Clinical trial results:
A Clinical Study to Evaluate the Safety and Effectiveness of NOVOCART® 3D plus Compared to Microfracture in the Treatment of Articular Cartilage Defects of the Knee.

Summary

EudraCT number	2011-005798-22
Trial protocol	DE AT GB CZ PL HU LV LT FR
Global end of trial date	28 February 2023

Results information

Result version number	v1 (current)
This version publication date	07 December 2023
First version publication date	07 December 2023

Trial information

Trial identification

Sponsor protocol code	AAG-G-H-1202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01656902
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TETEC – Tissue Engineering Technologies – AG
Sponsor organisation address	Aspenhaustrasse 18, Reutlingen, Germany, 72770
Public contact	Chief Medical Officer, TETEC – Tissue Engineering Technologies – AG, christoph.gaissmaier@tetec-ag.de
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001823-PIP01-15
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	24 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Objectives of the final analysis: 60 months efficacy and safety of the matrix-associated autologous chondrocyte implantation product NOVOCART 3D plus (N3D plus) in comparison to microfracture (MFx) for the treatment of cartilage defects of the knee (defect size 2 - 6 cm2).
Primary Objective: To demonstrate superiority of N3D plus versus MFx based on the IKDC subjective score improvement from baseline to the score measured at the 24-months post treatment.
Secondary objectives: Assessment of several efficacy variables for all follow-up time points until 60 months: change of IKDC subjective score and IKDC objective physician score, change of overall KOOS and KOOS subscores, KOOS and IKDC responder rates, MOCART MRI score, change of SF-36 score, proportion of treatment failures, safety variables

Protection of trial subjects:

Allowed concomitant medications: Outside the time windows specified in the trial protocol (washout, 2 weeks post MFx/N3D plus transplantation) normal standard of care should be followed. All concomitant medications were to be documented.
Regular follow-up visits were performed to monitor efficacy and safety after treatment. All adverse events were to be documented.
Regular on-site monitoring as well as several quality-assurance audits by TETEC AG or its designees were performed.
Safety data were reviewed by TETEC AG/the medical monitor and an external Clinical Safety Board on a regular basis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 May 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Czechia: 47
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	Latvia: 7

Country: Number of subjects enrolled	Lithuania: 69
Worldwide total number of subjects	263
EEA total number of subjects	255

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)	2
Adults (18-64 years)	261
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled and treated between May 2013 and February 2018 at 35 clinical sites in 10 European countries.

Pre-assignment

Screening details:

All patients with cartilage defects consulting the investigator during the recruitment phase of this clinical trial were informed of the trial. Patients who were interested in study participation, and had read the Patient Information and signed and dated the Patient Informed Consent form, were screened for eligibility (348 patients screened).

Pre-assignment period milestones

Number of subjects started	263
Number of subjects completed	263

Period 1

Period 1 title	Treatment and follow-up period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	N3D group

Arm description:

Autologous chondrocyte implantation with NOVOCART 3D plus

Arm type	Experimental
Investigational medicinal product name	NOVOCART 3D plus
Investigational medicinal product code	M09AX02 (ATC code)
Other name	
Pharmaceutical forms	Implant, Implantation matrix
Routes of administration	Implantation, Intraarticular use, Intralesional use, Local use

Dosage and administration details:

The product NOVOCART® 3D plus contains a total of 8.25 - 44 x 106 articular chondrocytes as active substance, seeded on a biphasic bioresorbable collagen-based scaffold (matrix) of bovine origin consisting of a membrane cover and a cell-carrying porous sponge lying underneath. Matrix-associated chondrocyte implantation (M-ACI) treatment with NOVOCART® 3D plus requires 2 surgeries. During arthroscopy small cartilage biopsies are taken from a non-weight bearing area of the knee and sent to TETEC AG for NOVOCART® 3D plus transplant production. About 3 to 4 weeks later, the transplantation takes place in a second surgery. NOVOCART® 3D plus is implanted via a minimally invasive approach (mini-arthrotomy). The cell-seeded matrix is cut or punched intraoperatively by the surgeon to fit the defect size and shape. The transplant is sutured into the defect area with absorbable suture material applied in simple interrupted sutures or fixed with absorbable minipins.

Arm title	Microfracture

Arm description:

Microfracture

Arm type	Active comparator

Investigational medicinal product name	No IMP assigned in this arm
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Intraarticular use

Dosage and administration details:

During microfracturing, the defect is cleansed from diseased or destroyed cartilage tissue down to the subchondral bone plate (debridement). Defect rims have to be debrided into the healthy cartilage tissue. An instrument set of two different angled microfracture picks (20° and 40°) is provided by TETEC AG to perform the microfracture procedure. The exposed bone plate is then perforated preferably by one of these picks until focal bleeding occurs or fat droplets appear. In order to avoid a fracture of the bone plate, the perforation distances should exceed 3-4 mm (Steadman et al., 1999).

Number of subjects in period 1	N3D group	Microfracture
Started	178	85
Completed	158	72
Not completed	20	13
Consent withdrawn by subject	3	4
Adverse event, non-fatal	1	-
Not specified	9	2
Lost to follow-up	7	7

Baseline characteristics

Reporting groups	
Reporting group title	N3D group
Reporting group description:	
Autologous chondrocyte implantation with NOVOCART 3D plus	
Reporting group title	Microfracture
Reporting group description:	
Microfracture	

Reporting group values	N3D group	Microfracture	Total
Number of subjects	178	85	263
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)	2	0	2
Adults (18-64 years)	176	85	261
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	41	40	
full range (min-max)	17 to 64	18 to 61	-
Gender categorical Units: Subjects			
Female	49	24	73
Male	129	61	190

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) comprised all patients randomized who had undergone surgery (i.e., arthroscopy and microfracture for MFx patients; transplantation of NOVOCART® 3D plus for N3D patients), and with at least one primary efficacy assessment after surgery / transplantation (IKDC subjective score).	
Subject analysis set title	Safety set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Defined as all randomized patients who had received surgery with arthroscopy (i.e., microfracture in the MFx group and tissue harvest in the N3D group, respectively).	

Reporting group values	Full analysis set	Safety set (SAF)	
Number of subjects	262	263	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	260	261	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	40.5	40.5	
full range (min-max)	17 to 64	17 to 64	
Gender categorical Units: Subjects			
Female	73		
Male	189		

End points

End points reporting groups

Reporting group title	N3D group
Reporting group description:	
Autologous chondrocyte implantation with NOVOCART 3D plus	
Reporting group title	Microfracture
Reporting group description:	
Microfracture	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) comprised all patients randomized who had undergone surgery (i.e., arthroscopy and microfracture for MFx patients; transplantation of NOVOCART® 3D plus for N3D patients), and with at least one primary efficacy assessment after surgery / transplantation (IKDC subjective score).	
Subject analysis set title	Safety set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Defined as all randomized patients who had received surgery with arthroscopy (i.e., microfracture in the MFx group and tissue harvest in the N3D group, respectively).	

Primary: IKDC subjective score change from baseline (24 mo)

End point title	IKDC subjective score change from baseline (24 mo)
End point description:	
The IKDC subjective score is an established, knee-specific, patient-reported outcome measure. The questionnaire covers 3 separate categories: "symptoms" (7 questions), "sports activity" (2 questions), and "current knee function" (1 question). The IKDC subjective total transformed score has a span from 0 to 100, with higher values indicating higher levels of function and lower levels of symptoms. Data for 24 months follow-up (primary endpoint, main analysis) is reported here.	
End point type	Primary
End point timeframe:	
24 months	

End point values	N3D group	Microfracture		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	85		
Units: points				
arithmetic mean (standard deviation)	32.31 (± 21.285)	32.00 (± 23.544)		

Statistical analyses

Statistical analysis title	IKDC change from baseline (main analysis 24 mo)
Comparison groups	N3D group v Microfracture

Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0226
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.02
Confidence interval	
level	95.48 %
sides	2-sided
lower limit	-4.17
upper limit	6.21

Secondary: Change from baseline in IKDC objective score (60 mo)

End point title	Change from baseline in IKDC objective score (60 mo)

End point description:

The IKDC objective score is performed by the investigator to evaluate a variety of knee conditions including ligament, meniscal, articular cartilage, arthritis, and patellofemoral injuries. The assessment consists of a functional assessment of the knee (range of motion, rotation, crepitation), as well as instrumental and/or imaging-based evaluation of the different compartments.
The form contains items that fall into one of 7 measurement domains. The 7 domains assessed by the knee examination form are:
1. Effusion
2. Passive Motion Deficit
3. Ligament Examination
4. Compartment Findings
5. Harvest Site Pathology
6. X-ray Findings
7. Functional Test
Each item is evaluated using a 4-grade classification into "normal", "nearly normal", "abnormal", and "severely abnormal". For the current analysis only the first 3 domains were considered and analyzed categorically.
Here the results after 60 months follow-up are presented.

End point type	Secondary

End point timeframe:

60 months

End point values	N3D group	Microfracture		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	85		
Units: patients				
Normal	131	56		
Nearly normal	16	8		
Abnormal	4	4		
Severely abnormal	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Knee Injury and Osteoarthritis Outcome Score (KOOS) change from baseline

End point title	Overall Knee Injury and Osteoarthritis Outcome Score (KOOS) change from baseline

End point description:

The KOOS has been developed as an instrument to assess the patients' opinion about their knee and associated problems. The KOOS consists of 5 subscales; pain, other symptoms, function in daily living (ADL), function in sport and recreation (sport/rec) and knee-related quality of life QoL. The last week is taken into consideration when answering the questions. Standardized answer options are given (5 Likert boxes) and each question gets a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. In addition, the overall KOOS score, defined as the average of the 5 subscale scores (ensuring equal weighting of all subscales), can be calculated.
Data for 60 months follow-up is reported here. The statistical analysis at 24 and 60 months is provided in the attachment.

End point type	Secondary

End point timeframe:

60 months

End point values	N3D group	Microfracture		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	85		
Units: points				
least squares mean (confidence interval 95%)	32.23 (29.56 to 34.91)	29.04 (25.25 to 32.84)		

Attachments (see zip file)	Overall KOOS changes from baseline/Overall KOOS LS mean

Statistical analyses

No statistical analyses for this end point

Secondary: KOOS subscore changes from baseline

End point title	KOOS subscore changes from baseline

End point description:

The KOOS has been developed as an instrument to assess the patients' opinion about their knee and associated problems. The KOOS consists of 5 subscales; pain, other symptoms, function in daily living (ADL), function in sport and recreation (sport/rec) and knee-related quality of life QoL. The last week is taken into consideration when answering the questions. Standardized answer options are given (5 Likert boxes) and each question gets a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. In addition, the overall KOOS score, defined as the average of the 5 subscale scores (ensuring equal weighting of all subscales), can be calculated.
Data for subscore "sports/rec" after 60 months follow-up is reported here. The statistical analysis of all subscores at 24 and 60 months is provided in the attachment.

End point type	Secondary

End point timeframe:

60 months

End point values	N3D group	Microfracture		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	85		
Units: points				
least squares mean (standard deviation)	45.55 (± 28.777)	40.14 (± 28.722)		

Attachments (see zip file)	KOOS subscores LS mean changes from baseline/KOOS

Statistical analyses

No statistical analyses for this end point

Secondary: SF-36 component summary score changes from baseline

End point title	SF-36 component summary score changes from baseline

End point description:

The SF-36 (version 2 used in this study) asks 36 questions to measure functional health and well-being from the patient's perspective.
A physical (PCS) and mental (MCS) component summary score is calculated based on the data of 8 health domains.
Data for the MCS after 60 months follow-up is reported here. The statistical analysis at 24 and 60 months for both the MCS and PCS is provided in the attachment.

End point type	Secondary

End point timeframe:

60 months

End point values	N3D group	Microfracture		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	79		
Units: points				
least squares mean (confidence interval 95%)	3.54 (2.10 to 4.98)	2.47 (0.40 to 4.54)		

Attachments (see zip file)	SF-36 LS mean changes from baseline/SF-36 LS mean changes

Statistical analyses

No statistical analyses for this end point

Secondary: MOCART score

End point title	MOCART score

End point description:

The Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score version 2.0 was used to assess in vivo performance of cartilage repair. The MOCART 2.0 total score consists of 7 items and ranges from 0 points (no repair) to 100 score points (normal cartilage).
The results of the MOCART sum score after 60 months are presented here. MOCART subscores after 60 months and MOCART sum scores for other timepoints are given in the attachment.

End point type	Secondary

End point timeframe:

60 months

End point values	N3D group	Microfracture		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	35		
Units: points				
least squares mean (confidence interval 95%)	74.09 (69.36 to 78.81)	72.53 (66.11 to 78.96)		

Attachments (see zip file)	MOCART sum and subscores analysis.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Treatmentfailure rate

End point title	Treatmentfailure rate

End point description:

Definition 1: Treatment failures were defined as all graft/microfracture-related conditions requiring surgical re-intervention
Definition 2: Intraoperatively diagnosed treatment failures were defined as all conditions that required surgical re-interventions affecting the closed surface of the transplant/microfracture area (the surface was not closed when the defect area was grade 3 or 4 ICRS) and/or required additional cartilage repair modalities on the target defect.
The numbers of treatment failures according to definition 1 are presented. Rates according to definition 2 are provided in the attachment.

End point type	Secondary

End point timeframe:

60 months

End point values	N3D group	Microfracture		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	72		
Units: Patients	8	2		

Attachments (see zip file)	Treatment failure rate/Treatment failure rate.docx

Statistical analyses

No statistical analyses for this end point

Secondary: IKDC subjective score change from baseline (60 mo)

End point title	IKDC subjective score change from baseline (60 mo)

End point description:

The IKDC subjective score is an established, knee-specific, patient-reported outcome measure. The questionnaire covers 3 separate categories: "symptoms" (7 questions), "sports activity" (2 questions), and "current knee function" (1 question). The IKDC subjective total transformed score has a span from 0 to 100, with higher values indicating higher levels of function and lower levels of symptoms.

End point type	Secondary

End point timeframe:

60 months

End point values	N3D group	Microfracture		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	85		
Units: points				
arithmetic mean (standard deviation)	37.20 (± 21.06)	35.51 (± 19.69)		

Statistical analyses

Statistical analysis title	IKDC subjective change from baseline (60 mo)
Comparison groups	N3D group v Microfracture
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3
upper limit	6.4

Other pre-specified: IKDC subjective score reponder rates

End point title	IKDC subjective score reponder rates

End point description:

Responder I: Response defined as an improvement of >20.5 points from baseline.
Responder II: Response defined as an improvement of ≥11.5 points from baseline.
Results for responder rate definition I after 60 months is given here. Results for both responder definitions at all measured timepoints is presented in the attachment.

End point type	Other pre-specified

End point timeframe:

60 months

End point values	N3D group	Microfracture		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	70		
Units: Patients				
Responder	127	56		
Non-responder	30	14		

Attachments (see zip file)	IKDC subjective reponder rate/IKDC subjective reponder rate.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall KOOS responder rate

End point title	Overall KOOS responder rate

End point description:

Response for overall KOOS is defined as an improvement of at least 10 points from baseline.
KOOS reponder rates after 60 months are reported here, other timepoints are given in the attachment.

End point type	Other pre-specified

End point timeframe:

60 months

End point values	N3D group	Microfracture		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	71		
Units: Patients				
Responder	138	63		
Non-responder	18	8		

Attachments (see zip file)	Overall KOOS responder rate/Overall KOOS reponder rate.docx

Statistical analyses

No statistical analyses for this end point

Post-hoc: KOOS subscore substantial clinical benefit

End point title	KOOS subscore substantial clinical benefit

End point description:

For each KOOS subscale, a substantial clinical benefit (SCB) rate (referred to as SCB responder rate) was defined based on the following SCB thresholds (Ogura et al. 2018):

Pain: 27.7
Symptoms: 14.28
Function in daily living (ADL): 29.4
Function in sport and recreation (Sport/Rec): 30
Knee related quality of life QoL: 37.5

SCB rate for subscore "sports/rec" after 60 months follow-up is reported here. SCB rates of all subscores at 24 and 60 months are provided in the attachment.

End point type	Post-hoc

End point timeframe:

60 months

End point values	N3D group	Microfracture		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	71		
Units: Patients				
Responder (SCB)	120	40		
Non-responder (SCB)	36	31		

Attachments (see zip file)	KOOS subscore substantial clinical benefit.docx

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

60 months

Adverse event reporting additional description:

Please not that frequency thresholds for reporting non-serious adverse events was ≥5.0% at the PT level in either treatment group (SAF) and also includes serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	N3D plus

Reporting group description: -

Reporting group title	Microfracture (MFx)

Reporting group description: -

Serious adverse events	N3D plus	Microfracture (MFx)	
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 177 (23.73%)	13 / 86 (15.12%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Testicular seminoma (pure)			

subjects affected / exposed	0 / 177 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Acquired hydrocele			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Meniscus injury			

subjects affected / exposed	3 / 177 (1.69%)	4 / 86 (4.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft delamination			
subjects affected / exposed	6 / 177 (3.39%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant failure			
subjects affected / exposed	5 / 177 (2.82%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis postoperative			
subjects affected / exposed	3 / 177 (1.69%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone contusion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft complication			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft loss			

subjects affected / exposed	0 / 177 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 177 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricle rupture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebral infarction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 177 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 177 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chondropathy			

subjects affected / exposed	7 / 177 (3.95%)	2 / 86 (2.33%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	5 / 177 (2.82%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthrofibrosis			
subjects affected / exposed	3 / 177 (1.69%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 177 (1.13%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exostosis			
subjects affected / exposed	2 / 177 (1.13%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee deformity			
subjects affected / exposed	2 / 177 (1.13%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondromalacia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint adhesion			

subjects affected / exposed	0 / 177 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loose body in joint			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patellofemoral pain syndrome			
subjects affected / exposed	0 / 177 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 177 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 177 (1.13%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			

subjects affected / exposed	0 / 177 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 86 (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	N3D plus	Microfracture (MFx)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	172 / 177 (97.18%)	82 / 86 (95.35%)	
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	12 / 177 (6.78%)	6 / 86 (6.98%)	
occurrences (all)	14	6	
Ligament sprain			
subjects affected / exposed	9 / 177 (5.08%)	1 / 86 (1.16%)	
occurrences (all)	11	2	
Ligament rupture			
subjects affected / exposed	4 / 177 (2.26%)	5 / 86 (5.81%)	
occurrences (all)	5	5	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 177 (6.21%)	7 / 86 (8.14%)	
occurrences (all)	12	7	
Blood and lymphatic system disorders			
Bone marrow oedema			
subjects affected / exposed	11 / 177 (6.21%)	2 / 86 (2.33%)	
occurrences (all)	14	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	149 / 177 (84.18%)	72 / 86 (83.72%)	
occurrences (all)	371	121	

Joint effusion			
subjects affected / exposed	60 / 177 (33.90%)	18 / 86 (20.93%)	
occurrences (all)	109	39	
Joint swelling			
subjects affected / exposed	46 / 177 (25.99%)	20 / 86 (23.26%)	
occurrences (all)	73	27	
Joint range of motion decreased			
subjects affected / exposed	18 / 177 (10.17%)	7 / 86 (8.14%)	
occurrences (all)	21	7	
Osteoarthritis			
subjects affected / exposed	14 / 177 (7.91%)	8 / 86 (9.30%)	
occurrences (all)	16	9	
Joint crepitation			
subjects affected / exposed	12 / 177 (6.78%)	6 / 86 (6.98%)	
occurrences (all)	17	7	
Chondropathy			
subjects affected / exposed	12 / 177 (6.78%)	5 / 86 (5.81%)	
occurrences (all)	16	7	
Joint lock			
subjects affected / exposed	8 / 177 (4.52%)	5 / 86 (5.81%)	
occurrences (all)	10	5	
Patellofemoral pain syndrome			
subjects affected / exposed	7 / 177 (3.95%)	6 / 86 (6.98%)	
occurrences (all)	7	6	
Back pain			
subjects affected / exposed	3 / 177 (1.69%)	5 / 86 (5.81%)	
occurrences (all)	4	7	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 177 (7.34%)	10 / 86 (11.63%)	
occurrences (all)	19	14	
Corona virus infection			
subjects affected / exposed	11 / 177 (6.21%)	3 / 86 (3.49%)	
occurrences (all)	11	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2012	• Slight changes in inclusion criteria to avoid contradictions to exclusion criteria; • Details on consequences of patients requiring subsequent surgery were added (patients with subsequent surgery were allowed to remain in the study); • Specifications on confirmatory hypothesis tests of secondary efficacy endpoints were added; • An additional MRI assessment was scheduled for the screening visits (to assess eligibility criteria).
25 July 2013	• Participating countries were updated (France, Poland, Netherlands, Czech Republic); • Inclusion criterion No. 2 was generalized from "patient has symptomatic knee pain indicative of articular cartilage defects of the knee unsuccessfully treated with conservative care (e.g., analgesics, rest, and physical therapy)" to the current wording: "Patient has a localized articular cartilage defect of the femoral condyle or the trochlea of the knee. 2 localized cartilage defects are accepted if the total defect size is ≤ 6 cm2, both cartilage defects are located at the femoral condyle and/or the trochlea and both cartilage defects are to be treated with NOVOCART® 3D plus or microfracture."; • The allowed defect size was extended from "≥3 and ≤5 cm2" to "≥2 and ≤6 cm2 post debridement"; • The maximum allowed meniscus resection was extended from 33% to 50%; • The exclusion criterion "patient has had prior release and excision of scar tissue except isolated lateral release in the target knee." was deleted, as this criterion would have created an artificial situation; • A couple of exclusion criteria were deleted, as their clinical relevance and impact on study results was not evident. However, the exclusion criterion concerning prior surgical treatments of clinical relevance in the target knee was added instead; • The excluded use of steroids within the past 3 months prior to screening was limited to systemic or intraarticular steroids within 30 days prior to tissue harvest/MFx; • Low-dose treatment with NSAIDs (not capable of pain relief) was allowed; • The accepted BMI was increased from 30 kg/m2 to 35 kg/m2;

16 November 2015	• Based on supporting literature data showing the full evolvement of the beneficial treatment effects of MACT and MFx already after 24 months post-surgery, it was decided to prepone the time point for the primary efficacy analyses from 36 months to 24 months post-treatment. • A definition for treatment failure was included and the proportion of treatment failures was added as a secondary endpoint; • The originally planned patient number for the MRI sub-study (64 in each arm) was adapted to match the actual randomization ratio of 2:1 • Biomarker sampling (blood and urine) was limited from all patients to a subset of patients from pre-selected sites; • The screening period (which was previously unlimited in time) was restricted to a maximum of 3 months from screening visit 1 to visit 2 (arthroscopy); • Clarifications and slight changes in in- and exclusion criteria, e.g., clarification that, if 2 localized defects have to be treated, the size of each individual lesion had to be ≥2 cm2; permission to include patients with known history of diabetes, primary hyperparathyroidism or hyperthyroidism, provided these conditions were sufficiently controlled; the exclusion criterion "known history of cancer" was limited to the past 5 years; in the original protocol, patients taking indomethacin or other NSAIDs were not to be included into the study. This exclusion criterion was deleted and the concomitant medication section was revised accordingly to cover washout periods; • For unscheduled visits, the IKDC objective physician score, physical examination and vital signs, SF-36, KOOS, IKDC subjective score, activity level and functional status were added as mandatory assessments; • The post-treatment rehabilitation regimen according to Hirschmüller et al. was changed from a mandatory to an optional (although still recommended) procedure. Still, patients were to undergo post-treatment rehabilitation according to the standard of care in the respective site/country at least
05 October 2016	• In the context of the "Pediatric Investigational Plan" (PIP) discussions, the Pediatric Committee (PDCO) requested prospective data on the efficacy and safety of NOVOCART® 3D in skeletally mature pediatric patients. As suggested by the PDCO, the protocol was amended to include pediatric patients with closed epiphyseal growth plates. The inclusion criteria were expanded accordingly and the statistical section updated to include the subgroup analyses; • The definition of treatment failures was amended to make clear that only graft/MFx-related conditions requiring surgical re-intervention should be considered treatment failures (in the previous definition the relatedness was missing); • Latvia, Lithuania, Hungary, and Turkey were added as participating countries to the study; • HTLV-I antibody testing was introduced for all patients living in, or originating from, high-prevalence areas, or with sexual partners originating from those areas, or where the patient’s parents originated from those areas; • Cryopreservation was explicitly allowed as an exception in the event that the originally agreed transplantation date had to be postponed; • It was added that patients in the MFx arm receiving other subsequent treatments on the target lesion (e.g., other ACT, total knee replacement etc.) were to be withdrawn from the study, whereas patients in the N3D arm were to remain in the study (but only adverse events related to NOVOCART® 3D plus treatment and serious adverse events (irrespective of relationship) were to be collected in these patients after change in therapy);

11 September 2018	• The group of "further exploratory endpoints" (i.e., KOOS total responder rate, IKDC responder rate, rate of surgical re-intervention on the target knee) was added to the set of efficacy analyses; • A second definition of treatment failure (definition No. 2) was introduced to the effect that surgical re-interventions not affecting the closed surface of the transplant / microfracture area were not automatically classified as treatment failure; • Advanced T2 mapping analyses using GLCM features were added to the MRI analyses, since these features serve as a robust quantitative marker for collagen fiber organization; • The length of incision was omitted as key secondary endpoint (because this variable is recorded only in the N3D group); • Following an EMA recommendation, the IUDR procedure was used as replacement strategy for missing values in the primary and key secondary analyses. The linear mixed effect model for repeated measurements (MMRM) without imputation of missing values was implemented as a sensitivity analysis. The imputation of missing values due to treatment failure by "last observation carried forward (LOCF)" was omitted; • The nominal significance levels at the interim and main (final) analysis were fixed in order to ensure independency from the actual information available after the interim analysis (as recommended by the EMA); • A supplementary NI analysis was implemented in the case of a failed superiority test of NOVOCART® 3D plus vs. microfracture.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported