Clinical trial results:
A phase I/II trial of IMA970A plus CV8102 following a single pre-vaccination infusion of cyclophosphamide in patients with very early, early and intermediate stage of hepatocellular carcinoma after any standard treatments

Summary

EudraCT number	2015-003389-10
Trial protocol	DE BE ES IT
Global end of trial date	20 December 2019

Results information

Result version number	v1 (current)
This version publication date	07 April 2021
First version publication date	07 April 2021

Trial information

Trial identification

Sponsor protocol code	HepaVac-101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03203005
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale"
Sponsor organisation address	Via Mariano Semmola 142, Naples, Italy, 80131
Public contact	Clinical Trial Information, HepaVac Consortium @ Istituto Nazionale Tumori G. "Pascale", 0039 0815903624, info@hepavac.eu
Scientific contact	Clinical Trial Information, HepaVac Consortium @ Istituto Nazionale Tumori G. "Pascale", 0039 0815903624, info@hepavac.eu

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	20 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2019
Global end of trial reached?	Yes
Global end of trial date	20 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the present phase I/II study is to investigate whether treatment with IMA970A plus CV8102 following a single pre-vaccination infusion of cyclophosphamide (CY) is safe and tolerable, and able to induce a T-cell response in very early, early and intermediate stage hepatocellular carcinoma (HCC) patients after any standard treatment and without any evidence of active disease that warrant further treatment.

Protection of trial subjects:

The study was performed in accordance with Declaration of Helsinki, International Council on Harmonization/GCP guidelines and all applicable and ethical regulatory requirements. The study was approved by national regulatory agencies and the Independent Ethics Committee (IEC) competent for the coordinating investigator and the IECs responsible for each study site in accordance with the local legislation in each participating country.

All subjects were fully informed about nature, scope and possible consequences of the clinical trial in a language appropriate for the subject and they provided written informed consent before study-related procedures were performed.

Following precautionary safety measures were implemented into the trial to assure the safety of patients:
- Facilities and equipment for resuscitation have to be in place when performing vaccinations with IMA970A and CV8102 to shorten reaction times in case of life- threatening anaphylactic reactions.
- Staggered enrollment of the first 3 patients
- Early Data Safety Monitroing Board (DSMB) meeting, regular DSMB meetings throughout the trial and ad hoc DSMB meetings
- Reporting of adverse events of special interest (AESIs) according to the reporting rules of serious adverse events
- Dose de-escalation rules for CV8102 are implemented into the clinical trial for patients experiencing CTCAE Grade ≥ 3 adverse drug reactions
- Premature withdrawal from study treatment in case of unacceptable toxicities
- Capturing of selected safety data including autoimmune diseases, adverse drug reactions and outcome after liver transplantation during non-interventional follow-up
- Patients with a history of or active autoimmune diseases were excluded from treatment with IMA970A and CV8102.

Additionally, special precautions for IMA970A and CV8102 vaccinations and CY treatment were specified in detail in the protocol and the Investigator's Brochure and explained to investigators during Site Initiation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 14
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	10
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 2017 and 2019, 82 patients were screened at six study centers in Italy, Germany, Belgium, The United Kingdom, and Spain of whom 22 were assigned to receive study treatment.

Pre-assignment

Screening details:

In Screening S1, patients were screened for HLA typing, demographics and disease characteristics either before (S1.1) or during (S1.2) standard treatment for HCC and recovery phase. Still eligible patients entered the main Screening S2 for final eligibility check and baseline assessments (e.g. CT/MRI, medical history, blood sampling, ECG, ECOG).

Period 1

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

Blinding implementation details:

No blinding procedures were performed in this open-label, single arm trial.

Arms

Arm title	Trial Treatment (IMA970A, CV8102 and CY)

Arm description:

Within this single arm trial to investigate safety, tolerability and immunogenecity , all eligible patients were assigned to receive a pre-treatment wirh CY followed by vaccinations with IMA970A and CV8102.

Arm type	Experimental
Investigational medicinal product name	IMA970A
Investigational medicinal product code	IMA970A
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

IMA970A is a cocktail of 17 synthetic TUMAPs with the ability to elicit T-cell responses. It consists of 7 human HLA-A*02 Class I-binding peptides, 5 HLA-A*24 Class I-binding peptides, 4 HLA-DR Class II-binding peptides, and 1 HLA-A*02 Class I-binding peptide from HBV core antigen (marker peptide). The dose per each intradermal vaccination was 400 µg of each peptide. Overall, a total of 9 vaccinations were scheduled; the first 4 vaccinations were applied at weekly intervals (Days 1, 8, 15, and 22), and the remaining 5 vaccinations were given in 3-weekly intervals (Days 43, 64, 85, 106, and 127). All vaccinations were preferably to be applied intradermally to the same initially selected vaccination site (the skin of the inner side of the thighs or the upper arms) in order to target the same draining lymph nodes with all vaccinations. IMA970A was to be injected first, followed by CV8102 as close as possible to the injection site of IMA970A about 10 minutes later.

Investigational medicinal product name	CV8102
Investigational medicinal product code	CV8102
Other name	RNAdjuvant
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

CV8102 is a novel RNA-based immuno-stimulatory adjuvant. It is composed of a purified, single-stranded, non-coding, long-chain RNA (R2025) and a small, arginine-rich cationic peptide (CR12C) that form particles (complexes) of approximately 100 nm size optimized for enhanced immune-stimulatory activity. The starting dose was 50 µg per intradermal injection, which could be reduced to 25 µg in the case of intolerability.Overall, a total of 9 vaccinations were scheduled; the first 4 vaccinations were applied at weekly intervals (Days 1, 8, 15, and 22), and the remaining 5 vaccinations were given in 3-weekly intervals (Days 43, 64, 85, 106, and 127). All vaccinations were preferably to be applied intradermally to the same initially selected vaccination site (the skin of the inner side of the thighs or

the upper arms) in order to target the same draining lymph nodes with all vaccinations. IMA970A was to be injected first, followed by CV8102 10 minutes later.

Investigational medicinal product name	Endoxan
Investigational medicinal product code	Cyclophosphamide
Other name	CY
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide (CY) is an immunomodulatory agent and was administered intravenously as a single pre-vaccination infusion at a low dose of 300 mg/m2 body surface area in order to enhance the immune response to vaccination by means of reducing inhibitory regulatory T cells.

Number of subjects in period 1	Trial Treatment (IMA970A, CV8102 and CY)
Started	22
Completed	20
Not completed	2
Consent withdrawn by subject	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	10	
From 65-84 years	12	12	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	65.7		
standard deviation	± 8.8	-	
Gender categorical Units: Subjects			
Female	2	2	
Male	20	20	
HLA-A*02 status			
Patients were to be HLA-A*02 and/or HLA-A*24 positive.			
Units: Subjects			
Negative	5	5	
Positive	16	16	
No result	1	1	
HLA-A*24 status			
Patients were to be HLA-A*02 and/or HLA-A*24 positive.			
Units: Subjects			
Negative	16	16	
positive	5	5	
No result	1	1	
HBV status			
Enrollment of patients infected with Hepatitis B virus (HBV) was possible. Infected patients were to be treated with antiviral therapy before enrolment. Serology was done to assess HBV infection and to determine viral load in patients infected. Direct-acting antivirals were allowed to be applied as medically indicated.			
Units: Subjects			
Negative	15	15	
Positive	7	7	
HCV status			

Enrollment of patients infected with Hepatitis C virus (HCV) was possible. Infected patients were to be treated with antiviral therapy before enrolment. Serology was done to assess HCV infection and to determine viral load in patients infected. Direct-acting antivirals were allowed to be applied as medically indicated.			
Units: Subjects			
Negative	18	18	
Positive	4	4	
Confirmation of Hepatocellular Carcinoma (HCC)			
HCC diagnosis was to be confirmed by biopsy or resected tissue (histopathological diagnosis) or imaging findings (non-invasive criteria).			
Units: Subjects			
by biopsy or resected tissue	5	5	
by imaging	16	16	
by both	1	1	
BCLC status			
The study population consisted of adult patients with confirmed HCC at very early, early, and intermediate "Barcelona Clinic Liver Cancer" (BCLC) stage after adequate standard treatment for HCC.			
Units: Subjects			
0 (very early stage)	1	1	
A (early stage)	11	11	
B (intermediate stage)	10	10	
Child-Pugh Stage			
One main main criterion for inclusion was Child-Pugh A5-6 and B7 disease or no liver function impairment			
Units: Subjects			
5-6 points	19	19	
7 points	3	3	
Anti-tumor therapy (before start of trial treatment)			
Anti-tumor medication administered prior to start of study treatment was reported in only 1 SAF patient (4.5%; sorafenib administered about 2 years before study enrollment), while anti-tumor procedures prior to treatment start were documented as: TACE in 10 patients (45.6%), hepatectomy in 9 patients (40.9%), microwave therapy in 7 patients (31.8%), highfrequency ablation in 6 patients (27.3%), PEI in 3 patients (13.6%), thermal ablation in 2 patients (9.1%), radioembolization in 1 patient (4.5%), and radiotherapy in 1 patient (4.5%; multiple specifications per patient were possible).			
Units: Subjects			
one previous therapy	12	12	
2 previous therapies	7	7	
3 previous therapies	2	2	
4 previous therapies	0	0	
5 previous therapies	1	1	
Currently indicated standard therapy			
Patients to be enrolled after any standard treatment (e.g., hepatic resection, RFA, TACE, and SIRT) and without any evidence of active disease that warrant further treatment. Thus, no standard anti-tumor therapy was to be indicated for the next 3 months. Please note that patients listed on the liver transplantation waiting list were allowed to be enrolled in the study.			
Units: Subjects			
None	21	21	
liver transplantation	1	1	
any anti-tumor treatment indicated	0	0	
Body height			
Units: cm			
arithmetic mean	169.2		
standard deviation	± 7.7	-	
Body weight			

Units: kg			
arithmetic mean	78.68		
standard deviation	± 13.47	-	
Body mass index			
Units: kg/m2			
arithmetic mean	27.49		
standard deviation	± 4.38	-	

Subject analysis sets	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled patients having received at least once study drug (i.e. CY, IMA970A, or CV8102)	
Subject analysis set title	Immune-response evaluable population (IRE)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All patients who had received the first 7 vaccinations.	

Reporting group values	Safety analysis set (SAF)	Immune-response evaluable population (IRE)	
Number of subjects	22	21	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	10	
From 65-84 years	12	11	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	65.7	65.5	
standard deviation	± 8.8	± 9.0	
Gender categorical			
Units: Subjects			
Female	2	2	
Male	20	19	
HLA-A*02 status			
Patients were to be HLA-A*02 and/or HLA-A*24 positive.			
Units: Subjects			
Negative	5	4	
Positive	16	16	
No result	1	1	
HLA-A*24 status			
Patients were to be HLA-A*02 and/or HLA-A*24 positive.			
Units: Subjects			

Negative	16	16	
positive	5	4	
No result	1	1	
HBV status			
Enrollment of patients infected with Hepatitis B virus (HBV) was possible. Infected patients were to be treated with antiviral therapy before enrolment. Serology was done to assess HBV infection and to determine viral load in patients infected. Direct-acting antivirals were allowed to be applied as medically indicated.			
Units: Subjects			
Negative	15	14	
Positive	7	7	
HCV status			
Enrollment of patients infected with Hepatitis C virus (HCV) was possible. Infected patients were to be treated with antiviral therapy before enrolment. Serology was done to assess HCV infection and to determine viral load in patients infected. Direct-acting antivirals were allowed to be applied as medically indicated.			
Units: Subjects			
Negative	18	17	
Positive	4	4	
Confirmation of Hepatocellular Carcinoma (HCC)			
HCC diagnosis was to be confirmed by biopsy or resected tissue (histopathological diagnosis) or imaging findings (non-invasive criteria).			
Units: Subjects			
by biopsy or resected tissue	5	5	
by imaging	16	15	
by both	1	1	
BCLC status			
The study population consisted of adult patients with confirmed HCC at very early, early, and intermediate "Barcelona Clinic Liver Cancer" (BCLC) stage after adequate standard treatment for HCC.			
Units: Subjects			
0 (very early stage)	1	1	
A (early stage)	11	10	
B (intermediate stage)	10	10	
Child-Pugh Stage			
One main main criterion for inclusion was Child-Pugh A5-6 and B7 disease or no liver function impairment			
Units: Subjects			
5-6 points	19	18	
7 points	3	3	
Anti-tumor therapy (before start of trial treatment)			
Anti-tumor medication administered prior to start of study treatment was reported in only 1 SAF patient (4.5%; sorafenib administered about 2 years before study enrollment), while anti-tumor procedures prior to treatment start were documented as: TACE in 10 patients (45.6%), hepatectomy in 9 patients (40.9%), microwave therapy in 7 patients (31.8%), highfrequency ablation in 6 patients (27.3%), PEI in 3 patients (13.6%), thermal ablation in 2 patients (9.1%), radioembolization in 1 patient (4.5%), and radiotherapy in 1 patient (4.5%; multiple specifications per patient were possible).			
Units: Subjects			
one previous therapy	12	12	
2 previous therapies	7	6	
3 previous therapies	2	2	
4 previous therapies	0	0	
5 previous therapies	1	1	
Currently indicated standard therapy			
Patients to be enrolled after any standard treatment (e.g., hepatic resection, RFA, TACE, and SIRT) and			

without any evidence of active disease that warrant further treatment. Thus, no standard anti-tumor therapy was to be indicated for the next 3 months. Please note that patients listed on the liver transplantation waiting list were allowed to be enrolled in the study.			
Units: Subjects			
None	21	20	
liver transplantation	1	1	
any anti-tumor treatment indicated	0	0	
Body height			
Units: cm			
arithmetic mean	169.2	169.1	
standard deviation	± 7.7	± 7.9	
Body weight			
Units: kg			
arithmetic mean	78.68	78.90	
standard deviation	± 13.47	± 13.76	
Body mass index			
Units: kg/m2			
arithmetic mean	27.49	27.59	
standard deviation	± 4.38	± 4.46	

End points

End points reporting groups

Reporting group title	Trial Treatment (IMA970A, CV8102 and CY)

Reporting group description:

Within this single arm trial to investigate safety, tolerability and immunogenecity , all eligible patients were assigned to receive a pre-treatment wirh CY followed by vaccinations with IMA970A and CV8102.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

All enrolled patients having received at least once study drug (i.e. CY, IMA970A, or CV8102)

Subject analysis set title	Immune-response evaluable population (IRE)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All patients who had received the first 7 vaccinations.

Primary: Safety: Overview of TEAEs by maximum severity

End point title	Safety: Overview of TEAEs by maximum severity[1]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing),
Repeatedly occurring AEs (i.e., same preferred term) with similar intensity were counted only once in the severity analyses.
Severity grading according to the US National Cancer Institute’s Common Terminology Criteria for Adverse Events to (NCI-CTCAE, Version 4.0).

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
CTC Grade 1	21			
CTC Grade 2	11			
CTC Grade 3	5			
CTC Grade 4	1			
CTC Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Overview of SAEs by maximum severity

End point title	Safety: Overview of SAEs by maximum severity[2]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing),
Repeatedly occurring AEs (i.e., same preferred term) with similar intensity were counted only once in the severity analyses.
Severity grading according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events to (NCI-CTCAE, Version 4.0).

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AEs)				
CTC Grade 1	1			
CTC Grade 2	2			
CTC Grade 3	0			
CTC Grade 4	1			
CTC Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Overview of TEAEs leading to any action with any study drug

End point title	Safety: Overview of TEAEs leading to any action with any study drug[3]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing),

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
delay of further vaccinations	2			
premature discontinuation of vaccinations	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Overview of TEAEs by relation to study drugs

End point title	Safety: Overview of TEAEs by relation to study drugs[4]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing),

'Study drug' includes IMA970A, CV8102 and CY.

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
related to CY, IMA970A and/or CV8102	20			
related to IMA970A and/or CV8102	20			
related to CY	4			
related to CV8102	20			
related to IMA970A	20			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Overview of SAEs by relation to study drugs

End point title	Safety: Overview of SAEs by relation to study drugs[5]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing),

'Study drug' includes IMA970A, CV8102 and CY.

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
related to CY, IMA970A and/or CV8102	2			
related to IMA970A and/or CV8102	2			
related to CY	1			
related to CV8102	2			
related to IMA970A	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Overview of TEAEs related to CY, IMA970A and/or CV8102 by maximum severity

End point title	Safety: Overview of TEAEs related to CY, IMA970A and/or CV8102 by maximum severity[6]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing),
Repeatedly occurring AEs (i.e., same preferred term) with similar intensity were counted only once in the severity analyses.
Severity grading according to the US National Cancer Institute’s Common Terminology Criteria for Adverse Events to (NCI-CTCAE, Version 4.0).

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
CTC Grade 1	20			
CTC Grade 2	5			
CTC Grade 3	2			
CTC Grade 4	1			
CTC Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Overview of TEAEs related to IMA970A and/or CV8102 by maximum severity

End point title	Safety: Overview of TEAEs related to IMA970A and/or CV8102 by maximum severity[7]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing),
Repeatedly occurring AEs (i.e., same preferred term) with similar intensity were counted only once in the severity analyses.
Severity grading according to the US National Cancer Institute’s Common Terminology Criteria for Adverse Events to (NCI-CTCAE, Version 4.0).

The causality assessments made for IMA970A and CV8102 separately were almost always identical.

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
CTC Grade 1	20			
CTC Grade 2	4			
CTC Grade 3	2			
CTC Grade 4	1			
CTC Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Overview of TEAEs related to CY by maximum severity

End point title	Safety: Overview of TEAEs related to CY by maximum

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing),
Repeatedly occurring AEs (i.e., same preferred term) with similar intensity were counted only once in the severity analyses.
Severity grading according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events to (NCI-CTCAE, Version 4.0).

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
CTC Grade 1	3			
CTC Grade 2	2			
CTC Grade 3	0			
CTC Grade 4	0			
CTC Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Overview of SAEs related to CY, IMA970A and/or CV8102 by maximum severity

End point title	Safety: Overview of SAEs related to CY, IMA970A and/or CV8102 by maximum severity[9]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing),
Repeatedly occurring AEs (i.e., same preferred term) with similar intensity were counted only once in the severity analyses.
Severity grading according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events to (NCI-CTCAE, Version 4.0).

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
CTC Grade 1	1			
CTC Grade 2	0			
CTC Grade 3	0			
CTC Grade 4	1			
CTC Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Overview of SAEs related to IMA970A and/or CV8102 by maximum severity

End point title	Safety: Overview of SAEs related to IMA970A and/or CV8102 by maximum severity[10]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing),
Repeatedly occurring AEs (i.e., same preferred term) with similar intensity were counted only once in the severity analyses.
Severity grading according to the US National Cancer Institute’s Common Terminology Criteria for Adverse Events to (NCI-CTCAE, Version 4.0).

The causality assessments made for IMA970A and CV8102 separately were almost always identical.

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
CTC Grade 1	1			
CTC Grade 2	0			
CTC Grade 3	0			
CTC Grade 4	1			
CTC Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: Overview of SAEs related to CY by maximum severity

End point title	Safety: Overview of SAEs related to CY by maximum

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing),
Repeatedly occurring AEs (i.e., same preferred term) with similar intensity were counted only once in the severity analyses.
Severity grading according to the US National Cancer Institute’s Common Terminology Criteria for Adverse Events to (NCI-CTCAE, Version 4.0).

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
CTC Grade 1	1			
CTC Grade 2	0			
CTC Grade 3	0			
CTC Grade 4	0			
CTC Grade 5	0			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: All TEAEs by System of Organ Class (SOC), if at least 2 patients were involved

End point title	Safety: All TEAEs by System of Organ Class (SOC), if at least 2 patients were involved[12]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing).
Repeatedly occurring AEs (i.e., same SOC) were counted only once.

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
Gen. disorders and administration site conditions	21			
Gastrointestinal disorders	8			
Infections and infestations	4			
Vascular disorders	4			
Respiratory, thoracic and mediastinal disorders	3			
Skin and subcutaneous tissue disorders	2			
Endocrine disorders	2			
Hepatobiliary disorders	2			
Investigations	2			
Musculoskeletal a. connective tissue disorders	2			
Nervous system disorders	2			
Reproductive system and breast disorders	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: All TEAEs by Preferred Term (PT), if at least 2 patients were involved

End point title	Safety: All TEAEs by Preferred Term (PT), if at least 2 patients were involved[13]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing).
Repeatedly occurring AEs (i.e., same preferred term) were counted only once

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
Injection site erythema	16			
Injection site oedema	10			
Fatigue	9			
Injection site pruritus	6			
Pyrexia	5			
Influenza like illness	4			
Injection site pain	4			
Injection site warmth	3			
Nausea	2			
Vomiting	2			
Ascites	2			
Diarrhoea	2			
Hypertension	2			
Injection site induration	2			
Skin hyperpigmentation	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: All TEAEs related to IMA970A and/or CV8102 by SOC, if at least 2 patients were involved

End point title	Safety: All TEAEs related to IMA970A and/or CV8102 by SOC, if at least 2 patients were involved[14]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing).
Repeatedly occurring AEs (i.e., same SOC) were counted only once

End point type	Primary

End point timeframe:

AEs occurring between start of CY and Visit 10/EOV (or last vaccination, if Visit 10/EOV is missing).

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
Gen. disorders and administration site conditions	20			
Skin and subcutaneous tissue disorders	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety: All TEAEs related to IMA970A and/or CV8102 by PT, if at least 2 patients were involved

End point title	Safety: All TEAEs related to IMA970A and/or CV8102 by PT, if at least 2 patients were involved[15]

End point description:

The main safety analysis is based on treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing).
Repeatedly occurring AEs (i.e., same preferred term) were counted only once.

End point type	Primary

End point timeframe:

All TEAEs by Preferred Term (PT), if at least 2 patients were involved

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'safety' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Patients withs adverse events (AE)				
Injection site erythema	16			
Injection site oedema	10			
Fatigue	6			
Injection site pruritus	6			
Pyrexia	4			
Injection site pain	4			
Injection site warmth	3			
Influenza like illness	2			

Injection site induration	2			
Skin hyperpigmentation	2			

Statistical analyses

No statistical analyses for this end point

Primary: Tolerability: Evaluation of local tolerability 5 min. after injections

End point title	Tolerability: Evaluation of local tolerability 5 min. after injections[16]

End point description:

The evaluation of local tolerability was performed in 21 SAF patients (i.e., completely missing data for 1 patient).

End point type	Primary

End point timeframe:

Pre-defined signs of local reactions (intolerability) were assessed after vaccination at each vaccination day (i.e., both 5 minutes and 2 hours after the CV8102 injection).

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'tolerability' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Patients with specific local sign				
Erythema	15			
Itching	3			
Induration	1			
Warmth	2			
Edema	9			
Ulceration / necrosis	1			
Pain	0			
Other	5			

Statistical analyses

No statistical analyses for this end point

Primary: Tolerability: Evaluation of local tolerability 2 hours after injection

End point title	Tolerability: Evaluation of local tolerability 2 hours after injection[17]

End point description:

The evaluation of local tolerability was performed in 21 SAF patients (i.e., completely missing data for 1 patient).

End point type	Primary

End point timeframe:

Pre-defined signs of local reactions (intolerability) were assessed after vaccination at each vaccination day (i.e., both 5 minutes and 2 hours after the CV8102 injection).

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'tolerability' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Patients with specific local sign				
Erythema	14			
Itching	0			
Induration	0			
Warmth	2			
Edema	6			
Ulceration / necrosis	0			
Pain	0			
Other	2			

Statistical analyses

No statistical analyses for this end point

Primary: Tolerability: Evaluation of systemic tolerability 2 hours after injections

End point title	Tolerability: Evaluation of systemic tolerability 2 hours after injections[18]

End point description:

The evaluation of systemic tolerability was performed in 21 SAF patients (i.e., completely missing data for 1 patient).

End point type	Primary

End point timeframe:

Pre-defined signs of systemic reactions (intolerability) were assessed after vaccination at each vaccination day (2 hours after the CV8102 injection).

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'tolerability' and no statistical testing were performed.

End point values	Safety analysis set (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: Patients with specific systemic sign				
Inflammatory symptoms	0			
Flu-like symptoms	0			
Signs of autoimmune reactions	0			
Other	0			

Statistical analyses

No statistical analyses for this end point

Primary: Immunogenicity: Vaccine-induced TUMAP responses (Class I TUMAPs)

End point title	Immunogenicity: Vaccine-induced TUMAP responses (Class I TUMAPs)[19]

End point description:

Primary immunomonitoring analysis (immunogenicity of study treatment) was performed in a total of 19 immune-response evaluable (IRE) patients that were evaluable for immune responses to the 12 Class I and 4 Class II TUMAPs contained in IMA970A.
At least one VI response to Class I was observed in 13 (68.4%) patients, respectively; more than one VI response was seen in 7 (36.8%) patients, respectively. Expressed as a total sum, 21 Class I responses (9.2% relative to the 228 Class I TUMAP exposures among the 19 evaluable patients) were mounted by the vaccinations. Mean number of vaccine-induced responses was 1.1 ± 0.9 (Median: 1.0; range: 1 to 3).
Thus, the ex vivo measured immunogenicity of the Class I TUMAPs contained in IMA970A turned out to be rather moderate.

End point type	Primary

End point timeframe:

A vaccine-induced (VI) TUMAP response was regarded as "positive", if a positive VI TUMAP response was observed for at least one post-vaccination time point (visit pool).

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'immunogenicity' and no statistical testing were performed.

End point values	Immune-response evaluable population (IRE)			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: Patients with response				
Patients with ≥ 1 VI response	13			
Patients with > 1 VI response	7			

Statistical analyses

No statistical analyses for this end point

Primary: Immunogenicity: Vaccine-induced TUMAP responses (Class II TUMAPs)

End point title	Immunogenicity: Vaccine-induced TUMAP responses (Class II TUMAPs)[20]

End point description:

Primary immunomonitoring analysis (immunogenicity of study treatment) was performed in a total of 19 immune-response evaluable (IRE) patients that were evaluable for immune responses to the 12 Class I and 4 Class II TUMAPs contained in IMA970A.
At least one VI response to Class II TUMAPs were observed in 10 (52.6%) patients; more than one VI response was seen in 5 (26.3%) patients. Expressed as a total sum, 18 Class II responses (23.7% relative to the 76 Class II TUMAP exposures) were mounted by the vaccinations. Mean number of vaccine-induced responses was 0.9 ± 1.1 (Median: 1.0; range: 1 to 3).
Thus, the ex vivo measured immunogenicity of the Class II TUMAPs contained in IMA970A turned out to be rather moderate.

End point type	Primary

End point timeframe:

A vaccine-induced (VI) TUMAP response was regarded as "positive", if a positive VI TUMAP response was observed for at least one post-vaccination time point (visit pool).

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All study analyses were done descriptively, i.e., no confirmatory hypothesis testing was performed, during this single-arm first-in-man phase I/II trial.
Only descriptive summary analysis for this end point 'immunogenicity' and no statistical testing were performed.

End point values	Immune-response evaluable population (IRE)			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: Patients with response				
Patients with ≥ 1 VI response	10			
Patients with > 1 VI response	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All treatment-emergent AEs (TEAEs) defined as any AE that started or deteriorated on/after the day of the 1st administration of any study medication (i.e. CY pre-treatment 2-4 days before 1st vaccination) until EOV or last vaccination, if EOV is missing.

Adverse event reporting additional description:

AEs were recorded by asking specifically whether patients had noticed any unexpected or unusual symptoms or because of relevant findings in clinical assessments (e.g. blood sampling, vitals signs, phys. examinations). All AEs were documented in CRF; SAEs and AEs of Special Interest (AESIs) were additionally to be reported within 24 hours to sponso

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Safety analysis set (SAF)

Reporting group description:

all enrolled patients having received at least once study drug (i.e. CY, IMA970A, or CV8102)

Serious adverse events	Safety analysis set (SAF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 22 (18.18%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Lipase increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety analysis set (SAF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 22 (40.91%)		
occurrences (all)	11		
Influenza like illness			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	8		
Injection site erythema			
subjects affected / exposed	16 / 22 (72.73%)		
occurrences (all)	128		
Injection site induration			

subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Injection site oedema			
subjects affected / exposed	10 / 22 (45.45%)		
occurrences (all)	52		
Injection site pain			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	7		
Injection site pruritus			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences (all)	12		
Injection site warmth			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	7		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			

Skin hyperpigmentation subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2015	With this Amendment, the following changes from the original protocol (Version 1.1) were implemented:: - The protocol was amended to only include patients with Child-Pugh A5-6 and B7 disease. Thus, patients with Child-Pugh B8 and B9 were no longer allowed to be enrolled. - It was clarified that, according to medical practice, patients with HBV infection should be treated with antiviral therapy before enrolment. - An additional sentence was added in the section on special precautions for CY to indicate that "Cyclophosphamide should not be administered to patients with a leukocyte count below 2,500 cells/microliter (cells/mm3) and/or a platelet count below 50,000 cells/mm3". - Administrative changes in study personnel were implemented.
24 September 2018	The Amendment implemented the following changes from the protocol: - New Screening 1 sequence to enable S1 during the standard treatment and recovery phase (screening option S1.2 added) - Exclusion Criterion No. 1 was modified to additionally allow for screening Option 1.2, where patients might have been to sign their first informed consent during or immediately after the standard treatment. - Time window between screening 1 (S1 procedures according to screening option S1.1) and start of the currently indicated standard treatment was extended by additional 4 weeks. - Duration of standard treatment and recovery phase, for both screening options S1.1 and S1.2, was extended by additional 4 weeks - A statement was added that a sample size of about 20 patients would be sufficient to estimate safety- and immunogenicity-related endpoints - Tumor assessment according to mRECIST is no longer mandatory but optional. Additionally, imaging of pelvis is only mandatory at baseline, thereafter optional, if no lesion was found in this area. - Enrollment timelines were prolonged to allow patient enrollment as expected. - The allocation of a patient ID could be done before signing IC1 for individual patients due to organizational needs (e.g., coordination of PBMC sampling). - The use of use of paracetamol (acetaminophen) for the treatment or prophylaxis of flu-like symptoms was permitted Further clarifications and minor adjustments that patients were allowed to be re-screened (e.g. for HLA-typing) and to have more than one standard therapy and that inhaled or nasally applied steroids, as well as topical steroids outside the planned vaccination area, during S2 and paracetamol (acetaminophen) for the treatment or prophylaxis of flu-like symptoms were permitted. description of drug preparation/application was improved and more detailed. Minor re-phrasing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported