 weeks** (± 2 weeks) after last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.

7 Patient satisfaction with the treatment **12** (± 2) weeks after the last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.

8 Physician assessment of treatment success **12** (± 2) weeks after the last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.

9 Assessment of improvement of veins on a 5-grade scale evaluated **26 weeks** (± 4 weeks) after last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.

10 Patient satisfaction with the treatment **26** (± 4) weeks after the last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.

11 Physician assessment of treatment success **26** (± 4) weeks after the last injection. Comparison between Aethoxysklerol® and Sodium Tetradecyl Sulfate.

Protocol Change: Patient satisfaction. At the time of their evaluation of satisfaction with treatment, patients will be provided with the digital images of the treatment taken at Visit 1.

Protocol Change: Patient Estimation of treatment. Patients will be asked at visit 4 and 5 for their estimation of what drug (one of the liquid sclerosants or placebo) they think they have received.

Safety Variable - No changes.

5.8.12 Electronic CRFs

Protocol Change. All of the clinical data will be captured via electronic data capture (EDC) using a web-based tool. The sponsor's CRO, (b) (4), uses the software Marvin from the company XClinical (www.xclinical.com/) as their preferred EDC software. The sponsor contended that Marvin is compliant with all legislation relevant to electronic data capture (FDA 21 CRF Part 11, GCP), that all data will be stored remote on the central server of the CRO, and that investigators will have access to their data at all times.

5.8.13 Sample size

No Change.

However, the level of statistical significance to be used for analysis is **"two-sided with a significance level of 5%**." A pooled stratified analysis between Group S and Group R will be done, followed by a separate analysis in each stratum. A similar statistical analysis plan will be used for comparison of Aethoxysklerol® vs sodium tetradecyl sulphate and Aethoxysklerol® vs placebo.

The Division has stated that the EASI study needs to demonstrated a "very high success rate (i.e., a statistical significance level much smaller than 5%). The sponsor is worried that if the statistical significance level is not at 1% but, for example at 1.5% or some other value below 5%, a new study to evaluate dose response might become necessary.

5.8.14 Statistical Considerations

Protocol change: To limit the overall significance level to 5%, an *a priori* ordered hypothesis testing will be applied.

The primary statistical hypothesis for efficacy is to show that Aethoxysklerol® is superior to Placebo. A pooled, stratified analysis between Group S and R will be done assuming that the effect of Aethoxysklerol® 0.5% in spider veins is equal to the effect of Aethoxysklerol® 1% in reticular veins.

Only if the result of this test is statistically significant at a 5% level, the secondary ordered hypothesis (as listed in section 5.8.11) and endpoints will be also tested at the same 5% level. The testing procedure will stop once a non-significant result is found. Then the remaining endpoints will only be compared descriptively and no confirmatory testing will be applied.

The sponsor also stated that patient satisfaction after 12 and 26 weeks will be compared between treatment groups using the Wilcoxon Mann-Whitney-U test, and that the assessment of improvement of veins according to a 5-grade scale will be correlated with the patient satisfaction scores.

A subgroup analysis within each stratum (Group S or Group R) will be done if evidence of differences, if any, between vein types is found.

5.9 **Safety Considerations**

Please see discussion of safety considerations in review dated 14-Apr-2006.

5.9.1 Clinical and laboratory studies

The clinical and lab evaluation schedule is shown in the study flow chart (Item 5.8.8).

5.9.2 Indications for discontinuation

No change.

5.9.3 Dropouts

Drop outs will not be replaced (***Protocol Change***: Exception = screening failures, i.e.,

patients who have not received study medication.)

5.10	**Efficacy Considerations**	
	5.10.1 Efficacy Variables	See item 5.8.11.
	5.10.2 Substudy evaluations	Not applicable.
5.12	**Proposed observation period**	Patients enrolled into the study will be followed for a duration of 26±4 weeks (from the day of the last injection).
6.	**DOES THE STUDY PROVIDE USEFUL INFORMATION?**	Yes. This study will provide efficacy and safety information, particularly the incidence of post-treatment DVT so far not available prospectively in the medical literature.

Answers to comments and questions raised by the sponsor are in a separate document attached.

7.	RECOMMENDED REGULATORY ACTION	Communicate with the sponsor to provide answers to their questions and comments, and advise the sponsor to make minor amendments to the protocol.

Khin Maung U, MBBS, MMedSc, MD (NSW, Australia), MD, FACP
Medical Officer, DCaRP, ODE I, CDER, FDA

cc: orig.
HFD-110 / N. Stockbridge / A. Karkowsky / A. Sermon / Robert O. Kumi / Valeria Friedlin / K.M.U

***Question 1.1:* Are these (following) procedures sufficient to satisfy the points raised by FDA regarding standardization of digital images?**

The sponsor provided a summary of the key issues of the system to standardize procedures for taking digital images in the EASI-study. The "microDERM®" system will be used, which consists of a digital image recording hardware device and a software system ensuring that the procedure for taking digital images will be identical in all centers. All centers will be provided with identical devices (PC notebooks, digital cameras with front attachment and software). The microDERM® software runs under the Microsoft® Windows XP operating system.

The system hardware ensures that (i) the distance to the skin is constant and reproducible, (ii) surrounding light is kept away, and (iii) the position (viewing angle) is constant and reproducible

The microDERM software ensures that the following image parameters are controlled and standardized: (i) Magnification (Zoom), (ii) White Balance, (iii) Exposure Control, (iv) Focus, (v) Color, (vi) Flash, and (vii) Shutter.

To standardize the readings and interpretation of the digital images, representative examples of C1 varicose veins will be transformed into black and white images and modified electronically to illustrate examples of the five different grades.

Answer: Yes. To improve standardization of digital photographic images I would also suggest using color reference cards in each image (as communicated to you in my e-mail dated 03-May-2006). These color reference cards can then be used to correct for lighting differences so that the final printed images will be more comparable.

***Question 1.2:* Is this modification of the EASI-protocol (below) sufficient to comply with FDA's suggestion regarding adjudication of images that result in disagreement among the assessors?**

Study protocol was changed so that the FINAL adjudication made would be the WORST CASE scenario as requested by FDA (see *Chapter 8.5.3.1* of protocol).

Answer: Yes.

***Question 1.3:* Is this (following) assumption (of FDA's comments) correct?**

Kreussler stated they did not exactly understand the meaning of FDA-comment: *"we suggest that the 'blinded' primary endpoint evaluations should be supported by the evaluations of patient satisfaction with treatment (secondary efficacy variable)"*.

But the sponsor interpreted that the two criteria "*improvement of digital images pre- versus post-treatment*" and "*subjective finding of patient satisfaction with treatment*" should both be positive for Aethoxysklerol independently.

Answer: The two efficacy endpoints should be positive independently, and the positive findings should go hand in hand. This means there should be a positive correlation between the digital image and patient satisfaction (i.e., patients who are highly satisfied should also show grade 5 or 4 improvement in the digital images).

***Question 1.4:* Do you agree with the (following) described procedure (to evaluate patient satisfaction)?**

The detailed procedure for the secondary efficacy variable "patient satisfaction" is described in *Chapter 8.5.3.2* of the attached revised Study protocol. We recommend that at the time of the evaluation of treatment success, patients will be provided with digital images of the treatment area taken before the treatment.

Answer: Yes.

***Question 1.5:* Is this (following) modification of the protocol sufficient (to address FDA's suggestion regarding what drug (one of the liquid sclerosants or placebo) they think they have received)?**

The Study protocol was changed as requested by FDA (*Chapter 8.5.3.3 "patient estimation of drug used (placebo or active drug)"*).

Answer: Yes.

***Question 1.6:* Will such a number of study sites (10-20 sites) be satisfactory (to address FDA's suggestion that the trial is conducted at multiple sites that enroll < 10-15% of the total sample size for the trial, rather than one or two large sites)?**

The sponsor agreed with the Division's suggestion and stated they planned to enroll 10-20 study sites.

Answer: Yes.

***Question 1.7:* Is this additional information (below, regarding eCRFs and electronic data) and the procedure described in Chapter 8.6.1 sufficient (to address the FDA's bulleted point below)? If not, what other information would you like to receive?**

- Regarding eCRFs and electronic data: We suggest that when you use eCRFs and direct web-entry of patient data to servers, these data must be stored at the clinical trial sites under the control of the clinical investigator. There must be a system of passwords that limit access or tampering by unauthorized personnel and audit trails that can be verified. The protocol needs to provide a more detailed description of the equipment and procedures for electronic data entry, validation, and maintenance of data integrity. We want to emphasize the importance of the need to adhere to FDA §21 CFR Part 11 - Electronic Records; Electronic Signatures.

Our CRO, (b) (4) uses the software Marvin from the company XClinical (www.xclinical.com/) as preferred EDC software. Marvin is compliant with all legislation relevant to electronic data capture (FDA 21 CRF Part 11, GCP) (see Study protocol *Chapter 8.6.1*). In this context, we want to mention that with this software, all data will be stored remote on the central server of the CRO. Investigators will at all time have access to their own data.

Answer: Yes.

***Question 2.1:* Do you agree with this (following) summary?**

According to our clarifying phone call, the data from the other four studies mentioned in the table below can be used for safety. Therefore, after the EASI-study, only approximately 700 patients will be needed from the French registry, and the request for "*1 year follow-up for safety*" only applies for the French registry.

Total number of patients involved in efficacy studies submitted with Kreussler 's NDA

Concentration	OHIO	ASK-94-002	ASK-96-001	ASK-97-01-00	EASI-study	Total
0.5%	25	18	50	14	54	161
1.0%	25	44	29	16	54	168
Total	50	62	79	30	108	329

Answer: Yes.

***Question 2.2:* Do you agree with this (following) summary?**

The sponsor stated as follows: As pointed out in the last clarifying telephone call with you, it should be reminded that the French registry reports safety results from 12,173 sclerotherapy *sessions*, not 12,173 patients. Therefore, according to the coordinator of the French registry, Dr. J.J. Guex, only approx. a *total of 4000 patients* were treated, mostly during several sessions. Most of these patients were not only treated with liquid Aethoxysklerol but sometimes also with foamed sclerosing agents during another session or a different liquid sclerosing agent. It is also possible that some of these patients have received further treatments after the observation period.

We made clear that we will of course continue to collect in the first place data from as many patients as possible who have been treated only with liquid Aethoxysklerol (please note that in France Aethoxysklerol 0.25%, 0.5%, 2% and 3% are approved, in practice sometimes these concentrations are diluted by the physician), but that it may be difficult to find approx. 700 patients who have been treated only with liquid Aethoxysklerol.

Therefore, you suggested that the Division would also accept data from patients who have not been treated exclusively with liquid Aethoxysklerol in all sessions, provided that this panel of patients does not show less adverse events than the only liquid patients.

Answer: Yes.

***Question 2.3:* Do you agree with this (following) summary?**

In our clarifying telephone call, you agreed that "re-canalization" is not a safety parameter, but an efficacy parameter and, in addition, could therefore methodologically not be evaluated in a Registry. Therefore, also considering the discussion during the November 30, 2005-meeting, re-canalization/durability will only have to

be prospectively evaluated in the EASI-study.

Answer: Yes.

***Question 2.4:* Do you agree with this (following) summary?**

As requested by you during the last telephone communication, we send you the questionnaire to be asked by the treating physicians to the patients, for review by the FDA. As soon as we receive your comments we will start with the collection of post-treatment data.

Answer: Yes.

Question 3.1: Do you agree (to the following comment to FDA's answer to Question 3 below)?

Question 3: **Efficacy considerations**: *In November 30, 2005-meeting the Division and Sponsor agreed that approval will only be sought for Aethoxysklerol 0.5% (spider veins) and Aethoxysklerol 1% (reticular veins). Therefore, EASI study will be valuable as pivotal study with sufficient sample size for the requested indication C1-veins (see also question 2 above conc. Sample size).*

Does the Division agree?

Answer: Please refer to our response to Questions 1 and 2, above.

We would like to reiterate the Division's position stated in previous meetings and telecons that the EASI study needs to demonstrate a "very high success rate (i.e., a statistical significance level much smaller than 5%)" using fairly objective endpoints. Otherwise, you will need to conduct clinical studies to demonstrate a dose-response and/or support the EASI study. This aspect of efficacy considerations will need to be revisited as a review issue when the NDA is submitted.

Kreussler's comments:

Requesting again a "very high success rate" in this answer is inconsistent with an answer already given by the division after review of the package submitted on January 30, 2006, that the "dose-response"-question is answered and an additional confirmation of "dose-response" is no longer necessary: In fact the division had already acknowledged in the FDA-fax dated 24. February 2006:

"We would not require better dose-response than you have shown in your studies, provided safety in the proposed studies show no cause for concern compared to safety data at the higher dose. Your previous studies contained dose-related safety data on a small number of verifiable patients."

Perhaps this inconsistency was due to the fact that we did not ask an explicit confirmatory question on page 8 of our SPA-request in which we referred to the a m. FDA-statement.

We would like to emphasize that sample size calculation is based on the 1% significance level and that it is our aim to reach a level close to 1%. (see *Chapter 8.7.4* of EASI-protocol).

However, the answer given to question 3 would lead to the result that even if Aethoxysklerol® is superior to placebo in a statistically significant manner, a new study evaluating dose response would automatically become necessary, only because the significance level is not at 1% but for example at 1.5% or another value below 5%. This would again hold up the registration-procedure after more than 15 years. Based on the a.m. FDA-statement and the overall knowledge of and experience with this drug, such a dramatic consequence would not be justified.

Therefore, we continue to believe that - unlike your answer to question 3 – "a very high success rate" (significance level=1%) is not be necessary for approval, but that it is sufficient that Aethoxysklerol® is statistically significantly superior to placebo (significance level=5%) because dose response studies already do exist and were accepted by the FDA by fax dated February 24, 2006.

Answer: Yes, we agree with your "aim to reach a level close to 1%". However, we do NOT agree with your statement that "it is sufficient that Aethoxysklerol® is statistically significantly superior to placebo (significance level=5%) because dose response studies already exist and were accepted by the FDA by fax dated February 24, 2006." The FDA letter faxed 24-Feb-2006 merely states "*Your previous studies contained dose-related safety data on a small number of verifiable patients."*

Question 5.1: Do you agree (to the proposed statistical plan in response to FDA's suggestion for a pre-specified adjustment for multiple comparisons and FDA's question as to how α will be spent with

statistical analysis)?

FDA requests a correction for multiple testing of secondary endpoints. This is not usual (because correction for multiple testing is usually only needed for primary parameters), however can be done. We propose a hierarchical testing procedure with *a priori*-ordered hypotheses. Secondary endpoints will be put in order and the testing procedure stops once a non-significant result was found. This procedure limits the overall significance level to 5% (*see also question 3.1*).

The primary efficacy analysis will include the stratification factor, and an analysis for each stratum will not be done within the frame of the primary analysis. The analysis per stratum can be done as additional subgroup analysis and is mentioned in *Chapter 8.7.1.10* of the protocol. This avoids correcting the significance level for multiplicity of testing of the primary efficacy parameter.

Chapter 1 and *Chapter 8.5.3.1* and *Chapter 8.7.1.3* "secondary efficacy variables" were changed accordingly.

Answer: Yes.

Question 5.2: Do you agree (to the protocol change to comply with FDA's suggestion that a copy of the randomization code for all study centers be submitted to the Division before the clinical trial starts)?

Protocol was changed as requested by FDA (see *Chapter 8.4.4* of protocol).

Answer: Yes.

Question 5.3: Do you agree (to the protocol change to comply with FDA's suggestion to use intra-class correlation coefficient instead of the Pearson correlation coefficient)?

Protocol was changed as requested by FDA (see *Chapter 8.7.1.2* of protocol).

Answer: Yes.

Question 5.4: Do you agree (that the assessments made by each assessor will be part of the final study report)?

Answer: Yes.

Question 6.1: Do you agree (to the following protocol changes to address FDA's suggestions to obtain post-treatment safety data related to DVT at one week ±3 days)?

Protocol was changed as requested by FDA under No. 1 (your first suggestion above) (see *Chapter 1.2 [study flow chart]* and *Chapter 8.1* of protocol). A new visit 1a was added 1 week ± 3 days after the first injection in order to reveal ongoing DVTs. During visit 1a DVT scanning as described in appendix 8 will be performed. DVT scanning was deleted from the 2nd and 3rd treatment visits as suggested. DVT scanning during visit 0 and visit 3 remains unchanged.

(Please note, that due to this change the names and numbering of the different visits has been slightly changed.)

Answer: Yes.

There is no Question 7.

Question 8.1: Do you agree that a modification of the study protocol concerning the statistical significance level is not necessary (as stated below)?

It goes without saying that our aim is to reach a very high success rate. However, we refer to our comment and *Question 3.1* above, reiterating that a statistical significance level below 1% is not necessary following FDA-fax dated February 24, 2006.

Answer: Yes, we agree with your aim "to reach a very high success rate". However, as stated in our response to Question 3.1, we do NOT agree with your statement that "a statistical significance level below 1% is not necessary following FDA-fax dated February 24, 2006." The FDA letter faxed 24-Feb-2006 merely states "*Your previous studies contained dose-related safety data on a small number of verifiable patients.*" The Division's recommendation remains as a statistical significance level way below 5%, preferably at 1 % (two-sided).

There is no Question 9 or 10.

Question 11: Is this "guideline for sclerosing technique" (which will be binding for all investigators during the EASI-study (see Appendix 9 of EASI protocol)) adequate for the study?

Answer: Yes in general. However, the final document is not yet in Appendix 9 of EASI protocol.

Question 12.1: Do you agree to our understanding that only the EASI-study but not the French registry will be subject to an FDA GCP audit?

> According to our clarifying phone call, only the EASI-study but not the French registry will be subject to an FDA GCP audit. Therefore, you made clear that the last part of the sentence "and must be verifiable through a FDA GCP audit" only applies to the EASI-study (see also our last comment before *Question 2*).

Answer: Yes.

Question 12.2: (identical to Question 3.1) Do you agree?

Answer: Please see answer to Question 3.1.

Question 12.3: (identical to Question 2.1) Do you agree (that the request for "1 year follow-up for safety" only applies for the French registry)?

Answer: Yes.

Question 12.4: (identical to Question 2.3) Do you agree (with our opinion that "re-canalization" is not a safety parameter, but an efficacy parameter and, that re-canalization/durability will only be prospectively evaluated in the EASI-study?

Answer: Yes.

Question 13: Do you agree that blood sampling is no longer necessary?

Answer: No. The Clin-Pharm Reviewer, Dr. Robert O Kumi, states in his review that per 21 CFR Part 320.21, NDA applications should include "evidence measuring the *in vivo* bioavailability of the drug product that is the subject of the application or information to permit FDA to waive the submission of evidence measuring in vivo bioavailability". The assay used in Study ASK 00-01-00 was able to detect drug following doses up to 2.0 mg/kg, and therefore, for the proposed study that employs lower doses (0.3 and 0.4 mg/kg), drug levels should still be detectable, at least at early time points, even at these lower doses based on the reported assay sensitivity. The sponsor should show a documented effort to develop an assay with lower sensitivity than the existing assay; if such an assay cannot be developed, the existing assay is acceptable.

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/s/

Khin U
7/17/2006 04:55:18 PM
MEDICAL OFFICER
This is just copy of review of post-SPA amended EASI-protocol. Most issues ae resolved. Sponsor informed by letter re: requirement for (1) alpha level at 0.001 or a dose-response study (2) blood sampling & (3) safety data from French registry.

Background

Polidocanol was developed in the 1950's as a local anesthetic. It has been marketed outside of the United States and used as a sclerosant since the 1960's for various indications such as hemorrhoids, gastric and esophageal varices, and the treatment of varicose veins. In the United States, sclerosant choice is limited. Currently available products include hypertonic saline (used off-label); sodium morrhuate (not listed in the Orange Book, but listed on the National Drug Code Directory; one manufacturer, Glenwood, LLC, sells a product containing sodium morrhuate as Scleromate; according to the American College of Phlebology this drug substance was introduced in the 1920s and "is exempted from the need for FDA approval"; and sodium tetradecyl sulfate (NDA 5-970 for Sotradecol was withdrawn from the U.S. market by the manufacturer, Elkins-Sinn, Inc., in 2003); however, Sotradecol was recently approved in 2004 under ANDA.

NDA 21-201 is for use of Aethoxysklerol (polidocanol) solution as a sclerosant intended for intravenous administration for treatment of (b) (4) mm diameter (b) (4) varicose veins of the lower extremities. The application was opened under IND 35,139 on May 21, 1990 (see Appendix A – Regulatory History).

Pivotal Studies

Originally, the sponsor undertook a single study with three study sites; however, it was agreed by the Agency that the Applicant could merge two of the centers due to slow enrollment. The two merged centers were then considered as one study, while the third center was considered as another study. The protocols were identical designed double-blind, prospective, randomized, parallel-design comparative studies of the efficacy and safety of Aethoxysklerol as compared to diluted Sotradecol (used at a lower concentration than labeled).

The Phase 3 study population consists of a total of 320 female and 4 male patients between 21 and 65 years of age. Altogether, there were 153 patients treated with Aethoxysklerol and 156 patients treated with Sotradecol. Patients were stratified according to the vein size (≤1 mm in diameter, >1-3 mm in diameter, or >3-6 mm in diameter) and randomized 1 to 1 to either receive either Aethoxysklerol or diluted Sotradecol.

Patients were treated according to the sclerotherapy technique commonly used by the investigator. Each patient received 1 to 3 treatments as determined by the investigator based on clinical judgment. The maximum dose of polidocanol was 2.0 mg/kg body weight per day.

Efficacy Variables

The primary efficacy variable was dichotomized Disappearance of Varicosities (Yes/No) as per the September 23, 1998 Guidance Meeting # 3143 minutes. The Applicant's original primary efficacy endpoint was Disappearance of Varicosities 16 weeks after the last treatment as judged by three blinded vascular surgeons who compared baseline and end of study photographs using a 5-point scale. The rating scale was: 1 (worse than

before treatment), 2 (same as before), 3 (minority of varicosities disappeared), 4 (the majority disappeared), and 5 (complete disappearance).

Secondary efficacy variables were (1) overall clinical improvement based on disappearance of varicosities, hyperpigmentation, and neovascularization and (2) overall patient satisfaction. These variables were compared between treatment groups for each vein-size group and across all vein-size groups.

A determination was made by the review team that the primary analysis would best be a superiority comparison of complete disappearance of varicosities; although both superiority and non-inferiority analyses had at various times been discussed with the Applicant. Demonstration of superiority of Aethoxysklerol over Sotradecol is thought to be most clinically and regulatorily appropriate for the following reasons:

1) The original protocol was designed as a superiority protocol.
2) Sotradecol was diluted and used at concentrations less than labeled and was considered to be a placebo for the purposes of the study.

Safety Database

The Applicant proposed to market Aethoxysklerol in (b) (4) concentrations: 0.5%, 1.0% (b) (4) The pivotal studies enrolled 329 subjects, 324 of whom received study drug. Of the 324 subjects who were treated, 158 received Aethoxysklerol and 166 received Sotradecol. Of the Aethoxysklerol-treated subjects, 53 received the 0.5% concentration, 53 received 1% and 52 subjects 3%.

Across the Applicant's development program, a total of 514 subjects were exposed to polidocanol, 415 of whom were exposed to the Applicant's formulation at concentrations (b) (4): 0.5%: 126 subjects; 1.0%: 132 subjects; 2.0%: 73 subjects; 3.0%: 84 subjects.

Safety Variables in the Pivotal Trials

Adverse event data were principally captured by use of a checklist. Pre-treatment doppler or duplex ultrasound was performed to rule out valvular incompetence.

Inspections of Clinical Trial Sites

DSI issued a Form 483 (List of Observations) from the California site (See Attachment, Clinical Inspection Summary dated July 13, 2004). Observations cited includes not conducting the study in accordance with the investigational plan, inadequate drug disposition records inadequate record keeping, inadequate assurance of IRB oversight, inadequate drug records, inadequate supervision of the study by the PI, and inadequate informed consent.

Regulatory Action

A Not Approvable action was issued by the Division on August 8, 2004 under section 505(d) of the Act and 21 CFR 314.125(b) as superiority was not demonstrated for the primary efficacy parameter, complete disappearance of varicosities. An adequate risk-

benefit analysis has not been supported by the data provided in this application. (See Attachment, Not Approvable Letter in DFS).

Post Action Meetings

Two post action meetings were held between the Applicant and the Division on October 13, 2004 and February 10, 2005. (See Attachments). The Applicant was advised to conduct either two vehicle controlled studies or one robust study which should be powered to achieve statistical significance much below the (b) (4) level. Safety procedures in the new clinical study(s) should include specific plans for assessment for deep vein thrombosis.

Appendix A
Regulatory History NDA 21-201

1990 (HFD-160)

- May 21, 1990: Memorandum of In-House meeting (HFD-160 and Compliance) for Division input regarding the wide distribution and illegal use of aethoxysklerol (a sclerosing agent) by over 100 doctors who are treating patients with this unapproved drug product.
- July 19, 1990: Date of receipt by the Agency for IND 35,139 assigned to HFD-160 to the Division of Medical Imaging, Surgical and Dental Drug Products (July 2, 1990 submission date)
- August 13, 1990: Protocol received for a single, open label and uncontrolled study was received (MOR review completed 01-30-91).
- August 10, 1990 (CDER date): Submission Chemistry submitted was insufficient to initiate the proposed clinical studies.
- July 19, 1990: Pilot study submitted for IV use of aethoxysklerol 10 patients. J. L. Villavicencio, M.D. is listed as Principal Investigator (the protocol was reviewed as a consult in HFD 540 with a review date of January 10, 1994 and a stamp date of September 24, 1994.)
- August 16, 1990: T-con provided a two-week extension of the 30-day safety was granted.
- November 14, 1990: Meeting with Jobst Institute (according to a December 5, 1990 stamp dated HFD-160 memo from chemistry)
- November 16, 1990: Certified letter from the Agency to (b) (4) regarding violation of FDA regulations governing use of the unapproved medication aethoxysklerol. (b) (4)

  (b) (4)

1991 (HFD-160)

- January 30, 1991: MO Review of the 08-31-90 pilot study. According to the review, while the study was safe to proceed, sufficient data would not be collected to support regulatory requirements for an NDA. Minutes of a meeting between the Agency and the sponsor were not available; however based on the MO's recollection, "...that the sponsor was advised to re-write the protocol in such a fashion that the data may be ultimately submitted as two, separate and independent, well controlled clinical studies.". According to the MO's recommendation regarding a well controlled, blinded study,"...This protocol may be employed at two separate study locations in order to fulfill; the requirement for two independent studies."
- January 30, 1991: A Memorandum of A Telephone Conversation between Jobst (the Sponsor) and HFD-160 indicated that a more detailed protocol (preferably blinded clinical study) in collaboration with Dr. Villavicencio was close to being submitted. Request was made of the sponsor to consider individual investigators who are interested in studying the drug under the IND.
- February 07, 1991: Clinical trials may proceed from standpoint of pharmacology with deficiencies noted.

- March 08, 1991: Reasonably safe to proceed from Chemistry. Clinical requested a protocol to describe a well controlled preferably blinded, clinical study. The protocol should be employed at a minimum of two separate study locations in order to fulfill the requirement for two independent studies.

1993 (HFD 160)

- January 6, 1993: Phase 3 protocol initiation date
- February 23, 1993: Submission date of the protocol titled "Double-Blind, Prospective, Randomized, Comparative Multicenter Trial Between Aethoxysklerol® (Polidocanol) and Sotradecol® (Sodium Tetradecyl Sulfate) in the Management of Varicose Veins of the Lower Extremities".
- December 30, 1993: The Amendment was reviewed by HFD-520 as a consult, with a review date of December 30, 1993). PIs listed as Mitchell P. Goldman, MD (Encinitas, CA), John C. Cranley, MD (Logan, Ohio), and John R. Pfeifer, MD (Southfield, MI). Three centers enrolling a total of 450 subjects were planned. The planned study was double-blind, six week active control study with a four month follow-up. Study participants were to be stratified into three groups according to vessel size.

1994 (HFD 540)

- January 1994: IND 35,139 was assigned to HFD-540 (Steve's notes)
- February 8, 1994: Major problem with efficacy rating scale with inclusion of adverse events (e.g., neovascularization and pigmentation). Needed to evaluate efficacy separately from AEs.
- April 12, 1994 (Source NDA submission) Memorandum from Biostatistics to the Sponsor regarding Merging of two centers due to slow enrollment.
- May 5, 1994 (Source NDA Submission) Memorandum from Biostatistics to the Sponsor regarding proper Meta-Analysis
- December 30, 1994 (Stamp Date): Statistical Consultation IND 35, 139 Annual Report Review (date of Document 12-15-92, Date received by Biometrics 11-21-94) recommending an Amendment addressing the multiple comparisons issue and that the protocol planned sample size and analysis plan seem to be statistically appropriate to meet the sponsor's stated objectives.

1995 (HFD 540)

- January 25, 1995: (Document Date: 12/15/94) Statistical Consultation (requested by the FDA) to review submission of all written communications referencing IND #35, 139 between Dr. Leonel Villavicencio (PI for the study) and the Division of Dermatology and all records pertaining IND #35, 139 that were in the possession of Dr, Ralph Harkins of the FDA.
- October 17, 1995: Comments from Statistician regarding 07-26-95 submission regarding request to begin data analysis at one center
- December 4, 1995: Meeting?
- January 31, 1996: E-mail from Joanne Holmes (PM) noting that Paul Cowden (Jobst) was informed that without a formal End of Phase 2 meeting, they have not

received commitments by the Agency. Reference was made regarding 12/92 and 7/95 Protocols.

1996 (HFD-540)

- February 2, 1996: meeting?
- February 19, 1996: Clinical trial completion date
- April 1, 1996: Primary Efficacy Endpoint from Ralph Hawkins, Ph.D. Disappearance of varicose veins will be recognized as the primary efficacy endpoint. Pigmentation and neovascularization are adverse events.
- April 15, 1996: Meeting Minutes Ms. Farr noted that the sponsor agreed upon disappearance as the primary endpoint. The sponsor would combine the Michigan and California data. Suggested DSI audit of the Michigan site. Could not compare an approved comparator agent at an unapproved dose. The sponsor would need to be able to beat placebo in the study.
- October 4, 1996: Statistical Analysis Procedures from Ralph Hawkins, Director Biometrics IV

1997 (HFD-540)

- March 25, 1997: Statistical comments Dr. Srinivasan regarding non-inferiority analysis
- June 23, 1997: Division advice regarding a shortage of STS and a request by Jobst to make atheoxysklerol available for physician use under IND 35,139
- June 23, 1997: Pharm/Tox review comments regarding adverse pregnancy outcome report

1998 (HFD-540)

- January 12, 1998: Guidance meeting, The only primary endpoint variable should be disappearance of vascularization as determined by three readers on a 5-point scale. In addition, the sponsor should analyze the proportion of subjects who had complete disappearance vs. partial disappearance.
- August 7, 1998: Pharm/Tox review
- September 23, 1998: Guidance meeting

1999 (HFD-540)

- October 1, 1999: NDA 21-201 submitted to the Agency
- December 1, 1999: NDA 21-201 was withdrawn due issues with pharmacokinetic data (according to November 24, 2003 Filing Memo)

2002 (HFD-540)

- October 21, 2002: Pre-NDA meeting (Content and format)

2003 (HFD-540)

- September 29, 2003: NDA 21-201 was resubmitted
- December 15, 2003: 74-Day Filing Letter issued

2004 (HFD-540)

- May 14, 2004: Regulatory Briefing
- August 8, 2004: Not Approvable Action issued
- October 13, 2004: Post approval meeting between the sponsor and the Division (HFD-540)

2005 (HFD-540)

- February 10, 2005: Post approval meeting between the sponsor and the Division (HFD-540)

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/s/

Brenda Carr
3/10/05 10:39:19 AM
MEDICAL OFFICER

Markham Luke
3/10/05 10:56:25 AM
MEDICAL OFFICER
Memo to file regarding NDA history (Background information) from Drs. Vaughan and Carr.

Jonathan Wilkin
4/1/05 12:11:10 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS

MEMORANDUM

DATE: July 30, 2004

TO: NDA 21-201 File

FROM: Stanka Kukich, M.D.
Deputy, Division of Dermatologic and Dental Drug Products

SUBJECT: Deputy Division Director's Memorandum for NDA 21-201, Aethoxysklerol (polidocanol) Injectable, 0.5%, 1%, (b) (4) for the sclerotherapy of varicose veins of the lower extremities

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The applicant has requested approval for Aethoxysklerol (polidocanol) Injectable, 0.5%, 1%, (b) (4) for the sclerotherapy of varicose veins of the lower extremities. In support of this indication, the applicant has submitted the results of two clinical trials initially designed as a single clinical trial but during the conduct of the study seperated into OHIO and MICA studies. The objective of the trials was to demonstrate safety and efficacy of Aethoxysklerol when used as sclerosing agent at different concentrations for varicose veins $\leq$ 1 mm in diameter, 1 to 3 mm, (b) (4)

The review team has recommended a Non-Approvable action for this NDA. This regulatory action is based on the absence of efficacy and inadequate safety evaluation of study subjects determined by a multidisciplinary review of the data contained in NDA 21-201. This memorandum will focus on the pivotal issues that supported a Non-Approvable action.

1. Limited data in support of safety and efficacy:

The efficacy of Aethoxysklerol for sclerotherapy of varicose veins of the lower extremities has not been demonstrated in two pivotal trials. Initially, these studies were designed to demonstrate the superiority of Aethoxysklerol over Sotradecol. However, the superiority has not been demonstrated for the complete disappearance of varicosities, the

primary efficacy parameter. A post-hoc non-inferiority comparison failed to establish that Aethoxysklerol was clinically similar to Sotradecol because the treatment effect of active control was not well characterized in a similar patient population. Sotradecol was approved in 1946 when demonstration of efficacy was not necessary, and later found to be probably effective for the treatment of varicose veins. As previously stated, the data provided do not permit the conclusion that Aethoxysklerol is superior to Sotradecol for this indication, nor support the conclusion that Aethoxysklerol is non-inferior to diluted Sotradecol.

The safety database is limited to a small number of patients who received different concentrations of Aethoxysklerol. The submitted safety data did not provide adequate information about the risk of deep vein thrombosis following the treatment with Aethoxysklerol. Specifically, the study design did not include adequate assessment of deep vein thrombosis post-treatment.

2. Data Quality and Data Integrity:

The clinical inspection to validate data in support of the NDA 21-201 indicated that there were multiple deficiencies in proper record keeping at the Michigan and California sites that included but were not limited to an inadequate drug disposal record, inadequate informed consent process, inadequate reporting to the local IRB, and inadequate supervision of the study by the principal investigator. Therefore, the data from these sites could not be used to support the efficacy or safety analyses in this NDA.

3. Product Quality:

Because Aethoxysklerol is intended for intravenous use as sclerosing agent, a product quality microbiology review was conducted to evaluate the manufacturing process with regard to sterilization procedures. The information regarding the methods used to control and monitor production sterilization cycles, information to prove that the sterilization cycle has been adequately validated, and the incubation parameters for the biological indicators following sterilization validation cycles has not been provided. Therefore, it can not be reasonably assured that microorganisms would not survive the sterilization procedures.

In summary, the benefit of Aethoxysklerol for the treatment of varicose veins of the lower extremities has not been demonstrated and the safety database is limited to permit evaluation of the potential risk of asymptomatic deep vain thrombosis post-treatment.

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/s/

Stanka Kukich
7/30/04 02:39:50 PM
MEDICAL OFFICER

Office Director Memorandum
Office of Drug Evaluation V
Date: July 30, 2004

Re: NDA 21-201
Proposed Trade Name: Aethoxysklerol
Generic Name: Polidocanol

Applicant: Chemische Fabrik Kreussler and Col., GmbH

Pharmacologic Category: Sclerosant

Dosage Form and Route of Administration: Intravenous

This memorandum provides for my concurrence with the recommendations of the review team for this NDA. The details of the trials will not be reiterated and are well summarized in the reviews.

The action letter for this NDA clearly outlines the grounds for the non-approval. This is based on significant clinical trial design flaws leading to an inadequate body of evidence for safety and efficacy. In addition, there are significant concerns based on the finding of the Division of Scientific Investigations on the data integrity.

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/s/

Jonca Bull
7/30/04 03:44:04 PM
MEDICAL OFFICER

Lead Medical Officer Addendum
NDA 21-201
Aethoxysklerol (polidocanol)

June 23, 2004 (revised July 13, 2004)

Both of the primary Medical Officer reviewers, Dr. Brenda Vaughan and Dr. Brenda Carr, are in agreement that this product should not be approved (a Non-Approval recommendation). The Dermatology TL is also in agreement that this recommendation is the most appropriate given the informational needs that remain outstanding upon review of this submission.

Regarding the Efficacy of this Drug Product

The pivotal studies failed to demonstrate that Aethoxysklerol was superior to diluted Sotradecol, a comparator of unknown efficacy. A post-hoc non-inferiority comparison also does not result in a clear demonstration of non-inferiority of one product vs. the other in the two studies submitted.

Further, the studies were done in a manner that fails to assure confidence in the results. There was a failure to use consistent and standardized procedures. Such procedures are needed for a clinical study that is seeking approval for a new drug so that we can be certain that it is the effect of the drug itself that is being measured and not some variation in the procedure.

While not factored into the Medical Officers' decision, the initial DSI inspection reports suggest a significant concern that may be sufficient to recommend not using two of the three sites at which this drug was evaluated.

Regarding the Safety of this Drug Product

Reiterating the primary Medical Officer's safety evaluation, the methods for assessing safety did not appear to permit adequate evaluation of safety. Laboratory data were not collected in the pivotal studies for this intravenously administered drug. Safety assessments used targeted checklists so would miss any unexpected adverse events.

The single case report of a patient who died minutes post injection of Aethoxyskelerol (page 17 of MOR, IND 35,139) could be attributable to an anaphylaxis or a cardiac response to the "reversible cardiac arrest" reported in the reference described on page 13 of the Medical Officer Review. Given the relatively small numbers of patients studied during the development of this drug, this safety consideration will need further evaluation.

Other anesthetics have been reported to cause arrythmias and bradycardia. It appears that this is a concern for polidocanol as well and should be further evaluated by the Sponsor before resubmission.

In addition, while not factored into the Medical Officers' recommendation, it appeared from the clinical site inspections that unqualified personnel may have been doing post-treatment evaluations.

While the CMC review is still pending at this time, it appears that the CMC Microbiologist has concerns about documentation of sterility of this product. These concerns will need to be addressed in sufficient detail.

Regarding the Risk vs. Benefit in a Cosmetic Indication

The indication of treatment of varicose veins (b) (4) appears to be largely a cosmetic indication. There are instances of patients for whom an argument could be made that the indication is more than cosmetic (the degree of non-cosmesis may vary but will usually involve minor discomfort).

Given these premises to be true, it would be best that a product used for sclerotherapy have a minimum of side effects other than those coincident with sclerosant activity (e.g. ecchymosis, bruising, local discomfort).

It is not clear that polidocanol has the best safety profile for all patients. Some work should go into identifying patients who would be at greater risk to receiving this drug (e.g. congenital heart defect, concomitant medications or anesthetics).

Regarding the Pharmacokinetics of this Drug Product

The majority of the effect of this drug product is local, i.e. it is used in order to provide sclerosant activity to the unwanted varicose vein. The local gradient effect that results immediately after injection may be more of a concern that the generalized redistribution of the drug over the minutes after injection. Thus, an appropriate PK study could be to evaluate the gradient of drug from the site of injection in a pre-clinical model to evaluate how far up the circulation this drug product may have an effect.

At the time of this secondary review, the Clinical Pharmacology PK review is still pending.

Additional Information Needed Prior to Approval

I concur with the Medical Officers' recommendations that additional studies are needed prior to approval and the following specifics be conveyed in the Non-Approval letter:

"Conduct two well designed multi-center, randomized, double blind, active versus vehicle superiority studies demonstrating safety and efficacy of Aethoxysklerol for treatment of varicosities (stratified by vein size) of the lower extremities. Durability of treatment effect at one year after the last sclerotherapy session should be submitted at the time of NDA submission. [Provision for two year follow-up with reporting either pre- or post-approval. *My addition.*] Sclerotherapy technique and safety monitoring for deep vein thrombosis should be well-delineated in the protocol. Blinded efficacy assessment should be based on clinical observation rather than photographs alone.

Structured and open-ended approaches should be employed in the collection of adverse event data, and the data should be collected at specified time-points post-treatment to permit assessment of the status of the event at a particular time-point. Safety monitoring should include collection of laboratory data (hematology, chemistries, urinalysis), electrocardiograms, and posttreatment assessment for deep vein thrombosis (e.g. duplex ultrasound). It is recommended that safety data for a minimum of 300 subjects treated with the highest concentration proposed for marketing be included in the application."

Further, such studies should also evaluate for the specific location of each vein with regard to the major veins treated. Consideration should be given towards the safety and efficacy associated with treating each of these veins. Purely basing approvability on size may discount the potential for larger veins below the knee to respond differently than larger veins above the knee. The known science of venous anatomy of the lower extremities should be used to our maximum advantage in evaluating this product.

As above, it is also recommended that the Applicant further address the sterility documentation needed as per the CMC Micro reviewer. Also, the Applicant should work on obtaining additional information regarding 1) cardiac arrhythmias that result from exposure to this drug product and 2) the gradient effect of intravenous injection of this drug. The Applicant should work to further define the population for which this product should be used or should be contraindicated in (e.g. patients taking disulfuram, patients with certain congential heart defects, patients who are also being treated with certain anesthetics).

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

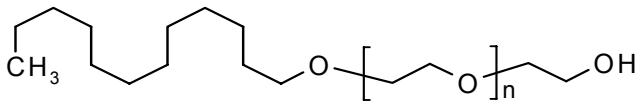
/s/

Markham Luke
7/13/04 11:55:47 AM
MEDICAL OFFICER
TL comments for NDA 21-201.

Jonathan Wilkin
7/13/04 07:13:01 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 21-201
Original

NDA Submission number/type	NDA 21-201
Applicant Name:	Chemische Fabrik Kreussler & Co., GmbH Rheingaustrasse 87-93 D-65203 Wiesbaden Germany
Name of Company Official Or Contact Person:	Howard M. Smith INC Research, Inc. 675 Peter Jefferson Parkway, Suite 120 Charlottesville, VA 22911 434-244-5165; (Fax: 434-295-7209)
Submission/Review Dates	
Date of submission (date of applicant's letter)	
CDER stamp date	10-02-03
Filing Date:	12-13-04
Review Completed:	06-16-04
Drug Identification	
Generic name	Polidocanol
Proposed trade name	Aethoxysklerol
Chemical structure	



n = 0 to ~22

Chemical name	Polyethylene glycol monododecyl ether
Molecular formula:	$C_{12}H_{25}(OCH_2CH_2)_nOH$
Mean Molecular weight:	Approximately 600
Pharmacological Category:	Sclerosant
Dosage form:	
Route of Administration:	Intravenous
Reviewers: Efficacy:	Brenda Vaughan, M.D., Medical Officer
Safety:	Brenda Carr, M.D., Medical Officer
Division:	Dermatologic and Dental Drug Products
Documents Reviewed:	NDA 21-201 Volumes 1.1, 1.2, and
	NDA 21-201 C 12-23-03
	NDA 21-201 SU 02-09-04
	NDA 21-201 C 02-13-04

NDA 21-201 C	02-21-04
NDA 21-201C	02-13-04
NDA 21-201BZ	03-10-04
NDA 21-201BZ	03-29-04
NDA 21-201BZ	04-01-04
NDA 21-201BL	04-09-04
NDA 21-201BM	05-27-04
NDA 21-201BM	06-03-04

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CLINICAL REVIEW of NDA 21-201

Executive Summary Section

Executive Summary

I. Recommendations

A. Recommendation on Approvability

A *Non-Approvable* recommendation is being made for use of Aethoxysklerol (polidocanol), a sclerosant intended for intravenous administration for treatment of (b) (4) diameter varicosities of the lower extremities. Safety and efficacy are being reviewed separately.

The Applicant failed to establish superiority for the dichotomized Complete Disappearance of Varicosities efficacy endpoint as proposed by the Division or Disappearance of Varicosities on a 5-point scale as proposed by the Applicant when Aethoxysklerol is compared to diluted Sotradecol (STS). The attempt to demonstrate superiority or non-inferiority was flawed because the treatment effect of the Sotradecol comparator is unknown; thereby making power calculations determination difficult. Sotradecol was approved in 1946 when efficacy did not have to be established; therefore, use as an active comparator is problematic in establishing superiority or non-inferiority in that the treatment effect of the approved or diluted concentrations of Sotradecol is unknown. It is of note that non-inferiority was also not established for the dichotomized Complete Disappearance of Varicosities efficacy endpoint.

It is recommended that the application is Not-Approvable. While the submitted safety data revealed an adverse event profile consistent with sclerotherapy and the pharmacologic class of sclerosants, and raised no new safety concerns or apparent polidocanol-specific effect, efficacy was not demonstrated. Thus, the risk-benefit analysis does not favor approval.

B. Recommendation on Studies Needed Prior to Approval

Conduct two well designed multi-center, randomized, double blind, active versus vehicle superiority studies demonstrating safety and efficacy of Aethoxysklerol for treatment of varicosities (stratified by vein size) of the lower extremities. Durability of treatment effect at one year after the last sclerotherapy session should be submitted at the time of NDA submission. Sclerotherapy technique and safety monitoring for deep vein thrombosis should be well delineated in the protocol. Blinded efficacy assessment should be based on clinical observation rather than photographs alone.

Structured and open-ended approaches should be employed in the collection of adverse event data, and the data should be collected at specified time-points post-treatment to permit assessment of the status of the event at a particular time-point. Safety monitoring should include collection of laboratory data (hematology, chemistries, urinalysis), electrocardiograms, and post-treatment assessment for deep vein thrombosis (e.g. duplex ultrasound). It is recommended that safety data for a minimum of 300 subjects treated with the highest concentration proposed for marketing be included in the application.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Aethoxysklerol (polidocanol) is a sclerosant intended for intravenous administration for treatment of (b) (4) diameter varicosities of the lower extremities. Data from two centers (OHIO and merged California /Michigan (MICA) were submitted to support approval of the

NDA. The study design was double-blind, prospective, randomized, parallel-design comparative study of the efficacy and safety of Aethoxysklerol as compared to Sotradecol (an FDA approved sclerosant). Identical protocols were followed at all study sites.

In the sponsor's development program, 415 subjects received the formulation proposed for marketing in the range of concentrations proposed for marketing. Of these 415 subjects, 342 were treated with the formulation (b) (4), in the concentrations (b) (4) (b) (4): 0.5%, 1.0% and 3.0%, with 126, 132, and 84 receiving treatment, respectively. An additional 73 subjects in a supportive study received a 2.0% concentration.

Originally 450 patients were planned to be treated at 3 study sites (Ohio, Michigan, and California). Originally the trial was constructed with a sample size such that statistical significant results within each center were possible. According to a February 14, 1995 statistical review, it seemed to be suggested that the sponsor intends to claim that each center is an independent trial, however, that regulations require two adequate and well-controlled trials (not centers) for approval. Subsequently, the current application (with assistance from the Agency's Statistical Team Leader) consists of two one-center clinical trials. The study design has remained consistent in that patients were stratified according to the vein size, as follows: small cutaneous blemishes (≤1 mm in diameter), superficial venules (>1-3 mm in diameter), or varicose veins (>3-6 mm in diameter) and randomized 1 to 1 to either receive either Aethoxysklerol or diluted Sotradecol.

The study plan included an unblinded investigator whose responsibilities included providing the randomization numbers, making necessary dilutions of Sotradecol, and filling the syringes for injection. All other study personnel were blinded to study-drug assignments. Treatments were not standardized and patients were treated according to the sclerotherapy technique commonly used by the investigator. Each patient received 1 to 3 treatments and the number of treatments was determined by the investigator based on clinical judgment. The maximum dose of polidocanol was 2.0 mg/kg body weight per day.

The application has a complex regulatory history and it is unclear whether End-of-Phase 2 types of agreements were ever reached between the Applicant and the Agency. The primary efficacy variable is the dichotomized version of the Disappearance of Varicosities (Yes/No) as per September 23, 1998 Guidance Meeting Minutes (# 3143). The Applicant's original primary efficacy endpoint was Disappearance of Varicosities 16 weeks after the last treatment as judged by three blinded vascular surgeons who compared baseline and end of study photographs using a 5 point scale. The rating scale was as follows: 1 (worse than before treatment), 2 (same as before), 3 (minority of varicosities disappeared), 4 (the majority disappeared), and 5 (complete disappearance).

The secondary efficacy variables were (1) overall clinical improvement based on disappearance of varicosities, hyperpigmentation, and neovascularization and (2) overall patient satisfaction. These variables were compared between treatment groups for each vein-size group and across all vein-size groups. The Applicant was advised that hyperpigmentation, and neovascularization were adverse events and as should not be included in the efficacy evaluation.

Data from two supportive concentration-controlled studies (Studies ASK 94-002, ASK 96-001) conducted in Japan, and one supportive uncontrolled "study" (AET-AS25) conducted in Germany were also submitted. All studies assessed the efficacy of Aethoxysklerol in patients with varicose veins of the lower extremities. These studies were not conducted under the IND, were open-labeled studies, and are being reviewed for safety. The total study population consists of total of 669 patients.

The clinical trial was initiated on January 6, 1993 and completed February 19, 1996. The NDA was resubmitted to the Agency letter date of December 22, 2003. The 10 month PUDFA goal date is August 2, 2004 (See Appendix for Regulatory History).

B. Efficacy

The Phase 3 study population consisted of a total of 324 (320 females and 4 males) patients age 21 to 65 years were initially treated at three study sites in the U.S; however, the Michigan study site was closed and data from California and Michigan study sites were merged (MICA). There were 153 patients treated with Aethoxysklerol and 156 patients treated with Sotradecol. The primary efficacy endpoint was complete disappearance of varicosities based on assessment of photographs taken at baseline and 16 weeks after the last sclerotherapy session.

The primary efficacy variable is the dichotomized version of the Disappearance of Varicosities (Yes/No) as per September 23, 1998 Guidance Meeting Minutes (# 3143). Photographic technique was to be standardized; however, photographic quality is poor and the technique was not standardized (e.g., angle, distance, lighting, etc.). For the OHIO Study, no statistically significant difference overall or for each vein size was demonstrated ($p \leq 0.2698$ and all ≥ 0.1793). For the MICA Study, no statistically significant difference overall or for each vein size was demonstrated ($p \leq 0.3127$ and all ≥ 0.1758).

The current Review Team recommended a superiority comparison of Complete Disappearance of Varicosities; although the both superiority and non-inferiority analyses were discussed with the Applicant. Demonstration of superiority of Aethoxysklerol over Sotradecol was based on the following: 1) regulatory history suggests that the initial intent was a superiority trial, 2) the comparator was diluted for all vein sizes studied, and 3) the Applicant was advised as per a February 9, 1996 communication from the Agency that analysis of the data from the efficacy portion of the study as designed in this protocol will require that Aethoxysklerol demonstrate results superior to Sotradecol. Efficacy of the diluted Sotradecol has not been established; therefore, diluted Sotradecol will be considered a placebo for purposes of efficacy evaluation as per and the Applicant was advised that the STS study arms would be viewed as a placebo for purposes of the study. In fact, the treatment effect of the approved concentrations of STS is not known because STS was approved prior to the requirement to demonstrate efficacy.

The Regulatory history is complex and spans over 13 years prior to filing of the initial NDA application. A March 25, 1997 communication indicates that Bioequivalence rule analysis recommendation was forwarded to the Applicant providing for a non-inferiority margin of 20%.

A result of simple comparisons on success proportions indicates that it cannot be concluded that Aethoxysklerol has been shown non-inferior to Sotradecol. According to the statistical review, the Applicant achieves the non-inferiority bound overall in the OHIO Study but not in the MICA Study in results of analysis of the simple mean scores, ignoring other factors. The Applicant achieves the non-inferiority bound for each vein size in each study (See Statistical Review for details).

Due to the complex regulatory history and what appeared to be conflicting recommendations from the Agency, additional statistical analyses were undertaken; however, the Applicant filed to establish superiority on the 5-point Disappearance of Varicosities scale or non-inferiority for the dichotomized primary efficacy endpoint, Complete Disappearance of Varicosities, when Aethoxysklerol is compared to Sotradecol. The Applicant did establish non-inferiority on the 5-point scale for Mean Scores for Disappearance of Varicosities.

The secondary variables were Clinical Improvement (determined by the same panel of surgeons and graded on an 11-point scale, Patient Satisfaction (determined by the patients on a 4-point scale).

There may be some irregularities of significant concern with the pivotal trials; however, at this time, the final report from DSI is still pending.

C. Safety

In the pivotal studies, 147 of 158 subjects (93.0%) in the Aethoxysklerol groups and 158 of 166 subjects (95.2%) in the Sotradecol comparator groups experienced at least one adverse event. Irrespective of drug treatment group, the most common adverse events in the pivotal studies were pain and hyperpigmentation. Superficial vein thrombosis was a common event in all treatment groups, occurring at an overall rate of approximately 51-52% for each drug treatment group. Thirteen subjects (6 treated with Aethoxysklerol and 7 with Sotradecol) experienced systemic reactions that included taste perversion, paresthesia, fainting, dizziness, asthenia, visual field deficit, and palpitation, and none were clinically significant.

While laboratory data were not collected in the pivotal studies, such data were collected in supportive studies. All studies that included clinical laboratory testing, revealed some potential for red blood cell (RBC) parameters and platelets to be affected following treatment; however, no changes were considered to be clinically significant.

No subjects died in the development program, and no subjects withdrew from any study because of an adverse event.

Review of the safety data did not reveal any adverse events that have not been previously reported with sclerotherapy or sclerosants in general, or polidocanol in particular. However, the safety assessments were largely targeted at capturing the occurrence of known sclerotherapy-associated adverse events through use of checklists.

The submitted safety data permitted no assessment for risk of deep vein thrombosis (DVT) following treatment with the sponsor's product, since none of the studies specifically assessed for DVT post-treatment.

D. Dosing

According to the sponsor, Aethoxysklerol is marketed in six concentrations: 0.25%, 0.5%, 1.0%, 2.0%, 3.0%, and 4.0%. Given that the dose-finding study ASK 94-002 appears to have been conducted after the pivotal trials, it is not clear how the sponsor determined the concentrations to evaluate for safety and efficacy in Phase 3, or that the selected concentrations represent the optimal choices for the proposed indication.

According to the proposed label, (b) (4)

(b) (4).

E. Special Populations

Gender

Analysis by gender was not performed because only for 4 males were enrolled in the study. Too few males were enrolled to be able to draw valid efficacy conclusions; however, there were 3 males with scores above 4 (majority disappeared) and one scored above 3 (minority disappeared) on the Disappearance of Varicosities Scale. Patients 1105, 2343, and 3309 had scores of 4.7 each and Patient 1227 had a score of 3.7.

Ethnic/Racial

Ethnic/racial safety and efficacy differences could not be assessed due to lack of obtaining these baseline demographic data. Post-inflammatory hyperpigmentation is of particular concern in certain ethic/racial populations. According to Weiss and Dover (Atlas of Cosmetic Surgery 2002) the rate of hyperpigmentation after sclerotherapy varies from 10 % to 80% (rare in vessels <1 mm) due to both postinflammatory hyperpigmentation and hemosiderin deposits.

Geriatric

Geriatric patients older than 65 yrs were excluded from study. The Applicant provided an age split performed at 45 yrs, and the results from those patients ≥ 45 yrs of age were compared with those from patients < 45 yrs of age with no efficacy difference being identified for age, center, vein size, and treatment –by-center.

Pediatric

A pediatric waiver was requested and should be granted because varicose veins of the lower extremities are extremely uncommon in children; therefore, study of pediatric patients is not needed.

Pregnancy Use Information
Sclerotherapy of varicose veins is contraindicated in case of pregnancy and the procedure is listed as a precaution. According to the proposed label, [redacted]. Pregnant females were excluded from study participation. The Agency received a reported adverse pregnancy outcome that appears consistent with findings in animal studies (Pharm/Tox review dated June 12, 1997); however, the conclusion stated that additional epidemiologic data on children born to mothers treated with Aethoxysklerol would be needed to confirm that the birth was not due to a random premature birth.

The pharmacology/toxicology reviewer has recommended Pregnancy Category "C" (the sponsor proposed (b) (4) "Polidocanol has been shown to have an embryocidal effect in rabbits when given in doses approximately equal to the human dose (following normalization of the exposures on the basis of body surface area). This effect may have been secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Polidocanol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus." The clinical reviewer agrees with the recommendation for Pregnancy Category "C".

There were no pregnancies reported in the development program.

Clinical Review
I. Introduction and Background
Polidocanol was developed by Badische Anilin and Sodafabrik (BASF) and was introduced in Germany as a local anesthetic in 1936 and soon it became apparent that IV administration caused sclerosis of small blood vessels. Scientist at Chemische Fabric Kreussler & Co. (hereafter Kreussler) studied the sclerosant properties of the drug. In 1966 Aethoxysklerol was registered with the Bundesgesundheitsant (BGA; Federal Health Office) as a sclerosant and the drug has been marketed in Germany since that time. According to the Applicant, the drug is currently marketed in more than 50 countries in Europe, Asia, Australia, and South America. Aethoxysklerol is used as a sclerosant for various indications such as hemorrhoids, gastric and esophageal varices, and treatment of varicose veins. Creating permanent fibrosis of a varicose segment is the goal of sclerotherapy. Sclerosing solutions are classified into three groups based on their mechanisms of endothelium destruction as detergents agents, osmotic agents, or chemical irritants. Polidocanol is considered a detergent agent.

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

- Established Name Polidocanol
- Proposed Trade Name Aethoxysklerol
- Sponsor's Proposed Indication(s) sclerotherapy of varicose veins of the lower extremities

- Age 18 to 65 years of age

Proposed Dose/Regimen:
Aethoxysklerol is indicated in the sclerotherapy of varicose veins of the lower extremities. Different concentrations of Aethoxysklerol are required, depending on the size of the varicose veins (see Dosage and Administration for appropriate injection volumes). In general, the dosage [redacted] Extensive varicosities [redacted] be treated in multiple sessions. The principle of lower concentrations for smaller vein sizes should always be followed.

For the ***sclerotherapy of varicose veins (spider veins) ≤1 mm in diameter***, give 0.1 to 0.3 mL Aethoxysklerol 0.5% per injection.

For the ***sclerotherapy of varicose veins [redacted] 1 to 3 mm in diameter***, give 0.1 to [redacted] mL Aethoxysklerol 1% per injection.

[redacted] (b) (4)

B. State of Armamentarium for Indication(s)
Small vessel sclerotherapy treatment modalities include sclerotherapy, surgery, laser, and broad flash-lamp light sources. Sclerosing agents are classified into three groups (detergent, osmotic, and chemical irritants) based on their mechanisms of destruction on the endothelium. Polidocanol and Sotradecol are detergent sclerosing agents. Two concentrations of Sotradecol were available at the time of the study; however, the NDA was withdrawn without prejudice from the US market in March 5, 2003 due to a withdrawal request from the Applicant (letter date February 5, 2003).

Currently there are no approved drugs approved for treatment of varicosities of the extremities. Sodium tetradecyl sulfate (STS) was previously a sclerosant of choice in the U.S.; however, is no longer available. Non-approved sclerosing agents include chromated glyerine (Scleremo), mixture of 25% dextrose and 10% sodium chloride (Sclerodex), and polyiodinated iodine (Variglobin, Sclerodine). Sodium morrhuate came into use in the 1930s and is available; however, sodium morrhuate is not FDA approved. Hypertonic saline is a FDA approved drug that is used off-label as a sclerosing agent. Pharmacy compounding has also been a source of sclerosants in the United States.

C. Important Milestones in Product Development
Regulatory Background (Regulatory history timeline is located in Appendix 1.)
The regulatory history is complex with multiple interactions between the Applicant and the Agency. Pivotal studies were initiated in 1994 and completed in 1996. The application does not meet today's evidentiary standard of submission of data from at least two independent multicenter clinical trials in support of efficacy and that data from two study sites were merged.

Important dates include initial submission of IND 35,139 on July 19, 1990 to the Division of Medical Imaging, Surgical and Dental Drug Products (HFD-160), NDA submission and withdrawal in 1999, and resubmission December 22, 2003. Communications were conveyed to the Applicant supporting acceptability of a minimum of two separate study locations in order to fulfill the requirement for two independent studies (March 8, 1991) and concurrence with a request to combine a non-productive center with a more productive center (although not usually recommended) providing that proper Meta-Analysis procedures were used (April 12, 1994 Division memo). IND 35,139 was transferred to Dermatology (HFD-520) in January 1994, and then to the newly formed HFD-540 (Division of Topical Drug Products) in September 1994.

It should be noted that in 1993 the clinical trial was already on going at the time of protocol review and prior to receipt of comments from the Division. According to the MO Review, the protocol submission date was February 22, 1993; therefore pivotal studies were ongoing at time of the review. Also of note is a January 31, 1996 e-mail from Project Management noting that Paul Cowden (Jobst) was informed that without a formal End of Phase 2 meeting, they have not received commitments by the Agency at which time one study was completed and the other study was nearing completion.

D. Other Relevant Information

Because Aethoxysklerol contains ethanol (5%), its use has been reported to be contraindicated in patients receiving treatment with disulfuram or similar products (Goldman, PM, J Dermatol Surg Oncol 1989;15:204-209). However, other authors do not believe use of disulfuram to necessarily be a contraindication (absolute or relative) to Aethoxysklerol treatment, although, as with any medication, its use in relation to disulfuram should be "reviewed carefully for its appropriateness" (Rabe E, et al. Dermatol Surg 2004;30:687-693). Also, these authors note that other injectables contain alcohol and do not carry a disulfuram contraindication (Note: The article was from Germany, so it is not clear how broadly this observation would apply).

Comment: It is difficult to envisage a scenario where disulfuram treatment and sclerotherapy of varicose veins of the lower extremities would need to coincide. When treatment of varicose veins is undertaken for strictly cosmetic purposes, it would not appear reasonable or appropriate to risk a disulfuram reaction. Even when a medical need for treatment of varicose veins exists, treatment is not done on an emergent basis, and, if sclerotherapy is chosen as the treatment approach, it could be scheduled to allow for clearance of disulfuram. It is recommended that the label reflect use of disulfuram to be a contraindication to Aethoxysklerol treatment.

Foreign Experience

Aethoxysklerol (polidocanol) has been used in Europe and South America since the 1970s and more recently in Asia and Australia. Aethoxysklerol was available in 5 different concentrations at the time of the study; 6 concentrations (0.25%, 0.5%, 1%, 2%, 3%, and 4%) have been available since 1996. The application is not specific regarding European and South American availability of Aethoxysklerol; however the presumption is that these data refer to the Chemische

Fabrik Kreussler & Co., GmbH drug product. Copies of patient information leaflet and expert information documents for Aethoxysklerol from 26 foreign countries were submitted; however, marketing authorization dates were not provided.

United States
Polidocanol 1% microfoam (VARISOL) is being studied under IND by a different sponsor as a sclerosant (b) (4)

E. Important Issues with Pharmacologically Related Agents

In the American College of Phlebology publication "Complications of Sclerotherapy," adverse events associated with the procedure are reported to include hyperpigmentation, swelling, telangiectatic matting, localized urticaria, localized hirsutism, cutaneous necrosis, systemic allergic reactions, superficial thrombophlebitis, deep vein thrombosis and nerve damage. Additional reported complications include orthostatic collapse and scotoma (Rabe E, et al.). These adverse events are reported as being associated with sclerotherapy in general, rather than with any particular sclerosant.

Hemolysis has also been reported with several sclerosants including sodium tetradecyl sulfate (Goldman MP, Dermatol Surg 2002;28:52-55), hypertonic saline (Feied CF, American College of Phlebology, "Sclerosing Solutions Part Two"), ethanolamine oleate (Feied CF, eMedicine, "Varicose Veins and Spider Veins"), and polidocanol (Marrocco-Trischitta MM, et al., Dermatol Surg 2002;28:153-155). Hemoglobinuria may accompany the hemolysis, and renal failure may result if the hemolysis is sufficiently severe (Feied and Marrocco-Trischitta MM, et al.). Because of the risk of hemoglobinuria-related renal failure, Marrocco-Trischitta MM, et al. recommend that patients be hydrated during and immediately following sclerotherapy.

Reversible cardiac arrest has been reported following injection of 4 mL of 1% polidocanol (40 mg) into a peripheral venous malformation (Klippel-Trenaunay syndrome). Cardiac arrest was preceded by rapidly progressive sinus bradycardia. The authors hypothesized that the event was attributable to the local anesthetic properties of polidocanol with the attendant potential to interfere with the electrical activity of the heart if there is sufficient systemic absorption (Marrocco-Trischitta, MM et al.).

Comment: The reported cardiac arrest occurred under circumstances that would not be at all typical of those for the sponsor's proposed indication of treatment of varicose veins of the lower extremities, including:

- *The patient was in the pediatric age group (5-year-old).*
- *The diagnosis was a peripheral venous malformation.*
- *The treatment area included the buttock.*

- *Sclerotherapy was performed under general anesthesia (because of the patient's age). The patient was pre-medicated with oral midazolam and atropine, anesthesia was induced with thiopental, tracheal intubation was facilitated by vecuronium bromide, and anesthesia was maintained with sevoflurane and a mixture of oxygen and nitrous oxide. It is not clear whether there might have been any drug-drug interaction effects operative.*

Also, at 40 mg, the 20 kg patient received what is reported to be the upper limit of the manufacturer's maximum daily recommended dosing of 2mg/kg (Feied CF, et al. J Dermatol Surg Oncol 1994;20:466-468).

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Chemistry

CMC Review is pending. No chemistry issues are anticipated.

B. Animal Pharmacology and Toxicology

The PharmTox Reviewer recommends an approvable action with respect to pharmacologic and toxicologic concerns stating that no additional nonclinical studies are recommended at this time.

C. Clinical Pharmacology and Biopharmaceutics

Biopharmaceutics review is pending; however, verbal communication with the PK reviewer on May 17, 2004 indicates that there no outstanding PK issues.

D. Statistics

According to the draft statistical review conclusion, even without an adjustment for the multiplicity of tests, in both nominal studies, no overall or within vein size comparisons of the dichotomized complete disappearance were statistically significant (all $p \geq 0.1758$). Further, in neither study did any of these comparisons of this dichotomous endpoint meet the requirements to show non-inferiority

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics (Biopharm review pending)

B. Pharmacodynamics

According to the proposed label, [redacted] disappeared.

Data were not submitted to support this precaution; however, Biopharm's recommendation follows: "Besides being a sclerosing agent, polidocanol also has local anesthetic properties. As such, it can have an additive effect with other systemically administered anesthetics on cardiac

functions, i.e., bradycardia. Treatment of varicose veins with polidocanol should be done separately from surgical treatment of varicose veins to avoid potentials of cardiac side-effects."

IV. Description of Clinical Data and Sources

A. Overall Data

Data sources for this review were from the clinical trials conducted by the Applicant and submitted literature reports.

B. Tables Listing the Clinical Trials

Table 1 (Applicant's Table 8.G.1) Studies Used to Determine Efficacy

Reviewer comments:

Although the Applicant considers the following studies as efficacy studies, only the Ohio and MICA studies are being reviewed for efficacy. The two concentration controlled studies (ASK 94-002 and ASK 96-001) listed in the following table are randomized dose ranging studies that were initiated in 1995 and 1996; respectively. The two concentration controlled studies were initiated 2 to 3 years after the pivotal studies initiation (1993), did not contribute to dose selection for the pivotal studies, and are being reviewed only for safety. Study AET-AS25 was also not randomized and was reviewed for safety.

Table 1

TABLE 8.G.1 STUDIES USED TO DETERMINE EFFICACY

Study No./ Centers/Location[a]	Principal/ Coordinating Investigator	Start Date/ Status	Formulation	Design	Treatment/ Dose[b]	No. Entered	Age Range (mean)	Gender M/F	Duration of Treatment	Location Report	Location Data	Location CRFs
Pivotal Studies												
OHIO/ 1/US	Villavicencio/ Lohr	6 Jan 1993/ Completed	0.50%, 1.0%, 3.0% Aet.[c] 0.25%, 0.50%, 1.5% Sotr.[c]	Randomized, double-blind, active-controlled	Drug/0.50% /1.0% /3.0% Control[e]/0.25% /0.50% /1.5%	25 25 25 25 25 25	21-65 yrs (41.0)	1/149	NA[d]			NA
MICA/ 2/US	Villavicencio /Pfeifer /Goldman	3 Mar 1993/ Completed	0.50%, 1.0%, 3.0% Aet. 0.25%, 0.50%, 1.5% Sotr.	Randomized, double-blind, active-controlled	Drug/0.50% /1.0% /3.0% Control/0.25% /0.50% /1.5%	29 31 27 33 32 27	24-65[f] yrs (42.8)	3/176	NA			
Concentration-Controlled Studies												
ASK 94-002/ 21/JPN	(b) (4)	3 Feb 1995/ Completed	0.5%, 1.0%, 2.0%, 3.0% Aet.	Randomized, open-label, concentration-controlled	Drug/0.50% /1.0% /2.0% /3.0%	22 50 63 26	20-75 yrs (48.0)	11/150	NA			NA
ASK 96-001/ 21/JPN		27 Aug 1996/ Completed	0.25%, 0.5%, 1.0% Aet.	Randomized, open-label, concentration-controlled	Drug/0.25% /0.50% /1.0%	20 51 29	29-79 yrs (49.6)	2/98	NA			NA
Uncontrolled "Study" (AWB)												
AET-AS25/ 4/GER	Rabe	Dec 1995/ Completed	0.25%, 0.25%G[g] Aet.	Open-label, uncontrolled	Drug/0.25% /0.25%G	40 39	19-62 yrs (40.6)	0/79	NA			NA

US = United States; JPN = Japan; GER = Germany; AWB = *Anwendungsbeobachtung* (a treatment observation done under the German drug law that permits such a treatment observation with registered and marketed drugs to be done without informed consents, Institutional Review

Board/Ethics Committee approval, or case report forms. It was a safety and tolerability "study" of 2 formulations of Aethoxysklerol, and no control was specified. Therefore, it is classified here as an uncontrolled "study.").

[b] Dose was determined for individual patients; a maximum of 2.0 mg/kg could be administered. Concentrations are presented in this column.

[c] Aet. = Aethoxysklerol, Sotr. = Sotradecol

[d] NA = Not Applicable

[e] The control solution was Sotradecol.

[f] Age range and mean for the MICA study are calculated based on 174 patients who received drug (see Section 2.1).

[g] An alternative formulation with 20% glycerin instead of ethanol as the (b) (4); the active ingredient for both formulations was polodcanol.

C. Post-marketing Experience

According to the sponsor, Aethoxysklerol has been marketed since 1966, and is currently marketed in more than 50 countries (Europe, Asia, Australia, and South America). The sponsor reports that Aethoxysklerol is marketed in six concentrations: 0.25%, 0.5%, 1.0%, 2.0%, 3.0%, and 4.0% for three indications: esophageal varices, hemorrhoids and varicose veins (Volume 30, p. 27). Its total use for these three indications from 1987 to February 2003 is reported to have been (b) (4) mL.

From 1987 until April 2003 (data lock), 358 spontaneous reports of adverse events in connection with Aethoxysklerol and treatment of varicose veins of the lower extremities were recorded from healthcare professionals and patients. These 358 reports involving 450 subjects are said to represent all adverse events reported in association with the use of Aethoxysklerol in the treatment of varicose veins for the time period covered. The sponsor states that the number of reports and patients are different because more than one patient could have been reported in some cases. Select events are presented in the table below:

Reported Event	# of Reports	# of Patients
Necrosis/ulceration	64	123
"Pigmentations"	21	50
Suspicious of allergy	11	11
Cerebrovascular incident,aphasia	1	3
Vision disorders/scotoma	13	13
Circulation problems/blood pressure changes	12	12
Unconciousness/collapse	7	7
Breathing difficulties	15	15
Pressure in the chest	10	14
Pulmonary edema	2	2
Thrombosis*	6	6
Deep vein thrombosis	6	6
Pulmonary embolism	5	5
Thrombocytopenia	3	3
Phlebitis/thrombophlebitis	4	4
Anaphylaxis	8	9
Generalized allergic reaction	4	4
"state of shock"	1	1

Source: ISS Table 8.H.21

*Thrombosis was not further defined

Comment: 1) The database would have been more comprehensive had the sponsor included information on all spontaneous adverse event reports, rather than only those submitted in

association with treatment of varicose veins of the lower extremities. However, the post-marketing data submitted did not reveal any new or unexpected events. 2) An e-mail communication from the Office of Drug Safety (date May 14, 2004) indicated that there were no post-marketing adverse event reports in the AERS database.

D. Safety Update

On February 6, 2004, the sponsor submitted the 120-Day Safety Update to the NDA. The update consisted entirely of spontaneously reported adverse events. From May 1, 2003 to January 26, 2004, there were 22 such reports pertaining to patients who received treatment of varicose veins of the lower extremities. The Safety Update contained one report of death, which is believed to represent the report of a death from France that had been submitted to IND 35,139. The death occurred on January 10, 2003, and the report was received by the manufacturer on November 21, 2003. It was submitted to the sponsor's IND on November 24, 2003 (Serial 057):

A 35 y/o female, without known allergies, received 0.5 ml x 2 of 0.5% Aethoxysklerol for sclerosis of an "inferior member." Minutes following treatment, while arising from the table, she apparently collapsed with loss of conciousness, progressive cyanosis and eventual cardiac arrest. Resuscitation efforts were unsuccessful. There were reportedly no precursor signs. Available autopsy findings, limited only to gross examination of the undissected heart, were submitted in a follow-up report on February 2, 2004 (Serial 059). The heart was reported to weigh 300 g, and external examination revealed dilation of the right ventricle.

Comment: While the temporal relationship is obvious, an investigator's assessment of the degree of relatedness to treatment was not provided.

The types of events reported were otherwise similar to those previously submitted in the NDA

E. Literature Review

The submitted literature supports efficacy and safety with use of polidocanol, treatment of varicosities, and comparison of treatment modalities.

V. Clinical Review Methods

A. How the Review was Conducted

Data from only two studies (OHIO and MICA) were submitted in support of efficacy. As previously indicated, open-labeled studies ASK 94-002, ASK 96-001 (concentration controlled), and AET-AS25 were reviewed for only for safety.

All seven studies submitted in support of safety were reviewed separately.

B. Overview of Materials Consulted in Review

Materials reviewed include: Divisional File for regulatory history and NDA 21-201 (Vol. 1.1, 1.2, 1.30 – 1.50.). In addition, for the safety review, IND 35,139 was reviewed, as were minutes of the meetings the Division had with the sponsor.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations (DSI) report of inspections at the Ohio, Michigan, and California study sites are pending at this time. In April 2004, a List of Observations (Form 483) was issued for California site on inspection by DSI.

DSI draft recommendations (dated June 10, 2004) stated that the data submitted in support of this application by Drs. Pfeifer and Goldman were inadequate and should not be relied upon in making any decisions regarding the approvability of this submission. These draft recommendations are derived solely from a review of the Form 483 issued to Dr. Pfeifer and from a brief overview of the Form 483 and the inspection report for Dr. Goldman. If these draft recommendations are made final, then data from only one study site that studied 73 patients with Aethoxysklerol would be eligible for efficacy assessment.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Studies OHIO, MICA, ASK96-001, ASK-94-002, and ASK-00-01-00 were conducted in accordance with the Ethical principles in the Declaration of Helsinki and its amendments. However, "Study" AET-AS25 was an *Anwendungsbeobachtung* (AWB). An AWB is a treatment observation done under the German drug law that permits such a treatment observation with registered and marketed drugs to be done without informed consents.

There did not appear to be any obvious breaches of ethics from review of the safety data submitted.

E. Evaluation of Financial Disclosure

The Applicant certified that there were no financial arrangements with the listed clinical investigators as defined in 21 CFR 54.2(a), 21 CFR 54.2(b), and 21 CFR 54.2(f)."

Reviewer comments:

Financial disclosure was not provided for the photographic review panel. Financial disclosure for the photographic review panel was requested in the 74-Day Filing letter and is still pending.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

From an efficacy prospective a *Non-Approvable* recommendation is being made for use of Aethoxysklerol (polidocanol), a sclerosant intended for intravenous administration for treatment of (b) (4) diameter varicosities of the lower extremities.

The Applicant failed to establish superiority for the dichotomized Complete Disappearance of Varicosities efficacy endpoint as proposed by the Division or Disappearance of Varicosities on a 5-point scale as proposed by the Applicant when Aethoxysklerol is compared to diluted Sotradecol (STS). The attempt to demonstrate superiority or non-inferiority was flawed because the treatment effect of the Sotradecol comparator is unknown; thereby making power calculations determination difficult.

Sotradecol was approved in 1946 when efficacy did not have to be established therefore use as an active comparator is problematic in establishing superiority or non-inferiority in that the treatment effect of the approved or diluted concentrations of Sotradecol is unknown. It is of note that non-inferiority was not established for the dichotomized Complete Disappearance of Varicosities efficacy endpoint.

B. General Approach to Review of the Efficacy of the Drug
OHIO and MICA are the clinical trials being reviewed in depth to support efficacy.

C. Detailed Review of Trials by Indication
Indication #1 Treatment of Varicose Veins of the Lower Extremities
Treatment of Varicose Veins of the Lower Extremities of three vessel sizes is the only indication studied. Study protocols were identical for all pivotal studies (MICA and OHIO); however, there is only one multicenter clinical trial.

Applicant's OHIO Protocol

Title: "Double-Blind, Prospective, Randomized, Comparative Multicenter Trial Between Aethoxysklerol® (Polidocanol) and Sotradecol® (Sodium Tetradecyl Sulfate) in the Management of Varicose Veins of the Lower Extremities"

Selection of Study Population
Inclusion Criteria

- Male or female patients, at least 18 years of age, who gave written informed consent were eligible to enroll.
- Only patients suffering from the following types of varicose veins and in whom no valvular insufficiency had been detected during the venous examination were enrolled in the study:
  1. Small cutaneous blemishes: telangiectasia, venous stars, venous lakes (veins ≤1 mm in diameter)
  2. Superficial venules: >1-3 mm in diameter in the standing patient
  3. Varicose veins: >3-6 mm in diameter distributed over different areas of the extremity

Exclusion Criteria
Patients with any of the following conditions were not included in the study.

- Large varicose veins (>6 mm in diameter).
- Pregnant women. Women who were sexually active were treated within the first 10 days post-menstrual period, or while they were practicing an acceptable method of birth control;
- Elderly or sedentary patients (>65 years of age);
- Generalized systemic disease (cardiac, renal, hepatic, pulmonary, collagen) and malignancies;
- Advanced rheumatic disease, osteoarthritis, or any disease that interfered with a patient's mobility;

- Arterial insufficiency of the lower extremities as evidenced by intermittent claudication, coldness of the extremity, skin atrophy, and absence of foot pulses. In questionable cases, ankle/brachial index (arm blood pressure/ankle blood pressure) were investigated. Normal index should be ≤1;
- Bronchial asthma or demonstrated allergies;
- Acute, superficial, or deep thrombophlebitis;
- Acute febrile illness as manifested by fever (≥38 C) and signs and symptoms of acute systemic disease;
- Obesity as manifested by a body weight in excess of 20% of the ideal body weight;
- Varicose veins that are in communication with a source of venous reflux as demonstrated by non-invasive venous examination (these have been demonstrated to have a high incidence of recurrence after sclerotherapy); or,
- Concomitant use of anticoagulants.

Reviewer comments:

- Use of oral contraceptives is listed in the proposed label as an exclusion criterion; however, was not listed in the protocol.
- Rationale for exclusion of patients >65 years of age who are not sedentary was not provided.

Prior and Concomitant Therapy

With the exception of the concomitant use of anticoagulants, there were no restrictions placed upon prior or concomitant therapies.

Reviewer comments:

Use of oral contraceptives was addressed under exclusion criteria.

Pre-Study Evaluation

Each patient was approved by the principal investigator before entry into the study. Venous diameters were measured with a caliper at entry. A medical history and physical examination including Doppler examination of the venous system was performed prior to treatment. Color photographs of the affected area were taken before, at one month, and 4 months after the last treatment.

Reviewer comments:

The protocol did not address how the target varicosity was selected for study if patients had more than one size varicosity.

Study procedures

Patients were classified according to vein size, and the randomization numbers were assigned sequentially to the patients as they entered the study. Sexually active females were treated within the first 10 days post-menstrual period, or while they were practicing an acceptable method of birth control. Patients were treated according to the sclerotherapy technique commonly used by the investigator rather than a standardized treatment method.

The unblinded investigator provided the blinded physician with a randomization number for each patient entered into the study. The unblinded investigator was also responsible for:

- making necessary dilutions of Sotradecol,
- filling the syringes for injection. (The 2 drugs were identical in appearance.)
- maintaining a code envelope for each patient in which was kept patient information and the drug assignment.

Treatments Administered
The two sclerosing agents used in this study were Aethoxysklerol (Chemische Fabrik Kreussler & Co. GmbH, Wiesbaden, Germany) and Sotradecol (Elkins-Sinn Inc., Cherry Hill, NJ). The investigator determined, on a patient-by-patient basis, the amount of intravenously administered sclerosing agent necessary to treat the affected area and the number of sclerotherapy sessions required.

Identity of Investigational Product
According to the submission, Aethoxysklerol was provided in boxes containing 5 glass ampules. Each ampule contained 2 mL of either 0.5%, 1.0%, or 3.0% Aethoxysklerol, the concentration of polidocanol in each of these was 5 mg/mL, 10 mg/mL, and 30 mg/mL, respectively. All concentrations contained 5% ethanol by volume. Aethoxysklerol ampules were labeled B-0.5%, B-1%, and B-3%.

Sotradecol was provided in boxes of 5 glass ampules each containing 2 mL each. Each ampule contained either 10 mg (for 1.0% solution) or 30 mg (for 3.0% solution) of sodium tetradecyl sulfate. Each concentration contained 0.02 mL benzyl alcohol per mL of solution. Sotradecol ampules were labeled A-1% and A-3%.

The lot numbers for Aethoxysklerol were the following:
B-0.5%: 03535
B-1%: 03135
B-3%: 04535
The lot numbers for Sotradecol were the following:
A-1%: 052236
A-3%: 052220

Reviewer comments:
Sotradecol was not used as labeled.

Sclerotherapy Technique
The sclerotherapy technique was not described in detail in the protocol. The technique commonly used by the coordinating investigator in his or her department was used to treat patients in this study. Details of the technique were to be described and recorded on the CRF.

According to the protocol, after the injection treatment, external pressure was to be applied with an elastic stocking and that compression was to be maintained for at least 1 week. At the end of

the compression period, the limb was to be examined, and the locations of areas of venous thrombosis, ecchymosis, or any other local phenomena were to be recorded in the CRF.

Any thrombus that might have formed was to be evacuated through multiple micro-incisions, and external compression was to be maintained for 2 to 3 days. The goal of the microthrombectomy was to diminish the incidence of hyperpigmentation (an undesirable side effect following sclerotherapy). The thrombectomized areas were to be recorded on the CRFs pages containing drawings of the legs. Josbt Institute provided the elastic stockings for patients in the study (Vol. 35, pg. 2429).

Reviewer comments

1. According to N. Sadick and C. Li (Small-vessel Sclerotherapy, Fundamentals of Cosmetic Surgery, Volume 19, Number 3, July 2001) there are four basic techniques of sclerotherapy and other perhaps standard procedures (e.g., proper visualization, angle of needle insertion, skin tension, etc.). These basic injection techniques are listed as follows: air bolus, aspiration, puncture "feel", and empty vein techniques. The protocol should have addressed the specified sclerotherapy technique to be used or provided subgroup analysis based on the different sclerotherapy technique used by the investigators.
2. Perivascular injections and the length of post sclerotherapy compression were not addressed in the study report. According to the information provided, at concentrations of 0.5%, it can be infiltrated perivascularly without inducing skin necrosis. The protocol stated that compression was to be maintained for at least 1 week; however, compression times differed based on vessel size. According to the Applicant (06-03-04), only one subject was unintentionally injected perivascularly; however, this patient was not identified.

A summary description of the sclerotherapy technique used at each site is summarized as follows (According to Attachment 4, Submission N000 (BZ), received March 29, 2004):

Positioning of Patient during injection:

Patient was placed in a recumbent position with the leg to be injected in a horizontal position.

Types of syringes or needles:

Smooth-moving syringes with fine-gauge needles (30G) were used (Dr. Goldman). Drs. Lohr and Pfeifer specified that 30 G were used for spider veins, bigger needles for larger veins were used.

Injection technique:

Injection was performed by slow injection with gentle pressure and intravenous positioning of the needle tip.

Post-treatment procedure/Compression

Immediately following injection, a gradient compression was applied. The patient was instructed to walk for at least half an hour and to maintain the compression for up to 2 days (spider veins) or a minimum of 1 week (for larger veins).

Reviewer comments:
Sclerotherapy technique and compression gradient are minimally described. Additional information has been requested (04-16-04). Additionally, post sclerotherapy compression times for varicosities are different from the duration proposed in the label. The compression times proposed in the label are:

- 2 – 3 days for spider veins ≤1mm
- 5 – 7 days for varicosities 1-3 mm

Random review of the CRFs submitted on 05-26-04 confirms that sclerotherapy techniques were minimally described; therefore, subgroup analysis could not be performed and adequate details are not available for labeling.

Selection of Doses in the Study
Concentrations of study drug administered were dependent upon the sizes of veins to be injected and are displayed in the table below:

Table 2: Dosing

Sclerosing Agent	**Vein Size**		
	≤1mm	> 1-3 mm	> 3-6 mm
Aethoxysklerol	0.50%	1.0%	3.0%
Sotradecol	0.25%	0.50%	1.5%

According to the protocol (Vol. 37, pg. 3125), " At each treatment session, the maximum dose of polidocanol was to be 2 mg/kg body weight; the maximum volume of Sotradecol 1.0% was to be 4 mL; and the maximum volume of Sotradecol 3.0% was to be 2 mL. The concentrations of Sotradecol were obtained by diluting the drug with physiologic saline (0.9%)".

Reviewer comments:
Sotradecol was not used as approved. Use of Sotradecol is problematic in that efficacy at the approved concentrations and diluted concentrations are unknown; therefore, it is difficult to estimate the treatment effect. STS was approved prior to 1946 where only establishing safety was needed.

Sotradecol was approved in two concentrations, 1% and 3%, according to the 1996 label. The indication is in the treatment of small uncomplicated varicose veins of the lower extremities that show simple dilation with competent valves. The risk-to-benefit ratio should be considered in selected patients who are great surgical risk.

According to the Dosage and Administration Section for Sotradecol, the sclerosing agent was for intravenous use only and in general, the 1% solution will be found most useful with the 3% solution preferred for larger varicosities; however, vessel diameter was not provided.

The rationale for diluting Sotradecol was not provided. According to the submission Vol. 37, pg. 3125), use of specific concentrations were obtained from the clinical published literature; however, these references were not identified in the submission.

Randomization
The unblinded investigator provided the blinded physician with a randomization number for each patient entered into the study. Patients were classified according to vein size, and the randomization numbers were assigned sequentially to the patients as they entered the study. The randomization number was a 4-digit number; the first digit indicated the study center (1=California site and 3=Michigan site), the second digit indicated the vein size category, and the third and fourth digits indicated the patient number.

The randomization schedule was generated by computer and provided to the study site by the Department of Preventive Medicine and Biometrics of the Uniformed Services University of the Health Sciences (USUHS). When the Sponsor decided to merge the data from the Michigan and California sites, a new randomization schedule was prepared for the California site. According to the protocol, the schedule was maintained in strict confidence by the unblinded investigator.

Reviewer comments:
Identification and qualification of the unblinded investigator at each study site has been requested.

Selection and Timing of Dose for Each Patient
The investigator determined, on a patient-by-patient basis, the amount of sclerosing agent necessary to treat the affected area and the number of sclerotherapy sessions required. Based upon previous experience, it was expected that 1 to 6 or more treatments would be necessary. Individual veins usually require from 1 to 3 treatments.

Blinding
With the exception of an unblinded investigator, all other study personnel were blinded to study-drug assignments. Study drugs were identical in appearance.
Reviewer comments:
Randomization and maintaining the study blind are at issue since the unblinded investigator recorded AKs and took the photographs (according to initial DSI report at the California site) from which efficacy was ultimately assessed.

Removal of Patients from Therapy
Patients were removed from the study if they refused to continue treatment or if they experienced any allergic reactions, either local or systemic.

Reviewer comments:
During NDA review, it is noted that patients who received the incorrect concentration or dilution of Sotradecol were discontinued from the studies. It is not clear when the protocol violations occurred or when the patients were withdrawn from efficacy evaluation.

Treatment Compliance
According to the submission, since study drug had to be administered by the blinded physician, patient compliance was ensured.
Reviewer comments:
Protocol compliance should have been monitored (e.g., dilution, study drug volume administered, duration of compression, photographic assessment, microthrombectomy, etc.) Sotradecol dilution and the amount injected should have been monitored and documented. Aethoxysklerol amount and vein size compliance should have been provided. Compliance with compression should have been monitored and reported. According to the proposed label, [redacted] Photographic assessments, follow-up visits, and concomitant medications are all compliance issues that may have affected the accurate evaluation of safety and efficacy with use of the study drug.

Photography
Color photographs of the affected area were taken before, at one month, and 4 months after the last treatment. The photographic technique was to be standardized, using the same distance and the same film and photographic equipment (Kodac Color Print Film Gold 100 ASA). Color prints 5 x 7 were to be attached to the patient's file in special transparent sheets. Copies were to be kept by the Study Coordinator. In Amendment 1, the size of the color prints was changed from 5 X 7 to 4 X 6.

Although photographs were taken at one month, these photographs were not used in any efficacy or safety evaluations of subjects (N-000 BZ, pg. 1, received March 10, 2004). Standardized photographic technique and superior quality were crucial for adequate efficacy evaluation since efficacy outcome was based on solely on photographs.

According to the submission (N-000 BZ, received February 10, 2004):
1. To ensure uniformity of photographic quality, each center had a training session on how photographic equipment (camera, lenses, dual flash system, filters, film, and guide to appropriate distance between the subject and the camera).
2. All films were developed in the same laboratory by the same technician following pre-set standards.

Photographs for each subject judged to have complete disappearance of varicosities were submitted for the OHIO and MICA study sites.
Reviewer comments:
Efficacy was based on review of the photographs. Photographic quality (consistency of distance, angle, sharpness, and lighting) was poor based an informal assessment of baseline and 16 weeks after the last sclerotherapy session. Photographic assessment alone may not be the best method for determining efficacy.

Duration of Treatment:
Each treatment was a single dose of Aethoxysklerol or Sotradecol, but each patient received 1 to 3 treatments. The number of treatments necessary was determined by the investigator based on clinical judgment.

Criteria for Evaluation:
Efficacy: The primary efficacy variable was the disappearance of varicosities as determined by 3 vascular surgeons who were blinded to treatment and independent from the study center. They based their evaluation on photographs taken with a standard technique before and after injection. The variable was compared between treatment groups for each vein-size group and across all vein-size groups.

Disappearance of Varicosities, based on a scale from 1 to 5 where
1=worse than before treatment,
2=same as before,
3=the minority disappeared,
4=the majority disappeared, and
5=complete disappearance of varicosities.
The average of the "disappearance" scores from the 3 reviewers was used for the analyses of the primary efficacy variable. Based on this score, a categorical "complete disappearance" variable was derived, where a value of "yes" was given for those cases which received a score of 5 on the disappearance score, and all others were given a value of "no." Results are presented for both the disappearance score and the categorical variable.

The secondary efficacy variables were (1) overall clinical improvement based on disappearance of varicosities, hyperpigmentation, and neovascularization and (2) overall patient satisfaction. Clinical improvement rating scale follows: 0 – 2 = poor, 2 – 4 = f air, 4 – 6 = moderate, 6-8 = good, and 8 – 10 = excellent. Each of the 3 independent reviewers graded the photographs by comparing and evaluating the following 3 variables:

- vein disappearance,
- hyperpigmentation, and
- neovascularization (called matting in the CRF).

According to the submission, although hyperpigmentation and neovascularization were independently analyzed as adverse events, they were to be taken into consideration when judging the overall clinical improvement of the treated limb.

An additional efficacy variable was overall patient satisfaction that was based on a 4-point scale where 1=unsatisfied, 2=moderately satisfied, 3=satisfied, and 4=very satisfied. At the final visit, the patients filled out a CRF provided by the investigator on which they recorded and signed their degree of overall satisfaction with the end result of treatment.

These variables were compared between treatment groups for each vein-size group and across all vein-size groups.

Statistical Analysis Plan (See also Statistical Review)
The primary analysis is the superiority comparison of complete disappearance of varicosities 16 weeks after the last sclerotherapy treatment; although the both superiority and non-inferiority analyses were discussed with the Applicant. Demonstration of superiority of Aethoxysklerol over Sotradecol was based on the fact that the Applicant was advised as per a February 9, 1996

communication from the Agency that analysis of the data from the efficacy portion of the study as designed in this protocol will require that Aethoxysklerol demonstrate results superior to Sotradecol, regulatory history suggested that the initial intent was a superiority trial, and that the comparator was diluted for all vein sizes studied. Efficacy of the diluted Sotradecol has not been established; therefore, diluted Sotradecol will be considered a placebo for purposes of efficacy evaluation as per and the Applicant was advised that the STS study arms would be viewed as a placebo for purposes of the study. However, a March 25, 1997, communication indicates that Bioequivalence rule analysis was forwarded to the Applicant from an FDA biostatistician providing for a 20% non-inferiority margin.

Efficacy and Safety Variables
Efficacy Measurements
The clinical response to treatment was evaluated by assessing the 3 variables; one primary efficacy variable, disappearance of varicosities, and two secondary variables, overall clinical improvement and overall patient satisfaction. Disappearance of varicosities and overall clinical improvement were investigator efficacy assessments based on before and after photographs.

Reviewer comments:
The Applicant was advised that the recommended that the sole primary efficacy endpoint should be the dichothomized version (Yes/No) of Disappearance of Varicosities according to minutes from a September 23, 1998 Guidance meeting between the Division and the Applicant (Beirsdorf-Josbt). It is also noted that the primary population is the per protocol population since this is a non-inferiority/equivalence trial (Please refer to E9 of the ICH document). If superiority is demonstrated, then there is no adjustment for multiple comparisons.

Based on the following factors the Clinical Team decided superiority statistical analysis should to the primary statistical analysis with Compete Disappearance of Varicosity dichothomized (Yes/No) as the primary efficacy endpoint. However, an efficacy endpoint at 16 weeks after the last treatment is not sufficient to establish durability of treatment effect. Since the treating investigator was blinded to treatment assignment it is unclear why clinical efficacy assessment were not performed and supported by the 3 independent evaluators determining efficacy from photographs.

It should be noted that all protocol and statistical discussions with the Applicant were after initiation of the studies (e.g., study dates of January 6, 1993 to July 26, 1995 and March 3, 1993 to February 19, 1996 for the OHIO and MICA sites; respectively).

The 3 independent reviewers were instructed in a preparatory training session with the principal investigator and the study biostatistician.

Reviewer comments:
The same 3 independent reviewers provided efficacy assessments for both pivotal studies (OHIO and MICA) from before and 16 weeks after photographs. This efficacy evaluation makes the two studies less independent.

Secondary Efficacy Variable
The secondary efficacy variable was overall clinical improvement of the treated area from baseline and 16 weeks after photographs on a scale from 0 to 10 where 0 = no improvement or worse than before and 10 = perfect cosmetic result. Intermediate values at intervals of 0.5 could also be assigned. The average of the clinical improvement scores from the 3 reviewers was the basis for the analyses of this secondary efficacy variable.

Longevity of Effect
According to the Applicant, once a vein is successfully treated by sclerotherapy, it is permanently transformed into a fibrous cord that cannot open. Aethoxysklerol achieves this effect by damaging the endothelium of the vein by interfering with the lipids on the cell surface which results in desquamation of these cells. Subsequent intravascular reactions such as vasospasm and local platelet aggregation occlude the vein. Compression of the treated veins helps ensure the permanent transformation of the vein into fibrotic tissue.

Reviewer comments:
The Applicant did not provide data to support duration of effect past 4 months and there is no documentation that the need for data supporting longevity of effect beyond 16 weeks after the last sclerotherapy session was discussed. Based on today's standards, minimally, one year follow up is needed and two year follow-up is desirable.

Statistical and Analytical Plans
See the Statistical Review for details of the statistical and analytical plan. This application has a complex regulatory history. Unique to this application is the recommendation that one multicenter clinical trial was acceptable, the merging of two centers (Michigan and California or MICA), and conflicting post hoc recommendations for data analysis (superiority versus non-inferiority) from the Division and the Biostat Team Leader.

Determination of Sample Size
Patients in Treatment Group A were to have received Sotradecol and patients in Treatment Group B were to have received Aethoxysklerol. Based upon sample-size calculations in Appendix 4 of the protocol, 25 patients of each vein size in each treatment group were to be enrolled (N=150). This sample size would provide a sufficient number of patients to distinguish between the treatment groups with 90% power and a significance level of 0.05. For this calculation, the ratio of the difference between the 2 treatment group means to the pooled standard deviation was assumed to be approximately 1.

Reviewer comments:
At this juncture (Memorandum dated 22 April 1994, Vol. 37, pg. 3322), achieving statistical significance appears to have been the statistical goal which could be achieved with 300 patients rather than the 450 originally plan prior to merging of the CA and MI centers (MICA).

Changes in the Conduct of the Study or Planned Analyses
Amendment #011 (Date: July 6, 1995)

The protocol was amended as follows:

- Study design. In the original protocol, a total of 450 patients (150 patients at each of 3 research centers, in California, Michigan, and Ohio) were to be enrolled. Fifty patients with varicosities < 1 mm in diameter, 50 patients with varicosities > 1 and ≤ 3 mm in diameter, and 50 patients with varicosities >3 and ≤ 6 mm in diameter were to be enrolled in each arm of the study. Under the amendment to the protocol, 300 patients, 150 for the MICA study and 150 from the OHIO study, were to be enrolled. This report is limited to the discussion of results of patients enrolled at the MICA study.
- Exclusion criteria. The amendments clarified 3 sections of the exclusion criteria by defining the following terms:

1) "Arterial insufficiency of the lower extremities" was defined as "as evidenced by: intermittent claudication coldness of the extremity, skin atrophy and absence of foot pulses. In questionable cases, ankle/brachial index (arm blood pressure/ankle blood pressure) should be investigated. Normal index should be 1 or > 1."
2) "Acute febrile illness" was defined as "as manifested by fever (38° C or above) and signs and symptoms of acute systemic disease."
3) "Obesity" was defined as "as manifested by a body weight in excess of 20%over the ideal body weight."

- Efficacy variables. The primary efficacy variable was changed from overall clinical improvement to disappearance of varicosities. Overall clinical improvement was maintained as a secondary efficacy variable.
- Safety assessment rating scales. The 4-point scale for the assessment of pain was modified such that "1 = none" replaced "1 = no pain" in the original protocol. The other 3 levels were unchanged. For the variables skin necrosis, hyperpigmentation, and systemic reactions, the initial protocol had called for descriptive assessments. The amendment added the 4-point scales for assessment of all these variables, as outlined above.
- Photographic analyses. In the amendment, the size of the color prints was changed from 5 X 7 to 4 X 6.
- Statistical methods. The criteria for determining efficacy were altered. The protocol had called for evaluation based on 6 endpoints, as follows: the photographic score; evaluation of overall patient satisfaction; assessment of subjective variables; incidence of systemic effects; discrete variables, such as swelling and inflammation; and the incidence of delayed phenomena, such as ecchymosis and vein thrombosis.

  These were replaced by the following 7 endpoints: disappearance of varicosities; overall level of clinical improvement; evaluation of overall patient satisfaction; assessment of subjective variables, such as pain; incidence of systemic effects; discrete variables, such as swelling and inflammation; and the incidence and extent of delayed phenomena, such as ecchymosis and vein thrombosis. The evaluation of photographs was altered such that these evaluations would provide the bases for the endpoints "disappearance of varicosities" and "overall level of improvement."
- Statistical considerations were modified to reflect the merging of the 2 sites and the consequent reduction in sample size.

Reviewer comments:
According to the submission, there were two protocol amendments. The date of Amendment 1 was July 6, 1995 (according to communication N-000(BL) received April 13, 2004. Amendment 1 is summarized above. According to communication dated April 22, 1994 (pg. 603), recruitment of patients was discontinued on April 20, 1994 and Dr. Goldman will continue to recruit patients after receiving the new randomization schedule.

Agreement to combine two centers (a non-productive with a productive center) is documented (Vol. 35 of 50, page 2499); however, the communication from Ralph Hawkins also states that this is not usually recommended.

According to the April 22, 1994 communication (page 2501), statistical significance in the study comparing Sotradecol and Polidocanol could be achieved with a smaller of patients (300 rather than 450). Enrollment at CA and MI Study sites was suspended between April 12, 1994 communication from the Ralph Hawkins, Vol. 37, pg. 3320 and April 25, 1994 communication from Dr. Villavicencio).

Amendment #012 (Date: sometime after April 6, 1996)
According to Submission N-000 (BL) (dated April 7, 2004, received April 13, 2004), Amendment 2 is not dated therefore a precise date is not available. According to the submission, the FDA requested the Amendment be done in an April 6, 1996 memo. The Amendment concerned only data analysis and not actual conduct of the study.

Study Results: OHIO Study Site
Principal Investigator:
J. Leonel Villavicencio, MD, FACS
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814-4799

Coordinating Investigator and Study Center:
Joann M. Lohr, MD
Kachelmacher Memorial Clinic, Inc.
755 St. Rt. 664 North
P.O. Box 348
Logan, OH 43138

Study Period: 6 January 1993 through 26 July 1995

Reviewer comment:
1. It should be noted that the study initiation date January 6, 1993. Protocol submission date is February 22, 1993 to the Agency (based on the Medical Officer's review). The Medical Officer's protocol review date is December 30, 1993; therefore, these studies were ongoing prior to feedback from or agreements with the Agency.

2. The term principal investigator is used loosely in the application. Investigator data listed above is as per the original submission. According to N-000 (C) received 02-13-04, J. Leonel Villavicencio, MD, FACS is the Coordinating Investigator for OHIO, MICIGAN, and CALIFORNIA study sites. Dr. Villavicencio was responsible for general project administration, training of the investigators and the monitor, and review of CRFs. He also over saw the data management, including the entry of the data into a database.
3. Joann M. Lohr, MD is the PI for the OHIO study site.

Co-Investigators are listed as (b) (4) and John J. Cranley, M.D., FACS

Reviewer comments:
Number of patients treated per co-investigator is unknown. Identification and qualifications of the unblinded investigator have been requested (04-16-04).

Study Population
A total of 150 patients were randomized to study medication (75 to Aethoxysklerol and 75 to Sotradecol).

Reviewer comments:
The number of patients screened was not provided. According to the protocol, each patient was approved by the principal investigator prior to study entry.

Disposition of Patients
In the Aethoxysklerol group, 73/75 (97.3%) patients completed the study per protocol, while in the Sotradecol group, 69/75 (92.0%) patients completed the study per protocol. Two (2.7%) patients in each group were lost to follow-up. Four (5.3%) patients in the Sotradecol group received study drug that was diluted with an incorrect saline concentration.

Table 3 (Sponsor's Table 1, Vol. 35, pg. 2317) Study Medication Assignment (OHIO)

Vein Size	A* N (%)	B* N (%)
≤ 1 mm	25 (33.3%)	25 (33.3%)
> 1 - 3 mm	25 (33.3%)	25 (33.3%)
> 3 - 6 mm	25 (33.3%)	25 (33.3%)
Total	75	75

* A: Sotradecol; B**:** Aethoxysklerol

Reviewer comments:
The Drug Randomization Sheet (Vol. 35, pg. 2779) is blank. Additional information is requested. This center appears adapt at perfect recruitment with even study subject distribution across vein size. Some variation would be expected; however according to the FDA Statistician, randomization was poorly described.

Demographics, Evaluability
Baseline demographics consisted of gender, age, height, weight, and vein size. Only one male subject was treated. Patients randomized to Aethoxysklerol were significantly older than patients randomized to Sotradecol in both the ≤ 1 mm and > 3 - 6 mm vein size.

Table 4 (Table A.5.2) Ohio Demographics

	Sotradecol	Aethoxysklerol	Total
Gender Male	0	1 (1.3%)	1 (0.7%)
Female	75 (100 %)	74 (98.7%)	149 (99.3%)
Age groups			
21 to 35 years	33 (44. 0 %)	16 (21.3 %)	49 (32.7%)
36 to 50 years	29 (38.7 %)	43 (57.3 %)	72 (48.0%)
51 to 65 years	13 (17.3 %)	16 (21.3 %)	29 (19.3%)
Age Mean (SD)	38.8 (10.4)	43.1 (9.5)	40.1 (10.1)

There were no significant differences between subjects treated with Aethoxysklerol and those treated with Sotradecol for any vein size for any other demographic variable (age, height, or weight).

Reviewer comments:
Baseline history and physicals were performed; however, no baseline data other than gender, age, height, weight, and vein size were provided.

Reviewer comments
Racial demographics were not collected. Patient population should reflect demographics of the US population in which the drug product will be used. Post-inflammatory hyperpigmentation is of particular concern certain patient populations.

Table 5 (Sponsor's Table 2, Vol. 35, pg. 2317) Summary of Patient Disposition

Disposition	A* N=75 n (%)	B* N=75 N (%)	Total N=150 n (%)
Entered	75 (100%)	75 (100%)	150 (100%)
Completed per protocol	69 (92.0)	73 (97.3)	142 (94.7%)
Lost to follow-up	2 (2.7)	2 (2.7)	4 (2.7)
Protocol Violation (wrong diluent)	4 (5.3)	0 (0)	4 (2.7)

* A: Sotradecol; B**:** Aethoxysklerol

Table 6 (Sponsor's Table 3, Vol. 35, pg. 2318) Number (%) of Patients Completing the Study Per Protocol

Completed Study	Vein Size ≤ 1 mm		Vein Size > 1 - 3 mm		Vein Size > 3 - 6 mm	
	A* N=25 n (%)	B* N=25 n (%)	A* N=25 n (%)	B* N=25 n (%)	A* N=25 n (%)	B* N=25 n (%)
Yes	21 (84)	25 (100)	23 (92)	23 (92)	25 (100)	25 (100)
No	4 (16.0)	0 (0.0)	2 (8.0)	2 (8.0)	0 (0.0)	0 (0.0)

- A: Sotradecol; B**:** Aethoxysklerol

Reviewer comments:
Documentation was extremely deficient in this study. The protocol was loosely constructed; therefore, completion per protocol criteria may have been post hoc since compliance was minimally addressed. It is unclear how dilutions were verified and veins were appropriately treated by size, concentration, and amount.

Treatment Compliance
According to the submission treatment compliance was ensured.

Reviewer comments
Eight patients were not included in efficacy evaluation. Four patients in the Sotradecol study arm received an incorrect diluent, hypertonic saline (23.4%), instead of physiologic saline (0.9%). Four patients were lost to follow-up (2 in the Aethoxysklerol study arm and 2 in the Sotradecol study arm).
Reviewer comments:
How and when the incorrect diluents were discovered was not provided.

Protocol Violations
Four patients, Patients 2101, 2103, 2106, and 2201 were injected with Sotradecol that was diluted in hypertonic saline (23.4%) rather than physiologic saline (0.9%). According to the Applicant no adverse events were reported in these patients.

Analysis of Efficacy
Primary Efficacy Endpoint Complete Disappearance of Varicosities
Table 7 : (Statistical Table 7. Complete Disappearance of Varicosities)

Vein sizes	Ohio		
	Sotradecol	Aethoxysklerol	p-values
Overall	12/69 (17.4%)	18/73 (24.7%)	0.2908[1]
< 1 mm	5/21 (23.5%)	4/25 (16.0%)	0.5060[2]
1 mm - 3 mm	3/23 (13.0%)	6/23 (26.1%)	0.2648[2]

[1] MH test stratified on vein size.
[2] Chi-Square test.

No statistically significant difference was demonstrated overall or for each vein size individually between treatment groups ($p \leq 0.2908$ and all $p \geq 0.1853$ respectively). These results were obtained even without an adjustment for multiplicity overall or for each vein size individually. The overall success rate was numerically higher for 24.7% for Aethysklerol versus 17.4% Sotradecol.

The FDA Statistician performed additional data analyses: GLM nested Model, two-sample t-test within each vein size (as specified in the original protocol), and non-inferiority analyses. This approach was recommended by the review team due to the complex regulatory history. Both superiority and non-inferiority statistical analyze plans were discussed in analyzing the mean disappearance scale. As previously stated, here have been numerous interactions between the Agency (individual reviewers as well as scheduled meetings with the Division) and the Applicant's representatives.

No statistically significant difference was demonstrated between treatment groups ($p \leq 0.1203$ and all $p \geq 0.1039$ respectively) overall or for each vein size individually using a GLM nested Model. Thus, using the two-sample t-test within each vein size (as specified in the original protocol), No statistically significant difference was demonstrated between treatment groups (all $p \geq 0.1055$ respectively). According to the statistical review, an adjustment for multiplicity would only exaggerate the non-significance.

Regulatory history is complex and recommendations varied over time therefore in order to look at the data in different ways, clinical team requested additional data analyses. (See the Statistical Review for details). Non-inferiority analysis was preformed for the primary efficacy endpoint, Complete Disappearance of Varicosities. None of the confidence intervals are completely above the lower bound; therefore, Aethoxysklerol has not been shown to be non-inferior to Sotradecol. In a similar analysis using the 5-point Disappearance of Varicosities scale was performed. Non-inferiority is achieved in each comparison for simple comparisons on mean scores for contrast comparisons on mean scores.

Secondary Efficacy Endpoints:
Investigator's Level of Clinical Improvement and Patient's Satisfaction

The original protocol specified an analysis stratified within vein size; therefore to control family-wise Type I error, the FDA Statistician performed Holm's Step-down method for evaluating Investigator's Level of Clinical Improvement. According to the Statistical Review, the smallest p-value is 0.0205 in the Ohio Study and does not fall below its bound (.05/6 = 0.0083). After adjusting for multiplicity, no differences in the Ohio Study are statistically significant for Investigator's Level of Clinical Improvement.

Patient Satisfaction
Mean satisfaction was assessed and no differences were statistically significant after adjusting for multiplicity.

Applicant's Conclusion
Aethoxysklerol was as effective as Sotradecol in causing the disappearance of varicosities, in causing clinical improvement, and in resulting in overall patient satisfaction with treatment.

Reviewer Conclusion
The Applicant failed to establish either superiority or non-inferiority for Complete Disappearance of Varicosities when Aethoxysklerol is compared to Sotradecol.

Protocol: MICA Study Phase: Phase III Study
Title: "Double-Blind, Prospective, Randomized, Comparative Multicenter Trial Between Aethoxysklerol® (Polidocanol) and Sotradecol® (Sodium Tetradecyl Sulfate) in the Management of Varicose Veins of the Lower Extremities"

Study Initiation Date: March 3, 1993
Completion Date: February 19, 1996
J. Leonel Villavicencio, MD, FACS is listed as Principal Investigator

Coordinating Investigators and Study Centers:
John R. Pfeifer, MD
Institute for Vein Diseases
22250 Providence Drive
Southfield, MI 48075
Mitchel P. Goldman, MD
Dermatology Associates of San Diego County, Inc.
477 North El Camino Real, Suite B-303
Encinitas, CA 92024
Study Period: 3 March, 1993 through 19 February, 1996

Number of Patients: A total of 174 patients were entered in the study; 61 patients in the ≤1 mm vein-size group, 59 in the >1-3 mm vein-size group, and 54 in the >3-6 mm vein-size group. The patients in each vein-size group were equally randomized to receive either Aethoxysklerol or Sotradecol. All 174 patients received study drug. There were 149 patients who completed the study per protocol, 72 patients in the Aethoxysklerol group and 77 patients in the Sotradecol group; 16 patients were protocol violators, 8 in each treatment group. Nine patients did not complete the study; 3 patients in the Aethoxysklerol group and 6 patients in the Sotradecol group.

MICA Study Initiation Date: 6 January 1993
Study Phase: Phase III Study Completion Date: 26 July 1995
Principal Investigator:
J. Leonel Villavicencio, MD, FACS
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814-4799

Coordinating Investigator and Study Center:
Mitchel P. Goldman, MD
Dermatology Associates of San Diego County, Inc.
477 North El Camino Real, Suite B-303
Encinitas, CA 92024

Study Period: 3 March 1993 through 19 February 1996

The data from the site in Michigan were merged with the data from the California study site to Michigan/California or MICA. Study protocols were identical and were double-blind, prospective, randomized, parallel-design study of the efficacy and safety of Aethoxysklerol and Sotradecol administered intravenously for the treatment of varicose veins of the lower extremities

Number of Patients: A total of 174 patients were entered in the study; 61 patients in the ≤1 mm vein-size group, 59 in the >1-3 mm vein-size group, and 54 in the >3-6 mm vein-size group. The patients in each vein-size group were equally randomized to receive either Aethoxysklerol or Sotradecol. All 174 patients received study drug. There were 149 patients who completed the study per protocol, 72 patients in the Aethoxysklerol group and 77 patients in the Sotradecol group; 16 patients were protocol violators, 8 in each treatment group. Nine patients did not complete the study; 3 patients in the Aethoxysklerol group and 6 patients in the Sotradecol group.

Diagnosis and Main Criteria for Inclusion: Patients who were between the ages of 18 and 65 years; suffering from small cutaneous blemishes, superficial venules, or varicose veins of the lower extremities; and without valvular insufficiency, were included in the study.

Table 8 (Sponsor's Table 1, Vol. 37, pg. 3133) Study Medication Assignment

Vein Size	A* n (%)	B* n (%)
≤ 1 mm	33 (36.3%)	28 (33.7%)
> 1 - 3 mm	31 (34.1%)	28 (33.7%)
> 3 - 6 mm	27 (29.7%)	27 (32.5%)
Total	91	83

* A: Sotradecol; B**:** Aethoxysklerol

A summary of patient disposition is in Table 2. In the Aethoxysklerol group, 72/83 (86.7%) patients completed the study per protocol, while in the Sotradecol group, 77/91 (84.6%) patients completed the study per protocol.

Table 9 (Sponsor's Table 2, Vol. 37, pg. 3134) Summary of Patient Disposition

Disposition	A* N=91 n (%)	B* N=83 n (%)	Total N=174 n (%)
Entered	91 (100%)	83 (100%)	174 (100%)
Completed	85 (93.4)	80 (96.4)	165 (94.8)
Completed per protocol	77 (84.6)	72 (86.7)	149 (85.6%)
Protocol Violation+	8 (8.8)	8 (9.6)	16 (9.2)
Discontinued	6 (6.6)	3 (3.6)	9 (5.2)
Lost to follow-up	1 (1.1)	3 (3.6)	4 (2.3)
Protocol Violation (wrong diluent)	5 (5.5)	0 (0)	5 (2.9)

* A: Sotradecol; B: Aethoxysklerol

Eight patients in each group were protocol violators, but they completed the study. Three (3.6%) patients in the Aethoxysklerol group and 1 (1.1%) patient in the Sotradecol group were lost to follow-up. Five (5.5%) patients in the Sotradecol group were protocol violators, and they did not complete the study.

Five patients were enrolled in the study and randomized to treatment, but never received study drug. Therefore, these 5 patients are not included in any analyses, tables, or listings.

Protocol Violations

Five patients, Patients 3102, 3107, 3201, 3203, and 3205, were injected with a higher concentration of Sotradecol than that recommended in the protocol for the size of the varicosities being treated. None of these patients received more than the maximum protocol-recommended daily dose of Sotradecol. All of these patients were withdrawn from the study.

Reviewer comments:

More than one sclerotherapy session could be conducted and it is unknown when the protocol violations occurred, were detected, or when these patients were discontinued from the study.

The amount of study drug administered exceeded the maximum, protocol-recommended, daily dose for a total of 7 patients (5 in the Aethoxysklerol group and 2 in the Sotradecol group). Patients 1303, 1308, 1312, 1323, and 1324 were treated with Aethoxysklerol 3%, and they received more than 2 mg/kg body weight of the study drug. Patients 1305 and 1307 were treated with Sotradecol, and they received more than 4 mL of study drug. All of these patients were continued in the study.

Reviewer comments:

The protocol did not address selection of a target area for treatment. Non-study areas were treated in some patients with some receiving amounts exceeding the maximum daily dose recommended per protocol.

Eleven patients were treated with Diprolene cream, a high-potency corticosteroid cream, was used to minimize the inflammatory changes following sclerotherapy. The Aethoxysklerol-treated patients who were treated with Diprolene Cream were 1104, 1119, 1204, and 1312. The Sotradecol-treated patients who were treated with Diprolene cream were 1103, 1106, 1108, 1121, 1210, 1305, and 1314. These patients continued in the study.

Reviewer comments:
None of the patients listed were in the Complete Disappearance category on the Disappearance of Varicosities scoring scale; however, all are in category 4 (majority disappeared). With the exception of concomitant use of anticoagulants, there were no restrictions on placed upon prior or concomitant therapies in the protocol. Diprolene Cream was not used at the OHIO or Michigan study sites. no information was provided regarding use of Diprolene Cream at the California study site (e.g.; selection of patients, after initial treatment, 4 weeks after treatment, etc.).

Efficacy Evaluation
Data Sets Analyzed
The efficacy data set used for the evaluation of the primary and secondary efficacy variables consisted of data from 167 patients. This data set included the data from the 165 patients who completed the study. In addition, efficacy data were available from 2 of the patients who were protocol violators who did not complete the study. These patients were also included in the efficacy data set.

Demographic Variables
Table 5 is a summary of demographic variables for patients in the efficacy data set.
Since only 3 patients were male, the demographic information was not summarized for gender.

Table 10 (Applicant's Table A.5.1) MICA Demographics

	California		Michigan		
	Sotradecol	Aethoxysklerol	Sotradecol	Aethoxysklerol	Total
Gender Male	1 (1.4%)	1 (1.6%)	0	1 (5.0%)	3 (1.7%)
Female	69 (98.6%)	62 (98.4%)	21 (100%)	19 (95.0 %)	171 (98.3%)
Age groups					
24 to 35 years	12 (17. 1%)	19 (30.2%)	7 (33.3%)	9 (45.0%)	47 (27. 0%)
36 to 50 years	42 (60.0%)	25 (39.9%)	11 (52.4%)	10 (50.0%)	88 (50.6%)
51 to 65 years	16 (22.9%)	19 (30.2%)	3 (14.3%)	1 (5.0%)	39 (22.4%)
Age Mean (SD)	44.1 (8.7)	43.4 (11.3)	41.0 (9.1)	38.6 (8.7)	42.8 (9.9%)

Only three males were treated in the study. There were no significant differences between subjects treated with Aethoxysklerol and those treated with Sotradecol for any vein size for any demographic variable (age, height, or weight).

Table 11 (Statistical Table 4.) Complete Disappearance of Varicosities (Relative Success Rate & Percentage

Vein sizes	California		Michigan		
	Sotradecol	Aethoxysklerol	Sotradecol	Aethoxysklerol	p-values
Overall	16/69 (23.2%)	19/60 (31.7%)	3/18 (16.7%)	4/20 (20.0%)	0.3127[1]
< 1 mm	4/23 (17.4%)	7/19 (36.8%)	1/9 (11.1%)	1/7 (14.3%)	0.1758[2]
1 mm - 3 mm	5/22 (22.7%)	4/19 (21.1%)	2/6 (33.3%)	1/8 (12.5%)	0.5688[2]
		(b) (4)		(b) (4)	(b) (4)

[1] CMH test stratified on center x vein size
[2] CMH test stratified on center

According to the FDA Statistical analysis, no statistically significant difference was demonstrated between treatment groups (p≤ 0.3127 and all p≥ 0.1758 respectively) for either overall or each vein size individually (even without adjusting for the multiplicity of tests). Using Holm's method, adjusting for multiplicity over all four comparisons would lead to a minimum significance level of 0.7032.

According to the FDA Statistical Reviewer, an ANOVA of the mean of the 5-point varicosities scale was also discussed and an analysis using a GLM Model was performed. No statistically significant difference was demonstrated between treatment groups (p≤ 0.2698 and all p≥ 0.1793 respectively) either overall or for each vein size individually.

Mean Disappearance on 5-point Varicosities Scale (Protocol Analysis)
No differences were statistically significant (all p≥ 0.0646) within each vein size.

Non-inferiority Analyses (MICA)
Aethoxysklerol was not shown to be non-inferior to Sotradecol in complete Disappearance of varicosities, the primary efficacy endpoint. However, non-inferior was demonstrated for assessment of simple comparisons and contrast comparisons on the mean score.

Secondary Efficacy Endpoints
Table 12 (Statistical Table A.3.2) Mean Satisfaction: MICA Study

Treatment	California		Michigan		
	Sotradecol	Aethoxysklerol	Sotradecol	Aethoxysklerol	p-values
Overall	3.0 (1.0)	3.2 (1.0)	3.5 (0.7)	3.1 (1.0)	0.8171
< 1 mm	3.1 (0.9)	2.7 (1.1)	3.5 (0.8)	3.0 (1.2)	0.3851
1 mm - 3 mm	3.1 (0.9)	3.3 (0.8)	3.8 (0.4)	3.0 (0.8)	0.7193
		(b) (4)		(b) (4)	

[1] CMH test stratified on center x vein size.
[2] CMH test stratified on center.

No differences were statistically significant in the MICA Study even without adjust for multiplicity.

D. Efficacy Conclusions

Applicant's Conclusion

Disappearance of Varicosities – Pivotal Studies

According to the Applicant's analysis, in neither of the 2 pivotal studies for the primary efficacy variable, Disappearance of Varicosities was there a significant difference between Aethoxysklerol and Sotradecol, and the confidence intervals indicate that the same results are expected following treatment with either compound.

Aethoxysklerol was as effective as Sotradecol in causing the disappearance of varicosities. Across all vein sizes, treatment with Aethoxysklerol resulted in significantly higher overall clinical-improvement scores compared with Sotradecol (p=0.020). When individual vein-size groups were compared across treatments, there were no significant treatment-group differences seen in the clinical improvement scores. Both Aethoxysklerol and Sotradecol were equally effective with regard to overall patient satisfaction with treatment.

Reviewer Conclusion

A total of 324 (320 females and 4 males) patients age 21 to 65 years were treated at three study sites in the U.S. The primary efficacy endpoint was complete disappearance of varicosities based on photographs taken at baseline and 16 weeks after the last sclerotherapy session. Photographic quality is poor and the technique was not standardized (e.g., angle, distance, lighting, etc.). Due to the complex regulatory history and what appeared to be conflicting recommendations from the Agency, additional statistical analyses were undertaken; however, the Applicant failed to establish superiority or non-inferiority for Complete Disappearance of Varicosities, the primary efficacy endpoint when Aethoxysklerol is compared to diluted Sotradecol.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Review of the safety database revealed no apparent polidocanol-specific safety signal. Adverse events were generally consistent with those seen with sclerotherapy and the pharmacologic class of sclerosants. However, some adverse events may not have been captured because of the sponsor's general approach to collection of safety data across the development program, which largely relied on checklists. Also, the submitted safety data permit little to no assessment for risk of deep vein thrombosis (DVT) following treatment with the sponsor's product, since none of the studies specifically assessed for DVT post-treatment. The frequent occurrence of superficial vein thrombosis in both treatment groups of all vein sizes might indicate a systemic deficiency in study conduct, e.g. insufficiently detailed study procedures.

All studies that included clinical laboratory testing, revealed some potential for RBC parameters and platelets to be affected following treatment (decrease), irrespective of dose received or vessel size treated; however, there was no particular pattern identified, and no changes appeared to be clinically significant.

While the safety database may be supportive of the 0.5% and 1.0% concentrations,(b) (4)

B. Description of Patient Exposure

Safety Database

Seven studies were intended to support the safety of Aethoxysklerol in the treatment of varicose veins of the lower extremities. All studies enrolled affected subjects:

- Two pivotal trials: OHIO and MICA, were randomized, double-blind, active-controlled, studies comparing the safety of Aethoxysklerol to Sotradecol in patients with varicose veins.
- Five supportive studies:
  - two concentration-controlled studies: ASK 94-002 and ASK 96-001 were randomized, open-label, concentration-controlled studies conducted in Japan. ASK 94-002 was a dose-finding study intended to determine the optimal usage of the study drug based on change in diameter of the treated vein. ASK 96-001 investigated the efficacy and safety of study drug by parallel group comparison of different concentrations of the study drug.
  - three uncontrolled studies: AET-AS25 (safety study), AET-P2 (safety study) and ASK-00-01-00 (pharmacokinetic study)

In these seven studies, 514 subjects received polidocanol, 415 of whom were treated with concentrations within the ranges of those proposed for marketing. Of these 415 subjects, 342 were treated with the formulation (b) (4), in the concentrations (b) (4) (b) (4): 0.5% (5 mg of polidocanol/mL), 1.0% (10 mg/mL) and 3.0% (30 mg/mL), with 126, 132, and 84 receiving treatment, respectively. An additional 73 subjects in a supportive study (AET-P2) received a 2.0% concentration. Lastly, 99 subjects received a concentration lower than any proposed for marketing (0.25%), 39 of whom received a formulation different from that proposed for marketing. The alternative formulation contained 20% glycerin as an (b) (4), instead of 5% ethanol. In all studies, except the supportive study AET-P2, the investigator determined the dose for each subject on an individual basis. In AET-P2, all subjects received 2 mL of 2% Aethoxysklerol.

Number of Subjects Exposed to Polidocanol in the Development Program

Study/No. Centers/ Location	Concentration					
	0.25%	**0.5%**	**1.0%**	**2.0%**	**3.0%**	**Total**
OHIO/1/US (pivotal)	-	25	25	-	25	75
MICA/2/US (pivotal)	-	28	28	-	27	83
ASK 94-002/21/JPN	-	22	50	63	26	161
ASK 96-001/21/JPN	20	51	29	-	-	100
AWB AET-AS25/4/GER*	40/39*	-	-	-	-	79
AET-P2/1/US	-	-	-	10	-	10
ASK-00-01-00/1/JPN	-	-	-	-	6	6
Total # per concentration	99*	126	132	73	84	514*

Sources: ISS Tables 8.H.1 and 8.H.2

* 39 subjects were treated with a polidocanol formulation different from the one proposed for marketing.

Study Procedures/Safety Assessments in the Pivotal Trials (MICA and OHIO)

Determination of dosing was described in Section 8.2.0 of the protocol found in Volume 31 (p. 471): "Each study center will determine the amount of sclerosing agent necessary to treat the affected area and the number of sclerotherapy sessions necessary to obtain results. The maximum dose of 2 mg/kg/day of Aethoxysklerol; 4 ml of Sotracecol 1.0% or 2 ml Sotracecol 3.0% per session will be strictly observed." Sotradecol was the comparator, diluted from the marketed concentrations of 1.0% and 3.0% to concentrations of 0.25%, 0.5% and 1.5%.

Comment: It is unclear what impact the diluting of Sotradecol might have had on the adverse event profile in this treatment group.

Safety was assessed by evaluating immediate local and systemic reactions, adverse events, and vital signs taken before treatment and within one hour after treatment. Delayed events were captured one week post-treatment and at all subsequent follow-up visits. Post-treatment assessments were also specified for one month and four months after the final treatment.

A medical history and physical examination were performed prior to treatment. Additionally, the pre-study evaluation included Doppler examination of the venous system in order to establish the diagnosis and suitability of the patient for enrollment. Significant venous reflux, where "significant" was not defined, detected either with Doppler or Duplex scanner, was a basis for exclusion from the study.

Within 60 minutes post-injection, subjects were assessed for "immediate" reactions. Assessment for these reactions employed a checklist in the case report form, designed to capture the following (also see Section 8.1.2. of the protocol):

1. Immediate local reactions:
   - Pain
   - Inflammation of the injected vein surrounding tissues, as assessed by the intensity of the redness and sensitivity of the injected vein
   - Swelling
   - "Local allergic reactions" (per case report form, these reactions included "hives, itching, other")

2. Immediate systemic reactions
   - dizziness
   - blurred vision or other visual disturbances
   - nausea or vomiting
   - dyspnea or other respiratory disturbances
   - tachycardia, arrhythmias, or other cardiac manifestations
   - hypotension
   - fainting

- asthma or bronchospasm
- allergies (skin rashes or similar manifestations)
- anaphylactic shock
- other reactions

3. Delayed local reactions (recorded by checklist one week after injection and after each follow-up visit):
   - Vein thrombosis (superficial)
   - Ecchymoses
   - Skin necrosis
   - Hyperpigmentation
   - Neovascularization

   "Any other delayed reactions" were to have been described.

Comment: The post-treatment assessments appeared to have been targeted at capturing the occurrence of adverse events that are commonly reported as being associated with sclerotherapy. While use of the checklist may have allowed for some standardization of the post-treatment assessments, this approach may not have capture all non-listed events.

As described in Section 8.2.3 of the protocol, microthrombectomy was to have been performed if a thrombus was detected during follow-up. The stated goal of this procedure was to "diminish the incidence of hyperpigmentation."

Patient Accountability in the Pivotal Studies (MICA and OHIO)

Modified TABLE 8.H.3 PIVOTAL STUDIES: PATIENT DISPOSITION

	Sotradecol N(%)	Aethoxysklerol N(%)	Total N(%)
Disposition			
Entered	167 (100.0)	162 (100.0)	329 (100.0)
Received Drug	166 (99.4)	158 (97.5)	324 (98.5)
Completed*	154 (92.8)	153 (96.8)	307 (94.8)
Per protocol	146 (88.0)	145 (91.7)	291 (89.8)
Protocol violation	8 (4.8)	8 (5.1)	16 (4.9)
Discontinued*	12 (7.2)	5 (3.2)	17 (5.2)
Lost to follow-up	3 (1.8)	5 (3.2)	8 (2.5)
Protocol violation	9 (5.4)	0 (0.0)	9 (2.8)

*based on the number of patients who received drug.

ITT Presented by Treatment Group

	Aethoxysklerol n=158			Sotradecol n=166		
Concentration/ Vessel size	0.5%/ ≤1mm	1.0%/ >1-3mm	3.0%/ > 3-6 mm	0.25%/ ≤1mm	0.5%/ >1-3mm	1.5%/ > 3-6 mm
# subjects	53	53	52	58	56	52

Source: Table 8.H.5 ISS, p.2004

Three-hundred twenty-nine subjects were enrolled in the pivotal studies, and 324 received treatment with study drug. Of these 324 subjects, 158 received Aethoxysklerol and 166 received Sotradecol. Subjects who did not receive study drug are not included in the analyses of safety.

Protocol Violations

Four subjects in the OHIO study received Sotradecol that was diluted with saline said to be of an "incorrect concentration."

Comment: Per Table 4 and Section 7.2 of the OHIO study report (Volume 35), the "incorrect concentration" of saline used for dilution of Sotradecol was hypertonic saline, rather than physiologic saline. However, the protocol did not appear to specify the diluent for the Sotradecol: Section 7.1.5 states only that, "Parenteral solutions for dilution of the drug will be provided by the investigator." Given the caustic nature of hypertonic saline, it is possible that its use in combination with Sotradecol could have had an additive effect in regard to adverse events, particularly as pertains to skin necrosis. However, none of the four subjects who received the hypertonic saline/Sotradecol combination were reported to have experienced skin necrosis (Volume 36, Appendix 12.2.6, "Listing of Safety Variables").

There were a number of protocol violations in the MICA study (Section 7.2 of the study report):

- Seven subjects (five in the Aethoxysklerol group and two in the Sotradecol group), were administered an amount of study drug that exceeded the maximum, protocol-recommended daily dose (this will be further addressed in the discussion of serious adverse events). Per the MICA "CRF Tabulations-Demography" (begins on p. 198 in Volume 47), all seven subjects were from the California site.
- Eleven subjects (four in the Aethoxysklerol group and seven in the Sotradecol group) used Diprolene ® cream to minimize the inflammatory changes following sclerotherapy (two subjects whose treatment exceeded the maximum dose were also subjects who used Diprolene, one Aethoxysklerol-treated subject and one Sotradecol-treated subject). Per the MICA "CRF Tabulations-Demography," all 11 subjects were from the California site.
- An additional five subjects received a higher concentration of Sotradecol than was specified for their vein-size group (but did not exceed the maximum daily dose) and were discontinued from the study. Per the MICA "CRF Tabulations-Demography," all five subjects were from the Michigan site.

Eight subjects were lost-to-follow-up and did not complete the studies: four Aethoxysklerol-treated subjects in the MICA study; two Aethoxysklerol-treated subjects and two Sotradecol-treated subjects in the OHIO study.

All available data for all patients who received study drug were included in the Integrated Summary of Safety, even if they did not complete the study.

Extent of Exposure (MICA and OHIO)

Exposure was expressed as the cumulative volume of solution injected for all injections into the target vein for each patient. Patients received similar volumes in all vein-size groups, regardless of treatment group.

Extent of Exposure (Combined MICA and OHIO; modified Table 8.H.4, ISS)[a]

Statistic	Vein Size ≤1 mm		Vein Size >1-3 mm		Vein Size >3-6 mm		All Vein Sizes	
	Sotra.	Aethoxy.	Sotra.	Aethoxy.	Sotra.	Aethoxy.	Sotra.	Aethoxy.
n	57*	53	55*	53	52	52	164	158
Mean	1.63	1.43	1.79	1.63	1.69	1.73	1.70	1.60
STDb	1.37	1.58	1.37	1.31	1.69	1.49	1.47	1.46
Min	0.08	0.13	0.15	0.30	0.10	0.22	0.08	0.13
Max	7.0	10.0	6.0	6.0	8.0	9.0	8.0	10.0

a Total volume of study drug injected (mL) into the target vein.
b STD = Standard deviation.
*Exposure not found for one subject

Comment: A slight progressive increase in the mean volume of exposure to Aethoxysklerol was noted as diameter of target vessel increased. However, because of the differences in the concentrations of study drug, a slight mean volume increase translated into a considerable difference in mean Aethoxysklerol exposures per vein size group: 7.15 mg, 16.3 mg and 51.9 gm, respectively. Maximum exposure was 270 mg.

Extent of Exposure (MICA)[a] (Modified Table 10, Volume 37)

Statistic	Vein Size ≤1 mm		Vein Size >1-3 mm		Vein Size >3-6 mm		All Vein Sizes	
	Sotra.	Aethoxy.	Sotra.	Aethoxy.	Sotra.	Aethoxy.	Sotra.	Aethoxy.
n	32*	28	30*	28	27	27	89	83
Mean	2.22	2.00	2.40	2.12	2.51	2.46	2.37	2.19
STDb	1.49	1.95	1.29	1.56	1.95	1.71	1.57	1.73
Min	0.08	0.50	0.50	0.50	0.50	0.75	0.08	0.50
Max	7.0	10.0	6.0	6.0	8.0	9.0	8.0	10.0

a Total volume of study drug injected (mL) into the target vein.
b STD = Standard deviation.
*Exposure not found for one subject

Extent of Exposure (OHIO)[a] (Modified Table 10, Volume 35)

Statistic	Vein Size ≤1 mm		Vein Size >1-3 mm		Vein Size >3-6 mm		All Vein Sizes	
	Sotra.	Aethoxy.	Sotra.	Aethoxy.	Sotra.	Aethoxy.	Sotra.	Aethoxy.
n	25	25	25	25	25	25	75	75
Mean	0.87	0.79	1.05	1.09	0.80	0.95	0.91	0.94
STDb	0.68	0.62	1.08	0.63	0.64	0.60	0.82	0.62
Min	0.15	0.13	0.15	0.30	0.10	0.22	0.10	0.13

Max	2.7	2.1	5.4	2.6	2.0	2.0	5.4	2.6

a Total volume of study drug injected (mL) into the target vein.
b STD = Standard deviation.

Comment: Reported mean exposures were higher for all dosing groups in MICA, when compared to OHIO, and this was not addressed by the sponsor in the Integrated Summary of Safety. Review of select case report forms suggests that some subjects received treatment of additional vessels beyond the target vessel; however, "extent of exposures" reflect only the amount of drug injected into the target vein. Therefore, the true extent of exposure is unclear, and may be higher. Also, given that the reported exposures are said to reflect only treatment of the target vessel, it is unclear how mean volumes could be so similar across vessels sizes that are so dissimilar.

Demographic Characteristics

Per vein-size group, the two treatment groups were not reported to differ significantly for age, height, or weight. The mean ages across treatment groups were between 40.8 and 43.1 years. The mean heights were between 64.7 and 65.4 inches, and the mean weights were between 138.7 and 146.1 pounds. Only 4 of the patients who entered the pivotal studies were male. Race data were not collected.

C. Methods and Specific Findings of Safety Review

ADVERSE EVENTS

In the pivotal studies, 147 subjects (93.0%) in the Aethoxysklerol group and 158 subjects in the Sotradecol (95.2%) group experienced at least one adverse event. The most common adverse events were hyperpigmentation, ecchymosis, superficial vein thrombosis, and pain (p. 2010).

Immediate Reactions in OHIO and MICA Trials

1. Immediate Local Reactions (Sources ISS Tables 8.H.5 and 8.H.6)

Reaction	Vein size ≤ 1mm		Vein size >1-3mm		Vein size >3-6 mm		All Vein Sizes	
	Aethoxy n=53	Sotra n=58	Aethoxy n=53	Sotra n=56	Aethoxy n=52	Sotra n=52	Aethoxy n=158	Sotra n=166
Pain	43.4% (23)	32.8% (19)	32.1% (17)	46.4% (26)	46.2%(24)	26.9% (14)	40.5% (64)	35.5% (59)
Inflammation	24.5% (13)	44.8% (26)	28.3% (15)	28.6% (16)	11.5% (6)	28.8% (15)	21.5% (34)	34.3% (57)
Local Allergy	13.2% (7)	22.4% (13)	20.8% (11)	19.6% (11)	11.5% (6)	23.1% (12)	15.2% (24)	21.7% (36)
Swelling	9.4% (5)	24.1% (14)	13.2% (7)	17.9% (10)	7.7% (4)	23.1% (12)	10.1% (16)	21.7% (36)

Comment: The combined results for immediate local reactions are largely driven by reports from the MICA study:

- *All reports of inflammation for Aethoxysklerol-treated subjects were from the MICA study. For Sotradecol-treated subjects, of the 54 of the 57 reports (94.7%) of inflammation were from the MICA study.*

- *Nineteen of the 24 reports (79.2%) of local allergy for Aethoxysklerol-treated subjects were from the MICA study. For Sotradecol-treated subjects, 33 of the 36 reports (91.2%) of local allergy were from the MICA study.*
- *All reports of swelling were from the MICA study.*

Mean concentrations of study drug were higher in the MICA group, and it is not clear whether this might have contributed to the higher rate of adverse events reported in the MICA study.

It is unclear to what extent local adverse events might have been a function of technique, particularly as pertains to the ≤ 1 mm veins where investigators had the option of injecting Aethoxysklerol 0.5% either perivascularly or intravenously (Section 5.3.2 of the protocol). It is possible that the higher rate of inflammation seen in the smaller Aethoxysklerol-treated vessels relates to certain technical aspects of injecting smaller vessels, e.g. risk of "blowing out" the vessel (although this pattern did not hold in for the Sotradecol groups). Also, given that the assessment of inflammation reflected the intensity of redness, the reported inflammation could have represented transient urtication, reported to be common with polidocanol (Goldman, PM,1989; 15:204-209). It is possible, however, that urtication would have been captured under "local allergy."

2. Immediate Systemic Reactions in OHIO and MICA trials

Immediate systemic reactions were reported for 13 subjects: 3 subjects in OHIO and 10 subjects in MICA. Of these 13, 6 subjects received Aethoxysklerol and 7 received Sotradecol. Three of these 6 subjects (all in the MICA study) were also protocol violators who had received more than the recommended dose of study drug.

All systemic reactions in OHIO occurred in Aethoxysklerol-treated subjects group: taste perversion (two subjects), paresthesia (one subject).

As stated, ten subjects in the MICA study were reported to have experienced systemic reactions. Three Aethoxysklerol-treated subjects experienced paresthesia; all three were also protocol violators who received more than the protocol-specified maximum daily dose of Aethoxysklerol. Seven Sotradecol-treated subjects experienced the following reactions: dizziness (#1114) paresthesia (#1121); taste perversion (#1231); fainting, dizziness (#1232); paresthesia, asthenia (#1315); visual field deficit (#1331); palpitation, dry mouth, nervousness, vasodilation , vascular disease peripheral (#1333).

Comment: None of the systemic adverse events appeared to qualify as serious adverse events.

<u>Delayed Reactions (Sources ISS Tables 8.H.5 and 8.H.7)</u>

Reaction	Vein size ≤ 1mm		Vein size >1-3mm		Vein size >3-6 mm		All Vein Sizes	
	Aethoxy n=53	Sotra n=58	Aethoxy n=53	Sotra n=56	Aethoxy n=52	Sotra n=52	Aethoxy n=158	Sotra n=166
Hyperpigmentation	35.8% (19)	67.2% (39)	67.9% (36)	66.1%(37)	73.1% (38)	69.2% (36)	58.9% (93)	67 5% (112)
Ecchymoses	42.3% (24)	65.5% (38)	49.1% (26)	69.6% (39)	67.3% (35)	65.4% (34)	53.8% (85)	66 9% (111)
Vein thrombosis*	35.8%(19)	48.3% (28)	58.5% (31)	62.5% (35)	59.6% (31)	44.2% (23)	51.3% (81)	51.8% (86)
Neovascularization	7.5% (4)	6.9% (4)	7.5% (4)	5.4% (3)	9.6% (5)	13.5% (7)	8.2% (13)	8.4% (14)
Skin necrosis	0 (0)	10.3% (6)	1.9% (1)	1.8% (1)	1.9% (1)	1.9% (1)	1.3% (2)	4.8% (8)

*superficial

Comments: Unlike with immediate local reactions, delayed events did not appear to be driven by one study.

As with immediate local reactions, it is unclear to what extent delayed local adverse events might have been a function of technique. Generally, delayed reactions in Aethoxysklerol-treated subjects tended to increase as vessel size and drug concentration increased. A similar pattern was not identified in Sotradecol-treated subjects.

The highest rate of skin necrosis was in Sotradecol-treated subjects in the ≤ 1mm vein-size group (0.25%). There were no reports of skin necrosis in Aethoxysklerol-treated subjects in this vein-size group; these subjects received the 0.5% concentration of study drug. Section 5.3.2 of the protocol states that, "at concentrations of 0.5% (Aethoxysklerol) may be injected perivascularly…", and it has been reported that paravenous injections of 0.25% to 1.% polidocanol may not result in skin necrosis (Rabe et al.). It is not clear that the same holds for paravenous injection of Sotradecol. However, if paravenous injection of Sotradecol is poorly tolerated (skin necrosis) and was administered in this manner, this might explain the higher rate of skin necrosis in Sotradecol-treated subjects in the ≤ 1mm group. It is noted that the protocol only addressed perivascular injection of Aethoxysklerol; it is not clear whether any subjects received perivasular treatment.

"Delayed reactions" did not include an assessment for deep vein thrombosis (DVT) and DVT has been reported following sclerotherapy, even in the treatment of telangiectasias.

Adverse Events

Sponsor Table 8.H.8. PIVOTAL STUDIES: NUMBER (%) OF PATIENTS EXPERIENCING ADVERSE EVENTS [a], SUMMARIZED BY BODY SYSTEM

Body System Preferred Term [c]	A [b] N=166	B [b] N=158	Total N=324
Any Body System	158 (95.2)	147 (93.0)	305 (94.1)
Skin And Appendages	119 (71.7)	98 (62.0)	217 (67.0)
Hyperpigmentation	112 (67.5)	93 (58.9)	205 (63.3)
Rash	8 (4.8)	9 (5.7)	17 (5.2)
Skin Necrosis	8 (4.8)	2 (1.3)	10 (3.1)

Urticaria	2 (1.2)	1 (0.6)	3 (0.9)
Necrosis Skin [c]	2 (1.2)	0 (0.0)	2 (0.6)
Ulcer Skin	1 (0.6)	0 (0.0)	1 (0.3)
Rash Vesiculobullous	1 (0.6)	0 (0.0)	1 (0.3)
Hemic And Lymphatic	111 (66.9)	85 (53.8)	196 (60.5)
Ecchymosis	111 (66.9)	85 (53.8)	196 (60.5)
Cardiovascular System	97 (58.4)	92 (58.2)	189 (58.3)
Vein Thrombosis [d]	86 (51.8)	81 (51.3)	167 (51.5)
Neovascularization (Matting)	14 (8.4)	13 (8.2)	27 (8.3)
Neovascularization	3 (1.8)	3 (1.9)	6 (1.9)
Vasodilation	1 (0.6)	0 (0.0)	1 (0.3)
Vascular Disorder	1 (0.6)	0 (0.0)	1 (0.3)
Vascular Disease Peripheral	1 (0.6)	0 (0.0)	1 (0.3)
Thrombophlebitis	1 (0.6)	0 (0.0)	1 (0.3)
Phlebitis	0 (0.0)	1 (0.6)	1 (0.3)
Palpitation	1 (0.6)	0 (0.0)	1 (0.3)
Fainting	1 (0.6)	0 (0.0)	1 (0.3)
Body As A Whole	91 (54.8)	98 (62.0)	189 (58.3)
Pain Duration	59 (35.5)	69 (43.7)	128 (39.5)
Pain Scale	59 (35.5)	64 (40.5)	123 (38.0)
Inflammation	57 (34.3)	34 (21.5)	91 (28.1)
Local Allergy	36 (21.7)	24 (15.2)	60 (18.5)
Pain	5 (3.0)	0 (0.0)	5 (1.5)
Asthenia	1 (0.6)	0 (0.0)	1 (0.3)
Allergic Reaction	0 (0.0)	1 (0.6)	1 (0.3)
Metabolic And Nutrition	37 (22.3)	16 (10.1)	53 (16.4)
Swelling	36 (21.7)	16 (10.1)	52 (16.0)
Edema	2 (1.2)	0 (0.0)	2 (0.6)
Nervous System	5 (3.0)	3 (1.9)	8 (2.5)
Paresthesia	2 (1.2)	4 (2.5)	5 (1.5)
Dizziness	2 (1.2)	0 (0.0)	2 (0.6)
Paresthesia Circumoral	0 (0.0)	1 (0.6)	1 (0.3)
Nervousness	1 (0.6)	0 (0.0)	1 (0.3)
Dry Mouth	1 (0.6)	0 (0.0)	1 (0.3)
Special Senses	2 (1.2)	2 (1.3)	4 (1.2)
Taste Perversion	1 (0.6)	2 (1.3)	3 (0.9)
Visual Field Defect	1 (0.6)	0 (0.0)	1 (0.3)

[a] If a patient experienced more than 1 event in a given body system or preferred term, that patient was only counted once for that body system or preferred term; a single patient may be counted under more than 1 body system or preferred term. [b] A: Sotradecol; B: Aethoxysklerol. [c] The terms in bold-faced type are COSTART-coded terms for events described in comments written on the CRF.

Comment: Adverse Event Table 8.H.8 may not represent a comprehensive adverse event database, since it appears to essentially reflect only immediate and delayed reactions, as captured by use of the checklists in the case report forms. The extent to which the study allowed for spontaneous adverse event reporting and open-ended inquiry is unclear, but appears to have been limited.

Serious Adverse Events and Deaths (OHIO and MICA)

No subjects died, and no subjects withdrew from either study because of adverse events.

Seven subjects (five in the Aethoxysklerol group and two in the Sotradecol group) received more than the maximum protocol-recommended daily dosage of study medication and were considered by the sponsor, on this basis alone, to have experienced serious adverse events. All seven subjects were in the MICA study, and all were in the highest dosing groups i.e., 3% Aethoxysklerol and 1.5% Sotradecol. All seven subjects completed the study.

Comment: The sponsor's definition of what constituted a serious adverse event differs from the regulatory definition (CFR 312.32). Instead, a determination of a serious adverse event appears to have been solely based on a subject's having received an excessive amount of study drug; clinical outcome did not appear to factor into this determination. None of the seven subjects were reported to have required hospitalization or other special intervention to treat any reaction (e.g. epinephrine). Based on review of the information provided in the narratives and case report forms for these seven subjects, the reviewer does not consider any of the seven subjects to have experienced serious adverse events, however, the following reactions may be of some significance:

- *Subject 1305 received 8 mL of 1.5% Sotradecol and experienced "mild pain…, mild inflammation, mild itching, and moderate swelling immediately after study drug was injected." Diprolene cream was applied to the area post-treatment.*
- *Subject 1308 received 5 ml of 3.0% Aethoxysklerol and was reported to have experienced "mild pain, moderate inflammation, serious hives, and mild swelling." Additionally, five minutes after the injection, the subject experienced numbness of the tongue of two minutes duration. On the case report form, all reactions were reported as being local, with no immediate systemic reactions recorded. No intervention was reported.*
- *Subject 1312 received 8 mL of 3.0% Aethoxysklerol and experienced "mild pain, moderate hives and itching, and mild swelling immediately after the study drug was injected." This subject also experienced numbness in her tongue that lasted approximately 5 minutes. On the case report form, all reactions were reported as being local; however the numbness in the tongue might be considered a systemic reaction. No intervention was reported.*
- *Subject 1324 received 7 mL of 3.0% Aethoxysklerol and experienced numbness of the tongue and lips following injection of study drug. The subject also experienced a sneezing attack that lasted 5 minutes. No intervention was reported.*

Transient urtication is reported to be common following treatment with polidocanol, usually resolving within 30 minutes (Goldman PM). However, it also reportedly can occur following treatment with any sclerosant solution and may be due to endothelial irritation (American College of Phlebology, "Complications of Sclerotherapy"). Systemic allergy and anaphylaxis have also been reported following sclerotherapy. It has been recommended that emergency equipment be immediately available when sclerotherapy is undertaken (American College of Phlebology, "Technique for Sclerosing Veins").

The remaining three subjects who received excessive study drug were reported to have experienced no immediate or local or systemic reactions.

Vital signs (temperature, pulse rate, respiration rate, and systolic and diastolic blood pressures) were collected before and within 1 hour after the injection. In the > 3-6 mm vein size group, patients in the Sotradecol group had a significantly higher mean pulse than did patients in the Aethoxysklerol group (74.7 vs. 71.9 beats/min, p = 0.043). There were no other significant between-group differences in any vital signs measure. There was no indication of any systematic change in vital signs values following treatment with either sclerosing agent.

Comment: The difference in mean pulse rate is not clinically meaningful.

Safety Data from Supportive Studies:

Concentration-Controlled Studies: ASK 94-002 and ASK 96-001

These were randomized, open-label, concentration-controlled studies of Aethoxysklerol conducted in Japan in subjects with varicose veins. In both studies, subjects were randomized to one of two dosing groups according to varicose vein diameter. Subjects in all categories were said to have received Aethoxysklerol intravenously at multiple sites, and while a specific volume was not specified for administration, as with the pivotal trials, the maximum dose was 2.0 mg/kg body weight per day. In both studies, safety was assessed by evaluating adverse events, clinical laboratory tests, and vital signs.

No subjects died or experienced serious adverse events during the concentration-controlled studies. No patients withdrew because of adverse events during the studies.

ASK 94-002

Start date: February 3, 1995 **Completion date:** January 11, 1996

This was a phase 2 dose-finding study conducted to determine the optimal dosage and dose range of the study drug based on the change in diameter of the vein in subjects with varicose veins of the lower extremity. Similar to the pivotal trials, subjects with varicose veins of the lower extremity were categorized into three groups according to vein diameter. The concentrations of Aethoxysklerol (ASK) studied were 0.5%, 1.0%, 2.0%, and 3.0%, and subjects in each of the three vein-size groups were allotted (by envelope method) to receive one of two concentrations of ASK (see table below).

Comment: It is noted that this dose-finding study was commenced approximately two years after the pivotal trials were begun (OHIO: January 6, 1993 to July 26, 1995; MICA: March 3, 1993 to February 19, 1996).

Study drug was administered intravenously at 0.1-1.0 mL for each vein with a maximum total dosage of 2mg/kg at each treatment session. The change in vein was observed for one month. In this study, 161 subjects were exposed to study drug.

Assessments were conducted at baseline, one week after each treatment, one week after final treatment and one month after final treatment. The number of treatments did not appear to be specified. Safety was assessed by vital signs, adverse events, laboratory tests (hematology, chemistry, urinalysis). Labs were obtained at baseline, one week after final treatment and one month after final treatment.

Comment: The review will be limited to the safety data and will not address the submitted efficacy data.

Results

Number Exposed to Polidocanol in ASK 94-002

Category	Vein Diameter	Aethoxysklerol Concentration	# of Subjects
I	< 1 mm	0.5%	22
		1.0%	23
II	>1 and < 3 mm	1.0%	27
		2.0%	30
III	> 3 mm	2.0%	33
		3.0%	26

Source: ASK 94-002: Table 2 (Vol. 40 p. 4296);

Comment: 1) The extent of exposure was not found. 2) Several subjects in all three categories were reported to have had previous treatment of their varicose veins (e.g. ligation, sclerotherapy). It is not clear whether the vessels treated in the study were untreated or previously treated. It is not clear how the safety outcomes might have been impacted by treatment of previously treated veins.

Local adverse events were similar to those in the pivotal trials and were seen in all vein sizes and with all ASK concentrations. Reported verbatim local events were intravenous thrombi, pigmentation, induration, subcutaneous hemorrhage, internal hemorrhage, pigmentation/phlebitis, and skin itching sensation. No local adverse events required discontinuation of treatment.

Comment: While "internal hemorrhage" was not defined, it was reported as a local adverse event.

No systemic adverse events were noted.

Laboratory Results

Mean data were not found in the study report. On review of data listings in Volume 41, several subjects in each dosing group showed decreases in red blood cell (RBC) parameters and platelets. No consistent pattern was noted with any dosing group; however, observed patterns included:

- progressive decrease from baseline, to one week post-treatment, to one month post-treatment
- decrease in values at the one week post-treatment testing as compared to baseline testing, with apparent recovery at one-month post-treatment testing
- decrease in values seen only at the one month post-treatment testing

The sponsor reported that a significant difference in comparison to pre-treatment values was seen for RBC's, hematocrit and hemoglobin in both treatment groups (2.0% and 3.0%) in the > 3 mm group, and "hemolytic effect was suspected" (p. 4271).

White blood cells (WBC's) also sometimes showed some tendency to decreases; however, no particular pattern was discerned. Differentials were not included in the data listings reviewed.

While urinalyses were said to have been done (e.g. p. 4270, Vol. 40), those data were not found or did not appear to have been commented on in the study report.

No subjects were reported to have experienced clinically significant events.

ASK 96-001

Start date: August 27, 1996 **Completion date:** May 17, 1997

The study was conducted to investigate the effectiveness and safety of ASK in sclerotherapy of varicose veins of the lower extremity by parallel group comparison of three concentrations, 0.25%, 0.5% and 1.0%, for two vein size categories. Subjects were ≥ 20 and ≤ 75 years of age. Study drug was injected intravenously at 0.1-0.5 mL at one site. Maximum dose was 2.0 mg/kg body weight per day.

Comment: This study was undertaken after completion of the pivotal trials.

The follow-up schedule was the same as was described for ASK 94-002. Safety was assessed by vital signs, adverse events, laboratory tests (hematology, chemistry, urinalysis). Labs were obtained at baseline, one week after final treatment and one month after final treatment.

Comment: As with study ASK 94-002, the review will be limited to the safety data and will not address the submitted efficacy data.

Number Exposed to Polidocanol in ASK 96-001

Category	Vein Diameter	Aethoxysklerol Concentration	# of Subjects
I	< 1 mm	0.25%	20
		0.5%	24
II	≥ 1 and < 3 mm	0.5%	27
		1.0%	29

Sources: ASK 96-001:Appenidx 16.1 (p.5438);

The most common local adverse events were "intravaricose thrombosis" and "pigmentation." (The Integrated Summary of Safety identifies these events as superficial intravenous thrombosis and hyperpigmentation, respectively). Other reported local adverse events included "dermatitis" and intradermal hemorrhage, and the most adverse events were reported in subjects who received the 1% concentration of study drug. Additionally, eight subjects, distributed across each vein-size group and study drug concentration, were reported to have developed "bulla due to elastic bandage/pillow." No additional information was provided about this reaction, so its nature is unclear (e.g. contact dermatitis).

No deaths or serious adverse events were reported. No systemic events were reported.

Laboratory Tests

As with ASK 94-002, mean data were not found in the study report. Also, similar to ASK 94-002, several subjects in each dosing group showed decreases in RBC parameters and platelets. No consistent pattern was noted with any dosing group or vein category. WBC's showed some tendency to decrease irrespective of dosing group or vein category. Urinalyses also were not found.

Uncontrolled Studies: AWB AET-AS25 and AET-P2

AWB AET-AS25

This open-label study was conducted in Germany under a special law that permits a treatment observation with registered and marketed drugs to be done without case report forms (also without informed consent, or Institutional Review Board/Ethics Committee approval). Study period was December 1995 until June 1996. This study enrolled 79 subjects. Two formulations of 0.25% Aethoxysklerol were compared in subjects with vein diameters of < 1mm. One formulation was the formulation proposed for marketing (40 subjects) and the other formulation "0.25%G Aethoxysklerol" contained 20% glycerin as the (b) (4) instead of 5% ethanol (39 subjects). Study duration for each subject was unclear. The mean numbers of injections and amounts of study drug varied between the study centers.

"Pigmentation" was "the most frequently occurring attendant temporary phenomenon." Thrombophlebitis was reported in five subjects, all treated at one center and with the formulation proposed for marketing. "Intravascular coagula" were also reported. The study report indicates that "no allergic reactions were observed, nor any inflammatory response" (Vol.44, p. 6071), and no subject required discontinuation of therapy. Also, no skin necrosis or telangiectatic matting were reported.

No reference to laboratory data was found in the study report.

Comments: The concentration studied in this trial is lower than proposed for marketing, and for 39 subjects, the formulation differed from that proposed for marketing.

AET-P2

This was an open-label, safety study of 2.0% Aethoxysklerol in which all subjects received 2.0 ml of drug (40 mg of polidocanol). The study enrolled 10 subjects with superficial varicosities 2-4 mm in diameter distributed over different areas of one extremity. This is the only study in which subjects received a specified amount of amount of study drug (in all other studies, dosing was determined by the investigator on an individual basis for each subject). The amount was distributed between several varicosities of one of the extremities.

Comment: J. Leonel Villavicencio, M.D. was the principal investigator in this study. Per the Integrated Summary of Safety, the study was undertaken in April 1991. The completion date was not found.

Baseline screening included Doppler examination of the venous system. Safety assessments included immediate and delayed reactions (same signs/symptoms as assessed in the pivotal trials), adverse events, clinical laboratory tests, vital signs, pulmonary function tests (PFT's), electrocardiograms (ECG's) (Vol. 44, pp 6154-2). Post-treatment assessments were conducted at 2 hours, 1, 4, and 8 weeks after treatment. Per review of case report form (Vol. 44, p. 6197), labs were to have been obtained at 2 hours and one week post-treatment; however, Listing 5 in Appendix 3 (Vol. 44) suggests that a different schedule may have been followed for some subjects, e.g. labs were obtained 2-3 days post-treatment and approximately one week post-treatment.

Four subjects experienced immediate local reactions (occurred up to 2 hours after injection): pain, inflammation (2 reports) and local allergy. No immediate systemic reactions were reported. Reported delayed reactions included pain, hyperpigmentation, thrombosis, ecchymosis, neovascularization,. Five subjects showed slight decreases in hematologic parameters post-treatment. However, there were no reported statistically or clinically significant differences in laboratory data or in vital signs, PFT's or ECG's obtained before treatment compared with after treatment.

One subject had mild airflow obstruction pre-treatment, which was considered indicative of chronic obstructive pulmonary disease (COPD). One week post-treatment, this subject had a 22% decline in forced expiratory flow, "that bordered on being a significant change" (no change had been seen 2 hours post-treatment). All other subjects had baseline PFT's within normal limits, and none of these subjects had abnormal values after treatment.

Comment: Based on these "inconclusive" results seen in the one subject, the sponsor indicated that there may be a "necessity for evaluating the susceptibility of patients with COPD or asthma." (Vol. 44, p. 6155). No explanation for this reaction was proposed.

One subject, who had sinus bradycardia pre-treatment, was said to have abnormal ECG's at two hours and one week post-treatment. The nature of the changes was not described.

Three female subjects (66, 44 and 56 years) had trace occult blood on at least one post-treatment urinalysis, two of whom also had 1-2 RBC reported. The 66 and 56 year olds had baseline negative testing for blood; however, the 44 year old had a large amount of blood and 30-49 RBC's counted, which suggests she may have been menstruating. All three subjects also had decrease in some hematologic parameters post-treatment.

ASK-00-01-00

This was an open-label, uncontrolled pharmacokinetic study conducted in Japan in six subjects to determine the concentrations of polidocanol in the plasma of subjects with varicose veins of the lower extremities. Subjects with varicose veins > 3mm received a single dose of 3% Aethoxysklerol in an amount of 1.5 to 2.0 mg/kg body weight. Safety was assessed by evaluating adverse events, clinical laboratory tests, and vital signs for up to seven days after treatment.

Two systemic adverse events were reported:

- Subject # 3 experienced an increase in total bilirubin; however this subject was also an asymptomatic carrier of type C hepatitis virus.
- Subject #4 experienced "mild" precordial pressure/pain immediately following injection. The sensation was of several seconds duration and of undetermined etiology.

Two subjects experienced decreases in RBC parameters, WBC (no differential) and platelets one week post dosing; however values remained in the normal range. A third subject had a decrease in platelets post-treatment.

Comment: See the Clinical Pharmacology review.

Supportive Safety Data from the Published Literature

The sponsor summarized data from 29,083 subjects who were treated with polidocanol and for whom safety data were published. Adverse events were reported to have been experienced by 6,357 subjects (21.9%). The most common adverse events were local allergy, hyperpigmentation, and neovascularization.

Serious adverse events were reported to have been experienced by 20 subjects (0.1%) and all of these events were reported to have evolved without sequelae. The sponsor considered an event to have been "serious" if, in their opinion, by the description in the article, the event required, or was likely to have required hospitalization. Based on that definition, serious adverse events in the literature included cardiac arrest, "cardiac ischemia", "blood pressure unrecordable" (one report each); "severe anaphylactic reaction" (5 patients), pulmonary embolism (2 patients), deep vein thrombosis (3 patients), and gangrene (one patient). Note: The reports of "cardiac arrest", "cardiac ischemia" occurred in the setting of anaphylaxis (i.e. these events occurred in subjects who are among the 5 who experienced anaphylaxis).

D. Adequacy of Safety Testing

The submitted safety data did not reveal any new or unexpected events for sclerotherapy treatment of varicose veins. Some adverse events may have been missed because of the sponsor's largely checklist approach to collection of safety data across the development program. Less emphasis appears to have been placed on collection of spontaneous observations, and the allowance for open-ended inquiries was unclear.

While the safety database may be supportive of the 0.5% and 1.0% concentrations, (b) (4) The sponsor was advised of the need for a minimum of 300 subjects treated with labeled dosing at the September 23, 1998 Guidance meeting, at which time the Division also referred the sponsor to the ICH-E1A guideline for additional discussion regarding sample size and safety.

The submitted safety data permit little to no assessment for risk of deep vein thrombosis (DVT) following treatment with the sponsor's product. None of the studies included specific assessments for DVT post-treatment (e.g. Duplex ultrasound), and DVT has been reported following sclerotherapy, including following treatment of telangiectasias (Bohler-Sommeregger K et al., J Dermtol Surg Oncol 1992;18 (5):403-406;abstract). Specific assessments are sometimes required for diagnosis, since DVT can be both asymptomatic and sub-clinical. Also, concomitant DVT have been reported in association with superficial thrombophlebitis (Ninia J, American College of Phlebology, "Thrombosis and Thrombophlebitis"), and given the frequent occurrence of superficial vein thrombosis in the pivotal trials, it is possible that DVT might also have been present in some subjects (Goldman MP, American College of Phlebology, "Complications of Sclerotherapy").

Given the laboratory results seen in AET-P2, a study of ten subjects conducted prior to the pivotal trials, it is unclear why laboratory testing was not incorporated into the design of the pivotal trials. Additional information regarding effects of the various concentrations of the study drug on laboratory parameters might be helpful in clarifying these effects and for informing labeling.

E. Summary of Critical Safety Findings and Limitations of Data

Review of the safety data did not reveal any adverse events that have not been previously reported with sclerotherapy and sclerosants in general. However, the safety assessments were largely targeted at capturing the occurrence of known sclerotherapy-associated adverse events. Some events could be procedure-related and not necessarily sclerosant-related, e.g. fainting from a vasovagal episode. Other events probably relate to the pharmacologic action of sclerosants, e.g. superficial thrombophlebitis. The data do not appear to have been collected, and were not presented, in a fashion that permitted an assessment of how the adverse event evolved over time, i.e. status at a particular time point, such as final evaluation. Use of a high potency corticosteroid post-treatment by some subjects, with the specific intent of minimizing inflammation, might have favorably influenced the adverse event profile.

The prevalence of superficial thrombophlebitis in all treatment groups was generally higher than what some others have reported. Goldman, for instance, reported superficial thrombophlebitis to have occurred in approximately 0.5% of some 1500 patients treated with poildocanol, occurring mostly in vessels >3-5 mm and when post-treatment compression had been inadequate (Goldman PM, J Dermatol Surg Oncol 1989;15:204-209). The American College of Phlebology's syllabus "Complications of Sclerotherapy," also addresses the role of post-treatment compression in relation to superficial thrombophlebitis stating that it (superficial thrombophlebitis) "is observed less often if compression is maintained for an adequate period of time." It is unclear to what extent the lack of detail in the protocol, including post-treatment compression procedures, might have been contributory to the frequency with which this event was seen.

The true extent of exposure was somewhat difficult to characterize for several of the studies, since subjects could have treatment of other vessels in addition to the target vessel. Also, the target vessel, could itself have been treated repeatedly. The extent of exposure tended to be presented only in regard to the volume of study drug injected into the target vessel and not total volume injected into all treated vessels.

Pertaining to the pivotal trials, more detailed procedures for identification and tracking of the treated vessel(s) would have been helpful, since it is not clear, from review of photographs and case report forms in the original submission, that the vessel treated at baseline was necessarily the same one assessed at follow-up. For study purposes, it might be more useful to limit treatment to a specified target vessel (or vessels) or to vessels within a specified treatment region (e.g. telangiectasias within a 25 cm^2 area). Tracings on transparencies, similar to what was done in study AWB AET-AS25, may be helpful in localizing the treatment sites at follow-up visits in future studies.

Photographs can also be very useful tools for documenting treatment site and outcome from both a safety and efficacy perspective. However, their usefulness is a function of the consistency of the procedures followed, as well as the quality of the images generated. The submitted photographs indicated that there was no standardization of photographic techniques. The photographs were generally grainy and often inconsistent in angle, lighting, distance and sometimes even the field photographed. The "graininess" appeared to be at least partly due to most of the submissions being photocopies of photographs, rather than the photographs themselves. Ultimately, however, safety (and efficacy) should be evaluated by clinical assessment; photographs would be supplemental to, and not a substitute for, the clinical evaluation.

All studies that included clinical laboratory testing, revealed some potential for RBC parameters and platelets to be affected following treatment; however, there was no particular pattern identified, and no changes appeared to be clinically significant. Alterations in RBC parameters were also observed in the preclinical studies. Additionally, hemolysis has been reported with other sclerosing agents. In some instances, the extent of exposure when laboratory testing was done was unclear, since labs were at one week and one month after final injection, so not everyone had labs done after the same number of exposures.

It may be prudent to avoid use of Aethoxyskelerol when other local anesthetics are in use because there may be a potential additive effect on the electrical activity of the heart.

No subjects died in the development program, and no subjects withdrew from any study because of adverse events.

VIII. Dosing, Regimen, and Administration Issues

According to the sponsor, Aethoxysklerol is marketed in six concentrations: 0.25%, 0.5%, 1.0%, 2.0%, 3.0%, and 4.0% (Volume 30, p. 27). Given that the dose-finding study ASK 94-002 appears to have been conducted after the pivotal trials, it is not clear how the sponsor determined the concentrations to evaluate for safety and efficacy in Phase 3, or that the selected concentrations represent the optimal choices for the proposed indication. At least one author considers it "difficult to justify using concentrations of polidocanol higher than 0.25% overall for most patients with telangiectasias and superficial venules. Results over the last 10 years using 0.25%, 0.5%, and 0.75% seem quite similar…" (Goldman PM). It is not clear that the 0.25% was sufficiently assessed in the development program to determine any potential role in marketing for the proposed indication.

The effect of chronic or recurrent use of polidocanol is not known.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Gender effects could not be analyzed, since there were only 21 males treated across the sponsor's development program.

The pharmacology/toxicology reviewer has recommended Pregnancy Category "C" (the sponsor proposed (b) (4) "Polidocanol has been shown to have an embryocidal effect in rabbits when given in doses approximately equal to the human dose (following normalization of the exposures on the basis of body surface area). This effect may have been secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Polidocanol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

There were no pregnancies reported in the development program.

Comment: The clinical reviewer agrees with the recommendation for Pregnancy Category "C".

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Mean ages in all studies conducted were less than <60 yrs. Race data were not collected in either pivotal study. Three of the five supportive studies were conducted in Japan, and a fourth was conducted in Germany.

Comment: In response to a Clinical Pharmacology information request, the sponsor asserted in a submission dated February 9, 2004 that, "There are no data to suggest that systemic exposure to polidocanol would increase in a representative US population (compared to Japanese patients)." The response includes a discussion of the metabolism of the drug in Japanese subjects as compared to Caucasians, e.g. alcohol dehydrogenase. See the Clinical Pharmacology review.

C. Evaluation of Pediatric Program

The indication is not typically seen in the pediatric population.

D. Comments on Data Available or Needed in Other Populations

Additional information may be needed regarding the safety of use of the product in subjects with COPD and asthma, given the PFT findings in one subject in study AET-P2.

Because Aeothoxysklerol contains alcohol, it may not be appropriate for use in patients receiving treatment with disulfuram.

Gender
Analysis by gender was not performed because only for 4 males were enrolled in the study. Too few males were enrolled to be able to draw valid efficacy conclusions; however, there were 3 males with scores above 4 (majority disappeared) and one scored above 3 (minority disappeared) on the Disappearance of Varicosities Scale. Patients 1105, 2343, and 3309 had scores of 4.7 each and Patient 1227 had a score of 3.7.

Ethnic/Racial
Ethnic/racial safety and efficacy differences could not be assessed due to lack of obtaining these baseline demographic data. Post-inflammatory hyperpigmentation is of particular concern in certain ethic/racial populations; therefore, studies participation should reflect the intended popluation. According to Weiss and Dover (Atlas of Cosmetic Surgery 2002) the rate of hyperpigmentation after sclerotherapy varies from 10 % to 80% (rare in vessels <1 mm) due to both postinflammatory hyperpigmentation and hemosiderin deposits.

Geriatric
Geriatric patients older than 65 yrs were excluded from study. The Applicant provided an age split performed at 45 yrs, and the results from those patients ≥ 45 yrs of age were compared with those from patients < 45 yrs of age with no efficacy difference being identified for age, center, vein size, and treatment –by-center. In the pivotal studies, mean ages ranged from 40.8 to 43.1 years. Data are needed for geriatric patients (65 yrs) since the incidence of varicose veins increases with each decade of life. Patients who were ≥65 years of age were excluded per protocol, and the rationale for exclusion of patients older than 65 years old was provided.

Pediatric
A pediatric waiver was requested and should be granted because varicose veins of the lower extremities are extremely uncommon in children; therefore, study of pediatric patients is not needed.

Pregnancy
Sclerotherapy of varicose veins is contraindicated in case of pregnancy and the procedure is listed as a precaution. According to the proposed label, (b) (4) (b) (4) Aethoxysklerol is proposed as a Pregnancy Category (b) drug by the Applicant; however, Pharm/Tox recommends the classification as Pregnancy Category C. Pregnant females were excluded from study participation. The Agency received a reported adverse pregnancy outcome that appears consistent with findings in animal studies (Pharm/Tox review dated June 12, 1997); however, the conclusion stated that additional epidemiologic data on children born to mothers treated with Aethoxysklerol would be needed to confirm that the birth was not due to a random premature birth.

X. Conclusions and Recommendations

A. Conclusions

Efficacy Conclusions
The Applicant's study design was flawed in that the treatment effect of the comparator arm was not unknown and failed to establish superiority or non-inferiority for Complete Disappearance of Varicosities, the primary efficacy endpoint when Aethoxysklerol is compared to Sotradecol. Thus, the efficacy of Aethoxysklerol has not been adequately demonstrated for the proposed indication.

Safety Conclusions
The submitted safety data revealed an adverse event profile consistent with what has been reported with sclerotherapy and sclerosants, with no new or unexpected events reported. From the data submitted, there was no apparent signal of an adverse event that might suggest a polidocanol-specific effect. However, known sclerotherapy-related adverse events were specifically sought in the clinical trials, with less emphasis placed on establishing a more general, comprehensive adverse event profile for the study drug.

The submitted safety data permit little to no assessment for risk of deep vein thrombosis (DVT) following treatment with the sponsor's product. None of the studies specifically assessed for DVT post-treatment (e.g. Duplex ultrasound), and DVT has been reported following sclerotherapy, including following treatment of telangiectasias. The frequent occurrence of superficial vein thrombosis in both treatment groups of all vein sizes might indicate a systemic deficiency in study conduct, e.g. insufficiently detailed study procedures in regard to post-treatment compression.

(b) (4)
The database may be supportive of the 0.5% and 1.0% concentrations.

Additional information regarding effects of the various concentrations of the study drug on laboratory parameters might be helpful in clarifying these effects and for informing labeling. Also, as the sponsor has suggested, additional information might be needed regarding the use of the product in patients with COPD or asthma, given the decrease in forced expiratory flow experienced post-treatment by one subject in the one study in which pulmonary function tests were performed.

Additive risk from use of the product in a setting with other local anesthetics is unclear. It might, therefore, be prudent to avoid use when other local anesthetics are also planned for use.

B. Recommendations

Recommendation on Approvability

A *Non-Approvable* recommendation is being made for use of Aethoxysklerol (polidocanol), a sclerosant intended for intravenous administration for treatment of (b) (4) diameter varicosities of the lower extremities. Safety and efficacy are being reviewed separately.

The Applicant failed to establish superiority for the dichotomized Complete Disappearance of Varicosities efficacy endpoint as proposed by the Division or Disappearance of Varicosities on a 5-point scale as proposed by the Applicant when Aethoxysklerol is compared to diluted Sotradecol (STS). The attempt to demonstrate superiority or non-inferiority was flawed because the treatment effect of the Sotradecol comparator is unknown; thereby making power calculations determination difficult. Sotradecol was approved in 1946 when efficacy did not have to be established therefore use as an active comparator is problematic in establishing superiority or non-inferiority in that the treatment effect of the approved or diluted concentrations of Sotradecol is unknown. It is of note that non-inferiority was also not established for the dichotomized Complete Disappearance of Varicosities efficacy endpoint.

It is recommended that the application is Not Approvable. The submitted safety data revealed an adverse event profile consistent with sclerotherapy and the general pharmacologic class of sclerosants; however, efficacy was not demonstrated. Thus, the risk-benefit analysis does not favor approval. The safety database revealed no apparent signal of a polidocanol-specific effect. Also, while not the basis of the Not-Approvable recommendation, additional information is needed to inform labeling regarding the risk of systemic effects, including the effect of the drug on laboratory parameters, and the risk of deep vein thrombosis, and possibly the risk of use in patients with COPD or asthma.

XI. Appendix

A. Other Relevant Materials

Regulatory History NDA 21-201

1990 (HFD-160)

- May 21, 1990: Memorandum of In-House meeting (HFD-160 and Compliance) for Division input regarding the wide distribution and illegal use of aethoxysklerol (a sclerosing agent) by over 100 doctors who are treating patients with this unapproved drug product.
- July 19, 1990: Date of receipt by the Agency for IND 35,139 assigned to HFD-160 to the Division of Medical Imaging, Surgical and Dental Drug Products (July 2, 1990 submission date)
- August 13, 1990: Protocol received for a single, open label and uncontrolled study was received (MOR review completed 01-30-91).
- August 10, 1990 (CDER date): Submission Chemistry submitted was insufficient to initiate the proposed clinical studies.
- July 19, 1990: Pilot study submitted for IV use of aethoxysklerol 10 patients. J. L. Villavicencio, M.D. is listed as Principal Investigator (the protocol was reviewed as a consult in HFD 540 with a review date of January 10, 1994 and a stamp date of September 24, 1994.)
- August 16, 1990: T-con provided a two-week extension of the 30-day safety was granted.
- November 14, 1990: Meeting with Jobst Institute (according to a December 5, 1990 stamp dated HFD-160 memo from chemistry)
- November 16, 1990: Certified letter from the Agency to (b) (4) regarding violation of FDA regulations governing use of the unapproved medication aethoxysklerol.

1991 (HFD-160)

- January 30, 1991: MO Review of the 08-31-90 pilot study. According to the review, while the study was safe to proceed, sufficient data would not be collected to support regulatory requirements for an NDA. Minutes of a meeting between the Agency and the sponsor were not available; however based on the MO's recollection, "...that the sponsor was advised to re-write the protocol in such a fashion that the data may be ultimately submitted as two, separate and independent, well controlled clinical studies.". According to the MO's recommendation regarding a well controlled, blinded study,"…This protocol may be employed at two separate study locations in order to fulfill; the requirement for two independent studies."
- January 30, 1991: A Memorandum of A Telephone Conversation between Jobst (the Sponsor) and HFD-160 indicated that a more detailed protocol (preferably blinded clinical study) in collaboration with Dr. Villavicencio was close to being submitted. Request was made of the sponsor to consider individual investigators who are interested in studying the drug under the IND.

- February 07, 1991: Clinical trials may proceed from standpoint of pharmacology with deficiencies noted.
- March 08, 1991: Reasonably safe to proceed from Chemistry. Clinical requested a protocol to describe a well controlled preferably blinded, clinical study. The protocol should be employed at a minimum of two separate study locations in order to fulfill the requirement for two independent studies.

1993 (HFD 160)

- January 6, 1993: Phase 3 protocol initiation date
- February 23, 1993: Submission date of the protocol titled **"**Double-Blind, Prospective, Randomized, Comparative Multicenter Trial Between Aethoxysklerol® (Polidocanol) and Sotradecol® (Sodium Tetradecyl Sulfate) in the Management of Varicose Veins of the Lower Extremities".
- December 30, 1993: The Amendment was reviewed by HFD-520 as a consult, with a review date of December 30, 1993). PIs listed as Mitchell P. Goldman, MD (Encinitas, CA), John C. Cranley, MD (Logan, Ohio), and John R. Pfeifer, MD (Southfield, MI). Three centers enrolling a total of 450 subjects were planned. The planned study was double-blind, six week active control study with a four month follow-up. Study participants were to be stratified into three groups according to vessel size.

1994 (HFD 540)

- January 1994: IND 35,139 was assigned to HFD-540 (Steve's notes)
- February 8, 1994: Major problem with efficacy rating scale with inclusion of adverse events (e.g., neovascularization and pigmentation). Needed to evaluate efficacy separately from AEs.
- April 12, 1994 (Source NDA submission) Memorandum from Biostatistics to the Sponsor regarding Merging of two centers due to slow enrollment.
- May 5, 1994 (Source NDA Submission) Memorandum from Biostatistics to the Sponsor regarding proper Meta-Analysis
- December 30, 1994 (Stamp Date): Statistical Consultation IND 35, 139 Annual Report Review (date of Document 12-15-92, Date received by Biometrics 11-21-94) recommending an Amendment addressing the multiple comparisons issue and that the protocol planned sample size and analysis plan seem to be statistically appropriate to meet the sponsor's stated objectives.

1995 (HFD 540)

- January 25, 1995: (Document Date: 12/15/94) Statistical Consultation (requested by the FDA) to review submission of all written communications referencing IND #35, 139 between Dr. Leonel Villavicencio (PI for the study) and the Division of Dermatology and all records pertaining IND #35, 139 that were in the possession of Dr, Ralph Harkins of the FDA.
- October 17, 1995: Comments from Statistician regarding 07-26-95 submission regarding request to begin data analysis at one center
- December 4, 1995: Meeting?

- January 31, 1996: E-mail from Joanne Holmes (PM) noting that Paul Cowden (Jobst) was informed that without a formal End of Phase 2 meeting, they have not received commitments by the Agency. Reference was made regarding 12/92 and 7/95 Protocols.

1996 (HFD-540)
- February 2, 1996: meeting?
- February 19, 1996: Clinical trial completion date
- April 1, 1996: Primary Efficacy Endpoint from Ralph Hawkins, Ph.D. Disappearance of varicose veins will be recognized as the primary efficacy endpoint. Pigmentation and neovascularization are adverse events.
- April 15, 1996: Meeting Minutes Ms. Farr noted that the sponsor agreed upon disappearance as the primary endpoint. The sponsor would combine the Michigan and California data. Suggested DSI audit of the Michigan site. Could not compare an approved comparator agent at an unapproved dose. The sponsor would need to be able to beat placebo in the study.
- October 4, 1996: Statistical Analysis Procedures from Ralph Hawkins, Director Biometrics IV

1997 (HFD-540)
- March 25, 1997: Statistical comments Dr. Srinivasan regarding non-inferiority analysis
- June 23, 1997: Division advice regarding a shortage of STS and a request by Jobst to make atheoxysklerol available for physician use under IND 35,139
- June 23, 1997: Pharm/Tox review comments regarding adverse pregnancy outcome report

1998 (HFD-540)
- January 12, 1998: Guidance meeting, The only primary endpoint variable should be disappearance of vascularization as determined by three readers on a 5-point scale. In addition, the sponsor should analyze the proportion of subjects who had complete disappearance vs. partial disappearance.
- August 7, 1998: Pharm/Tox review
- September 23, 1998: Guidance meeting

1999 (HFD-540)
- October 1, 1999: NDA 21-201 submitted to the Agency
- December 1, 1999: NDA 21-201 was withdrawn due issues with pharmacokinetic data (according to November 24, 2003 Filing Memo)

2002 (HFD-540)
- October 21, 2002: Pre-NDA meeting (Content and format)

2003 (HFD-540)
- September 29, 2003: NDA 21-201 was resubmitted
- December 15, 2003: 74-Day Filing Letter issued

2004 (HFD-540)

- May 14, 2004: Regulatory Briefing
- August 2, 2004: 10-month Goal date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brenda Vaughan
7/8/04 06:06:39 PM
MEDICAL OFFICER

Brenda Carr
7/12/04 07:23:28 AM
MEDICAL OFFICER

Markham Luke
7/12/04 03:43:37 PM
MEDICAL OFFICER
Concur with MO recommendation for Not Approvable. See also TL addendum for additional comments.

Jonathan Wilkin
7/13/04 07:10:14 PM
MEDICAL OFFICER