Clinical trial results:
A randomised, double-blind, placebo-controlled study of celecoxib after collagenase injection for adults with Dupuytren's disease at high risk of recurrence

Summary

EudraCT number	2014-000717-31
Trial protocol	BE
Global end of trial date	27 May 2019

Results information

Result version number	v1 (current)
This version publication date	10 July 2022
First version publication date	10 July 2022

Trial information

Trial identification

Sponsor protocol code	WI187847

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	UZ Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Clinial Trial Information Desk , Research Orthopedie - IORT, 0032 16338818, orthopedic.research@uz.kuleuven.be
Scientific contact	Clinial Trial Information Desk , Research Orthopedie - IORT, 0032 16338818, orthopedic.research@uz.kuleuven.be

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	08 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2019
Global end of trial reached?	Yes
Global end of trial date	27 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the ability of celecoxib to improve the treatment result (improved finger extension) of collagenase in Dupuytren's patients at high risk for disease recurrence, when administered after the collagenase injection.

Protection of trial subjects:

This study was conducted adhering to the CONSORT standards, with double blinding and strict randomization. Strict selection of patients with a high recurrence risk ensured that enough change would occur in order to detect any difference between the two groups. Compared to tamoxifen (that demonstrated to have some effects on contractures and satisfaction scores after limited fasciectomy) COX-2 selective non-steroidal anti-inflammatory drugs such as celecoxib have a more safe pharmacological profile for patients.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2015
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	Belgium: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	17
From 65 to 84 years	18

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment of the patients will occur in the out-patient clinic of Prof. Dr. Luc De Smet and Prof. Dr. Ilse Degreef in the University Hospitals of the KU Leuven, Campus Leuven and Pellenberg. It is expected that 30 high risk patients will be recruited within one year. Recruitment was between December 2015 and May 2017.

Pre-assignment

Screening details:

Inclusion criteria: Dupuytren's patients with risk score D of Abe > 4; treatment with collagenase injections scheduled, >18 years
Exclusion criteria: contra-indication as per characteristics of celecoxib; taking another NSAID or anticoagulant; any other clinically significant disorder that would be a risk to subject safety or study completion

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 investigator enrols the participants and assign them blindly to the celecoxib or to the placebo group. Number of the box is noted on the informed consent form and other study related documents. All sealed randomisation envelopes, each stating the real content of a given box are kept in a sealed enveloped at the study office. Both investigators an the hospital pharmacist received an envelope with the randomisation data in case of emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Celecoxib

Arm description:

The first dose of celecoxib will be administered after the injection at a dose of 200 mg peroral. Thereafter, once a day in the morning during 12 weeks. This is done blinded.

Arm type	Experimental
Investigational medicinal product name	Celebrex
Investigational medicinal product code	LI900005
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

dosage: 200 mg peroral
Administration details:
- first dose administered after the collagenase injection
- Starting from day 2: one dose of 200mg peroral a day in the morning during 12 weeks

Arm title	Placebo

Arm description:

The first dose of placebo will be administered after the injection at a matched-dose (with celecoxib of 200 mg) peroral . Thereafter, once a day in the morning during 12 weeks.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dosage: matched with 200mg celecoxib
Administration details:
- first dose administered after the collagenase injection
- Starting from day 2: one dose peroral a day in the morning during 12 weeks

Number of subjects in period 1	Celecoxib	Placebo
Started	19	16
Completed	14	15
Not completed	5	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	4	1

Baseline characteristics

Reporting groups

Reporting group title	Celecoxib

Reporting group description:

The first dose of celecoxib will be administered after the injection at a dose of 200 mg peroral. Thereafter, once a day in the morning during 12 weeks. This is done blinded.

Reporting group title	Placebo

Reporting group description:

The first dose of placebo will be administered after the injection at a matched-dose (with celecoxib of 200 mg) peroral . Thereafter, once a day in the morning during 12 weeks.

Reporting group values	Celecoxib	Placebo	Total
Number of subjects	19	16	35
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	65	63	
full range (min-max)	38 to 78	43 to 78	-
Gender categorical Units: Subjects			
Female	1	4	5
Male	18	12	30

Subject analysis sets

Subject analysis set title	Subjects with complete dataset for analysis
Subject analysis set type	Full analysis

Subject analysis set description:

A total of 6 drop-outs within the trial, but 3 were late drop-outs with a complete dataset. These were included in the analysis

Reporting group values	Subjects with complete dataset for analysis		
Number of subjects	32		
Age categorical Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	64		
full range (min-max)	38 to 78		
Gender categorical Units: Subjects			
Female	5		
Male	27		

End points

End points reporting groups

Reporting group title	Celecoxib

Reporting group description:

The first dose of celecoxib will be administered after the injection at a dose of 200 mg peroral. Thereafter, once a day in the morning during 12 weeks. This is done blinded.

Reporting group title	Placebo

Reporting group description:

The first dose of placebo will be administered after the injection at a matched-dose (with celecoxib of 200 mg) peroral . Thereafter, once a day in the morning during 12 weeks.

Subject analysis set title	Subjects with complete dataset for analysis
Subject analysis set type	Full analysis

Subject analysis set description:

A total of 6 drop-outs within the trial, but 3 were late drop-outs with a complete dataset. These were included in the analysis

Primary: The Total Passive Extension Deficit per RAY: TPED/RAY

End point title	The Total Passive Extension Deficit per RAY: TPED/RAY

End point description:

The Total Passive Extension Deficit (TPED) of the MCP, PIP and DIP joints of each affected ray will be measured with an electronic goniometer, by two independent orthopaedic surgeons. The study will focus on individual rays, rather than on patients, especially for computation of the data.

End point type	Primary

End point timeframe:

This TPED will be measured before surgery (clinical data sheet) and 4 and 12 weeks, 6 months, 1 and 2 years after surgery.

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: degrees				
arithmetic mean (standard deviation)	28.47 (± 22.98)	25.61 (± 29.20)		

Statistical analyses

Statistical analysis title	multilevel mixed-effects linear regression

Statistical analysis description:

a repeated measures mixed model was used, with an unstructured residual covariance matrix and restricted maximum likelihood.

Comparison groups	Celecoxib v Placebo

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Median difference (final values)

Secondary: Tubiana index

End point title	Tubiana index

End point description:

Tubiana grading of the most affected finger was determined as a secondary outcome parameter at each visit (grade I: 0°- 45° passive extension deficit, grade II: 45°-90°, grade III: 90°-135°, grade IV: ≥ 135°. The Tubiana index (correction divided by initial grade) was calculated to evaluate relative gain.

End point type	Secondary

End point timeframe:

before surgery (clinical data sheet) and 4 and 12 weeks, 6 months, 1 and 2 years after surgery

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: %				
arithmetic mean (standard deviation)	41.67 (± 31.73)	27.28 (± 27.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: The DASH questionnaire

End point title	The DASH questionnaire

End point description:

It consists of 30 questions about the activities of daily living. The scores are added and transformed into a 100-point scale. The higher the result, the worse the condition of the patient.

End point type	Secondary

End point timeframe:

preoperatively, and after 1 and 2 years

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: 100 point scale				
arithmetic mean (standard deviation)	43.36 (± 11.69)	36.00 (± 14.20)		

Statistical analyses

Statistical analysis title	multilevel mixed-effects linear regression

Statistical analysis description:

a repeated measures mixed model was used, with an unstructured residual covariance matrix and restricted maximum likelihood.

Comparison groups	Celecoxib v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: The visual analogue satisfaction score

End point title	The visual analogue satisfaction score

End point description:

End point type	Secondary

End point timeframe:

Before surgery, 6 weeks, 12 weeks, 6 months, 1 and 2 years after surgery

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: scale between 0 and 10				
arithmetic mean (standard deviation)	8.68 (± 2.05)	7.93 (± 2.81)		

Statistical analyses

Statistical analysis title	multilevel mixed-effects linear regression

Statistical analysis description:

a repeated measures mixed model was used, with an unstructured residual covariance matrix and restricted maximum likelihood.

Comparison groups	Celecoxib v Placebo

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Recurrence rate TPED

End point title	Recurrence rate TPED

End point description:

End point type	Secondary

End point timeframe:

Recurrence will be noted during every visit after surgery

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: yes or no	8	8		

Statistical analyses

Statistical analysis title	Kaplan-Meier failure analysis

Statistical analysis description:

a Kaplan-Meier failure analysis was performed, with log-rank test to detect a difference between the groups

Comparison groups	Celecoxib v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Logrank

Secondary: The visual analogue pain score

End point title	The visual analogue pain score

End point description:

End point type	Secondary

End point timeframe:

Before surgery, 6 weeks, 12 weeks, 6 months, 1 and 2 years after surgery

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: 0 to 10 scale				
arithmetic mean (standard deviation)	0.98 (± 0.89)	1.84 (± 2.35)		

Statistical analyses

Statistical analysis title	multilevel mixed-effects linear regression

Statistical analysis description:

a repeated measures mixed model was used, with an unstructured residual covariance matrix and restricted maximum likelihood.

Comparison groups	Celecoxib v Placebo
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Median difference (final values)

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During every visit and self-repporting by participants	
Assessment type	Systematic

Dictionary used	
Dictionary name	UZ Leuven guidelines
Dictionary version	1

Reporting groups	
Reporting group title	Celecoxib
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Celecoxib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	6 / 16 (37.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Surgical and medical procedures			
Stent placement			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot operation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
nesbitt operation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stapedotomy			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fasciectomy	Additional description: Fasciectomy ray 3-4-5 right hand & Fasciectomy ray 2-4-5 lefthand		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 19 (5.26%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Celecoxib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 19 (47.37%)	3 / 16 (18.75%)	
Injury, poisoning and procedural complications			
Tooth fracture			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Second collagenase injection			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 19 (5.26%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Stomach complications	Additional description: infection of stomach & problems with function of stomach		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 19 (10.53%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cold			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Muscle discomfort	Additional description: hand and feet		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Infections	Additional description: Infection of shoulder Infection of cheeck with NSAID treatment Gout with pain medication treatment		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 19 (10.53%)	1 / 16 (6.25%)	
occurrences (all)	2	1	

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