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SYNOPTIC CLINICAL STUDY REPORT:

full version FOR REGULATORY SUBMISSION

A Prospective Randomized Multicentre Phase I/II Clinical Trial to Evaluate Safety and Efficacy of NOVOCART® Disc plus Autologous Disc Chondrocyte Transplantation (ADCT) in the Treatment of Nucleotomized and Degenerative Lumbar Discs to Avoid Secondary Disease

Protocol Number:	AAG-G-H-1102
EudraCT Number:	2010-023830-22
ClinicalTrials.gov Identifier:	NCT01640457
IND Number:	Not applicable
Test Product:	NOVOCART® Disc plus autologous disc chondrocyte transplantation (ADCT) and NOVOCART® Disc basic (no active cell component)
Indication:	herniated, nucleotomized lumbar discs, and adjacent degenerated discs (ADDs), if present
Development Phase of Study:	Phase I/II
Sponsor and Sponsor's	TETEC AG
Responsible Medical Officer:	Dr. med. Christoph Gaissmaier
Coordinating Investigators:	**O. Univ.-Prof. Dr. med. Claudius Thomé** University Clinic for Neurosurgery, Innsbruck, Austria **Prof. Dr. med. Hans Jörg Meisel** Clinic for Neurosurgery, Halle, Germany
Study initiation (FPFV):	07-OCT-2012
Study completion (LPLV):	14-JUN-2021

FPFV = first patient's first visit; LPLV = last patient's last visit

COVID-19 Impact: 1 patient had a delayed final visit; 1 patient was unwilling to attend the final study visit, which was then performed by phone; and 1 patient was unable to attend the final visit due to a COVID-19 infection and was lost to follow-up.

Report Version, Date: FINAL/24-MAY-2022

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3 STUDY SYNOPSIS

Name of company: TETEC AG
Name of finished investigational medicinal products (IMPs): NOVOCART® Disc plus ADCT and NOVOCART® Disc basic (no active cell component)
Name of active ingredient: ADCT

Title of study:

A prospective randomized multicentre phase I/II clinical trial to evaluate safety and efficacy of NOVOCART® Disc plus Autologous Disc Chondrocyte Transplantation (ADCT) in the treatment of nucleotomized and degenerative lumbar discs to avoid secondary disease

Study ID: AAG-G-H-1102; **EudraCT Number:** 2010-023830-22;
ClinicalTrials.gov identifier: NCT01640457; **IND Number**: Not applicable

Coordinating Investigators, number of study centres and countries:

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Centres: 10

Countries: Austria and Germany

Publications

Tschugg A, Diepers M, Simone S, et al. 2017.[1]

Tschugg A, Michnacs F, Strowitzki M, Meisel HJ, Thomé C. 2016.[2]

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Study period:

First patient's first visit (FPFV): 07-OCT-2012
Last patient's last visit (LPLV): 14-JUN-2021

Reporting periods:

Safety: Same as study period

- 13-MAR-2014 (interim analysis and report, safety only)
- 07-OCT-2016 (analysis only)
- 27-OCT-2017 (analysis only)
- 26-OCT-2018 (analysis only)

Phase of development of study: Phase I/II

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Background and rationale for the study

The aim of this study was to explore the clinical applicability, safety, and efficacy of NOVOCART® Disc plus (NDplus) in the repair of a herniated disc with an indication for an elective sequestrectomy, and of the ADD, if present. NDplus was developed to provide rehydration and biological integrity of degenerative lumbar discs to prevent secondary disease such as disc herniation and segmental instability. It was hypothesized that by transplanting disc derived chondrocytes into degenerative discs, where the cells will be held in situ re-differentiate and produce new cartilaginous tissue. Thus patients were expected to experience better outcomes as compared to control (standard care [SC] sequestrectomy). Although NOVOCART® Disc basic (NDbasic) alone has no active cell component, its hydrophilic characteristics and specific ingredients for influencing cell metabolism and anti-inflammatory as well as anti-angiogenic, anti-osteogenic, and anti-neurotropic milieu conditioning has a potential for disc regeneration and effective pain treatment. The influence of NDbasic on outcome effects was also investigated. The known risks of adverse reactions to the IMP (outlined in the protocol) or associated with the medical procedures that were used during the study in order to handle the IMP were very small when taking into account the expected improvement to the individual participant or the entire group of patients suffering from this disease. Methods to minimise bias (e.g., randomisation) were incorporated into the study and patient protection measures included rigorous monitoring and a Clinical Safety Board to review data.

Note: Final safety results and a brief summary of efficacy are reported in this synoptic clinical study report due to the Sponsor's decision to permanently discontinue the NDplus and NDbasic development programme. Further reporting details are provided in the Methodology section below.

Objectives and endpoints:

Objectives	Endpoints
Primary (Safety)	
• To characterize the safe use of the IMP and the transplantation/implantation procedures.	• Prevalence of subsequent surgical interventions. • Adverse events (AEs) by event category, intensity, seriousness, and relationship to the graft and/or procedure. • Any unanticipated AE. • Specific laboratory parameters according to product compatibility and availability (only in Phase I): C-reactive protein (CRP), interleukin-6 (IL-6), leukotriene E4 (LTE-4)
Primary (Efficacy)	**Primary Endpoints**
• To characterize the cumulative functional and radiological effects of NDplus over NDbasic and SC.	• Oswestry Disability Index (ODI): Mean total score changes for NDplus, NDbasic, and SC from baseline (Visit [V] 2a) to - V3a (pre-implantation NDplus and NDbasic only) - 1.5 months - 3 months - 6 months - 12 months (V7) - 24 months (V8) - 60 months (V11, end of study)
• To characterize the effect of NDbasic alone over SC.	• ODI: Differences in changes of ODI total scores between NDbasic and SC from baseline (V2a) to - V3a (NDbasic only) - 1.5 months - 3 months - 6 months - 12 months (V7) - 24 months (V8) - 60 months (V11, end of study)
• To characterize the effect of the IMP on the ADDs.	• ODI: Differences in changes of ODI total scores between NDplus, NDbasic, and SC from baseline (V2a) to the following time points in patients with ADDs: - V3a (NDplus and NDbasic only)

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	- 1.5 months - 3 months - 6 months - 12 months (V7) - 24 months (V8) - 60 months (V11, end of study)
• To define metabolic parameters that measure identity, purity, and potency of the extracted tissue, of the isolated cells, and of the in vitro expanded cells.	• 21 analytes measured in cell culture supernatants: Interleukin-1β, -4, -6, -8, -10, Interleukin-1 receptor antagonist, VEGF (Vascular endothelial growth factor), IFN-γ (Interferon-γ), TNF-α (Tumour necrosis factor-α), RANTES (Regulated and Normal T cell expressed and secreted), BAP (Bone alkaline phosphatase), BMP-2 (bone morphogenetic protein-2), Cathepsin-K, COMP (Cartilage oligomeric matrix protein), CS 846 (chondroitin sulfate-846 epitope of aggrecan), HA (Hyaluronic acid), MMP-3 (matrix metalloproteinase-3), TGF (Transforming growth factor) -β1, -β2, β3, YKL-40 (Chitinase-3-like protein 1, CHI3L1)
• To define metabolic parameters in patients to control the status of tissue repair.	• 20 analytes measured in serum samples: Interleukin-1β, -4, -6, -8, -10, Interleukin-1 receptor antagonist, VEGF (Vascular endothelial growth factor), IFN-γ (Interferon-γ), TNF-α (Tumour necrosis factor-α), RANTES (Regulated and Normal T cell expressed and secreted), COMP (Cartilage oligomeric matrix protein), CS 846 (chondroitin sulfate-846 epitope of aggrecan), HA (Hyaluronic acid), YKL-40 (Chitinase-3-like protein 1, CHI3L1), C2C (Collagen Type II Cleavage), CPII (Procollagen Type II propeptide synthesis), CTX-I (C-terminal telopeptides of type I collagen), CTX-II (C-terminal telopeptides of type II collagen), NTX-I (N-terminal telopeptides of type I collagen), PIIANP (type IIA collagen N-propeptide)

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	• CTX-I, CTX-II, NTX-I and creatinine (for normalization) were analysed in the urine samples.
• To define the prognostic value of metabolic and radiological parameters in the context of disc degeneration, functional status, and quality of life.	• No correlation between metabolic and radiological parameters and clinical outcome was performed due to discontinuation of product development.
Secondary (Efficacy)	
• To quantify parameters of surgical procedures	• Surgical parameters, including length of procedure
• To evaluate the sensitivity and effectiveness of methods in measuring the treatment effects.	• Efficacy will be evaluated using the following clinical and morphological outcome measures comparing baseline (V2a) data to follow-up data at t0 (V2b), t5 (V3a, V3b, only NDplus, NDbasic), 1.5-, 3-, 6-, 12 (V7), 24- (V8), and 60-month (V11, end of study) follow-up assessments: - Magnetic resonance imaging (MRI) signal (disc height, disc volumetry, signal intensity) - ODI - Visual analogue scale (VAS) for back pain and leg pain - Health-related quality of life as measured by the SF-36 - Functional status (Finger-ground distance and Schober's sign) - Neurological status (Jenny Scale) - Return to work (days) - Analgesic medication use - Health Questionnaire EQ-5D
• To estimate the variability in outcomes.	• Efficacy will be explored using the following clinical outcome measures comparing baseline data to follow-up data at the 36 and 48-months follow-up assessments via telephone interview: - ODI

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	- Health-related quality of life as measured by the SF-36. - Health Questionnaire EQ-5D.
• To gauge physician acceptability and ease of use of the investigational product.	• Physician assessments of ease of transplantation/implantation.

Estimand: Estimand was not defined for this study.

Methodology:

This was a non-confirmatory, prospective, multicentre, unmasked, clinical trial conducted in 2 parts: Phase I focussed on safety and Phase II analysed both safety and efficacy, including outcomes to develop and validate biological markers. In Phase I, 24 patients were to be assigned to either NDplus or NDbasic in a 1:1 ratio. In Phase II, 96 eligible patients were to be randomized to NDplus, NDbasic, or SC sequestrectomy as control in a 2:1:1 ratio. Patients with a lumbar disc herniation were classified according to the presence (ADD, adjacent degenerative disc) or absence (HD, herniated disc) of a degenerative disc at the adjacent level.

In Phase I, visits included screening (V1); baseline (V2a, time point [t]0, pre-surgery, maximum 45 days post screening); sequestrectomy/tissue explant (V2b, time t0, operative, maximum 45 days post screening); a post operative examination for all sequestrectomy patients as well as pre-implant examination for patients randomised to NDplus or NDbasic (V3a, time t5, 90 d ± 15 d post t0); and transplant/implant for patients randomised to NDplus or NDbasic (V3b, time t5, operative, 90 days ± 15 d post t0).

In Phase II, visits included the same visits as in Phase I and post-surgical follow-up for post 2b SC group and post 3b NDplus/NDbasic groups as follows: V4 at 1.5 months (42 days ± 7 days, t16); V5 at 3 months (90 days ± 7 days, t17); V6 at 6 m (180 days ± 14 days, t18); V7 at 12 months (365 d ± 14 d, t19); V8 at 24 months (730 days ± 30 days, t20); V9 at 36 months (1095 days ± 30 days, t21); V10 at 48 months (1460 days ± 30 days, t22); and V11 at 60 months (1825 days ± 30 days, t23).

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All patients were evaluated at the 1.5-, 3-, 6-, 12-, 24-, 36-, and 48-months post-t0 examination in the SC study arm and 1.5-, 3-, 6-, 12-, 24-, 36-, and 48-months post-t5 examination in the NDplus and NDbasic study arms, and then 5 years post-t0/t5 to collect long-term clinical data. Efficacy measurements for functional improvement were evaluated among NDplus, NDbasic and SC. Physiological effects observed from MRI measurements were compared between appropriate treatments depending on expected treatment mechanisms. Safety data of NDplus was also combined with NDbasic to contrast against SC on procedure related risks and NDplus against NDbasic and SC together on graft-related adverse experiences. Further details are available in Section 4 of the study protocol and amendments.

Note: Although this study was completed as planned, final results are reported in this synoptic clinical study report because the Sponsor has decided to permanently discontinue the NDplus and NDbasic development programme due to lack of a clear efficacious benefit of the IMP over SC (see details in efficacy results below). Thus, the main focus of this report is safety. Laboratory safety tables from Phase I and the full set of final tables and listings, including safety data from the start of treatment (V2a) to the end of study (V11), are attached as appendices.

Number of patients (Phases 1 and II):

Planned: 120 (60 NDplus, 36 NDbasic, 24 SC)
Enrolled: 139
Randomised and treated (i.e., sequestrectomy performed): 120 (58 NDplus, 37 NDbasic, 25 SC)
Treated with at least one primary efficacy assessment: (NDplus or NDbasic implantation in the NDplus and NDbasic groups and sequestrectomy in the SC group): 98 (47 NDplus, 27 NDbasic, 24 SC)

Diagnosis and main criteria for inclusion and exclusion

Diagnosis: disc herniation with back and/or leg pain with an indication for sequestrectomy.

Main inclusion criteria:

- Aged 18 to 60 years
- Single-level lumbar disc herniation with more than 50% remaining disc height in the herniated disc in comparison to unaffected discs or at least 5 mm disc height if all discs affected.

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- Radiological inclusion criteria: Patients with ADDs must have had additional degenerative signs in the proximal adjacent lumbar level and patients without an ADD (HD) must have had no degenerative signs.

Main exclusion criteria:

- Concomitant diseases or functional impairments of specific organs:
  - Degenerative muscular or neurological conditions
  - Disease with chronically inflammable character
  - Primary hyperparathyroidism or hyperthyroidism, chronic renal failure or previous fragility fractures.
  - Systemic connective tissue or collagen disease
  - Known osteoporosis or drug-treated diabetes
  - Hereditary ocular degenerations with unclear diagnosis, retinopathies based on connective tissue-defined causes, macular corneal dystrophy
  - History of blood coagulation disease of different genesis, including known haemorrhagic diathesis of unknown cause
- Immune suppression or immune defects or the affinity for infections of known or unknown causes
- Chemo or radiotherapy within the past 5 years, or had any cancer other than non-melanoma skin cancer treated with curative intent within the past 5 years
- Radiological exclusion criteria: apparent degenerative changes in the lumbar spine; one or more dysplastic vertebral bodies within the lumbar spine; sacralised lumbar vertebra LWK5 at the level to be treated; previous or acute spondylodiscitis; segmental instability; ankylosing spondylitis or spondylolysis, lumbar scoliosis; previous trauma; discography or any other surgical intervention at the lumbar spine; previous compression or burst fracture at the level(s) to be treated; central spinal canal stenosis with evidence of a narrowing; spinal tumour; metabolic bone disease; facet ankylosis or severe facet degeneration; lumbar kyphosis

A full list of exclusion criteria is available in Section 7 of the protocol.

Test Product, dose, mode of administration, batch number(s)

Test products: NDplus and NDbasic consist of in situ cross-linking modified albumin-hyaluronic acid gel. NDplus also consists of autologous disc cells. The test product

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procurement process (sequestrectomy/tissue explant) and application (transplant/implant) are described in Section 6 of the protocol.

Dosage forms and strengths: Each NDplus product carrier contains 1 million +/- 10% viable chondrocytes per mL cell suspension. The dosage is individual. The volume of injection is dependent on the capability of the treated disc. It may vary between 0.5 and 2 mL cell suspension volume.

Mode of administration: Injection

Batch numbers: Each product has been assigned an individual batch number, which is also the patient ID number. Each patient ID/batch number has its own individual expiry date. A list of these patient ID/batch numbers and their expiry dates is available from the Sponsor upon request.

Control product, dose, mode of administration, batch number(s)

SC sequestrectomy was the control. Sequestrectomy is described in Section 6 of the protocol. There are no doses or batch numbers associated with the control.

Duration of treatment

Not applicable (as each patient received only one single batch of NDplus or NDbasic).

Statistical methods

This was a non-confirmatory study without pre-specified decision-making rules or hypotheses. All statistical analyses were descriptive and exploratory and there were no adjustment of significance levels for multiple testing or interim analyses. Confidence intervals (CIs) were calculated to estimate treatment effects and differences between treatment arms. Continuous data were summarised by means of descriptive statistics, i.e., number of patients, mean, standard deviation (SD), median, quartiles and range (minimum and maximum). Categorical variables were summarised using number and percentages of patients by category. CIs and p-values were interpreted as descriptive measures of treatment group differences in an exploratory sense. If not stated otherwise, two-sided statistical tests were performed on a nominal level of significance of 0.05 and corresponding two-sided 95%-CIs were reported. The significance level of one-sided tests was divided by two to ensure comparability with two-sided tests. The confidence level for calculation of CIs were chosen as (1-significance level) of the respective statistical test. The statistical analysis was conducted following the principles as specified in the ICH Topic E9 [ICH, 1998]. Statistical planning and evaluation of the trial were carried out by a

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qualified statistician in accordance with the ICH-guidelines and adequate biostatistical standard operating procedures. Detailed Statistical Analysis Plans (SAPs) were prepared for the interim analyses and the final analysis. The following statistical analysis sets were defined:

Enrolled set: All patients enrolled into the study, i.e., gave their informed consent.

Safety set: All patients who received surgery with sequestrectomy for tissue explant.

Full analysis set (FAS): All patients randomised who underwent surgery (sequestrectomy for SC patients; transplantation/implantation in case of NDplus or NDbasic patients) and with at least one primary efficacy assessment after surgery/implantation (ODI). This is equivalent to the ITT population.

Summary of results and conclusions

Subject disposition

A total of 139 patients were enrolled in the study. Of these, 120 patients were randomized (58 NDplus, 37 NDbasic, and 25 SC). All 120 patients were in the Safety set and of these, 98 (81.7%) patients were in the FAS (47 [81.0%] NDplus, 27 [73.0] NDbasic, and 24 [96.0] SC). Of the 120 patients in the Safety set, 32 (26.7%) discontinued the study prematurely with the most frequently reported reasons of withdrawn consent (10 patients), ineligibility due to inclusion/exclusion criteria (7 patients), and lack of compliance (5 patients). One patient in the SC group was withdrawn due to a COVID-19 infection. The patient did not attend a final visit and was lost to follow up.

COVID-19: This study was conducted through the COVID-19 pandemic period and as a result, COVID-19-related protocol deviations occurred that are summarized as follows:

One patient in the SC group (08/0808) was unwilling to attend the final study visit due to COVID-19. The on-site study visit was postponed for 3 months. However, the site sent the patient questionnaires to the patient and the documentation was performed in the time window. The final visit was conducted by phone.

The final visit of one patient in the SC group (07/0702) was not done completely – the patient did not come to visit as planned due to a COVID-19 infection but was at the site for the MRI the day before the final visit was planned. After the COVID-19 infection, the patient was lost to follow-up.

The final visit of one patient in the NDplus group (07/0703) had to be postponed due to COVID-19 and was performed 34 days after the time window.

Demography and baseline characteristics

Of the 120 patients in this study, 72 (60.0%) were men and 48 (40.0%) were women. The mean (SD) age was 41.7 (10.54) years. Mean (SD) weight was 78.9 (13.56) kg. Mean (SD) height was 177.0 (9.62) cm (Table 14.1.2.1). An ADD was present in 11 (19.0%) patients in the NDplus group, 10 (27.0%) patients in the NDbasic group and 2 (8.0%) patients in the SC group (Table 14.1.2.4).

Efficacy results

Efficacy data are available in Appendix 14 (Study Summary Tables 14.2.1.1.1 to 14.2.9.2.2) and Appendix 16.2 (Subject Data Listings 16.2.2.1 to 16.2.2.6). Data collected for biomarker analysis were analysed by the Sponsor and a summary of results are available upon request.

The primary efficacy variable, the ODI, is the patient's estimate of his or her level of function. The final score/index ranges from 0-100. A score of 0-20 reflects minimal disability, 21-40 moderate disability, 41-60 severe disability, 61-80 crippled, and 81-100 bed-bound. Primary endpoint results for mean ODI total score changes from baseline

(V2a) to V3a (pre-implantation NDplus and NDbasic only), 12 months (V7), 24 months (V8), and 60 months (V11 end of study) showed no statistically significant differences between the treatment groups (Table 1). In addition, an analysis of covariance (ANCOVA) model was performed to investigate whether changes in ODI from V2a (baseline) were influenced by independent variables. Least square (LS) means and p-values were calculated. The change in ODI from V2a was used as the dependent variable, with the following influencing factors added to the model: treatment group (NDplus, NDbasic and SC, where SC was used as reference category); presence or absence of ADD (versus absence of ADD [HD], where HD was used as reference category); and size of annulus defect (0-3 mm, 3-6 mm and >6 mm, where 0-3 mm was used as reference category); and with influencing covariables ODI total score at baseline, number of cigarettes on baseline, age, Pfirrmann score at baseline, amount of tissue, and pain score as assessed on VAS at baseline. The ANCOVA showed no statistically significant differences between NDplus or NDbasic compared with SC (p-values >.05).

Other primary ODI endpoint results (differences in changes NDbasic vs SC from baseline; and differences in changes between NDplus, NDbasic, and SC from baseline in patients with ADDs) also showed no statistically significant differences between any of the groups.

MRI results for changes in disc height (from volume), volumetry, and signal intensity (T2 relation time) showed either a lower or comparable result between NDplus and NDbasic compared with SC.

The lack of a clear efficacious benefit of the IMP over SC at most of the time points and at the end of study prompted the Sponsor's decision to permanently stop the NOVOCART® Disc development programme.

Table 1 Brief summary of efficacy results (FAS)

Efficacy Endpoint	Time Point	Parameter/ Statistic	NDplus N= 47	NDbasic N=27	SC N=24
ODI total score changes from baseline (V2a))	V3a*	Mean (SD)	n=47 -27.2 (19.99)	n=27 -35.8 (16.22)	-
	V7 12 m	Mean (SD)	n=46 -33.7 (19.91)	n=26 -39.6 (19.20)	n=20 -33.8 (24.63)
		LS Mean [a] p-value n=66	-27.7 0.3062	-35.7 0.1506	-30.8 -
	V8 24 m	Mean (SD)	n=44 -32.4 (20.00)	n=26 -41.3 (19.22)	n=22 -36.7 (22.46)
		LS Mean[a] p-value n=67	-27.4 0.0788	-35.2 0.4161	-32.5 -
	V11 60 m	Mean (SD)	n=41 -32.6 (21.69)	n=26 -39.1 (20.54)	n=21 -34.6 (21.33)

		LS Mean[a] p-value n=64	-27.8 0.2400	-32.0 0.9826	-32.0 -
ODI total score differences in changes (NDbasic vs. SC) from baseline (V2a) to end of study	V7 12 m	Point estimate[b] (95% CI)		-6.00 (-20.00, 8.00)	
	V8 24 m	Point estimate[b] (95% CI)		-5.78 (-18.00, 8.00)	
	V11 60 m	Point estimate[b] (95% CI)		-6.00 (-18.00, 6.67)	
ODI total score: differences in changes between NDplus, NDbasic, and SC from baseline (V2a) in patients with ADDs	V7 12 m	NDplus vs. SC Point estimate[b] (95% CI)		2.00 (-42.00, 46.00)	
	V8 24 m	NDplus vs. SC Point estimate[b] (95% CI)		3.00 (-40.00, 46.00)	
	V11 60 m	NDplus vs. SC Point estimate[b] (95% CI)		12.11 (-38.00, 70.00)	
	V7 12 m	NDbasic vs. SC Point estimate[b] (95% CI)		-8.00 (-50.00, 34.00)	
	V8 24 m	NDbasic vs. SC Point estimate[b] (95% CI)		-9.00 (-50.00, 32.00)	
	V11 60 m	NDbasic vs. SC Point estimate[b] (95% CI)		-4.00 (-42.00, 34.00)	
	V3a*	NDplus vs. NDbasic Point estimate[b] (95% CI)		14.00 (-7.78, 34.00)	
	V7 12 m	NDplus vs. NDbasic Point estimate[b] (95% CI)		7.00 (-14.00, 30.00)	
	V8 24 m	NDplus vs. NDbasic Point estimate[b] (95% CI)		11.00 (-14.00, 38.00)	
	V11 60 m	NDplus vs. NDbasic Point estimate[b] (95% CI)		19.00 (-8.00, 52.22)	
MRI changes from screening or baseline (V2a)[c] : disc height (from volume)	V3a*	Caudal disc height (mm) Mean (SD)	n=20 -0.1 (1.91)	n=13 0.3 (0.98)	-
	V7 12 m	Caudal disc height (mm) Mean (SD)	n=21 0 (2.01)	n=12 0.4 (0.98)	7 0.2 (0.90)

	V8 24 m	Caudal disc height (mm) Mean (SD)	n=18 -0.2 (1.52)	n=12 0.6 (0.99)	n=7 1.0 (0.86)
	V11 60 m	Caudal disc height (mm) Mean (SD)	n=18 -0.5 (2.57)	n=11 2.1 (6.99)	n=6 0.1 (1.67)
	V3a*	Central disc, disc height (mm) Mean (SD)	n=47 0.3 (1.27)	n=27 -0.3 (1.67)	-
	V7 12 m	Central disc, disc height (mm) Mean (SD)	n=45 0 (1.35)	n=25 -0.4 (1.76)	n=20 0.1 (1.38)
	V8 24 m	Central disc, disc height (mm) Mean (SD)	n=41 -0.1 (1.81)	n=24 -0.6 (1.98)	n=21 0.4 (1.39)
	V11 60 m	Central disc, disc height (mm) Mean (SD)	n=37 -0.9 (1.91)	n=22 -0.9 (2.19)	n=19 -0.6 (1.70)
	V3a*	Cranial disc, ADD treated disc height (mm) Mean (SD)	n=7 0.7 (0.92)	n=4 0.3 (0.69)	-
	V7 12 m	Cranial disc, ADD treated disc height (mm) Mean (SD)	n=6 0.6 (1.41)	n=4 -0.2 (1.57)	n=2 2.7 (1.71)
	V8 24 m	Cranial disc, ADD treated disc height (mm) Mean (SD)	n=5 0.3 (1.25)	n=4 0 (1.67)	n=2 1.8 (0.31)
	V11 60 m	Cranial disc, ADD treated disc height (mm) Mean (SD)	n=4 0.4 (1.13)	n=3 -1.0 (1.76)	n=1 2.4 (0)
MRI changes from screening or baseline (V2a)[c] : disc volumetry	V3a*	Caudal disc volume (mm^3) Mean (SD)	n=20 25.3 (902.43)	n=12 428.7 (786.56)	-
	V7 12 m	Caudal disc volume (mm^3) Mean (SD)	n=21 169.9 (971.39)	n=12 319.9 (1346.64)	n=6 496.9 (1280.50)
	V8 24 m	Caudal disc volume (mm^3) Mean (SD)	n=18 -180.1 (1166.15)	n=12 1.8 (1689.02)	n=7 802.7 (1364.16)

	V11 60 m	Caudal disc volume (mm³) Mean (SD)	n=18 -488.6 (1378.36)	n=11 128.3 2212.52)	n=6 -479.0 (711.81)
	V3a*	Central disc, volume (mm³) Mean (SD)	n=46 43.9 (1239.90)	n=25 -148.4 (1070.02)	-
	V7 12 m	Central disc, volume (mm³) Mean (SD)	n=44 168.9 (1382.25)	n=25 -334.6 (1360.99)	n=19 442.7 (1843.39)
	V8 24 m	Central disc, volume (mm³) Mean (SD)	n=39 -434.6 (1529.06)	n=24 -521.3 (1465.73)	n=21 384.8 (1817.02)
	V11 60 m	Central disc, volume (mm³) Mean (SD)	n=37 -1056.1 (1989.63)	n=22 -927.0 (2131.08)	n=19 -1030.7 (2040.71)
	V3a*	Cranial disc, ADD treated volume (mm³) Mean (SD)	n=7 407.5 (1015.90)	n=4 144.0 (1470.53)	-
	V7 12 m	Cranial disc, ADD treated volume (mm³) Mean (SD)	n=5 155.1 (937.00)	n=4 -943.1 (1791.03)	n=2 2367.5 (1984.85)
	V8 24 m	Cranial disc, ADD treated volume (mm³) Mean (SD)	n=4 -324.8 (1657.72)	n=4 -940.1 (1462.13)	n=2 309.0 (1965.05)
	V11 60 m	Cranial disc, ADD treated volume (mm³) Mean (SD)	n=4 84.6 (1636.25)	n=3 -3627.2 (2731.24)	n=1 2721.0 (-)
MRI changes from screening or baseline (V2a)[c] : signal intensity (T2 relaxation time)	V3a*	Caudal disc T2 (ms) Mean (SD)	n=18 0 (4.99)	n=13 2.1 (4.95)	-
	V7 12 m	Caudal disc T2 (ms) Mean (SD)	n=19 -1.6 (8.89)	n=12 0 (7.12)	n=7 2.9 (10.93)
	V8 24 m	Caudal disc T2 (ms) Mean (SD)	n=16 -3.3 (9.64)	n=13 -1.3 (7.04)	n=7 5.9 (15.42)
	V11 60 m	Caudal disc T2 (ms) Mean (SD)	n=15 -6.5 (8.27)	n=13 -3.0 (11.82))	n=6 1.9 (13.55)
	V3a*	Central disc T2 (ms) Mean (SD)	n=44 0.5 (7.440)	n=27 0.5 (7.20)	-
	V7 12 m	Central disc T2 (ms) Mean (SD)	n=42 -2.2 (9.39)	n=25 -1.4 (8.00)	n=20 3.0 (6.64)

V8 24 m	Central disc T2 (ms) Mean (SD)	n=40 -0.9 (9.48)	n=25 -1.3 (9.35)	n=21 4.0 (9.34)
V11 60 m	Central disc T2 (ms) Mean (SD)	n=34 -2.0 (8.97)	n=24 -3.1 (10.40)	n=19 1.5 (11.78)
V3a*	Cranial disc, ADD treated T2 (ms) Mean (SD)	n=7 2.1 (6.57)	n=4 0.4 (2.31)	-
V7 12 m	Cranial disc, ADD treated T2 (ms) Mean (SD)	n=6 1.1 (5.51)	n=4 -4.5 (6.46)	n=2 4.3 (6.66)
V8 24 m	Cranial disc, ADD treated T2 (ms) Mean (SD)	n=5 -3.3 (14.05)	n=4 -9.3 (11.74)	n=2 -0.6 (10.06)
V11 60 m	Cranial disc, ADD treated T2 (ms)) Mean (SD)	n=5 -1.4 (16.97)	n=3 6.7 (8.79)	n=1 1.7 (-)

ADD: adjacent degenerated disc; CI: confidence interval; FAS: full analysis set; LS: least square; m: months; MRI: magnet resonance imaging; N: number of patients in treatment group; n: number of patients with data available; ODI: Oswestry Disability Index; SC: standard care; SD: standard deviation; T2: transverse relaxation time; V: visit.
*NDplus and NDbasic only (pre-implantation)
a p-value for LS means only available for NDplus and NDbasic; p-value refers to NDplus vs. SC and NDbasic vs. SC, respectively.
b Hodges-Lehmann CIs
c Screening (Visit 1) or Baseline (Visit 2a) used as baseline, whatever was available. If both visits were available, the latest one was taken into account.
Source: Table 14.2.1.2.1, 14.2.1.2.2, 14.2.1.3.2, 14.2.1.4, 14.2.7.1, 14.2.7.2, 14.2.7.4

Safety results

An interim report of this study, “Key Result Report – Safety” dated 05-MAY-2014 after 24 patients completed Phase I was submitted for safety review via the Voluntary Harmonisation Procedure to the Paul-Ehrlich-Institut, an agency of the German Federal Ministry of Health located in Langen, Germany and to the Austrian Federal Office for Safety in Health Care (BASG)/Austrian Agency for Health and Food Safety (AGES) located in Vienna, Austria. A positive review enabled the study to continue. The interim report is available upon request from the Sponsor.

Unless otherwise indicated, this synoptic report includes all safety data until the end of the study. Except for safety laboratory, data are not separated by phase; no safety laboratory

was performed in Phase II. Summary tables are available in Appendix 14 and individual subject data listings are available in Appendix 16.2.

Adverse events (AEs)

Brief summary of AEs

An overview of the study's AEs, including treatment-emergent AEs (TEAEs) (i.e., that started or worsened on or after the date of V2b/sequestrectomy), pre-transplant TEAEs (i.e., that started or worsened on or after the date of V2b/sequestrectomy to 90 d post sequestrectomy) and post-transplant TEAEs (i.e., that started on or after the date of V3b for NDplus and NDbasic and on or after 90 d post sequestrectomy for SC to the end of study) is presented in Table 2.

From study start to finish, 106 (88.3%) patients experienced an AE and 104 (86.7%) experienced a TEAE. The percentages of patients experiencing a TEAE were comparable across all treatment groups (difference of <5%).

Higher percentages of patients in the NDplus and NDbasic groups than in the SC group experienced pre-transplant TEAEs (44.8%, 45.9%, 36.0%, respectively) and serious TEAEs (37.9%, 32.4%, and 24.0%, respectively). However, lower percentages of patients in the NDplus and NDbasic groups than in the SC group experienced post transplant TEAEs (79.3%, 70.3%, 88.0%, respectively).

Occurrence of related pre-transplant TEAEs in patients were comparable between the NDplus and SC groups (13.8%, 12.0%, respectively), and higher than in the NDbasic group (5.4%).

Percentages of patients who had related post-transplant TEAEs (i.e, related to IMP) were comparable between the NDplus and NDbasic groups (15.5% and 13.5%, respectively). In the SC group there were no patients with related post-transplant TEAEs (i.e., TEAEs related to medical intervention beyond 90 days after sequestrectomy). Occurrence of serious TEAEs in patients was highest in the NDplus group (NDplus 37.9%, NDbasic 32.4% and SC 24.0%), but only a small percentage of patients in the NDplus group (6.9%) had related post transplant serious TEAEs assessed by the Investigator as related to the IMP.

Table 2 Brief summary of adverse events (Safety set)

Patients with	NDplus N=58	NDbasic N=37	SC N=25	Overall N=120
		n (%)		
Any AE[a]	53 (91.4)	31 (83.8)	22 (88.0)	106 (88.3)
Any TEAE[b]	51 (87.9)	31 (83.8)	22 (88.0)	104 (86.7)
Pre-transplant TEAEs[c]	26 (44.8)	17 (45.9)	9 (36.0)	52 (43.3)

Post transplant TEAEs[d]	46 (79.3)	26 (70.3)	22 (88.0)	94 (78.3)
Related* pre-transplant TEAEs	8 (13.8)	2 (5.4)	3 (12.0)	13 (10.8)
Related* post-transplant TEAEs	9 (15.5)	5 (13.5)	0	14 (11.7)
Serious TEAEs	22 (37.9)	12 (32.4)	6 (24.0)	40 (33.3)
Related* pre-transplant serious TEAEs	0	0	1 (4.0)	1 (0.8)
Related* post-transplant serious TEAEs	4 (6.9)	1 (2.7)	0	5 (4.2)
TEAEs leading to death	0	0	0	0

AE: adverse event; N: number of patients in treatment group; n: number of patients within treatment group; SC: standard care; TEAE: treatment-emergent AE.

[a] Any AE that occurred on or after signing of informed consent.

[b] TEAE: Any AE that started or worsened on or after the date of V2b/sequestrectomy

[c] Pre-transplant TEAE: Any AE that started or worsened on or after the date of V2b/sequestrectomy, but before the date of V3b (transplant/implant: 90 d after sequestrectomy) for patients of the NDplus and NDbasic groups and before V5 (90 d after sequestrectomy) for patients of the SC group

[d] Post transplant TEAE: Any AE that started or worsened on or after the date of V3b (transplant/implant) for patients of the NDplus and NDbasic groups and on or after the date of V5 (90 d after sequestrectomy) for patients of the SC group

* Related: Pre-transplant TEAEs are related to medical intervention. Post-transplant TEAEs are related to medical intervention for patients in the SC group and to IMP for patients of the NDplus and NDbasic group.

Source: Table 14.3.1.1

Most frequently reported system organ classes (SOCs) and TEAEs

The most frequently reported SOCs overall (≥15%) that started or worsened on or after the date of V2b/sequestrectomy were musculoskeletal and connective tissue disorders with 75 (62.5%) patients; infections and infestations with 61 (50.8%) patients; nervous system disorders with 49 (40.8%) patients; injury, poisoning and procedural complication with 32 (26.7%) patients; and gastrointestinal disorders with 21 (17.5%) patients (Table 14.3.1.2).

The most frequently reported TEAEs (i.e., that started or worsened on or after the date of V2b/sequestrectomy) during the study, and that occurred pre-transplant (i.e., that started on or after the date of V2b/sequestrectomy to 90 days post sequestrectomy) and post transplant (i.e., that started on or after the date of V3b for NDplus and NDbasic and on or after 90 days post sequestrectomy for SC to the end of study) are presented in Table 3.

Overall, the most frequently reported preferred terms (PTs) ≥5% in any treatment group were back pain, nasopharyngitis, intervertebral disc protrusion, and sciatica. In general, reports of back pain, intervertebral disc protrusion, and sciatica were infrequent pre-transplant. The number of patients reported with back pain post transplant were 35 (29.2%) patients overall (24.1% NDplus, 24.3% NDbasic, and 48% SC). The number of patients with post transplant intervertebral disc protrusion were 23 (19.2%) patients overall (24.1% NDplus, 21.6% NDbasic, 4.0% SC). Details of intervertebral disc protrusion in individual

patients are available in Listing 16.2.3.2. The incidence of sciatica was 17.5% of patients overall (19.0% NDplus, 13.5% NDbasic, 20.0% SC) post transplant.

Table 3 Most frequently reported TEAEs in ≥5% of patients in any treatment group (Safety set)

PT	NDplus N=58	NDbasic N=37	SC N=25	Overall N=120
During the study[a]		**n (%)**		
Back pain	16 (27.6)	9 (24.3)	12 (48.0)	37 (30.8)
Nasopharyngitis	20 (34.5)	9 (24.3)	7 (28.0)	36 (30.0)
Intervertebral disc protrusion	17 (29.3)	10 (27.0)	1 (4.0)	28 (23.3)
Sciatica	12 (20.7)	6 (16.2)	6 (24.0)	24 (20.0)
Headache	5 (8.6)	4 (10.8)	2 (8.0)	11 (9.2)
Arthralgia	5 (8.6)	3 (8.1)	1 (4.0)	9 (7.5)
Depression	4 (6.9)	3 (8.1)	2 (8.0)	9 (7.5)
Procedural pain	1 (1.7)	4 (10.8)	1 (4.0)	6 (5.0)
Bacterial infection	1 (1.7)	1 (2.7)	3 (12.0)	5 (4.2)
Facet joint syndrome	2 (3.4)	2 (5.4)	1 (4.0)	5 (4.2)
Hypertension	2 (3.4)	1 (2.7)	2 (8.0)	5 (4.2)
Influenza	2 (3.4)	2 (5.4)	1 (4.0)	5 (4.2)
Pain in extremity	2 (3.4)	2 (5.4)	1 (4.0)	5 (4.2)
Contusion	2 (3.4)	2 (5.4)	0	4 (3.3)
Erythema	1 (1.7)	2 (5.4)	1 (4.0)	4 (3.3)
Gastritis	3 (5.2)	1 (2.7)	0	4 (3.3)
Ligament sprain	2 (3.4)	2 (5.4)	0	4 (3.3)
Meniscus injury	3 (5.2)	1 (2.7)	0	4 (3.3)
Nausea	3 (5.2)	0	1 (4.0)	4 (3.3)
Radiculopathy	3 (5.2)	1 (2.7)	0	4 (3.3)
Respiratory tract infection	1 (1.7)	1 (2.7)	2 (8.0)	4 (3.3)
Toothache	3 (5.2)	0	1 (4.0)	4 (3.3)
Urinary tract infection	4 (6.9)	0	0	4 (3.3)
Bronchitis	3 (5.2)	0	0	3 (2.5)
Diarrhoea	1 (1.7)	2 (5.4)	0	3 (2.5)
Skin laceration	1 (1.7)	2 (5.4)	0	3 (2.5)
Gastroesophageal reflux disease	0	0	2 (8.0)	2 (1.7)
Pre-transplant TEAEs[b]				
Back pain	3 (5.2)	0	(2 (8.0)	5 (4.2)
Intervertebral disc protrusion	3 (5.2)	2 (5.4)	0	5 (4.2)
Headache	1 (1.7)	2 (5.4)	0	3 (2.5)

Seasonal allergy	0	1 (2.7)	2 (8.0)	3 (2.5)
Post-transplant TEAEs[c]				
Back pain	14 (24.1)	9 (24.3)	12 (48.0)	35 (29.2)
Nasopharyngitis	20 (34.5)	9 (24.3)	6 (24.0)	35 (29.2)
Intervertebral disc protrusion	14 (24.1)	8 (21.6)	1 (4.0)	23 (19.2)
Sciatica	11 (19.0)	5 (13.5)	5 (20.0)	21 (17.5)
Depression	4 (6.9)	3 (8.1)	2 (8.0)	9 (7.5)
Headache	4 (6.9)	3 (8.1)	2 (8.0)	9 (7.5)
Arthralgia	4 (6.9)	3 (8.1)	1 (4.0)	8 (6.7)
Bacterial infection	1 (1.7)	1 (2.7)	3 (12.0)	5 (4.2)
Facet joint syndrome	2 (3.4)	2 (5.4)	1 (4.0)	5 (4.2)
Influenza	2 (3.4)	2 (5.4)	1 (4.0)	5 (4.2)
Contusion	2 (3.4)	2 (5.4)	0	4 (3.3)
Muscle tightness	0	1 (2.7)	3 (12.0)	4 (3.3)
Osteoarthritis	1 (1.7)	3 (8.1)	0	4 (3.3)
Procedural pain	1 (1.7)	3 (8.1)	0	4 (3.3)
Radiculopathy	3 (5.2)	1 (2.7)	0	4 (3.3)
Respiratory tract infection	1 (1.7)	1 (2.7)	2 (8.0)	4 (3.3)
Toothache	3 (5.2)	0	1 (4.0)	4 (3.3)
Urinary tract infection	4 (6.9)	0	0	4 (3.3)
Bronchitis	3 (5.2)	0	0	3 (2.5)
Skin laceration	1 (1.7)	2 (5.4)	0	3 (2.5)

AE: adverse event; d: day(s); IMP: investigational medicinal product; N: number of patients in treatment group; n: number of patients within treatment group; PT: preferred term; SC: standard care; TEAE: treatment-emergent AE; V: visit.

[a] TEAE: Any AE that started or worsened on or after the date of V2b/sequestrectomy

[b] Pre-transplant TEAE: Any AE that started or worsened on or after the date of V2b/sequestrectomy, but before the date of V3b (transplant/implant: 90 d after sequestrectomy) for patients of the NDplus and NDbasic groups and before V5 (90 d after sequestrectomy) for patients of the SC group

[c] Post transplant TEAE: Any AE that started or worsened on or after the date of V3b (transplant/implant) for patients of the NDplus and NDbasic groups and on or after the date of V5 (90 d after sequestrectomy) for patients of the SC group

Source: Table 14.3.1.2, 14.3.1.4, and 14.3.1.5

Related TEAEs (either related to IMP or medical intervention)

TEAEs assessed by the Investigator as related in the pre-transplant period, i.e., TEAEs that started or worsened on or after the date of V2b/sequestrectomy, but before the date of V3b (transplant/implant: 90 days after sequestrectomy) for patients of the NDplus and NDbasic groups and before V5 (90 days after sequestrectomy) for patients of the SC group, were considered related to medical intervention.

TEAEs assessed by the Investigator as related in the post-transplant period, i.e., TEAEs that started or worsened after the date of V3b (transplant/implant) for patients of the

NDplus and NDbasic groups and on or after the date of V5 (90 days after sequestrectomy) for patients of the SC group, were considered related to medical intervention for patients in the SC group and related to IMP for patients of the NDplus and NDbasic group.

Related TEAEs in the pre-transplant period were reported in a total of 13 (10.8%) patients (Table 4). Except for sciatica, which occurred in a total of 3 patients, all related pre-transplant TEAEs each occurred in only 1 or 2 patients. Medical intervention-related TEAEs were comparable between the NDplus and SC groups (13.8 vs. 12.0%, respectively), which were higher than in the NDbasic group (5.4%).

Related TEAEs in the post-transplant period were reported in a total of 14 (11.7%) patients. The most frequently reported related post-transplant TEAEs were intervertebral disc protrusion in 8 patients and sciatica in 5 patients. The incidence of post-transplant TEAEs were comparable between the NDplus and NDbasic groups (15.5 vs. 13.5%, respectively). In the SC group there were no patients with related post-transplant TEAEs (i.e., TEAEs related to medical intervention beyond 90 days after sequestrectomy).

Table 4 Related pre-transplant and post transplant TEAEs (Safety set)

PT	NDplus N=58	NDbasic N=37	SC N=25	Overall N=120
	n (%) patients			
Pre-transplant (or medical intervention-related) TEAEs[a]				
Any	8 (13.8)	2 (5.4)	3 (12.0)	13 (10.8)
Sciatica	2 (3.4)	0	1 (4.0)	3 (2.5)
Intervertebral disc protrusion	2 (3.4)	0	0	2 (1.7)
Procedural nausea	0	1 (2.7)	1 (4.0)	2 (1.7)
Procedural pain	0	1 (2.7)	1 (4.0)	2 (1.7)
Procedural vomiting	0	1 (2.7)	1 (4.0)	2 (1.7)
Back pain	1 (1.7)	0	0	1 (0.8)
C-reactive protein increased	1 (1.7)	0	0	1 (0.8)
Dural tear	1 (1.7)	0	0	1 (0.8)
Dysaesthesia	0	1 (2.7)	0	1 (0.8)
Post procedural constipation	1 (1.7)	0	0	1 (0.8)
Post procedural haemorrhage	0	0	1 (4.0)	1 (0.8)
Sleep disorder	1 (1.7)	0	0	1 (0.8)
Post-transplant (IMP-related for the NDplus and NDbasic groups, medical intervention-related in the SC group) TEAEs[b]				
Any	9 (15.5)	5 (13.5)	0	14 (11.7)
Intervertebral disc protrusion	5 (8.6)	3 (8.1)	0	8 (6.7)
Sciatica	4 (6.9)	1 (2.7)	0	5 (4.2)
Back pain	1 (1.7)	0	0	1 (0.8)
Monoparesis	0	1 (2.7)	0	1 (0.8)
Pain in extremity	0	1 (2.7)	0	1 (0.8)

Paraesthesia	0	1 (2.7)	0	1 (0.8)
Procedural pain	0	1 (2.7)	0	1 (0.8)
Spinal pain	0	1 (2.7)	0	1 (0.8)

IMP: investigational medicinal product; N: number of patients in treatment group; n: number of patients within treatment group; PT: preferred term; SC: standard care; TEAE: treatment-emergent AE; V: visit.

[a] Pre-transplant TEAE: Any AE that started or worsened on or after the date of V2b/sequestrectomy, but before the date of V3b (transplant/implant: 90 d after sequestrectomy) for patients of the NDplus and NDbasic groups and before V5 (90 d after sequestrectomy) for patients of the SC group

[b] Post transplant TEAE: Any AE that started or worsened on or after the date of V3b (transplant/implant) for patients of the NDplus and NDbasic groups and on or after the date of V5 (90 d after sequestrectomy) for patients of the SC group

Source: Table 14.3.1.6 and 14.3.1.7

Severity of TEAEs

The severity of TEAEs for each individual patient is available in Listing 16.2.3.1. Most TEAEs were assessed by the Investigator as mild or moderate, except for the following TEAEs assessed as severe:

- Intervertebral disc protrusion: 4 patients in the NDplus group (4 episodes resolved with no sequalae, one after 9 days [06/0614], one after 7 days [01/0118], one after 3 days [11/1101], one after 5 days [11/1101], and one was resolving [09/0905]);1 patient in the NDbasic group (resolved with no sequalae after 6 days [01/0112]); and 1 patient in the SC group (resolved with no sequalae after 14 days [11/1103])
- Gastritis: 1 patient in the NDplus group (resolved with no sequalae after 3 days [06/0610])
- Sciatica: 2 patients in the NDplus group (one resolved with no sequalae after 37 days [06/0614] and one was resolving [11/1101])
- Depression: 1 patient in the NDbasic group (not resolved [06/0619])
- Erysipelas: 1 patient in the NDbasic group (resolved with no sequalae after 13 days [06/0619])
- Meniscus injury: 1 patient in the NDbasic group (resolved with sequalae after 2 days [08/0805])
- Renal colic: 1 patient in the NDplus group (resolved with no sequalae after 12 days [09/0911])
- Urinary tract infection: 1 patient in the NDplus group had 3 episodes that resolved with no sequalae (the first episode resolved after 12 days, the second episode resolved after 2 days, and the third episode resolved after 19 days [09/0911])
- Ureteric stenosis: 1 patient in the NDplus group had 2 episodes (the first episode did not resolve and the second episode resolved after 19 days [09/0911])

Name of company: TETEC AG
Name of finished investigational medicinal products (IMPs): NOVOCART® Disc plus ADCT and NOVOCART® Disc basic (no active cell component)
Name of active ingredient: ADCT

- Arrested labour: 1 patient in the NDplus group (resolved with no sequalae after 5 days [09/0911])
- Pneumonia: 1 patient in the SC group (resolved with no sequalae with no definitive date range given [09/0916])
- Idiopathic generalised epilepsy: 1 patient in the NDplus group (resolved with no sequalae after 5 days [11/1101])
- Procedural pain: 1 patient in the NDplus group (resolved with no sequalae after 88 days [12/1201]) and 1 patient in the NDbasic group (resolved with no sequalae after 1 day [11/1102])
- Post procedural haemorrhage: 1 patient in the SC group (resolved with no sequalae after 11 days [11/1103])
- Hypoesthesia: 1 patient in the SC group (resolved with no sequalae, no definitive date range given [11/1103])
- Muscular weakness: 1 patient in the SC group (resolved with no sequalae, no definitive date range given [11/1103])
- Facet joint syndrome: 1 patient in the SC group (resolved with no sequalae after 17 days [11/1103])
- Hypersomnia: 1 patient in the SC group had 2 episodes (one episode resolved with no sequalae after 4 days and one episode did not resolve [11/1103])
- Back pain: 1 patient in the NDplus group had 2 episodes (one episode did not resolve and one episode resolved with no sequalae after 4 days [12/1201])

Analysis of deaths, other serious TEAEs, and other clinically meaningful TEAEs

Deaths

No TEAEs led to death in this study (Table 14.3.1.1).

Other serious TEAEs

A total of 40 (33.3%) patients overall experienced a TEAE assessed by the Investigator as serious: 22 (37.9%) in the NDplus group; 12 (32.4%) in the NDbasic group; and 6 (24.0%)

in the SC group (Table 5). Outcome and relatedness of Serious TEAEs are available in (Listing 16.2.3.1).

The most frequently reported SOC for patients with serious TEAEs overall was Musculoskeletal and connective tissue disorders with 22 (18.3%) patients (Table 14.3.1.3).

Overall, the most frequently reported PTs >1 patient in any treatment group were intervertebral disc protrusion, back pain, osteoarthritis, and sciatica.

Table 5 Serious TEAEs in >1 patient in any treatment group (Safety set)

PT	NDplus N=58	NDbasic N=37	SC N=25	Overall N=120
		n (%)		
Any serious TEAE[a]	22 (37.9)	12 (32.4)	6 (24.0)	40 (33.3)
Intervertebral disc protrusion	11 (19.0)	4 (10.8)	1 (4.0)	16 (13.3)
Back pain	2 (3.4)	0	0	2 (1.7)
Osteoarthritis	0	2 (5.4)	0	2 (1.7)
Sciatica	2 (3.4)	0	0	2 (1.7)

N: number of patients in treatment group; n: number of patients within treatment group; PT: preferred term; SC: standard care; TEAE: treatment-emergent AE; V: visit.

[a] TEAE: Any AE that started or worsened on or after the date of V2b/sequestrectomy

Source: Table 14.3.1.3

Discontinuations due to TEAEs

No patients discontinued the study due to TEAEs (Listing 16.2.1.1).

Unanticipated TEAEs – reherniations

Reherniations are defined as recurrent herniations of the index disc. Herniations that occur in a disc for the first time are referred to as new herniations.

Although reherniation was expected to occur infrequently in this study, the number of patients with reherniation after the initial sequestrectomy was unanticipated. A total of 28 patients were reported to have had intervertebral disc protrusion during the study (Listing 16.2.3.2). Various terms were reported, including “herniated disc”, “recurrent herniation of lumbal discus”, “reherniation”, “discus prolaps”, “disc herniation”, “relapse”, and others, but all were considered to be reherniations.

After sequestrectomy and before implantation (for the SC group, those patients within 90 days of sequestrectomy), 3 patients in the NDplus group, 2 patients in the NDbasic group, and no patients in the SC group were reported to have had reherniations (Listing 16.2.3.2).

After implantation (in the SC group, those patients beyond 90 days after sequestrectomy), 13 patients in the NDplus group, 6 patients in the NDbasic group, and 1 patient in the SC group were reported to have had reherniations (Listing 16.2.3.2). In addition, 2 patients (01/0104 and 02/0203) in the NDbasic group who had their adjacent disc co-treated developed a new disc herniation in the treated adjacent disc (Listing 16.2.1.7 and Listing 16.2.3.2). In the NDplus group a total of 11 patients had the adjacent disc co-treated and no patient experienced a disc herniation in the treated adjacent disc. No herniations were reported for untreated ADDs.

Only a portion of reherniations required a reoperation. Only 1 patient in the NDbasic group (01/0112) and 1 patient in the NDplus group (01/0133) had a reherniation requiring reoperation early after sequestrectomy and before implantation, which were clearly unrelated to the study (Listings 16.2.3.1 and 16.2.3.2).

After implantation (in the SC group, those patients beyond 90 days after sequestrectomy), 9 patients in the NDplus group (01/0118, 01/0123, 01/0139, 02/0201, 02/0208, 06/0610, 06/0614, 09/0905, and 11/1101) had a reherniation requiring reoperation with 2 patients (02/0201, 02/0208) in this group whose reherniation was assessed by the Investigator as related to both medical intervention and the IMP, and 3 patients (06/0610, 06/0614, 09/0905) in this group whose reherniation was assessed by the Investigator as related to the medical intervention, but not related to the IMP (Listings 16.2.3.1 and 16.2.3.2). After implantation, 4 patients (01/0112, 01/0113, 01/0126, and 08/0805) in the NDbasic group had a reherniation requiring reoperation with only 1 patient (08/0805) in this group whose reherniation was assessed by the Investigator as related to both medical intervention and the IMP. Only 1 patient (11/1103) in the SC group had a reherniation requiring reoperation that was assessed by the Investigator as not related to medical intervention (Listings 16.2.3.1 and 16.2.3.2).

Clinical laboratory evaluations

Because inflammatory markers were expected to increase temporarily after surgical procedures, the focus of laboratory safety signals was therefore on their return to normal values in the follow-up period after transplant/implant surgery.

In Phase I only, the laboratory values IL-6, CRP, and LTE-4 were measured and analysed. Laboratory summary tables are available in Appendix 14, Summary Tables – Phase I, Tables 6.1 to 6.13. Laboratory individual data are available in Appendix 16.2, Subject Data Listings – Phase I Laboratory, Listing 9.5.

Median changes in safety laboratory parameters from transplant/implant surgery to the end of Phase I were zero and there were no differences between the treatment groups (Tables 6.1, 6.2, and 6.3).

In the time frame from transplant/implant surgery to 48 h post surgery, laboratory parameters for most patients did not change (Tables 6.4, 6.6, 6.7, 6.9, 6.10, and 6.12). Only 1 patient in the NDplus group had a shift from an increased to a normal CRP value and 2 patients in each treatment group had shifts from normal to increased IL-6 values. In the

time frame from transplant/implant surgery to 1.5 months post surgery (end of Phase I),
1 patient in the NDplus group had a shift from an increased to a normal IL-6 value,
2 patients in the NDbasic group had a shift from normal to increased CRP values, and
1 patient in the NDbasic group had a shift from a normal to an increased IL-6 value.

Laboratory parameters were screened for abnormal values considered medically important by the Sponsor according to predefined criteria. The only clinically noteworthy criterion was a CRP value of >50 mg/L (specified in the SAP for the Phase I interim safety report) or >5 mg/dL. Only 3 patients (2 in the NDplus group and 1 in the NDbasic group) experienced clinically significant abnormalities in CRP values up to 36 h after sequestrectomy surgery, which all returned to normal at later sampling times (Table 6.13 and Listing 9.5).

Vital signs and other observations related to safety

Vital signs

No clinically significant changes were observed in systolic or diastolic blood pressure and pulse rate from baseline to the end of the trial (Table 14.3.2.1). Vital sign data for individual patients are available in Listing 16.2.3.3).

Other observations related to safety

The prevalence of subsequent surgical interventions (reoperations) was a primary safety endpoint. Patients in all three treatment groups had unscheduled visits for repeated surgeries to treat reherniations (Listing 16.2.3.6). Subsequent surgical interventions occurred in a total of 15 patients: 9 patients in the NDplus group (01/0118, 01/0123, 01/0133, 02/0201, 02/0208, 06/0610, 06/0614, 09/0905, 11/1101), 4 patients in the NDbasic group (01/0112, 01/0113, 01/0126, 08/0805), and 2 patients in the SC group (01/0129, 11/1103). According to an Investigator comment, one patient (01/0139) in the NDplus group had an additional surgical intervention (sequestrectomy) in another clinic and was not willing to give more information, therefore, no unscheduled visit could be documented (Listing 16.2.3.6 and patient profile available from the Sponsor).

Discussion

The purpose of Phase I of this clinical trial of NDplus ADCT in the treatment of nucleotomized and degenerative lumbar discs to avoid secondary disease focused on the safety and feasibility of this treatment approach. Phase II continued to assess safety and a number of efficacy endpoints were to be explored.

Routine treatment (elective sequestrectomy) in the target patient population is considered to be associated with AEs such as recurrent disc herniation or ongoing or recurrent low back pain or sciatica in up to 25% of patients within 2 years. Recurrent symptoms due to disc degeneration, osteochondrosis, etc. also termed post-discectomy syndrome occur over time. In this trial on or after approximately 3 months post sequestrectomy up to the follow-up of 60 months, intervertebral disc protrusion occurred in a total of 19.2% patients, back pain in 29.2% patients, and sciatica in 17.5% patients. Although intervertebral disc

protrusion was more frequently reported in the NDplus and NDbasic groups compared with SC (24.1%, 21.6%, and 4.0%, respectively), the percentage of patients with sciatica in the NDplus group was comparable to the SC group (19.0% and 20.0%, respectively) and lower in the NDbasic group compared with the SC group (13.5% and 20.0%, respectively). Of note during this same time period was the lower percentages of patients reporting back pain in the NDplus and NDbasic groups (24.1% and 24.3%, respectively) compared with the SC group (48.0% patients).

Reoperations due to reherniation were expected at a rate of approximately 10% within 2 years with a tendency to occur early after index surgery. The numbers of reherniations requiring another operation were slightly higher than anticipated: 1 patient each in the NDplus and NDbasic groups after sequestrectomy and before implantation, and 9 patients in the NDplus, and 4 patients in the NDbasic groups after implantation, and 1 patient in the SC group (beyond 90 days after sequestrectomy) (Listings 16.2.3.1, 16.2.3.2, and 16.2.3.6).

Laboratory testing revealed some cases of increased CRP levels after sequestrectomy but no significant changes after implantation. Therefore, there is no indication of relevant immunological consequences of the intradiscal injection at short-term follow-up.

After efficacy data were analysed, the lack of a clear benefit of the IMP over SC at most of the primary ODI and MRI time points and at the end of study prompted the Sponsor's decision to permanently stop the NOVOCART® Disc development programme.

Conclusions

Overall, the observed TEAE pattern in this trial was consistent with the safety pattern observed after elective disc surgery The rates of conservatively and surgically treated recurrences over the entire observation period were within the range reported in the literature (0% to 29.5% for high-risk patients with large annular defect; the range of the reoperation rate is 0% to 24.8%; see supporting literature in Appendix 16.1.4). However, there is an imbalance in the number of recurrences that occurred in the treatment groups: the reherniation rate in the SC group was in the lower range of what is reported in the literature while reherniation rates in the NDplus and NDbasic groups were in the upper range. No indications of harmful material extrusion or immunological consequences due to the study procedures were evident and incidences of back pain and sciatica in Phase II were either lower or comparable in the NDplus and NDbasic groups compared with the SC group. The conduct of this study was impacted by the COVID-19 pandemic as follows: 1 patient had a delayed final visit; 1 patient was unwilling to attend the final study visit, which was then performed by phone; and 1 patient was unable to attend the final visit due to a COVID-19 infection and was lost to follow-up.

As no clear efficacious benefit of the IMP over SC was observed in this study, the Sponsor has permanently stopped the NOVOCART® Disc development programme.

Name of company: TETEC AG
Name of finished investigational medicinal products (IMPs): NOVOCART® Disc plus ADCT and NOVOCART® Disc basic (no active cell component)
Name of active ingredient: ADCT

Date and version of this report

Regulatory Review Version 1, 24-MAY-2022

4 REFERENCE LIST

1. Tschugg A, Diepers M, Simone S, et al. A prospective randomized multicenter phase I/II clinical trial to evaluate safety and efficacy of NOVOCART disk plus autologous disk chondrocyte transplantation in the treatment of nucleotomized and degenerative lumbar disks to avoid secondary disease: safety results of Phase I-a short report [published correction appears in Neurosurg Rev. 2017 Jan;40(1):177]. Neurosurg Rev. 2017;40(1):155-162. doi:10.1007/s10143-016-0781-0.

2. Tschugg A, Michnacs F, Strowitzki M, Meisel HJ, Thomé C: A prospective multicenter phase I/II clinical trial to evaluate safety and efficacy of NOVOCART Disc plus autologous disc chondrocyte transplantation in the treatment of nucleotomized and degenerative lumbar disc to avoid secondary disease: study protocol for a randomized controlled trial. Trials. 2016 Feb 26;17(1):108. doi: 10.1186/s13063-016-1239-y.

5 APPENDICES

Appendix 14 Study Summary Tables

Summary Tables – Phase I and Phase II

14.1.1.1 Overall subject accounting

14.1.1.2 Subjects disposition – safety set

14.1.2.1 Demographics – safety set

14.1.2.2 Tobacco Uses – safety set

14.1.2.3 Employment during healthy status – safety set

14.1.2.4 Anamnesis – location and presence of adjacent degenerated disc – safety set

14.1.2.5 Relevant medical history during the last year – safety set

14.1.2.6 Relevant surgical history (except lumbar spinal history) – safety set

14.1.3.1 Feasibility of surgery and tissue explant (Visit 2b) – safety set

14.1.3.2 Feasibility of transplantation (Visit 3b) – safety set

14.1.3.3 Fluoroscopy at surgical transplant/implant (Visit 3b) – safety set

14.1.4.1 Previous medications – safety set

14.1.4.2 Concomitant medications – safety set

14.1.4.3 Previous pain medications – safety set

14.1.4.4 Previous opioid pain medications – safety set

14.1.4.5 Concomitant pain medications – safety set

14.1.4.6 Concomitant opioid pain medications – safety set

14.2.1.1.1 Frequency on ODI Section 1 (Pain Intensity) and changes from Baseline (Visit 2a) – full analysis set

14.2.1.1.2 Frequency on ODI Section 2 (Personal Care) and changes from Baseline (Visit 2a) – full analysis set

14.2.1.1.3 Frequency on ODI Section 3 (Lifting) and changes from Baseline (Visit 2a) – full analysis set

14.2.1.1.4 Frequency on ODI Section 4 (Walking) and changes from Baseline (Visit 2a) - full analysis set

14.2.1.1.5 Frequency on ODI Section 5 (Sitting) and changes from Baseline (Visit 2a) - full analysis set

14.2.1.1.6 Frequency on ODI Section 6 (Standing) and changes from Baseline (Visit 2a) - full analysis set

14.2.1.1.7 Frequency on ODI Section 7 (Sleeping) and changes from Baseline (Visit 2a) - full analysis set

14.2.1.1.8 Frequency on ODI Section 8 (Sexual Life) and changes from Baseline (Visit 2a) - full analysis set

14.2.1.1.9 Frequency on ODI Section 9 (Social Life) and changes from Baseline (Visit 2a) - full analysis set

14.2.1.1.10 Frequency on ODI Section 10 (Traveling) and changes from Baseline (Visit 2a) - full analysis set

14.2.1.2.1 Summary of ODI total score and changes in ODI total score from Baseline (Visit 2a) - full analysis set

14.2.1.2.2 Differences in changes of ODI total scores between treatment groups - full analysis set

14.2.1.3.1 Summary of ODI total score and changes in ODI total score from Baseline (Visit 2a) separately for HD and ADD patients - full analysis set

14.2.1.3.2 Differences in changes of ODI total scores between treatment groups separately for HD and ADD patients - full analysis set

14.2.1.4 Ancova of changes in ODI total scores from Baseline (Visit 2a) - full analysis set

14.2.2.1 Summary of subject's pain assessment and changes in subject's pain assessment from Baseline (Visit 2a) - full analysis set

14.2.2.2 Differences in changes of subject's pain assessment from Baseline (Visit 2a) between treatment groups - full analysis set

14.2.3.1 Summary of neurological examination for items assessed on both sides (Jenny Scale) - full analysis set

14.2.3.2 Improvement of motor deficits (Jenny Scale) compared to Baseline (Visit 2a/Visit 1) - full analysis set

14.2.3.3 Change in sensory deficits (Jenny Scale) compared to Baseline (Visit 2a/Visit 1) - full analysis set

14.2.3.4 Frequencies of quality and reflexes (Jenny Scale) - full analysis set

14.2.3.5 Change in sciatic stretch test (Jenny Scale) compared to Baseline (Visit 2a/Visit 1) - full analysis set

14.2.3.6 Change in cauda equina syndrome (Jenny Scale) compared to Baseline (Visit 2a/Visit 1) - full analysis set

14.2.3.7 Summary of walking range (Jenny Scale) - full analysis set

14.2.4.1 Summary of Finger-Ground Distance (cm) and changes in Finger-Ground Distance (cm) from Baseline (Visit 2a) - full analysis set

14.2.4.2 Summary of Schober's sign (cm) and changes in Schober's sign (cm) from Baseline (Visit 2a) - full analysis set

14.2.5.1 Incidence of pain medication (mean cumulative function) - full analysis set

14.2.5.2 Extent of exposure to pain medication - full analysis set

14.2.5.3 Extent of exposure to opioids - full analysis set

14.2.6.1 Change in work status - full analysis set

14.2.7.1 Summary of volume (mm^3) and changes in volume (mm^3) from Screening (Visit 1) or Baseline (Visit 2a) - full analysis set

14.2.7.2 Summary of height from volume (mm) and changes in height from volume (mm) from Screening (Visit 1) or Baseline (Visit 2a) - full analysis set

14.2.7.3 Summary of height(manual, mm) and changes in height(manual, mm) from Screening (Visit 1) or Baseline (Visit 2a) - full analysis set

14.2.7.4 Summary of T2 (ms) and changes in T2 (ms) from Screening (Visit 1) or Baseline (Visit 2a) - full analysis set

14.2.7.5 Frequencies of T2 relaxation time (ms) in comparison with Screening (Visit 1) or Baseline (Visit 2a) - full analysis set

14.2.7.6 Frequencies of T2 relaxation time (ms) in comparison with Visit 3a - full analysis set

14.2.7.7 Ancova of changes in T2 relaxation time from Baseline (Visit 2a) - full analysis set

14.2.8.1 Frequencies of SF-36 items - full analysis set

14.2.8.2.1 Summary of SF-36 domain score 'physical functioning' and changes from Baseline (Visit 2a) - full analysis set

14.2.8.2.2 Summary of SF-36 domain score 'role limitations due to health problems' and changes from Baseline (Visit 2a) - full analysis set

14.2.8.2.3 Summary of SF-36 domain score 'role limitations due to emotional problems' and changes from Baseline (Visit 2a) - full analysis set

14.2.8.2.4 Summary of SF-36 domain score 'vitality' and changes from Baseline (Visit 2a) - full analysis set

14.2.8.2.5 Summary of SF-36 domain score 'mental health' and changes from Baseline (Visit 2a) - full analysis set

14.2.8.2.6 Summary of SF-36 domain score 'social functioning' and changes from Baseline (Visit 2a) - full analysis set

14.2.8.2.7 Summary of SF-36 domain score 'bodily pain' and changes from Baseline (Visit 2a) - full analysis set

14.2.8.2.8 Summary of SF-36 domain score 'general health perceptions' and changes from Baseline (Visit 2a) - full analysis set

14.2.8.2.9 Summary of SF-36 summary score 'physical component summary' and changes from Baseline (Visit 2a) - full analysis set

14.2.8.2.10 Summary of SF-36 summary score 'mental component summary' and changes from Baseline (Visit 2a) - full analysis set

14.2.8.2.11 Summary of SF-36 question 'Reported Health Transition' and changes from Baseline (Visit 2a) - full analysis set

14.2.9.2.1 Summary of EQ-5D-3L utility index score and changes from Baseline (Visit 2a) - full analysis set

14.2.9.2.2 Summary of EQ VAS score and changes from Baseline (Visit 2a) - full analysis set

14.3.1.1 Summary of adverse events - safety set

14.3.1.2 TEAEs by system organ class and preferred term - safety set

14.3.1.3 Serious TEAEs by system organ class and preferred term - safety set

14.3.1.4 Pre-transplant TEAEs by system organ class and preferred term - safety set

14.3.1.5 Post-transplant TEAEs by system organ class and preferred term - safety set

14.3.1.6 Related pre-transplant TEAEs by system organ class and preferred term - safety set

14.3.1.7 Related post-transplant TEAEs by system organ class and preferred term - safety set

14.3.2.1 Vital signs - safety set

14.3.3.1 MRI parameters - change in extradiscal fluid collection from Screening (Visit 1) or Baseline (Visit 2a) - safety set

14.3.3.2 MRI parameters - change in fracture from Screening (Visit 1) or Baseline (Visit 2a) - safety set

14.3.3.3 MRI parameters - change in normal lordotic LS from Screening (Visit 1) or Baseline (Visit 2a) - safety set

14.3.3.4 MRI parameters - change in relevant scoliosis from Screening (Visit 1) or Baseline (Visit 2a) - safety set

14.3.3.5 MRI parameters - change in dorsal disc extrusion from Baseline (Visit 2a) - safety set

14.3.3.6 MRI parameters - change in spondylolisthesis > Meyerding grade I from Screening (Visit 1) or Baseline (Visit 2a) - safety set

14.3.3.7 MRI parameters - change in protruding osteophyte from Screening (Visit 1) or Baseline (Visit 2a) - safety set

14.3.3.8 Change in distinct sclerosis from Screening (Visit 1) or Baseline (Visit 2a) - safety set

14.3.3.9 Change in more than moderate degenerative spinal stenosis from Screening (Visit 1) or Baseline (Visit 2a) - safety set

14.3.3.10 Change in more than moderate degenerative foraminal stenosis right or left from Screening (Visit 1) or Baseline (Visit 2a) - safety set

14.3.3.11 MRI parameters - change in osteochondrosis grading (modic) from Screening (Visit 1) or Baseline (Visit 2a) - safety set

14.3.3.12 Change in disc degeneration grading (Pfirrmann) from Screening (Visit 1) or Baseline (Visit 2a) - safety set

Summary Tables – Phase I Laboratory

6.1 Laboratory Safety Variables: CRP (mg/dL) - summary statistics - safety set

6.2 Laboratory Safety Variables: IL6 (pg/mL)- summary statistics - safety set

6.3 Laboratory Safety Variables: LTE-4 (pg/mL) - summary statistics - safety set

6.4 Laboratory Safety Variables CRP: Shift table with respect to normal range between Visit 3a and Visit 3k - safety set

6.5 Laboratory Safety Variables CRP: Shift table with respect to normal range between Visit 3a and Visit 3l - safety set

6.6 Laboratory Safety Variables CRP: Shift table with respect to normal range between Visit 3a and Visit 4 - safety set

6.7 Laboratory Safety Variables IL6: Shift table with respect to normal range between Visit 3a and Visit 3k - safety set

6.8 Laboratory Safety Variables IL6: Shift table with respect to normal range between Visit 3a and Visit 3l - safety set

6.9 Laboratory Safety Variables IL6: Shift table with respect to normal range between Visit 3a and Visit 4 - safety set

6.10 Laboratory Safety Variables LTE 4: Shift table with respect to normal range between Visit 3a and Visit 3k - safety set

6.11 Laboratory Safety Variables LTE 4: Shift table with respect to normal range between Visit 3a and Visit 3l - safety set

6.12 Laboratory Safety Variables LTE 4: Shift table with respect to normal range between Visit 3a and Visit 4 - safety set

6.13 Laboratory Safety Variables: Number and frequency of subjects satisfying clinically significant criteria - safety set

Appendix 16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Protocol Version 2.0, 06-MAR-2012 (first protocol used in the study)

Protocol Amendment No. 2, 11-OCT-2012

Protocol Version 3.0, 11-OCT-2012

Protocol Amendment No. 4 to Clinical Study Protocol Version 4.1, 25-JUN-2014

Protocol Version 4.1, 25-JUN-2014 (redline)

Protocol Version 4.1, 25-JUN-2014

Protocol Amendment No. 5 to Clinical Study Protocol Version 5.0, 29-MAR-2016

Protocol Version 5.0, 29-MAR-2016

Protocol Version 6.0, 18-FEB-2019 (redline)

Protocol Version 6.0, 18-FEB-2019

16.1.2 Signatures

Signature of Sponsor's responsible Medical Officer

Signature of responsible Biostatistician

16.1.3 Statistical Analysis Plan Version Final 1.0, 19-OCT-2021

16.1.4 Supporting Literature

DSUR No. 9 (NOVOCART® Disc Plus), 06.05.2021, Appendix 7: Reherniation and reoperation rate of patients with lumbar disc herniation after microdiscectomy or sequestrectomy: overview of literature data

Appendix 16.2 Subject Data Listings

Subject Data Listings – Phase I and Phase II

16.2.1.1 Subject Disposition – all enrolled subjects

16.2.1.2 Demographic data – all enrolled subjects

16.2.1.3 Tobacco use – all enrolled subjects

16.2.1.4 Work status – all enrolled subjects

16.2.1.5 Anamnesis at Screening – all enrolled subjects

16.2.1.6 Medical and Surgical History during the last year – all enrolled subjects

16.2.1.7 Surgery and Tissue Explant – all enrolled subjects

16.2.1.8 Serology – all enrolled subjects

16.2.1.9 Feasibility of transplantation – all enrolled subjects

16.2.1.10 Wound assessment – all enrolled subjects

16.2.1.11 Previous and concomitant medication – all enrolled subjects

16.2.1.12 Previous and concomitant pain medication – all enrolled subjects

16.2.1.13 Previous and concomitant non-drug therapies – all enrolled subjects

16.2.2.1 Oswestry Disability Questionnaire – all enrolled subjects

16.2.2.2 Visual Analog Scale for Pain – all enrolled subjects

16.2.2.3 Neurological Status (Jenny Scale) – all enrolled subjects

16.2.2.4 Function Status – all enrolled subjects

16.2.2.5 SF-36 Questionnaire – all enrolled subjects

16.2.2.6 EQ-5D-3L Questionnaire – all enrolled subjects

16.2.3.1 Adverse Events – all enrolled subjects

16.2.3.2 Subjects with adverse event ‘intervertebral disc protrusion’ (preferred term) – all enrolled subjects

16.2.3.3 Vital signs – all enrolled subjects

16.2.3.4 MRI parameters – all enrolled subjects

16.2.3.5 Unscheduled Visits – Anamnesis – all enrolled subjects

16.2.3.6 Unscheduled Visits – Repeating Surgery – all enrolled subjects

Subject Data Listings – Phase I Laboratory

9.5 Subject listings of laboratory data - all enrolled subjects