Clinical trial results:
The use of topical Glyceryl Trinitrate (GTN) and eccentric exercises in the treatment of mid portion Achilles Tendinopathy: a randomised placebo controlled trial

Summary

EudraCT number	2015-005421-40
Trial protocol	IE
Global end of trial date	01 December 2018

Results information

Result version number	v1 (current)
This version publication date	28 April 2022
First version publication date	28 April 2022

Trial information

Trial identification

Sponsor protocol code	RCSI-1764

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02499484
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Royal College of Surgeons Ireland
Sponsor organisation address	111 St Stephens Green, dublin, Ireland, Dublin 2
Public contact	School of Physiotherapy, Royal College of Surgeons Ireland, 353 014022397no, sponsorship@rcsi.ie
Scientific contact	School of Physiotherapy, Royal College of Surgeons Ireland, 353 014022397no, paulkirwin@rcsi.ie

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2018
Global end of trial reached?	Yes
Global end of trial date	01 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective
The primary objective of this research is to determine if the addition of topical GTN over 24 weeks to a 12 week exercise programme improves clinical outcomes more than placebo GTN for people with Achilles Tendinopathy.

Secondary Objective

To determine at which time point (week 6, 12 or 24) changes in clinical outcomes occur in those with Achilles tendinopathy undergoing a programme of topical GTN and eccentric exercise.

To determine which baseline measures and patient specific factors can predict response to treatment (GTN and eccentric exercise)

Protection of trial subjects:

By way of a phone interview, the principal investigator informed the potential participants of the nature of the study in order to ascertain their willingness to be involved or to decline participation. Potential participants were screened for inclusion and exclusion criteria at this point. All those who declined to participate or did not fulfill the inclusion criteria received their treatment as normal in the hospital physiotherapy department. Participants that were willing to partake in the study were posted an envelope containing a Participant Information Leaflet on the nature and purpose of the study, a consent letter for review, which was then signed in the presence of the principal investigator at time of initial assessment and an appointment to attend for their initial assessment. In addition, patients could withdraw from the study at any time without providing a reason and this did not have any affect on their clinical care.

Background therapy:

N/A

Evidence for comparator:

n/a

Actual start date of recruitment	02 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 76
Worldwide total number of subjects	76
EEA total number of subjects	76

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	75
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial aimed to recruit 240 subjects (120 in each treatment arm) that presented to Connolly Hospital Physiotherapy department with Achilles tendinopathy. The original sample size was 76 and although the protocol in use at the time of recruitment stipulated that 240 patients be recruited, the investigator reverted to the original sample size (76)

Pre-assignment

Screening details:

All patients referred to Connolly Hospital Physiotherapy department with a diagnosis of Achilles tendinopathy were considered eligible for the trial (once they met eligibility criteria). A pre-screening phone interview initially took place with potential subjects & an in person screening visit followed (at hospital site).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The principal investigator performing visit assessments was fully blinded. Unblinded personnel performed the randomisation and prescribing of the investigational medicinal product for each subject. Subjects were unaware of the treatment allocation (as the Percutol and placebo tubes were not identical, they were wrapped in a covering which obscured the details). At each assessment timepoint, subjects were advised not to bring their medication so as not to unblind the investigator.

Arms

Are arms mutually exclusive?	Yes
Arm title	Glyceryl Trinitrate (GTN)

Arm description:

0.5cm Glyceryl Trinitrate to be delivered to subjects. The topical GTN to be used for the purpose of this trial was Percutol. This delivered the GTN in ointment form. Participants were instructed to measure 0.5cm of Percutol ointment by applying 0.5cm of Percutol to a paper applicator/strip, which had the amount required indicated in a circular outline, measuring approximately the same size as a pea.

Arm type	Experimental
Investigational medicinal product name	Glyceryl Trinitrate Ointment
Investigational medicinal product code	
Other name	Percutol
Pharmaceutical forms	Ointment
Routes of administration	Topical

Dosage and administration details:

Subjects applied 0.5cm of the GTN once daily (for a 12-14 hour duration per day) for a total of 24 weeks.

Arm title	Placebo Arm

Arm description:

Participants were instructed in how to measure 0.5cm of aqueous cream and applied 0.5cm of the aqueous cream to a paper applicator/strip, which had the amount required indicated in a circular outline, measuring approximately the same size as a pea.

Arm type	Placebo

Investigational medicinal product name	Aqueous Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical

Dosage and administration details:

The placebo ointment to be used in this trial was aqueous cream, contained in a 100g collapsible tube. Subjects applied this daily (for a 12-14 hour duration each day) for a total of 24 weeks.

Number of subjects in period 1	Glyceryl Trinitrate (GTN)	Placebo Arm
Started	37	39
Completed	33	33
Not completed	4	6
Lost to follow-up	4	6

Baseline characteristics

Reporting groups	
Reporting group title	Glyceryl Trinitrate (GTN)
Reporting group description:	
0.5cm Glyceryl Trinitrate to be delivered to subjects. The topical GTN to be used for the purpose of this trial was Percutol. This delivered the GTN in ointment form. Participants were instructed to measure 0.5cm of Percutol ointment by applying 0.5cm of Percutol to a paper applicator/strip, which had the amount required indicated in a circular outline, measuring approximately the same size as a pea.	
Reporting group title	Placebo Arm
Reporting group description:	
Participants were instructed in how to measure 0.5cm of aqueous cream and applied 0.5cm of the aqueous cream to a paper applicator/strip, which had the amount required indicated in a circular outline, measuring approximately the same size as a pea.	

Reporting group values	Glyceryl Trinitrate (GTN)	Placebo Arm	Total
Number of subjects	37	39	76
Age categorical			
Patients 65-84 in GTN arm			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	36	39	75
From 65-84 years	1	0	1
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	16	14	30
Male	21	25	46

End points

End points reporting groups

Reporting group title	Glyceryl Trinitrate (GTN)

Reporting group description:

0.5cm Glyceryl Trinitrate to be delivered to subjects. The topical GTN to be used for the purpose of this trial was Percutol. This delivered the GTN in ointment form. Participants were instructed to measure 0.5cm of Percutol ointment by applying 0.5cm of Percutol to a paper applicator/strip, which had the amount required indicated in a circular outline, measuring approximately the same size as a pea.

Reporting group title	Placebo Arm

Reporting group description:

Participants were instructed in how to measure 0.5cm of aqueous cream and applied 0.5cm of the aqueous cream to a paper applicator/strip, which had the amount required indicated in a circular outline, measuring approximately the same size as a pea.

Primary: Victorian Institute of Sport Assessment – Achilles

End point title	Victorian Institute of Sport Assessment – Achilles

End point description:

VISA-A was a self administered questionnaire which rated the severity of the Achilles tendon pain, function and activity. It is currently the only validated reliable tool for assessing pain and function in Achilles tendinopathy, it is the current gold standard outcome tool.

End point type	Primary

End point timeframe:

Assessed at 24 weeks

End point values	Glyceryl Trinitrate (GTN)	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: 0-100				
arithmetic mean (standard deviation)	87.1 (± 13.9)	85.1 (± 16.8)		

Statistical analyses

Statistical analysis title	Statistical analysis of primary endpoint

Statistical analysis description:

Data were entered into Excel Version 16 and imported to SPSS 26 for analysis. Linear regression was used to analyse the between-group difference in the primary outcome in order to compare the effectiveness of GTN versus placebo on Achilles symptoms as measured by the change in the primary outcome measure from baseline to 6 weeks, 12 weeks and 24 weeks.

Comparison groups	Glyceryl Trinitrate (GTN) v Placebo Arm

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.09
upper limit	9.1

Notes:

[1] - Where baseline differences existed between the two groups, baseline scores for the outcome measures were used as the covariate in the analysis, due to baseline differences between the two groups. The independent variables selected were group allocation (GTN or placebo), and the baseline outcome measure being analysed (e.g. VISA-A at baseline). The dependent variable selected was the outcome measure being analysed at week 6, 12 and 24 (e.g. VISA-A scores at week 6, 12 and 24).

Secondary: Numerical Rating Scale (NRS)

End point title	Numerical Rating Scale (NRS)

End point description:

This was a numerical rating scale (NRS) for subjects to rate their Achilles pain from zero to ten,

End point type	Secondary

End point timeframe:

assessed at 24 weeks

End point values	Glyceryl Trinitrate (GTN)	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: 0-10				
arithmetic mean (standard deviation)	3.2 (± 2.9)	2.9 (± 2.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Lower Extremity Functional Scale (LEFS)

End point title	Lower Extremity Functional Scale (LEFS)

End point description:

The LEFS is a self reported measure of functional ability in relation to their Achilles tendinopathy, which was completed by participants

End point type	Secondary

End point timeframe:

Assessment at 24 weeks

End point values	Glyceryl Trinitrate (GTN)	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: 0-80				
arithmetic mean (standard deviation)	72.9 (± 9.9)	71.9 (± 10.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Heel Raise for Endurance Test

End point title	Heel Raise for Endurance Test

End point description:

End point type	Secondary

End point timeframe:
assessment at 24 weeks

End point values	Glyceryl Trinitrate (GTN)	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: 0-100				
arithmetic mean (standard deviation)	28.1 (± 10.3)	31.6 (± 13.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hopping Test

End point title	Hopping Test

End point description:

End point type	Secondary

End point timeframe:
assessment at 24 weeks

End point values	Glyceryl Trinitrate (GTN)	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: 0-100				
arithmetic mean (standard deviation)	77.6 (± 42.8)	79.8 (± 42.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: AP Ultrasound Measure of Achilles thickness

End point title	AP Ultrasound Measure of Achilles thickness

End point description:

End point type	Secondary

End point timeframe:
assessment at 24 weeks

End point values	Glyceryl Trinitrate (GTN)	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: 0-20				
arithmetic mean (standard deviation)	7.7 (± 2.4)	7.9 (± 2.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pressure Pain Threshold (PPT) Scores

End point title	Pressure Pain Threshold (PPT) Scores

End point description:

End point type	Secondary

End point timeframe:
assessment at 24 weeks

End point values	Glyceryl Trinitrate (GTN)	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: 0-10				
arithmetic mean (standard deviation)	6.3 (± 2.9)	5.9 (± 2.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Star Excursion Balance Test (SEBT) Anterior Reach

End point title	Star Excursion Balance Test (SEBT) Anterior Reach

End point description:

End point type	Secondary

End point timeframe:
assessment at 24 weeks

End point values	Glyceryl Trinitrate (GTN)	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: 0-120				
arithmetic mean (standard deviation)	62.6 (± 8.4)	64.2 (± 6.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Star Excursion Balance Test (SEBT) Posteromedial Reach

End point title	Star Excursion Balance Test (SEBT) Posteromedial Reach

End point description:

End point type	Secondary

End point timeframe:
assessment at 24 weeks

End point values	Glyceryl Trinitrate (GTN)	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: 0-120				
arithmetic mean (standard deviation)	97.7 (± 10.7)	98.7 (± 10.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Star Excursion Balance Test (SEBT) Posterolateral Reach

End point title	Star Excursion Balance Test (SEBT) Posterolateral Reach

End point description:

End point type	Secondary

End point timeframe:
assessment at 24 weeks

End point values	Glyceryl Trinitrate (GTN)	Placebo Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: 0-120				
arithmetic mean (standard deviation)	88.7 (± 9.2)	90.2 (± 12.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Week 3 to week 24	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22
Reporting groups	
Reporting group title	Glyceryl Trinitrate Group
Reporting group description: Six adverse reactions were noted in the GTN group and four adverse events.	
Reporting group title	Placebo Group
Reporting group description: Four adverse reactions and two adverse events occurred in the placebo	

Serious adverse events	Glyceryl Trinitrate Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 37 (2.70%)	0 / 39 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
achilles tendon rupture			
subjects affected / exposed	1 / 37 (2.70%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Glyceryl Trinitrate Group	Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 37 (27.03%)	4 / 39 (10.26%)	
Injury, poisoning and procedural complications			
Injury			
subjects affected / exposed	2 / 37 (5.41%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	2 / 39 (5.13%) 2	
Eye disorders Eye Swelling subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 39 (0.00%) 0	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 39 (0.00%) 0	
Skin and subcutaneous tissue disorders Skin Irritation subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3	0 / 39 (0.00%) 0	
Musculoskeletal and connective tissue disorders Muscle Soreness subjects affected / exposed occurrences (all) Ankle Swelling subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0 1 / 37 (2.70%) 1	1 / 39 (2.56%) 1 0 / 39 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported