Clinical trial results:
PROOF OF CONCEPT STUDY OF HYQVIA IN PATIENTS WITH IMMUNOGLOBULIN DEFICIENCY AND RECURRENT INFECTIONS WITH CHRONIC FATIGUE SYNDROME

Summary

EudraCT number	2016-002370-12
Trial protocol	DE
Global end of trial date	27 August 2018

Results information

Result version number	v1 (current)
This version publication date	09 July 2022
First version publication date	09 July 2022

Trial information

Trial identification

Sponsor protocol code	IMI2016-2

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charité Universitätsmedizin Berlin
Sponsor organisation address	Augustenburger Platz 1, Berlin, Germany, 13353
Public contact	Frau Prof. Dr. Carmen Scheibenbogen, Institut für Medizinische Immunologie, 49 030450524062 , carmen.scheibenbogen@charite.de
Scientific contact	PD Dr. med. Patricia Grabowski, Medizinische Klinik m.S. Hämatologie, Onkologie und Tumorimmunologie, patricia.grabowski@charite.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 August 2018
Global end of trial reached?	Yes
Global end of trial date	27 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to improve chronic fatigue syndrome in patients with chronic immunodeficiency and recurrent infections

Protection of trial subjects:

Patients are monitored for AE and SAE during IgG infusion as well as the periods between infusions. At home patients are requested to keep a diary where they document all infusions, complaints and problems. Side effects will be documented according to CTC criteria.

This clinical study will be conducted in accordance with the principles of Good Clinical Practice (ICH-GCP) and the regulations of the actual Arzneimittelgesetz (AMG) and in accordance with the Declaration of Helsinki version October 1996 (48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

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)	16

From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

ME/CFS patients were selected who were diagnosed at the outpatient clinic for immunodeficiencies at the Institute of Medical Immunology at the Charité Universitätsmedizin Berlin (Berlin, Germany) and fulfilled the inclusion criteria.
Start of recruitment: 01.09.2016
End of recruitment:

Pre-assignment

Screening details:

It was planned to include 15 patients in the trial and replace patients receiving less than 3 months of treatment. All 17 patients who were approached agreed to participate in the trial.
Assessed for eligibility:17
Allocation: 17

Period 1

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

Arms

Arm title	ME/CFS patients
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	HyQvia
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Solution for infusion

Dosage and administration details:

0.2-0.8g/kg body weight / month

Month 1, day 0: total 0.2 g/kg body weight per month (one infusion).
Month 2: total 0.4 g/kg body weight per month (given as one or bi-weekly infusion).
Months 3–12: total 0.8 g/kg body weight per month (given as bi-weekly infusion).

Number of subjects in period 1	ME/CFS patients
Started	17
Completed	12
Not completed	5
Adverse event, non-fatal	3
Lack of efficacy	2

Baseline characteristics

Reporting groups	
Reporting group title	ME/CFS patients

Reporting group description: -

Reporting group values	ME/CFS patients	Total	
Number of subjects	17	17	
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)	16	16	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
median	46		
full range (min-max)	18 to 70	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	8	8	
infection-triggered onset Units: Subjects			
received infections	12	12	
no infections	5	5	
age at disease onset Units: years			
median	36		
full range (min-max)	15 to 61	-	
Bell’s Functionality Score (Disability Scale Assessment)			
Bell score (max 100 points)			
Units: Bell score			
median	30		
full range (min-max)	20 to 50	-	

End points

End points reporting groups

Reporting group title	ME/CFS patients
Reporting group description: -	
Subject analysis set title	Completers
Subject analysis set type	Per protocol
Subject analysis set description:	
A total of 12 patients received the scheduled 12-months treatment	

Primary: change of the Chalder fatigue scale

End point title	change of the Chalder fatigue scale[1]
End point description:	
Univariate comparison of two independent groups was performed using the Mann–Whitney-U test, comparison of two dependent groups was done using the Wilcoxon matched-pairs signed-rank test. A two-tailed p-value of <0.05 was considered statistically significant.	
End point type	Primary
End point timeframe:	
up to 12 months follow up	

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 was an investigator-initiated one arm trial

End point values	Completers			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Scale				
median (full range (min-max))				
pre	27.50 (21.00 to 31.00)			
3 Months	26.50 (19.00 to 33.00)			
6 months	22.50 (8.00 to 29.00)			
9 months	20.50 (14.00 to 28.00)			
12 months	23.00 (15.00 to 31.00)			

Statistical analyses

No statistical analyses for this end point

Primary: change of the SF-36

End point title	change of the SF-36[2]
End point description:	
Univariate comparison of two independent groups was performed using the Mann–Whitney-U test, comparison of two dependent groups was done using the Wilcoxon matched-pairs signed-rank test. A two-tailed p-value of <0.05 was considered statistically significant.	
End point type	Primary

End point timeframe:

up to 12 months fallow up

Notes:

[2] - 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 was an investigator-initiated one arm trial

End point values	Completers			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Scale				
median (full range (min-max))				
pre	20.00 (0.00 to 60.00)			
3 months	30.00 (0.00 to 50.00)			
6 months	45.00 (10.00 to 65.00)			
9 months	42.50 (10.00 to 85.00)			
12 months	42.50 (5.00 to 80.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: improvement of the autonomic dysfunction

End point title	improvement of the autonomic dysfunction

End point description:

All patients reported moderate to severe symptoms of autonomic dysfunction assessed by the COMPASS-31 questionnaire.
The COMPASS-31 is a questionnaire validated by the Mayo Clinic to assess and quantify symptoms of autonomic dysfunction. 6 categories of organ dysfunction will be assessed with a maximum of 100 being the most severe disturbance.

End point type	Secondary

End point timeframe:

15months

End point values	Completers			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Score				
median (full range (min-max))				
at baseline	50.9 (12.9 to 73.8)			
6 months	37.14 (6.99 to 60.06)			
9 months	36.05 (20.16 to 54.72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Assessment

End point title	Functional Assessment

End point description:

One Patient lost the tracker device.
All responding patients at month 12 (patients 2, 11, 13 and 16) and also patients 4 and 8 with a response at
month 6 and 9 walked more steps during IgG treatment. The number of steps in the five non-responder patients (patients 5, 6, 7, 10, 17) did not
increase. There was no seasonal variation in numbers of steps. (See attachment)

End point type	Secondary

End point timeframe:

15 months

End point values	Completers			
Subject group type	Subject analysis set			
Number of subjects analysed	6[3]			
Units: steps per day				
median (full range (min-max))				
pretreatment	4565 (1062 to 7756)			
at 6 months	6067 (3017 to 10411)			

Notes:

[3] - Values only from the responders

Statistical analyses

No statistical analyses for this end point

Secondary: Effectiveness to control infections

End point title	Effectiveness to control infections

End point description:

End point type	Secondary

End point timeframe:

12 months before treatment and 12 mont during the treatment

End point values	Completers			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: Infections				
median (full range (min-max))				
Before During 12 months	6 (4 to 12) 3.5 (0 to 6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

15 months

Adverse event reporting additional description:

Patients are monitored for AE and SAE during IgG infusion as well as the periods between infusions. At home patients are requested to keep a diary where they document all infusions, complaints and problems. Side effects will be documented according to CTC criteria. Grade 1 and 2 are non SAEs and Grade 3 are SAE.

Assessment type	Non-systematic

Dictionary used

Dictionary name	own
Dictionary version	1

Reporting groups

Reporting group title	treatment completed
Reporting group description: -	
Reporting group title	treatment not completed

Reporting group description: -

Serious adverse events	treatment completed	treatment not completed	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 5 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	treatment completed	treatment not completed	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	5 / 5 (100.00%)	
Injury, poisoning and procedural complications			
injection site reaction			
subjects affected / exposed	12 / 12 (100.00%)	5 / 5 (100.00%)	
occurrences (all)	12	5	
General disorders and administration site conditions			
headache			

subjects affected / exposed	5 / 12 (41.67%)	5 / 5 (100.00%)	
occurrences (all)	5	5	
Blood and lymphatic system disorders			
liver toxicity (ALT/GPT increase)			
subjects affected / exposed	3 / 12 (25.00%)	1 / 5 (20.00%)	
occurrences (all)	3	1	
Gastrointestinal disorders			
abdominal pain			
subjects affected / exposed	1 / 12 (8.33%)	4 / 5 (80.00%)	
occurrences (all)	1	4	
diarrhea			
subjects affected / exposed	2 / 12 (16.67%)	2 / 5 (40.00%)	
occurrences (all)	2	2	
Infections and infestations			
flu-like symptoms			
subjects affected / exposed	12 / 12 (100.00%)	3 / 5 (60.00%)	
occurrences (all)	12	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

Taken together, our study has several limitations, including a small patient number and a lack of a control arm.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34072494