

**Clinical trial results:
NEUORIMPA - Intraarticular Application of Opioids in Chronic Arthritis
of the knee joint****Summary**

EudraCT number	2015-000538-31
Trial protocol	DE
Global end of trial date	27 August 2021

Results information

Result version number	v1 (current)
This version publication date	20 March 2023
First version publication date	20 March 2023

Trial information**Trial identification**

Sponsor protocol code	Neuroimpa2015
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02967302
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00011113

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
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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	17 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 August 2021
Global end of trial reached?	Yes
Global end of trial date	27 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate pain and inflammatory parameters (cytokines, immune cells) in knee joint tissue of chronic arthritis patients following intraarticular (i.a.) injections of morphine, a standard steroid or placebo.

The primary hypothesis is that i.a. morphine results in significantly lower pain scores and supplemental analgesic consumption than placebo during the first week after injection, an efficacy comparable to standard i.a. steroid (tri-aminolone) medication.

Primary efficacy endpoint:

Reduction of pain intensity (on a 100mm VAS) at 8 a.m. on day 7 compared to baseline.

Protection of trial subjects:

The study was conducted according to the ethical principles of the Declaration of Helsinki.

Daily activities, intensity and quality of pain are monitored for 2 weeks after intervention. Biopsies and synovial fluid aspiration are repeated after 7 days. Supplemental DMARDs are maintained at a stable dosage.

Rescue medication: Patients have access to supplemental oral diclofenac (up to 150mg/day) or tramadol (up to 100 mg).

Background therapy:

Patients with chronic inflammatory arthritis (e.g. rheumatoid arthritis; RA) or inflammatory exacerbations of chronic degenerative joint diseases (e.g. osteoarthritis; OA) suffer from recurrent pain, restricted function and reduction of daily activities. Such diseases are difficult to treat and lead to job loss, disability, premature retirement and increased compensatory expenses. Current standard treatments with nonsteroidal antiinflammatory drugs (NSAIDs), steroids or disease-modifying anti-rheumatic drugs (DMARDs) (e.g. methotrexate, biologicals) are partially effective, but can produce severe side effects (gastrointestinal ulcers, bleeding, thromboembolic complications, nephrotoxicity, hepatotoxicity, cartilage degeneration; Cushing's syndrome, infections). A novel approach without such complications is the activation of peripheral opioid receptors, e.g. by i.a. application of small, systemically inactive doses of morphine. In a large number (> 60) of published randomized controlled trials (RCT), we and others have shown that i.a. morphine produces significant analgesia in acute postoperative pain with similar efficacy to local anesthetics or steroids without systemic or local side effects.

Evidence for comparator: -

Actual start date of recruitment	06 October 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	Germany: 93
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Worldwide total number of subjects	93
EEA total number of subjects	93

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)	54
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at department of rheumatology , Charity, from October 6th 2015 to 27th August 2021.

Pre-assignment

Screening details:

114 patients were screened.

93 patients were randomised.

Period 1

Period 1 title	Treatment + follow up (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	placebo

Arm description:

patient recieved i.a. injection 5ml of 0.9 % NaCl

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

Dosage and administration details:

0.9 % NaCl (5 ml; placebo) were i.a injected

Arm title	Morphin
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Arm description:

patients received i.a. morphine (3 mg/5 ml)

Arm type	Experimental
Investigational medicinal product name	Morphinsulfat
Investigational medicinal product code	SUB14597MIG
Other name	Morphine Hexal
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

morphine (3 mg/5 ml) was i.a. injected

Arm title	TRIAMCINOLONE
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Arm description:

triamcinolone for benchmarking to current active standard medication were i.a. injected

Arm type	Active comparator
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Investigational medicinal product name	TRIAMCINOLONACETONID
Investigational medicinal product code	SUB41525
Other name	Triam 40 mg Lichtenstein
Pharmaceutical forms	Solution for injection
Routes of administration	Injection

Dosage and administration details:

5ml (40 mg/ml) TRIAMCINOLONACETONID were i.a injected

Number of subjects in period 1	placebo	Morphin	TRIAMCINOLONE
Started	18	35	40
Completed	18	33	38
Not completed	0	2	2
Consent withdrawn by subject	-	1	-
no more interest	-	-	1
Lost to follow-up	-	1	1

Baseline characteristics

Reporting groups

Reporting group title	placebo
Reporting group description:	patient recieved i.a. injection 5ml of 0.9 % NaCl
Reporting group title	Morphin
Reporting group description:	patients received i.a. morphine (3 mg/5 ml)
Reporting group title	TRIAMCINOLONE
Reporting group description:	triamcinolone for benchmarking to current active standard medication were i.a. injected

Reporting group values	placebo	Morphin	TRIAMCINOLONE
Number of subjects	18	35	40
Age categorical			
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)	10	21	23
From 65-84 years	8	14	17
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	59.33	59.37	57.35
standard deviation	± 14.56	± 13.07	± 15.32
Gender categorical			
Units: Subjects			
Female	11	16	21
Male	7	19	19
Height			
Units: cm			
arithmetic mean	173.22	172.6	172.93
standard deviation	± 9.79	± 9.22	± 10.98
Weight			
Units: kg			
arithmetic mean	81.39	85.11	81.98
standard deviation	± 20.44	± 15.14	± 14.74
CRP			
Units: mg/l			
arithmetic mean	2.8	5.69	8.01
standard deviation	± 2.67	± 6.26	± 14.34
VAS Pain last 7 days			

Units: mm			
arithmetic mean	64	65.6	61.9
standard deviation	± 14.78	± 16.62	± 13.15

Reporting group values	Total		
Number of subjects	93		
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)	54		
From 65-84 years	39		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	-		
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	48		
Male	45		
Height			
Units: cm			
arithmetic mean	-		
standard deviation	-		
Weight			
Units: kg			
arithmetic mean	-		
standard deviation	-		
CRP			
Units: mg/l			
arithmetic mean	-		
standard deviation	-		
VAS Pain last 7 days			
Units: mm			
arithmetic mean	-		
standard deviation	-		

End points

End points reporting groups

Reporting group title	placebo
Reporting group description:	patient recieved i.a. injection 5ml of 0.9 % NaCl
Reporting group title	Morphin
Reporting group description:	patients received i.a. morphine (3 mg/5 ml)
Reporting group title	TRIAMCINOLONE
Reporting group description:	triamcinolone for benchmarking to current active standard medication were i.a. injected

Primary: difference of VAS pain intensity on day 7 compared to baseline

End point title	difference of VAS pain intensity on day 7 compared to baseline
End point description:	In the first step, superiority of the experimental treatment vs. the placebo arm was tested (one sided test, type 1 error = 0.025). If this test was not significant, the procedure terminates and the result of the study was negative. In case of significance, a noninferiority test vs. the standard therapy was performed (one sided test, type 1 error = 0.025). A linear model including baseline as a continuous covariate was used for both steps of testing. In a sensitivity analysis, supplementary analgesic medication was included as an additional continuous covariate We expected that the adjustment of baseline as covariate will decrease the error term. Therefore, we did not anticipate less power due to the reduction of degrees of freedom by one of the error terms.
End point type	Primary
End point timeframe:	from baseline to week 1

End point values	placebo	Morphin	TRIAMCINOLO NE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	33	38	
Units: mm				
arithmetic mean (standard error)	-19.83 (\pm 6.33)	-22.85 (\pm 4.18)	-37.69 (\pm 3.45)	

Attachments (see zip file)	primary-secondary-endpoints_NEUROIMPA/Primary and
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Statistical analyses

Statistical analysis title	Differences VAS at 8 a.m on day 7/baseline
Comparison groups	Morphin v TRIAMCINOLONE v placebo

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Confidence interval	
sides	2-sided
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

overall study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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Reporting groups

Reporting group title	Morphine
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Reporting group description: -

Reporting group title	Triamcinolone
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Morphine	Triamcinolone	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)	0 / 45 (0.00%)	0 / 22 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Morphine	Triamcinolone	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 45 (26.67%)	14 / 45 (31.11%)	5 / 22 (22.73%)
Injury, poisoning and procedural complications			
Haematoma			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	1 / 22 (4.55%)
occurrences (all)	2	0	1
pain at site of injection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			

Hypertension/ hypertensive crisis subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	0 / 45 (0.00%) 0	0 / 22 (0.00%) 0
Surgical and medical procedures elective stomache operation subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 45 (0.00%) 0	0 / 22 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	2 / 45 (4.44%) 2	1 / 22 (4.55%) 1
General disorders and administration site conditions tiredness subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	1 / 45 (2.22%) 1	0 / 22 (0.00%) 0
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	2 / 45 (4.44%) 2	1 / 22 (4.55%) 1
Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	1 / 45 (2.22%) 1	0 / 22 (0.00%) 0
Skin and subcutaneous tissue disorders Exanthema on feet subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 45 (2.22%) 1	0 / 22 (0.00%) 0
Psychiatric disorders hyperventilation subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 45 (0.00%) 0	0 / 22 (0.00%) 0
exitement subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 45 (2.22%) 1	0 / 22 (0.00%) 0
sleeplessness subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 45 (2.22%) 1	0 / 22 (0.00%) 0
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 5	2 / 45 (4.44%) 3	1 / 22 (4.55%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 45 (6.67%) 3	1 / 45 (2.22%) 1	1 / 22 (4.55%) 1
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	0 / 45 (0.00%) 0	1 / 22 (4.55%) 1
herpes labialis subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	0 / 45 (0.00%) 0	1 / 22 (4.55%) 1
Nail bed infection subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 45 (2.22%) 1	0 / 22 (0.00%) 0
elevated ESR subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	1 / 45 (2.22%) 1	0 / 22 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2015	Deletion of the inclusion criterion Maximum weight 90 kg

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported