Post Authorisation Safety Study final report for Fibrovein 3% and 1%

EU PAS register number: EUPAS8260

A voluntary non-interventional post-authorisation safety study to define the incidence of and potential risk factors for procedure-related neurological adverse events in patients undergoing ultrasound guided foam sclerotherapy for the treatment of varicose veins using Fibrovein 3% and 1% incorporating a drug utilisation study.

Author

Mike Watkins BSc PhD

STD Pharmaceutical Products Ltd, Plough Lane, Hereford, UK.

Signature: 

Chief Clinical Investigator

Professor Andrew W. Bradbury BSc MB ChB (Hons) MD MBA FEBVS FRCSEd FRCSEng Sampson Gamgee Professor of Vascular Surgery, University of Birmingham, UK and Consultant Vascular and Endovascular Surgeon, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

Signature: 

EU QPPV

Maikel Hofwijks

Drug Safety Solutions Limited, Sleper 11, Brunssum, 6446 BW, Netherlands.

Signature: 

Title	A voluntary non interventional post-authorisation safety study (PASS) to define the incidence of and potential risk factors for procedure-related neurological adverse events (AE) in patients undergoing ultrasound guided foam sclerotherapy (UGFS) for the treatment of lower limb varicose veins (VV) using Fibrovein 3% and 1% (sodium tetradecyl sulfate, STS, injection) incorporating a drug utilisation study.
Version identifier of the final study report	Version 1
Date of last version of the final study report	18 December 2020
EU PAS register number	EUPAS8260
Active substance	Sodium tetradecyl sulfate
Medicinal product	Fibrovein 3% and 1%
Product reference	UK/H/2775/001-004/DC (NB product reference is now CZ/H/0944/001-004/DC)
Procedure number	Not applicable
Marketing authorisation holder(s)	STD Pharmaceutical Products Limited, Plough Lane, Hereford, HR4 0EL, United Kingdom. STD Pharmaceutical (Ireland) Limited, Block 1, Blanchardstown Corporate Park, Ballycoolen Road, Blanchardstown. D15 AKK1 Dublin 15. Ireland.
Joint PASS	No
Research question and objectives	Research Questions: 1. What is the incidence, type, severity, duration, treatment (where required), and clinical outcome of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam? 2. To what extent, if any, are these procedure-related neurological AE associated with identifiable patient and treatment characteristics? 3. Post-marketing authorisation (PMA), how is UGFS with Fibrovein 3% and 1% being used in the "real world" to treat lower limb VVs (nested drug utilisation study)? Objectives: 1. Define the incidence of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam 2. Further characterise these AE in terms of type, severity, duration, treatment (where required), and clinical outcome 3. To describe the relationship, if any, between procedure related neurological AE and identifiable patient and treatment characteristics 4. Describe the PMA "real world" use Fibrovein 3% and 1% foam for the treatment of lower limb VVs (nested drug utilisation study)
Countries of study	United Kingdom, France
Author	Mike Watkins BSc., PhD.

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1. Abstract:

Title

A voluntary non interventional post-authorisation safety study (PASS) [as defined by Directive 2001/83/EC (DIR) Art 1(15)] to define the incidence of and potential risk factors for procedure-related neurological adverse events (AE) in patients undergoing ultrasound guided foam sclerotherapy (UGFS) for the treatment of lower limb varicose veins (VV) using Fibrovein 3% and 1% (sodium tetradecyl sulfate, STS, injection) incorporating a drug utilisation study.

Date of report: 18 Dec 2020

Author: Mike Watkins BSc., PhD.

Affiliation: STD Pharmaceutical Products Ltd., Plough Lane, Hereford, HR4 0EL, UK.

Keywords

Foam sclerotherapy, neurological adverse events

Rationale and Background

Across Europe, patients with lower limb varicose veins (VV) were increasingly being treated without surgery. In the UK, the National Institute of Clinical and Health Excellence (NICE) had recommended endothermal ablation (ETA) and ultrasound-guided foam sclerotherapy (UGFS) in preference to surgery for the treatment of VV.

(http://www.nice.org.uk/Guidance/QS67)

(http://www.nice.org.uk/guidance/CG168)

Randomised controlled trials and observational studies had indicated that the incidence of procedure-related neurological adverse events (AE) (including visual disturbance, migraine, transient ischaemic attack (TIA) and stroke) during and following UGFS was very low.

However, their exact incidence and cause had not yet been defined.

Fibrovein 3% and 1% were granted a UK license for the treatment of VV by means of UGFS in 2012 as part of a DCP (UK/H/2775/001-4/DC).

One of the post approval commitments was to perform a voluntary non-interventional PASS to assess the incidence and potential risk factors for procedure-related neurological AE.

Nested within this study was a drug utilisation study to examine the “real world” use of Fibrovein for UGFS.

Research questions and objectives

Research Questions:

1. What was the incidence, type, severity, duration, treatment (where required), and clinical outcome of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam?
2. To what extent, if any, were these procedure-related neurological AE associated with identifiable patient and treatment characteristics?
3. Post-marketing authorisation (PMA), how is UGFS with Fibrovein 3% and 1% being used in the “real world” to treat lower limb VVs (nested drug utilisation study)?

Objectives

To:

1. Define the incidence of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam

2. Further characterise these AE in terms of type, severity, duration, treatment (where required), and clinical outcome
3. To describe the relationship, if any, between procedure related neurological AE and identifiable patient and treatment characteristics
4. Describe the PMA "real world" use Fibrovein 3% and 1% foam for the treatment of lower limb VVs (nested drug utilisation study)

Study Design

This was a non-interventional prospective, multicentre, PASS of patients undergoing UGFS for lower limb VV incorporating a nested drug utilisation study.

The study was purely observational and had no impact on the:

1. Decision to treat with UGFS
2. Nature of any aspect of the UGFS treatment provided
3. Management of any procedure-related neurological AE

Furthermore:

1. The results of the PASS are not generalisable to patients having UGFS using other sclerosants or to other types of VV treatment
2. No access to medical records was required and patient identifiable data was be recorded outside the clinical care team

For these reasons, the NHS Health Research Authority (HRA) did not consider this type of non-interventional PASS study to:

1. Be "research" (http://www.hra-decisiontools.org.uk/research/)
2. Require NHS Research Ethical Committee (REC) approval (http://www.hra-decisiontools.org.uk/ethics/)
3. Require NHS R&D Management permission (http://www.hra.nhs.uk/documents/2013/09/approval-of-medical-devices-research-version-2-april-2008.pdf)

Setting

Place: public and private hospitals in the UK, France

Data collection period: 1 January 2015 to 31 January 2020

Inclusion criteria: all non-pregnant, non-breast-feeding patients aged 18 years or over, undergoing Fibrovein UGFS (either alone or in combination with another modality such as endothermal ablation) for varicose veins

Exclusion criteria: patient under 18 years of age; not undergoing Fibrovein UGFS as part of their varicose veins' treatment; pregnancy, breast-feeding

Sampling: none, all suitable patients were included

Subjects and study size

Persons: non-pregnant, non-breastfeeding, patients aged 18 years or over, undergoing Fibrovein UGFS for lower limb varicose veins

Study size: 10,274 legs treated in 8,058 sessions.

Variables and data sources

Variables

Outcome of interest: procedure-related neurological AE

Exposures: 1% and/or 3% Fibrovein used as foam

Patient variables:

1. Age
2. Gender
3. Height, weight, and body mass index (BMI)
4. Primary versus recurrent VV
5. Co-existing deep venous disease / history of deep vein thrombosis (DVT)
6. CEAP clinical grade (C1-C6)
7. Type of VV: great saphenous vein (GSV), small saphenous vein (SSV), and anterior accessory saphenous vein (AASV), tributary veins
8. History of migraine / transient ischaemic Attack (TIA) / stroke / diabetes mellitus (DM) / hypertension (high blood pressure, BP)
9. Smoking status
10. Known to have a patent foramen ovale (PFO) (symptomatic or asymptomatic)
11. Previous Fibrovein UGFS

Treatment variables:

1. Unilateral vs. bilateral
2. Method of preparation of Fibrovein foam
3. Concentration of Fibrovein used
4. Fibrovein to gas ratio
5. Gas used: air vs. physiological gases (O_2/CO_2)
6. Volume of each concentration of Fibrovein used
7. Number of injection sites
8. Aliquot size (volume of foam injected at each injection site)
9. Concomitant surgical and non-surgical treatments for VV
10. Compression regime and duration following UGFS

Data sources:

The occurrence (and if present the type, severity, duration, treatment [where required] and clinical outcome) or absence of procedure-related neurological AE associated with Fibrovein UGFS for lower limb VV, together with patient and treatment characteristics, was collected using Fibrovein PASS Proforma 1 (Appendix 1) at the end of each UGFS treatment session.

Each separate UGFS treatment session generated a separate proforma.

In patients undergoing bilateral treatment a Fibrovein PASS Proforma 1 was completed for each leg.

UGFS was used either as the sole treatment for the patient's VV or in combination with another treatment modality.

In keeping with post-marketing pharmacovigilance (PV) requirements, in addition to completing Fibrovein PASS Proforma 1, co-investigators were asked to contact the UK co-ordinating centre should a serious adverse event (SAE) occur at the time of the UGFS or if they become aware that a SAE has occurred subsequently. SAE details were recorded on Fibrovein PASS Proforma 2 (Appendix 2).

SAE were defined by the UK Medicines and Healthcare Products Regulatory Agency (MRHA) (www.mhra.gov.uk) as those which:

- Result in death
- Are immediately life threatening
- Require in-patient hospitalisation or prolongation of existing hospitalisation

- Result in persistent of significant disability / incapacity or substantial disruption of the ability to conduct normal life functions
- Result in a congenital abnormality or birth defect
- Represent an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Co-investigators were provided with instructions on how to complete the Fibrovein PASS Proformas 1 and 2 and telephone help was available during normal office hours from the UK Co-ordinating Centre.

Results

The table below compares the patient demographics and past medical history of patients who did and did not experience an adverse event. The statistical significance was calculated using two tailed t-tests for continuous data and Pearson's chi-squared test for categorical variables.

Statistical analysis was also performed on the other variables collected e.g. CEAP classification, treatment type, vein treated etc. The only variable suggesting a significant difference between patients who did and did not experience and adverse event was the volume of foam injected and this is analysed further below.

Patient Demographics – comparing no adverse event to patients experiencing an adverse event			
Variable	**No AE n=8,010**	**With AE n=46**	**p-value**
Age – median (IQR)	56 (46, 66) n=7,713	54 (46, 59.3) n=44	0.170
Female, n (%)	5,231 (66.2%) n=7,901	30 (65%) n=46	0.890
Male, n (%)	2,670 (33.8%) n=7,901	16 (35%) n=46	0.890
BMI – median (IQR)	26.8 (23.7, 30.9) n=4,158	26.9 (23.4, 30.3), n=32	0.537
Past Medical History			
Migraine, n (%)	543 (6.8%), n=8,010	26 (56. 5%), n=46	<0.0001
Migraine with aura, n (%)	186 (2.3%), n=8,010	21 (45.7%), n=46	<0.0001
Transient Ischaemic Attack (TIA), n (%)	68 (0.3%), n=8,010	2 (4.3%), n=46	0.011
Stroke, n (%)	47 (0.6%), n=8,010	0 (0%), n=46	0.602
Smoker, n (%)	392 (4.9%), n=8,010	0 (0%), n=46	0.124
Diabetic, n (%)	342 (4.3%), n=8,010	1 (2.2%), n=46	0.483
High Blood Pressure, n (%)	1,076 (13.4%), n=8,010	5 (10.9%), n=46	0.611
Deep Vein Thrombosis, n (%)	194 (2.4%), n=8,010	1 (2.2%), n=46	0.913
DVT same leg, n (%)	88 (1.1%), n=8,010	0 (0%), n=46	0.487
Known Patent Foramen Ovale, n (%)	5 (0.06%), n=8,010	0 (0%), n=46	0.865
Symptomatic PFO, n (%)	1 (0.01%), n=8,010	0 (0%), n=46	0.940

The results show that a history of migraine with or without aura ($p < 0.0001$) and TIA ($p = 0.011$) are significantly associated with the occurrence of an adverse event.

The table below shows that a history of migraine and TIA and the use of foam in excess of the SmPC recommendations, are associated with a greatly increased chance (odds ratio) of an adverse event.

Variable	Odds Ratio	Upper 95% CI	Lower 95% CI	p-value
History of migrane	17.92	32.32	9.94	0.000000
History of migraine/aura	35.33	64.26	19.43	0.000000
History of TIA	5.31	22.34	1.26	0.022615
Foam volume over 16ml	3.77	7.46	1.91	0.000154

There were twelve cases of an AE after volumes of foam in excess of SmPC recommendations was administered however ten of the patients also had a history of migraine. The data indicates that a high volume of foam alone is less of a predictor but high volumes in patients with a history of migraine is a very strong predictor of an adverse event.

Discussion

The study objectives as defined in the protocol were:

1. Define the incidence of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam
2. Further characterise these AE in terms of type, severity, duration, treatment (where required), and clinical outcome
3. To describe the relationship, if any, between procedure related neurological AE and identifiable patient and treatment characteristics
4. Describe the post marketing authorisation “real world” use of Fibrovein 3% and 1% foam for the treatment of lower limb VVs (nested drug utilisation study).

The study has achieved the objectives with data collected on 48 patient and treatment variables for over 8,000 treatment sessions and over 10,000 legs.

Incidence of procedure related adverse events

Looking firstly at defining the incidence of procedure related adverse events and comparing them with expected frequencies as defined in the SmPC.

There were 46 adverse events.

The events with the highest frequency were migraine/headache with or without visual disturbance/aura followed by visual disturbance alone. The results are slightly confused by some patients receiving much higher doses of foam than the recommended maximum of 16ml. Here the incidence will be discussed including the high doses but also without the high doses because it is important when comparing results with the SmPC that we consider the treatments that conformed to the SmPC recommendations.

The SmPC lists the frequency for migraine and headache using foam as ‘rare’ defined as >1 in 10,000 to < 1 in 1,000 (>0.01% to <0.1%).

Visual disturbance is not listed specifically in the SmPC but scotoma, scintillating scotoma is listed with a frequency of uncommon defined as >1 in 1,000 to < 1 in 100 (>0.1% to <1%).

The tables below compare the frequency of the adverse event with the expected frequency listed in the SmPC

Adverse event	Incidence all cases	Incidence normal dose	SmPC frequency
Migraine ± aura/ visual disturbance	19/8056 = 0.24%	15/8056 = 0.19%	>0.01% to <0.1%
Headache ± visual disturbance	8/8056 = 0.099%	5/8056 = 0.062%	>0.01% to <0.1%
Scotoma/visual disturbance	NA	10/8056 = 0.12%	>0.1% to <1%
Key point - the incidence of migraine is higher than the frequency listed in the SmPC			

Looking at the other adverse events there were two cases of stroke, one TIA, one arm weakness (hemiparesis) and one allergic reaction all of which are listed as very rare (<10,000). There were two vasovagal cases which is listed as rare (>1 in 10,000 to < 1 in 1,000).

Adverse event	Incidence including high doses	Incidence normal dose	SmPC frequency
Vaso vagal e.g. fainting, confusion	NA	2/8056 = 0.025%	>0.01% to <0.1%
Allergic reaction	NA	1 in 8056	< 1 in 10,000
Weakness (hemiparesis)	NA	1 in 8056	< 1 in 10,000
Transient ischaemic attack	NA	1 in 8056	< 1 in 10,000
Stroke/CVA	2 in 8056	1 in 8056	< 1 in 10,000
Hyperventilation Carpo-pedal spasm	1 in 8056	NA	

Looking at the cases in more detail the vaso-vagal cases are within the frequencies listed in the SmPC.

There was one of each of the following adverse events, allergic reaction, weakness, transient ischaemic attack in the data set of 8,056 sessions and 10,274 legs. It is reasonable to propose that the listed frequency of very rare for these adverse events is commensurate with the data collated in this study.

Looking at the stroke cases it seems likely that one was not related to the sclerotherapy treatment. Cases reported in the literature tend to occur at the time of treatment or within 3-4 days whereas this one was 19 days after treatment. The patient's medical history included hypertension and elevated cholesterol. Given the late onset and patient history it therefore seems reasonable to exclude this case.

The second stroke case was definitely related to the treatment, but the patient received 32mL of foam which is twice the recommended maximum.

Given the mitigating factors in the two stroke cases it is reasonable to propose that the listed frequency of very rare for a stroke remains commensurate with the data collated in this study.

The case of hyperventilation leading to carpo-pedal spasm it was felt with this case that the patient suffered from anxiety which led to hyperventilation, this thinking is based on the fact that once the symptoms had been explained and the patients breathing was regulated there was a rapid resolution of the symptoms.

In summary the individual case data suggests the frequencies listed in the SmPC remain adequate for all of the adverse events except for migraine. The data suggests that the frequency for migraine should be changed from 'rare' to 'uncommon'.

Looking at the relationship between procedure related neurological AE and identifiable patient and treatment characteristics.

The statistical analysis identified three predictors that increase the likelihood of an adverse event occurring.

A history of migraine with or without aura, higher than recommended foam volumes and TIA.

Section 4.4 of the SmPC 'Special warnings and precautions for use' already lists migraine the recommendations in the SmPC are as follows:

'Previous migraine sufferers should be treated with care. Patients with previous migraine have been shown to be more likely to suffer from visual disturbances and migraine, particularly following injections with foamed sclerosant. Use smaller volumes in patients with history of migraine.'

Based on this recommendation, the warnings regarding previous migraine sufferers and the need to be careful with the volume of foam injected is adequately covered in the current SmPC.

Regarding TIA as a possible predictor of an adverse event, it is not mentioned in the SmPC. However, there were only two patients with a history of TIA who experienced an adverse event. One experienced a headache the other experienced a visual disturbance (flashing lights). It is difficult to be certain that the adverse events were related to the patients having had a TIA previously however a special warning could be added to the SmPC.

Conclusion and impact on benefit-risk balance of the product

The study objectives were well met and the real-world frequencies of neurological adverse events following UGFS using 3% and 1% Fibrovein has been accurately determined.

The main conclusions are that the current SmPC lists the neurological adverse events and the frequencies listed accurately reflects the frequencies of occurrence with the exception of migraine.

The recommendation is that the frequency for migraine listed in the SmPC is changed from 'rare' to 'uncommon'.

A past medical history of migraine is a strong predictor for a neurological adverse event especially when larger volumes of foam are administered. A past medical history of migraine is addressed in the current SmPC as a special warning which urges caution and to use low volumes of foam.

The recommendation is to leave the special warning as it is.

A past medical history of a TIA was a significant predictor for a neurological adverse event. The current SmPC has no warnings regarding a past medical history of TIA.

The recommendation is to add a past medical history of TIA to section 4.4 'Special warnings and precautions for use' with a statement such as:

TIA

Patients with a past medical history of TIA should be treated with care.

Patients with previous TIA have been shown to be more likely to suffer from visual disturbances and migraine, particularly following injections with foamed sclerosant.

Large volumes of foam also are a strong predictor for a neurological adverse event especially where the patient has a history of migraine. Large volumes of foam on it own is not a particularly strong predictor. Most centres treated patients stayed within the SmPC recommended volumes of foam with only 610 sessions exceeding them.

Recommendation is that the current maximum dose listed in the SmPC (16ml) is safe and should remain the same and should not be increased or decreased.

Marketing Authorisation Holder

STD Pharmaceutical Products Ltd., Plough Lane, Hereford, HR4 0EL, UK.

STD Pharmaceutical (Ireland) Limited, Block 1, Blanchardstown Corporate Park, Ballycoolen Road, Blanchardstown. D15 AKK1 Dublin 15. Ireland.

Principal Investigators

Chief clinical investigator: Professor Andrew W. Bradbury BSc MB ChB (Hons) MD MBA FEBVS FRCSEd FRCSEng Sampson Gamgee Professor of Vascular Surgery, University of Birmingham, UK and Consultant Vascular and Endovascular Surgeon, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

Co-ordinating Clinical Investigator: Mr Huw Davies BSc (Hons), MBBS, FRCS (Vasc), MD

Address for correspondence: University Department of Vascular Surgery, Netherwood House, Solihull Hospital, Lode Lane, Solihull, B91 2JL, UK.

Chief Scientific Investigators

Mr Bruce Gardiner BSc, Managing Director

Mike Watkins BSc PhD, Qualified Person Pharmacovigilance (QPPV)

STD Pharmaceutical Products Ltd., Plough Lane, Hereford, HR4 0EL, UK

2. List of abbreviations:

AASV – anterior accessory vein
AE – adverse event
BMI – body mass index
CVA – cerebrovascular accident
CT - computerized tomography
DVT – deep vein thrombosis
ETA - endovenous thermal ablation
GSV – Great saphenous vein
IQR – interquartile range
NICE – National Institute Clinical Excellence
NHS – National Health Service
PFO – patent foramen ovale
PMA – post marketing authorisation
SAE – serious adverse event
SmPC – Summary product characteristics
SSV – small saphenous vein
TIA – transient ischaemic attack
UGFS – ultrasound guided foam sclerotherapy
VV – varicose veins

3. Investigators:

Chief Clinical Investigator (UK)

Professor Andrew W. Bradbury BSc MB ChB (Hons) MD MBA FEBVS FRCSEd FRCSEng

Sampson Gamgee Professor of Vascular Surgery, University of Birmingham, UK and

Consultant Vascular and Endovascular Surgeon, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

Address for correspondence: University Department of Vascular Surgery, Netherwood House, Solihull Hospital, Lode Lane, Solihull, B91 2JL, UK.

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Mr Huw Davies BSc (Hons), MBBS, FRCS (Vasc), MD

Address for correspondence: University Department of Vascular Surgery, Netherwood House, Solihull Hospital, Lode Lane, Solihull, B91 2JL, UK.

Chief Scientific Investigators

Mr Bruce Gardiner BSc, Managing Director

Dr Mike Watkins BSc PhD, Qualified Person Pharmacovigilance (QPPV)

STD Pharmaceutical Products Ltd., Plough Lane, Hereford, HR4 0EL, UK

Collaborating centres:

A list of all collaborating centres and investigators will be made available upon request.

4. Other responsible parties

Not applicable

5. Milestones:

	Planned	Actual	Comments
Date of registration in EU PAS	NA	19 December 2014	
Start of data collection	01 January 2015	01 January 2015	
End of data collection	31December 2017	31 December 2019	Study was extended to collect >10,000 leg treatments
Date of final report	02 April 2018	18/12/2020	As above

6. Rationale and background:

Across Europe, patients with lower limb varicose veins (VV) were increasingly being treated without surgery. In the UK, the National Institute of Clinical and Health Excellence (NICE) had recommended endothermal ablation (ETA) and ultrasound-guided foam sclerotherapy (UGFS) in preference to surgery for the treatment of VV.

(http://www.nice.org.uk/Guidance/QS67)

(http://www.nice.org.uk/guidance/CG168).

Randomised controlled trials and observational studies had indicated that the incidence of procedure-related neurological adverse events (AE) (including visual disturbance, migraine, transient ischaemic attack (TIA) and stroke) following UGFS was low [Beckitt et al 2011, Bradbury et al 2010, Coleridge-Smith 2006, Guex 2005, Jia et al 2007].

However, their exact incidence and cause had not yet been defined [Parsi 2012, Adatia et al 2013, Asbjornsan et al 2012, Willenburg 2013].

Fibrovein 3% and 1% were granted a UK license for the treatment of varicose veins by means of UGFS in 2012 as part of DCP (UK/H/2775/001-4/DC).

One of the post approval commitments was to perform a voluntary non-interventional PASS to assess the frequency and nature of procedure-related neurological AE.

Nested within this study was a drug utilisation study to examine the “real world” use of Fibrovein for UGFS.

Data on AE was collected in accordance with post-marketing pharmacovigilance requirements.

7. Research question and objectives:

Research Questions:

1. What was the incidence, type, severity, duration, treatment (where required), and clinical outcome of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam?
2. To what extent, if any, were these procedure-related neurological AE associated with identifiable patient and treatment characteristics?
3. Post-marketing authorisation (PMA), how is UGFS with Fibrovein 3% and 1% being used in the “real world” to treat lower limb VVs (nested drug utilisation study)?

Objectives

To:

1. Define the incidence of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam
2. Further characterise these AE in terms of type, severity, duration, treatment (where required), and clinical outcome

3. To describe the relationship, if any, between procedure related neurological AE and identifiable patient and treatment characteristics
4. Describe the PMA "real world" use Fibrovein 3% and 1% foam for the treatment of lower limb VVs (nested drug utilisation study)

8. Amendments and updates to the protocol:

Italy amended the protocol for local use to include thrombotic events on proforma 1.

9. Research methods:

9.1 Study design:

This was a non-interventional prospective, multicentre, PASS [as defined by Directive 2001/83/EC (DIR) Art 1(15)] of patients undergoing UGFS for lower limb varicose veins with a nested drug utilisation study.

9.2. Setting:

Place: public and private hospitals in the UK, France

Data collection period: 1 January 2015 to 31 January 2020

9.3. Subjects:

Persons: non-pregnant, non breast-feeding, patients aged 18 years or over, undergoing Fibrovein UGFS for lower limb varicose veins

Inclusion criteria: all non-pregnant, non-breast-feeding patients aged 18 years or over, undergoing Fibrovein UGFS (either alone or in combination with another modality such as endothermal ablation) for varicose veins

Exclusion criteria: patient under 18 years of age; not undergoing Fibrovein UGFS as part of their varicose veins' treatment; pregnancy, breast-feeding

Sampling: none, all suitable patients to be included

9.4. Variables:

Outcome of interest: procedure-related neurological AE

Exposures: 1% and/or 3% Fibrovein used as foam

Patient variables:

1. Age
2. Gender
3. Height, weight, and body mass index (BMI)
4. Primary versus recurrent VV
5. Co-existing deep venous disease / history of deep vein thrombosis (DVT)
6. CEAP clinical grade (C1-C6)
7. Type of VV: great saphenous vein (GSV), small saphenous vein (SSV), and anterior accessory saphenous vein (AASV), tributary veins
8. History of migraine / transient ischaemic Attack (TIA) / stroke / diabetes mellitus (DM) / hypertension (high blood pressure, BP)
9. Smoking status
10. Known to have a patent foramen ovale (PFO) (symptomatic or asymptomatic)
11. Previous Fibrovein UGFS

Treatment variables:

1. Unilateral vs. bilateral
2. Method of preparation of Fibrovein foam
3. Concentration of Fibrovein used
4. Fibrovein to gas ratio
5. Gas used: air vs. physiological gases (O_2/CO_2)
6. Volume of each concentration of Fibrovein used
7. Number of injection sites
8. Aliquot size (volume of foam injected at each injection site)
9. Concomitant surgical and non-surgical treatments for VV
10. Compression regime and duration following UGFS

9.5. Data sources:

The occurrence (and if present the type, severity, duration, treatment [where required], and clinical outcome) or absence of procedure-related neurological AE associated with Fibrovein UGFS for lower limb VV, together with patient and treatment characteristics, was collected using Fibrovein PASS Proforma 1 (Appendix 1) at the end of each UGFS treatment session.

Each separate leg treated with UGFS generated a separate proforma.

In patients undergoing bilateral treatment a Fibrovein PASS Proforma 1 was completed for each leg.

UGFS was used either as the sole treatment for the patient's VV or in combination with another treatment modality.

In keeping with post-marketing pharmacovigilance (PV) requirements, in addition to completing Fibrovein PASS Proforma 1, co-investigators were asked to contact the UK co-ordinating centre should a serious adverse event (SAE) occur at the time of the UGFS or if they become aware that a SAE has occurred subsequently. SAE details were recorded on Fibrovein PASS Proforma 2 (Appendix 2).

SAE were defined by the UK Medicines and Healthcare Products Regulatory Agency (MRHA) (www.mhra.gov.uk) as those which:

- Result in death
- Are immediately life threatening
- Require in-patient hospitalisation or prolongation of existing hospitalisation
- Result in persistent of significant disability / incapacity or substantial disruption of the ability to conduct normal life functions
- Result in a congenital abnormality or birth defect
- Represent an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Co-investigators were provided with instructions on how to complete the Fibrovein PASS Proformas 1 and 2 and telephone help was available during normal office hours from the UK Co-ordinating Centre.

9.6. Bias:

No sources of bias were expected.

9.7. Study size:

A review of the literature indicated that procedure-related neurological AE in patients undergoing Fibrovein UGFS for varicose veins are either rare (< 1:1,000) or very rare (1:1,000-10,000).

Statistical advice was, therefore, sought regarding the sample size required to define, within reasonable confidence intervals, the prevalence of such AE.

A procedure-related neurological AE event rate of 0.3% equates to the observation of 30 such AE in association with 10,000 UGFS treatment sessions.

However, there was a 50% chance of observing > 30 such AE, and binomial theorem indicates that there was a 20% chance of observing > 35 such AE, in association with 10,000 UGFS treatments.

There was, therefore, an 80% chance (similar to 80% power) of observing < 35 such AE in association with 10,000 UGFS treatments.

If 35 such AEs were observed in association with 10,000 UGFS treatments, the 95% confidence intervals would range from 0.24% to 0.49%.

This provided significant (P<0.05) evidence that the rate was less than 0.5%.

In other words, if the incidence of procedure-related neurological AE in association with UGFS was 0.35%, a sample size of 10,000 treatment sessions would provide the study with an 80% chance (power) of showing that the rate was significantly below 0.5% at the 5% significance level.

9.8. Data transformation:

Each completed Fibrovein PASS Proforma 1 was transmitted to the UK Co-ordinating Centre where non-patient identifiable data was held confidentially and entered into a password-protected computerised database for later analysis. The data was analysed from the spreadsheet without being transformed.

9.9 Statistical methods

9.9.1 Main summary measures

The dataset was cleaned and deduplicated. The total number of legs treated was assigned to treatment sessions comprising single leg and bilateral treatment sessions. This dataset served as the master whole dataset (n=8,056) which was further subdivided into sessions with adverse events (n=46) and sessions without adverse events (n=8,010). Continuous variables were presented as median and interquartile range. Categorical variables were presented as counts and percentages.

9.9.2 Main statistical methods

The patients with and without adverse events were compared using two tailed t-tests for continuous data and Pearson's chi-squared test for categorical variables. Odds ratios and 95% confidence intervals were calculated for potential risk factors for an adverse event from the patient's previous medical histories and volumes of sclerosing foam used.

9.9.3 Missing values

Missing values from the submitted proformas were coded so that they were easily identifiable in the whole dataset. The number of missing data points was 16,348 out of a total of 482,878 data points (47 variables, 10,274 legs treated) which is 3.39% of the total. The mean percentage of missing data of the whole dataset was 4.32% (4.32% for the group without adverse events and 1.49% for the group with adverse events). The largest proportion of missing data was the height and weight (and therefore body mass index) and possibly reflects the clinical practice of many clinics not routinely performing these measures for out patient treatments; a high BMI is a known risk factor for the development of varicose veins but not the development of neurological adverse events in relation to sclerotherapy. If this data is removed, the mean percentage of missing data in the whole dataset was 1.65%.

9.9.4 Sensitivity analyses

Sensitivity analysis was not undertaken for this non-interventional PASS.

9.9.5 Amendments to the statistical analysis plan

No amendments were made to the statistical analysis plan

9.10. Quality control:

Data was collected on standardised proformas.

Participating centres were provided with instructions to ensure uniformity of data entry to the questionnaire. Telephone support was provided during normal office hours.

Questionnaires were verified for completeness by analysing centre.

The entry of non-patient-identifiable data to a password protected computerised database and analysis of collated data was performed by suitably qualified individuals to ensure validity of results and reporting of trial findings.

10. Results:

10.1. Participants:

Data was collected on non-pregnant, non-breastfeeding, patients aged 18 years or over, undergoing ultrasound guided foam sclerotherapy for lower limb varicose veins with Fibrovein 3% and Fibrovein 1%.

All eligible patients were included.

Data was collected for 8,056 treatment sessions during which 10,274 legs were treated.

There were 5,838 unilateral leg treatment sessions and 2,218 bilateral treatment sessions.

10.2. Descriptive data:

Tables below describe patient demographics, relevant medical history and treatment characteristics.

The data are presented as either:

- the median, (interquartile range), number of sessions with data for that variable.
- or number of patients, (percentage of data set), number of sessions with data for that variable.

Patient Demographics	**Whole dataset.** **Sessions = 8,056**
Variable	**n = number with data**
Age – median (IQR)	56 (46, 67), n=7,757
Female, n (%)	5,261 (66.2%), n=7,947
Male, n (%)	2,686 (33.8%), n=7,947
BMI – median (IQR)	26.8 (23.7, 30.9), n=4,550
Past Medical History (Risk Factors)	
Migraine, n (%)	569 (7.1%), n=8,056
Migraine with aura, n (%)	207 (2.6%), n=8,056
Transient Ischaemic Attack (TIA), n (%)	70 (0.9%), n=8,056
Stroke, n (%)	47 (0.6%), n=8,056
Smoker, n (%)	392 (4.9%), n=8,056
Diabetes mellitus, n (%)	343 (4.3%), n=8,056
Hypertension, n (%)	1,081 (13.4%), n=8,056
Deep Vein Thrombosis, either leg, n (%)	195 (2.4%), n=8,056
DVT same leg, n (%)	88 (1.1%), n=8,056
Known Patent Foramen Ovale (PFO), n (%)	5 (0.06%), n=8,056
Known symptomatic PFO, n (%)	1 (0.01%), n=8,056

Treated patients were relatively young with typical demographics and past medical history. Twice as many women were treated as men which is discussed in more detail in section 10.5.

Leg treated, n (%)	n=6,926 (100%)
Right	2,416 (34.9%)
Left	2,292 (33.1%)
Bilateral	2,218 (32.0%)

Treatment sessions were evenly split between the left leg, right leg and both legs.

***CEAP classification,* n (%)**	n=7,873 (100%)
1	272 (3.5%)
2	4,806 (61.0%)
3	766 (9.7%)
4	1,298 (16.5%)
5	371 (4.7%)
6	360 (4.6%)
Normal deep veins, n (%)	7,234 (96.5%), n=7,495

The majority treated patients had a CEAP clinical grade 2 (visible varicose veins) or 4 (skin changes). See also section 10.5.

Treatment, n (%)	n=7,723 (100%)
Foam only (UGFS)	4,077 (52.8%)
UGFS & endovenous laser ablation	2,930 (37.9%)
UGFS & radiofrequency ablation	523 (6.8%)
UGFS & other treatment	128 (1.7%)
UGFS & liquid sclerotherapy	56 (0.7%)
UGFS and phlebectomy	9 (0.1%)

UGFS was the only treatment modality in 52.8% of cases with another 44.7% also having endothermal ablation (laser & RFA).

Veins treated, n (%)	
Primary veins	n=9,198 (100%)
GSV above knee	3,713 (40.4%)
GSV below knee	2,417 (26.3%)
SSV	981 (10.7%)
Anterior Accessory Saphenous vein	1,040 (11.3%)
Above knee perforator	212 (2.3%)
Below knee perforator	835 (9.1%)
Recurrent veins	n=2,598 (100%)
GSV above knee	867 (33.4%)
GSV below knee	767 (29.5%)
SSV	381 (14.7%)
Anterior Accessory Saphenous vein	246 (9.5%)
Above knee perforator	101 (3.9%)
Below knee perforator	236 (9.1%)

In total 11,796 veins were treated as more than one vein type can be treated in a single treatment session. Veins treated were primary in 78% and recurrent in 22% of cases. The above and below knee GSV accounted for 66.7% and 62.9% primary and recurrent veins treated respectively.

Foam Preparation Technique, n (%)	n=8,008 (100%)
Tessari	5,404 (67.5%)
Tessari and 5 micron filter	2,064 (25.8%)
Double syringe	429 (5.4%)
Steriven	15 (0.2%)
Easyfoam	8 (0.1%)
Other	88 (1.1%)

The Tessari technique used in 95.3% of sessions with the addition of a 5-micron filter in 25.8% of cases. The double syringe method uses a straight connector rather than a three way tap and this was used in 5.4% of sessions.

Liquid to gas ratio, n (%)	n=7,850 (100%)
1:2	290 (3.7%)
1:3	1,435 (18.3%)
1:4	6,084 (77.5%)
1:5	41 (0.5%)

The gas:liquid ratio was concordant with the SmPC recommendations (1:3 or 1:4) in 95.8% of treatments.

Gas type, n (%)	n=7,918 (100%)
Air	7,487 (94.6%)
O_2/CO_2	431 (5.4%)

Air was used to make the foam in 94.6% of treatments with a physiological gas mixture (O_2/CO_2) being used for 5.4% of treatments.

Foam volume	n=7,687
Foam volume 3% – median (IQR)	8ml (4, 12) n=3,244
Foam volume 1% – median (IQR)	6ml (4, 10) n=5,838
Total foam volume per session – median (IQR)	8ml (5, 12) n=7,687
Max volume in a session	112ml

The median volume of foam injected is concordant with the SmPC recommendations (16ml maximum) however there were higher than recommended doses in some cases which is discussed in section 10.5.

Compression	n=7,925 (100%)
None	69 (0.9%)
Bandage	629 (7.9%)
Stocking	4,834 (55.3%)
Bandage & Stocking	2,843 (35.9%)

Compression was applied post treatment in 99.1% of cases.

10.3. Outcome data:

There were 46 adverse reactions reported following the treatment of 10,274 legs in 8,056 treatment sessions with foam sclerotherapy. The adverse reactions details are in section 10.6.

Here the data is presented as a summary and the adverse reactions have been grouped into similar events.

The adverse reactions are grouped as follows: migraine and/or headaches only, migraine and/or headaches plus a visual disturbance or scotoma, visual disturbance or scotoma only and other adverse reactions.

Patients experiencing migraine, migraine with aura, and/or headache								
Case ref	**History Migraine**	**History Aura**	**Known TIA**	**History PFO**	**Gas used**	**Volume foam**	**No. inj'n sites**	**Adverse reaction**
SADR-255	Y	N	N	N	Air	10ml	7	Migraine/aura
SADR-271	Y	Y	N	N	Air	20ml*	5	Migraine
SADR-273	N	N	N	N	Air	8ml	1	Headache
SADR-276	N	N	Y	N	Air	10ml	2	Headache
SADR-279	Y	Y	Stroke	Y	O_2/CO_2	52ml*	10	Mig'/Hed'
SADR-284	N	N	N	N	Air	4ml	1	Migraine/aura
SADR-291	Y	Y	N	N	O_2/CO_2	28ml*	7	Headache
SADR-293	Y	Y	N	N	Air	4ml	1	Migraine
SADR-300	Y	N	N	N	O_2/CO_2	32ml*	10	Migraine
SADR-312	Y	N	N	N	O_2/CO_2	6ml	8	Headache
SADR-316	Y	Y	N	N	Air	8ml	4	Migraine
SADR-328	Y	N	N	N	O_2/CO_2	32ml*	10	Migraine
SADR-338	Y	Y	N	N	O_2/CO_2	52ml*	33	Headache
SADR-350	N	N	N	N	Air	4ml	1	Headache
SADR-352	Y	Y	N	N	Air	8ml	2	Migraine
SADR-376	Y	Y	N	N	Air	10ml	4	Migraine
** more than the maximum recommended (SmPC) volume of 16ml of foam was administered* *Bilateral treatment SADR-312 and SADR-338*								
Migraine/headache only in 16/8,056 = 0.2% (1 in 500) for all cases. Migraine/headache only in 10/8,056 = 0.12% (1 in 833) for volume within SmPC recommendations								
History of migraine in 12/16 = 75% for all cases History of migraine in 6/10 = 60% for volume within SmPC recommendations								
Volume foam exceeding SmPC recommendations 6/16 = 37.5%								

Patients experiencing migraine and/or headache plus visual disturbance/scotoma								
Case ref	**History Migraine**	**History Aura**	**Known TIA**	**History PFO**	**Gas used**	**Volume foam**	**No. inj'n sites**	**Adverse reaction**
SADR-219	Y	Y	N	N	Air	12ml	6	Migraine Scotoma
SADR-222	Y	Y	N	N	Air	10ml	4	Headache Visual dis'
SADR-295	N	N	N	N	Air	10ml	3	Migraine Scotoma
SADR-308	Y	Y	N	N	Air	5ml	5	Migraine Scotoma
SADR-327	Y	Y	N	N	Air	8ml	3	Migraine Scotoma
SADR-330	Y	Y	N	N	Air	6ml	2	Migraine Visual dis'
SADR-331	Y	Y	N	N	Air	4ml	1	Migraine Visual dis'
SADR-332	Y	Y	N	N	Air	8ml	3	Migraine Visual dis'
SADR-363	Y	-	N	N	Air	15ml	8	Migraine Scotoma
SADR-364	Y	Y	N	N	Air	10ml	3	Migraine Scotoma
Bilateral treatments SADR-330 and SADR-364								
Migraine and a visual disturbance in 10/8,056 = 0.12% (1 in 833)								
History of migraine 9/10 = 90.0%								

Of the 26 patients undergoing UGFS with any volume of foam who experienced a migraine/headache with or without a visual disturbance 21 (80.8%) had a history of migraine.

Of the 20 patients undergoing UGFS with the volume of foam in accordance with the SmPC and who experienced a migraine/headache with or without a visual disturbance 14 (70%) had a history of migraine.

Patients experiencing visual disturbance or scotoma only								
Case ref	**History Migraine**	**History Aura**	**Known TIA**	**History PFO**	**Gas used**	**Volume foam**	**No. inj'n sites**	**Adverse reaction**
SADR-278	N	N	Y	N	Air	14ml	4	Flashing lights
SADR-283	N	N	N	N	Air ?	10ml	2	Scotoma
SADR-287	Y	Y	N	N	Air	8ml	2	Visual dis'
SADR-288	N	N	N	N	Air	12ml	3	Blurred vision
SADR-334	Y	Y	N	N	O_2/CO_2	36ml*	12	Scotoma
SADR-336	N	N	N	N	Air	3ml	1	Visual dis'
SADR-337	N	N	N	N	O_2/CO_2	28ml*	16	Scotoma
SADR-340	Y	Y	N	N	O_2/CO_2	32ml*	13	Scotoma
SADR-341	N	N	N	N	O_2/CO_2	32ml*	17	Visual dis'
SADR-342	Y	Y	N	N	Air	10ml	4	Scotoma
SADR-358	N	N	N	N	Air	12.5ml	4	Scotoma
SADR-395	N	N	N	N	Air	8ml	2	Flashing lights
** more than the maximum recommended (SmPC) volume of 16ml of foam was administered* *Bilateral treatments SADR-287, SADR-334, SADR-337 and SADR-395*								
Visual disturbance alone occurred in 12/8,056 = 0.15% (1 in 667) of patients undergoing UGFS with any volume of foam. Visual disturbance alone occurred in 8/8,056 = 0.10% (1 in 1000) of patients who received a volume of foam that was concordant with the SmPC recommendations.								
A history of migraine was present in 4/12 = 33.3% patients undergoing UGFS with any volume of foam. History of migraine is 2/8 = 25% of patients who received a volume of foam that was concordant with the SmPC recommendations.								
Volume foam exceeding SmPC recommendations 4/12 = 33.3%								

Patients experiencing other adverse reactions								
Case ref	**History Migraine**	**History Aura**	**Known TIA**	**History PFO**	**Gas used**	**Volume foam**	**No Inj's**	**Adverse reaction**
SADR-221[#]	-	-	-	-	Air	10ml	3	CVA/weakness
SADR-379[#]	-	-	-	-	Air	32ml*	12	CVA
SADR-349[#]	Y	Y	-	-	Air	8ml	2	TIA
SADR-254	headache	-	-	-	Air	2ml	2	Right arm weakness
SADR-277[#]	-	-	-	-	Air	12	2	Anaphylaxis
SADR-282	Y	Y	-	-	O_2/CO_2	48ml*	12	Hyper ventil'n Carpo-pedal spasm
SADR-302[#]	-	-	-	-	Air	6ml	1	Vasovagal syncope, loss consciousness
SADR-396	-	-	-	-	Air	5	4	Feeling faint & nauseous
[#] *serious cases (CVA = cerebrovascular accident. TIA = transient ischaemic attack)* ** more than the maximum dose of 16ml of foam was administered* *Both legs treated SADR-282 and SADR-379*								

Patients with a history of migraine (n=27) made up 58.7% of the total adverse events. The incidence of patients with a history of migraine was 9.7% in the whole data set.

Patients who received more than the SmPC recommended volume of foam who experienced an adverse event was 12/46 = 26.1%, however ten of the twelve also had a history of migraine.

What the results suggest is that when volumes of foam in excess of the SmPC recommendations are administered to patients with a history of migraine an adverse event is more likely than if recommended foam volumes are used. Of the patients experiencing a migraine/headache approximately one third had received a much higher than recommended volume of foam

10.4. Main results:

The table below compares the patient demographics and past medical history of patients who did and did not experience an adverse event. The statistical significance was calculated using two tailed t-tests for continuous data and Pearson's chi-squared test for categorical variables.

Statistical analysis was also performed on the other variables as presented in the tables in section 10.2 e.g. CEAP classification, treatment type, vein treated etc. The only variable suggesting a significant difference between patients who did and did not experience and adverse event was the volume of foam injected and this is analysed further below.

Patient Demographics – comparing no adverse event to patients experiencing an adverse event			
Variable	**No AE n=8,010**	**With AE n=46**	**p-value**
Age – median (IQR)	56 (46, 66) n=7,713	54 (46, 59.3) n=44	0.170
Female, n (%)	5,231 (66.2%) n=7,901	30 (65%) n=46	0.890
Male, n (%)	2,670 (33.8%) n=7,901	16 (35%) n=46	0.890
BMI – median (IQR)	26.8 (23.7, 30.9) n=4,158	26.9 (23.4, 30.3), n=32	0.537
Past Medical History			
Migraine, n (%)	543 (6.8%), n=8,010	26 (56. 5%), n=46	<0.0001
Migraine with aura, n (%)	186 (2.3%), n=8,010	21 (45.7%), n=46	<0.0001
Transient Ischaemic Attack (TIA), n (%)	68 (0.3%), n=8,010	2 (4.3%), n=46	0.011
Stroke, n (%)	47 (0.6%), n=8,010	0 (0%), n=46	0.602
Smoker, n (%)	392 (4.9%), n=8,010	0 (0%), n=46	0.124
Diabetic, n (%)	342 (4.3%), n=8,010	1 (2.2%), n=46	0.483
High Blood Pressure, n (%)	1,076 (13.4%), n=8,010	5 (10.9%), n=46	0.611
Deep Vein Thrombosis, n (%)	194 (2.4%), n=8,010	1 (2.2%), n=46	0.913
DVT same leg, n (%)	88 (1.1%), n=8,010	0 (0%), n=46	0.487
Known Patent Foramen Ovale, n (%)	5 (0.06%), n=8,010	0 (0%), n=46	0.865
Symptomatic PFO, n (%)	1 (0.01%), n=8,010	0 (0%), n=46	0.940

The results show that a history of migraine with or without aura ($p < 0.0001$) and TIA ($p = 0.011$) are significantly associated with the occurrence of an adverse event.

The table below shows that a history of migraine and TIA and the use of foam in excess of the SmPC recommendations, are associated with a greatly increased chance (odds ratio) of an adverse event.

Variable	Odds Ratio	Upper 95% CI	Lower 95% CI	p-value
History of migrane	17.92	32.32	9.94	0.000000
History of migraine/aura	35.33	64.26	19.43	0.000000
History of TIA	5.31	22.34	1.26	0.022615
Foam volume over 16ml	3.77	7.46	1.91	0.000154

There were twelve cases of an AE after volumes of foam in excess of SmPC recommendations was administered however ten of the patients also had a history of migraine. The data indicates that a high volume of foam alone is less of a predictor but high volumes in patients with a history of migraine is a very strong predictor of an adverse event.

10.5. Other analyses:

Outcomes have been anonymously analysed by centres.

The table below shows foam volume injected analysed by centre, divided into UK NHS Trust, UK private vein clinic and French centres.

Centre	Centre type	No. sessions n = 8,056	Median volume (IQR)	Min' volume	Max' volume	Sessions with data
A	Private	3,641 (45.2%)	7 (4, 10)	0.5	40	3,396
B	NHS	2,079 (25.8%)	12 (8, 14)	1	42	2,029
C	France	533 (6.6%)	5 (3, 7.5)	0.5	20	498
D	NHS	499 (6.2%)	8 (6, 12)	2	32	499
E	Private	430 (5.3%)	28 (18, 36)	1	112	402
F	NHS	176 (2.2%)	14 (10, 18)	2	21	172
G	France	139 (1.7%)	3 (2, 4)	2	9	138
H	NHS	100 (1.2%)	10 (8, 12)	4	16	99
I	NHS	82 (1.0%)	10 (5.75, 10)	4	15	82
J	France	77 (1.0%)	5 (3, 7.5)	2.5	13	77
K	NHS	69 (0.9%)	10 (7.5, 12.5)	2	15	68
L	NHS	53 (0.7%)	8 (8, 10)	4	12	53
M	NHS	32 (0.4%)	10 (7.5, 12.5)	2	20	31
N	NHS	29 (0.4%)	12 (5.4, 16)	4	33	28
O	Private	26 (0.3%)	10 (10, 13)	1	16	26
P	NHS	24 (0.3%)	15 (9, 18)	4	22	23
Q	NHS	21 (0.3%)	6 (5, 8)	3	12	21
R	France	21 (0.3%)	3 (3, 3)	2	8	21
S	NHS	16 (0.2%)	10 (7, 10)	2	16	15
T	NHS	7 (0.1%)	12 (8, 12)	8	12	7
U	NHS	1 (0.0%)	2 (NA)	2	2	1
V	NHS	1 (0.0%)	6 (NA)	6	6	1

The data was then subdivided to look at which centres exceeded the recommended SmPC maximum volume of foam (16ml) and to see what volumes were used in those sessions.

Centre	Type	Total number sessions	Sessions over max dose, %	Median volume over max'	Max dose ml
E	Private	430	303 (70.5%)	32 (24, 40)	112
B	NHS	2079	134 (6.4%)	18 (18, 20)	42
A	Private	3641	90 (2.5%	20 (18, 20)	40
F	NHS	176	61 (34.7%)	20 (18, 20)	21
P	NHS	24	9 (37.5%)	20 (18, 20)	22
N	NHS	29	6 (20.7%)	20.5 (17.8, 23.3)	33
D	NHS	499	4 (0.8%)	24 (23, 26)	32
C	FR	533	2 (0.4%)	18.5 (17.8, 19.3)	20
M	NHS	32	1 (3.1%)	20 (20, 20)	20

There were 610 sessions (7.6%) where more than the SmPC recommended maximum dose was administered.

Only centre 'E' used foam volumes in excess of 16ml in morethan half of their treatment sessions. There were 90 sessions where over 40ml of foam was injected. Centre E accounts for eleven (24%) of the total reported adverse events. In ten of the eleven sessions where there was an adverse event the foam volume was 28-52ml.

CEAP classification by centre type.

The table below shows the CEAP clinical grade of varicose veins being treated by centre type.

CEAP classification, **n (%)**	**NHS n=3130**	**Private clinic n=3975**	**France n=767**
1	41 (1.3%)	229 (5.8%)	0 (0.0%)
2	1,253 (40.0%)	3,082 (77.5%)	472 (61.5%)
3	445 (14.2%)	278 (7.0%)	43 (5.6%)
4	776 (24.8%)	339 (8.5%)	183 (23.9%)
5	300 (9.6%)	38 (1.0%)	33 (4.3%)
6	315 (10.1%)	9 (0.2%)	36 (4.7%)
Average CEAP	3.32	2.22	2.85
missing data	n=59	n=122	n=3

The results indicate that the level of venous disease treated is quite different for each centre type. In the NHS patients 44.5% of patients treated are C4-6 (C4 = skin changes, C5 = healed ulcer, C6 = open ulcer) whereas in the private vein clinics patients with C4-6 only make up 9.7% of the treatments. The majority of the patients treated privately (77.5%) are C2 (C2 = visible varicose veins). The French clinics fall somewhere between the NHS and private UK clinics 61.5% of patients were C2 but patients with CEAP 4-6 make up 32.9% of treatments.

This is what we would expect based on personal knowledge. Vein treatments in the NHS are 'rationed' by funding and many Trusts don't treat patients until they have advanced venous disease e.g. C4-6. In the private clinics the patients being treated earlier before the venous disease progresses because they have access to treatment.

In France patients tend to be treated sooner which is reflected in the results. Comparatively more patients are treated when they have visible varicose veins, but the clinic load is also made up of about one third of patients with advanced venous disease.

The table below further analyses the CEAP clinical grade by centre type and gender.

Centre type CEAP	NHS Ave' (n=data, n=missing)	Private clinic Ave' (n=data, n=missing)	France Ave' (n=data, n=missing)
Male	3.62 (1,333, 21)	2.42 (1,037, 25)	3.02 (270, 0)
Female	3.09 (1767, 38)	2.15 (2874, 90)	2.76 (490, 2)

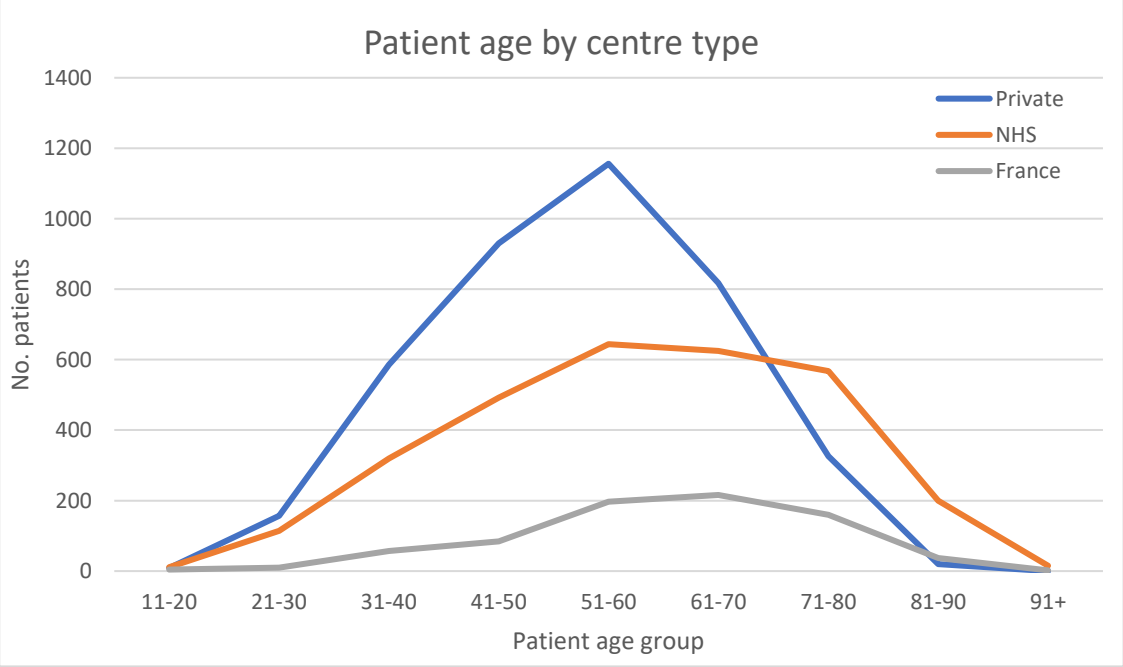
The data suggests patients being treated in the private clinics have less advanced venous disease and women seek treatment earlier than men.

Age of patient by centre type.

The table below analyses the ages of patients treated in each centre.

Centre type	Average age	min	max	n =	missing n=
NHS	58.5	17	98	2,989	200
Private	52.7	16	89	4,001	96
France	60.9	14	94	767	3

The data was also analysed by age group to see the age range treated for each centre.



Age	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91+
NHS	11	114	320	492	644	625	568	200	15
Private	9	157	586	930	1156	817	326	20	0
France	4	10	57	84	197	216	160	37	2

The results show that patients treated in the private clinics are generally younger than those treated in the NHS and French centres.

Patient gender by centre type

The table below analyses the data by centre type and gender.

Centre type	Male	Female	missing data n=
NHS	1,354 (42.8%)	1,805 (57.2%)	71
Private	1,062 (26.4%)	2,964 (73.6%)	30
France	270 (35.4%)	492 (64.6%)	8

The data indicates that more women than men are treated in the UK private clinics and French centres. In the NHS there is less of a difference.

10.6. Adverse events and adverse reactions:

System Organ Class				
MedDRA PT		**Serious**	**Non-serious**	**Total**
Immune system disorders		**1**	**0**	**1**
	Anaphylactic reaction	1		1
Metabolism and nutrition disorders		**0**	**1**	**1**
	Tetany		1	1
Nervous system disorders		**6**	**42**	**48**
	Cerebrovascular accident	2		2
	Dizziness		1	1
	Headache		9	9
	Hypoaesthesia	1	1	2
	Migraine		16	16
	Migraine with aura		2	2
	Migraine without aura		1	1
	Monoplegia	1		1
	Scotoma		1	1
	Syncope	1		1
	Transient ischaemic attack	1		1
	Visual field defect		11	11
Eye disorders		**0**	**10**	**10**
	Photopsia		2	2

	Vision blurred		1	1
	Visual impairment		7	7
Respiratory, thoracic and mediastinal disorders		**0**	**1**	**1**
	Hyperventilation		1	1
Gatrointestinal disorders		**0**	**1**	**1**
	Nausea		1	1
Musculoskeletal, connective tissue and bone disorders		**1**	**2**	**3**
	Muscle twitching		1	1
	Muscular weakness	1	1	2
Injury and poisoning		**0**	**6**	**6**
	Intentional product use issue		1	1
	Product use issue		5	5
Total		**8**	**63**	**71**

11. Discussion:

11.1. Key results:

The study objectives as defined in the protocol were:

1. Define the incidence of procedure-related neurological AE in patients undergoing UGFS for lower limb VV using Fibrovein 3% and 1% foam
2. Further characterise these AE in terms of type, severity, duration, treatment (where required), and clinical outcome
3. To describe the relationship, if any, between procedure related neurological AE and identifiable patient and treatment characteristics
4. Describe the post marketing authorisation “real world” use of Fibrovein 3% and 1% foam for the treatment of lower limb VVs (nested drug utilisation study).

The study has achieved the objectives with data collected on 48 patient and treatment variables for over 8,000 treatment sessions and over 10,000 legs.

Incidence of procedure related adverse events

Looking firstly at defining the incidence of procedure related adverse events and comparing them with expected frequencies as defined in the SmPC.

There were 46 adverse events, the summary of the cases is presented in section 10.3 Outcome data.

The events with the highest frequency were migraine/headache with or without visual disturbance/aura followed by visual disturbance alone. The results are slightly confused by some patients receiving much higher doses of foam than the recommended maximum of 16ml. Here the incidence will be discussed including the high doses but also without the high doses because it is important when comparing results with the SmPC that we consider the treatments that conformed to the SmPC recommendations.

The SmPC lists the frequency for migraine and headache using foam as ‘rare’ defined as >1 in 10,000 to < 1 in 1,000 (>0.01% to <0.1%).

Visual disturbance is not listed specifically in the SmPC but scotoma, scintillating scotoma is listed with a frequency of uncommon defined as >1 in 1,000 to < 1 in 100 (>0.1% to <1%).

The tables below compare the frequency of the adverse event with the expected frequency listed in the SmPC

Adverse event	Incidence all cases	Incidence normal dose	SmPC frequency
Migraine ± aura/ visual disturbance	19/8056 = 0.24%	15/8056 = 0.19%	>0.01% to <0.1%
Headache ± visual disturbance	8/8056 = 0.099%	5/8056 = 0.062%	>0.01% to <0.1%
Scotoma + visual disturbance	NA	10/8056 = 0.12%	>0.1% to <1%
Key point - the incidence of migraine is higher than the frequency listed in the SmPC			

Looking at the other adverse events there were two cases of stroke, one TIA, one arm weakness (hemiparesis) and one allergic reaction all of which are listed as very rare (<10,000). There were two vasovagal cases which is listed as rare (>1 in 10,000 to < 1 in 1,000).

Adverse event	Incidence including high doses	Incidence normal dose	SmPC frequency
Vaso vagal e.g. fainting, confusion	NA	2/8056 = 0.025%	>0.01% to <0.1%
Allergic reaction	NA	1 in 8056	< 1 in 10,000
Weakness (hemiparesis)	NA	1 in 8056	< 1 in 10,000
Transient ischaemic attack	NA	1 in 8056	< 1 in 10,000
Stroke/CVA	2 in 8056	1 in 8056	< 1 in 10,000
Hyperventilation Carpo-pedal spasm	1 in 8056	NA	

Looking at the cases in more detail the vaso-vagal cases are within the frequencies listed in the SmPC.

There was one of each of the following adverse events, allergic reaction, weakness, transient ischaemic attack in the data set of 8,056 sessions and 10,274 legs. It is reasonable to propose that the listed frequency of very rare for these adverse events is commensurate with the data collated in this study.

The stroke cases require a more detailed discussion.

SADR-221 the patient was treated with 10ml of 1% Fibrovein foam and had no complications on the day but experienced a non-disabling cerebrovascular accident (CVA) 19 days later. He presented to A&E with left arm/hand weakness and was admitted to hospital with a non-disabling CVA. A CT scan confirmed right internal capsule infarct.

The patient recovered without sequelae and was discharged seven days later on aspirin, clopidogrel, statin and his usual antihypertensive medication. The patient's medical history included hypertension and elevated cholesterol, with no history of cardiovascular events or CVA. Concomitant medications included amlodipine andramipril, further details unspecified.

The reporting investigator felt that the foam treatment was not directly related to the event, particularly given the 19 day delay to onset.

SADR-379 - the patient was treated with 1% Fibrovein foam and 16ml was administered to each leg a total of 32ml of foam. Soon after the sclerotherapy treatment the patient experienced cerebrovascular accident.

When the stockings were being applied at the end of the procedure, the patient lost control of the left side of her body and developed facial droop. The patient did not lose consciousness completely but was drowsy and she was talking throughout. A CT scan showed air embolus in the middle cerebral artery, and the patient was transferred for hyperbaric oxygen therapy. The patient was recovering on the hyperbaric oxygen. At the time of the follow-up report, the outcome was recovered with sequelae. The patient had very slight loss of sensation in the left shoulder and face.

Looking at the stroke cases it seems likely that SADR-221 was not related to the sclerotherapy treatment. Cases reported in the literature tend to occur at the time of treatment or within 3-4 days, it therefore seems reasonable to exclude this case.

Case -379 is definitely related to the treatment, but the patient received 32mL of foam which is twice the recommended maximum.

Given the mitigating factors in the two stroke cases it is reasonable to propose that the listed frequency of very rare for a stroke remains commensurate with the data collated in this study.

Case -282 hyperventilation leading to carpo-pedal spasm.

The patient underwent ultrasound guided foam sclerotherapy (UGFS) of the great saphenous vein (recurrent) below the knee, of the right leg with Fibrovein converted to foam with O_2/CO_2 (1:3) using the Tessari preparation method. She also received Fibrovein treatment of some peripheral veins and of the labia (off label use), further details unspecified. The total number of injection sites was 12 with aliquot sizes of 3-5ml. The total volume of foam prepared was 32ml 3% and 16ml 1%. Following Fibrovein treatment, the patient developed hyperventilation which led to carpopedal spasm. An explanation of the symptoms and regularisation of her breathing resulted in rapid resolution of the event.

It was felt with this case that the patient suffered from anxiety which led to hyperventilation, this thinking is based on the fact that once the symptoms had been explained and the patients breathing was regulated there was a rapid resolution of the symptoms.

In summary the individual case data suggests the frequencies listed in the SmPC remain adequate for all of the adverse events except for migraine. The data suggests that the frequency for migraine should be changed from ‘rare’ to ‘uncommon’.

Looking at the relationship between procedure related neurological AE and identifiable patient and treatment characteristics.

The statistical analysis identified three predictors that increase the likelihood of an adverse event occurring.

A history of migraine with or without aura, higher than recommended foam volumes and TIA.

Section 4.4 of the SmPC ‘Special warnings and precautions for use’ already lists migraine the recommendations in the SmPC are as follows:

‘Previous migraine sufferers should be treated with care. Patients with previous migraine have been shown to be more likely to suffer from visual disturbances and migraine, particularly following injections with foamed sclerosant. Use smaller volumes in patients with history of migraine.’

Based on this recommendation, the warnings regarding previous migraine sufferers and the need to be careful with the volume of foam injected is adequately covered in the current SmPC.

Regarding TIA as a possible predictor of an adverse event, it is not mentioned in the SmPC. However, there were only two patients with a history of TIA who experienced an adverse event. One experienced a

headache the other experienced a visual disturbance (flashing lights). It is difficult to be certain that the adverse events were related to the patients having had a TIA previously however a special warning could be added to the SmPC.

11.2. Limitations:

The missing data was from mainly in the demographic data over all the missing data amounted to 4.6%.

Adverse events are fully reported.

11.3. Interpretation:

The results are good and compare well with results from other studies. The frequencies of the adverse events listed in the SmPC were originally calculated from published clinical series using sodium tetradecyl sulfate and the similar class active polidocanol. This study has a large data set and confirms the incidence of the neurological adverse events as being in line with what has been previously published. The incidence of migraine is slightly higher than expected but the published clinical series were not as large.

11.4. Generalisability:

The external validity of the results is good.

12. Other information:

No other information.

13. Conclusions:

The study objectives were well met and the real-world frequencies of neurological adverse events following UGFS using 3% and 1% Fibrovein has been accurately determined.

The main conclusions are that the current SmPC lists the neurological adverse events and the frequencies listed accurately reflects the frequencies of occurrence with the exception of migraine.

The recommendation is that the frequency for migraine listed in the SmPC is changed from ‘rare’ to ‘uncommon’.

A past medical history of migraine is a strong predictor for a neurological adverse event especially when larger volumes of foam are administered.

A past medical history of migraine is addressed in the current SmPC as a special warning which urges caution and to use low volumes of foam.

The recommendation is to leave the special warning as it is.

A past medical history of a TIA was a significant predictor for a neurological adverse event. The current SmPC has no warnings regarding a past medical history of TIA.

The recommendation is to add a past medical history of TIA to section 4.4 ‘Special warnings and precautions for use’ with a statement such as:

TIA

Patients with a past medical history of TIA should be treated with care.

Patients with previous TIA have been shown to be more likely to suffer from visual disturbances and migraine, particularly following injections with foamed sclerosant.

Large volumes of foam also are a strong predictor for a neurological adverse event especially where the patient has a history of migraine. Large volumes of foam on it own is not a particularly strong predictor.

Most centres treated patients stayed within the SmPC recommended volumes of foam with only 610 sessions exceeding them.

Recommendation is that the current maximum dose listed in the SmPC (16ml) is safe and should remain the same and should not be increased or decreased.

14. References.

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Appendix 1: Fibrovein PASS Proforma 1 (neurological AE)

Centre, date and patient details ***(please complete a form for each patient and each leg)***

Centre number: ☐☐ Date (dd/mmm/yy): ☐☐ / ☐☐☐ / ☐☐ Initials: ☐☐☐

Age ☐☐ M ☐ F ☐ Height (m): ☐.☐☐ Weight (kg): ☐☐☐ BMI: ☐☐.☐

Patient history ***(please tick all that apply)***

Migraine ☐ if yes, aura? ☐ TIA ☐ Stroke ☐ Smoker ☐ Diabetes ☐ High BP ☐

DVT ☐ if yes, same leg? ☐ Known PFO: ☐ if yes, is it symptomatic? ☐

Details of treatment – which leg? R ☐ L ☐ ***(please complete a separate form for each leg)***

CEAP: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐

Foam only Y ☐ N ☐ If no, what other?

RFA ☐ LASER ☐ phlebectomy ☐

liquid sclerotherapy ☐ other ☐

Vein treated	Primary	Recurrent
GSVAK	☐	☐
GSVBK	☐	☐
AASV	☐	☐
SSV	☐	☐

Deep veins normal: Y ☐ N ☐

Previous Fibrovein foam treatments:

1 ☐ 2 ☐ 3 ☐ ≥4 ☐

Preparation: Tessari ☐ Double syringe ☐

Tessari + 5 micron filter ☐

Steriven ☐ Easyfoam ☐ Other ☐

Liquid to gas ratio 1 to: 2 ☐ 3 ☐ 4 ☐ 5 ☐

Air ☐ CO_2/O_2 ☐ Other gas ☐

Total volume foam (ml) 3% ☐☐ 1% ☐☐

Number of injection sites ☐☐

Aliquot size: 2-3ml ☐ 3-5ml ☐ >5ml ☐

Compression type: Bandage ☐ Stocking ☐

Stocking compression class: 1 ☐ 2 ☐

Duration (days): Bandage☐☐ Stocking☐☐

Was there a procedure-related neurological AE? Y ☐ N ☐

If, yes please inform the UK Co-ordinating Centre and complete rest of the form

Migraine ☐ Headache ☐ Scotoma ☐ Other visual ☐ One eye ☐ Both eyes ☐

Stroke ☐ TIA ☐ Hemiparesis ☐ Language disturbances ☐ loss of consciousness ☐

Outcome: Recovered without sequelae ☐ Recovered with sequelae ☐ Recovering ☐

Not recovered ☐ Died due to the adverse event ☐ Unknown ☐

Signed: Date (dd/mmm/yy): / /

Please report SAE to the UK Co-ordinating centre WITHIN 1 WORKING DAY

+44 (0)121 424 5570 or fibroveinpass@heartofengland.nhs.uk

Appendix 2: Fibrovein PASS Proforma 2 (SAE)

Centre, date and patient details
Centre number: ☐☐ Date (dd/mmm/yy): ☐☐ / ☐☐☐ / ☐☐
Patient ID ☐☐☐☐☐☐☐☐☐☐ Initials: ☐☐☐ Age ☐☐ M ☐ F ☐
Details of SAE: patient outcome, comments & follow up taken
Treatment date: ☐☐ / ☐☐☐ / ☐☐ Date of reaction: ☐☐ / ☐☐☐ / ☐☐ Description of SAE:
Outcome: Recovered without sequelae ☐ Recovered with sequelae ☐ Recovering ☐ Not recovered ☐ Died due to the adverse event ☐ Unknown ☐
Signed: Date (dd/mmm/yy): ☐☐ / ☐☐☐ / ☐☐
Please report SAE to the UK Co-ordinating centre WITHIN 1 WORKING DAY **+44 (0)121 424 5570 or fibroveinpass@heartofengland.nhs.uk**