Clinical trial results:
EuroNet-Paediatric Hodgkin's Lymphoma Group

First international Inter-Group Study
for classical Hodgkin's Lymphoma in Children and Adolescents

Summary

EudraCT number	2006-000995-33
Trial protocol	DE CZ GB SE AT FR IE ES DK PL BE NL SI
Global end of trial date	30 October 2018
Results information	
Result version number	v1 (current)
This version publication date	10 June 2021
First version publication date	10 June 2021
Summary attachment (see zip file)	Final report (EuroNet-PHL-C1_trial_report_Final 2.0_2020-07-07.pdf)

Trial information

Trial identification	
Sponsor protocol code	EuroNet-PHL-C1
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Martin-Luther-University of Halle-Wittenberg
Sponsor organisation address	Magdeburger Str. 27, Halle (Saale), Germany, 06097
Public contact	Prof Dr Dieter Körholz (Coordinating chairperson), UK Giessen und Marburg GmbH; Standort Giessen - Zentrum f. Kinderheilkunde u. Jugendmedizin, Dieter.Koerholz@paediat.med.uni-giessen.de
Scientific contact	Prof Dr Dieter Körholz (Coordinating chairperson), UK Giessen und Marburg GmbH; Standort Giessen - Zentrum f. Kinderheilkunde u. Jugendmedizin, Dieter.Koerholz@paediat.med.uni-giessen.de

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	07 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2018
Global end of trial reached?	Yes
Global end of trial date	30 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. Are 5 year event free survival (EFS) rate estimates in patients with adequate response after 2 OEPA treated without radiotherapy consistent with a target EFS rate of 90% in all treatment groups?
2. Can Procarbazine be safely replaced by Dacarbazine in therapy groups TG-2 and TG-3 without a deterioration of EFS (randomised comparison of COPDAC and COPP)?
3. Description of treatment outcome to a standardised risk adapted relapse strategy

Protection of trial subjects:

Patients werde closely monitored by the trating staff with regard to safety during the course of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2007
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: 33
Country: Number of subjects enrolled	Norway: 39
Country: Number of subjects enrolled	Poland: 98
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Spain: 105
Country: Number of subjects enrolled	Sweden: 56
Country: Number of subjects enrolled	United Kingdom: 289
Country: Number of subjects enrolled	Austria: 87
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Czechia: 52
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	France: 487
Country: Number of subjects enrolled	Germany: 693
Country: Number of subjects enrolled	Ireland: 41
Country: Number of subjects enrolled	Slovakia: 35

Country: Number of subjects enrolled	Switzerland: 45
Worldwide total number of subjects	2102
EEA total number of subjects	1768

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)	455
Adolescents (12-17 years)	1647
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Within this clinical trial N=2131 patients have been recruited in 188 trial centres in 16 European countries. The first patient within this clinical trial has been recruited on 2007-01-31, the last patient on 2013-01-29. Accrual to the study closed on 2013-01-29.

Pre-assignment

Screening details:

Screening included: confirmation of the diagnosis by the local pathologist; FDG-PET scan before start of treatment; confirmation of local pathology result by reference pathologist; medical history; previous and concomitant disease status; clinical, laboratory and functional examinations; pubertal assessment, if appl.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TG-1

Arm description:

TG-1 (treatment group 1): patients of stages I A/B and II A without bulk>=200 ml and without ESR>=30mm/hr
All patients receive two cycles of OEPA. Patients in TG-1 with adequate response (response groups AR1 and AR2) receive no further therapy. Patients with inadequate response (IR and IRU) receive involved field radiotherapy .

Arm type	stratification group
Investigational medicinal product name	Prednisone/prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OEPA scheme
Prednisone/prednisolone
60 mg/m2/day p.o. divided into 3 doses
day 1 – 15

Investigational medicinal product name	Vincristine sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

OEPA scheme
Vincristine
1.5 mg/m2 i.v., max. SD 2 mg
day 1 + 8 + 15

Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

OEPA scheme
Doxorubicine
40 mg/m2 as 1-6 hour infusion
day 1 + 15

Investigational medicinal product name	Etoposide/Etopophos
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

OEPA scheme
Etoposide/Etopophos
125 mg/m² as 1-2 hour infusion
day 1 – 5

Arm title	TG-2

Arm description:

TG-2 (treatment group 2): patients of stages IEA/B, IIEA, II B or III A and patients of stages I A/B and II A with bulk>=200 ml and/or ESR>=30mm/hr
All patients receive two cycles of OEPA. After initial staging and assignment to treatment groups 2 or 3, patients are randomised between COPP and COPDAC. Following completion of 2 cycles of OEPA and after early response assessment including FDG-PET, patients in TG-2 receive two cycles, patients in TG-3 four cycles of either COPP or COPDAC.
Patients in TG-2 / TG-3 with adequate response in early response assessment (response groups AR1 and AR2) receive no radiotherapy.

Arm type	stratification group
Investigational medicinal product name	Procarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

COPP scheme
Procarbazine
100 mg/m²/day, p.o. divided into 2 – 3 doses
day 1 – 15

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

Dosage and administration details:

COPP / COPDAC scheme
Cyclophosphamide
500 mg/m2, 60-min. inf.
day 1 + 8

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

COPDAC scheme
Dacarbazine
250 mg/m2 as 15 - 30-min. inf.
day 1 – 3

Investigational medicinal product name	Prednisone/prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OEPA scheme
Prednisone/prednisolone
60 mg/m2/day p.o. divided into 3 doses
day 1 – 15

Investigational medicinal product name	Vincristine sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

OEPA scheme
Vincristine
1.5 mg/m2 i.v., max. SD 2 mg
day 1 + 8 + 15

Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

OEPA scheme
Doxorubicine
40 mg/m2 as 1-6 hour infusion
day 1 + 15

Investigational medicinal product name	Etoposide/Etopophos
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

OEPA scheme
Etoposide/Etopophos
125 mg/m² as 1-2 hour infusion
day 1 – 5

Arm title	TG-3

Arm description:

TG-3 (treatment group 3): patients of stages IIEB, IIIEA/B, III B or IV A/B
All patients receive two cycles of OEPA. After initial staging and assignment to treatment groups 2 or 3, patients are randomised between COPP and COPDAC. Following completion of 2 cycles of OEPA and after early response assessment including FDG-PET, patients in TG-2 receive two cycles, patients in TG-3 four cycles of either COPP or COPDAC.
Patients in TG-2 / TG-3 with adequate response in early response assessment (response groups AR1 and AR2) receive no radiotherapy.

Arm type	stratification group
Investigational medicinal product name	Procarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

COPP scheme
Procarbazine
100 mg/m²/day, p.o. divided into 2 – 3 doses
day 1 – 15

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

Dosage and administration details:

COPP / COPDAC scheme
Cyclophosphamide
500 mg/m2, 60-min. inf.
day 1 + 8

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

COPDAC scheme
Dacarbazine
250 mg/m2 as 15 - 30-min. inf.
day 1 – 3

Investigational medicinal product name	Prednisone/prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

OEPA scheme
Prednisone/prednisolone
60 mg/m2/day p.o. divided into 3 doses
day 1 – 15

Investigational medicinal product name	Vincristine sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

OEPA scheme
Vincristine
1.5 mg/m2 i.v., max. SD 2 mg
day 1 + 8 + 15

Investigational medicinal product name	Doxorubicine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

OEPA scheme
Doxorubicine
40 mg/m2 as 1-6 hour infusion
day 1 + 15

Investigational medicinal product name	Etoposide/Etopophos
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

OEPA scheme
Etoposide/Etopophos
125 mg/m² as 1-2 hour infusion
day 1 – 5

Number of subjects in period 1	TG-1	TG-2	TG-3
Started	714	479	909
Completed	713	478	904
Not completed	1	1	5
Consent withdrawn by subject	1	-	1
early death	-	1	-
disease progression	-	-	4

Baseline characteristics

Reporting groups	
Reporting group title	TG-1
Reporting group description:	
TG-1 (treatment group 1): patients of stages I A/B and II A without bulk>=200 ml and without ESR>=30mm/hr All patients receive two cycles of OEPA. Patients in TG-1 with adequate response (response groups AR1 and AR2) receive no further therapy. Patients with inadequate response (IR and IRU) receive involved field radiotherapy .	
Reporting group title	TG-2
Reporting group description:	
TG-2 (treatment group 2): patients of stages IEA/B, IIEA, II B or III A and patients of stages I A/B and II A with bulk>=200 ml and/or ESR>=30mm/hr All patients receive two cycles of OEPA. After initial staging and assignment to treatment groups 2 or 3, patients are randomised between COPP and COPDAC. Following completion of 2 cycles of OEPA and after early response assessment including FDG-PET, patients in TG-2 receive two cycles, patients in TG-3 four cycles of either COPP or COPDAC. Patients in TG-2 / TG-3 with adequate response in early response assessment (response groups AR1 and AR2) receive no radiotherapy.	
Reporting group title	TG-3
Reporting group description:	
TG-3 (treatment group 3): patients of stages IIEB, IIIEA/B, III B or IV A/B All patients receive two cycles of OEPA. After initial staging and assignment to treatment groups 2 or 3, patients are randomised between COPP and COPDAC. Following completion of 2 cycles of OEPA and after early response assessment including FDG-PET, patients in TG-2 receive two cycles, patients in TG-3 four cycles of either COPP or COPDAC. Patients in TG-2 / TG-3 with adequate response in early response assessment (response groups AR1 and AR2) receive no radiotherapy.	

Reporting group values	TG-1	TG-2	TG-3
Number of subjects	714	479	909
Age categorical Units: Subjects			
Age under 13	236	142	243
Age over 13	478	337	666
Gender categorical Units: Subjects			
Female	390	236	383
Male	324	243	526
Stage Units: Subjects			
Stage I	45	3	0
Stage II	668	315	133
Stage III	1	159	247
Stage IV	0	2	529

Reporting group values	Total		
Number of subjects	2102		
Age categorical Units: Subjects			
Age under 13	621		

Age over 13	1481		

Gender categorical Units: Subjects			
Female	1009		
Male	1093		
Stage Units: Subjects			
Stage I	48		
Stage II	1116		
Stage III	407		
Stage IV	531		

End points

End points reporting groups

Reporting group title	TG-1

Reporting group description:

TG-1 (treatment group 1): patients of stages I A/B and II A without bulk>=200 ml and without ESR>=30mm/hr
All patients receive two cycles of OEPA. Patients in TG-1 with adequate response (response groups AR1 and AR2) receive no further therapy. Patients with inadequate response (IR and IRU) receive involved field radiotherapy .

Reporting group title	TG-2

Reporting group description:

TG-2 (treatment group 2): patients of stages IEA/B, IIEA, II B or III A and patients of stages I A/B and II A with bulk>=200 ml and/or ESR>=30mm/hr
All patients receive two cycles of OEPA. After initial staging and assignment to treatment groups 2 or 3, patients are randomised between COPP and COPDAC. Following completion of 2 cycles of OEPA and after early response assessment including FDG-PET, patients in TG-2 receive two cycles, patients in TG-3 four cycles of either COPP or COPDAC.
Patients in TG-2 / TG-3 with adequate response in early response assessment (response groups AR1 and AR2) receive no radiotherapy.

Reporting group title	TG-3

Reporting group description:

TG-3 (treatment group 3): patients of stages IIEB, IIIEA/B, III B or IV A/B
All patients receive two cycles of OEPA. After initial staging and assignment to treatment groups 2 or 3, patients are randomised between COPP and COPDAC. Following completion of 2 cycles of OEPA and after early response assessment including FDG-PET, patients in TG-2 receive two cycles, patients in TG-3 four cycles of either COPP or COPDAC.
Patients in TG-2 / TG-3 with adequate response in early response assessment (response groups AR1 and AR2) receive no radiotherapy.

Primary: Event free survival (EFS)

End point title	Event free survival (EFS)[1]

End point description:

EFS = time from registration until the first of the following events:
- progression/relapse of disease
- occurrence of a secondary malignancy
- death by any cause

End point type	Primary

End point timeframe:

60 months

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: See attached final trial report

End point values	TG-1	TG-2	TG-3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	713	478	904	
Units: months				
number (confidence interval 95%)	87.4 (85.0 to 89.9)	91.7 (89.2 to 94.2)	85.5 (83.2 to 87.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) = time period from registration until death of any cause

End point type	Secondary

End point timeframe:

60 months

End point values	TG-1	TG-2	TG-3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	713	478	904	
Units: months				
number (confidence interval 95%)	99.1 (98.4 to 99.8)	98.9 (98.0 to 99.9)	97.9 (97.0 to 98.9)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 3 months after application of last trial therapy	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: See attached final trial report

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2007	1. Data of the interim analysis of the GPOH-HD2002 pilot study support that COPDAC is an effective and safe treatment option. Relevant safety information is updated. 2. Treatment of study patients who refuse randomisation. (In the event of refusal of randomisation between COPP and COPDAC the recommendation of the trial chairpersons is that COPP is considered as the standard arm. In these situations these patients will remain on the study. These patients will be informative concerning the STAR question and add to the safety data. Patients should not be treated on the COPDAC arm outside the study.) 3. SAE reporting: Time horizon and clarification in order avoid unnecessary SAE – reporting. (SAE reporting is restricted to events occurring within 3 month after the end of the study treatment; addition of expected toxicities for each IMP and RT) 4. Administrative data (update of contact data, correction of typos)
17 November 2009	1. Clarification of discrepancies between patient information and informed consent declaration concerning time of archiving 2. Change of members in the central review team and in the panel of referenpathologists. 3. Title of patient information and informed consent for relapse treatment is adjusted to the protocol. The inclusion criteria do not contain an age limit for patients with relapse of childhood and adolescent Hodgkin`s Lymphoma 4. Clarification in patient information for primary and relapse treatment that depending on the treatment center either prednisone or prednisolon will be used as prescribed in the final version of the treatment protocol 5. Clarification of antibacterial prophylaxis since the use of these drugs is differently handled in the various countries and institutions. However, this will not affect the study results, since all patients will receive a necessary prophylaxis. 6. The protocol prescribes either Prednisone or Prednisolone. In the abbreviation section only prednisone was listed, Therefore prednisolone was added for formal correctness. 7. Administrative data (update of contact data)
22 February 2012	1. Stop randomisation COPP vs COPDAC: Further to a Clinical Board Meeting of EuroNet-PHL and the Annual EuroNet-PHL Clinicians Meeting (from 09.02.2012 to 11.02.2012), a decision was made to end the randomisation between COPP and COPDAC for eligible Patients in the EuroNet-PHL-C1 trial. This decision was made on the basis of the results of the second interim data analysis which showed emerging evidence that COPP and COPDAC are similarly efficacious. In view of the evidence that emerged from the interim data analysis of EuroNet PHL-C1 the Clinical Board and associated parties saw a change in the risk-benefit assessment for the trial and decided that randomisation should be stopped on 13.02.2012. Although the data was immature, it was clear that the sample size was sufficient to answer the randomised question on efficacy and that furthermore it was essential to avoid the potentially detrimental effects of COPP on male fertility. All Patients in EuroNet-PHL-C1 (in TG-2 and TG-3) should now receive COPDAC. The trial remained open to recruitment (outside of Germany) because that data was required to fully answer the other important questions in the protocol relating to the STAR approach to treatment and whether it is safe to omit radiotherapy. 2. Administrative data: Update of contact data

13 April 2015	1. Addition of global scientific side projects: a) DETERMINATION OF ANTI MULLERIAN AND OTHER GONADAL HORMONES IN FEMALE PATIENTS OF THE EURONET-PHL-C1 PATIENTS; b) QUALITY CONTROL IN RADIOTHERAPY; c) INCIDENCE OF OSTEONECROSES IN CHILDREN AND ADOLESCENTS TREATED WITHIN THE EURONET-PHL-C1 TRIAL 2. Addition of country-specific scientific side projects: a) IDENTIFICATION OF A PROGNOSTIC GENE EXPRESSION SIGNATURE IN PEDIATRIC HODGKIN'S LYMPHOMA IN CONTEXT OF THE EURONET-PHL-C1 TRIAL; b) IDENTIFICATION OF DISTINCTIVE PATHOLOGIC FEATURES OF PEDIATRIC HODGKIN'S LYMPHOMAS WITH ABNORMAL CHEMO RESPONSE IN CONTEXT OF THE EURONET-PHL-C1 TRIAL c) ASSESSMENT OF LATE EFFECTS IN PATIENTS TREATED ACCORDING TO EURONET-PHL-C1

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported