Clinical trial results:
Randomized, open-label, parallel-group, multi-centre phase II clinical trial of active cellular immunotherapy DCVAC/PCa in patients with localized prostate cancer after primary radical prostatectomy

Summary

EudraCT number	2011-004985-14
Trial protocol	CZ
Global end of trial date	22 May 2017

Results information

Result version number	v1 (current)
This version publication date	01 April 2018
First version publication date	01 April 2018

Trial information

Trial identification

Sponsor protocol code	SP003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02107404
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sotio a.s.
Sponsor organisation address	Jankovcova 1518/2, Prague, Czech Republic, 17000
Public contact	Clinical Trials Sotio, Sotio a.s., +420 224175111, clinicaltrial@sotio.com
Scientific contact	Clinical Trials Sotio, Sotio a.s., +420 224175111, clinicaltrial@sotio.com

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	22 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 May 2017
Global end of trial reached?	Yes
Global end of trial date	22 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of the study SP003 were to evaluate prostate-specific antigen (PSA) doubling time (PSADT) in patients in the immunotherapy group and in the control group in the treatment phase of the study; to compare PSADT measured in the treatment phase with PSADT prior to randomization in patients in both groups; to evaluate PSADT in patients in the immunotherapy group and in the control group in the follow-up phase of the study; to monitor the incidence of adverse events (AEs); to determine the proportion of patients with biochemical relapse, progressive increase in PSA, objective disease progression, or further anticancer therapy introduction within 2 years of randomization; and to compare overall survival (OS) between the two groups.

Protection of trial subjects:

Not applicable

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	23 April 2012
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	Czech Republic: 150
Worldwide total number of subjects	150
EEA total number of subjects	150

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)	60
From 65 to 84 years	90
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Nineteen clinical study centers in the Czech Republic participated in the study SP003 and 15 recruited (screened) at least 1 patient. Recruitment started on 23-Apr-2012 (first patient signed the informed consent form) and ended on 25-May-2015 (last patient signed the informed consent form).

Pre-assignment

Screening details:

Screened: 169
Randomized: 150
Analyzed for efficacy: 150
Analyzed for safety: 137

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Immunotherapy group

Arm description:

DCVAC/PCa; patients in the immunotherapy group were treated with 50 mg/day of oral cyclophosphamide for 7 days before the first dose of DCVAC/PCa and applied imiquimod cream to the planned DCVAC/PCa injection sites 24 hours before each DCVAC/PCa administration

Arm type	Experimental
Investigational medicinal product name	DCVAC/PCa
Investigational medicinal product code	Not applicable
Other name	Not applicable
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of approximately 1×10e7 autologous dendritic cells; oral cyclophosphamide 50 mg/day for 7 days before the first dose of DCVAC/PCa; imiquimod cream applied to the planned DCVAC/PCa injection sites 24 hours before each DCVAC/PCa administration

Arm title	Control group

Arm description:

No investigational medicinal product assigned in this arm

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Immunotherapy group	Control group
Started	74	76
Completed	53	55
Not completed	21	21
Consent withdrawn by subject	3	5
Physician decision	1	1
Adverse event, non-fatal	3	-
Death due to underlying disease	1	-
Manufacturing failure	5	-
Progressive disease	7	11
Protocol deviation	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Immunotherapy group
Reporting group description:	
DCVAC/PCa; patients in the immunotherapy group were treated with 50 mg/day of oral cyclophosphamide for 7 days before the first dose of DCVAC/PCa and applied imiquimod cream to the planned DCVAC/PCa injection sites 24 hours before each DCVAC/PCa administration	
Reporting group title	Control group
Reporting group description:	
No investigational medicinal product assigned in this arm	

Reporting group values	Immunotherapy group	Control group	Total
Number of subjects	74	76	150
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	66.48	66.27	
full range (min-max)	50.36 to 78.38	47.73 to 79.4	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	74	76	150

End points

End points reporting groups

Reporting group title	Immunotherapy group

Reporting group description:

DCVAC/PCa; patients in the immunotherapy group were treated with 50 mg/day of oral cyclophosphamide for 7 days before the first dose of DCVAC/PCa and applied imiquimod cream to the planned DCVAC/PCa injection sites 24 hours before each DCVAC/PCa administration

Reporting group title	Control group

Reporting group description:

No investigational medicinal product assigned in this arm

Subject analysis set title	ITT-derived populations
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The ITT population consisted of all randomized patients except those for whom no data were available following randomization. Inclusion criterion 4 was changed in version 5.0 of the Protocol, and patients who did not fulfill this criterion were excluded from the primary efficacy analysis. For that reason, the ITT-eligible population according to inclusion criterion 4 (ITTe) was introduced. For endpoints where PSADT was the main interest, only patients who had 2 or more PSA values in the examined time period were taken into consideration. It means that for the treatment phase, the ITT population with 2 or more PSA values in the treatment phase (ITT2t) and the same population additionally being eligible according to inclusion criterion 4 in SP003 (ITT2te) were examined. The same applied to the follow-up phase with the populations ITT2f and ITT2fe. Patients who did not start treatment were not analyzed for PSADT in the follow-up phase.

Primary: PSADT in the treatment phase

End point title	PSADT in the treatment phase

End point description:

End point type	Primary

End point timeframe:

From randomization to visit (V)10 at week 40

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34[1]	37[2]		
Units: Months				
median (full range (min-max))	12.16 (3.33 to 100)	13.19 (3.26 to 100)		

Notes:

[1] - ITT2te

[2] - ITT2te

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

2-sided Wilcoxon Mann Whitney test

Comparison groups	Immunotherapy group v Control group

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4744
Method	Wilcoxon (Mann-Whitney)

Secondary: Comparing PSADT measured in the treatment phase with PSADT prior to randomization

End point title	Comparing PSADT measured in the treatment phase with PSADT prior to randomization

End point description:

End point type	Secondary

End point timeframe:

Treatment phase and prior to randomization

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34[3]	37[4]		
Units: Months				
median (full range (min-max))	8.62 (-2.97 to 97.7)	9.31 (-7.08 to 98.45)		

Notes:

[3] - ITT2te

[4] - ITT2te

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

2-sided Wilcoxon Mann Whitney test

Comparison groups	Immunotherapy group v Control group
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8765
Method	Wilcoxon (Mann-Whitney)

Secondary: Value of PSADT in the follow-up phase

End point title	Value of PSADT in the follow-up phase

End point description:

End point type	Secondary

End point timeframe:

From the completed visit at week 40 to 2 years from randomization

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54[5]	54[6]		
Units: Months				
median (full range (min-max))	22.03 (1.89 to 100)	24.3 (4.14 to 100)		

Notes:

[5] - ITT2f

[6] - ITT2f

Statistical analyses

Statistical analysis title	Secondary analysis
Statistical analysis description: 2-sided Wilcoxon Mann Whitney	
Comparison groups	Immunotherapy group v Control group
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6838
Method	Wilcoxon (Mann-Whitney)

Secondary: Proportion of patients with objective disease progression (metastatic disease development [distant failure])

End point title	Proportion of patients with objective disease progression (metastatic disease development [distant failure])

End point description:

- Progression free: patients for whom objective tumor assessment (CT scan and scintigraphy) at 2 years (-6 months) or later showed evidence of non-progressive disease
- Progressed: patients for whom objective tumor assessment (CT scan and scintigraphy) at 2 years (+4 weeks) or earlier showed evidence of disease progression, patients who died at 2 years (+4 weeks) or earlier, or patients who started further anticancer therapy within 2 years (+4 weeks) after randomization

Patients with an unknown status at 2 years were excluded from this analysis.

End point type	Secondary

End point timeframe:

Within 2 years of randomization

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[7]	76[8]		
Units: Proportion of pts with progression				
number (confidence interval 95%)	0.400 (0.260 to 0.570)	0.350 (0.240 to 0.490)		

Notes:

[7] - ITT

[8] - ITT

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

Fisher’s exact test

Comparison groups	Immunotherapy group v Control group
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.68
Method	Fisher exact

Secondary: Proportion of patients who required any further anticancer therapy

End point title	Proportion of patients who required any further anticancer therapy

End point description:

End point type	Secondary

End point timeframe:

Within 2 years of randomization

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[9]	76[10]		
Units: Proportion of pts with further therapy				
number (confidence interval 95%)	0.1892 (0.1075 to 0.2970)	0.2632 (0.1687 to 0.3768)		

Notes:

[9] - ITT

[10] - ITT

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description: Fisher’s exact test	
Comparison groups	Immunotherapy group v Control group
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3315
Method	Fisher exact

Statistical analysis title	Secondary analysis
Statistical analysis description: Fisher’s exact test	
Comparison groups	Immunotherapy group v Control group
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3315
Method	Fisher exact

Secondary: For the subgroup of patients who did not undergo salvage radiotherapy (only RPE), the proportion of patients who had biochemical relapse

End point title	For the subgroup of patients who did not undergo salvage radiotherapy (only RPE), the proportion of patients who had biochemical relapse
End point description:	
End point type	Secondary
End point timeframe: Within 2 years of randomization	

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52[11]	49[12]		
Units: Proportion of pts with PSA relapse				
number (confidence interval 95%)	0.530 (0.381 to 0.659)	0.497 (0.349 to 0.629)		

Notes:

[11] - ITT population without patients who had salvage radiotherapy

[12] - ITT population without patients who had salvage radiotherapy

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:	
Kaplan-Meier analysis and log-rank test	
Comparison groups	Immunotherapy group v Control group
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8826
Method	Logrank

Secondary: Proportion of patients who had progressive increase in PSA

End point title	Proportion of patients who had progressive increase in PSA
End point description:	
End point type	Secondary
End point timeframe:	
Within 2 years of randomization	

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[13]	24[14]		
Units: Proportion of pts with progressive PSA				
number (confidence interval 95%)	0.133 (0.042 to 0.278)	0.200 (0.069 to 0.380)		

Notes:

[13] - ITT with PSA values

[14] - ITT with PSA values

Statistical analyses

Statistical analysis title	Secondary analysis
Statistical analysis description:	
Kaplan-Meier analysis and log-rank test	
Comparison groups	Immunotherapy group v Control group
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6986
Method	Logrank

Secondary: Overall survival

End point title	Overall survival
End point description:	

End point type	Secondary
End point timeframe: 2 years after randomization	

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[15]	76[16]		
Units: Proportion of pts alive				
number (confidence interval 95%)	0.973 (0.896 to 0.993)	1.000 (1.000 to 1.000)		

Notes:
[15] - ITT
[16] - ITT

Statistical analyses

Statistical analysis title	Secondary analysis
Statistical analysis description: Kaplan-Meier analysis and log-rank test	
Comparison groups	Immunotherapy group v Control group
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6357
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs and SAEs: from V1 to 30 days after the last dose of DCVAC/PCa (immunotherapy group) or from V1 to 30 days after V10 (treatment phase discontinuation) (control group)
Deaths: from consent signature to trial termination

Adverse event reporting additional description:

The tables include information on treatment-emergent AEs, treatment-emergent SAEs, and all deaths. An event causally related to treatment was one which was assessed by investigators as causally related to DCVAC/PCa administration. The SAE 'Acute myocardial infarction' was later reported by the sponsor as a SUSAR.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Immunotherapy group
Reporting group description:	
DCVAC/PCa	
Reporting group title	Control group
Reporting group description:	
No treatment	

Serious adverse events	Immunotherapy group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 64 (12.50%)	1 / 73 (1.37%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colorectal cancer			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 64 (0.00%)	1 / 73 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Vestibular neuronitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 73 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Immunotherapy group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 64 (48.44%)	17 / 73 (23.29%)	

Investigations Antinuclear antibody positive subjects affected / exposed occurrences (all)	 2 / 64 (3.13%) 2	 1 / 73 (1.37%) 1	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	 5 / 64 (7.81%) 5	 1 / 73 (1.37%) 1	
General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	 1 / 64 (1.56%) 1 2 / 64 (3.13%) 2	 2 / 73 (2.74%) 2 0 / 73 (0.00%) 0	
Gastrointestinal disorders Inguinal hernia subjects affected / exposed occurrences (all)	 2 / 64 (3.13%) 2	 0 / 73 (0.00%) 0	
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	 2 / 64 (3.13%) 2	 0 / 73 (0.00%) 0	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 0 / 64 (0.00%) 0	 6 / 73 (8.22%) 6	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 2 / 64 (3.13%) 2	 1 / 73 (1.37%) 1	
Infections and infestations Cystitis subjects affected / exposed occurrences (all) Viral infection	 2 / 64 (3.13%) 2	 0 / 73 (0.00%) 0	

subjects affected / exposed occurrences (all)	1 / 64 (1.56%) 1	2 / 73 (2.74%) 2	
Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all)	 0 / 64 (0.00%) 0	 2 / 73 (2.74%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2011	- European Pharminvent Services to be responsible for pharmacovigilance (PV) services - Definition of disease progresion was detailed and the corresponding secondary endpoint was updated - Specification of vein access evaluation before leukapheresis for patients in the immunotherapy group - Specification of HIV tests (CE-marked kits; an accredited laboratory)
07 June 2012	- Extension of the time window for leukapheresis and for vein access evaluation before leukapheresis - Clarification of cyclophosphamide dosing - Screening phase prolonged to 4 weeks - Changed time window for visits in the screening phase (±14 days) - Added tests in the study schedule - Modified wording of inclusion criterion E-6 - Updated SAE reporting - Explanation added why leukapheresis was not performed in the control group - Details provided about CT/scintigraphy readings - Added criteria for premature termination of participation in the study - DCVAC/PCa transport and application description updated - Explanation added that missed DCVAC/PCa administration was not considered a reason for termination of a patient's participation in the trial - Extension of the time window for immunology and immunomonitoring sampling to 6 months
12 August 2013	- Added a secondary endpoint (PSADT on treatment vs PSADT pre-treatment) - The number of patients was changed to 150 - Terminology was separated for the investigational medicinal product (DCVAC/PCa) and stimulating medication (cyclophosphamide and imiquimod) - Detailed inclusion criterion Inc-5b - Added a reason for early termination of patient participation in the study due to the investigator's decision
15 August 2014	- Updated study objectives and added a detailed description of exploratory objectives - Updated primary and secondary endpoints - Modified inclusion criterion Inc-4 - Exclusion criterion E-6 was specified in more detail - Clearly distinguishing the IMP from stimulating medication - Detailed description of laboratory testing, including samples for research - Statistical analysis section updated in relation to modified inclusion criterion Inc-4 - Information about phase I/II clinical trials conducted by the University Hospital in Motol updated per current knowledge - Section on concomitant medication was updated - Updated safety reporting sections - Introduction of new terminology: EoT, End of study, EoS visit, follow-up, and follow-up after the EoS examinations visit - Updated section "Rationale for prostate cancer immunotherapy" - Terminology harmonization

23 July 2015	- Updated safety reporting sections to capture the transfer of safety monitoring responsibilities from the European Pharminvent Services to SOTIO a.s. - Implementation of the Pregnancy Data Collection Form and wording updates in the PV section - Wording for exploratory endpoints and analysis was detailed - Clarification of the CT/bone scintigraphy schedule

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported