



Clinical trial results:

A single arm, phase II open label trial to investigate the efficacy and safety of intra-dermal injection of etanercept for remission induction in discoid lupus erythematosus

Summary

EudraCT number	2015-001602-33
Trial protocol	GB
Global end of trial date	31 December 2017

Results information

Result version number	v1 (current)
This version publication date	05 March 2020
First version publication date	05 March 2020
Summary attachment (see zip file)	TARGET-DLE Final Report (TARGET-DLE_FinalReport.pdf)

Trial information

Trial identification

Sponsor protocol code	RR15/114
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02656082
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	Research & Innovation Centre, St James University Hospital, Beckett Street, Leeds, United Kingdom, LS9 7TF
Public contact	James Goulding, University of Leeds, +44 0113 39 24495, J.T.R.Goulding@leeds.ac.uk
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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	05 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 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 assess the proportion of patients with active discoid lupus erythematosus (DLE) that achieves a clinical response as assessed using the modified Limited Score of Activity and Damage in DLE (SADDLE) tool (ie: defined as reduction in modified limited SADDLE score by 20% or more from baseline in the discoid lesion) at Week 12 following treatment with weekly intra-dermal injection of etanercept.

Protection of trial subjects:

1. The intra-dermal injection of etanercept was administered by the investigators or qualified research nurses at the Day Case Unit (Ward 5), Chapel Allerton Hospital, Leeds. This site had full resuscitation facility.
2. For safety and tolerability purposes, the first dose acted as a test dose using etanercept 1mg dose irrespective of the size of the lesion. There was a 2-week gap between the first two doses (rather than the usual weekly dosing schedule) to monitor for safety.
3. As etanercept was used for an unlicensed condition in this trial, a ceiling therapy of 10mg per injection at one treatment visit for a discoid lesion ≥ 3.5 cm radius was put in place.
4. Participants attended the hospital on a weekly basis to receive the intra-dermal injection of etanercept. Hence, all adverse events were extensively collected. In addition, appropriate mechanism to contact the research/medical team (i.e. both during working hours and out of hours) were available for the participants should an adverse event occurred.
5. Safety report of the trial was provided to the Data Monitoring Ethics Committee (DMEC) on a quarterly basis and the DMEC met annually to review the overall safety conduct of the trial.
6. Participants were free to withdraw from the study at any time, without prejudice to their continued care.

Background therapy:

1. If participants were taking an oral corticosteroid for maintenance, the dose must have been ≤ 10 mg of oral prednisolone (or equivalent) and had been stable for at least 28 days prior to Baseline visit.
2. Participants receiving anti-malarials must have been receiving them for at least 3 months prior to Screening, with a stable dose regimen for at least 28 days (± 1 day) prior to Baseline visit.
3. Permitted other concomitant immunosuppressant includes methotrexate, azathioprine and mycophenolate mofetil. If the subject was receiving these immunosuppressants, they must have been at a stable dose for at least 28 days (± 1 day) prior to Baseline visit.

Evidence for comparator:

Not applicable since this was a single arm study.

Actual start date of recruitment	01 February 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 Kingdom: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	24
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period ran for 18 months with a run-in screening period within four weeks of the start of protocol treatment.

Recruitment start date: 1 Feb 2016.

Recruitment end date: 31 July 2017.

All 25 participants required in this study were recruited within this specified time-frame.

Pre-assignment

Screening details:

Screening Period lasted a maximum of 28 days (Day -28 to -1). Participants were screened against inclusion and exclusion criteria as per trial protocol. A total of 25 participants underwent Screening. Of these, 2 were initially deemed screening failures due to abnormal test and concurrent infection. However, they were included after re-screening.

Period 1

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

Blinding implementation details:

Not applicable as this was a single arm, open label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline Assessment

Arm description:

This is a single arm study. Unfortunately this EudraCT form cannot accommodate for this type of study. Hence this Arm 1 is considered as one group and is defined as the Baseline Assessment.

Arm type	Experimental
Investigational medicinal product name	Etanercept
Investigational medicinal product code	EU/1/99/126/022
Other name	Enbrel
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

One index lesion was identified (i.e. the lesion with the highest modified limited SADDLE score at baseline) for treatment and subsequent assessments throughout the study. The treatment involved weekly intra-dermal injection of etanercept for up to 12 weeks. The dose of etanercept was estimated based on the radius of the lesion (in cm) as specified in the trial protocol, with multiple injections spread across a larger lesion. For safety and tolerability purposes, the first dose will act as a test dose using etanercept 1mg dose irrespective of the size of the lesion. There was a 2-week gap between the first two doses (rather than the usual weekly dosing schedule) to monitor for safety. Any SAEs were recorded and communicated with Sponsor and Pfizer. As etanercept was used for an unlicensed condition in this trial, a ceiling therapy of 10mg per treatment visit was put in place.

Arm title	Endpoint Assessment
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Arm description:

This is a single arm study. Unfortunately this EudraCT form cannot accommodate for this type of study. Hence this Arm 2 is considered as one group and is defined as the Endpoint Assessment.

Arm type	Experimental
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Investigational medicinal product name	Etanercept
Investigational medicinal product code	EU/1/99/126/022
Other name	Enbrel
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

One index lesion was identified (i.e. the lesion with the highest modified limited SADDLE score at baseline) for treatment and subsequent assessments throughout the study. The treatment involved weekly intra-dermal injection of etanercept for up to 12 weeks. The dose of etanercept was estimated based on the radius of the lesion (in cm) as specified in the trial protocol, with multiple injections spread across a larger lesion. For safety and tolerability purposes, the first dose will act as a test dose using etanercept 1mg dose irrespective of the size of the lesion. There was a 2-week gap between the first two doses (rather than the usual weekly dosing schedule) to monitor for safety. Any SAEs were recorded and communicated with Sponsor and Pfizer. As etanercept was used for an unlicensed condition in this trial, a ceiling therapy of 10mg per treatment visit was put in place.

Number of subjects in period 1	Baseline Assessment	Endpoint Assessment
Started	1	24
Completed	1	17
Not completed	0	7
Adverse event, non-fatal	-	2
Personal reason	-	2
Pregnancy	-	1
Lack of efficacy	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description:	
Since this EudraCT form cannot accommodate for single arm study, two arms have to be created for this Trial Report i.e. Arm 1: Baseline and Arm 2: Endpoint Assessment. Hence, the number of subjects at baseline here is 50. The ACTUAL number of participant in this single arm study is 25.	

Reporting group values	Overall trial	Total	
Number of subjects	25	25	
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)	24	24	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous			
Mean age at baseline			
Units: years			
arithmetic mean	47.3		
standard deviation	± 12.2	-	
Gender categorical			
Units: Subjects			
Female	18	18	
Male	7	7	
Race			
Racial distribution			
Units: Subjects			
Caucasian	18	18	
South Asian	6	6	
Afro-Caribbean	1	1	
Previous Skin Biopsy for DLE			
Previous Skin Biopsy for DLE			
Units: Subjects			
Yes	19	19	
No	6	6	
Concurrent diagnosis of SLE			
Concurrent diagnosis of systemic lupus erythematosus (SLE)			
Units: Subjects			
Yes	6	6	
No	19	19	
Positive ANA test			

Positive anti-nuclear antibody (ANA) test			
Units: Subjects			
Yes	9	9	
No	16	16	
Low Complement Levels			
Either C3 or C4 level			
Units: Subjects			
Yes	1	1	
No	24	24	
Concomitant csDMARDs excluding anti-malarials only			
Concomitant therapy with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs)			
Units: Subjects			
Methotrexate	2	2	
Azathioprine	1	1	
Thalidomide	2	2	
Mycophenolate Mofetil	1	1	
No	19	19	
Concomitant anti-malarial agents			
Units: Subjects			
Yes	14	14	
No	11	11	
Concomitant oral prednisolone			
Units: Subjects			
Yes	7	7	
No	18	18	
Family history of autoimmune rheumatic disease			
Units: Subjects			
Yes	6	6	
No	19	19	
Smoking			
Units: Subjects			
Never	5	5	
Current	15	15	
Previous	5	5	
DLE Disease Duration			
DLE disease duration from Diagnosis to trial Baseline			
Units: Years			
median	9.8		
inter-quartile range (Q1-Q3)	3.3 to 16.0	-	
Number of previous DMARDs			
csDMARDs and/or biological DMARDs (bDMARDs)			
Units: Number			
median	5		
full range (min-max)	1 to 16	-	

End points

End points reporting groups

Reporting group title	Baseline Assessment
Reporting group description: This is a single arm study. Unfortunately this EudraCT form cannot accommodate for this type of study. Hence this Arm 1 is considered as one group and is defined as the Baseline Assessment.	
Reporting group title	Endpoint Assessment
Reporting group description: This is a single arm study. Unfortunately this EudraCT form cannot accommodate for this type of study. Hence this Arm 2 is considered as one group and is defined as the Endpoint Assessment.	

Primary: ML-SADDLE 20 Response Rate at Week 12

End point title	ML-SADDLE 20 Response Rate at Week 12
End point description: The proportion of patients who achieved a reduction in the modified limited Score of Activity and Damage in DLE (ML-SADDLE) score by 20% of the baseline score (ML-SADDLE 20) in the index lesion between the end of study treatment visit (Week 12) and the baseline visit was summarised as the proportion of cases with exact 95% confidence interval. If 6 or more of the combined 25 patients were considered responders by this definition, a phase III randomised controlled trial would be recommended.	
End point type	Primary
End point timeframe: From Baseline to Week 12	

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[1]	24 ^[2]		
Units: Percentage				
Responder	0	13		
Non-responder	0	4		
Missing Data	0	8		

Notes:

[1] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[2] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	ML-SADDLE 20 Response Rate at Week 12
Statistical analysis description: Using the conservative approach by assuming that those with missing data were non-responders, in the Full Analysis Set, the primary endpoint was met with 13/25 (52%, 95% CI 31-73) meeting the ML-SADDLE 20 response rate at week 12.	
Comparison groups	Baseline Assessment v Endpoint Assessment

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[3]
Parameter estimate	Proportion percentage
Point estimate	52
Confidence interval	
level	95 %
sides	2-sided
lower limit	31
upper limit	73

Notes:

[3] - *This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 25.

Secondary: Change in physician's VAS at Weeks 12

End point title	Change in physician's VAS at Weeks 12
End point description:	Change in physician's visual analogue scale (VAS) for global assessment of disease activity at Weeks 12
End point type	Secondary
End point timeframe:	From Baseline to Week 12

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[4]	24 ^[5]		
Units: mm				
arithmetic mean (standard deviation)				
Baseline	0 (± 0)	53.1 (± 16)		
Week 12	0 (± 0)	23.2 (± 20)		

Notes:

[4] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[5] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Change in physician's VAS at Weeks 12
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	< 0.001 ^[7]
Method	t-test, 2-sided

Notes:

[6] - Complete Case Analysis (N=17).

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 17.

[7] - There was a significant improvement in the physician's VAS at Week 12 from Baseline; mean

difference 29.9 (95% CI 19.4 to 40.4), $p < 0.001$.

Secondary: Change in Dermatology Life Quality Index (DLQI) at Weeks 12

End point title	Change in Dermatology Life Quality Index (DLQI) at Weeks 12
End point description:	Change in patient-reported outcome; the Dermatology Life Quality Index (DLQI) at Weeks 12
End point type	Secondary
End point timeframe:	From Baseline to Week 12

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[8]	24 ^[9]		
Units: score				
arithmetic mean (standard deviation)				
Baseline	0 ($\pm$ 0)	11.4 ($\pm$ 6.87)		
Week 12	0 ($\pm$ 0)	6.5 ($\pm$ 6.21)		

Notes:

[8] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[9] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Change in DLQI at Weeks 12
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[10]
P-value	< 0.001 ^[11]
Method	t-test, 2-sided

Notes:

[10] - Complete Case Analysis Set (N=17).

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 17.

[11] - There was a significant improvement in the DLQI at Week 12 from Baseline; mean difference 4.9 (95% CI 2.6 to 7.1), $p < 0.001$.

Secondary: Change in patient's VAS at Week 12

End point title	Change in patient's VAS at Week 12
End point description:	Change in patient's visual analogue scale (VAS) for global assessment of disease activity at Weeks 12
End point type	Secondary
End point timeframe:	From Baseline to Week 12

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[12]	24 ^[13]		
Units: mm				
arithmetic mean (standard deviation)				
Baseline	0 (± 0)	56.9 (± 28)		
Week 12	0 (± 0)	29.7 (± 28)		

Notes:

[12] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=17.

[13] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Change in patient's VAS at Weeks 12
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[14]
P-value	= 0.001 ^[15]
Method	t-test, 2-sided

Notes:

[14] - Complete Case Analysis (N=17).

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 17.

[15] - There was a significant improvement in the patient's VAS at Week 12 from Baseline; mean difference 27.2 (95% CI 12.2 to 40.1), p=0.001.

Secondary: Change in infrared thermography parameter at Week 12

End point title	Change in infrared thermography parameter at Week 12
End point description:	
Change in the the mean (SD) of the absolute difference in temperature between active DLE and non-active areas using thermography at Baseline and Week 12	
End point type	Secondary
End point timeframe:	
From Baseline to Week 12	

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[16]	24 ^[17]		
Units: Degree Celcius				
arithmetic mean (standard deviation)				
Baseline	0 (± 0)	1.92 (± 1.17)		
Week 12	0 (± 0)	1.08 (± 1.05)		

Notes:

[16] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[17] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Change in infrared thermography parameter at Week
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[18]
P-value	= 0.005 ^[19]
Method	t-test, 2-sided

Notes:

[18] - Complete Case Analysis (N=17).

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 17.

[19] - There was a significant improvement in the absolute difference in temperature between active DLE and non-active areas using thermography at Week 12 from Baseline; mean difference 0.84 (0.30 to 1.39), p=0.005.

Secondary: Change in Laser Doppler imaging (LDI) parameter at Week 12

End point title	Change in Laser Doppler imaging (LDI) parameter at Week 12
End point description:	
Change in the mean (SD) of the absolute difference in perfusion unit between active DLE and non-active areas using the LDI at Baseline and Week 12	
End point type	Secondary
End point timeframe:	
From Baseline to Week 12	

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[20]	24 ^[21]		
Units: perfusion unit (PU)				
arithmetic mean (standard deviation)				
Baseline	0 (± 0)	495.1 (± 224)		
Week 12	0 (± 0)	376.2 (± 223)		

Notes:

[20] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[21] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Change in LDI parameter at Week 12
Comparison groups	Baseline Assessment v Endpoint Assessment

Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[22]
P-value	= 0.018 ^[23]
Method	t-test, 2-sided

Notes:

[22] - Complete Case Analysis (N=17).

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 17.

[23] - There was a significant improvement in the absolute difference in perfusion unit between active DLE and non-active areas using the LDI at Week 12 from Baseline; mean difference 118.9 (23.7 to 214.0), p=0.018.

Secondary: Change in optical coherent tomography (OCT) score at Week 12

End point title	Change in optical coherent tomography (OCT) score at Week 12
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End point description:

Change in the the mean (SD) of the total OCT score in DLE lesions at Baseline and Week 12. Four OCT parameters (i.e. (i) thickening and disruption of the entrance signal correlated with hyperkeratosis (ii) thinning of layer below the entrance signal correlated with atrophy of epidermis (iii) patchy hyporeflective zones in the epidermis correlated with lymphocytic infiltrates in the upper dermis and (iv) wide signal free cavities in the upper dermis correlated with dilated vessels in the upper dermis) were each graded using a scale of 0-3; 0=none, 1=slight, 2=moderate and 3=strong; with a possible maximum total OCT score of 12.

End point type	Secondary
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End point timeframe:

From Baseline to Week 12

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[24]	24 ^[25]		
Units: score				
arithmetic mean (standard deviation)				
Baseline	0 (± 0)	4.4 (± 1.77)		
Week 12	0 (± 0)	3.7 (± 1.94)		

Notes:

[24] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[25] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Change in OCT score at Week 12
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[26]
P-value	= 0.144 ^[27]
Method	t-test, 2-sided

Notes:

[26] - Complete Case Analysis (N=17).

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 17.

[27] - There was no significant improvement in the total OCT score in DLE lesions at Week 12 from Baseline; mean difference 0.7 (-0.3 to 1.7), p=0.144.

Secondary: Change in daily oral prednisolone requirement at Weeks 12

End point title	Change in daily oral prednisolone requirement at Weeks 12
End point description:	
Change in daily oral prednisolone requirement at Weeks 12 from Baseline. Tapering of oral prednisolone after Week 3 (Visit 5) to a target dose of ≤ 5 mg/day prednisolone equivalent was encouraged during the study. Steroid dose adjustments was avoided during Weeks 9 to 12 (Visit 11 to 14).	
End point type	Secondary
End point timeframe:	
From Baseline to Week 12	

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[28]	24 ^[29]		
Units: Number				
Dose Increased	0	0		
Dose unchanged	0	7		
Dose Reduced	0	0		
Not on oral prednisolone	0	10		
Missing Data	0	8		

Notes:

[28] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[29] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Change in daily oral prednisolone at Week 12
Comparison groups	Endpoint Assessment v Baseline Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[30]
Parameter estimate	Proportion percentage
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	41

Notes:

[30] - In the Full Analysis Set, of 7/25 patients who were on daily oral prednisolone at baseline, none of them had their dose either reduced or increased at Week 12.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study

was 25.

Secondary: Change in the overall grade of histology score of skin biopsy at Week 12

End point title	Change in the overall grade of histology score of skin biopsy at Week 12
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End point description:

Change in the overall grade of histology score of skin biopsy at Week 12 from Baseline. The histopathologist scored the biopsy based on their classic histological features including (i) interface dermatitis; (ii) inflammatory cell infiltrate in a perivascular, periappendageal or subepidermal location; (iii) vacuolar alteration of the basal layer; (iv) thickening of the basement membrane; (v) follicular plugging; (vi) the presence of immunofluorescence and (vii) dermal mucin deposition. The first two parameters were rated using a graded scale of 0-2; 0=absent, 1=mild and 2=strong while the remaining five parameters were rated using a binary scale; 0=absent, 1=present, with a possible maximum total score of 9. Finally, since these parameters were not weighted for clinical significance, an overall histology grade was then assigned for each biopsy sample using a graded scale of 0-2; 0=non active 1=mild and 2=active.

End point type	Secondary
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End point timeframe:

From Baseline to Week 12

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[31]	24 ^[32]		
Units: Number				
Improved	0	2		
Unchanged	0	2		
Worsening	0	2		
No paired skin biopsy done	0	19		

Notes:

[31] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[32] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Change in skin biopsy score at Week 12
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[33]
Parameter estimate	Proportion percentage
Point estimate	33.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	4
upper limit	78

Notes:

[33] - 13 patients underwent skin biopsy procedures at baseline. Of these, 6/13 had paired pre- and post-biopsy samples. Of these, 2/6 had histology score improved, 2/6 remained the same and 2/6 had worsening score at week 12. The correlation between total histology score and ML-SADDLE score at baseline was $r=0.50$; $p=0.085$.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. Actual no of patients = 6.

Secondary: New development or worsening of positive auto-antibodies titres: anti-nuclear antigen (ANA) and anti-double stranded deoxyribonucleic acid (dsDNA), extractable nuclear antigen antibodies (anti-ENAs) and anti-cardiolipin antibody (ACA) at Week 7 and 15.

End point title	New development or worsening of positive auto-antibodies titres: anti-nuclear antigen (ANA) and anti-double stranded deoxyribonucleic acid (dsDNA), extractable nuclear antigen antibodies (anti-ENAs) and anti-cardiolipin antibody (ACA) at Week 7 and 15.
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End point description:

New development or worsening of positive auto-antibodies titres: anti-nuclear antigen (ANA) and anti-double stranded deoxyribonucleic acid (dsDNA), extractable nuclear antigen antibodies (anti-ENAs) and anti-cardiolipin antibody (ACA) at Week 7 and 15.

End point type	Secondary
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End point timeframe:

From Baseline to Week 7 and Week 15

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[34]	24 ^[35]		
Units: Number				
New autoantibodies	0	0		
Worsening autoantibodies	0	25		
Remained unchanged	0	25		

Notes:

[34] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[35] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Change in autoantibodies at Week 7 and Week 15
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[36]
Parameter estimate	Proportion percentage
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	14

Notes:

[36] - No patient had new development of ANA or clinically significant worsening of autoantibodies titres (anti-dsDNA, anti-ENAs and ACA) from Baseline to Week 15.

One patient (4%) had Anti-B2 glycoprotein antibody positivity detected at Week 7; 21.00 U/mL from 14.70 U/mL at Baseline (normal <19.99 U/mL). There was no history of venous or arterial thrombosis observed. Her ANA remained negative. At Week 15, the Anti-B2 glycoprotein antibody reverted back to normal.

Secondary: Change in complement (C3 and C4) levels below the normal limit (if normal at baseline) at Week 7 and 15

End point title	Change in complement (C3 and C4) levels below the normal limit (if normal at baseline) at Week 7 and 15
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End point description:

End point type	Secondary
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End point timeframe:

From Baseline to Visit 7 and 15

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[37]	24 ^[38]		
Units: Number				
Worsening	0	1		
Unchanged	0	23		
Improving	0	1		

Notes:

[37] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[38] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Change in complement levels at Week 7 and 15
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[39]
Parameter estimate	Proportion percentage
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	20

Notes:

[39] - The one patient with low baseline complement levels had his levels normalised at Early Withdrawal visit (week 7). Two patients (8%) had changes in complement levels to < lower limit of normal (LLN) at Week 7 but only one (4%) had persistently low levels at Week 15.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 25.

Secondary: For SLE patients, change in disease activity as assessed using the British Isles Lupus Activity Groups (BILAG)-2004 score at Week 7 and 15

End point title	For SLE patients, change in disease activity as assessed using the British Isles Lupus Activity Groups (BILAG)-2004 score at
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End point description:

Assessed in DLE patients with concurrent systemic lupus erythematosus (SLE) only.

End point type

Secondary

End point timeframe:

From Baseline to Week 7 and Week 15.

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[40]	24 ^[41]		
Units: Number				
Worsening	0	0		
Unchanged	0	5		
Improving	0	1		

Notes:

[40] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[41] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Changed in BILAG-2004 at Week 7 and Week 15
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[42]
Parameter estimate	Proportion percentage
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	46

Notes:

[42] - Of 6 patients with concurrent SLE, only 4 completed the study. Those who withdrew early did not have deterioration in BILAG-2004 score at the Withdrawal Visits. One patient had improvement in BILAG Mucocutaneous domain from Grade B at Baseline to Grade C at Week 15.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 6.

Secondary: For SLE patients, change in disease activity as assessed using the SLE Disease Activity Index (SLEDAI) score at Week 7 and 15

End point title	For SLE patients, change in disease activity as assessed using the SLE Disease Activity Index (SLEDAI) score at Week 7 and 15
End point description:	
Assessed only in DLE patients with concurrent SLE.	
End point type	Secondary
End point timeframe:	
From Baseline to Week 7 and Week 15.	

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[43]	24 ^[44]		
Units: Number				
Worsening	0	1		
Unchanged	0	5		
Improving	0	0		

Notes:

[43] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[44] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Change in SLEDAI score at Week 7 and Week 15
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[45]
Parameter estimate	Proportion percentage
Point estimate	16.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	64

Notes:

[45] - Of 6 patients with concurrent SLE, only 4 completed the study. Those who withdrew early did not have deterioration in SLEDAI-2K score at the Withdrawal Visits. only 1 patient had increased in SLEDAI-2K score from 8 to 10 points due to worsening of complement levels at week 7 and week 15.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 6.

Other pre-specified: ML-SADDLE 20 Response Rate at Week 15

End point title	ML-SADDLE 20 Response Rate at Week 15
End point description:	Reduction in modified limited Score of Activity and Damage in DLE (ML-SADDLE) score by 20% or more from baseline in the index lesion at Week 15
End point type	Other pre-specified
End point timeframe:	
From Baseline to Week 12	

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[46]	24 ^[47]		
Units: Percentage				
Responder	0	13		
Non-Responder	0	4		
Missing Data	0	8		

Notes:

[46] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[47] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	ML-SADDLE 20 Response Rate at Week 15
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[48]
Parameter estimate	Proportion percentage
Point estimate	52
Confidence interval	
level	95 %
sides	2-sided
lower limit	31
upper limit	73

Notes:

[48] - Full Analysis Set.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 25.

Other pre-specified: ML-SADDLE 50 Response Rate at Week 12

End point title	ML-SADDLE 50 Response Rate at Week 12
End point description:	Reduction in modified limited Score of Activity and Damage in DLE (ML-SADDLE) score by 50% or more from baseline in the index lesion at Week 12
End point type	Other pre-specified
End point timeframe:	From Baseline to Week 12

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[49]	24 ^[50]		
Units: Percentage				
Responder	0	12		
Non-Responder	0	5		
Missing Data	0	8		

Notes:

[49] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[50] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	ML-SADDLE 50 Response Rate at Week 12
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[51]
Parameter estimate	Proportion percentage
Point estimate	48
Confidence interval	
level	95 %
sides	2-sided
lower limit	27
upper limit	69

Notes:

[51] - Full Analysis Set.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 25.

Other pre-specified: ML-SADDLE 50 Response Rate at Week 15

End point title	ML-SADDLE 50 Response Rate at Week 15
End point description:	
Reduction in modified limited Score of Activity and Damage in DLE (ML-SADDLE) score by 50% or more from baseline in the index lesion at Week 15	
End point type	Other pre-specified
End point timeframe:	
From Baseline to Week 15	

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[52]	24 ^[53]		
Units: Percentage				
Responder	0	12		
Non-Responder	0	5		
Missing Data	0	8		

Notes:

[52] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[53] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	ML-SADDLE 50 Response Rate at Week 15
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[54]
Parameter estimate	Proportion percentage
Point estimate	48
Confidence interval	
level	95 %
sides	2-sided
lower limit	27
upper limit	69

Notes:

[54] - Full Analysis Set.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 25.

Other pre-specified: ML-SADDLE 70 Response Rate at Week 12

End point title	ML-SADDLE 70 Response Rate at Week 12
End point description:	
Reduction in modified limited Score of Activity and Damage in DLE (ML-SADDLE) score by 70% or more from baseline in the index lesion at Week 12	
End point type	Other pre-specified
End point timeframe:	
From Baseline to Week 12	

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[55]	24 ^[56]		
Units: Percentage				
Responder	0	5		
Non-Responder	0	12		
Missing Data	0	8		

Notes:

[55] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[56] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	ML-SADDLE 70 Response Rate at Week 12
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[57]
Parameter estimate	Proportion percentage
Point estimate	20

Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	37

Notes:

[57] - Full Analysis Set.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 25.

Other pre-specified: ML-SADDLE 70 Response Rate at Week 15

End point title	ML-SADDLE 70 Response Rate at Week 15
End point description:	
Reduction in modified limited Score of Activity and Damage in DLE (ML-SADDLE) score by 70% or more from baseline in the index lesion at Week 15	
End point type	Other pre-specified
End point timeframe:	
From Baseline to Week 15	

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[58]	24 ^[59]		
Units: Percentage				
Responder	0	6		
Non-Responder	0	11		
Missing Data	0	8		

Notes:

[58] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[59] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	ML-SADDLE 70 Response Rate at Week 15
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[60]
Parameter estimate	Proportion percentage
Point estimate	24
Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	42

Notes:

[60] - Full Analysis Set.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 25.

Other pre-specified: Complete Remission Rate at Week 12

End point title	Complete Remission Rate at Week 12
End point description: The proportion of patients who achieved complete remission (as defined as modified limited SADDLE activity score = 0) in the index lesion at Week 12.	
End point type	Other pre-specified
End point timeframe: From Baseline to Week 12	

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[61]	24 ^[62]		
Units: Percentage				
Complete	0	1		
Incomplete/No	0	16		
Missing Data	0	8		

Notes:

[61] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[62] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Complete Remission Rate at Week 12
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[63]
Parameter estimate	Proportion percentage
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	20

Notes:

[63] - Full Analysis Set.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 25.

Other pre-specified: Complete Remission Rate at Week 15

End point title	Complete Remission Rate at Week 15
End point description: The proportion of patients who achieved complete remission (as defined as modified limited SADDLE activity score = 0) in the index lesion at Week 15.	
End point type	Other pre-specified
End point timeframe: From Baseline to Week 12	

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[64]	24 ^[65]		
Units: Percentage				
Complete	0	2		
Incomplete/No	0	15		
Missing Data	0	8		

Notes:

[64] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[65] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Complete Remission Rate at Week 15
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[66]
Parameter estimate	Proportion percentage
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	26

Notes:

[66] - Full Analysis Set.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 25.

Other pre-specified: Detection of Serum Etanercept level during therapy

End point title	Detection of Serum Etanercept level during therapy
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End point description:

End point type	Other pre-specified
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End point timeframe:

Baseline and Visit 6 (Week 4). For the second sample, blood will be taken providing that the participants receive the treatment in the previous visit.

End point values	Baseline Assessment	Endpoint Assessment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1 ^[67]	24 ^[68]		
Units: Number				
Serum Etanercept detected	0	6		
Not detected	0	17		
Missing Paired Sample	0	1		

Notes:

[67] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

[68] - *This form cannot cater for single arm study. Two groups had to be created instead. Actual N=25.

Statistical analyses

Statistical analysis title	Serum Etanercept Level detected during therapy
Comparison groups	Baseline Assessment v Endpoint Assessment
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	other ^[69]
Parameter estimate	Proportion percentage
Point estimate	25
Confidence interval	
level	95 %
sides	2-sided
lower limit	10
upper limit	47

Notes:

[69] - At baseline, as expected, etanercept levels were undetected in all 24 patients with available data. Of 23 patients with pre- and post-trough serum etanercept levels available, 6/23 (26%) had detectable serum etanercept level post-therapy.

*This form cannot cater for single arm study. Therefore, two groups had to be created i.e. Baseline Assessment Group and Endpoints Assessment Group. The actual total number of patients in this study was 24.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline to Week 15.

Adverse event reporting additional description:

Methods for AE data collection and assessment: i) At each study visit (i.e. 15 visits in 12 weeks for this study); ii) participant report to stud team via telephone and iii) notification by medical team to the research team in the event of participant's hospitalisation episode.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.0
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Reporting groups

Reporting group title	Experimental group
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Reporting group description:

Single arm study. So, only one group is reported. Of the 25 participants recruited, 24 received the experimental treatment. 1 participant withdrew early (self-choice) at Baseline visit and hence, was not exposed to the experimental treatment.

Serious adverse events	Experimental group		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Heart failure	Additional description: Deemed possible treatment-related since patient was not known to have heart failure previously although he had background risk factors for heart failure including ischaemic heart disease, hypertension, high cholesterol and peripheral vascular disease		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Worsening of chilblains	Additional description: Deemed by the Investigator - Not related to the experimental drug.		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Presumed Infection source unidentified	Additional description: Deemed probable treatment-related by the investigators. As no source or organism was cultured despite a CRP of 235, he was treated as presumed infection empirically with broad spectrum antibiotics and intravenous anti-virals. Made a good recovery		

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia	Additional description: Deemed by the investigator - Not related to the experimental drug as the participant had missed two doses prior to hospitalisation episode.		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Experimental group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 24 (54.17%)		
Nervous system disorders			
Headache	Additional description: N = 4		
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	4		
Dizziness	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Pregnancy, puerperium and perinatal conditions			
Pregnancy	Additional description: N = 1. Not deemed related to the experimental drug. Received one injection exposure to experimental drug. She was withdrawn from study. Post-partum follow-up showed no effect of drug exposure to mother and the baby.		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Faecal incontinence	Additional description: N = 1		

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Cough	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Pleuritic pain	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Sore throat	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Injection site swelling	Additional description: N = 3		
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Pruritus	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Worsening of subacute cutaneous lupus	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Infections and infestations			
Lower respiratory tract infection	Additional description: N = 5		
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	5		
Urinary tract infection	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Injection site infection	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Pharyngitis	Additional description: N = 1		

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Otitis externa	Additional description: N = 1		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2016	Total no of Substantial Amendment = 1. a) Reason for Amendment: For safety purpose as etanercept was used in an unlicensed indication in this Trial. The establishment of a ceiling therapy was also in line with clinical practice of an intra-dermal injection of a drug to discoid lesion. Amendment to Selection of dose and dose modification: Section 12.4 (Selection of dose and dose modification) was updated in line with recent case, where the subject's size of discoid was unusually higher than anticipated; 6cm radius. The usual size of discoid rash was between 2-3 cm radius. The dose of IMP to be administered for this larger size was not specified in the previous Protocol V3.0. After mutual agreement with the CI, QA Sponsor and DMEC members, we had put a ceiling therapy of 10mg per injection at one treatment visit for a discoid lesion ≥ 3.5 cm radius. This was in line with clinical practice where up to 10mg of triamcinolone is injected intra-dermally to discoid or keloid at one session. The Dosing Guide table in Section 12.2 was also updated to cater for discoid size of 2.5 and 3.5cm radius (page 37 of the Trial Protocol V4.0).

11 November 2016	Total No of Substantial Amendments = 6. a) Reason for Amendment: In the previous version 4.0, an age limit of 65 years was established as an inclusion criterion. This was extended to 80 years old. Extension of the age limit would help us in enhancing recruitment for this study. Amendment: (i) Protocol Synopsis – Inclusion Criteria and (ii) Inclusion Criteria (Section 11.3.1). The upper limit of the participant's age was extended to 80 years old (18-80 years old). Page 14 and 29 respectively of Trial Protocol v5.0. b) Reason for Amendment: To clarify the window period between each scheduled visit to take place and specifically outline the procedures for treatment interruptions. Amendment to the Summary Schedule of Study Assessments (14.1). Page 49-50 of Trial Protocol v5.0. c) Reason for Amendment: To invite potential patients to participate in the study in order to enhance recruitment. Amendment: The Letters of Invitation to Participant V1.0 15 August 2016 was added to the initial application form to REC. d) Reason for Amendment: To update information on poster in line with the change in the inclusion criterion (upper limit of the participant's age). Amendment: Inclusion criteria in Poster V1.0 dated 01 April 2016 was changed to 18-80 years old. e) Reason for Amendment: To update information on leaflet in line with the change in the inclusion criterion (upper limit of the participant's age). Amendment: Inclusion criteria in Leaflet V1.0 dated 01 April 2016 was changed to 18-80 years old. f) Reason for Amendment: To update the Investigator's Brochure (IB) document as provided by Pfizer in the initial CT application. Amendment: Investigator's Brochure V1.0 dated January 2015 was updated accordingly. However, the Reference Safety Information document (V1.0 15 Sept 2015) used for determination of SAE/SUSAR for this trial this trial did not require an amendment as this was based on Etanercept SmPC instead.
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27 March 2017	Total no of Substantial Amendment = 4. a) Reason for Amendment: Based on original Simon's 2-stage design, recruitment to Stage 2 would need to be halted after the 15th participant had been recruited in Stage 1. A formal interim analysis would then took place. However, if recruitment was halted and allowing for a further 4 months follow-up as per study schedule, then it would be highly unlikely for us to recruit all patients in time. We were on a tight recruitment timeline i.e. 18 months as specified by our funder. Amendment: Therefore, we amended the trial design to "A prospective single arm, Simon's 2-stage minimax design with Hybrid adaptation, phase II open label trial." This would allow for recruitment to continue while the results from Stage 1 were generated as well as target recruitment to be met rather than due to any clinical or scientific imperative. b) Reason for Amendment: During the DMEC meeting, we reviewed the upcoming formal interim analysis process included the determination of the STOP/GO criteria. Amendment: We had increased the number of participants required to proceed with Stage 2 of recruitment and the total number of participants required for a Phase 3 trial to be recommended. This improvised criteria required the smallest sample size whilst having a type I error rate no more than 5% and power no less than 80%. c) Reason for Amendment: For Laser Doppler imaging (LDI), It was the relative difference of perfusion between the active DLE and non-active areas that was clinically meaningful to be measured rather than perfusion in DLE lesion only (as per previous protocol v5.0). Amendment to the Secondary Endpoint: LDI parameter (Section 8.2 of the Trial Protocol v6.0) d) Reason for Amendment: To minimise the need for a minor protocol deviation due to non-attendance to be reported. Amendment: We had also increased the window period between each scheduled visit to +/- 3 days (Section 14.1 on page 50 Trial Protocol v6.0)
31 December 2017	Total no of Substantial Amendment = 1. This amendment was undertaken post-end of trial date, prior to database locked. The exact date of approval of this amendment was 23/08/2018. The date above was entered as per EudraCT's rule. a) Reason for Amendment: The proposed change was in relation to the interpretation of scientific documents/value of the trial. Changes to the scoring system of the skin biopsy were made following a review by our histopathologist. An overall grade of activity of the discoid lesion needed to be added and used for analysis instead of the total score of each histopathologic features. This was because each of the histopathologic features from skin biopsy was not weighted for significance in terms of activity, hence the highest total score might not necessarily represent the most active DLE lesion. Additionally, since the trial protocol v6.0 was approved, a new information had emerged. We recently published the use of this proposed overall grade of activity as an outcome measure for the assessment of cutaneous lupus erythematosus. Amendment: An overall grade of activity using a graded scale of 0-2 (0=non active, 1=mild activity and 2=active) was added to the Trial Protocol v7.0 and used for secondary analysis.

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.

1. An open-label trial. Results could be influenced by reporting bias from participants and investigators. However, efficacy were supported by objective measures.
2. 76% were on DMARDs, thus efficacy might not be contributed to etanercept alone.

Notes: