Clinical trial results:
Evaluation of anthroposophic supportive medicine on treatment-related toxicity in children receiving cancer therapy

Summary

EudraCT number	2004-002711-83
Trial protocol	DE
Global end of trial date	23 March 2017

Results information

Result version number	v1 (current)
This version publication date	25 April 2022
First version publication date	25 April 2022
Summary attachment (see zip file)	CSR Summary of Results (CSR_Summary_of_Results_V1.0.pdf)

Trial information

Trial identification

Sponsor protocol code	09-2004 PaedonkoChar

Additional study identifiers

ISRCTN number	ISRCTN64676790
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Helixor Heilmittel GmbH
Sponsor organisation address	Fischermühle 1, Rosenfeld, Germany, 72348
Public contact	Sabine Rieger, Helixor Heilmittel GmbH, +49 7428 / 935 850, srieger@helixor.de
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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	21 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

influence of an anthroposophic supportive therapy concept on the chemotherapy-associated toxicity was investigated by means of a toxicity sumscore consisting of the NCI-CTC-scales hematology, mucositis, general condition and the GPOH-modified scale for infection

Protection of trial subjects:

- the study was conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of patients
- the investigator ensured pseudonymity of the patients, signed patient informed consent and patient enrolment log were kept striktly confidential to enable patient identification at the site
- minimisation of pain of subcutaneous injection by use of INJEX needle free injector (optional)
- further measures were not necessary

Background therapy:

participants of all groups received standard chemotherapy according to individual tumor type and stage

Evidence for comparator: -

Actual start date of recruitment	24 November 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 340
Worldwide total number of subjects	340
EEA total number of subjects	340

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)	22
Children (2-11 years)	205
Adolescents (12-17 years)	113
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period from 11/2005 until 11/2013 in 12 trial sites in Germany
Patients were assigned to the verum or control group by stratified randomization according to tumor entities and chemotherapy protocols.

Pre-assignment

Screening details:

Fulfilment of inclusion and non-fulfilment of exclusion criteria.
No further screening criteria defined.
Latest possible date of randomisation was the 10th day after start of chemotherapy protocol.
In total, 556 patients were screened.

Period 1

Period 1 title	treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	control group

Arm description:

standard therapy: chemotherapy according to underlying disease with standardised concomitant treatments

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	verum group

Arm description:

anthroposophic supportive therapy in addition to standard therapy (chemotherapy according to underlying disease with standardised concomitant treatments)

Arm type	Experimental
Investigational medicinal product name	Helixor A
Investigational medicinal product code	L01CH01
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections 2 times a week
stepwise dose increase starting with 1 mg until occurence of local or systemic reaction to investigational drug
maximum allowed dose: 100 mg

Investigational medicinal product name	Cichorium e planta tota 5% Globuli velati
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details:

Dose for children < 4 years: 3x5 globules per day
dose for children ≥ 4 years: 3x7 globules per day

Investigational medicinal product name	Oxalis Folium Rh D4 aqueous dilution
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Dose for children < 4 years: 3x5 drops per day
dose for children ≥ 4 years: 3x7 drops per day

Investigational medicinal product name	Phosphorus D8 Globuli velati
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details:

Dose for children < 4 years: 5 globules (in the morning)
dose for children ≥ 4 years: 10 globules (in the morning)

Investigational medicinal product name	Phosphorus D30 Globuli velati
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details:

Dose for children < 4 years: 5 globules (in the evening)
dose for children ≥ 4 years: 10 globules (in the evening)

Investigational medicinal product name	Aurum/Prunus liquid dilution for injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 ampoule as an intravenous infusion before each chemotherapy

Investigational medicinal product name	Aurum Valeriana Globuli velati
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details:

Dose for children < 4 years: 5 globules up to every 2 hours (except at night)
dose for children ≥ 4 years: 10 globules up to every 2 hours (except at night)

Investigational medicinal product name	Bryophyllum 5% solution for injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

In the recovery phase after sedation, anesthesia or punctures:
dose for children < 4 years: 5 ml as an intravenous infusion
dose for children ≥ 4 years: 10 ml as an intravenous infusion

Investigational medicinal product name	Bryophyllum 50%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder
Routes of administration	Oral use

Dosage and administration details:

For psychological and somatic side effects or at the end of steroid administration: 1 teaspoon 3 times a day;

for sleep disorders daily:
dose for children < 4 years: 1/2 teaspoon 3 times a day
dose for children ≥ 4 years: 1 teaspoon 3 times a day

Investigational medicinal product name	Calendula (mother tincture)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Dose for children < 4 years: 5 drops 3 times a day
Dose for children ≥ 4 years: 10 drops 3 times a day

Investigational medicinal product name	Nux vomica D4 liquid dilution for injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 ampoule as an intravenous infusion before each chemotherapy

Investigational medicinal product name	Nux vomica e semine D4 Globuli velati
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details:

Dose for children < 4 years: 3 globules daily to hourly
dose for children ≥ 4 years: 5 globules daily to hourly

Investigational medicinal product name	Oxalis ointment 30%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

if necessary or regularly moist warm wrap at noon

Investigational medicinal product name	Ratanhia comp.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Mouthwash
Routes of administration	Oral use

Dosage and administration details:

To be used only as a dilution (30 drops per 100 ml of water) Besides this mouthwash, no other conventional is allowed

Investigational medicinal product name	Solum Oil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pharmaceutical dose form not applicable
Routes of administration	Topical use

Dosage and administration details:

Rubbing of individual body parts (for example extremities / back); if necessary, ideally in the evening

Investigational medicinal product name	Meteoreisen Globuli velati
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pillules
Routes of administration	Oral use

Dosage and administration details: Dose for children < 4 years: 3x5 globules per day dose for children ≥ 4 years: 3x10 globules per day	
Investigational medicinal product name	Argentum metallicum praeparatum D30 (liquid dilution for injection)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: Dose for children < 4 years: 1 ampoule as an intravenous infusion once a day before intravenous antibiotic administration dose for children ≥ 4 years: 2 ampoules as an intravenous infusion once a day before intravenous antibiotic administration	
Investigational medicinal product name	Gentiana Magen Globuli velati
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pillules
Routes of administration	Oral use
Dosage and administration details: Dose for children < 4 years: 3x5 globules per day dose for children ≥ 4 years: 3x10 globules per day	
Investigational medicinal product name	Lachesis D8 Dilution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pillules
Routes of administration	Oral use
Dosage and administration details: Dose for children < 4 years: 3x5 drops per day (to be diluted) dose for children ≥ 4 years: 3x7 drops per day (to be diluted)	

Number of subjects in period 1	control group	verum group
Started	170	170
Completed	149	139
Not completed	21	31
Protocol deviation	21	31

Period 2	
Period 2 title	follow-up period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes

Arm title	Follow-up control group

Arm description:

Patients who have finished at least the first observation period of chemotherapy were observed up to five years
no limitations for treatment during follow-up period after conclusion of standard therapy

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Follow-up verum group

Arm description:

Patients, who have finished at least the first observation period of chemotherapy and have received basic remedies at least during this period, were observed up to five years
no limitations for treatment during follow-up period after conclusion of standard therapy

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Follow-up control group	Follow-up verum group
Started	149	139
Completed	135	135
Not completed	14	4
Lost to follow-up	14	4

Baseline characteristics

Reporting groups	
Reporting group title	control group
Reporting group description:	
standard therapy: chemotherapy according to underlying disease with standardised concomitant treatments	
Reporting group title	verum group
Reporting group description:	
anthroposophic supportive therapy in addition to standard therapy (chemotherapy according to underlying disease with standardised concomitant treatments)	

Reporting group values	control group	verum group	Total
Number of subjects	170	170	340
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	12	10	22
Children (2-11 years)	104	101	205
Adolescents (12-17 years)	54	59	113
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	82	59	141
Male	88	111	199

End points

End points reporting groups

Reporting group title	control group
Reporting group description:	
standard therapy: chemotherapy according to underlying disease with standardised concomitant treatments	
Reporting group title	verum group
Reporting group description:	
anthroposophic supportive therapy in addition to standard therapy (chemotherapy according to underlying disease with standardised concomitant treatments)	
Reporting group title	Follow-up control group
Reporting group description:	
Patients who have finished at least the first observation period of chemotherapy were observed up to five years no limitations for treatment during follow-up period after conclusion of standard therapy	
Reporting group title	Follow-up verum group
Reporting group description:	
Patients, who have finished at least the first observation period of chemotherapy and have received basic remedies at least during this period, were observed up to five years no limitations for treatment during follow-up period after conclusion of standard therapy	
Subject analysis set title	control group ITT subset
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This ITT population includes all patients enrolled in the study who have been randomised, regardless of protocol violations in the course of the study	
Subject analysis set title	verum group ITT subset
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This ITT population includes all patients enrolled in the study who have been randomised and who have received basic medications at least during one complete observation period, regardless of protocol violations in the course of the study.	
Subject analysis set title	Follow-up control group EFS
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
This modified ITT-population includes all patients enrolled in the study and randomised into the control group • with complete remission (CR) at the end of the intensive phase of chemotherapy (main study) • for which a follow-up documentation sheet is available 5 years after diagnosis. This documentation sheet must contain an indication (yes or no) on relapse, death and second malignancy	
Subject analysis set title	Follow-up verum group EFS
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
This modified ITT-population includes all patients enrolled in the study and randomised into the verum group • with complete remission (CR) at the end of the intensive phase of chemotherapy (main study) • for which a follow-up documentation sheet is available 5 years after diagnosis. This documentation sheet must contain an indication (yes or no) on relapse, death and second malignancy	
Subject analysis set title	Follow-up control group OS
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
This modified ITT-population includes all patients enrolled in the study and randomised into the control group for whom a follow-up documentation form has been completed 5 years after diagnosis	
Subject analysis set title	Follow-up verum group OS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

This modified ITT-population includes all patients enrolled in the study and randomised into the verum group for whom a follow-up documentation form has been completed 5 years after diagnosis

Subject analysis set title	control group PP subset
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population includes all patients enrolled in the study who have been randomised and have gone through all chemotherapy units until conclusion of last chemotherapy unit without occurrence of serious protocol violations.

Subject analysis set title	verum group PP subset
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population includes all patients enrolled in the study who have been randomised and have gone through all chemotherapy units until conclusion of last chemotherapy unit without occurrence of serious protocol violations. Additionally at least 75% of basic remedies of study medication have been administered.

Primary: Reduction of toxicity sum score of selected NCI-CTC-scales

End point title	Reduction of toxicity sum score of selected NCI-CTC-scales

End point description:

influence of an anthroposophic supportive therapy concept on the chemotherapy-associated toxicity was investigated by means of a toxicity sumscore consisting of the NCI-CTC-scales hematology, mucositis, general condition and the GPOH-modified scale for infection

End point type	Primary

End point timeframe:

Depending on the chosen chemotherapy schedule time frame lasted from beginning of first chemotherapy treatment unit until 28 days after termination of last chemotherapy treatment unit.

End point values	control group ITT subset	verum group ITT subset	control group PP subset	verum group PP subset
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	140	139	126	82
Units: unit(s)				
arithmetic mean (standard deviation)	11.8 (± 4.54)	12.1 (± 3.92)	11.5 (± 4.33)	11.4 (± 3.58)

Statistical analyses

Statistical analysis title	Comparison of toxicity sum score ITT group
Comparison groups	control group ITT subset v verum group ITT subset
Number of subjects included in analysis	279
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.257
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Comparison of toxicity sum score PP group
Comparison groups	control group PP subset v verum group PP subset

Number of subjects included in analysis	208
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.716
Method	Wilcoxon (Mann-Whitney)

Secondary: ALL-Non-HR; overall survival

End point title	ALL-Non-HR; overall survival

End point description:

Overall survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of death or end of 5-years observation period

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	47		
Units: months				
arithmetic mean (standard deviation)	56.9 (± 10.2)	59.0 (± 5.61)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS
Number of subjects included in analysis	101
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.185
Method	Logrank

Secondary: ALL-HR; overall survival

End point title	ALL-HR; overall survival

End point description:

Overall survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of death or end of 5-years observation period

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	5		
Units: months				
arithmetic mean (standard deviation)	60.0 (± 0)	57.6 (± 5.37)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS
Number of subjects included in analysis	8
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.439
Method	Logrank

Secondary: COALL-HR; overall survival

End point title	COALL-HR; overall survival
End point description:	
Overall survival within a period of 5 years	
End point type	Secondary
End point timeframe:	
Date of initial diagnosis until date of death or end of 5-years observation period	

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	9		
Units: months				
arithmetic mean (standard deviation)	53.0 (± 13.7)	55.3 (± 9.27)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS

Number of subjects included in analysis	16
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.756
Method	Logrank

Secondary: ALL-Rez; overall survival

End point title	ALL-Rez; overall survival

End point description:

Overall survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of death or end of 5-years observation period

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: months				
arithmetic mean (standard deviation)	50.2 (± 22.7)	46.2 (± 21.8)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS
Number of subjects included in analysis	12
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.992
Method	Logrank

Secondary: AML; overall survival

End point title	AML; overall survival

End point description:

Overall survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of death or end of 5-years observation period

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	8		
Units: months				
arithmetic mean (standard deviation)	55.3 (± 14.0)	46.8 (± 20.1)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS
Number of subjects included in analysis	17
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.229
Method	Logrank

Secondary: B-NHL; overall survival

End point title	B-NHL; overall survival
End point description:	
Overall survival within a period of 5 years	
End point type	Secondary
End point timeframe:	
Date of initial diagnosis until date of death or end of 5-years observation period	

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	8		
Units: months				
arithmetic mean (standard deviation)	57.6 (± 6.72)	40.4 (± 27.2)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS

Number of subjects included in analysis	16
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.063
Method	Logrank

Secondary: Rhabdomyosarcoma; overall survival

End point title	Rhabdomyosarcoma; overall survival

End point description:

Overall survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of death or end of 5-years observation period

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	2		
Units: months				
arithmetic mean (standard deviation)	60.0 (± 0)	34.0 (± 0)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS
Number of subjects included in analysis	5
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.221
Method	Logrank

Secondary: Osteosarcoma; overall survival

End point title	Osteosarcoma; overall survival

End point description:

Overall survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of death or end of 5-years observation period

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	3		
Units: months				
arithmetic mean (standard deviation)	56.8 (± 6.50)	42.3 (± 30.6)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS
Number of subjects included in analysis	7
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.728
Method	Logrank

Secondary: Morbus Hodgkin; overall survival

End point title	Morbus Hodgkin; overall survival
End point description:	
Overall survival within a period of 5 years	
End point type	Secondary
End point timeframe:	
Date of initial diagnosis until date of death or end of 5-years observation period	

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	11		
Units: months				
arithmetic mean (standard deviation)	55.1 (± 11.0)	59.4 (± 2.11)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS

Number of subjects included in analysis	28
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.407
Method	Logrank

Secondary: Ewing-Sarcoma; overall survival

End point title	Ewing-Sarcoma; overall survival

End point description:

Overall survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of death or end of 5-years observation period

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	10		
Units: months				
arithmetic mean (standard deviation)	56.9 (± 6.89)	47.4 (± 21.7)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS
Number of subjects included in analysis	21
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.441
Method	Logrank

Secondary: Medulloblastoma/Ependymoma; overall survival

End point title	Medulloblastoma/Ependymoma; overall survival

End point description:

Overall survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of death or end of 5-years observation period

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	3		
Units: months				
arithmetic mean (standard deviation)	60.0 (± 0)	29.0 (± 11.5)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS
Number of subjects included in analysis	4
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.182
Method	Logrank

Secondary: Neuroblastoma; overall survival

End point title	Neuroblastoma; overall survival
End point description:	
Overall survival within a period of 5 years	
End point type	Secondary
End point timeframe:	
Date of initial diagnosis until date of death or end of 5-years observation period	

End point values	Follow-up control group OS	Follow-up verum group OS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: months				
arithmetic mean (standard deviation)	48.4 (± 20.2)	33.0 (± 18.2)		

Statistical analyses

Statistical analysis title	Comparison of overall survival
Comparison groups	Follow-up control group OS v Follow-up verum group OS

Number of subjects included in analysis	14
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.025
Method	Logrank

Secondary: ALL-Non-HR; event-free survival

End point title	ALL-Non-HR; event-free survival

End point description:

Event-free survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	44		
Units: months				
arithmetic mean (standard deviation)	54.9 (± 13.4)	55.7 (± 12.5)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up control group EFS v Follow-up verum group EFS
Number of subjects included in analysis	93
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.686
Method	Logrank

Secondary: ALL-HR; event-free survival

End point title	ALL-HR; event-free survival

End point description:

Event-free survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	5		
Units: months				
arithmetic mean (standard deviation)	60.0 (± 0)	57.2 (± 6.26)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up control group EFS v Follow-up verum group EFS
Number of subjects included in analysis	8
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.436
Method	Logrank

Secondary: COALL-Non-HR; event-free survival

End point title	COALL-Non-HR; event-free survival

End point description:

Event-free survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: months				
arithmetic mean (standard deviation)	57.9 (± 6.33)	58.9 (± 3.33)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up control group EFS v Follow-up verum group EFS

Number of subjects included in analysis	18
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.967
Method	Logrank

Secondary: COALL-HR; event-free survival

End point title	COALL-HR; event-free survival

End point description:

Event-free survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	4	9		
Units: months				
arithmetic mean (standard deviation)	60.0 (± 0)	53.8 (± 12.8)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up control group EFS v Follow-up verum group EFS
Number of subjects included in analysis	13
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.331
Method	Logrank

Secondary: ALL-Rez; event-free survival

End point title	ALL-Rez; event-free survival

End point description:

Event-free survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	4		
Units: months				
arithmetic mean (standard deviation)	59.0 (± 1.73)	50.8 (± 18.5)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up control group EFS v Follow-up verum group EFS
Number of subjects included in analysis	7
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.919
Method	Logrank

Secondary: AML; event-free survival

End point title	AML; event-free survival
End point description:	
Event-free survival within a period of 5 years	
End point type	Secondary
End point timeframe:	
Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period	

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	4		
Units: months				
arithmetic mean (standard deviation)	49.9 (± 19.6)	50.8 (± 18.5)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up control group EFS v Follow-up verum group EFS

Number of subjects included in analysis	12
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.306
Method	Logrank

Secondary: B-NHL; event-free survival

End point title	B-NHL; event-free survival

End point description:

Event-free survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	6		
Units: months				
arithmetic mean (standard deviation)	60.0 (± 0)	51.5 (± 20.8)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up control group EFS v Follow-up verum group EFS
Number of subjects included in analysis	13
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.28
Method	Logrank

Secondary: Rhabdomyosarcoma; event-free survival

End point title	Rhabdomyosarcoma; event-free survival

End point description:

Event-free survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	1		
Units: months				
arithmetic mean (standard deviation)	60.0 (± 0)	9.0 (± 0)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up control group EFS v Follow-up verum group EFS
Number of subjects included in analysis	3
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.157
Method	Logrank

Secondary: Morbus Hodgkin; event-free survival

End point title	Morbus Hodgkin; event-free survival

End point description:

Event-free survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	9		
Units: months				
arithmetic mean (standard deviation)	53.5 (± 15.9)	52.0 (± 17.6)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up control group EFS v Follow-up verum group EFS

Number of subjects included in analysis	15
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.802
Method	Logrank

Secondary: Ewing-Sarcoma; event-free survival

End point title	Ewing-Sarcoma; event-free survival

End point description:

Event-free survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	4		
Units: months				
arithmetic mean (standard deviation)	56.0 (± 8.21)	55.0 (± 10.0)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up control group EFS v Follow-up verum group EFS
Number of subjects included in analysis	14
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.897
Method	Logrank

Secondary: Medulloblastoma/Ependymoma; event-free survival

End point title	Medulloblastoma/Ependymoma; event-free survival

End point description:

Event-free survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	3		
Units: months				
arithmetic mean (standard deviation)	60.0 (± 0)	22.7 (± 11.9)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up verum group EFS v Follow-up control group EFS
Number of subjects included in analysis	4
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.182
Method	Logrank

Secondary: Neuroblastoma; event-free survival

End point title	Neuroblastoma; event-free survival

End point description:

Event-free survival within a period of 5 years

End point type	Secondary

End point timeframe:

Date of initial diagnosis until date of event (relapse, death or second malignancy) or end of 5-years observation period

End point values	Follow-up control group EFS	Follow-up verum group EFS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	1		
Units: months				
arithmetic mean (standard deviation)	60.0 (± 0)	41.0 (± 0)		

Statistical analyses

Statistical analysis title	Comparion of event free survival
Comparison groups	Follow-up control group EFS v Follow-up verum group EFS

Number of subjects included in analysis	4
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.083
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

continuous reporting of adverse events by investigator via remote data entry, assessment of reports yearly within framework of annual safety reports (serious adverse reactions assessed quarterly)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	safety population

Reporting group description:

The safety population included all patients recruited into the study who were randomized and who received the basic medication at least once during the course of the study and/or on-demand remedies of the investigational medication. For this population adverse events (AE) and serious adverse events (SAEs) were assessed.

Serious adverse events	safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 163 (6.75%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Nervous system disorders			
Toxic encephalopathy			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral venous sinus thrombosis			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia viral				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 163 (1.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Neutropenic sepsis				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Febrile infection				
subjects affected / exposed	1 / 163 (0.61%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Soft tissue infection			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	123 / 163 (75.46%)		
Cardiac disorders			
Tachycardia paroxysmal			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Nervous system disorders			
Tremor			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
General disorders and administration site conditions			
Injection site inflammation			
subjects affected / exposed	106 / 163 (65.03%)		
occurrences (all)	453		
Inflammation			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Application site pain			
subjects affected / exposed	6 / 163 (3.68%)		
occurrences (all)	9		
Injection site necrosis			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		

Pyrexia			
subjects affected / exposed	32 / 163 (19.63%)		
occurrences (all)	81		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Immune system disorders			
Dermatitis allergic			
subjects affected / exposed	17 / 163 (10.43%)		
occurrences (all)	27		
Hypersensitivity			
subjects affected / exposed	8 / 163 (4.91%)		
occurrences (all)	9		
Urticaria			
subjects affected / exposed	3 / 163 (1.84%)		
occurrences (all)	4		
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	4 / 163 (2.45%)		
occurrences (all)	6		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Lung infiltration			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Apnoea			

subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 163 (0.61%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	4 / 163 (2.45%)		
occurrences (all)	4		
Pruritus			
subjects affected / exposed	2 / 163 (1.23%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2006	Essential changes were: - Updates, specifications and correction of chemotherapy protocols - Frequency of administration of an IV product - Addition of an investigation of mistletoe lectin-antibodies for a sample of n = 15 patients of verum group in order to get information about the application of Helixor® A - Specification for the early withdrawal of a patient from the study - Correction of expected end of study - Complete revision of the chapter on definition, recording and evaluation of adverse events
01 September 2008	Essential changes were: - Inclusion of new trial sites - Prolongation of recruitment time due to slow recruitment - Update of existing an new CT protocols - Specification of an exclusion criterion - Specification and supplementation of the analysis population - Supplement of side effects - Elimination of an additional analysis due to unsuitability
18 January 2010	Essential changes were: - Downsizing of the DSMC to exclude people directly involved in the study - Update and corrections of the CT protocols - Prolongation of recruitment time and study duration - Recruitment of further trial sites - Side effects: Adaption to SPC - Update of PIL and SPC - Supplement for control group regarding procedure after the end of the study - Specification of definition for follow up - Elimination of redundantinformation, statistical analysis: specification of analysis - Clear description for the documentation in case of early withdrawal of a patient

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 secondary endpoint Event-free Survival (EFS) could not be analysed for some subgroups due to too small analytical populations for valid comparison of verum vs control population

Notes: