Clinical trial results:
Double blind placebo controlled randomized intervention study to validate the beneficial effect of hydrocortisone on dexamethasone-induced neurobehavioral side effects in pediatric acute lymphoblastic leukemia

Summary

EudraCT number	2017-002738-22
Trial protocol	NL
Global end of trial date	27 March 2021

Results information

Result version number	v1 (current)
This version publication date	07 September 2022
First version publication date	07 September 2022
Summary attachment (see zip file)	Reason for late posting of results (EudraCt Results 2017-002738-22.pdf)

Trial information

Trial identification

Sponsor protocol code	62388

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Netherlands Trial Register: NL6507 (NTR6695)

Notes:

Sponsors

Sponsor organisation name	Princess Máxima Center for Pediatric Oncology
Sponsor organisation address	Heidelberglaan 25, Utrecht, Netherlands, 3584 CS
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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	09 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 November 2020
Global end of trial reached?	Yes
Global end of trial date	27 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To validate that addition of physiological doses of hydrocortisone to standard dexamethasone treatment reduces side effects in acute lymphoblastic leukemia patients who suffer from clinically relevant dexamethasone-induced neurobehavioral problems.

Protection of trial subjects:

The risk-benefit analysis for this 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 physiological dose. In addition, we previously performed preclinical in vitro and ex vivo studies to prove that adding hydrocortisone to treatment will not have any negative effects on the efficacy of dexamethasone and prednisone regarding cytotoxicity on leukemic 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. This included the regular assessment of the patient's physical condition and performance status.

Background therapy:

This study is a double blind placebo controlled randomized trial with cross-over design. Patients are included if they experience clinically significant dexamethasone-induced neurobehavioral problems. These patients received the IMP (hydrocortisone) or placebo during 4 periods of a 5-day dexamethasone treatment during maintenance therapy. All children were randomized to either start with dexamethasone + IMP or dexamethasone + placebo. After two courses (with a washout period of 2 weeks and 2 days between each period) cross over took place.
The IMP was hydrocortisone suspension, given orally in a physiological dose of 10 mg/m2/day. Patients used the hydrocortisone solution (1mg/ml) or placebo (equal in appearance and taste) 3 times per day in a 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.
52 patients were randomized to answer our primary objective. However, in total 105 patients were included in our trial to be able answer our secondary objectives as well.

Evidence for comparator:

NA

Actual start date of recruitment	17 May 2018
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: 105

Worldwide total number of subjects	105
EEA total number of subjects	105

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)	90
Adolescents (12-17 years)	15
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 17 May 2018 (first inclusion) and 27 March 2021 (last patient last visit) in the Princess Máxima Center in Utrecht, The Netherlands.

Pre-assignment

Screening details:

164 out of 278 ALL patients were eligible. 106 gave informed consent, 1 patient entered twice.

58 refused for these reasons:
- Burden/effort n=17
- No time n=10
- Few side effects: n=10
- Child refuses: n=5
- Too many studies n=3
- Not interested n=5
- Other n=5
- Unknown n=3

Of the 105 unique patients, 52 were included in our RCT.

Period 1

Period 1 title	Baseline measurement
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Blinding was only used in the RCT (the period after baseline measurement)

Arms

Are arms mutually exclusive?	Yes
Arm title	Start hydrocortisone

Arm description:

Patients who started with hydrocortisone during the RCT with cross-over design. After two courses of hydrocortisone, cross over to placebo took place.

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

Dosage and administration details:

10 mg/m2/day. Patients used hydrocortisone (1mg/ml) 3 times per day in a circadian rhythm: 5 mg/m2 in the morning, 3 mg/m2 in the afternoon and 2 mg/m2 in the evening.

Arm title	Start placebo

Arm description:

Patients who started with placebo during the RCT with cross-over design. After two courses of placebo, cross over to hydrocortisone took place.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	NA
Other name	
Pharmaceutical forms	Oral solution in bottle
Routes of administration	Oral use

Dosage and administration details:

10 mg/m2/day. Patients used the placebo in exactly the same way as the IMP: 5 mg/m2 in de morning, 3 mg/m2 in the afternoon and 2 mg/m2 in the evening.

Arm title	No intervention

Arm description:

Patients who did not have clinically significant dexamethasone-induced neurobehavioral problems (defined as a rise of 5 or more point on the Strengths and Difficulties Questionnaire (SDQ) Total Difficulties Score after 5 days of dexamethasone treatment) did not enter the randomized controlled trial. Also patients who only completed the baseline (dexamethasone-only) measurements after our RCT closed.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Start hydrocortisone	Start placebo	No intervention
Started	26	26	53
Completed	26	26	53

Period 2

Period 2 title	Randomized Controlled Trial (n=52)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Patients were allocated to start with hydrocortisone or placebo using the method of a prefixed randomization list. This randomization list was prepared by the Princess Maxima Center pharmacy, independent of the clinical investigators. Both the IMP (hydrocortisone) and placebo were produced by the A15 pharmacy and distributed through the Princess Maxima Center pharmacy.

Arms

Are arms mutually exclusive?	Yes
Arm title	Hydrocortisone

Arm description:

All patients in the RCT received two courses of hydrocortisone (cross-over design).

Arm type	Experimental

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

Dosage and administration details:

10 mg/m2/day. Patients used hydrocortisone (1mg/ml) 3 times per day in a circadian rhythm: 5 mg/m2 in the morning, 3 mg/m2 in the afternoon and 2 mg/m2 in the evening.

Arm title	Placebo

Arm description:

All patients in the RCT received two courses of placebo (cross-over design)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	NA
Other name	
Pharmaceutical forms	Oral solution in bottle
Routes of administration	Oral use

Dosage and administration details:

10 mg/m2/day. Patients used the placebo in exactly the same way as the IMP: 5 mg/m2 in de morning, 3 mg/m2 in the afternoon and 2 mg/m2 in the evening.

Number of subjects in period 2[1]	Hydrocortisone	Placebo
Started	52	52
Completed	51	52
Not completed	1	0
Adverse event, non-fatal	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: After the baseline (first) period, only patients with clinically relevant dexamethasone-induced neurobehavioral problems were included in the subsequent period. Patients under the category 'no intervention' did not enter the RCT, therefore the number of subjects starting the RCT is not consistent with the total number completing the preceding period.

Baseline characteristics

Reporting groups	
Reporting group title	Start hydrocortisone
Reporting group description:	
Patients who started with hydrocortisone during the RCT with cross-over design. After two courses of hydrocortisone, cross over to placebo took place.	

Reporting group title	Start placebo
Reporting group description:	
Patients who started with placebo during the RCT with cross-over design. After two courses of placebo, cross over to hydrocortisone took place.	

Reporting group title	No intervention
Reporting group description:	
Patients who did not have clinically significant dexamethasone-induced neurobehavioral problems (defined as a rise of 5 or more point on the Strengths and Difficulties Questionnaire (SDQ) Total Difficulties Score after 5 days of dexamethasone treatment) did not enter the randomized controlled trial. Also patients who only completed the baseline (dexamethasone-only) measurements after our RCT closed.	

Reporting group values	Start hydrocortisone	Start placebo	No intervention
Number of subjects	26	26	53
Age categorical			
Units: Subjects			
Age continuous			
Age at start of the study			
Units: years			
median	5.8	5.4	5.2
inter-quartile range (Q1-Q3)	4.1 to 9.1	4.1 to 8.0	4.0 to 10.5
Gender categorical			
Units: Subjects			
Female	7	13	21
Male	19	13	32
ALL subtype			
Type of ALL			
Units: Subjects			
B-ALL	25	21	48
T-ALL	1	5	5
CNS-status			
Central nervous system involvement at diagnosis			
Units: Subjects			
CNS-1	10	11	25
CNS-2	12	6	17
CNS-3	1	1	4
TLP+	2	6	5
TLP-	0	0	1
Undetermined	1	2	1

Week maintenance			
Week of maintenance at start of the RCT			
Units: week			
median	34	42	37
inter-quartile range (Q1-Q3)	25 to 44	27 to 53	23.5 to 47.5

Reporting group values	Total		
Number of subjects	105		
Age categorical			
Units: Subjects			

Age continuous			
Age at start of the study			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	41		
Male	64		
ALL subtype			
Type of ALL			
Units: Subjects			
B-ALL	94		
T-ALL	11		
CNS-status			
Central nervous system involvement at diagnosis			
Units: Subjects			
CNS-1	46		
CNS-2	35		
CNS-3	6		
TLP+	13		
TLP-	1		
Undetermined	4		
Week maintenance			
Week of maintenance at start of the RCT			
Units: week			
median			
inter-quartile range (Q1-Q3)	-		

End points

End points reporting groups

Reporting group title	Start hydrocortisone

Reporting group description:

Patients who started with hydrocortisone during the RCT with cross-over design. After two courses of hydrocortisone, cross over to placebo took place.

Reporting group title	Start placebo

Reporting group description:

Patients who started with placebo during the RCT with cross-over design. After two courses of placebo, cross over to hydrocortisone took place.

Reporting group title	No intervention

Reporting group description:

Patients who did not have clinically significant dexamethasone-induced neurobehavioral problems (defined as a rise of 5 or more point on the Strengths and Difficulties Questionnaire (SDQ) Total Difficulties Score after 5 days of dexamethasone treatment) did not enter the randomized controlled trial. Also patients who only completed the baseline (dexamethasone-only) measurements after our RCT closed.

Reporting group title	Hydrocortisone

Reporting group description:

All patients in the RCT received two courses of hydrocortisone (cross-over design).

Reporting group title	Placebo

Reporting group description:

All patients in the RCT received two courses of placebo (cross-over design)

Primary: Neurobehavioral problems

End point title	Neurobehavioral problems

End point description:

To answer our primary aim, we used the Dutch version of the parent-reported Strengths and Difficulties Questionnaire (SDQ). This 25-item questionnaire assesses psychological adjustment of children and youths and provides five subscales: emotional symptoms, conduct problems, hyperactivity and inattention, peer relationship problems and prosocial behavior. The Total difficulties score is the sum of the first four subscale scores (i.e. without prosocial behavior). A higher SDQ Total difficulties score reflects more problems. Like in our previous and current study a change of ≥5 points was considered clinically relevant. The effect of hydrocortisone was assessed by comparing the difference in SDQ scores of intervention day one and day five (delta score) of two consecutive hydrocortisone periods with two consecutive placebo periods.

End point type	Primary

End point timeframe:

Measurement for the RCT (n=52) took place between May 17, 2018 and August 5, 2020.

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	51		
Units: Points				
median (inter-quartile range (Q1-Q3))	5.0 (2.0 to 9.0)	5.8 (3.0 to 9.0)		

Statistical analyses

Statistical analysis title	Repeated measurement analysis

Statistical analysis description:

Due to the presence of repeated measures in our study design, a generalized mixed model was estimated to study the effect of therapy on all outcomes. Age, sex, start group (hydrocortisone/placebo), week of maintenance treatment, concomitant asparaginase treatment (yes/no), whether mother or father completed the questionnaire and an interaction term between intervention and time (maintenance week) were included in the models.

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	estimated effect
Point estimate	-2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	1.9

Notes:

[1] - Due to the cross-over design, hydrocortisone and placebo could be compared within patients in a repeated measurement model. We only included 51 patients in our analyses, but these patients had 102 measurements.

Secondary: Objective sleep problems

End point title	Objective sleep problems

End point description:

Children wore a wrist-worn actigraph (ActiGraph wGT3X-BT, Pensacola, FL, USA) for seven consecutive days twice: once during hydrocortisone and once during placebo. The parent kept an additional sleep-diary to document bedtimes, time of awakening and removal periods. The Sadeh algorithm was used to generate sleep outcomes. Total sleep time is reported.

End point type	Secondary

End point timeframe:

Measurement for the RCT (n=52) took place between May 17, 2018 and August 5, 2020.

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: min				
arithmetic mean (standard deviation)	512.0 (± 41.4)	504.2 (± 42.1)		

Statistical analyses

Statistical analysis title	Repeated measurement analysis

Statistical analysis description:

Due to the presence of repeated measures in our study design, a generalized mixed model was estimated to study the effect of therapy on all outcomes. Age, sex, start group (hydrocortisone/placebo), week of maintenance treatment, concomitant asparaginase treatment (yes/no), whether mother or father completed the questionnaire and an interaction term between intervention and time (maintenance week) were included in the models.

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	estimated effect
Point estimate	6.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.26
upper limit	21.01

Notes:

[2] - Due to the cross-over design, hydrocortisone and placebo could be compared within patients in a repeated measurement model. We only included 39 patients in our analyses, but these patients had 78 measurements.

Secondary: Subjective sleep

End point title	Subjective sleep

End point description:

To assess subjective sleep quality and sleep disturbances, we used the Sleep Disturbance Scale for Children (SDSC). This questionnaire contains 26 items and yields six subscales and a Total sleep score: a higher score reflects more problems. The effect of hydrocortisone was assessed by comparing the difference in SDSC scores of intervention day one and day five (delta score) of one hydrocortisone period with one placebo period.

End point type	Secondary

End point timeframe:

Measurement for the RCT (n=52) took place between May 17, 2018 and August 5, 2020.

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	42		
Units: Points				
median (inter-quartile range (Q1-Q3))	3.5 (0.8 to 10.0)	3.0 (1.0 to 8.0)		

Statistical analyses

Statistical analysis title	Repeated measurement analysis

Statistical analysis description:

Due to the presence of repeated measures in our study design, a generalized mixed model was estimated to study the effect of therapy on all outcomes. Age, sex, start group

(hydrocortisone/placebo), week of maintenance treatment, concomitant asparaginase treatment (yes/no), whether mother or father completed the questionnaire and an interaction term between intervention and time (maintenance week) were included in the models.

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	estimated effect
Point estimate	-1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.27
upper limit	5.35

Notes:

[3] - Due to the cross-over design, hydrocortisone and placebo could be compared within patients in a repeated measurement model. We only included 42 patients in our analyses, but these patients had 84 measurements.

Secondary: Eating and hunger satiety

End point title	Eating and hunger satiety

End point description:

To measure dexamethasone induced eating and hunger satiety we used an Eating Thermometer (ET): a visual analogue scale to indicate hunger. The scale ranged from 0 (no hunger at all) to 10 (terrible hunger). The effect of hydrocortisone was assessed by comparing the difference in thermometer score of intervention day one and day five (delta score) of one hydrocortisone period with one placebo period.

End point type	Secondary

End point timeframe:

Measurement for the RCT (n=52) took place between May 17, 2018 and August 5, 2020.

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	38		
Units: Points				
median (inter-quartile range (Q1-Q3))	2 (1 to 4)	2 (0.75 to 3)		

Statistical analyses

Statistical analysis title	Repeated measurement analysis

Statistical analysis description:

Due to the presence of repeated measures in our study design, a generalized mixed model was estimated to study the effect of therapy on all outcomes. Age, sex, start group (hydrocortisone/placebo), week of maintenance treatment, concomitant asparaginase treatment (yes/no), whether mother or father completed the questionnaire and an interaction term between intervention and time (maintenance week) were included in the models.

Comparison groups	Hydrocortisone v Placebo

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	estimated effect
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	3.6

Notes:

[4] - Due to the cross-over design, hydrocortisone and placebo could be compared within patients in a repeated measurement model. We only included 38 patients in our analyses, but these patients had 76 measurements.

Secondary: Quality of Life

End point title	Quality of Life

End point description:

The Pediatric Quality of Life Inventory (PedsQL), a 21- (for toddlers) or 23-item questionnaire, was used to assess health-related quality of life (HRQoL). A higher score reflects a better HRQoL in the child. The effect of hydrocortisone was assessed by comparing the difference in PedsQL scores of intervention day one and day five (delta score) of one hydrocortisone period with one placebo period.

End point type	Secondary

End point timeframe:

Measurement for the RCT (n=52) took place between May 17, 2018 and August 5, 2020.

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	41		
Units: Points				
median (inter-quartile range (Q1-Q3))	-14.1 (-23.8 to -4.2)	-15.2 (-25.6 to -7.1)		

Statistical analyses

Statistical analysis title	Repeated measurement analysis

Statistical analysis description:

Due to the presence of repeated measures in our study design, a generalized mixed model was estimated to study the effect of therapy on all outcomes. Age, sex, start group (hydrocortisone/placebo), week of maintenance treatment, concomitant asparaginase treatment (yes/no), whether mother or father completed the questionnaire and an interaction term between intervention and time (maintenance week) were included in the models.

Comparison groups	Hydrocortisone v Placebo

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	estimated effect
Point estimate	3.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.69
upper limit	20.2

Notes:

[5] - Due to the cross-over design, hydrocortisone and placebo could be compared within patients in a repeated measurement model. We only included 41 patients in our analyses, but these patients had 82 measurements.

Secondary: Parental distress

End point title	Parental distress

End point description:

We used the Distress Thermometer for parents (DT-P) to assess parental distress.21 Parents were asked to rate their overall distress from 0 (no distress) to 10 (extreme distress). The effect of hydrocortisone was assessed by comparing the difference in DT-P scores of intervention day one and day five (delta score) of one hydrocortisone period with one placebo period.

End point type	Secondary

End point timeframe:

Measurement for the RCT (n=52) took place between May 17, 2018 and August 5, 2020.

End point values	Hydrocortisone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	40		
Units: Points				
median (inter-quartile range (Q1-Q3))	2 (1 to 4)	2 (1 to 4)		

Statistical analyses

Statistical analysis title	Repeated measurement analysis

Statistical analysis description:

Due to the presence of repeated measures in our study design, a generalized mixed model was estimated to study the effect of therapy on all outcomes. Age, sex, start group (hydrocortisone/placebo), week of maintenance treatment, concomitant asparaginase treatment (yes/no), whether mother or father completed the questionnaire and an interaction term between intervention and time (maintenance week) were included in the models.

Comparison groups	Hydrocortisone v Placebo
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	estimated effect
Point estimate	0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	3.46

Notes:

[6] - Due to the cross-over design, hydrocortisone and placebo could be compared within patients in a repeated measurement model. We only included 40 patients in our analyses, but these patients had 80 measurements.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting took place between May 17, 2018 and August 5, 2020.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	5

Reporting groups

Reporting group title	Hydrocortisone

Reporting group description:

Adverse events of 51 patients during hydrocortisone treatment

Reporting group title	Placebo

Reporting group description:

Adverse events of 52 patients during placebo treatment

Serious adverse events	Hydrocortisone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 51 (3.92%)	1 / 52 (1.92%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Fever	Additional description: Fever and (prolongation of) hospitalization. Once during placebo course and two times between treatment courses, not related to study medication.		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 51 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: (Prolongation of) hospitalization between treatment courses, not related to study medication.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychosis	Additional description: Other medically important condition in one patient during hydrocortisone treatment		

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis	Additional description: (Prolongation of) hospitalization. During hydrocortisone course but unlikely related to study medication.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection	Additional description: (Prolongation of) hospitalization. SAE between courses, not related to study medication.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 51 (1.96%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Hydrocortisone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 51 (43.14%)	22 / 52 (42.31%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 51 (7.84%)	5 / 52 (9.62%)	
occurrences (all)	4	5	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	21 / 51 (41.18%)	19 / 52 (36.54%)	
occurrences (all)	21	19	
Fatigue			
subjects affected / exposed	20 / 51 (39.22%)	20 / 52 (38.46%)	
occurrences (all)	20	20	
Fever			

subjects affected / exposed	2 / 51 (3.92%)	3 / 52 (5.77%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 51 (21.57%)	10 / 52 (19.23%)	
occurrences (all)	11	10	
Constipation			
subjects affected / exposed	9 / 51 (17.65%)	9 / 52 (17.31%)	
occurrences (all)	9	9	
Nausea			
subjects affected / exposed	4 / 51 (7.84%)	6 / 52 (11.54%)	
occurrences (all)	4	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 51 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Pruritus			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 51 (11.76%)	7 / 52 (13.46%)	
occurrences (all)	6	7	
Psychiatric disorders			
Agitation			
subjects affected / exposed	7 / 51 (13.73%)	6 / 52 (11.54%)	
occurrences (all)	7	6	
Anxiety			
subjects affected / exposed	3 / 51 (5.88%)	0 / 52 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2018	Addition of several laboratory measurements in blood. Modification of number and timing of blood sampling. Addition of the 'time to rise from the floor' test. Addition of an alternative bioelectrical impedance analysis device.
18 February 2019	Addition of two exclusion criteria. Addition of muscle strength measurement. Possibility to start during concomittant asparaginase treatment. Possibility to visit patients at home.
28 September 2020	Continuation of the study after closure of the RCT to answer secondary research questions. Addition of short sarcopenia questionnaire. Addition of measurement from residual blood.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported