Clinical trial results:
Prevention of severe GVHD after allogeneic hematopoietic stem cell transplantation, applied as consolidation immunotherapy in patients with hematological malignancies. A prospective randomized phase III trial.

Summary

EudraCT number	2008-003540-11
Trial protocol	NL BE
Global end of trial date	07 January 2021

Results information

Result version number	v1 (current)
This version publication date	25 December 2022
First version publication date	25 December 2022

Trial information

Trial identification

Sponsor protocol code	HO96GVHD

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	HOVON
Sponsor organisation address	De Boelelaan 1117, Amsterdam, Netherlands,
Public contact	HOVON Data Center, HOVON, hdc@erasmusmc.nl
Scientific contact	HOVON Data Center, HOVON, hdc@erasmusmc.nl

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	05 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 July 2019
Global end of trial reached?	Yes
Global end of trial date	07 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Objectives:
- to increase the proportion of patients with non severe GVHD within 180 days post-allo-SCT,
- to reduce the progression rate and
- to improve the progression free survival
using a time restricted immunosuppressive regimen or a short-course post-transplant GVHD prophylaxis consisting of high-dose cyclophosphamide as compared to a prolonged, standard immunosuppressive regimen.

Protection of trial subjects:

Monitoring and Insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 April 2010
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: 491
Country: Number of subjects enrolled	Belgium: 3
Worldwide total number of subjects	494
EEA total number of subjects	494

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)	418
From 65 to 84 years	76
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects gave written informed consent and were screened according to the inclusion- and exclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Standard immunosuppression with Cyclosporin A and Myfortic.

Arm type	Standard treatment
Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft, Powder for infusion
Routes of administration	Infusion , Oral use

Dosage and administration details:

Cyclosporine A (CyA) immunosuppression: 9 mg/kg p.o. (in 2 doses) OR 3 mg/kg i.v. (in 2 doses) from day -5/-3 (depending on local procedures) till day 180.

Investigational medicinal product name	Myfortic
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Myfortic immunosuppression: (2x 16 mg/kg p.o.) from day 0 till day 84. Myfortic will be given with a maximum of 2160 mg/day.

Arm title	Arm B

Arm description:

Time-restricted immunosuppression with Cyclosporin A and Myfortic.

Arm type	Experimental
Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft, Powder for infusion
Routes of administration	Infusion , Oral use

Dosage and administration details:

Cyclosporine A time-restricted immunosuppression: 9 mg/kg p.o. (in 2 doses) OR 3 mg/kg i.v. (in 2 doses) from day -5/-3 (depending on local procedures) till day 84.

Investigational medicinal product name	Myfortic
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Myfortic time-restricted immunosuppression:(2x 16 mg/kg p.o.) from day 0 till day 28. Myfortic will be given with a maximum of 2160 mg/day.

Arm title	Arm C

Arm description:

Post-transplant cyclophosphamide

Arm type	Experimental
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide during conditioning: 14.5 mg/kg i.v. (day -6 and -5).
Cyclophosphamide during post-transplant immunosuppression: 50 mg/kg i.v. (day +3 and +4)

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Fludarabine during conditioning: 30 mg/m^2 i.v. (day -6 to -2) 5 days.

Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft, Powder for infusion
Routes of administration	Infusion , Oral use

Dosage and administration details:

Cyclosporine A during post-transplant immunosuppression: 9 mg/kg p.o. (in 2 doses) OR 3 mg/kg i.v. (in 2 doses) during day +5 till +70.

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	195	194	105
Completed	35	38	40
Not completed	160	156	65
Adverse Reaction	82	84	39
Other	21	15	7
At patients request	1	-	-
Lack of efficacy	56	57	19

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	494	494	
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)	418	418	
From 65-84 years	76	76	
85 years and over	0	0	
Age continuous Units: years			
median	56		
full range (min-max)	18 to 71	-	
Gender categorical Units: Subjects			
Female	201	201	
Male	293	293	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
Standard immunosuppression with Cyclosporin A and Myfortic.	
Reporting group title	Arm B
Reporting group description:	
Time-restricted immunosuppression with Cyclosporin A and Myfortic.	
Reporting group title	Arm C
Reporting group description:	
Post-transplant cyclophosphamide	

Primary: Primary endpoint

End point title	Primary endpoint[1]
End point description:	

End point type	Primary
End point timeframe:	
See publication	

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: Statistical analysis has been uploaded in the chart section.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	184	185	99	
Units: Whole	184	185	99	

Attachments (see zip file)	Statistical data section from publication/HO96_Statistical data List of reported non-SAE's/nonsaedata96-28Nov2022.pdf List of reported SAE's/saedata96-28Nov2022.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs CTCAE grade >= 2 have to be reported (with the exception of progression). However, GVHD of all grades has to be reported on the GVHD forms.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Control group (standard immunosuppression)
Reporting group description: -	
Reporting group title	Time-restricted immunosuppression
Reporting group description: -	
Reporting group title	Post-transplant cyclophosphamide

Reporting group description: -

Serious adverse events	Control group (standard immunosuppression)	Time-restricted immunosuppression	Post-transplant cyclophosphamide
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 184 (31.52%)	70 / 185 (37.84%)	26 / 99 (26.26%)
number of deaths (all causes)	92	97	43
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 184 (0.54%)	2 / 185 (1.08%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Vascular disorders			
Vascular disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	2 / 184 (1.09%)	3 / 185 (1.62%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	1 / 4	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	1 / 2	0 / 0
General disorders and administration site conditions			
General disorders and administration site conditions	Additional description: All combined, see SAE chart for details		

subjects affected / exposed	6 / 184 (3.26%)	6 / 185 (3.24%)	4 / 99 (4.04%)
occurrences causally related to treatment / all	2 / 6	1 / 6	1 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Immune system disorders			
Immune system disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	13 / 184 (7.07%)	14 / 185 (7.57%)	6 / 99 (6.06%)
occurrences causally related to treatment / all	3 / 15	3 / 14	0 / 6
deaths causally related to treatment / all	1 / 3	0 / 2	0 / 1
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	2 / 184 (1.09%)	2 / 185 (1.08%)	4 / 99 (4.04%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 4
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 3
Psychiatric disorders			
Psychiatric disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	0 / 184 (0.00%)	0 / 185 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Investigations	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	10 / 184 (5.43%)	8 / 185 (4.32%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	12 / 12	7 / 8	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	2 / 184 (1.09%)	1 / 185 (0.54%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Cardiac disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	4 / 184 (2.17%)	1 / 185 (0.54%)	3 / 99 (3.03%)
occurrences causally related to treatment / all	0 / 4	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			

Nervous system disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	4 / 184 (2.17%)	10 / 185 (5.41%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	3 / 4	8 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Blood and lymphatic system disorders			
Blood and lymphatic disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	4 / 184 (2.17%)	9 / 185 (4.86%)	3 / 99 (3.03%)
occurrences causally related to treatment / all	4 / 6	5 / 9	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	17 / 184 (9.24%)	15 / 185 (8.11%)	3 / 99 (3.03%)
occurrences causally related to treatment / all	14 / 20	10 / 16	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatobiliary disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	2 / 184 (1.09%)	2 / 185 (1.08%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 184 (0.54%)	0 / 185 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal and urinary disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 184 (0.54%)	2 / 185 (1.08%)	2 / 99 (2.02%)
occurrences causally related to treatment / all	1 / 1	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infections and infestations	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	11 / 184 (5.98%)	12 / 185 (6.49%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	1 / 12	2 / 14	0 / 1
deaths causally related to treatment / all	0 / 2	2 / 3	0 / 0
Metabolism and nutrition disorders			

Metabolism and nutrition disorders	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	5 / 184 (2.72%)	3 / 185 (1.62%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	2 / 5	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Control group (standard immunosuppression)	Time-restricted immunosuppression	Post-transplant cyclophosphamide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	149 / 184 (80.98%)	165 / 185 (89.19%)	89 / 99 (89.90%)
Vascular disorders			
Vascular	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	9 / 184 (4.89%)	7 / 185 (3.78%)	4 / 99 (4.04%)
occurrences (all)	12	8	4
Surgical and medical procedures			
Surgery/intra-operative injury	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	1 / 184 (0.54%)	0 / 185 (0.00%)	0 / 99 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Constitutional symptoms	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	27 / 184 (14.67%)	33 / 185 (17.84%)	6 / 99 (6.06%)
occurrences (all)	35	37	7
Pain	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	14 / 184 (7.61%)	19 / 185 (10.27%)	10 / 99 (10.10%)
occurrences (all)	14	20	11
Death	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	0 / 184 (0.00%)	1 / 185 (0.54%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Secondary malignancy	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	0 / 184 (0.00%)	1 / 185 (0.54%)	0 / 99 (0.00%)
occurrences (all)	0	1	0
Syndromes	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	0 / 184 (0.00%)	2 / 185 (1.08%)	1 / 99 (1.01%)
occurrences (all)	0	3	1
Immune system disorders			

Allergy/immunology	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	2 / 184 (1.09%)	0 / 185 (0.00%)	3 / 99 (3.03%)
occurrences (all)	2	0	5
Reproductive system and breast disorders			
Sexual/reproductive function	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	0 / 184 (0.00%)	1 / 185 (0.54%)	1 / 99 (1.01%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Pulmonary/upper respiratory	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	8 / 184 (4.35%)	12 / 185 (6.49%)	8 / 99 (8.08%)
occurrences (all)	9	15	11
Cardiac disorders			
Cardiac arrythmia	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	4 / 184 (2.17%)	4 / 185 (2.16%)	3 / 99 (3.03%)
occurrences (all)	4	4	3
Cardiac general	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	42 / 184 (22.83%)	43 / 185 (23.24%)	24 / 99 (24.24%)
occurrences (all)	45	46	24
Nervous system disorders			
Neurology	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	26 / 184 (14.13%)	22 / 185 (11.89%)	11 / 99 (11.11%)
occurrences (all)	31	28	13
Blood and lymphatic system disorders			
Blood/bone marrow	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	51 / 184 (27.72%)	42 / 185 (22.70%)	9 / 99 (9.09%)
occurrences (all)	90	92	15
Coagulation	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	3 / 184 (1.63%)	2 / 185 (1.08%)	1 / 99 (1.01%)
occurrences (all)	3	3	1
Hemorrhage/bleeding	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	4 / 184 (2.17%)	4 / 185 (2.16%)	1 / 99 (1.01%)
occurrences (all)	5	4	1
Lymphatics	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	4 / 184 (2.17%)	8 / 185 (4.32%)	2 / 99 (2.02%)
occurrences (all)	4	8	2
Ear and labyrinth disorders			

Auditory/ear	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	3 / 184 (1.63%)	1 / 185 (0.54%)	1 / 99 (1.01%)
occurrences (all)	3	1	1
Eye disorders			
Ocular/visual	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	6 / 184 (3.26%)	6 / 185 (3.24%)	6 / 99 (6.06%)
occurrences (all)	7	6	6
Gastrointestinal disorders			
Gastrointestinal	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	53 / 184 (28.80%)	50 / 185 (27.03%)	27 / 99 (27.27%)
occurrences (all)	65	70	29
Hepatobiliary disorders			
Hepatobiliary/pancreas	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	4 / 184 (2.17%)	1 / 185 (0.54%)	0 / 99 (0.00%)
occurrences (all)	4	2	0
Skin and subcutaneous tissue disorders			
Dermatology/skin	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	10 / 184 (5.43%)	21 / 185 (11.35%)	10 / 99 (10.10%)
occurrences (all)	10	25	12
Renal and urinary disorders			
Renal/genitourinary	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	11 / 184 (5.98%)	11 / 185 (5.95%)	4 / 99 (4.04%)
occurrences (all)	12	11	6
Endocrine disorders			
Endocrine	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	3 / 184 (1.63%)	7 / 185 (3.78%)	2 / 99 (2.02%)
occurrences (all)	3	7	2
Musculoskeletal and connective tissue disorders			
Musculoskeletal/soft tissue	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	6 / 184 (3.26%)	6 / 185 (3.24%)	7 / 99 (7.07%)
occurrences (all)	7	6	7
Infections and infestations			
Infection	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	87 / 184 (47.28%)	104 / 185 (56.22%)	71 / 99 (71.72%)
occurrences (all)	202	226	154
Metabolism and nutrition disorders			

Metabolic/laboratory	Additional description: All combined, see SAE chart for details		
subjects affected / exposed	74 / 184 (40.22%)	72 / 185 (38.92%)	40 / 99 (40.40%)
occurrences (all)	185	156	75

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2010	The study objective and statistical analysis of quality of life assessment are changed; Reporting of pregnancies is added; The grading of acute GvHD is corrected.
17 May 2011	Change of principal investigator; The registration of patients receiving a T-cell depleted allogenic SCT was added; An extra inclusion criterion for the second randomization was added; dose adjustment of cyclosporin A was added; deletion of a off protocol reason (infusion of donor lymphocytes);
13 March 2012	Change of principal investigator; Deletion of the section 'severe GvHD; The registration of patients receiving a T-cell depleted allogeneic SCT and that will be treated with immunosuppression according to local hospital policy is deleted form protocol. It was added in version 3, but has not been implemented; correction with regards to reporting of GvHD; Information requested at registering patient is corrected from “patient’s initials or code” into “local patient code (optional)”.
17 July 2013	Addition of an additional treatment arm with a short-course post-transplant GVHD prophylaxis consisting of high-dose cyclophosphamide. (introduction, objectives, study design, treatment, statistical considerations); Changed inclusion criterion regarding age; Changes in reason for going off protocol treatment with regards to development of GVHD; Added is the use of a Summary of Product Characteristics (SPC) for an authorized medicinal product in the definition of SUSAR.
22 April 2014	• Arm 3 Post transplant cyclophosphamide: Cyclosporine A treatment is extended to +70 days • Arm 3: Added option of cyclosporine A p.o. dose. • Arm 1 and 2: Date start cyclosporine A is changed to day -5 –day -3 (depending on local procedures). • Period of reporting adverse events is corrected (in accordance to earlier amendment • Exemptions of SAE reporting are clarified • Exemption of SAE reporting of chronic GvHD is limited to chronic GvHD not requiring systemic treatment. • Added is a monitoring of overall mortality to detect possible differences in relapse rate between arm 1 and arm 3.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported