



## Clinical trial results:

### Cyclophosphamide in Myalgic Encephalopathy/ Chronic Fatigue Syndrome.

An open label phase-II study with 6 infusions of cyclophosphamide 4 weeks apart.

#### Summary

EudraCT number	2014-004029-41
Trial protocol	NO
Global end of trial date	25 June 2020

#### Results information

Result version number	v1 (current)
This version publication date	29 August 2021
First version publication date	29 August 2021
Summary attachment (see zip file)	Frontiers in Medicine_290420 (Frontiers_290420.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	KTS-7-2015
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02444091
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Haukeland University Hospital
Sponsor organisation address	Jonas Lies vei 65, Bergen, Norway, 5021
Public contact	Øystein Fluge, Haukeland University Hospital, +47 5597358700, oystein.fluge@gmail.com
Scientific contact	Øystein Fluge, Haukeland University Hospital, +47 5597358700, oystein.fluge@gmail.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	20 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 July 2017
Global end of trial reached?	Yes
Global end of trial date	25 June 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective of this trial is to evaluate the efficacy, toxicity and feasibility of six infusions cyclophosphamide given four weeks apart, for patients with chronic fatigue syndrome (ME/CFS). The objective of part B of the trial is to evaluate feasibility of six infusions cyclophosphamide given six weeks apart with simplified follow-up for up to five patients with severe to very severe ME/CFS.

Protection of trial subjects:

Physical stress tests before and after intervention were only performed for patients deemed physically capable of completing such tests with regards to disease severity and post-exertional malaise. Treatment was administered in a single room at a designated clinical trial unit to minimise sensory input. Premedication was administered to prevent nausea. In order to limit number of hospital visits, the trial unit organised house calls for blood sampling upon request. For part B (two participants with very severe ME/CFS) the protocol was adjusted to make the trial less taxing on patients, including longer intervals between treatments and simplified patient reporting.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Scientific research
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	40
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment lasted from March 2015 to December 2015. All participants were included at Haukeland University Hospital in Western Norway. Seven of the participants received parts of their treatment and follow-up at Oslo University Hospital.

### Pre-assignment

Screening details:

Inclusion criteria were: a diagnosis of ME/CFS according to the Canadian criteria; age 18–66 years; disease duration more than 2 years; and disease severity mild-to-moderate, moderate, moderate-to-severe, or severe. Exclusion criteria and screening process are detailed in the trial protocol.

### Period 1

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

Blinding implementation details:

This was an unblinded trial.

### Arms

<b>Arm title</b>	Cyclophosphamide treatment
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Arm description:

Six 30-minute intravenous infusions of cyclophosphamide were administered at 4-week intervals with 600 mg/m<sup>2</sup> at the first and 700 mg/m<sup>2</sup> at further cycles.

Arm type	Experimental
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Six 30-minute intravenous infusions of cyclophosphamide were administered at 4-week intervals with 600 mg/m<sup>2</sup> at the first and 700 mg/m<sup>2</sup> at further cycles.

<b>Number of subjects in period 1</b>	Cyclophosphamide treatment
Started	40
Completed	38
Not completed	2
Consent withdrawn by subject	2

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment
Reporting group description: -	

Reporting group values	Treatment	Total	
Number of subjects	40	40	
Age categorical			
Age on date of consent.			
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)	40	40	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Age on date of consent			
Units: years			
arithmetic mean	41.7		
full range (min-max)	21.5 to 61.1	-	
Gender categorical			
Units: Subjects			
Female	31	31	
Male	9	9	
ME/CFS disease duration			
Number of years from symptom debut to inclusion in study			
Units: Subjects			
2-5 years	7	7	
5-10 years	13	13	
10-15 years	9	9	
>15 years	11	11	
ME/CFS disease severity			
Units: Subjects			
Mild/moderate	14	14	
Moderate	13	13	
Moderate/severe	7	7	
Severe	6	6	
Infection prior to ME/CFS			
Units: Subjects			
Yes	26	26	
No	14	14	
HLA typing			

Units: Subjects			
HLA-DQB1*03:03 and/or HLA-C*07:04 positive	12	12	
Negative for both HLA-DQB*03:03 and HLA-C*07:04	28	28	
SF-36 Physical Function			
Short Form 36 Physical Function subscale, raw scores (range 0-100)			
Units: Points			
arithmetic mean	33		
full range (min-max)	0 to 65	-	
SF-36 Physical Component summary score			
Short Form 36 Physical Component summary score, norm-based with population mean 50.			
Units: Points			
arithmetic mean	23.3		
full range (min-max)	13.5 to 41.6	-	
Steps per 24h			
Steps, mean per 24 hours. Continuous measurement by Sensewear activity armband for 5 to 7 consecutive days			
Units: Steps			
arithmetic mean	3199		
full range (min-max)	568 to 9637	-	
Total function level			
Baseline self-reported function level, scale 0 to 100%			
Units: Per cent			
arithmetic mean	16.9		
full range (min-max)	5 to 40	-	

## Subject analysis sets

Subject analysis set title	Rituximab-naïve
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants who had not received previous treatment with rituximab.	
Subject analysis set title	Responders
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants who were classed as responders according to study response criteria.	
Subject analysis set title	Non-responders
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants who were not classed as responders according to study response criteria.	

Reporting group values	Rituximab-naïve	Responders	Non-responders
Number of subjects	25	22	18
Age categorical			
Age on date of consent.			
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)	25	22	18
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age on date of consent			
Units: years			
arithmetic mean	40.5	41.4	42.2
full range (min-max)	21.5 to 60.3	21.5 to 60.3	23.4 to 61.1
Gender categorical			
Units: Subjects			
Female	18	18	13
Male	7	4	5
ME/CFS disease duration			
Number of years from symptom debut to inclusion in study			
Units: Subjects			
2-5 years	7	5	2
5-10 years	7	5	8
10-15 years	4	6	3
>15 years	7	6	5
ME/CFS disease severity			
Units: Subjects			
Mild/moderate	10	9	5
Moderate	7	9	4
Moderate/severe	5	4	3
Severe	3	0	6
Infection prior to ME/CFS			
Units: Subjects			
Yes	17	15	11
No	8	7	7
HLA typing			
Units: Subjects			
HLA-DQB1*03:03 and/or HLA-C*07:04 positive	6	10	2
Negative for both HLA-DQB*03:03 and HLA-C*07:04	19	12	16
SF-36 Physical Function			
Short Form 36 Physical Function subscale, raw scores (range 0-100)			
Units: Points			
arithmetic mean	34	35	30.6
full range (min-max)	0 to 65	10 to 65	0 to 65
SF-36 Physical Component summary score			
Short Form 36 Physical Component summary score, norm-based with population mean 50.			
Units: Points			
arithmetic mean	24.5	23.1	23.5
full range (min-max)	14.6 to 41.6	13.5 to 41.6	14.6 to 31.0
Steps per 24h			
Steps, mean per 24 hours. Continuous measurement by Sensewear activity armband for 5 to 7 consecutive days			

Units: Steps			
arithmetic mean	3282	3622	2681
full range (min-max)	568 to 9637	1083 to 8178	568 to 9637
Total function level			
Baseline self-reported function level, scale 0 to 100%			
Units: Per cent			
arithmetic mean	17	19.3	14.1
full range (min-max)	5 to 30	10 to 40	5 to 25



## End points

### End points reporting groups

Reporting group title	Cyclophosphamide treatment
Reporting group description: Six 30-minute intravenous infusions of cyclophosphamide were administered at 4-week intervals with 600 mg/m <sup>2</sup> at the first and 700 mg/m <sup>2</sup> at further cycles.	
Subject analysis set title	Rituximab-naïve
Subject analysis set type	Full analysis
Subject analysis set description: Participants who had not received previous treatment with rituximab.	
Subject analysis set title	Responders
Subject analysis set type	Full analysis
Subject analysis set description: Participants who were classed as responders according to study response criteria.	
Subject analysis set title	Non-responders
Subject analysis set type	Full analysis
Subject analysis set description: Participants who were not classed as responders according to study response criteria.	

### Primary: Overall response rate

End point title	Overall response rate <sup>[1]</sup>
End point description: Overall response: Fatigue score 4.5 or above for at least six consecutive weeks at any time during treatment or follow-up. Overall response rate: Proportion of patients fulfilling the response criteria.	
End point type	Primary
End point timeframe: 18 months from first treatment	

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This primary end point uses absolute numbers of patients with clinical response. There is no comparison within groups and so no statistical analysis is applied. Additional end points are based on changes from baseline to pre-specified time points during trial. They were assessed by a General Linear Model of repeated measures, which cannot be reported in this system. Details on endpoints and analyses can be found in the published article, attached herein.

End point values	Cyclophosphamide treatment	Rituximab-naïve		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40 <sup>[2]</sup>	25 <sup>[3]</sup>		
Units: Subjects				
number (not applicable)	22	14		

#### Notes:

[2] - Intention to treat

[3] - Intention to treat

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From date of first treatment through 12 months follow-up

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	Cyclophosphamide treatment
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Reporting group description:

Six 30-minute intravenous infusions of cyclophosphamide were administered at 4-week intervals with 600 mg/m<sup>2</sup> at the first and 700 mg/m<sup>2</sup> at further cycles.

Serious adverse events	Cyclophosphamide treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 40 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Other (olfactory meningioma)	Additional description: Admitted for elective procedure. Not related to treatment.		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Other (ME/CFS symptom exacerbation)			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Stomach pain	Additional description: Admitted to hospital for check-up. No pathology found. Possibly related to treatment.		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Urticaria	Additional description: Possibly related to treatment		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal calculi			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection	Additional description: Possible relation to treatment.		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis	Additional description: Complication after planned surgery. Not related to treatment.		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper respiratory infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration	Additional description: Admitted for rehydration. Probably related to treatment.		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

<b>Non-serious adverse events</b>	Cyclophosphamide treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 40 (97.50%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	8		
Headache			
subjects affected / exposed	12 / 40 (30.00%)		
occurrences (all)	21		
General disorders and administration site conditions			
Oedema	Additional description: Grade 1 oedema of face or limbs		
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	7		
Fatigue			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
Gastrointestinal disorders			
Constipation	Additional description: Grade 1-2. Probably related to treatment/premedication (anti-nausea medication).		
subjects affected / exposed	22 / 40 (55.00%)		
occurrences (all)	34		
Diarrhoea			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	7		
Dry mouth			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	7		
Nausea	Additional description: Grade 1-2 nausea lasting from two days to several weeks after individual treatments.		
subjects affected / exposed	36 / 40 (90.00%)		
occurrences (all)	106		
Gastroenteritis	Additional description: Unlikely relation to treatment		
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Stomach pain			

subjects affected / exposed occurrences (all)	8 / 40 (20.00%) 10		
Reproductive system and breast disorders Menstruation irregular subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 9		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	Additional description: Grade 1 hair loss. Probably related to treatment 4 / 40 (10.00%) 4		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	Additional description: Microscopic haematuria grade 1-2 6 / 40 (15.00%) 7		
Infections and infestations Common cold subjects affected / exposed occurrences (all)	Additional description: Unlikely relation to treatment 7 / 40 (17.50%) 10		
Sinusitis subjects affected / exposed occurrences (all)	Additional description: Grade 2, unlikely relation to treatment 4 / 40 (10.00%) 4		
Urinary tract infection subjects affected / exposed occurrences (all)	8 / 40 (20.00%) 11		
Urticaria subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Open trial, no placebo arm. Self-referral. Self-reported primary outcome measures with possible recall bias. Lack of specific biomarkers could cause unintended heterogeneity in patient sample.
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32411717>