



Clinical trial results:

Phase II feasibility study using ch14.18/CHO antibody and subcutaneous interleukin 2 after haploidentical stem cell transplantation in children with relapsed neuroblastoma

Summary

EudraCT number	2009-015936-14
Trial protocol	AT DE
Global end of trial date	21 October 2018

Results information

Result version number	v1 (current)
This version publication date	07 July 2023
First version publication date	07 July 2023
Summary attachment (see zip file)	preliminary results (Clinical Study Report_EMA.pdf) Adverse Events Evaluation (Safety-Evaluation_Adverse Events_ch14.18IL2.pdf)

Trial information

Trial identification

Sponsor protocol code	CH14.18-IL2 1021
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02258815
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital of Tübingen
Sponsor organisation address	Geissweg 3, Tübingen, Germany, 72076
Public contact	Prof. Dr. med. Peter Lang, Universitätsklinikum Tübingen, 49 7071290,
Scientific contact	Prof. Dr. med. Peter Lang, Universitätsklinikum Tübingen, 49 7071290,

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	28 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 October 2018
Global end of trial reached?	Yes
Global end of trial date	21 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of safety and feasibility of the chimeric 14.18 anti-GD2 monoclonal antibody (ch14.18/CHO) in combination with subcutaneous aldesleukin (IL-2, (Proleukin®))

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, 2008 and standard research practice at the Institutions, Good Clinical Practice (GCP) and applicable local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Germany: 52
Worldwide total number of subjects	68
EEA total number of subjects	68

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)	5
Children (2-11 years)	50
Adolescents (12-17 years)	13
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study population for this study included male and female patients aged less than or equal to 21 years, with relapsed neuroblastoma, who had previously received an allogeneic haploidentical SCT.

Pre-assignment

Screening details:

For screening, all scans including ultrasounds, CT scans, MRIs and X-rays were to be performed within two weeks prior to enrolment. CBC with platelets, human anti-chimeric antibodies and chemistries were to be done ≤ 2 weeks before study registration and meet eligibility criteria.

2 patients were excluded after the screening phase.

Period 1

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

Blinding implementation details:

Due to the exploratory nature of this trial, no active control treatment was administered in parallel to a comparator group.

Arms

Arm title	Treatment group
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Arm description:

This was a Phase II, open-label, uncontrolled, multi-center safety and exploratory efficacy study of ch14.18/CHO mAb plus IL-2 given in a single dose group not earlier than 60 days and maximally one year after haploidentical SCT to relapsed neuroblastoma patients. Due to the exploratory nature of this trial, no active control treatment was administered in parallel to a comparator group.

There was only one arm in the study

Arm type	Experimental
Investigational medicinal product name	ch14.18/CHO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ch14.18/CHO: 4.5 ± 0.25 mg/mL

Investigational medicinal product name	Interleukin-2 (IL-2)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use

Dosage and administration details:

1×10^6 IU/m²

Number of subjects in period 1	Treatment group
Started	68
Completed	39
Not completed	29
Adverse event, non-fatal	17
Progressive disease	12

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
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Reporting group description:

68 patients, with 1st to 5th relapse, were eligible for the study. The median age at study entry was 6,5 years (range 3-20 years) with a predominance of male participants (n=46; 67,6 %). The median time from initial diagnosis to haploidentical stem cell transplantation was 33 months (range 6-171 months)

All patients suffered from a stage IV relapse of a histologically confirmed neuroblastoma; most patients had also metastatic disease at initial diagnosis (94,1 %)

Reporting group values	Overall trial	Total	
Number of subjects	68	68	
Age categorical			
Units: Subjects			
≤ 1,5 years old	5	5	
>1,5 to 5 years old	50	50	
>5 years old	13	13	
Age continuous			
The median age at study entry was 6,5 years			
Units: years			
median	6.5		
full range (min-max)	1.5 to 20	-	
Gender categorical			
Units: Subjects			
Female	22	22	
Male	46	46	
Age at diagnosis			
Units: Subjects			
<18 months	6	6	
≥18 months	62	62	
MYCN amplification status			
Units: Subjects			
Not amplified	46	46	
Amplified	19	19	
Unknown	3	3	
Disease status			
Units: Subjects			
Primary refractory disease	3	3	
Local or combined relapse	24	24	
Distant relapse	41	41	
Time to first relapse			
Units: Subjects			
<18 months	19	19	
≥18 months	46	46	
Refractory disease	3	3	
mIBG Therapy			

Units: Subjects			
No	24	24	
Yes	43	43	
Unknown	1	1	
Time from first relapse to haplo-SCTb			
Units: Subjects			
<291 days	32	32	
≥291 days	33	33	
Unknown/refractory disease	3	3	

End points

End points reporting groups

Reporting group title	Treatment group
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Reporting group description:

This was a Phase II, open-label, uncontrolled, multi-center safety and exploratory efficacy study of ch14.18/CHO mAb plus IL-2 given in a single dose group not earlier than 60 days and maximally one year after haploidentical SCT to relapsed neuroblastoma patients. Due to the exploratory nature of this trial, no active control treatment was administered in parallel to a comparator group.

There was only one arm in the study

Subject analysis set title	Patients receiving full protocol treatment
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Subject analysis set type	Full analysis
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Subject analysis set description:

The patients who completed the full protocol treatment

Primary: Success of treatment

End point title	Success of treatment ^[1]
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End point description:

The primary end point 'success of treatment' was defined as patients receiving six cycles of dinutuximab beta (DB), alive 180 days after end of trial treatment, without progression, and unacceptable toxicity or acute GvHD \geq grade 3 or extensive chronic GvHD according to Glucksberg or Seattle classification, respectively.

Treatment success of $\geq 50\%$ was considered relevant with a minimum of 35 evaluable patients for assessing efficacy with a Simon's two-stage design (significance level 5%; power 80%), 22 followed by a validation group of 25 patients.

End point type	Primary
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End point timeframe:

180 days

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 the attached Clinical Trial Report

End point values	Treatment group			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: Patients	37			

Statistical analyses

No statistical analyses for this end point

Secondary: 5-year Overall Survival (OS)

End point title	5-year Overall Survival (OS)
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End point description:

EFS and OS were calculated from start of trial treatment (first antibody cycle in this trial, ie, first day of first dinutuximab beta (DB) cycle, after haplo-SCT).

End point type	Secondary
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End point timeframe:

5 years

End point values	Treatment group			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: Percentage				
number (confidence interval 95%)	53 (41 to 65)			

Statistical analyses

No statistical analyses for this end point

Secondary: 5-year Event-Free Survival (EFS)

End point title	5-year Event-Free Survival (EFS)
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End point description:

End point type	Secondary
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End point timeframe:

5 years

End point values	Treatment group			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: Percentage				
number (confidence interval 95%)	43 (31 to 55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission (maintained from before)

End point title	Complete Remission (maintained from before)
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End point description:

End point type	Secondary
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End point timeframe:

180 days

End point values	Treatment group	Patients receiving full protocol treatment		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	68	39		
Units: Percentage				
number (not applicable)	19.1	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Remission (improved compared to before treatment)

End point title	Complete Remission (improved compared to before treatment)
End point description: % of patients who experienced complete remission and meant an improvement compared to before the study treatment	
End point type	Secondary
End point timeframe: 180 days	

End point values	Treatment group	Patients receiving full protocol treatment		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	68	39		
Units: Percentage				
number (not applicable)	22.1	38.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Partial Remission (PR)

End point title	Partial Remission (PR)
End point description: % of patients who experienced Partial Remission (PR)	
End point type	Secondary
End point timeframe: 180 days	

End point values	Treatment group	Patients receiving full protocol treatment		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	68	39		
Units: Percentage				
number (not applicable)	8.8	15.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Mixed response (MR), Non-remission (NR) or Progressive disease (PD)

End point title	Mixed response (MR), Non-remission (NR) or Progressive disease (PD)
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End point description:

End point type	Secondary
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End point timeframe:

180 days

End point values	Treatment group	Patients receiving full protocol treatment		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	68	39		
Units: Percentage				
number (not applicable)	7.4	12.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

AEs were observed from the first dose of study medication within 30 days after the last study drug application or - if pre-existent - deteriorated after the first dose of study medication.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	CTC
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Dictionary version	4.0
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Frequency threshold for reporting non-serious adverse events: 0 %

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: The safety evaluation regarding the adverse events of the trial is attached as a PDF-document.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36854071>