Clinical trial results:
Phase II trial of metronomic treatment in children and adolescents with recurrent or progressive neuroblastoma

Summary

EudraCT number	2011-004593-29
Trial protocol	DE
Global end of trial date	29 June 2023

Results information

Result version number	v1 (current)
This version publication date	03 January 2024
First version publication date	03 January 2024

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-1495

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02641314
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Cologne, Germany, 50923
Public contact	Neuroblastomstudie, Children’s Hospital, University of Cologne, +49 2214786853, neuroblastomstudie@uk-koeln.de
Scientific contact	Neuroblastomstudie, Children’s Hospital, University of Cologne, +49 2214786853, neuroblastomstudie@uk-koeln.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	Interim
Date of interim/final analysis	10 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary trial objective is to demonstrate the non-inferiority of event free survival (EFS) in children and adolescents ≥ 2 and < 21 years of age with recurrent or progressive high risk neuroblastoma treated with low toxic metronomic celecoxib therapy in combination with low-dose metronomic cyclophosphamide, etoposide and vinblastine in comparison to a historical control group. Event free survival (EFS) defined as time from start of treatment up to: Progression (emerged from residual tumor, PD) or recurrence (developing from CR achieved by metronomic treatment), drop-out for unacceptable toxicity, secondary malignant neoplasm or death of any reason

Protection of trial subjects:

No relevant toxicities. No toxic deaths related to the metronomic treatment. No change of risk-benefit balance.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	01 December 2015
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	Germany: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	13
Adolescents (12-17 years)	1
Adults (18-64 years)	4

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

18 of a maximum of 26 patients have been recruited in 5 of 8 national test center in Germany.

Pre-assignment

Screening details:

1 screening failure

Period 1

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

Arms

Arm title	Metronomic treatment

Arm description:

The trial schedule consists of continuously administered cycles of metronomic therapy over 364 days. Treatment consists of eight alternating 28-day cycles of PCCVE and PCCV followed by five cycles PCCV. Vinblastine will be given every second week. Etoposide is only given in cycle PCCVE (cycle 1, 3, 5, 7).

The PCCVE cycle consists of propranolol, celecoxib, cyclophosphamide, vinblastine, and etoposide. On the first day of the very first PCCVE cycle, one single intravenous infusion of cyclophosphamide loading dose (500 mg/m2 i.v., duration 1 hour) is given.

The PCCV cycle consists of propranolol, celecoxib, cyclophosphamide, and vinblastine.

Arm type	Experimental
Investigational medicinal product name	Propranolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Propranolol
cycle 1:
0.5 mg/kgxd p.o. day 1,
1 mg/kgxd p.o. day 2,
2 mg/kgxd p.o. day 3-28;
all further cycles:
2 mg/kgxd p.o., day 1 – 28
(maximum total daily dose: 120 mg)
divided in 2 doses per day

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

Dosage and administration details:

400 mg/m2xd p.o.; day 1-28
(maximum total daily dose: 800 mg)
divided in 2 doses per day

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule, Solution for injection/infusion
Routes of administration	Oral use, Infusion

Dosage and administration details:

cycle 1, day 1:
loading dose: 500 mg/m2 intravenous 1-h-infusion,
single dose
cycle 1, day 2-28; all further cycles day 1-28:
25 mg/m2xd p.o
(maximum total daily dose: 50 mg)
as single daily dose

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

25 mg/m2xd p.o.; day 1-21
(maximum total daily dose: 50 mg)
as single daily dose

Investigational medicinal product name	Vinblastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

3 mg/m2xd i.v.
(maximum total daily dose: 6 mg)
administered day 1 and 15 (every two weeks)
as single daily dose

Number of subjects in period 1	Metronomic treatment
Started	18
Completed	18

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description: 11	

Reporting group values	Treatment	Total	
Number of subjects	18	18	
Age categorical Units: Subjects			
Children (2-11 years)	13	13	
Adolescents (12-17 years)	1	1	
Adults (18-64 years)	4	4	
Gender categorical Units: Subjects			
Female	7	7	
Male	11	11	

End points

End points reporting groups

Reporting group title	Metronomic treatment

Reporting group description:

The trial schedule consists of continuously administered cycles of metronomic therapy over 364 days. Treatment consists of eight alternating 28-day cycles of PCCVE and PCCV followed by five cycles PCCV. Vinblastine will be given every second week. Etoposide is only given in cycle PCCVE (cycle 1, 3, 5, 7).

The PCCVE cycle consists of propranolol, celecoxib, cyclophosphamide, vinblastine, and etoposide. On the first day of the very first PCCVE cycle, one single intravenous infusion of cyclophosphamide loading dose (500 mg/m2 i.v., duration 1 hour) is given.

The PCCV cycle consists of propranolol, celecoxib, cyclophosphamide, and vinblastine.

Subject analysis set title	Full dataset analysis
Subject analysis set type	Full analysis

Subject analysis set description:

All patients enrolled into the study.

Subject analysis set title	Population for sensitivity analysis
Subject analysis set type	Per protocol

Subject analysis set description:

patients who fulfilled the inclusion and exclusion criteria, have been registered in the study, and were treated conform to the protocol.

Subject analysis set title	Population for safety analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who entered the study and received at least the medication of the first day of the first treatment cycle.

Primary: Events

End point title	Events[1]

End point description:

End point type	Primary

End point timeframe:

until 30 days after the last treatment of the last patient

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: The final stastical analysis is ongoing. Values will be updated once the analysis is completed.

End point values	Metronomic treatment	Full dataset analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	18	18		
Units: number				
number (not applicable)	16	16		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

until 30 days after the last trial medication of the last patient

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Population for safety analysis

Reporting group description:

Patients reported with serious adverse events

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: Final analysis of adverse events is ongoing. Values will be updated once the analysis is completed.

Serious adverse events	Population for safety analysis		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Lung infiltration			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Population for safety analysis		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 17 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2017	METRO-NB2012 Trial Protocol Amendment Version 3.5.4
09 March 2020	METRO-NB2012 Trial Protocol Amendment Version 3.5.6
05 May 2021	METRO-NB2012 Trial Protocol Amendment 4.0

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported