Clinical trial results:
A Randomized Controlled Study of Extracorporeal Photopheresis (ECP) Therapy with UVADEX TM for the Treatment of Patients with Moderate to Severe Chronic Graft-versus-Host Disease (cGvHD).

Summary

EudraCT number	2010-022780-35
Trial protocol	GB DE AT ES IT HU
Global end of trial date	16 March 2015

Results information

Result version number	v1 (current)
This version publication date	23 February 2020
First version publication date	23 February 2020

Trial information

Trial identification

Sponsor protocol code	10-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01380535
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mallinckrodt
Sponsor organisation address	1425 U.S. Route 206, Bedminster, NJ, United States, 07921
Public contact	Medical Information Call Center, Mallinckrodt, +1 800-556-3314, ClinicalTrials@mnk.com
Scientific contact	Medical Information Call Center, Mallinckrodt, +1 800-556-3314, 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	19 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of ECP (Extracorporeal photopheresis) as determined by the incremental improvement in cGvHD (chronic graft-versus-host disease) according to National Institutes of Healt (NIH) Consensus Response Criteria versus a control population.

Protection of trial subjects:

The trial was conducted under the guidance of ICH E6 - Good Clinical Practices, which has its ethical foundation in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2011
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	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	60
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)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	56
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled in Austria, France, Germany, Italy, Hungary, Spain, the United Kingdom, and the United States. Enrollment started in November 2011, and the last patient visit occurred in March 2015.

Pre-assignment

Screening details:

All participants enrolled were included in the safety analysis set

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

It was not possible to blind patient or investigator to the use of a machine, so the outcomes assessor was the single blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	ECP Methoxsalen + SoC

Arm description:

Participants receive ECP methoxsalen in addition to standard of care

Arm type	Experimental
Investigational medicinal product name	Methoxsalen
Investigational medicinal product code	
Other name	UVADEX
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Extracorporeal use

Dosage and administration details:

UVADEX® (methoxsalen) Sterile Solution is a liquid methoxsalen (8-Methyoxypsoralen) for ex-vivo use in ECP therapy. It was developed to introduce methoxsalen as a liquid into the buffy coat bag during the ECP collection process followed by exposure of the cells to UVA light.

Investigational medicinal product name	Standard of Care (SoC)
Investigational medicinal product code	
Other name	Commonly oral prednizone with cyclosporine A (CsA) or tacrolimus (Tac)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Institutional standard of care, which may include oral prednisone, which may be used simultaneously or on an alternate day schedule with cyclosporine A (CsA) or tacrolimus (Tac), is the commonly used SOC.

Arm title	Standard of Care

Arm description:

Participants receive their institution's standard of care, commonly oral prednisone with cyclosporine A (CsA) or tacrolimus (Tac)

Arm type	Active comparator

Investigational medicinal product name	Standard of Care (SoC)
Investigational medicinal product code	
Other name	Commonly oral prednizone with cyclosporine A (CsA) or tacrolimus (Tac)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Institutional standard of care, which may include oral prednisone, which may be used simultaneously or on an alternate day schedule with cyclosporine A (CsA) or tacrolimus (Tac), is the commonly used SOC.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: It was not possible to blind patient or investigator to the use of a machine, so the outcomes assessor was the single blind.

Number of subjects in period 1	ECP Methoxsalen + SoC	Standard of Care
Started	29	31
Baseline Population	29	31
Intent-to-treat Population	29	24
Completed	22	16
Not completed	7	15
Consent withdrawn by subject	1	2
Adverse event, non-fatal	3	3
Death	3	-
Study site closed	-	5
Protocol deviation	-	2
Lack of efficacy	-	3

Baseline characteristics

Reporting groups	
Reporting group title	ECP Methoxsalen + SoC
Reporting group description:	
Participants receive ECP methoxsalen in addition to standard of care	
Reporting group title	Standard of Care
Reporting group description:	
Participants receive their institution's standard of care, commonly oral prednisone with cyclosporine A (CsA) or tacrolimus (Tac)	

Reporting group values	ECP Methoxsalen + SoC	Standard of Care	Total
Number of subjects	29	31	60
Age categorical Units: Subjects			
Adults (18-44) years	8	10	18
Adults (45-64) years	19	19	38
Adults (65 and over) years	2	2	4
Gender categorical Units: Subjects			
Female	7	13	20
Male	22	18	40
Race, Customized Units: Subjects			
White	22	24	46
Black	2	0	2
Other	1	1	2
Not recorded	4	6	10
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	4
Not Hispanic or Latino	24	24	48
Not Recorded	3	5	8

End points

End points reporting groups

Reporting group title	ECP Methoxsalen + SoC
Reporting group description:	
Participants receive ECP methoxsalen in addition to standard of care	
Reporting group title	Standard of Care
Reporting group description:	
Participants receive their institution's standard of care, commonly oral prednisone with cyclosporine A (CsA) or tacrolimus (Tac)	

Primary: Number of Patients With an Overall Response at Week 28

End point title	Number of Patients With an Overall Response at Week 28
End point description:	
Patients with overall response included those with partial response or complete response, according to study staff who did not know which treatment they received (blinded assessment).	
End point type	Primary
End point timeframe:	
28 Weeks	

End point values	ECP Methoxsalen + SoC	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[1]	24[2]		
Units: Patients	20	14		

Notes:

[1] - Intent to treat population

[2] - Intent to treat population

Statistical analyses

Statistical analysis title	Comparison Group
Comparison groups	ECP Methoxsalen + SoC v Standard of Care
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.373
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were recorded from the start of treatment through Week 28.

Adverse event reporting additional description:

Treatment emergent adverse events (TEAEs) are unpleasant events not there before the medical treatment, or that were there, but got worse or happened more often after the treatment. Both serious and non-serious adverse events reported here are TEAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	ECP Methoxsalen + SoC

Reporting group description:

Participants in the safety analysis set who receive ECP methoxsalen in addition to standard of care

Reporting group title	Standard of Care

Reporting group description:

Participants receive their institution's standard of care, commonly oral prednisone with cyclosporine A (CsA) or tacrolimus (Tac)

Serious adverse events	ECP Methoxsalen + SoC	Standard of Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 28 (28.57%)	9 / 28 (32.14%)	
number of deaths (all causes)	4	0	
number of deaths resulting from adverse events	3	0	
Cardiac disorders			
Cardiac Failure			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Graft versus host disease in liver			

subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord polyp			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Renal failure, acute			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroiditis subacute			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis, subacute			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (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			
Myopathy			
subjects affected / exposed	0 / 28 (0.00%)	2 / 28 (7.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			

subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Herpes simplex			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Toxoplasmosis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viraemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			

subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 28 (3.57%)	
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: 5 %

Non-serious adverse events	ECP Methoxsalen + SoC	Standard of Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 28 (92.86%)	24 / 28 (85.71%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 28 (32.14%)	4 / 28 (14.29%)	
occurrences (all)	9	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 28 (17.86%)	1 / 28 (3.57%)	
occurrences (all)	5	1	

Oedema peripheral			
subjects affected / exposed	2 / 28 (7.14%)	4 / 28 (14.29%)	
occurrences (all)	2	4	
Asthenia			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Pyrexia			
subjects affected / exposed	0 / 28 (0.00%)	4 / 28 (14.29%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 28 (21.43%)	1 / 28 (3.57%)	
occurrences (all)	6	1	
Dyspnoea			
subjects affected / exposed	5 / 28 (17.86%)	2 / 28 (7.14%)	
occurrences (all)	5	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 28 (7.14%)	3 / 28 (10.71%)	
occurrences (all)	2	3	
Sleep disorder			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 28 (14.29%)	3 / 28 (10.71%)	
occurrences (all)	4	3	
Platelet count decreased			
subjects affected / exposed	3 / 28 (10.71%)	2 / 28 (7.14%)	
occurrences (all)	3	2	
Blood cholesterol increased			
subjects affected / exposed	3 / 28 (10.71%)	1 / 28 (3.57%)	
occurrences (all)	3	1	
Blood creatinine increased			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
occurrences (all)	2	1	

Blood pressure increased			
subjects affected / exposed	1 / 28 (3.57%)	3 / 28 (10.71%)	
occurrences (all)	1	3	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Blood urea increased			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 28 (14.29%)	2 / 28 (7.14%)	
occurrences (all)	4	2	
Paraesthesia			
subjects affected / exposed	2 / 28 (7.14%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Headache			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Tremor			
subjects affected / exposed	2 / 28 (7.14%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 28 (7.14%)	4 / 28 (14.29%)	
occurrences (all)	2	4	
Anaemia			

subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	3 / 28 (10.71%)	0 / 28 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	1 / 28 (3.57%)	4 / 28 (14.29%)	
occurrences (all)	1	4	
Constipation			
subjects affected / exposed	1 / 28 (3.57%)	3 / 28 (10.71%)	
occurrences (all)	1	3	
Abdominal pain			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 28 (7.14%)	5 / 28 (17.86%)	
occurrences (all)	2	5	
Muscle spasms			
subjects affected / exposed	2 / 28 (7.14%)	4 / 28 (14.29%)	
occurrences (all)	2	4	
Myopathy			
subjects affected / exposed	2 / 28 (7.14%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Pain in extremity			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	

Arthralgia			
subjects affected / exposed	0 / 28 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	3	
Infections and infestations			
Rhinitis			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Epstein-Barr virus infection			
subjects affected / exposed	1 / 28 (3.57%)	3 / 28 (10.71%)	
occurrences (all)	1	3	
Respiratory tract infection			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 28 (10.71%)	4 / 28 (14.29%)	
occurrences (all)	3	4	
Hypertriglyceridaemia			
subjects affected / exposed	3 / 28 (10.71%)	1 / 28 (3.57%)	
occurrences (all)	3	1	
Hypokalaemia			
subjects affected / exposed	2 / 28 (7.14%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Hypomagnesaemia			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Hypoproteinaemia			
subjects affected / exposed	1 / 28 (3.57%)	2 / 28 (7.14%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2011	- Clarified NIH Criteria by amending the test related to the NIH Consensus Criteria Clinical Assessment (Modified version) throughout the protocol. - Added Consensus Clinical Assessment terminology. - Clarified that the TSS will be completed for all subjects in order to avoid confusion between subjects with or without cutaneous involvement and those for whom the eCRF may have been incorrectly completed. - Clarified that increases in CsA dosing should only be in the setting of serum levels which are below the therapeutic level. - Added "Relapse of underlying malignancy" to the Safety Endpoint and Subject Withdrawal and Replacement sections. - Clarified the time of randomization and assessment of study evaluations and treatments. - Increased allowed exposure to corticosteroids before the Baseline Visit from 3 days to 4 days. - Added information regarding the use of topical skin and ophthalmic corticosteroids as concomitant medication in order to reflect clinical practice as well as to control duration. - Clarified subject hospitalization, expedited reporting, and elective hospitalization. - Added information regarding the external DSMB. - Added information regarding Data Quality Assurance.
16 March 2012	- Provided changes in sponsor signatories and to safety reporting centers in the US and Europe throughout the protocol. - Clarified that CsA treatment may be continuing, rather, than initiated, at the start of study treatment. - Revised the study synopsis consistent with revisions to the study exclusion criteria. - Clarified: -the inclusion of subjects with moderate or severe cGvHD as defined by the NIH Consensus Criteria. -exclusion criteria regarding the duration of previous treatment with systemic steroids for mild and moderate to severe cGvHD. -that subjects who have discontinued treatment with low absorption steroids or enema preparations prior to or at screening are still eligible for the study. -that subjects who have received DLI in the past are still eligible for the study. - Provided examples of prohibited TKIs, indicated that PUVA is prohibited during the study, and included tapering requirements for MMF. - Added TKI, PUVA, and UK to List of Abbreviations and Definition of Terms. - Clarified: -for subjects with aphakia, that if the eye with aphakia has no vision capabilities then the subject may be included in the study. -that the Screening Visit platelet count will be used for stratification of treatment arms. - Added quantity of blood to process during each treatment for subjects in the SoC + ECP treatment arm. - Updated drugs/therapies prohibited during the study based on revisions to exclusion criteria. - Removed inaccurate sentence regarding baseline and randomization timing from Section 6. 1. 2. - Clarified: -that for subjects randomized to SoC + ECP treatment arm, additional blood samples will be collected for hematocrit and hemoglobin tests, and samples will be sent to local laboratory to perform testing before ECP therapy. -that all visits should occur within ± 3 days of the scheduled visit including ECP therapy visits. -the start corticosteroid treatment with occurrencof Baseline Visit. - Corrected for readability

02 December 2012	- Revised inclusion criteria for allowed dose of corticosteroids for cGvHD to be consistent with revised exclusion criteria. - Included new inclusion criteria for emphasis on the already existing 1.0 mg/kg corticosteroid dose at baseline study requirement. - Expanded the subject population by allowing subjects who develop cGvHD for up to 3 years after their transplant to be included. - Expanded the subject population to include a more common subject type by altering the requirement for allowed treatment for mild cGvHD in the exclusion criteria. - Revised exclusion criteria to allow a higher corticosteroid dose for moderate to severe cGvHD prior to baseline. - Allowed more time for early study logistics by revising the exclusion criteria. - Added information and instruction for the optional long-term 2-year follow-up. - Expanded the SoC treatment to include the use of either Tac or CsA. - Expanded the possible number of countries and study centers for the study. - Revised the study synopsis to be consistent with revisions to the body of the protocol. - Revised eligibility criteria to ease enrollment requirements. - Clarified method (using the instrument display or the manual calculation with rounding) for determining dose. - Added DSMB and Tac to the List of Abbreviations and Definition of Terms. - Phase corrected from 2b to Early phase 1 (Pilot)

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.

Long term follow-up (LTFU) safety data were provided to health authorities in safety reports; not the 28-week protocol.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31332045