End of Study Summary Report

Title of Study:	An assessment of intra-lesional 3% polidocanol solution in the treatment of digital myxoid cysts
EudraCT Number:	2013-005338-39
Name of Sponsor:	University of Edinburgh & NHS Lothian (ACCORD)
Name of Finished Product:	3% Polidocanol / Aethoxysclerol
Volume:	2ml vials
Name of Active Ingredient:	3% Polidocanol / Aethoxysclerol
Investigators:	Dr SA Holme, Ms L Webster and *Dr M Mowbray
Study Centre(s):	Department of Dermatology, Lauriston Building, Lauriston Place, Edinburgh, EH3 9HA *Department of Dermatology, Queen Margaret Hospital, Dunfermline. KY12 0SU
Studied Period:	3 months
Date of First Enrolment:	23 July 2015
Date of Last Completed	10 September 2015

Objectives:

Digital myxoid cysts (DMC) arise from degeneration in the connective tissue of the digit joint, usually the last joint of the finger or toe, often due to underlying joint arthritis. They may connect with the joint. Pressure from the cyst can result in deformity of the digit's nail and trauma to the cyst results in leakage of the fluid, representing a potential source of entry for infection. Cysts can be tender and interfere with the digit's function. A variety of treatments are available, from simple extrusion which is rarely successful, to more destructive cryotherapy, infra-red coagulation and formal excision under local anaesthetic. These latter three approaches can result in considerable scarring. Sclerosant injection of polidocanol in one small non-randomised trial has been reported to be a well tolerated efficacious treatment with minimal scarring and long-term resolution. The purpose of this study was to find out whether polidocanol was an effective treatment for the management of digital myxoid cysts, and whether it was comparable to the standard treatments available for treating this condition. We also aimed to assess if polidocanol had more or less side effects than the standard treatments available.

The primary objective was to determine if there was a difference in the percentage of participants with cyst resolution at 6 weeks post treatment in those treated with polidocanol compared to those treated with the current conventional treatments of cryotherapy and infra-red coagulation.

The secondary objective was to determine in those participants treated with polidocanol compared to cryotherapy, and also compared to infra-red coagulation, if there was a difference in:

1) The percentage of participants with cyst resolution at 12 and 52 weeks post initial treatment
2) Clinically apparent scarring
3) Procedure pain/discomfort
4) Procedure satisfaction

The primary endpoint was to be the point at which cyst resolution was achieved.

The secondary endpoints were;

1) Patient were reviewed at 6, 12 and 52 weeks to assess for cyst resolution, failure to respond, or recurrence.
2) At 6, 12 and 52 weeks, the degree of any scarring was to be assessed.
3) At 6 weeks, subjects were to be asked to assess the degree of pain and discomfort experienced.
4) At 6 weeks, subject's satisfaction was to be assessed.

Methodology:

This was an open label, three treatment arm, randomised two-centre trial. Patients referred to secondary care Dermatology in Lothian and Fife with possible DMC were to be preferentially booked into clinics of one of the two study investigators. The investigators also accepted referrals from secondary care dermatology colleagues.

Once a diagnosis of DMC was made by a dermatologist, subjects were given an information sheet about the condition and study. Written consent was obtained. A consented medical photograph of the cyst was to be taken. In the situation where more than one cyst was present, only one was assessed for the purposes of the study.

Subjects were to be randomised to one of the three treatments in equal numbers using a computer generated randomisation schedule produced using random block design. This schedule was to be translated into one series of sequentially numbered envelopes containing the allocation for each participant. Subjects were to be allocated randomly to:

1. Infra-red coagulation (injection with a local anaesthetic to numb the affected skin, pricking of the cyst to allow removal of the jelly-like contents, both operator and participant put on a pair of goggles, glass tip of the coagulator was pressed against the deflated cyst and a 1.25 second flash f the infra-red light applied.)
2. Polidocanol sclerotherapy (does not require local anaesthetic. The cyst was pricked to allow removal of the jelly-like contents, 3% polidocanol was injected into the deflated cyst and a Duoderm extra-thin dressing applied).
3. Cryotherapy (The cyst was pricked to allow removal of the jelly-like contents, and the area treated with double-freeze liquid nitrogen for 2 X 30 second freeze-thaw cycles).

Number of Participants and Diagnosis:

We aimed to recruit 120 participants, over 24 months, from patients referred to dermatology in NHS Lothian or NHS Fife who had visible DMC affecting the distal phalynx of toes or fingers.

Inclusion Criteria:

All patients referred to dermatology in NHS Lothian or NHS Fife who had a visible Digital Myxoid Cyst affective the dital phalynx of the toes or fingers. The patient must have had the ability to give informed consent.

Exclusion Criteria:

History of sensitivity to polidocanol or other sclerosants, age less than 18, inability to give informed consent, inability to report side effects experienced, pregnant or breastfeeding women, cyst not clearly visible, cyst not fluid-filled.

Investigational Medicinal Product:

Polidocanol/3% Aethoxysklerol (3% Aethoxysklerol/60mg Lauromacrogol 400), solution for injection, was provided by the manufacturer/marketing authorisation holder;
Chemische Fabrik Kreussler & Co GmbH
Rheingaustr. 87-93
65203 Wiesbaden
Germany

Polidocanol was labelled and packaged for this trial by;
Investigational Supplies Group (ISG)
1 George Square
Edinburgh
EH8 9JZ
MIA(IMP) 1384, site no. 7203285

Polidocanol was stored in a locked cabinet in the dermatology outpatients minor surgery treatment area.

Dosing Regime:

A maximum of two percutaneous injections of between 0.1 and 0.3ml of 3% polidocanol; 2nd injection to be done 6-8 weeks after 1st injection if cyst still present. The volume to be injected was dependent on the size of the cyst.

Criteria for Evaluation:

Study Assessments & Data Collection

Base line epidemiological data was gathered at start of study: participant age, sex, position of DMC, size of DMC, length of time present, nail effect, symptoms, previous treatments, evidence from history of arthritis, clinical evidence of arthritis or other localised medical Patient identifiable data such as name and date of birth are not required. A unique identifier was used to identify the participant for the duration of the study, but was to be deleted from the database prior to data analysis.

Subjects were reviewed as currently standard after 6-8 weeks. The response to treatment was assessed and they were to be asked about side-effects. They were asked to score discomfort of the procedure on a visual analogue scale of 1-10. They were also asked to score satisfaction with the treatment on a visual analogue scale of 1-10. If the cyst was still present, a second treatment was offered using the same method as the original treatment.

All participants were to be reviewed again at 12-14 weeks to review response and ask about side-effects, with scoring of discomfort and satisfaction, as above, of those who have undergone a second treatment.

All participants were to be reviewed finally at about 52 weeks. If the cyst failed to resolve after two treatments, participants were to continue as they would normally if they were a non-trial patient in the event of a failure. The new treatment was to be documented, along with the reasons for that treatment and treatment result. Thus the 6 and 12 week points will not be affected by treatment failure, but the results for the 52 week point will be presented separately.

Serial medical photographs of the cysts were to be taken at weeks 0, 6, 12 and 52 to allow assessment of final clinical appearance and change from the base-line photograph. All photographs were to be undertaken by medical photography staff using standard NHS Lothian and NHS Fife consent and request forms and stored on the secure NHS medical illustrations system.

Outcomes for cysts were to be recorded as clinically completely resolved, partial response or no evident response. Scarring was to be assessed as either present or not present. Photographs were to be reviewed at the end of the study by an independent dermatologist to confirm the study assessments. Results were to be entered into a secure database overseen by the University of Edinburgh.

Statistical analysis and health economic analysis were to be conducted by appropriately trained University of Edinburgh staff.

No safety assessments were conducted in this trial.

Statistics and Data Analysis

It was planned to recruit 120 subjects, expecting an approximately 70% resolution at 6 weeks in those receiving polidocanol. With a sample size of 35 per group using a two-sided test with 80% power, 5% level of significance, we would be able to detect a statistically significant difference if the comparator had 34% resolution or less. To take into account expected dropouts, 40 subjects per group will be recruited. The proposed statistical analyses was as follows;

1. To compare the proportion of participants with cyst resolution at 6 weeks in those receiving polidocanol to infra-red and separately to cryotherapy, a binomial test for the comparison of proportions and present the difference as a proportion with a 95% confidence interval was to be used.
2. To compare the proportion of participants with cyst resolution at 12 weeks in those receiving polidocanol to infra-red and separately to cryotherapy, a binomial test for the comparison of proportions and present the difference as a proportion with a 95% confidence interval was to be used.
3. To compare the proportion of participants with cyst resolution at 52 weeks in those receiving polidocanol to infra-red and separately to cryotherapy, a binomial test for the comparison of proportions and present the difference as a proportion with a 95% confidence interval was to be used.
4. To compare the proportion of participants with clinically apparent scarring at 6, 12 and 52 weeks in those receiving polidocanol to infra-red and separately to cryotherapy, a binomial test for the comparison of proportions and present the difference as a proportion with a 95% confidence interval was to be used.
5. To compare differences in pain scores, two sample-tests or non-parametric equivalent were to be used as appropriate to compare polidocanol to infra-red and separately for polidocanol with cryotherapy.
6. To compare differences in subject satisfaction score, two sample-tests or non-parametric equivalent were to be used as appropriate to compare polidocanol to infra-red and separately for polidocanol to cryotherapy.
7. A descriptive analysis was to be presented of treatment failure and subsequent treatment/outcome. Analysis of results from 52 week time point were to be take into account treatment failure. To compare the length of time for function to return and also for pain to settle, two-sample t-test or non-parametric equivalent were to be used as appropriate to compare those treated with polidocanol with those treated with infra-red and separately for polidocanol compared to cryotherapy

Summary Results & Conclusion:

Efficacy Results

This clinical trial was halted early. Unable to assess efficacy.

Safety Results

No safety issues were encountered. Following randomisation, one participant's lesion did not extrude clear jelly when pricked. The lesion was excluded from the study as per protocol and the Chief Investigator (CI) informed the sponsor of the event. The CI excised the lesion with narrow margins under standard practice of care. Histology revealed a rare tumour which was subsequently treated with wider excision.

Conclusion

No conclusions can be drawn from this clinical trial as the study was halted early as a result of a suspected serious breach of the protocol and Good Clinical Practice (GCP), and withdrawal of sponsorship by the sponsors. The serious breach was reported to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC).

Details of the serious breach as provided below;

As a result of a routine monitoring visit from the sponsors clinical trial monitors, several issues, subsequently reported as protocol/GCP violations, were identified which combined constituted a serious breach of GCP. These fell under 3 main areas:

1) IMP accountability

Use of 'off the shelf' polidocanol and not the IMP; Due to the lack of IMP accountability we were unable to reconstruct what was given to participants which therefore has a potential to affect the validity of the study data.

2) Randomisation

Use of a randomisation procedure which did not match that described in the protocol; A randomisation schedule was not used and opened envelopes were discarded. It is therefore not possible to reconstruct the randomisation process and prove that participants were given the correct allocated treatment. This has the potential to affect the validity of the study data.

3) Trial Management and Study Data

The lack of a Trial Steering Committee (TSC), which was tasked in the protocol with reviewing safety data on a bimonthly basis; This had the potential to affect participant safety if there had been safety events for review.

In addition, the serious breach report to the MHRA included other areas of concerns raised by the sponsor clinical trials monitors around study documentation e.g. the use of case report forms and study logs.

The serious breach report triggered an inspection from the MHRA (7 & 8 December 2015). The MHRA assessed various aspects identified in serious breach GCP-15-76 reported on 23 September 15 and made the following conclusions;

There were 3 main issues identified by the sponsor following a monitoring visit: randomisation creation and procedure, Investigational Medicinal Product (IMP) accountability and trial management (including source data/case report form (CRF) data and the study file).

During the inspection the Source Data/CRF Data, consent issues, investigator site file issues and protocol deviations identified by the sponsor were verified, therefore these are not reported as findings in the report. However, issues which had not either been identified or fully identified and assessed by the sponsor are reported.

In summary, it would appear there were failings on the part of both the Chief Investigator (CI) and the sponsor. It was clear that the CI was inexperienced in Clinical Trials of Investigational Medicinal Products (CTIMP) trials (he had never conducted any CTIMPs previously within the requirements of the clinical trial regulations), and this had not been identified and mitigated for sufficiently by the sponsor. Therefore, many of the non-compliances identified may have resulted from the combination of an inexperienced investigator with a lack of oversight and support provided by the sponsor.

As a well-established sponsor for numerous CTIMP trials, ACCORD has the ability to provide mechanisms to support and provide mentoring to new CTIMP investigators in order to develop and expand good quality research. It is expected that the errors identified in this trial can help improve identification and mitigation via the risk assessment up front and that new investigators are provided with sufficient assistance either by ACCORD or an assigned CTIMP experienced mentor to ensure compliance with GCP in future trials.

No critical findings were identified in the report issued by the MHRA following the triggered inspection. There were three major findings identified in the report from the MHRA relating to Protocol Compliance, IMP Management / Pharmacy and Sponsor's Oversight of Clinical Trials of IMP. The GCP Inspection statement (04 February 2016) from the MHRA states 'The organisation has provided corrective and preventative actions in response to the inspection report. These have been reviewed by the GCP Inspectorate and are considered acceptable. This inspection can be considered closed.