



Clinical trial results:

A Randomized, Single-blinded, Cross-over Study investigating the Non-inferiority of Efficacy and Safety of HyQvia in comparison with Conventional Subcutaneous Ig Therapy in Multifocal Motor Neuropathy

Summary

EudraCT number	2015-003453-18
Trial protocol	DK
Global end of trial date	03 May 2018

Results information

Result version number	v1 (current)
This version publication date	18 December 2020
First version publication date	18 December 2020
Summary attachment (see zip file)	Abstract (HyQvia, Abstract, EudraCT.docx)

Trial information

Trial identification

Sponsor protocol code	RH-2015-200
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02556437
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet - Department of Neurology
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark,
Public contact	Ali Al-Zuhairy, Rigshospitalet - Department of Neurology, 0045 22981147, al_zuhairy@hotmail.com
Scientific contact	Ali Al-Zuhairy, Rigshospitalet - Department of Neurology, 0045 22981147, al_zuhairy@hotmail.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	03 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 May 2018
Global end of trial reached?	Yes
Global end of trial date	03 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of immunoglobulin administered together with hyaluronidase (HyQvia) in large doses subcutaneously compared to conventional treatment with subcutaneous immunoglobulin (Subcuvia) in patients with MMN

Protection of trial subjects:

This study was conducted in accordance with the recommendations of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice and was monitored by the the local GCP units throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2015
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	Denmark: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was conducted at all three departments in Denmark responsible for the treatment of multifocal motor neuropathy, the Department of Neurology, Aarhus University Hospital, the Department of Neurology, Odense University Hospital and Department of Neurology, Rigshospitalet, Copenhagen University Hospital.

Pre-assignment

Screening details:

Thirty-eight patients with MMN were screened. Eleven did not meet inclusion criteria and 7 declined to participate. Twenty were included.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind ^[1]
Roles blinded	Data analyst, Assessor ^[2]

Arms

Arm title	Baseline
Arm description: -	
Arm type	Pre-study conventional SCIG
Investigational medicinal product name	Pre-study conventional subcutaneous immune globuline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients receiving their regular conventional subcutaneous immune globuline at a stable dose for at least three months prior to inclusion.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: The same blinded person assessed the patients during study and upon study completion was unblinded and analyzed data.

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

Justification: The same blinded person assessed the patients during study and upon study completion was unblinded and analyzed data.

Number of subjects in period 1	Baseline
Started	20
Completed	20

Period 2

Period 2 title	First period of treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind ^[3]
Roles blinded	Data analyst, Assessor ^[4]

Blinding implementation details:

All patients throughout the study were examined by the same assessor, who was blinded during the entire study.

Arms

Are arms mutually exclusive?	Yes
Arm title	fSCIG --> cSCIG

Arm description:

Patients receiving facilitated subcutaneous immune globulin during the first 24 weeks of the study before crossing over

Arm type	Experimental
Investigational medicinal product name	facilitated subcutaneous immune globuline
Investigational medicinal product code	
Other name	HyQvia
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Recombinant human hyaluronidase was manually injected at a dose of 80 U/g IgG followed by infusion of a 10% solution of human normal immunoglobulin (HyQvia, Shire, Lexington, MA, USA) [3] using an electronic peristaltic pump (Mini Rythmic PN+ R, Micrel Medical Devices, Athens, Greece). The maximum volume infused at one site was 600 ml at a rate of 300 ml/h.

Arm title	cSCIG --> fSCIG
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Arm description:

Patients receiving conventional subcutaneous immune globulin for the first 24 weeks before crossing over

Arm type	Experimental
Investigational medicinal product name	conventional subcutaneous immune globuline
Investigational medicinal product code	
Other name	Subcuvia
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Conventional SCIG was infused at a concentration of 16% human normal immunoglobulin (Subcuvia, Shire) [5] at the abdomen or the thighs using one or two mechanical pumps (Freedom Pump, RMS Medical Products, Chester, NY, USA), one or two 60 ml syringes and a maximum of four subcutaneous lines per pump. The average infusion speed was 20 ml/h with a maximum infusion volume of 20 ml at each site.

Notes:

[3] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: The same blinded person assessed the patients during study and upon study completion was unblinded and analyzed data.

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

Justification: The same blinded person assessed the patients during study and upon study completion was unblinded and analyzed data.

Number of subjects in period 2	fSCIG --> cSCIG	cSCIG --> fSCIG
Started	10	10
Completed	9	10
Not completed	1	0
Adverse event, non-fatal	1	-

Period 3

Period 3 title	Second period of treatment, cross-over
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind ^[5]
Roles blinded	Data analyst, Assessor ^[6]

Arms

Are arms mutually exclusive?	Yes
Arm title	fSCIG --> cSCIG

Arm description:

Patients treated with facilitated subcutaneous immune globulin for the first 24 weeks of study cross-over to 24 weeks of treatment with conventional subcutaneous immune globulin

Arm type	Experimental
Investigational medicinal product name	conventional subcutaneous immune globuline
Investigational medicinal product code	
Other name	Subcuvia
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Please refer to previous description

Arm title	cSCIG --> fSCIG
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Arm description:

Patients treated with conventional subcutaneous immune globulin for the first 24 weeks of study cross-over to 24 weeks of treatment with facilitated subcutaneous immune globulin

Arm type	Experimental
Investigational medicinal product name	facilitated subcutaneous immune globuline
Investigational medicinal product code	
Other name	HyQvia
Pharmaceutical forms	Infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Please refer to previous description

Notes:

[5] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: The same blinded person assessed the patients during study and upon study completion was unblinded and analyzed data.

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

Justification: The same blinded person assessed the patients during study and upon study completion was unblinded and analyzed data.

Number of subjects in period 3	fSCIG --> cSCIG	cSCIG --> fSCIG
Started	9	10
Completed	9	10

Baseline characteristics

Reporting groups

Reporting group title	Baseline period
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Reporting group description: -

Reporting group values	Baseline period	Total	
Number of subjects	20	20	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	54		
inter-quartile range (Q1-Q3)	46.5 to 62.5	-	
Gender categorical			
Units: Subjects			
Female	10	10	
Male	10	10	

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description: -	
Reporting group title	fSCIG --> cSCIG
Reporting group description: Patients receiving facilitated subcutaneous immune globulin during the first 24 weeks of the study before crossing over	
Reporting group title	cSCIG --> fSCIG
Reporting group description: Patients receiving conventional subcutaneous immune globulin for the first 24 weeks before crossing over	
Reporting group title	fSCIG --> cSCIG
Reporting group description: Patients treated with facilitated subcutaneous immune globulin for the first 24 weeks of study cross-over to 24 weeks of treatment with conventional subcutaneous immune globulin	
Reporting group title	cSCIG --> fSCIG
Reporting group description: Patients treated with conventional subcutaneous immune globulin for the first 24 weeks of study cross-over to 24 weeks of treatment with facilitated subcutaneous immune globulin	
Subject analysis set title	fSCIG
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All patients following 24 weeks of treatment with facilitated subcutaneous immune globuline	
Subject analysis set title	cSCIG
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All patients following 24 weeks of treatment with conventional subcutaneous immune globuline	

Primary: Normalized isometric strength

End point title	Normalized isometric strength
End point description:	
End point type	Primary
End point timeframe: 24 weeks	

End point values	fSCIG	cSCIG		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: Percentage				
arithmetic mean (confidence interval 95%)	100.8 (94.5 to 107.1)	105.9 (99.8 to 112.0)		

Statistical analyses

Statistical analysis title	Non-inferiority test with a 15% margin
Comparison groups	fSCIG v cSCIG
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.0014
Method	t-test, 1-sided

Notes:

[1] - Since this is a paried design, the values of 19 patients following each therapy were compared.

Secondary: Medical Research Council (MRC)

End point title	Medical Research Council (MRC)
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	fSCIG	cSCIG		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: au				
median (inter-quartile range (Q1-Q3))	88.0 (86.0 to 89.0)	87.0 (84.0 to 89.0)		

Statistical analyses

Statistical analysis title	Non-inferiority test with a 15% margin
Comparison groups	fSCIG v cSCIG
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
P-value	< 0.0001
Method	t-test, 1-sided

Notes:

[2] - Since this is a paried design, the values of 19 patients following each therapy were compared.

Secondary: Overall Disability Sum Score (ODSS)

End point title	Overall Disability Sum Score (ODSS)
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	fSCIG	cSCIG		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: au				
median (inter-quartile range (Q1-Q3))	2.0 (2.0 to 4.0)	2.0 (2.0 to 4.0)		

Statistical analyses

Statistical analysis title	Non-inferiority test with a 15% margin
Comparison groups	fSCIG v cSCIG
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
P-value	= 0.0007
Method	t-test, 1-sided

Notes:

[3] - Since this is a paried design, the values of 19 patients following each therapy were compared.

Secondary: 9-Hole Peg Test (9-HPT)

End point title	9-Hole Peg Test (9-HPT)
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	fSCIG	cSCIG		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: second				
median (inter-quartile range (Q1-Q3))	25.4 (18.4 to 28.5)	24.8 (18.1 to 28.4)		

Statistical analyses

Statistical analysis title	Non-inferiority test with a 15% margin
Comparison groups	fSCIG v cSCIG

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[4]
P-value	= 0.0085
Method	t-test, 1-sided

Notes:

[4] - Since this is a paired design, the values of 19 patients following each therapy were compared.

Secondary: Grip strength

End point title	Grip strength
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	fSCIG	cSCIG		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: kgf				
arithmetic mean (confidence interval 95%)	23.7 (17.1 to 30.3)	22.6 (16.8 to 28.5)		

Statistical analyses

Statistical analysis title	Non-inferiority test with a 15% margin
Comparison groups	fSCIG v cSCIG
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[5]
P-value	< 0.0001
Method	t-test, 1-sided

Notes:

[5] - Since this is a paired design, the values of 19 patients following each therapy were compared.

Secondary: Sixt Spot Step Test

End point title	Sixt Spot Step Test
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	fSCIG	cSCIG		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: second				
arithmetic mean (confidence interval 95%)	6.5 (5.4 to 7.6)	6.7 (5.6 to 7.7)		

Statistical analyses

Statistical analysis title	Non-inferiority test with a 15% margin
Comparison groups	fSCIG v cSCIG
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[6]
P-value	< 0.0001
Method	t-test, 1-sided

Notes:

[6] - Since this is a paried design, the values of 19 patients following each therapy were compared.

Secondary: EQ-5D-5L Index value

End point title	EQ-5D-5L Index value
End point description:	

End point type	Secondary
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End point timeframe:

24 weeks

End point values	fSCIG	cSCIG		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: au				
arithmetic mean (confidence interval 95%)	0.84 (0.78 to 0.91)	0.81 (0.76 to 0.86)		

Statistical analyses

Statistical analysis title	Non-inferiority test with a 15% margin
Comparison groups	fSCIG v cSCIG

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[7]
P-value	< 0.0001
Method	t-test, 1-sided

Notes:

[7] - Since this is a paired design, the values of 19 patients following each therapy were compared.

Secondary: EQ-5D-5L VAS

End point title	EQ-5D-5L VAS
End point description:	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	fSCIG	cSCIG		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: percent				
median (inter-quartile range (Q1-Q3))	82.0 (65.0 to 95.0)	85.0 (80.0 to 95.0)		

Statistical analyses

Statistical analysis title	Non-inferiority test with a 15% margin
Comparison groups	fSCIG v cSCIG
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[8]
P-value	= 0.0001
Method	t-test, 1-sided

Notes:

[8] - Since this is a paired design, the values of 19 patients following each therapy were compared.

Secondary: Headache or nausea

End point title	Headache or nausea
End point description:	
Number of patients experiencing headache or nausea at least once during the 24 weeks of therapy	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	fSCIG	cSCIG		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: At least once	7	7		

Statistical analyses

Statistical analysis title	McNemar's test
Statistical analysis description: Only 16 subjects logged specifically every infusion and whether any systemic adverse event occurred or not. Since this is a paired design, only 16 subjects were compared.	
Comparison groups	fSCIG v cSCIG
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	McNemar

Secondary: Percentage of infusions causing local side-effects

End point title	Percentage of infusions causing local side-effects
End point description:	
End point type	Secondary
End point timeframe: 24 weeks	

End point values	fSCIG	cSCIG		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	14		
Units: percent				
median (inter-quartile range (Q1-Q3))	62.6 (23.1 to 100.0)	9.4 (0.0 to 21.7)		

Statistical analyses

Statistical analysis title	Wilcoxon Signed Rank Test
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Statistical analysis description:

Only 14 patients had systematically logged all their infusions during both treatment periods with respect

to any side-effects. Since this is a paired design, the values of the 14 patients following each therapy were compared.

Comparison groups	fSCIG v cSCIG
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Wilcoxon Signed Rank Test

Secondary: Total infusions associated with local side-effects during the 24 weeks of each treatment

End point title	Total infusions associated with local side-effects during the 24 weeks of each treatment
End point description:	Total infusions associated with local side-effects during the 24 weeks period of each treatment
End point type	Secondary
End point timeframe:	24 weeks

End point values	fSCIG	cSCIG		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	14		
Units: Infusions				
median (inter-quartile range (Q1-Q3))	6.0 (3.0 to 13.0)	2.5 (0.0 to 6.0)		

Statistical analyses

Statistical analysis title	Wilcoxon Signed Rank Test
Statistical analysis description:	Only 14 patients had systematically logged all their infusions during both treatment periods with respect to any side-effects. Since this is a paired design, the values of the 14 patients following each therapy were compared.
Comparison groups	fSCIG v cSCIG
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon Signed Rank Test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 weeks

Adverse event reporting additional description:

Interviews every 6 weeks + patient logs

Assessment type	Systematic
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Dictionary used

Dictionary name	SNOMED CT
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Dictionary version	20200930
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Reporting groups

Reporting group title	fSCIG
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Reporting group description: -

Reporting group title	cSCIG
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Reporting group description: -

Serious adverse events	fSCIG	cSCIG	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	fSCIG	cSCIG	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)	10 / 19 (52.63%)	
General disorders and administration site conditions			
Systemic and local side-effects			
subjects affected / exposed	16 / 20 (80.00%)	10 / 19 (52.63%)	
occurrences (all)	16	10	

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

None reported