Clinical trial results:
Regeneration of ischemic damages in cardiovascular system using Wharton's jelly as an unlimited source of mesenchymal stem cells for regenerative medicine.
Project of the National Centre for Research and Development (Poland) 'STRATEGMED II'
Randomized Clinical Trial to Evaluate the Regenerative Capacity of CardioCell in patients with Chronic Ischaemic Heart Failure (CIHF)

Summary

EudraCT number	2016-004683-19
Trial protocol	PL
Global end of trial date	10 March 2021

Results information

Result version number	v1 (current)
This version publication date	14 October 2022
First version publication date	14 October 2022

Trial information

Trial identification

Sponsor protocol code	CIHF-Study

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03418233
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Krakowski Szpital Specjalistyczny im. Jana Pawła II
Sponsor organisation address	Pradnicka 80, Krakow, Poland, 31-202
Public contact	Gąsior, Ewa, 48 126142000, e.gasior@szpitaljp2.krakow.pl
Scientific contact	MD, PhD, Piotr Musiałek, 48 126142000, badaniakliniczne@szpitaljp2.krakow.pl

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	30 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the regenerative capacity of CardioCell in patients with Chronic Ischaemic Heart Failure (CIHF) based on the evaluation of Left ventricle ejection fraction assessed by SPECT

Protection of trial subjects:

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorized, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

The Sponsor has ethical, legal and scientific obligations to carefully follow this project in a detailed and orderly manner in accordance with established research principles and applicable regulations. The investigator, as part of his responsibilities, is expected to cooperate with the Sponsor in ensuring that the project adheres to the protocol and GCP requirements. As part of a concerted effort to fulfil these obligations, the Sponsor will authorize a Clinical research Organization (CRO) to perform monitoring tasks and visit the centers during the project. The processes reviewed can relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection. The investigator will permit the Sponsor' authorized CRO personnel to monitor the project as frequently as is deemed necessary and provide access to medical records.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 115
Worldwide total number of subjects	115
EEA total number of subjects	115

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	58
From 65 to 84 years	57
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All patients who provided informed consent and met inclusion criteria without any exclusion criteria were enrolled to the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	active group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cardio-Cell
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intracoronary use

Dosage and administration details:

Patients randomized to the active treatment group: Transcoronary or trans-bypass graft administration of 30 000 000 cells (suspended in 20 ml of 0.9% NaCl and 5% albumin) was performed using a dedicated cell delivery catheter.

Arm title	placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Cardio-Cell placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intracoronary use

Dosage and administration details:

Patients randomized to the placebo group: 0.9% NaCl and 5% albumin injections (in the same volumes as CardioCell) via the coronary arter(ies)/bypass grafts. The CardioCell and placebo are distributed encoded, in an indistinguishable form.

Arm title	labelled cardio-cell

Arm description:

active labelled product, not blinded, according to protocol

Arm type	active labelled product
Investigational medicinal product name	labeled Cardio-Cell
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intracoronary use

Dosage and administration details:

Patients randomized to the active labeled product treatment group: Transcoronary or trans-bypass graft administration of labeled Cardo-Cell at dosage of 30 000 000 cells (suspended in 20 ml of 0.9% NaCl and 5% albumin) will be performed using a dedicated cell delivery catheter.

Number of subjects in period 1	active group	placebo	labelled cardio-cell
Started	69	36	10
Completed	63	34	10
Not completed	6	2	0
Adverse event, serious fatal	4	1	-
Consent withdrawn by subject	1	-	-
Lost to follow-up	1	1	-

Baseline characteristics

End points

End points reporting groups

Reporting group title	active group
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	
Reporting group title	labelled cardio-cell
Reporting group description: active labelled product, not blinded, according to protocol	

Primary: Left ventricle ejection fraction (LVEF) increase

End point title	Left ventricle ejection fraction (LVEF) increase
End point description: Left ventricle ejection fraction (LVEF) increase, assessed by SPECT at 6M FU vs. during index (baseline) imaging – comparison between two groups (active vs placebo therapy)	
End point type	Primary
End point timeframe: baseline vs 6 M FU	

End point values	active group	placebo	labelled cardio-cell	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	27	8	
Units: percent				
median (inter-quartile range (Q1-Q3))	1.0 (-1.0 to 4.0)	3.0 (-1.0 to 5.0)	-2.0 (-5.75 to -0.25)	

Statistical analyses

Statistical analysis title	Left ventricle ejection fraction (LVEF) increase
Comparison groups	placebo v active group
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.912
Method	Wilcoxon (Mann-Whitney)

Secondary: An increase the result of 6 minute walk test at 3 and 6 month.

End point title	An increase the result of 6 minute walk test at 3 and 6 month.

End point description: total distance difference in 6 minute walk test between baseline and 6 month.	
End point type	Secondary
End point timeframe: baseline vs 6 months FU- total distance difference	

End point values	active group	placebo	labelled cardio-cell	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	29	7	
Units: metre				
median (inter-quartile range (Q1-Q3))	35.5 (5.0 to 76.0)	25.0 (0.0 to 76.5)	55.0 (15.0 to 60.0)	

Statistical analyses

Statistical analysis title	An increase the result of 6 minute walk test
Comparison groups	active group v placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7097
Method	t-test, 2-sided

Secondary: Myocardial perfusion improvement assessed in cardiac MRI at 6 month FU.

End point title	Myocardial perfusion improvement assessed in cardiac MRI at 6 month FU.
End point description: Difference between IS (infarct scar) [%left ventricle] in MRI at 6m FU and baseline	
End point type	Secondary
End point timeframe: baseline vs 6 months FU	

End point values	active group	placebo	labelled cardio-cell	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	13	0[1]	
Units: percent				
median (inter-quartile range (Q1-Q3))	-0.52 (-0.91 to -0.26)	-0.62 (-1.06 to -0.18)	(to)	

Notes:
[1] - endpoint in this population was not analysed according to protocol (labelled population)

Statistical analyses

Statistical analysis title	Myocardial perfusion improvement MR
Comparison groups	active group v placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9694
Method	Wilcoxon (Mann-Whitney)

Secondary: An improvement the result of spiroergometric test at 6 month FU.

End point title	An improvement the result of spiroergometric test at 6 month FU.
End point description: An improvement the result of spiroergometric test at 6 month FU - VOmax (mL/(kg·min)) difference	
End point type	Secondary
End point timeframe: baseline vs 6 months	

End point values	active group	placebo	labelled cardio-cell	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	14	4	
Units: varied				
median (inter-quartile range (Q1-Q3))	1.75 (0.3 to 3.2)	-0.2 (-2.88 to 1.83)	2.95 (-2.3 to 7.6)	

Statistical analyses

Statistical analysis title	An improvement the result of spiroergometric test
Statistical analysis description: An improvement the result of spiroergometric test at 6 month FU.	
Comparison groups	placebo v active group

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1761
Method	t-test, 2-sided

Secondary: echocardiography LVEF, EDV, ESV assesment

End point title	echocardiography LVEF, EDV, ESV assesment

End point description:

Left ventricle ejection fraction (LVEF) change against baseline, assessed in echocardiography at 6 months FU.

End point type	Secondary

End point timeframe:

baseline vs 6 months FU

End point values	active group	placebo	labelled cardio-cell	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	65	35	9	
Units: varied				
median (inter-quartile range (Q1-Q3))	2.0 (-1.0 to 4.0)	3.0 (1.0 to 5.0)	1.0 (-1.0 to 3.5)	

Statistical analyses

Statistical analysis title	echocardiography LVEF
Comparison groups	active group v placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1378
Method	Wilcoxon (Mann-Whitney)

Secondary: NT pro-BNP level a 6 months in comparison to the baseline level.

End point title	NT pro-BNP level a 6 months in comparison to the baseline level.

End point description:

NT pro-BNP level at 6 months in comparison to the baseline level

End point type	Secondary

End point timeframe:

baseline vs 6 months

End point values	active group	placebo	labelled cardio-cell	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	34	10	
Units: pg/ml				
median (inter-quartile range (Q1-Q3))	39 (-128.5 to 315.50)	-24.5 (-447.75 to 204.0)	-280.0 (-554.50 to 95.75)	

Statistical analyses

Statistical analysis title	NT pro-BNP level a 6 months in comparison
Comparison groups	active group v placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0619
Method	Wilcoxon (Mann-Whitney)

Secondary: The occurrence of major adverse cardiovascular events (MACE including death, myocardial infarction, and hospitalization for heart failure) at 6 month and 1 year FU.

End point title	The occurrence of major adverse cardiovascular events (MACE including death, myocardial infarction, and hospitalization for heart failure) at 6 month and 1 year FU.

End point description:

The occurrence of major adverse cardiovascular events (MACE including death, myocardial infarction, and hospitalization for heart failure) at 1 year FU

End point type	Secondary

End point timeframe:

baseline vs 1 year FU

End point values	active group	placebo	labelled cardio-cell	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	36	10	
Units: amount (n)	12	2	2	

Statistical analyses

Statistical analysis title	The occurrence of MACE
Comparison groups	active group v placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1312
Method	Fisher exact

Secondary: Quality of life improvement, assessed by SF-36 questionnaire or other dedicated for investigated population at 6 month and 1 year FU.	
End point title	Quality of life improvement, assessed by SF-36 questionnaire or other dedicated for investigated population at 6 month and 1 year FU.
End point description: Physical functioning: Baseline - 6M FU	
End point type	Secondary
End point timeframe: baseline vs 6 months vs 1 year FU	

End point values	active group	placebo	labelled cardio-cell	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	32	8	
Units: number				
median (inter-quartile range (Q1-Q3))	5.0 (-5.0 to 10)	5.0 (0.0 to 18.75)	2.5 (-17.5 to 15.0)	

Statistical analyses

Statistical analysis title	Quality of life improvement
Comparison groups	placebo v active group
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1998
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported in patients from personal consent and study enrollment to last visit in the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	trial population

Reporting group description: -

Serious adverse events	trial population		
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 115 (25.22%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
heart failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 115 (13.04%)		
occurrences causally related to treatment / all	0 / 21		
deaths causally related to treatment / all	0 / 1		
Acute myocardial infarction			

alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 115 (1.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
coronary artery disease				
alternative assessment type: Non-systematic				
subjects affected / exposed	3 / 115 (2.61%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
cardiac thrombus				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
LVAD implantation				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carotid artery stenosis				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 115 (0.87%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death	Additional description: no additional information from family was available			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Peritonitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Skin and subcutaneous tissue disorders			
necrotic ulceration of foot			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin lesion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
kidney failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 115 (1.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			

medical device site infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 115 (1.74%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	trial population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 115 (18.26%)		
Vascular disorders			
haemoptysis			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences (all)	1		
Cardiac disorders			
PCI	Additional description: PCI prior to procedure during control angiography		
subjects affected / exposed	5 / 115 (4.35%)		
occurrences (all)	5		
ICD implantation/reimplantation			
subjects affected / exposed	5 / 115 (4.35%)		
occurrences (all)	5		
heart failure optimalisation			
subjects affected / exposed	4 / 115 (3.48%)		
occurrences (all)	5		

CRT implantation			
subjects affected / exposed	2 / 115 (1.74%)		
occurrences (all)	2		
chest pain			
subjects affected / exposed	3 / 115 (2.61%)		
occurrences (all)	3		
transient no-reflow	Additional description: Transient no-reflow in the right coronary artery during administration of the study product.		
subjects affected / exposed	1 / 115 (0.87%)		
occurrences (all)	1		
Surgical and medical procedures			
planned operation			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences (all)	1		
visit in emergency unit			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences (all)	1		
Nervous system disorders			
mild stroke			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences (all)	1		
Gastrointestinal disorders			
abdominal pain			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Asthma exacerbation			
subjects affected / exposed	1 / 115 (0.87%)		
occurrences (all)	2		
Infections and infestations			
mild infection			
subjects affected / exposed	2 / 115 (1.74%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2019	Version 2.0- data of new study sites was added, description of study catheter was clarified, information about additional blood collections was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported