Clinical trial results:
Double blind placebo controlled randomized intervention study aiming at reducing dexamethasone related side effects in children with acute lymphoblastic leukemia (ALL).

Summary

EudraCT number	2011-003815-46
Trial protocol	NL
Global end of trial date	17 May 2016

Results information

Result version number	v1 (current)
This version publication date	21 August 2021
First version publication date	21 August 2021
Summary attachment (see zip file)	HC as intervention for dexamethason induced adverse effects (Warris HC as intervention for dexamethasone induced adverse effects JCO2016.pdf)

Trial information

Trial identification

Sponsor protocol code	37826

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Dutch trialregistry: NL3129

Notes:

Sponsors

Sponsor organisation name	Erasmus MC
Sponsor organisation address	Dr. Molewaterplein 60, Rotterdam, Netherlands, 3015 GJ
Public contact	ELT van den Akker, Erasmus MC, +31 107030703, e.l.t.vandenakker@erasmusmc.nl
Scientific contact	ELT van den Akker, Erasmus MC, +31 107030703, e.l.t.vandenakker@erasmusmc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2015
Global end of trial reached?	Yes
Global end of trial date	17 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To reduce dexamethasone induced cerebral side-effects on mood, behaviour, and cognition by intervention treatment with physiological doses of cortisol compared to placebo.

Protection of trial subjects:

The risk-benefit analysis for the study showed a favorable risk profile. The IMP that was studied is hydrocortisone, given in a physiological dose, NOT in a pharmacological dose. No side effects were expected in this dose. In addition, we performed preclinical in vitro and ex vivo studies to prove that adding cortisol to treatment will not have any negative effects on the efficacy of cytotoxic effect on leukemia cells. Since we did not expect major risks, we did not install a data and safety monitoring board (DSMB) for this study
Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug. They included the regular assessment of the patient's physical condition, and performance status

Background therapy:

This study is a double blind placebo-controlled randomized crossover study. Patients received the IMP or the placebo during 2 periods of a 5-day dexamethasone treatment. All children were randomized into two groups: either dexa + IMP or dexa + placebo first. After a washout period of 2 weeks and 2 days, a new medication period was started where the group that had a placebo in the first period received the study drug and the other group got the placebo.
The intervention product was hydrocortisone suspension, given orally. This drug was given in a physiological dose of 10 mg/m2/day. Patients used the hydrocortisone solution (1mg/ml) or placebo 3 times daily orally (5:3:2 ratio / circadian rhythm). Timing of intake: first dose after awakening. Second dose between 12am and 1pm, the third dose between 6pm and 8 pm.

Evidence for comparator:

Not applicable

Actual start date of recruitment	31 May 2012
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	Netherlands: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	50
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place between 31-may-2012 and 30-mar-2015
The study has a cross-over design. Participants were randomised to:
A: hydrocortisone for 5 days; after a wash-out period of 2 weeks and 2 days placebo for 5 days
B: placebo for 5 days; after a wash-out period of 2 weeks and 2 days hydrocortisone for 5 days

Pre-assignment

Screening details:

101 eligible patients were screened; 51 refused for following reasons:
- burden too high (37)
- no side effects of dexamethasone (8)
- no participation in studies (30
- refuse to drink oral solution (2)

Pre-assignment period milestones

Number of subjects started	50
Number of subjects completed	50

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

Patients were randomized electronically via the website ALEA
The Erasmus MC pharmacy prepared the IMP as well as the placebo suspension

Arms

Are arms mutually exclusive?	No
Arm title	Hydrocortisone

Arm description:

treatment with Hydrocortisone

Arm type	Experimental
Investigational medicinal product name	Hydrocortisone
Investigational medicinal product code	H02AB09 (CAS 50-23-7)
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

10 mg/m2/day. Patients used the hydrocortisone solution (1mg/ml) 3 times daily in a circadian rhythm (5:3:2 ratio)

Arm title	Placebo

Arm description:

Treatment with Placebo

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	not applicable
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

10 mg/m2/day. Patients used the placebo solution 3 times daily in a circadian rhythm (5:3:2 ratio)

Number of subjects in period 1	Hydrocortisone	Placebo
Started	50	50
completed all SDQ testmoments	46	48
Completed	46	48
Not completed	4	2
dexamethasone was stopped	2	-
Lost to follow-up	2	2

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	50	50	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	7.0		
full range (min-max)	5.5 to 12.0	-	
Gender categorical Units: Subjects			
Female	27	27	
Male	23	23	
ALL subtype Units: Subjects			
B-ALL	46	46	
T-ALL	4	4	
CNS status			
Involvement of CNS in the disease			
Units: Subjects			
CNS 1	22	22	
CNS 2	28	28	
CNS 3	0	0	
Week of maintenance phase			
At what week during the ALL11 maintenance treatment did the intervention take place			
Units: number			
arithmetic mean	37.0		
full range (min-max)	31.0 to 49.5	-	

End points

End points reporting groups	
Reporting group title	Hydrocortisone
Reporting group description: treatment with Hydrocortisone	
Reporting group title	Placebo
Reporting group description: Treatment with Placebo	

Primary: SDQ	
End point title	SDQ
End point description: SDQ is a questionnaire to measure emotional complaints/stress. The score is given in subcategories	
End point type	Primary
End point timeframe: SDQ is measured at 4 timepoints: at day 1 and 5 of hydrocortisone treatment and at day 1 and 5 of placebo treatment Number given are man delta for each arm	

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: amount				
arithmetic mean (standard error)				
SDQ overall stress	2.6 (± 0.61)	3.4 (± 0.80)		
SDQ EmoDis	0.9 (± 0.28)	1.5 (± 0.34)		
SDQ BehavDiff	0.5 (± 0.19)	0.5 (± 0.20)		
SDQ HypAttent	0.6 (± 0.24)	0.6 (± 0.30)		
SDQ GetAlong	0.6 (± 0.16)	0.8 (± 0.25)		
SDQ Helpful	-1.6 (± 0.33)	-1.5 (± 0.37)		
SDQ Impact	0.8 (± 0.32)	1.3 (± 0.35)		

Statistical analyses

Statistical analysis title	SDQ
Statistical analysis description: Paired T-test to compare delta of SDQ-scores between two arms	
Comparison groups	Hydrocortisone v Placebo

Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	≤ 0.01 [2]
Method	paired T-test
Parameter estimate	paired T-test

Notes:

[1] - DO SDQ differ significantly between the arms?

[2] - Not one p-vallue proved to be significant:

	P value
SDQ_overallstress	0.33
SDQ_EmoDis	0.08
SDQ_BehavDiff	1.00
SDQ_HypAttent	1.00
SDQ_GetAlong	0.61
SDQ_Helpful	0.71
SDQ_Impact	0.08

Primary: SDSC

End point title	SDSC

End point description:

DA, disorders of arousal;
DES, disorders of excessive somnolence;
DIMS, disorders of initiating and maintaining sleep; SBD, sleep breathing disorders; SHY, sleep hyperhidrosis; SWTD, sleep-wake transition disorders.

End point type	Primary

End point timeframe:

Questionnaire taken at day 1 and day 5 of hydrocortisone as well as placebo treatment

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: amount				
arithmetic mean (standard error)				
SDSC total	1.2 (± 1.2)	1.5 (± 1.1)		
DIMS	0.7 (± 0.5)	0.4 (± 0.7)		
DA	-0.1 (± 0.1)	-0.3 (± 0.1)		
SBD	-0.1 (± 0.1)	0.0 (± 0.1)		
DES	1.1 (± 0.4)	1.8 (± 0.5)		
SHY	0.0 (± 0.2)	0.3 (± 0.2)		
SWTD	-0.3 (± 0.3)	-0.7 (± 0.2)		

Statistical analyses

Statistical analysis title	SDSC

Statistical analysis description:

Does hydrocortisone decrease sleeping problems caused by dexamethasone

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.01 [3]
Method	paired T-test

Notes:

[3] - P value
(Paired T-test)
Total 0.84
DIMS 0.74
SWTD 0.29
DES 0.19
SBD 0.79
DA 0.45
SHY 0.19

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events according to the NCI CTCAE version 4.0 after 4 full days of hydrocortisone or placebo administration

Assessment type	Non-systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Hydrocortisone

Reporting group description:

All subjects receiving a course of hydrocortisone

Reporting group title	Placebo

Reporting group description:

All subjects receiving a course of placebo

Serious adverse events	Hydrocortisone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 48 (4.17%)	2 / 48 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	2 / 48 (4.17%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Hydrocortisone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 48 (2.08%)	2 / 48 (4.17%)	

General disorders and administration site conditions			
Tiredness			
subjects affected / exposed	1 / 48 (2.08%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 48 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2012	Addition of questionnaire for non-participants
19 June 2013	Addition of two participating sites in the Netherlands No hydrocortisone continuation after study completion
09 July 2013	Addition of another site in the Netherlands Changing SAE reporting to 16 days after last administration of study medication
16 October 2014	Addition of another site in the Netherlands

Notes:

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/27161966