



## Clinical trial results:

### Oral steroids for reducing renal scarring in infants with febrile urinary tract infections at high risk for renal scar development: a randomized controlled trial

#### Summary

EudraCT number	2013-000388-10
Trial protocol	IT
Global end of trial date	31 December 2017

#### Results information

Result version number	v1 (current)
This version publication date	28 September 2022
First version publication date	28 September 2022
Summary attachment (see zip file)	article 2021 (Article-OralSteroidsForReducingKidneyS.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	RF-2010-2318192
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	AZIENDA ULSS N.9 - TREVISO, UOC PEDIATRIA
Sponsor organisation address	Piazzale Ospedale 1, 31100 Treviso, Treviso, Italy,
Public contact	PROF.SSA LIVIANA DA DALT, AZIENDA ULSS N.9 - TREVISO, UOC PEDIATRIA, 0039 0422322263, liviana.dadalt@unipd.it
Scientific contact	PROF.SSA LIVIANA DA DALT, AZIENDA ULSS N.9 - TREVISO, UOC PEDIATRIA, 0039 0422322263, liviana.dadalt@unipd.it

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	31 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2017
Global end of trial reached?	Yes
Global end of trial date	31 December 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine the usefulness of steroid therapy (adjunctive to standard antibiotic treatment) in reducing renal scar development in infants with first febrile UTI, at higher risk based on PCT values  $\geq 1$  ng/mL, measured at the time of initial evaluation

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 June 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	48
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0



## Subject disposition

### Recruitment

Recruitment details:

total 437 assessed, 225 either did not meet inclusion criteria or met exclusion criteria. 131 did not complete study procedures, namely determination of serum PCT and/or urine collection through catheterization, 12 could not be approached by research staff and 21 declined consent; thus 48 patients underwent randomized and 18 completed follow-up

### Pre-assignment

Screening details:

Inclusion = age 2-24 months, fever > 37,5°C, positive dipstick (> = 1 leucocyte esterase and/or nitrites) on urine sample collected by catheterization. Exclusion: immunodeficit, antibiotics in 48 h before evaluation, known kidney disease, prematurity, contraindication to steroid therapy, recurrence or previous urinary tract infection

### Period 1

Period 1 title	june 2014-dicember 2017 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

two nuclear medicine physicians blinded to study allocation

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	dexamethasone +

Arm description:

dexamethasone plus routine therapy (antibiotic for 10 days)

Arm type	Experimental
Investigational medicinal product name	dexamethasone +
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution in bottle
Routes of administration	Oral use

Dosage and administration details:

0,15mg/kg per dose every 12 h for 4 days

<b>Arm title</b>	dexamethasone -
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Arm description:

Routine therapy for febrile urinary tract infection (antibiotic for 10 days)

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	dexamethasone +	dexamethasone -
Started	23	25
Completed	7	11
Not completed	16	14
Consent withdrawn by subject	1	-
Lost to follow-up	12	10

Protocol deviation	3	4
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## Baseline characteristics

### Reporting groups

Reporting group title	dexamethasone +
Reporting group description:	dexamethasone plus routine therapy (antibiotic for 10 days)
Reporting group title	dexamethasone -
Reporting group description:	Routine therapy for febrile urinary tract infection (antibiotic for 10 days)

Reporting group values	dexamethasone +	dexamethasone -	Total
Number of subjects	23	25	48
Age categorical			
Dexamethasone + (n.23): infants with age 2 months - 24 months Dexamethasone - (n.25): infants with age 2 months - 24 months			
Units: Subjects			
Infants and toddlers (28 days-23 months)	23	25	48
Age continuous			
Units: months			
median	9.4	7.4	
inter-quartile range (Q1-Q3)	5.3 to 12.3	3.7 to 13.7	-
Gender categorical			
Dexamethasone + (n.23): females 15, males 8 Dexamethasone - (n.25): females 14, males 11			
Units: Subjects			
Female	15	14	29
Male	8	11	19
principal variables			
Dexa group + (n= 23): race (caucasian) n. 18, fetal urinary tract abnormalities 1, Max body temperature (BT) in °C n. 39.5°, Weight in kg 8.5 Kg, PCT ng/ml 2.8, Leukocyturia on urine dipstick n. 23, Nitraturia on urine dipstick n. 15, Urine method collection for culture (Catheterization n. 22, Clean catch n. 1), Urine culture pos n. 20 Dexa group - (n= 25): race (caucasian) n. 22, fetal urinary tract abnormalities 0, BT in °C n. 39.3°, Weight in kg 8.0 Kg, PCT ng/ml 3.1, Leukocyturia n. 24, Nitraturia n.17, Catheterization n. 21, Clean catch n. 4, Urine culture pos 22			
Units: Subjects			
race	23	25	48

### Subject analysis sets

Subject analysis set title	Dexamethasone +
Subject analysis set type	Full analysis

Subject analysis set description:

The original sample size calculation on the hypothesis that dexamethasone would determine a renal scar reduction from 40% to 20%. Estimating a 10% rate of patients who did not fulfil the criteria for urinary tract infections diagnosis and 20% of lost to follow-up, a final number of 92 patients per group were required based on Freedman formula. Unanticipated difficult recruitment of patient in the study and their relevant loss to follow up prevented the completion of the study as originally designed. An interim assessment showed that based on the on the recruitment and attrition data, the completion of the study as initially planned was not feasible based on the available resources. We, therefore, used a Bayesian analysis to estimate the probability of treatment effect, given the limited number of patients we could enroll in the study based on the projection for patient enrolment and follow up estimated at the interim assessment.

Subject analysis set title	Dexamethasone -
Subject analysis set type	Full analysis

Subject analysis set description:

The original sample size calculation on the hypothesis that dexamethasone would determine a renal scar reduction from 40% to 20%. Estimating a 10% rate of patients who did not fulfil the criteria for urinary tract infections diagnosis and 20% of lost to follow-up, a final number of 92 patients per group were required based on Freedman formula. Unanticipated difficult recruitment of patient in the study and their relevant loss to follow up prevented the completion of the study as originally designed. An interim assessment showed that based on the on the recruitment and attrition data, the completion of the study as initially planned was not feasible based on the available resources. We, therefore, used a Bayesian analysis to estimate the probability of treatment effect, given the limited number of patients we could enroll in the study based on the projection for patient enrolment and follow up estimated at the interim assessment.

<b>Reporting group values</b>	Dexamethasone +	Dexamethasone -	
Number of subjects	23	25	
Age categorical			
Dexamethasone + (n.23): infants with age 2 months - 24 months Dexamethasone - (n.25): infants with age 2 months - 24 months			
Units: Subjects			
Infants and toddlers (28 days-23 months)	7	11	
Age continuous			
Units: months			
median	9.4	7.4	
inter-quartile range (Q1-Q3)	5.3 to 12.3	3.7 to 13.7	
Gender categorical			
Dexamethasone + (n.23): females 15, males 8 Dexamethasone - (n.25): females 14, males 11			
Units: Subjects			
Female	3	7	
Male	4	4	
principal variables			
Dexa group + (n= 23): race (caucasian) n. 18, fetal urinary tract abonormalities 1, Max body temperature (BT) in °C n. 39.5°, Weight in kg 8.5 Kg, PCT ng/ml 2.8, Leukocyturia on urine dipstick n. 23, Nitraturia on urine dipstick n. 15, Urine method collection for culture (Catheterization n. 22, Clean catch n. 1), Urine culture pos n. 20 Dexa group - (n= 25): race (caucasian) n. 22, fetal urinary tract abonormalities 0, BT in °C n. 39.3°, Weight in kg 8.0 Kg, PCT ng/ml 3.1, Leukocyturia n. 24, Nitraturia n.17, Catheterization n. 21, Clean catch n. 4, Urine culture pos 22			
Units: Subjects			
race	23	25	

## End points

### End points reporting groups

Reporting group title	dexamethasone +
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Reporting group description:

dexamethasone plus routine therapy (antibiotic for 10 days)

Reporting group title	dexamethasone -
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Reporting group description:

Routine therapy for febrile urinary tract infection (antibiotic for 10 days)

Subject analysis set title	Dexamethasone +
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Subject analysis set type	Full analysis
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Subject analysis set description:

The original sample size calculation on the hypothesis that dexamethasone would determine a renal scar reduction from 40% to 20%. Estimating a 10% rate of patients who did not fulfil the criteria for urinary tract infections diagnosis and 20% of lost to follow-up, a final number of 92 patients per group were required based on Freedman formula. Unanticipated difficult recruitment of patient in the study and their relevant loss to follow up prevented the completion of the study as originally designed. An interim assessment showed that based on the on the recruitment and attrition data, the completion of the study as initially planned was not feasible based on the available resources. We, therefore, used a Bayesian analysis to estimate the probability of treatment effect, given the limited number of patients we could enroll in the study based on the projection for patient enrolment and follow up estimated at the interim assessment.

Subject analysis set title	Dexamethasone -
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Subject analysis set type	Full analysis
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Subject analysis set description:

The original sample size calculation on the hypothesis that dexamethasone would determine a renal scar reduction from 40% to 20%. Estimating a 10% rate of patients who did not fulfil the criteria for urinary tract infections diagnosis and 20% of lost to follow-up, a final number of 92 patients per group were required based on Freedman formula. Unanticipated difficult recruitment of patient in the study and their relevant loss to follow up prevented the completion of the study as originally designed. An interim assessment showed that based on the on the recruitment and attrition data, the completion of the study as initially planned was not feasible based on the available resources. We, therefore, used a Bayesian analysis to estimate the probability of treatment effect, given the limited number of patients we could enroll in the study based on the projection for patient enrolment and follow up estimated at the interim assessment.

### Primary: Primary outcome

End point title	Primary outcome
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End point description:

Presence of renal scars on the Technetium 99m dimercaptosuccinic acid (DMSA) scan performed at the 6 months follow up. Outcome assessors were two nuclear medicine physicians, blinded to study allocation and unaware of patients clinical data, who interpreted the scans independently. Discrepancies were resolved by consensus if necessary.

End point type	Primary
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End point timeframe:

Follow up 6 months

<b>End point values</b>	dexamethason e +	dexamethason e -	Dexamethason e +	Dexamethason e -
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	7 <sup>[1]</sup>	11 <sup>[2]</sup>	7 <sup>[3]</sup>	11 <sup>[4]</sup>
Units: Presence of renal scars				
Presence of renal scar	0	2	0	2

Notes:

[1] - Given the limited number, we were unable to assess the frequency of renal scarring in the subgroup

[2] - Given the limited number, we were unable to assess the frequency of renal scarring in the subgroup

[3] - Given the limited number, we were unable to assess the frequency of renal scarring in the subgroup

[4] - Given the limited number, we were unable to assess the frequency of renal scarring in the subgroup

<b>Attachments (see zip file)</b>	Figure Patient selection Rescue trial.pdf
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## Statistical analyses

<b>Statistical analysis title</b>	bayesian analysis
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Statistical analysis description:

Bayesian analysis was used to estimate the probability of treatment effect, given the limited number of patients. In this analyses, the probability of treatment effect (posterior probability) is estimated considering the trial data and incorporating the prior probability distribution. The prior distribution includes treatment effect information provided by previous studies (clinical trial or pilot trials).

Comparison groups	dexamethasone - v dexamethasone +
Number of subjects included in analysis	18
Analysis specification	Post-hoc
Analysis type	other <sup>[5]</sup>
Method	bayesian analysis
Parameter estimate	bayesian analysis
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.29

Notes:

[5] - A sample size calculation was carried out for the Bayesian analysis, based on a Beta Binomial model for a difference in proportion outcome as suggested in the literature. We assumed an interval coverage of 0.9 with a length of 0.35. A Beta prior was considered for the computation based on previously published data on the proportion of renal scarring in both treatment and control groups. The achieved sample size consisted of 9 patients per group, for a total of 18 patients.

## Secondary: Secondary outcomes

<b>End point title</b>	Secondary outcomes
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End point description:

Secondary outcomes were the presence of renal scarring in the subgroup of children with higher PCT values; the acceptability of adjunctive steroids treatment, in terms of the rate of discontinuation of treatment and the reported side effects.

<b>End point type</b>	Secondary
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End point timeframe:

Follow up 6 months

<b>End point values</b>	dexamethason e +	dexamethason e -	Dexamethason e +	Dexamethason e -
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	7 <sup>[6]</sup>	11 <sup>[7]</sup>	7 <sup>[8]</sup>	11 <sup>[9]</sup>
Units: presence of renal scar				
presence of renal scar	0	0	0	2

Notes:

[6] - Given the limited number of recruited patients, we were unable to assess the frequency of renal scar

[7] - Given the limited number of recruited patients, we were unable to assess the frequency of renal scar

[8] - Given the limited number of recruited patients, we were unable to assess the frequency of renal scar

[9] - Given the limited number of recruited patients, we were unable to assess the frequency of renal scar

<b>Attachments (see zip file)</b>	Figure Patient selection Rescue trial.pdf
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### Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

From started therapy with dexamethasone until 10-15 days after diagnosis of urinary tract infection

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Adverse event reporting additional description:

Only 1 child present transient behavioural change.

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Assessment type	Non-systematic
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### Dictionary used

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Dictionary name	MedDRA
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Dictionary version	20.1
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Frequency threshold for reporting non-serious adverse events: 0.05 %

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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: Only one patient of dexamethasone + group presented irritability during the treatment.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2014	Modification of urine sample collection method for urine culture: previous study protocol described two different urine sample collection (catheterization or clean catch void). In this version of study protocol the urine sample method is only with catheterization to avoid methodology bias.
17 June 2015	Increase of participating centres because difficult recruitment of patients in the clinical study.
30 May 2017	<ol style="list-style-type: none"><li>1. Change of Principal study coordinator (from Prof. Liviana Da Dalt to DR. Floriana Scozzola)</li><li>2. Modification of clinical study participating centres (without Vicenza)</li><li>3. Change of name of clinical study sponsor (from AULSS9 to AULSS2)</li><li>4. Modification of the statistical analysis: use of a Bayesian analysis model</li></ol>

Notes:

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### 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.

Unanticipated difficult recruitment of patients in the study and their relevant loss to follow up prevented the completion of the study as originally designed.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34032923>