Clinical trial results:
A Phase Ib/IIa multi-centric study to determine the safety and efficacy of a combination of anti-CD3 & anti-CD7 ricin A immunotoxins (T-Guard) for the treatment of steroid-resistant acute Graft-versus-Host Disease.

Summary

EudraCT number	2013-000068-27
Trial protocol	NL DE
Global end of trial date	03 November 2016

Results information

Result version number	v1 (current)
This version publication date	19 October 2020
First version publication date	19 October 2020
Summary attachment (see zip file)	Publication T-Guard Ph1/2 study XEN/TG-001 (Groth et al 2019.pdf)

Trial information

Trial identification

Sponsor protocol code	XEN/TG-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02027805
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Xenikos BV
Sponsor organisation address	Wilhelminasingel 14, Nijmegen , Netherlands, 6524 AL
Public contact	Ypke van Oosterhout, Ypke van Oosterhout, +31 243000100, y.vanoosterhout@xenikos.com
Scientific contact	Ypke van Oosterhout, Ypke van Oosterhout, +31 243000100, y.vanoosterhout@xenikos.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	20 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy with which T-Guard, four weeks after the first infusion (study Day 28) induces an objective clinical response in patients with steroid-resistant acute GVHD.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The following additional measure(s) defined for this individual study was (were) in place for the protection of trial subjects:
- Patients were closely followed for symptoms which might have been indicative for the occurrence of esophagus or gastrointestinal toxicity.
- The occurrence of an anaphylactic reaction to T-Guard formed a contraindication for subsequent doses.
- No further doses should have been given when albumin levels decreased to 10.0 g/l or below. It was also recommended to consider an adjustment or halting of further doses if albumin levels dropped more than 5.0 g/l as compared to baseline, which decision was left to the Investigator's discretion.

Background therapy:

High dose steroids, which started at a level of 1-2 mg/kg

Evidence for comparator:

No comparator was used

Actual start date of recruitment	20 December 2013
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	Netherlands: 12
Country: Number of subjects enrolled	Germany: 8
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	17
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed at 2 transplantation sites, one in The Netherlands and one in Germany. In total, 20 evaluable patients were included over 29 months. First patient screened was 2014-03-04. Last patient last visit was 2016-11-03.

Pre-assignment

Screening details:

The study population consisted of patients who were treated for aGVHD that had developed following HSCT or DLI, and who did not respond to standard first-line therapy of 2 mg/kg methylprednisolone daily.

Period 1

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

Arms

Arm title	T-Guard treated patients

Arm description:

Subjects with steroid refractory acute Graft-vs-Host Disease who were treated with T-Guard

Arm type	Experimental
Investigational medicinal product name	T-Guard
Investigational medicinal product code	combination of anti-CD3/ CD7 ricin A immunotoxins
Other name	combination of SPV-T3a-RTA and WT1-RTA
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

T-Guard will be administered as an infusion at a dose of 4mg/m2 (actual body weight) over 4 hours every 2 calendar days on Days 0, 2, 4, and 6.

Number of subjects in period 1	T-Guard treated patients
Started	20
Completed	20

Baseline characteristics

Reporting groups

Reporting group title	overall trial period

Reporting group description: -

Reporting group values	overall trial period	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 52.5 18 to 74	 -	
Gender categorical Units: Subjects			
Female	11	11	
Male	9	9	

Subject analysis sets

Subject analysis set title	All Subjects Treated
Subject analysis set type	Full analysis

Subject analysis set description:
All patients that received at least one dose of T-Guard

Reporting group values	All Subjects Treated		
Number of subjects	20		
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 52,5 18 to 74		
Gender categorical Units: Subjects			
Female	11		
Male	9		

End points

End points reporting groups

Reporting group title	T-Guard treated patients
Reporting group description:	
Subjects with steroid refractory acute Graft-vs-Host Disease who were treated with T-Guard	
Subject analysis set title	All Subjects Treated
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients that received at least one dose of T-Guard	

Primary: Overall Response Rate at 4 weeks after the first infusion of TGuard (Day 28)

End point title	Overall Response Rate at 4 weeks after the first infusion of TGuard (Day 28)[1]
End point description:	
End point type	Primary
End point timeframe:	
28 days after administration of the first dose of T-Guard	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a non comparative single arm study; only descriptive statistics was performed. The estimated aGVHD response rates along with the 95% Clopper-Pearson exact CI were calculated.

End point values	T-Guard treated patients	All Subjects Treated		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20		
Units: 20	20	20		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
6 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1E

Reporting groups	
Reporting group title	All Subjects Treated
Reporting group description:	
All subjects who received at least one dose of T-Guard	

Serious adverse events	All Subjects Treated		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 20 (70.00%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	8		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post transplant lymphoproliferative disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
cardiac arrest			

subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiopulmonary failurenary				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
General disorders and administration site conditions				
Organ failure				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Immune system disorders				
Graft versus host diseases				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Acute graft versus host disease				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoeahea				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestinal haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
herpes virus infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Kidney infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pneumonia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Staphylococcal sepsis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All Subjects Treated		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 20 (90.00%)		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	6 / 20 (30.00%)		
occurrences (all)	10		
White blood cell count decreased			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	8 / 20 (40.00%)		
occurrences (all)	8		
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	11 / 20 (55.00%)		
occurrences (all)	21		
General disorders and administration site conditions			
edema peripheral			

subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) fatigue subjects affected / exposed occurrences (all)	8 / 20 (40.00%) 8 8 / 20 (40.00%) 11 6 / 20 (30.00%) 13		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopeniasis subjects affected / exposed occurrences (all)	 6 / 20 (30.00%) 11 6 / 20 (30.00%) 11		
Gastrointestinal disorders nausea subjects affected / exposed occurrences (all)	 5 / 20 (25.00%) 8		
Musculoskeletal and connective tissue disorders Muscular weakness subjects affected / exposed occurrences (all) Myopathy subjects affected / exposed occurrences (all)	 5 / 20 (25.00%) 5 5 / 20 (25.00%) 5		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	 5 / 20 (25.00%) 6		
Metabolism and nutrition disorders Hypoalbuminaemiab subjects affected / exposed occurrences (all) Hyperglycaemiacemia	 8 / 20 (40.00%) 10		

subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	8		
Hypokalaemia			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	15		
Hypophosphataemia			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2013	On request of the ethics committee, a provision has been added to the protocol that for reasons of risk mitigation first 8 patients should be treated sequentially, meaning that treatment should not be started until the previous patient has been observed for at least 48 hours after the last infusion. Furthermore, the collected personal demographic information of the study participants was restricted to 'month and year of birth', 'gender' and 'patient study number'.
08 April 2014	The following main changes were made to the protocol: - language regarding the potential cross-reactivity of SVP-T3a-RTA with esophagus epithelium was added and adequate safety measures were implemented - the severity of VLS was now scored according to the CTCAE V4.0 criteria for Capillary Leakage - 24 hours-delay of the dosage was recommended if Grade II or III toxicity occurred after the previous dosage, with the next dose given if toxicity improved to < grade II or ≤ grade II, respectively. Given the potentially life-threatening consequences of leaving steroid-resistant acute GVHD under-treated, the final decision to postpone the next dosage is left to the investigators discretion depending on the clinical status of the individual patient. Also, halving of the dosage could be considered - language was added regarding the consideration for adjustment or halting of further T-Guard doses if albumin levels decreased to 12.0 g/l or below, or dropped more than 5.0 g/l as compared to baseline, though in the end it was still left to the investigator's discretion.
13 November 2014	- No further T-Guard doses should be administered when the serum albumin level decrease to 10 g/l or lower. Furthermore it was also recommended to consider an adjustment or halting of further doses if albumin levels drop more than 5.0 g/l as compared to baseline, which decision was left to the Investigator's discretion.
01 December 2014	The German Arzneimittelgesetz (AMG) prohibited the mixing of the two drug products SPV-T3a-RTA and WT1-RTA by a Hospital Pharmacist without a manufacturing license. As a consequence, the preparation of the infusions and subsequent administration procedure of T-Guard differed slightly between the Radboudumc in The Netherlands and the University Hospital Münster in Germany. Of not, this had no effect on the composition, amount, or administration rate of the T-Guard IMP actually administered to the patient via the central intravenous catheter.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The samplesize was small, and no randomized comparator arm was included. In addition, the study population was heterogeneous with respect to e.g. age, donor type, and GVHD prophylaxis regimens used. Nonetheless the population was representative.