



Clinical trial results:

Prospective, Multicenter, Single-arm Phase III Clinical Trial to Evaluate the Efficacy and Safety of NOVOCART® Inject plus in the Treatment of Cartilage Defects of the Knee

Summary

EudraCT number	2016-002817-22
Trial protocol	HU CZ DE PL LT
Global end of trial date	22 February 2024

Results information

Result version number	v1 (current)
This version publication date	18 December 2024
First version publication date	18 December 2024

Trial information

Trial identification

Sponsor protocol code	AAG-G-H-1624
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03319797
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TETEC AG
Sponsor organisation address	Aspenhaustrasse 18, Reutlingen, Germany, 72770
Public contact	Chief Medical Officer, Christoph Gaissmaier, +49 71211626103, christoph.gaissmaier@tetec-ag.de
Scientific contact	Head of Clinical Development, Alexandra Kirner, +49 71211626103, alexandra.kirner@tetec-ag.de

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	12 April 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate efficacy of NOVOCART® Inject plus for the treatment of cartilage defects of the knee based on the Knee injury and Osteoarthritis Outcome Score (KOOS) responder rate 24 month after transplantation.

Protection of trial subjects:

Allowed concomitant medications: Outside the time windows specified in the trial protocol (washout, tissue harvest until 2 weeks post NOVOCART® Inject plus transplantation) normal standard of care had to be followed for pain management, deep vein thrombosis prophylaxis and for prophylactic antibiotics. Regular follow-up visits were performed to monitor efficacy and safety after treatment.

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	10 October 2017
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	Czechia: 35
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 24
Country: Number of subjects enrolled	Lithuania: 32
Country: Number of subjects enrolled	Switzerland: 1
Worldwide total number of subjects	102
EEA total number of subjects	101

Notes:

Subjects enrolled per age group

In utero	0
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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)	100
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled and treated between October 2017 and February 2019 for focal symptomatic cartilage defects of the knee at 6 Czech, 5 Hungarian, 3 Lithuanian, 2 German, and 1 Swiss centers.

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 (132 patients screened).

Period 1

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

Arms

Arm title	NOVOCART Inject plus
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Arm description:

All patients were treated with NOVOCART Inject plus (hydrogel-based autologous chondrocyte implantation)

Arm type	Experimental
Investigational medicinal product name	NOVOCART Inject plus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use, Local use

Dosage and administration details:

Treatment with NOVOCART® Inject plus required 2 surgeries. During the first surgery, autologous chondrocytes for transplant production were harvested arthroscopically. About 3 to 4 weeks later, the finished product was implanted by arthroscopy or (mini)-arthrotomy. The final product was administered using a double chamber syringe which allows mixing of the 2 components and subsequent cross-linking of the cell-carrying hydrogel at the site of administration.

NOVOCART® Inject plus contained 2 - 8 million cells per mL cell suspension (about 8 - 32 million cells per 4 mL cell suspension). The total volume of NOVOCART® Inject plus was 5 mL (4 mL cell suspension and 1 mL cross-linker). The volume to be administered depended on the size of the prepared defect. At an application height of 2.0 mm, the dosage of NOVOCART® Inject plus was 0.3 to 1.3 million cells per cm² defect area.

Number of subjects in period 1 ^[1]	NOVOCART Inject plus
Started	100
Main analysis (24 month follow-up)	100
Final analysis (60 months follow-up)	97
Completed	97
Not completed	3
Consent withdrawn by subject	1

Lost to follow-up	2
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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline data and treatment/follow-up period data are reported for the intent-to-treat population, i.e., all patients who were transplanted with Novocart Inject. The enrolled set corresponds to the safety population, i.e., all patients with cartilage tissue harvested for transplant production (102 patients). Two patients had cartilage harvested, but were finally not transplanted (1 withdrawal of consent, 1 unrelated AE requiring concomitant medication not compatible with surgery).

Baseline characteristics

Reporting groups

Reporting group title	Treatment and follow-up period
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Reporting group description:

All patients who had received NOVOCART Inject plus implantation

Reporting group values	Treatment and follow-up period	Total	
Number of subjects	100	100	
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)	98	98	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	39.8		
standard deviation	± 11.51	-	
Gender categorical			
Units: Subjects			
Female	37	37	
Male	63	63	
Prior surgeries on the target knee			
Units: Subjects			
yes	52	52	
No	48	48	
Failed prior cartilage repair at the target knee			
Units: Subjects			
Yes	8	8	
No	92	92	
Number of defects			
Units: Subjects			
One	70	70	
Two	30	30	
Defect location (larger lesion)			
Units: Subjects			
Femoral condyle	65	65	
Patellofemoral	33	33	
Tibial plateau	2	2	
ICRS defect grade (larger lesion)			

Units: Subjects			
III	67	67	
IV	33	33	
Defect aetiology (larger lesion)			
Units: Subjects			
Traumatic	59	59	
Osteochondritis dissecans	6	6	
Focal degenerative	35	35	
Body mass index			
Units: kg/m ²			
arithmetic mean	27.03		
standard deviation	± 4.095	-	
Time since diagnosis			
Units: Months			
arithmetic mean	11.292		
standard deviation	± 22.855	-	
Defect size			
Mean defect size of 130 defects.			
Units: cm ²			
arithmetic mean	4.82		
standard deviation	± 1.856	-	
Total defect size			
The mean total defect size is for the number of patients (N=100). In case of 2 lesions, both defect sizes were added to one value.			
Units: cm ²			
arithmetic mean	6.27		
standard deviation	± 2.080	-	

End points

End points reporting groups

Reporting group title	NOVOCART Inject plus
Reporting group description: All patients were treated with NOVOCART Inject plus (hydrogel-based autologous chondrocyte implantation)	

Primary: Overall KOOS responder rate at 24 mo

End point title	Overall KOOS responder rate at 24 mo ^[1]
End point description: 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. 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. The primary efficacy endpoint of the study was the responder rate based on the overall KOOS after 24 months of treatment. The KOOS responder rate was defined as the proportion of patients with ≥ 10 -point improvement in the overall KOOS from baseline. The responder rate is given here. The statistical analysis for timepoints up to 24 mo (95%-CI, p-values) is given in the attachment.	
End point type	Primary
End point timeframe: 24 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This was a single arm study, therefore no comparator group. Primary endpoint of the study was the overall KOOS responder rate at Month 24. A responder rate of 40% was the stipulated threshold for clinical relevance, and the statistical confirmation of a response rate $>40\%$ (i.e., lower 95% confidence interval boundary of $>40\%$ for the point estimate based on a binominal test) was required to conclude sufficient clinical efficacy of treatment in a confirmatory manner. Analysis given in attachment.

End point values	NOVOCART Inject plus			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: Responders				
Responder	93			
Non-responder	7			

Attachments (see zip file)	Primary analysis KOOS responder rate 24 mo/Primary analysis
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Statistical analyses

No statistical analyses for this end point

Secondary: Overall KOOS change from baseline

End point title	Overall KOOS change from baseline
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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 summary of KOOS over time (absolute values and mean changes from baseline) and statistical analysis (LS mean changes, 95%-CI) is provided in the attachment.

End point type	Secondary
End point timeframe:	
60 months	

End point values	NOVOCART Inject plus			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Change in KOOS (points)				
arithmetic mean (standard deviation)	44.86 (± 22.258)			

Attachments (see zip file)	Analysis of overall KOOS changes from baseline ove/Analysis of Summary of overall KOOS/Summary of overall KOOS.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: KOOS subscore changes from baseline

End point title	KOOS subscore changes from baseline
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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.

Data for subscore "sports/rec" after 60 months follow-up is reported here. The summary of all KOOS subscores (absolute values and mean changes from baseline) and statistical analysis (LS mean changes, 95%-CI) 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	NOVOCART Inject plus			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: KOOS subscore change (points)				
arithmetic mean (standard deviation)	58.16 (± 28.250)			

Attachments (see zip file)	Summary of KOOS subscores at 24 and 60 mo/Summary of Analysis of KOOS subscorechanges from baseline ove/Analysis
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Statistical analyses

No statistical analyses for this end point

Secondary: IKDC subjective score change from baseline

End point title	IKDC subjective score change from baseline
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 changes from baseline at 60 months (mean and SD) is reported here. The summary of IKDC scores (absolute values and mean changes from baseline) and statistical analysis (LS mean changes, 95% CI) over time is provided in the attachment.	
End point type	Secondary
End point timeframe:	
60 months	

End point values	NOVOCART Inject plus			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: IKDC change (points)				
arithmetic mean (standard deviation)	44.86 (± 22.264)			

Attachments (see zip file)	Analysis of IKDC changes from baseline ove/Analysis of IKDC Summary of IKDC subjective score/Summary of IKDC
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Statistical analyses

No statistical analyses for this end point

Secondary: IKDC subjective responder rate

End point title	IKDC subjective responder rate
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. IKDC responder rates are defined as follows. 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	Secondary
End point timeframe:	
60 months	

End point values	NOVOCART Inject plus			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Responders				
Responder	84			
Non-responder	13			

Attachments (see zip file)	IKDC responder rates over time through Mon/IKDC responder
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Statistical analyses

No statistical analyses for this end point

Secondary: IKDC objective physician score

End point title	IKDC objective physician score
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 In a final evaluation only the first 3 groups are evaluated and classified into "normal", "nearly normal", "abnormal", and "severely abnormal". The worst group grade determines the final evaluation. Here the results after 60 months follow-up are shown. Other timepoints are given in the attachment.	
End point type	Secondary
End point timeframe:	
60 months	

End point values	NOVOCART Inject plus			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: Patients				
Normal	88			
Nearly normal	4			
Abnormal	1			
Severely abnormal	0			

Attachments (see zip file)	IKDC objective score/Summary of IKDC objective score.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L index change from baseline

End point title	EQ-5D-5L index change from baseline
End point description:	
The EQ-5D is a standardized measure of health status. This measure consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The EQ-5D-5L health states can be converted to a single index value. The hypothetical range of the index value is from -0.661 (death) to 1 (perfect health) based on the validated national value set for Germany published in 2018. In addition to the assessment of the 5 dimensions, the EQ also includes a 20 cm vertical visual analogue scale (EQ-VAS), where the endpoints are labelled "best imaginable health state" (value 100) and "worst imaginable health state" (value 0).	
End point type	Secondary
End point timeframe:	
60 months	

End point values	NOVOCART Inject plus			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: Points				
arithmetic mean (standard error)	0.327 (± 0.321)			

Attachments (see zip file)	EQ-5D-5L change in index/Analysis of EQ-5D-5L index change Summary of EQ-5D-5L values/Summary of mean EQ-5D-5L
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Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L VAS change from baseline

End point title	EQ-5D-5L VAS change from baseline
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End point description:

The EQ-5D is a standardized measure of health status. This measure consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

The EQ-5D-5L health states can be converted to a single index value. The hypothetical range of the index value is from -0.661 (death) to 1 (perfect health) based on the validated national value set for Germany published in 2018.

In addition to the assessment of the 5 dimensions, the EQ also includes a 20 cm vertical visual analogue scale (EQ-VAS), where the endpoints are labelled "best imaginable health state" (value 100) and "worst imaginable health state" (value 0).

End point type	Secondary
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End point timeframe:

60 months

End point values	NOVOCART Inject plus			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: Points				
arithmetic mean (standard deviation)	27.4 (± 22.88)			

Attachments (see zip file)

Analysis EQ-5D-5L change in VAS/Analysis of EQ-5D-5L VAS. Summary of EQ-5D-5L VAS/Summary of mean EQ-5D-5L VAS.
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Statistical analyses

No statistical analyses for this end point

Secondary: MOCART 2.0 sum score

End point title	MOCART 2.0 sum score
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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 sum scores for other timepoints (separated by smaller and larger defects) are given in the attachment. Results refer to the number of lesions (not the number of patients).

End point type	Secondary
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End point timeframe:

60 months

End point values	NOVOCART Inject plus			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: points				
arithmetic mean (standard deviation)	64.6 (± 21.77)			

Attachments (see zip file)	MOCART 2.0 per lesion size /Summary of MOCART v2 sum
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Statistical analyses

No statistical analyses for this end point

Secondary: T2 mapping

End point title	T2 mapping
End point description:	
T2 relaxation time measurement is an established marker for cartilage water and collagen content as well as collagen organization that reflects the integrity and vitality of cartilage and cartilage regenerated tissue. The T2 relaxation time measured in the repair tissue can be set in relation to the T2 relaxation time measured in the surrounding healthy cartilage, thereby resulting in a "global" T2 ratio (if only the full-thickness tissue areas are measured) and in a "zonal" T2 ratio (if, in addition, the differences in T2 relaxation times in the superficial and deep zones of the cartilage areas are considered). Ideal global and zonal T2 ratios are "1" (indicating no difference between regenerate and normal tissue), and the ratio range of 0.8 to 1.2 is regarded as "normal" (and was therefore employed for the analyses of the T2 ratios). Here zonal T2 ratios at 60 months are given (based on the number of lesions). Zonal and global T2 ratios at all timepoints are given in the attachment.	
End point type	Secondary
End point timeframe:	
60 months	

End point values	NOVOCART Inject plus			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Ranges				
<0.8	3			
0.8-1.2	18			
>1.2	2			

Attachments (see zip file)	Summary of T2 global and zonal ratios/Summary of T2 global
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall KOOS responder rate up to 60 mo

End point title	Overall KOOS responder rate up to 60 mo
End point description:	
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. 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. The overall KOOS responder rate was defined as the proportion of patients with ≥ 10-point improvement in the overall KOOS from baseline. Here, the results at 60 months are given. Results of earlier timepoints are provided in the attachment.	
End point type	Other pre-specified
End point timeframe:	
60 months	

End point values	NOVOCART Inject plus			
Subject group type	Reporting group			
Number of subjects analysed	97			
Units: Responders				
Responder	90			
Non-responder	7			

Attachments (see zip file)	Overall KOOS responder rates over time through Mon/Overall
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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:

Adverse events were collected at each scheduled and unscheduled visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	NOVOCART Inject plus
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Reporting group description:

The safety population consists of all patients who have undergone tissue harvest for transplant production.

Serious adverse events	NOVOCART Inject plus		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 102 (17.65%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	3 / 102 (2.94%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple injuries			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic contusion			

subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenic rupture			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transplant failure			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia paroxysmal			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Cervicogenic headache			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple sclerosis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Acquired hydrocele			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Vocal cord cyst			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Hypertrophic scar			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chondropathy			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint adhesion			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint instability			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Knee deformity			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lateral patellar compression syndrome			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Osteoarthritis			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Rectal abscess			
subjects affected / exposed	1 / 102 (0.98%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	NOVOCART Inject plus		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 102 (78.43%)		
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	9 / 102 (8.82%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	43 / 102 (42.16%)		
occurrences (all)	66		
Joint swelling			
subjects affected / exposed	20 / 102 (19.61%)		
occurrences (all)	34		
Joint effusion			
subjects affected / exposed	19 / 102 (18.63%)		
occurrences (all)	27		
Joint crepitation			
subjects affected / exposed	10 / 102 (9.80%)		
occurrences (all)	10		
Infections and infestations			
Corona virus infection			

subjects affected / exposed	20 / 102 (19.61%)		
occurrences (all)	21		
Viral upper respiratory tract infection			
subjects affected / exposed	6 / 102 (5.88%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2017	- A single knee x-ray was added to the baseline examinations, since the Kellgren and Lawrence grade (needed for eligibility assessment) can only be assessed by plain radiography; - Correction of patella malalignment was additionally allowed to be performed during Visit 3/implantation visit (previously: only before Visit 3); - It was clarified that any concomitant surgeries performed at Visit 3 should be completed before the NOVOCART® Inject plus injection into the defect
06 June 2017	- It was added to pre-operative inclusion criterion No. 1 that the closure of the epiphyses in pediatric patients has to be confirmed by MRI or x-ray; - It was added to pre-operative exclusion No. 5 that patients, who had failed prior biologic reconstructive procedure, could only be included, if these procedures had been performed ≥ 24 months prior to Visit 1 (previously: 12 months); - A further sensitivity analysis taking into account the concomitant analgesic medication was added; - Time since start of target knee symptoms was added as a covariable to the covariate analyses. In addition, subgroups (dichotomized at the sample median) were formed based on the variables "time since diagnosis" and "time since start of target knee symptoms"
14 March 2018	- The treatment failure definition was changed (according to the old definition, any re-intervention on the transplant area was to be classified as treatment failure). The rationale for the change was the fact that corrective surgery without otherwise destroying the integrity of the transplant area (e.g., a removal of hypertrophic tissue) is not necessarily associated with treatment failure. This point was addressed with the revised treatment failure definition: "all surgical reinterventions affecting the closed surface of the transplant area (the surface is not closed when the defect area is grade 3 or 4 ICRS) and/or require additional cartilage repair modalities on the target defect" - Defect etiology in eligibility criteria was no longer limited to defects caused by trauma or osteochondritis dissecans but patients with focal cartilage defects irrespective of defect etiology could be included. - According to the preceding protocol version, target defects were not allowed to be located on articulating joint areas (e.g., trochlea and patella). With amendment No. 3, defects were accepted to be located on articulating joint areas, as long as the articulating joint surface opposite to the defect was intact; - It was added to the inclusion criteria that the defect(s) to be treated need to have a well-contained chondral structure surrounding the defect - According to the preceding protocol version, any diffuse chondromalacia was an exclusion criterion. With amendment No. 3, patients with Grade 1 chondromalacia according to the Outerbridge classification were allowed to be included; - The definition of the intent-to-treat (ITT) population was changed from "all patients having tissue harvested" to "all patients who have received NOVOCART® Inject plus implantation";
07 April 2020	An interim analysis of efficacy and safety data was originally planned once 66% of the planned number of patients had completed the 24-month period and could be evaluated for the primary endpoint. However, due to the exponential patient recruitment curve it turned out that the main analysis (=all patients have completed the 24-months period) would have been due only 3 months after the planned interim analysis. As the sole purpose of this interim look was to serve as a potential trigger for the start of marketing authorization application activities, an interim analysis 3 months prior to the main analysis was not considered reasonable. Therefore, it was decided to omit the interim analysis and to move directly to the main analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/35354310>

<http://www.ncbi.nlm.nih.gov/pubmed/37655236>

<http://www.ncbi.nlm.nih.gov/pubmed/38501741>