Clinical trial results:
Single-Arm Study to Assess the Efficacy of UVADEX® (Methoxsalen) Sterile Solution in Conjunction With the THERAKOS® CELLEX® Photopheresis System in Pediatric Patients With Steroid-Refractory Acute Graft Versus Host Disease (aGvHD)

Summary

EudraCT number	2014-004806-14
Trial protocol	DE HU GB IT ES AT
Global end of trial date	16 July 2019

Results information

Result version number	v2 (current)
This version publication date	09 September 2020
First version publication date	07 August 2020
Version creation reason	• Correction of full data set To correct three typographical errors

Trial information

Trial identification

Sponsor protocol code	TKS-2014-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02524847
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Therakos, Inc., a Mallinckrodt Company
Sponsor organisation address	1425 U.S. Route 206, Bedminster, NJ, United States, 07921
Public contact	Medical Information Call Center, Therakos, Inc., a Mallinckrodt Company, 1 800-844-2830 Ext 5, ClinicalTrials@mnk.com
Scientific contact	Medical Information Call Center, Therakos, Inc., a Mallinckrodt Company, 1 800-844-2830 Ext 5, ClinicalTrials@mnk.com

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	23 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 July 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of extracorporeal photopheresis (ECP) in pediatric participants with steroid-refractory aGvHD.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline, which has its foundation in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 January 2016
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	United States: 10
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 8
Worldwide total number of subjects	29
EEA total number of subjects	19

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)	2
Children (2-11 years)	17
Adolescents (12-17 years)	9

Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were recruited by multiple treatment centers in the United States and Europe.

Period 1

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

Arms

Arm title	Methoxsalen with ECP

Arm description:

Participants received methoxsalen 20 µg/ml in conjunction with ECP procedure three times per week for Weeks 1 to 4, and two times per week for Weeks 5 to 12.

Arm type	Experimental
Investigational medicinal product name	Methoxsalen
Investigational medicinal product code	298-81-7
Other name	Methoxalen Sterile Solution
Pharmaceutical forms	Solution for blood fraction modification
Routes of administration	Extracorporeal use

Dosage and administration details:

Participants received methoxsalen 20 µg/ml in conjunction with extracorporeal (ECP) use procedure three times per week for Weeks 1 to 4, and two times per week for Weeks 5 to 12.

Number of subjects in period 1	Methoxsalen with ECP
Started	29
Completed	15
Not completed	14
Condition no longer requires treatment	4
Adverse event, non-fatal	4
Death	1
Unsatisfactory therapeutic effect	4
Reason not specified	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	29	29	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	2	2	
Children (2-11 years)	17	17	
Adolescents (12-17 years)	9	9	
Adults (18-64 years)	1	1	
Age continuous Units: years			
arithmetic mean	8.6		
standard deviation	± 5.02	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	17	17	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	24	24	
Race Units: Subjects			
Asian	1	1	
Black or African American	2	2	
White	22	22	
Other	4	4	

End points

End points reporting groups

Reporting group title	Methoxsalen with ECP
Reporting group description: Participants received methoxsalen 20 µg/ml in conjunction with ECP procedure three times per week for Weeks 1 to 4, and two times per week for Weeks 5 to 12.	
Subject analysis set title	Stage 0 = No GvHD rash
Subject analysis set type	Full analysis
Subject analysis set description: No GvHD rash	
Subject analysis set title	Stage 1 = Maculopapular rash on < 25% body surface area (BSA)
Subject analysis set type	Full analysis
Subject analysis set description: Maculopapular rash on < 25% body surface area (BSA)	
Subject analysis set title	Stage 2 = Maculopapular rash on 25-50% BSA
Subject analysis set type	Full analysis
Subject analysis set description: Maculopapular rash on 25-50% BSA	
Subject analysis set title	Stage 3 = Maculopapular rash on >50% BSA
Subject analysis set type	Full analysis
Subject analysis set description: Maculopapular rash on >50% BSA	
Subject analysis set title	Stage 4 = Generalized erythroderma plus bullous formation
Subject analysis set type	Full analysis
Subject analysis set description: Generalized erythroderma plus bullous formation, which are blisters bigger than 5 mm across	
Subject analysis set title	Stage 0 = Bilirubin < 2.0 mg/dL
Subject analysis set type	Full analysis
Subject analysis set description: Bilirubin < 2.0 mg/dL	
Subject analysis set title	Stage 1 = Bilirubin 2.0-3.0 mg/dL
Subject analysis set type	Full analysis
Subject analysis set description: Bilirubin 2.0-3.0 mg/dL	
Subject analysis set title	Stage 2 = Bilirubin 3.1-6.0 mg/dL
Subject analysis set type	Full analysis
Subject analysis set description: Bilirubin 3.1-6.0 mg/dL	
Subject analysis set title	Stage 3 = Bilirubin 6.1-15.0 mg/dL
Subject analysis set type	Full analysis
Subject analysis set description: Bilirubin 6.1-15.0 mg/dL	
Subject analysis set title	Stage 4 = Bilirubin > 15.0 mg/dL
Subject analysis set type	Full analysis
Subject analysis set description: Bilirubin > 15.0 mg/dL	

Primary: Number of Participants Achieving Overall Response (OR) Using the Modified International Bone Marrow Transplant Registry (IBMTR) Severity Index at Week 4

End point title	Number of Participants Achieving Overall Response (OR) Using the Modified International Bone Marrow Transplant Registry (IBMTR) Severity Index at Week 4[1]

End point description:

OR using the modified IBMTR Severity Index is defined as complete response (CR) + partial response (PR) as follows:
• CR: complete resolution of all signs and symptoms of aGvHD in all evaluable organs without addition of next-line systemic treatment
• PR: improvement of 1 stage in 1 or more aGvHD target organs without progression in others and without addition of next-line systemic treatment

End point type	Primary

End point timeframe:

4 weeks

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: It was not possible to create an analysis module in this database because there was only one arm.

End point values	Methoxsalen with ECP			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Participants	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events

End point title	Number of Participants With Adverse Events

End point description:

Clinically significant changes in vital signs, laboratory values and investigations are reported as adverse events. Summary data are provided below, with details listed in the adverse events module.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Methoxsalen with ECP			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Participants				
Any serious AE	12			
Non-serious TEAE at 5% threshold	17			
Death for any cause	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Overall Response (OR) Using Modified IBMTR Severity Index at Week 8

End point title	Percentage of Participants Achieving Overall Response (OR) Using Modified IBMTR Severity Index at Week 8

End point description:

OR using the modified IBMTR Severity Index is defined as complete response (CR) + partial response (PR) as follows:
• CR: complete resolution of all signs and symptoms of aGvHD in all evaluable organs without addition of next-line systemic treatment
• PR: improvement of 1 stage in 1 or more aGvHD target organs without progression in others and without addition of next-line systemic treatment

End point type	Secondary

End point timeframe:

8 weeks

End point values	Methoxsalen with ECP			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: percentage of participants				
number (confidence interval 95%)	73.7 (48.8 to 90.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Overall Response (OR) Using Modified IBMTR Severity Index at Week 12

End point title	Percentage of Participants Achieving Overall Response (OR) Using Modified IBMTR Severity Index at Week 12

End point description:

OR using the modified IBMTR Severity Index is defined as complete response (CR) + partial response (PR) as follows:
• CR: complete resolution of all signs and symptoms of aGvHD in all evaluable organs without addition of next-line systemic treatment
• PR: improvement of 1 stage in 1 or more aGvHD target organs without progression in others and without addition of next-line systemic treatment

End point type	Secondary

End point timeframe:

12 weeks

End point values	Methoxsalen with ECP			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percentage of participants				
number (confidence interval 95%)	78.6 (49.2 to 95.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (Days) Within 16 Weeks Using Modified IBMTR Severity Index

End point title	Duration of Response (Days) Within 16 Weeks Using Modified IBMTR Severity Index

End point description:

Duration of first response is presented for participants whose disease progressed.
Duration of response is defined in the following way:
Participants whose response failed: Date at which 1st disease progression occurs - date of 1st response +1.
Participants whose response did not relapse: Date of 16-week follow-up or final assessment prior to week 16 (if participant withdrew early) - date of 1st response.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Methoxsalen with ECP			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: days				
median (full range (min-max))	13.5 (4 to 50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) According to the Modified Glucksberg Criteria

End point title	Overall Response Rate (ORR) According to the Modified

	Glucksberg Criteria

End point description:

ORR is defined as the percentage of participants who achieve an overall response after 4 weeks, 8 weeks, and 12 weeks of ECP treatment according to a scoring algorithm applied to calculate the grade of aGvHD using the modified Glucksberg Criteria.

End point type	Secondary

End point timeframe:

4 weeks, 8 weeks, and 12 weeks

End point values	Methoxsalen with ECP			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: percentage of participants				
number (confidence interval 95%)				
Week 4 (n=24)	50 (29.1 to 70.9)			
Week 8 (n=19)	63.2 (38.4 to 83.7)			
Week 12 (n=14)	78.6 (49.2 to 95.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative Dose of Daily Steroids

End point title	Cumulative Dose of Daily Steroids

End point description:

Steroids administered from diagnosis of aGvHD to 12 weeks after initiation of ECP treatment.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Methoxsalen with ECP			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: mg				
median (full range (min-max))	1917 (192 to 6895)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Skin Rated as Stage 0 - 4 Using the Modified Glucksberg Criteria

End point title	Number of Participants With Skin Rated as Stage 0 - 4 Using the Modified Glucksberg Criteria

End point description:

Number of participants whose skin was rated as Stage 0 - 4 using the modified Glucksberg criteria based on the Graft versus Host Disease (GvHD) rash - Stages are defined in the reporting group titles shown in the table.

End point type	Secondary

End point timeframe:

4 weeks, 8 weeks, and 12 weeks

End point values	Stage 0 = No GvHD rash	Stage 1 = Maculopapular rash on < 25% body surface area (BSA)	Stage 2 = Maculopapular rash on 25-50% BSA	Stage 3 = Maculopapular rash on >50% BSA
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	29	29	29
Units: Participants				
Week 4 (n=23)	9	8	3	3
Week 8 (n=18)	11	5	1	1
Week 12 (n=14)	10	2	1	1

End point values	Stage 4 = Generalized erythroderma plus bullous formation			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Participants				
Week 4 (n=23)	0			
Week 8 (n=18)	0			
Week 12 (n=14)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Liver Rated as Stage 0 - 4 Using the Modified Glucksberg Criteria

End point title	Number of Participants With Liver Rated as Stage 0 - 4 Using the Modified Glucksberg Criteria

End point description:

Number of participants whose liver was rated as Stage 0 - 4 on the modified Glucksberg criteria - Stages are based on level of bilirubin, as defined in the table's arm/group descriptions.

End point type	Secondary

End point timeframe:

4 weeks, 8 weeks, and 12 weeks

End point values	Stage 0 = Bilirubin < 2.0 mg/dL	Stage 1 = Bilirubin 2.0-3.0 mg/dL	Stage 2 = Bilirubin 3.1-6.0 mg/dL	Stage 3 = Bilirubin 6.1-15.0 mg/dL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	29	29	29	29
Units: Participants				
Week 4 (n=21)	19	1	1	0
Week 8 (n=13)	13	0	0	0
Week 12 (n=12)	12	0	0	0

End point values	Stage 4 = Bilirubin > 15.0 mg/dL			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Participants				
Week 4 (n=21)	0			
Week 8 (n=13)	0			
Week 12 (n=12)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 16 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Methoxsalen with ECP

Reporting group description:

Participants received methoxsalen 20 µg/ml in conjunction with ECP procedure three times per week for Weeks 1 to 4, and two times per week for Weeks 5 to 12.

Serious adverse events	Methoxsalen with ECP		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 29 (41.38%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage Intracranial			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General Physical Health Deterioration			

subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Autoimmune Haemolytic Anaemia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Acute Graft Versus Host Disease			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute Graft Versus Host Disease In Intestine			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute Graft Versus Host Disease In Liver			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Graft Versus Host Disease			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory Failure			

subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Failure			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Aspergilloma			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bk Virus Infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis Viral			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cytomegalovirus Infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device Related Infection			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis E			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Methoxsalen with ECP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 29 (58.62%)		
Investigations			
Immunoglobulins Decreased			

subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 3		
Vascular disorders Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all)	 4 / 29 (13.79%) 7 3 / 29 (10.34%) 6		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 3 / 29 (10.34%) 4		
Immune system disorders Hypogammaglobulinaemia subjects affected / exposed occurrences (all)	 3 / 29 (10.34%) 3		
Gastrointestinal disorders Abdominal Pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 4 / 29 (13.79%) 5 4 / 29 (13.79%) 8		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 4 / 29 (13.79%) 5		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	 2 / 29 (6.90%) 2		
Infections and infestations Clostridium Difficile Infection subjects affected / exposed occurrences (all) Cytomegalovirus Infection	 2 / 29 (6.90%) 2 		

subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Hypocalcaemia			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	4		
Hyperkalaemia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Hypophosphataemia			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Malnutrition			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2016	Changes made to provide more detailed information for the investigators and ensure study success. Extended the duration of the trial, adding time points at which to collect measurements. Adjusted inclusion/exclusion criteria and recording requirements, and added a risk/benefit statement.
27 July 2017	Modified inclusion and exclusion criteria and extended the recording period for adverse events.

Notes:

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.

This study did have a notable limitation in its single-group study design. This may limit a more robust assessment vs standard of care alone for primary endpoint of overall response and secondary endpoints steroid sparing and disease progression.

Notes: