Clinical trial results:
Keratinocyte Growth Factor - promoting thymic reconstitution and preventing autoimmunity after alemtuzumab (Campath-1H) treatment of multiple sclerosis. CAM-THY

Summary

EudraCT number	2011-005606-30
Trial protocol	GB
Global end of trial date	08 August 2017

Results information

Result version number	v1 (current)
This version publication date	23 August 2018
First version publication date	23 August 2018

Trial information

Trial identification

Sponsor protocol code	CAM-THY

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01712945
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Hills Road, Cambridge, United Kingdom, CB2 0QQ
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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	08 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2017
Global end of trial reached?	Yes
Global end of trial date	08 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to determine if Kepivance can prevent patients with multiple sclerosis from developing new autoimmune diseases after treatment with alemtuzumab.

Protection of trial subjects:

All subjects received IV methylprednisolone on days 1-3 immediately prior to each cycle of alemtuzumab (given at baseline and month 12) in order to reduce infusion associated reactions. If required, subjects were also treated with antihistamines and antipyretics.

Prior to starting the study, an open label Palifermin dose escalation sub-study was performed (n=10), to determine the highest dose of Palifermin that could be tolerated by out patient group. Three dosing levels were tested - 90mcg/kg/day; 120mcg/kg/day and 180mcg/kg/day. Ten patients were enrolled into this study (signing a separate ICF). Escalation between each dosing level only occurred if no AE greater than grade 2 occurred. Following the dose escalation sub-study, 180mcg/kg/day of Palifermin was selected for the main RCT.

Background therapy:

Alemtuzumab 12/mg per day for 5 days at baseline, and then for 3 days at month 12.
IV Methylprednisolone 1/day on days 1-3 at each cycle (baseline and month 12).

Evidence for comparator:

The comparator was Palifermin (Kepivance), which is recombinant human keratinocyte growth factor. Data from our group has shown that patients with the least thymic recovery of T-cells after treatment with alemtuzumab are most at risk of developing autoimmune complications. KGF has been shown in numerous animal models (murine and non-human primates) to increase thymic recovery, and in 2005 was licensed as Kepivance for use in humans to prevent mucositis induced by chemotherapy. In its pivotal licensing study, 60mcg/kg of palifermin was given for 3 days prior to conditioning, then for 3 days after shaematopoietic tem cell transplantation (HSCT). This regimen was well tolerated. Later a trial of 3 doses of palifermin (60mcg/kg) before conditioning and up to 9 doses after HSCT was shown to be safte, although it did not reduce the incidence of graft vs. host disease and did not increase lymphocyte recovery. Although thymic function was not directly studied in these patients, the results suggested that higher doses of palifermin might be required.
Therefore, we designed a study to explore the tolerability of higher doses of palifermin (tested in an open-label dose escalation sub-study), then tested the efficacy of 180mcg/kg/day in a placebo-controlled "main study" aimed at testing two hypothesess (i) that palifermin increases thymic T-cell reconstitution after alemtuzumab and (ii) that in doing so reduces the risk of alemtuzumab-induced autoimmunity. A planned "stop-go" interim analysis was performed when 28 "main study" patients reached month 6.

Actual start date of recruitment	01 May 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

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)	32
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a single centre (Addenbrooke's Hospital Cambridge UK) RCT. Patient were recruited to the RCT between June 2013 and February 2015.
The interim analysis was negative, so as per trial protocol recruitment halted.

Pre-assignment

Screening details:

Screening assessments included: EDSS, bloods (chemistry panel, full blood count, autoantibody screen, HIV, HepB and HepC), and where relevant a pregnancy test. Randomization occurred within 35 days of enrolment, or 56 days for patients who experienced a relapse or infection during screening or who required a 28 day washout of prior MS DMTs.

Period 1

Period 1 title	Main Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

Following randomisation pharmacy prepared the drug or placebo ready for preparation - both are clear colourless solutions for IV infusion, so there was no visual clue as to the identity of the IMP. Pharmacy was responsible for dispensing the trial drug based on unique randomisation codes. However, as Palifermin can cause side-effects that may compromise blinding (tongue whitening for example), all laboratory and imaging assessments were performed on link-anonymised samples in batches.

Arms

Are arms mutually exclusive?	Yes
Arm title	Palifermin

Arm description:

Experimental group who received Palifermin

Arm type	Experimental
Investigational medicinal product name	Palifermin
Investigational medicinal product code	
Other name	Kepivance, recombinant human keratinocyte growth factor
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received 180mcg/kg/day of Palifermin for 3 consecutive days immediate before and after each cycle of alemtuzumab and at months 1 and 3 after each cycle.

Arm title	Placebo

Arm description:

Control group who received placebo

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	Normal Saline
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Volume of saline to match volume of Palifermin required for 180mcg/kg/day 3 consecutive days immediate before and after each cycle of alemtuzumab and at months 1 and 3 after each cycle

Number of subjects in period 1	Palifermin	Placebo
Started	16	16
Interim analysis	14 [1]	14 [2]
Completed	16	15
Not completed	0	1
Lost to follow-up	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: As per the trial protocol the interim analysis was performed when 14 vs. 14 subjects reached month 6. Whilst the interim analysis was being performed subjects could still be recruited to the study, and 4 additional participants were (2 vs 2). Hence in total 16 participants were treated in each arm, whereas only 14 vs. 14 were included in the interim analysis.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: As per the trial protocol the interim analysis was performed when 14 vs. 14 subjects reached month 6. Whilst the interim analysis was being performed subjects could still be recruited to the study, and 4 additional participants were (2 vs 2). Hence in total 16 participants were treated in each arm, whereas only 14 vs. 14 were included in the interim analysis.

Baseline characteristics

Reporting groups	
Reporting group title	Palifermin
Reporting group description:	
Experimental group who received Palifermin	
Reporting group title	Placebo
Reporting group description:	
Control group who received placebo	

Reporting group values	Palifermin	Placebo	Total
Number of subjects	16	16	32
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	16	16	32
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	10	13	23
Male	6	3	9

Subject analysis sets	
Subject analysis set title	Palifermin Interim Group
Subject analysis set type	Per protocol
Subject analysis set description:	
The interim primary endpoint (number of naive CD4+ T cells at M6) was performed when 14 vs. 14 patients reached M6 (as recruitment was allowed to continue whilst the interim analysis was performed a further 2 vs. 2 patients were recruited making the total main study number 16 vs. 16)	
Subject analysis set title	Placebo Interim Group
Subject analysis set type	Per protocol
Subject analysis set description:	
The interim primary endpoint (number of naive CD4+ T cells at M6) was performed when 14 vs. 14 patients reached M6 (as recruitment was allowed to continue whilst the interim analysis was performed a further 2 vs. 2 patients were recruited making the total main study number 16 vs. 16)	

Reporting group values	Palifermin Interim Group	Placebo Interim Group	
Number of subjects	14	14	
Age categorical Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	8	12	
Male	6	2	

End points

End points reporting groups

Reporting group title	Palifermin
Reporting group description:	
Experimental group who received Palifermin	
Reporting group title	Placebo
Reporting group description:	
Control group who received placebo	
Subject analysis set title	Palifermin Interim Group
Subject analysis set type	Per protocol
Subject analysis set description:	
The interim primary endpoint (number of naive CD4+ T cells at M6) was performed when 14 vs. 14 patients reached M6 (as recruitment was allowed to continue whilst the interim analysis was performed a further 2 vs. 2 patients were recruited making the total main study number 16 vs. 16)	
Subject analysis set title	Placebo Interim Group
Subject analysis set type	Per protocol
Subject analysis set description:	
The interim primary endpoint (number of naive CD4+ T cells at M6) was performed when 14 vs. 14 patients reached M6 (as recruitment was allowed to continue whilst the interim analysis was performed a further 2 vs. 2 patients were recruited making the total main study number 16 vs. 16)	

Primary: Autoimmunity

End point title	Autoimmunity
End point description:	
For the purposes of this study secondary autoimmunity is defined as: i) the development of a novel autoimmune disease following treatment with alemtuzumab and/or ii) the generation of persistent novel autoantibodies (ANA, anti-smooth muscle, anti-TPO, and anti-mitochondrial antibodies) after treatment. Persistent is defined as present on at least 2 occasions at least 3 months apart.	
End point type	Primary
End point timeframe:	
Month 30	

End point values	Palifermin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15[1]		
Units: Yes or No				
Yes No	6	8		

Notes:

[1] - One subject in the Placebo arm of the study was lost to follow up prior to Month 30.

Attachments (see zip file)	Contingency of Data 1_CAMTHY_EOTD_AUTO.pdf

Statistical analyses

Statistical analysis title	Fisher Exact Test - Autoimmunity -Full data Set
Statistical analysis description:	
Occurrence of autoimmunity in the Palifermin full data set vs. autoimmunity in those randomised to receive Placebo.	

Comparison groups	Palifermin v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.4795 [2]
Method	Fisher exact

Notes:

[2] - Not statistically significant (but note, as recruitment to the study was halted - in keeping with the protocol following failure of the interim analysis, the trial was not powered to pick up differences in autoimmunity.

Other pre-specified: Naive CD4 T cell count

End point title	Naive CD4 T cell count

End point description:

The endpoint measured was number of circulating CD4+ naive T-cells defined as CD4+ T cells that co-express CD45RA and CCR7.

End point type	Other pre-specified

End point timeframe:

The interim analysis was performed when 14 vs. 14 of the main study patients reached month 6

End point values	Palifermin Interim Group	Placebo Interim Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	14		
Units: 10^7/L				
arithmetic mean (standard deviation)	2.229 (± 1.997)	7.733 (± 5.473)		

Attachments (see zip file)	Eudract_InterimResults.pdf

Statistical analyses

Statistical analysis title	Multivariate Linear Regression

Statistical analysis description:

The analysis estimates the the difference Placebo minus Palifermin in naive CD4 count at 6 months, adjusting for age, baseline naive CD 4 count, total palifermin dose.

The intercept represents the estimated naive CD4 T-cell count at 6 months for a 31 year old patient receiving Placebo, with a baseline CD4 T-cell count of 4 and a total Palifermin dose of 155mg (see attached document).

Comparison groups	Palifermin Interim Group v Placebo Interim Group
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [3]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-5.132

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.3
upper limit	-1.96

Notes:

[3] - The results of this analysis demonstrated that Palifermin significant reduced naive CD4 T cell counts at month 6.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing the ICF to Month 30.

Adverse event reporting additional description:

Patients were assessed daily throughout their IMP infusions and all AEs captured. Patients were then assessed clinically every 3 months(including blood tests to screen for thyroid autoimmunity and ITP; those being the most common autoimmune complications of alemtuzumab)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Palifermin

Reporting group description:

Experimental group who received Palifermin

Reporting group title	Placebo

Reporting group description:

Control group who received placebo

Serious adverse events	Palifermin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	2 / 16 (12.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Autoimmune Haemophilia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophagocytic Syndrome			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction to alemtuzumab			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Tonsillitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	Palifermin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)	16 / 16 (100.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 16 (31.25%)	8 / 16 (50.00%)	
occurrences (all)	6	8	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 16 (18.75%)	4 / 16 (25.00%)	
occurrences (all)	3	4	
Fatigue			
subjects affected / exposed	3 / 16 (18.75%)	3 / 16 (18.75%)	
occurrences (all)	3	3	
Chills			
subjects affected / exposed	3 / 16 (18.75%)	3 / 16 (18.75%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Tongue discolouration			
subjects affected / exposed	7 / 16 (43.75%)	0 / 16 (0.00%)	
occurrences (all)	11	0	
Oral discomfort			
subjects affected / exposed	13 / 16 (81.25%)	3 / 16 (18.75%)	
occurrences (all)	25	4	
Respiratory, thoracic and mediastinal			

disorders			
Chest tightness			
subjects affected / exposed	2 / 16 (12.50%)	8 / 16 (50.00%)	
occurrences (all)	2	8	
Skin and subcutaneous tissue disorders			
Hair Loss			
subjects affected / exposed	13 / 16 (81.25%)	2 / 16 (12.50%)	
occurrences (all)	13	2	
Peeling Skin			
subjects affected / exposed	3 / 16 (18.75%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Rash erythematous			
subjects affected / exposed	16 / 16 (100.00%)	6 / 16 (37.50%)	
occurrences (all)	30	7	
Rash urticarial			
subjects affected / exposed	7 / 16 (43.75%)	9 / 16 (56.25%)	
occurrences (all)	7	9	
Oedema - face			
subjects affected / exposed	10 / 16 (62.50%)	0 / 16 (0.00%)	
occurrences (all)	17	0	
Oedema peripheral (hands)			
subjects affected / exposed	7 / 16 (43.75%)	0 / 16 (0.00%)	
occurrences (all)	14	0	
Skin sensitivity			
subjects affected / exposed	5 / 16 (31.25%)	2 / 16 (12.50%)	
occurrences (all)	9	2	
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	8 / 16 (50.00%)	6 / 16 (37.50%)	
occurrences (all)	8	8	
Urinary tract infection			
subjects affected / exposed	2 / 16 (12.50%)	2 / 16 (12.50%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2012	To allow advertising on our group website
20 August 2012	1. Change of inclusion criterion - initially the inclusion criteria included selecting patients based on high serum IL-21 (in order to try and select patients most at risk of developing autoimmunity). In this amendment this was changed to selecting patients on low IL-7 for the same reasons; changed because of poor reproducibility in commercially available IL-21 ELISA assay kit. Please note this amendment occurred well before patients were selected for involvement in the main, randomized control trial part of the study, whilst we were recruiting patients to the open label dose escalation part of the study. 2. To remove advice regarding yearly pap smears (no longer advised by DOH) 3. To clarify preparation of alemtuzumab
26 November 2012	1. Legal status of alemtuzumab amended following withdrawal of MA by Genzyme in August 2012. 2. Clarification of statistical operational analysis 3. Correction of minor typographical error
20 May 2013	1. Change of CI from Prof Alasdair Coles to Dr Joanne Jones. 2. To refine the definition of secondary autoimmunity to include novel autoantibodies after alemtuzumab (namely ANA, anti-smooth muscle, anti-TPO, and anti-mitochondrial antibodies) present on at least 2 occasions and detected at least 3 months apart. 3. To remove IL-7 from inclusion criteria 4. To measure anti-nuclear, smooth muscle, mitochondrial and TPO antibodies pre and 3 monthly following alemtuzumab. 5. The addition of an interim analysis statistician and temporary member of the independent trial steering committee for futility analysis Please note this amendment occurred before patients were selected for involvement in the main, randomized control trial part of the study, whilst we were recruiting patients to the open label dose escalation part of the study.
01 October 2013	1. To change the formulation of IMP from Alemtuzumab 30mg/mL to Alemtuzumab 10mg/mL (either supplied as unlicensed drug, or Lemtrada) 3. To update the Legal status of alemtuzumab (to reflect new MA of alemtuzumab as Lemtrada as a treatment for relapsing remitting MS). 4. To modify the rules around repeat FBC testing following a platelet count below the LLN but >100 - in order to prevent unnecessary repeat testing for individuals whose platelet counts dipped just below the low limit of normal. 5. To correct an omission of baseline autoantibodies from the trial synopsis 6. To update the adverse effects seen following administration of Kepivance (PIS change only) - in order to inform potential participants of the range of AEs we had seen in the dose escalation phase of the study. This was the only amendment to occur during recruitment of individuals to the main/RCT part of the study.

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.

The interim milestone (14 vs. 14 patients at M6) was not passed so as per protocol recruitment to the trial was stopped. Therefore although the trial has clearly shown that Palifermin reduces thympopoesis, it is underpowered to assess autoimmunity.

Notes: