Clinical trial results:
Neodolpasse® Infusion Solution versus diclofenac 75 mg infusion in the treatment of postoperative pain after elective knee surgery - an exploratory placebo-controlled clinical study to investigate the analgesic properties of the combination of diclofenac and orphenadrine versus diclofenac alone.

Summary

EudraCT number	2016-001056-22
Trial protocol	AT
Global end of trial date	20 May 2019

Results information

Result version number	v1 (current)
This version publication date	11 September 2020
First version publication date	11 September 2020

Trial information

Trial identification

Sponsor protocol code	NDOL-001-2016

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University Clinic for Anaesthesiology, Medical Univerity Vienna
Sponsor organisation address	Währinger Gürtel 18-20, Vienna, Austria, 1090
Public contact	Principle Investigator, University Clinic for Anaesthesiology, Medical Univerity Vienna, 0043 140400 41030, oliver.kimberger@meduniwien.ac.at
Scientific contact	Principle Investigator, University Clinic for Anaesthesiology, Medical Univerity Vienna, 0043 140400 41030, oliver.kimberger@meduniwien.ac.at

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	20 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Trial objective is to investigate the use of additional analgesic medication via PCA during the first 24 hours postoperatively.

Protection of trial subjects:

The local and systemic tolerability and safety of the clinical study medications was assessed, as were possible neurological side effects using the Delirium Detection Score 2h and 24h after the first infusion. Overall pharmacological safety of the infusion solution was assessed via laboratory safety values. All patients were provided with a PCA as postoperative rescue pain medication. Consequently the possibility of an inadequate postoperative pain treatment in the study patients was very low, even in the placebo group. In case of PONV standard of care treatment with ondansetron was established. Furthermore, pregnancy was ruled out via a pregnancy test (hCG) in female patients prior to enrollment in this study.

Background therapy:

Included were patients receiving elective cruciate ligament surgery. Patients received a standard of care total intravenous anesthesia consisting of an induction with propofol, remifentanil and, if relaxation required, rocuronium followed by a maintenance with remifentanil and propofol. PCA was established after the patient awoke, containing 20 mg hydromorphone in 50 ml saline solution.

Evidence for comparator:

A multimodal approach including opiates and nonsteroidal anti-inflammatory drugs (NSAIDs), coxibs or paracetamol (acetaminophen) as well as an around-the-clock regimen of NSAIDs, coxibs, or paracetamol (acetaminophen) is standard of care. Intravenous diclofenac has an established role in the treatment of acute and chronic pain as well as in postoperative pain and has been in use for several decades in Europe.
Placebos are typically used as controls for the active treatment under investigation in RCTs.

Actual start date of recruitment	01 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 72
Worldwide total number of subjects	72
EEA total number of subjects	72

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)	72
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients undergoing elective cruciate ligament surgery at the general hospital of Vienna and who meet all enrollment criteria received detailed oral information about the study as well as a patient information leaflet. The patients were given amble time (but at minimum 24 hours) for consideration before enrollment in the study.

Pre-assignment

Screening details:

enrollment criteria: Age 18 to ≤ 85 years, No analgesics within 48 hours prior to surgery (surgery-related medication excluded), Absence of congestive heart failure classes 2 or higher (NYHA), Absence of ischemic heart disease, Absence of cerebro-vascular disease, Absence of risk factors for card. vasc. events (e.g. aHT, DM II)

Pre-assignment period milestones

Number of subjects started	72
Intermediate milestone: Number of subjects	Registration, Randomisation: 72
Number of subjects completed	72

Period 1

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

Blinding implementation details:

Patients were randomized pre-surgery using the web-based randomizer provided by the Institute for Medical Informatics, Statistics and Documentation, Medical University Graz.(https://www.randomizer.at/) to one of the three study arms. The study arms were numbered 1, 2, 3 and received according study medications, provided and labelled in accordance with the requirements of the AMG by the hospital pharmacy. Unblinding of the groups occured after conclusion

Arms

Are arms mutually exclusive?	Yes
Arm title	investigational medicinal products

Arm description:

Patients in this arm received the investigational product containing 75 mg diclofenac and 30 mg orphenadrine citrate as active ingredients in 250 ml saline solution

Arm type	Experimental
Investigational medicinal product name	Neodolpasse® Infusion Solution (250 mL)
Investigational medicinal product code	
Other name	diclofenac and orphenadrine
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

A single bottle (250 mL) of the investigational product contained 75 mg diclofenac and 30 mg orphenadrine citrate as active ingredients.
Total treatment durationwas less than 24 hours. Each patient received two (2) infusions. The first infusion of investigational medicinal product was administered directly after fixation of the graft replacement. The second infusion was started after an interval of 8 hours +/- 30 minutes counted from the start of the first infusion. Both were administered as an intravenous drip.

Arm title	Active comparator

Arm description:

Patients in this arm received the active comparator

Arm type	Active comparator
Investigational medicinal product name	Diclofenac
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

A single bottle (250 mL) of the active comparator product contains 75 mg diclofenac as active ingredient. Total treatment duration was less than 24 hours. Each patient received two (2) infusions. The first infusion of comparator was administered directly after fixation of the graft replacement. The second infusion was started after an interval of 8 hours +/- 30 minutes counting from the start of the first infusion. The comparator was provided as an intravenous drip.

Arm title	placebo

Arm description:

patients in this arm received a placebo infusion.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Physiologic saline infusion (250 mL). Total treatment duration was less than 24 hours. Each patient in this arm received two (2) infusions. The first infusion of placebo was administered directly after fixation of the graft replacement. The second infusion was started after an interval of 8 hours +/- 30 minutes counting from the start of the first infusion. The placebo was administered as an intravenous drip.

Number of subjects in period 1	investigational medicinal products	Active comparator	placebo
Started	24	24	24
recovery room	23	24	23
24h	23	21	21
Completed	23	21	21
Not completed	1	3	3
Consent withdrawn by subject	-	2	1
Protocol deviation	1	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	72	72	
Age categorical Units: Subjects			
Adults (18-64 years)	72	72	
Age continuous Units: years			
arithmetic mean	31.4		
standard deviation	± 9.25	-	
Gender categorical Units: Subjects			
Female	23	23	
Male	49	49	

End points

End points reporting groups

Reporting group title	investigational medicinal products
Reporting group description:	
Patients in this arm received the investigational product containing 75 mg diclofenac and 30 mg orphenadrine citrate as active ingredients in 250 ml saline solution	
Reporting group title	Active comparator
Reporting group description:	
Patients in this arm received the active comparator	
Reporting group title	placebo
Reporting group description:	
patients in this arm received a placebo infusion.	

Primary: mean dose of hydromorphone required via PCA in the first 2h

End point title	mean dose of hydromorphone required via PCA in the first 2h
End point description:	

End point type	Primary
End point timeframe:	
2h after surgery	

End point values	investigational medicinal products	Active comparator	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	21	
Units: mg				
arithmetic mean (standard deviation)	1.37 (± 0.78)	1.56 (± 1.19)	1.54 (± 0.57)	

Statistical analyses

Statistical analysis title	ANOVA for mean dose of hydromorphon 2h
Comparison groups	Active comparator v placebo v investigational medicinal products
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.737
Method	ANOVA
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2732
upper limit	1.7053
Variability estimate	Standard deviation
Dispersion value	0.8718

Primary: total dose of hydromorphone required via PCA (24h)

End point title	total dose of hydromorphone required via PCA (24h)
End point description:	
End point type	Primary
End point timeframe:	
24h post-surgery	

End point values	investigational medicinal products	Active comparator	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	21	
Units: mg				
arithmetic mean (standard deviation)	4.13 (± 2.57)	5.73 (± 4.75)	5.90 (± 2.90)	

Statistical analyses

Statistical analysis title	ANOVA for mean dose of hydromorphon 24h
Comparison groups	investigational medicinal products v Active comparator v placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.188
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3378
upper limit	6.0991
Variability estimate	Standard deviation
Dispersion value	3.55417

Adverse events

Adverse events information

Timeframe for reporting adverse events:

48h post-surgery

Adverse event reporting additional description:

The local and systemic tolerability and safety of the clinical study medications was assessed, as were possible neurological side effects using the Delirium Detection Score 2h and 24h after the first infusion. Overall pharmacological safety of the infusion solution was assessed via laboratory safety values.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	investigational medicinal products

Reporting group description:

Patients in this arm received the investigational product containing 75 mg diclofenac and 30 mg orphenadrine citrate as active ingredients in 250 ml saline solution

Reporting group title	Active comparator

Reporting group description:

Patients in this arm received the active comparator

Reporting group title	placebo

Reporting group description:

patients in this arm received a placebo infusion.

Serious adverse events	investigational medicinal products	Active comparator	placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	0 / 21 (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	investigational medicinal products	Active comparator	placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 23 (8.70%)	2 / 21 (9.52%)	2 / 21 (9.52%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Paraesthesia	Additional description: paraesthesia all fingertips right hand for several hours		
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Itching scar	Additional description: itching around infusion site		
subjects affected / exposed	0 / 23 (0.00%)	1 / 21 (4.76%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 21 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Hypokalaemia	Additional description: laboratory finding		
subjects affected / exposed	1 / 23 (4.35%)	0 / 21 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	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