Clinical trial results:
A multi-centre, double blind, randomised, placebo-controlled, parallel group, phase II trial to determine the efficacy of intra-nodular injection of anti-TNF to control disease progression in early Dupuytren's disease, with a dose response.

Summary

EudraCT number	2015-001780-40
Trial protocol	GB
Global end of trial date	10 December 2020

Results information

Result version number	v1 (current)
This version publication date	19 May 2022
First version publication date	19 May 2022

Trial information

Trial identification

Sponsor protocol code	11069

Additional study identifiers

ISRCTN number	ISRCTN27786905
ClinicalTrials.gov id (NCT number)	NCT03180957
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Kennedy Institute of Rheumatology, Oxford, United Kingdom, OX7 7LD
Public contact	Nicola Kenealy, University of Oxford, 44 01865610612, nicola.kenealy@kennedy.ox.ac.uk
Scientific contact	Prof Jagdeep Nanchahal, University of Oxford, 44 01865 612633, jagdeep.nanchahal@kennedy.ox.ac.uk

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	02 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 2: To determine if injection with adalimumab is superior to placebo injection of normal saline in controlling disease progression in participants with early Dupuytren’s disease.

Protection of trial subjects:

This study was conducted in accordance with local regulatory requirements, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and the ethical principles described in the current revision (2002) of Declaration of Helsinki.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	10 August 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 140
Worldwide total number of subjects	140
EEA total number of subjects	0

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)	94

From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment to RIDD was opened in December 2016, and the first participant was recruited in February 2017.
181 participants from the UK and NL were randomised over the period of 26 months. After excluding 8 randomisation that were in error, 173 (140 in the UK, 33 in NL) were included in the trial.

Pre-assignment

Screening details:

A total of 284 participants were screened for the RIDD trial out of these 284, 147 were randomised and 137 were ineligible. Participants were ineligible for the following reasons:
o Not eligible (n = 112) (of which 8 failed safety screening)
o Declined to participate (n = 20)
o Not included due to end of recruitment (n = 5)

Period 1

Period 1 title	Baseline Trial - UK
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

A non-blinded member of the research team, who was not involved in administering the IMP or assessing the participant, prepared the adalimumab or normal saline in a syringe according to the randomisation, and labelled the syringes with the participant's ID. The label did not reveal the identity of the IMP. Both the IMP and placebo have a similar viscosity and appearance so that the two treatments, adalimumab or saline, were indistinguishable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab Baseline

Arm description:

Anti-TNF
Participants received the anti-TNF agent Adalimumab 40 mg in 0.4ml into the nodule at baseline, 3, 6 and 9 months after randomisation.

Arm type	Experimental
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

40mg adalimumab in 0.4 ml

Arm title	Placebo Baseline

Arm description:

Placebo
Participants received an injection of saline (placebo) of equivalent volume at baseline, 3, 6 and 9 months after
randomisation

Arm type	Placebo

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

0.4 ml

Number of subjects in period 1	Adalimumab Baseline	Placebo Baseline
Started	70	70
Completed	59	54
Not completed	11	16
Lost to follow-up	11	16

Period 2

Period 2 title	12 Months Follow up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab - 12 Months

Arm description:

Anti-TNF Participants received the anti-TNF agent Adalimumab 40 mg in 0.4ml into the nodule at baseline, 3, 6 and 9 months after randomisation

Arm type	Experimental
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

40mg adalimumab in 0.4 ml

Arm title	Placebo - 12 months

Arm description:

Placebo Participants received an injection of saline (placebo) of equivalent volume at baseline, 3, 6 and 9 months after randomisation

Arm type	Placebo

Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

0.4 ml

Number of subjects in period 2	Adalimumab - 12 Months	Placebo - 12 months
Started	59	54
Completed	59	54

Baseline characteristics

Reporting groups	
Reporting group title	Baseline Trial - UK

Reporting group description: -

Reporting group values	Baseline Trial - UK	Total	
Number of subjects	140	140	
Age categorical Units: Subjects			
Adults (18-64 years)	94	94	
From 65-84 years	46	46	
Age continuous Units: years			
arithmetic mean	59.7		
standard deviation	± 10.0	-	
Gender categorical Units: Subjects			
Female	47	47	
Male	93	93	
Manual Occupation Units: Subjects			
Yes	16	16	
No	124	124	
Alcohol Consumption (units/week) Units: Subjects			
Non- Drinker	16	16	
up to 13	77	77	
14-35	43	43	
Over 35	4	4	
Current smoker Units: Subjects			
yes	7	7	
no	133	133	
Hand Dominance Units: Subjects			
right	124	124	
left	15	15	
Missing	1	1	
Epilepsy Units: Subjects			
no	137	137	
yes	3	3	
Liver Disease Units: Subjects			
no	140	140	
significant exposure to occupational vibration Units: Subjects			

no	130	130	
yes	10	10	
Previous significant trauma to affected hand Units: Subjects			
no	113	113	
yes	27	27	
Diabetes Units: Subjects			
no	131	131	
type 1	1	1	
type 2	8	8	
Frozen Shoulder Units: Subjects			
none	103	103	
right	12	12	
left	15	15	
both sides	10	10	
Ray affected by study nodule Units: Subjects			
index	2	2	
middle	21	21	
ring	78	78	
little	39	39	
affected joint Units: Subjects			
metacarpophalangeal	114	114	
proximal interphalangeal	26	26	
Bilateral Dupuytren's disease Units: Subjects			
no	65	65	
yes	75	75	
Treatment for Dupuytren's disease in other hand Units: Subjects			
no	109	109	
yes	31	31	
Associated medical conditions Units: Subjects			
no	72	72	
yes	67	67	
missing	1	1	
Plantar (Ledderhose) disease Units: Subjects			
no	117	117	
yes	22	22	
missing	1	1	
Peyronie's disease Units: Subjects			
no	134	134	
yes	6	6	
Garrod's knuckle pads			

Units: Subjects			
no	109	109	
yes	31	31	
Family history (any relatives, self reported) Units: Subjects			
no	75	75	
yes	65	65	
Family history (1st Degree relatives) Units: Subjects			
no	85	85	
yes	55	55	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants analysed in their randomised groups with available outcome data.
(Due to missing data for the primary endpoint (standard durometer) analysis multiple imputation by chained equations using predictive mean matching were used).

Reporting group values	ITT		
Number of subjects	140		
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age continuous Units: years			
arithmetic mean	59.7		
standard deviation	± 10.0		
Gender categorical Units: Subjects			
Female			
Male			
Manual Occupation Units: Subjects			
Yes			
No			
Alcohol Consumption (units/week) Units: Subjects			
Non- Drinker			
up to 13			
14-35			
Over 35			
Current smoker Units: Subjects			
yes			
no			
Hand Dominance Units: Subjects			

right left Missing			
Epilepsy Units: Subjects			
no yes			
Liver Disease Units: Subjects			
no			
significant exposure to occupational vibration Units: Subjects			
no yes			
Previous significant trauma to affected hand Units: Subjects			
no yes			
Diabetes Units: Subjects			
no type 1 type 2			
Frozen Shoulder Units: Subjects			
none right left both sides			
Ray affected by study nodule Units: Subjects			
index middle ring little			
affected joint Units: Subjects			
metacarpophalangeal proximal interphalangeal			
Bilateral Dupuytren's disease Units: Subjects			
no yes			
Treatment for Dupuytren's disease in other hand Units: Subjects			
no yes			
Associated medical conditions Units: Subjects			

no yes missing			
Plantar (Ledderhose) disease Units: Subjects			
no yes missing			
Peyronie's disease Units: Subjects			
no yes			
Garrod's knuckle pads Units: Subjects			
no yes			
Family history (any relatives, self reported) Units: Subjects			
no yes			
Family history (1st Degree relatives) Units: Subjects			
no yes			

End points

End points reporting groups

Reporting group title	Adalimumab Baseline

Reporting group description:

Anti-TNF
Participants received the anti-TNF agent Adalimumab 40 mg in 0.4ml into the nodule at baseline, 3, 6 and 9 months after randomisation.

Reporting group title	Placebo Baseline

Reporting group description:

Placebo
Participants received an injection of saline (placebo) of equivalent volume at baseline, 3, 6 and 9 months after
randomisation

Reporting group title	Adalimumab - 12 Months

Reporting group description:

Anti-TNF Participants received the anti-TNF agent Adalimumab 40 mg in 0.4ml into the nodule at baseline, 3, 6 and 9 months after randomisation

Reporting group title	Placebo - 12 months

Reporting group description:

Placebo Participants received an injection of saline (placebo) of equivalent volume at baseline, 3, 6 and 9 months after randomisation

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All participants analysed in their randomised groups with available outcome data.
(Due to missing data for the primary endpoint (standard durometer) analysis multiple imputation by chained equations using predictive mean matching were used).

Primary: Change in nodule hardness

End point title	Change in nodule hardness

End point description:

measured using a standard durometer
Baseline were mean imputed, 12 Months: Adalimumab n=63, Saline n =64.

End point type	Primary

End point timeframe:

Baseline to 12 Months

End point values	Adalimumab Baseline	Placebo Baseline	Adalimumab - 12 Months	Placebo - 12 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	70	59[1]	54[2]
Units: Durometer Arbitrary Units				
arithmetic mean (standard deviation)	63.2 (± 8.4)	61.4 (± 9.7)	58.1 (± 11.8)	61.2 (± 9.8)

Notes:

[1] - Measurements were available on 70 participants, the remainder were imputed

[2] - Measurements were available on 54 participants, the remainder were imputed

End point values	ITT			

Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: Durometer Arbitrary Units				
arithmetic mean (standard deviation)	59.56 (± 10.95)			

Statistical analyses

Statistical analysis title	Primary analysis for the treatment effect
Statistical analysis description: Difference between adalimumab and saline adjusted for baseline values site and age.	
Comparison groups	Adalimumab - 12 Months v Placebo - 12 months
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00024
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	-2.2

Secondary: Nodule Size

End point title	Nodule Size
End point description: Baseline were mean imputed, 12 months: Adalimumab n=61, Saline n =63.	
End point type	Secondary
End point timeframe: Baseline to 12 Months	

End point values	Adalimumab Baseline	Placebo Baseline	Adalimumab - 12 Months	Placebo - 12 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	70	59	54
Units: mm2				
arithmetic mean (standard deviation)	27.7 (± 17.6)	32.2 (± 22.2)	21.8 (± 18.7)	35.9 (± 28.9)

End point values	ITT			

Subject group type	Subject analysis set			
Number of subjects analysed	113			
Units: mm2				
arithmetic mean (standard deviation)	30.0 (± 20.0)			

Statistical analyses

Statistical analysis title	treatment effect adjusted for site and age
Comparison groups	Adalimumab - 12 Months v Placebo - 12 months
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0025
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-8.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	-2.9

Secondary: Grip Strength

End point title	Grip Strength
End point description: Baseline were mean imputed, 12 Months: Adalimumab n=63, Saline n =64.	
End point type	Secondary
End point timeframe: Baseline to 12 months	

End point values	Adalimumab Baseline	Placebo Baseline	Adalimumab - 12 Months	Placebo - 12 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	70	59	54
Units: kg				
arithmetic mean (standard deviation)	33.5 (± 10.7)	38.0 (± 12.1)	34.5 (± 10.7)	38.3 (± 11.9)

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	124			
Units: kg				

arithmetic mean (standard deviation)	35.8 (± 11.7)			

Statistical analyses

Statistical analysis title	treatment effect adjusted for site and age
Comparison groups	Adalimumab Baseline v Placebo Baseline
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.5

Secondary: Extension deficit of affected joint

End point title	Extension deficit of affected joint
End point description:	
Overall active extension deficit of joint affected by treated nodule (degrees) Baseline were mean imputed, 12 Months: Adalimumab n=63, Saline n =65.	
End point type	Secondary
End point timeframe:	
Baseline to 12 months	

End point values	Adalimumab Baseline	Placebo Baseline	Adalimumab - 12 Months	Placebo - 12 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	70	59	54
Units: degree				
arithmetic mean (standard deviation)	-6.7 (± 15.9)	-3.9 (± 18.3)	-2.3 (± 20.4)	0.3 (± 25.1)

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	140			
Units: degree				

arithmetic mean (standard deviation)	-5.3 (± 17.2)			

Statistical analyses

Statistical analysis title	treatment effect adjusted for site and age
Comparison groups	Adalimumab Baseline v Placebo Baseline
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	3.9
Variability estimate	Standard deviation

Secondary: Participant reported outcomes	
End point title	Participant reported outcomes
End point description: MHQ - overall hand function Baseline were mean imputed, 12 Months: Adalimumab n=64, Saline n =66.	
End point type	Secondary
End point timeframe: Baseline to 12 months	

End point values	Adalimumab Baseline	Placebo Baseline	Adalimumab - 12 Months	Placebo - 12 months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	70	59	54
Units: Michigan Hand Questionnaire				
arithmetic mean (standard deviation)	83.6 (± 14.9)	81.9 (± 16.8)	83.5 (± 16.1)	78.8 (± 16.0)

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	140			

Units: Michigan Hand Questionnaire				
arithmetic mean (standard deviation)	82.8 (± 15.8)			

Statistical analyses

Statistical analysis title	treatment effect adjusted for site and age
Comparison groups	Adalimumab Baseline v Placebo Baseline
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	7.5
Variability estimate	Standard deviation

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
12 Months	
Adverse event reporting additional description:	
AEs graded 3 and above occurring during the trial until 28 days after the last injection that were considered to be attributed to trial medication or the injection of the trial were reported. There were no AEs reported for the RIDD Trial.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	2015

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No related SAEs were reported in the trial. One unrelated SAE (pericarditis [recorded as "chest infection"], saline arm, UK) was reported during the follow-up.

No related grade 3+ AEs were reported during the follow-up for this trial.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2015	Resubmission to MHRA: wording for abstinence section 7.2; unblinding procedure section 8.4. REC also sent pregnancy notification leaflet and consent form, and GP letter with PI details
20 January 2016	Participant burden in part 1 reduced by removing some secondary outcomes and visits. Grip strength, range of motion, MHQ and activity-most-restricted dropped. Added in measuring COL-3A1. Dropped visit one week after injection and one and four weeks after surgery. Also will not rate the scar and have removed mention of western blotting and histology. In part 2 there will be a blood sample at 12 months.
29 March 2016	To remove ´safety´ and ´run-in´ from the title. To allow dose cohorts to be done in different order and with lower or intermediate doses. To randomise via RRAMP not sealed envelopes for Part 1.
17 May 2016	To do RCT with 35mg into the nodule – not dependent on dose response results, To remove 1 week visit in RCT. Some modifications to inclusion/exclusion criteria. (protocol V7.0)
17 October 2016	New formulation of adalimumab to be used in Part 2 – impact on blinding and dosage (using 40mg instead of 35 mg). New formulation will be a cohort in Part 1. Changes to outcomes. (protocol V8.0)
05 January 2018	Protocol V9.0
02 July 2018	Amendment to protocol: IMP preparation section; to implement REC 3 contract rule required by REC in response to Amendment 12; change to mandate screening blood tests & increase max volume blood; removal of parenteral steroid exclusion criteria from part 2
06 November 2018	Change to target recruitment from 138 to maximum of 200. 7.3 Exclusion criteria - Removal of exclusion criteria: Part 2. Scheduled elective surgery or other procedures requiring general anaesthesia during the study Section 15.5 has been updated in line with GDPR.
29 August 2019	Updated RSI SmPC, Protocol amendment: increase of trial duration to 45 months; additional options for data collection; addition of information in case surgery occurs; changes to stats methods; increase of archiving period to 15 years; change to definition of RSI.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

23 March 2020	COVID -19 pandemic caused the 18 month follow up for 76 participants to be delayed. Participants were sent the questionnaires to complete through the post and the follow up Case Report Forms were completed over the telephone meaning that that physical measures could not be taken. When lockdown restrictions were lifted the participants were invited back to the clinic to have physical measures taken and they complete the questionnaires once more.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Data from the UK and NL could not be combined for analysis - different durometers were used. The NL data showed similar trends to those for the UK participants, but the small number of NL participants and missing data precluded statistical analyses.

Notes: