Clinical trial results:
Fatigue in Sarcoidosis - A feasibility study investigating the treatment of fatigue in stable sarcoidosis patients using methylphenidate

Summary

EudraCT number	2016-000342-60
Trial protocol	GB
Global end of trial date	09 July 2018

Results information

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

Trial information

Trial identification

Sponsor protocol code	190280

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02643732
WHO universal trial number (UTN)	U1111-1180-0191

Notes:

Sponsors

Sponsor organisation name	Norfolk and Norwich University Hospital
Sponsor organisation address	Colney Lane, Norwich, United Kingdom, NR4 7UY
Public contact	Lisa Chalkley, Norfolk and Norwich University Hospital NHS Foundation Trust, +44 01603286611, lisa.chalkley@nnuh.nhs.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	10 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2018
Global end of trial reached?	Yes
Global end of trial date	09 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives for this trial is to determine whether it is feasible to perform a suitably large randomised controlled trial investigating whether methylphenidate is a clinically effective treatment for fatigue in sarcoidosis, and how best to design this trial to successfully answer this question.

As a result, the main research questions are:
(1) What is the recruitment rate of participants/how quickly can we recruit people into the trial? (How many studies might need to be involved in a future trial?)
(2) How many patients with sarcoidosis are excluded from the study and for what reason? (as above)
(3) How many people who are included in the study manage to complete the study? (How many participants extra do we need to ensure statistical power is maintained allowing for drop-outs)
(4) Why are potential participants excluded from the study, and why do participants withdraw/drop-out of the study? (as above, as well as generalisability of the results – is the population i

Protection of trial subjects:

Monitoring of all high risks during the trial - blood pressure, liver function, ECG. These were done at all visits through the trial where participants were potentially receiving the IMP (weeks 2,4,6,12,18 and 24).

Background therapy:

None

Evidence for comparator:

Comparator is placebo - identical gel caps containing lactose powder only (compared with gel caps including the active methylphenidate pill, then packed with lactose powder.

Actual start date of recruitment	25 April 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: 22
Worldwide total number of subjects	22
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	18
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from the Norfolk and Norwich University Hospital (Norwich, Norfolk, UK) with patients referred from other centres for consideration of trial inclusion. Recruitment was open between 07/11/2016 and 02/03/2018.

Pre-assignment

Screening details:

Participants were screened via medical notes (all patients with sarcoidosis under the care of the Norfolk and Norwich University Hospital against eligibility criteria; A proven diagnosis of sarcoidosis, stable disease, able to give informed consent and a Fatigue Assessment Scale score >21 points.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Placebo and active treatments appeared identical. Trial pharmacists at NNUH were aware of the treatment group due to unequal arm size; they did not disclose the group allocation and medication labels did not reference the allocated group; this data was contained on a tear-off strip which was removed prior to dispensing to the study team. During study monitoring and auditing, pharmacy monitoring was performed by a member of staff from Norwich CRTU to maintain blinding of the study team.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active treatment

Arm description:

Methylphenidate, up to 20mg BD

Arm type	Experimental
Investigational medicinal product name	Methylphenidate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft + tablet
Routes of administration	Oral use

Dosage and administration details:

10mg BD for 2 weeks then increased to 20mg BD to the end of the trial. Participants could opt-out of the up titration if they felt they had adequate benefit at the lower dose. Down-titration to the lower dose could occur if certain side effects occurred; following this, it was not possible to uptitrate back to the higher dose.

Arm title	Placebo

Arm description:

Placebo medication - identical capsule to the active treatment arm

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Identical placebo to active treatment (methylphenidate) - this was a soft capsule containing lactose

powder.
Started at 1 tablet BD, increased to 2 tablets BD after 2 weeks if no side effects had occurred.
Participants could opt out of the dose increase if adequate clinical improvement had already occurred.
Down-titration from the higher dose could occur if side effects became apparent on the higher dose; once this occurred it was not possible to uptitrate back up to the higher dose.

Number of subjects in period 1	Active treatment	Placebo
Started	15	7
Completed	15	7

Baseline characteristics

Reporting groups	
Reporting group title	Active treatment
Reporting group description:	
Methylphenidate, up to 20mg BD	
Reporting group title	Placebo
Reporting group description:	
Placebo medication - identical capsule to the active treatment arm	

Reporting group values	Active treatment	Placebo	Total
Number of subjects	15	7	22
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			
Age			
Units: years			
arithmetic mean	55.5	55.4	
standard deviation	± 10.1	± 7.7	-
Gender categorical			
Sex			
Units: Subjects			
Female	5	4	9
Male	10	3	13
Smoking status			
Smoking status			
Units: Subjects			
Current	0	0	0
Ex	4	3	7
Never	11	4	15
Disease duration			
Length of diagnosis of sarcoidosis			
Units: Subjects			
>3 years	9	4	13
1-3 years	2	2	4
<1 year	4	1	5
Ethnicity			
Units: Subjects			

Caucasian	15	7	22
Current treatment			
Current immunosuppressive treatment for sarcoidosis			
Units: Subjects			
Prednisolone	3	1	4
Methotrexate	1	2	3
Azathioprine	0	1	1
No current treatment	11	3	14
Pulmonary disease present			
Number of patients with pulmonary disease present			
Units: Subjects			
Yes	15	7	22
No	0	0	0
Extra-pulmonary disease present			
Number of patients with extra-pulmonary disease present			
Units: Subjects			
Yes	9	3	12
No	6	4	10
Fatigue assessment scale (stratified)			
Severity of fatigue by FAS score			
Units: Subjects			
Fatigued (Score 22-34)	7	3	10
Severe (35-50)	8	4	12
BMI			
Body mass index			
Units: kg/m^2			
arithmetic mean	30.3	33.8	
standard deviation	± 4.5	± 7.6	-
Weight			
Weight			
Units: kg			
arithmetic mean	94.0	94.0	
standard deviation	± 16.8	± 21.3	-
BP - systolic			
Systolic blood pressure			
Units: mmHg			
arithmetic mean	145.4	135.6	
standard deviation	± 16.3	± 24.7	-
BP - diastolic			
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	88.7	85.9	
standard deviation	± 10.7	± 9.7	-
Pulse			
Units: bpm			
arithmetic mean	73.5	75.9	
standard deviation	± 16.4	± 9.8	-
Pack-year smoking history			
Number of pack-years smoking history			
Units: pack-years			
arithmetic mean	17.5	6.7	

standard deviation	± 14.2	± 4.9	-
Alcohol intake			
Units of alcohol per week intake			
Units: units per week			
arithmetic mean	5.3	4.7	
standard deviation	± 7.6	± 10.3	-
Baseline FAS score			
Fatigue (FAS score)			
Units: points			
arithmetic mean	35.9	35.9	
standard deviation	± 7.7	± 8.8	-
Fatigue (FACIT-Fatigue Score)			
Fatigue (scored by FACIT-Fatigue)			
Units: units			
arithmetic mean	19.9	20.0	
standard deviation	± 11.0	± 10.8	-
Anxiety score			
HADS-A			
Units: points			
arithmetic mean	7.8	8.0	
standard deviation	± 3.3	± 4.9	-
Depression			
HADS-D			
Units: points			
arithmetic mean	7.9	6.6	
standard deviation	± 2.9	± 4.5	-
Health Utility (EQ5D)			
Health utility score by EQ5D utility score			
Units: units			
arithmetic mean	0.694	0.679	
standard deviation	± 0.271	± 0.244	-
EQ-VAS			
VAS score from EQ5D utility			
Units: mm			
arithmetic mean	62.5	68.0	
standard deviation	± 21.9	± 12.9	-
Health Utility (SF6D)			
Health utility scored by SF6D			
Units: units			
arithmetic mean	0.613	0.559	
standard deviation	± 0.094	± 0.164	-
KSQ General health status			
Kings Sarcoid questionnaire general health status			
Units: points			
arithmetic mean	48.8	47.1	
standard deviation	± 12.8	± 11.8	-
KSQ Lung			
Kings sarcoidosis questionnaire lung symptoms			
Units: points			
arithmetic mean	58.8	43.7	
standard deviation	± 16.5	± 15.8	-
KSQ Medications			

Kings sarcoidosis questionnaire medication related symptoms			
Units: points			
arithmetic mean	86.0	85.6	
standard deviation	± 20.3	± 23.2	-
KSQ Skin			
Kings sarcoidosis questionnaire skin symptoms			
Units: points			
arithmetic mean	86.0	87.5	
standard deviation	± 21.4	± 17.3	-
KSQ Eyes			
Kings sarcoidosis questionnaire eye symptoms			
Units: points			
arithmetic mean	66.7	62.6	
standard deviation	± 21.5	± 22.5	-
KSQ Composite			
Kings sarcoidosis questionnaire overall score			
Units: points			
arithmetic mean	54.2	50.0	
standard deviation	± 7.7	± 6.7	-
PSQI			
Pittsburgh sleep questionnaire inventory score			
Units: points			
arithmetic mean	8.9	13.5	
standard deviation	± 4.1	± 3.4	-
Sleep efficiency			
Overall sleep efficiency (% of night asleep)			
Units: percentage points			
arithmetic mean	86.9	55.4	
standard deviation	± 27.7	± 15.9	-
FEV1			
Forced expiratory volume in 1 seconds (percentage predicted)			
Units: percentage points			
arithmetic mean	99.5	79.1	
standard deviation	± 24.1	± 19.0	-
FVC % predicted			
Forced vital capacity (percentage predicted)			
Units: percentage points			
arithmetic mean	104.3	88.6	
standard deviation	± 21.7	± 18.4	-
MSWT			
Modified shuttle walk test distance			
Units: metres			
arithmetic mean	522.7	438.6	
standard deviation	± 330.9	± 353.6	-
Sedentary time			
Sedentary time per day			
Units: Minutes			
arithmetic mean	644.4	602.5	
standard deviation	± 152.8	± 118.7	-
MVPA			
Moderate and vigorous physical activity per day			
Units: Minutes			

arithmetic mean	105.7	87.4	
standard deviation	± 68.3	± 43.9	-
MVPA-10			
Moderate and vigorous activity per day (10 minute block time)			
Units: minutes			
arithmetic mean	19.0	4.6	
standard deviation	± 25.4	± 5.0	-

End points

End points reporting groups

Reporting group title	Active treatment
Reporting group description: Methylphenidate, up to 20mg BD	
Reporting group title	Placebo
Reporting group description: Placebo medication - identical capsule to the active treatment arm	

Primary: Medication adherence

End point title	Medication adherence[1]
End point description: Percentage of doses taken using pill counts at each visit to determine the number of doses that should have been taken, the number of pills expected to remain and the actual remaining pills. No participant took more than their expected number of doses. The overall count across the entire study period is reported.	
End point type	Primary
End point timeframe: 24 weeks total, though those recruited after December 2017 had a reduced follow-up period. (18 weeks if recruited between December and February 2018, 12 weeks if recruited after February 2018).	

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: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Percentage of doses taken				
median (inter-quartile range (Q1-Q3))	98 (90 to 100)	99 (97 to 100)		

Statistical analyses

No statistical analyses for this end point

Primary: Questionnaire missing data

End point title	Questionnaire missing data[2][3]
End point description: A total of 1142 data points across 12 questionnaires. Data is for BOTH arms, not just active treatment arm. As this was a measure of feasibility it was not split by arm.	
End point type	Primary
End point timeframe: 8 visits across 30 weeks	

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: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.
[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.

End point values	Active treatment			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Missing data	15			

Statistical analyses

No statistical analyses for this end point

Primary: Adverse event rate

End point title	Adverse event rate[4]

End point description:

Number of adverse events in any organ system reported during the 30 week trial.

End point type	Primary

End point timeframe:

30 weeks

Notes:

[4] - 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: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: Adverse events	14	7		

Statistical analyses

No statistical analyses for this end point

Primary: Activity monitor wear periods

End point title	Activity monitor wear periods[5][6]

End point description:

Feasibility end-point; number of wear periods for the accelerometer activity devices and number of devices with valid data. ASA. FEASIBILITY END-POINT THE DATA IS REPORTED FOR BOTH ARMS AND

WAS NOT SPLIT.

End point type	Primary

End point timeframe:

24 weeks - three wear periods per individual (fewer for individuals randomised from December 2017 onwards).

Notes:

[5] - 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: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.
[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.

End point values	Active treatment			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Number of wear periods				
Devices returned	59			
Any data on device	55			
Minimum valid data	54			
Complete 24h wear periods	49			

Statistical analyses

No statistical analyses for this end point

Primary: Exit Questionnaire - Wished to continue study drug at end of trial

End point title	Exit Questionnaire - Wished to continue study drug at end of trial[7]

End point description:

Participants were asked their perception of study enrolment

End point type	Primary

End point timeframe:

Week 24 - Exit questionnaire

Notes:

[7] - 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: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	7		
Units: Individuals	11	5		

Statistical analyses

No statistical analyses for this end point

Primary: Exit questionnaire - was participation in the study useful?

End point title	Exit questionnaire - was participation in the study useful?[8]

End point description:

End point type	Primary

End point timeframe:

Week 24 - Exit questionnaire

Notes:

[8] - 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: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	7		
Units: Individuals	12	7		

Statistical analyses

No statistical analyses for this end point

Primary: Exit questionnaire - Given the chance again would you participate in the study?

End point title	Exit questionnaire - Given the chance again would you participate in the study?[9]

End point description:

Number of participants who would take part in the trial again if given the chance again

End point type	Primary

End point timeframe:

Week 24 - Exit questionnaire

Notes:

[9] - 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: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	7		
Units: Individuals	12	7		

Statistical analyses

No statistical analyses for this end point

Primary: Exit Questionnaire - Would you recommend future trials including methylphenidate?

End point title	Exit Questionnaire - Would you recommend future trials including methylphenidate?[10]

End point description:

Number of participants who would recommend future trials investigating methylphenidate

End point type	Primary

End point timeframe:

Week 24 - Exit questionnaire

Notes:

[10] - 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: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	7		
Units: Individuals	12	7		

Statistical analyses

No statistical analyses for this end point

Primary: Participants correctly predicting allocation (exit questionnaire)

End point title	Participants correctly predicting allocation (exit

End point description:

Participants were asked to predict their allocation at the end of the trial

End point type	Primary

End point timeframe:

Week 24 - Exit questionnaire

Notes:

[11] - 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: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Individual	14	4		

Statistical analyses

No statistical analyses for this end point

Primary: Investigator correctly predicting allocation at end of trial

End point title	Investigator correctly predicting allocation at end of trial[12]

End point description:

Number of participants where the investigator correctly predicted the allocation of the participant whilst still blinded.

End point type	Primary

End point timeframe:

Week 24 - Exit questionnaire

Notes:

[12] - 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: The primary outcomes are feasibility outcomes and therefore do not relate to active vs placebo. It was pre-specified that no statistical analysis would take place on these primary feasibility outcomes and only exploratory statistical analysis would occur for the secondary clinical outcomes.

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Individuals	11	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Fatigue (FAS score) - 12 weeks

End point title	Fatigue (FAS score) - 12 weeks

End point description:

Change in FAS score

End point type	Secondary

End point timeframe:

Week 12

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: FAS score				
arithmetic mean (standard deviation)	29.1 (± 9.4)	27.1 (± 12.9)		

Statistical analyses

Statistical analysis title	Adjusted mean difference
Statistical analysis description:	
Mean difference between groups, adjusted for baseline scores	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority[13]
Parameter estimate	Mean difference (net)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	8.7
Variability estimate	Standard deviation

Notes:

[13] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Fatigue (FAS) - Week 24

End point title	Fatigue (FAS) - Week 24
End point description:	
FAS score at week 24	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: FAS score				
arithmetic mean (standard deviation)	28.2 (± 8.7)	22.0 (± 8.6)		

Statistical analyses

Statistical analysis title	Adjusted mean difference
Statistical analysis description:	
Mean difference between arms adjusted for baseline values	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[14]
Parameter estimate	Mean difference (net)
Point estimate	6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	13.7
Variability estimate	Standard deviation

Notes:

[14] - Mean difference between groups, adjusted for baseline scores
Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Fatigue (FAS) Week 30

End point title	Fatigue (FAS) Week 30
End point description:	
Final data, taken 6 weeks after completing medications	
End point type	Secondary
End point timeframe:	
Week 30 (6 weeks post completion of medications)	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: FAS score				
arithmetic mean (standard deviation)	32.7 (± 9.5)	27.6 (± 12.1)		

Statistical analyses

Statistical analysis title	Adjusted mean difference
Statistical analysis description:	
Mean difference 0 week 30 fatigue (FAS) score	
Comparison groups	Active treatment v Placebo

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence[15]
Parameter estimate	Mean difference (net)
Point estimate	7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	12.8
Variability estimate	Standard deviation

Notes:

[15] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: FACIT-Fatigue Week 12

End point title	FACIT-Fatigue Week 12
End point description:	
FACIT-Fatigue score	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: FACIT-Fatigue score				
arithmetic mean (standard deviation)	28.6 (± 13.1)	29.3 (± 17.6)		

Statistical analyses

Statistical analysis title	Mean difference (adjusted)
Statistical analysis description:	
Adjusted mean difference (for baseline FAS scores) between arms	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[16]
Parameter estimate	Mean difference (net)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	8.2

Variability estimate	Standard deviation

Notes:

[16] - Planned analysis at week 12 of difference between arms
1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group,
negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: FACIT-Fatigue Week 24

End point title	FACIT-Fatigue Week 24

End point description:

End point type	Secondary

End point timeframe:

Week 24 (Final data point whilst receiving medication)

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: FACIT-Fatigue score				
arithmetic mean (standard deviation)	29.0 (± 10.7)	39.2 (± 11.8)		

Statistical analyses

Statistical analysis title	Adjusted between-group mean difference

Statistical analysis description:

Between-group mean difference (adjusted for baseline fatigue FAS scores)

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[17]
Parameter estimate	Mean difference (net)
Point estimate	-9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	-0.6
Variability estimate	Standard deviation

Notes:

[17] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group,
negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: FACIT-Fatigue Week 30

End point title	FACIT-Fatigue Week 30

End point description:

FACIT-Fatigue score at week 30 (6 weeks after ceasing medications)

End point type	Secondary
End point timeframe:	
Week 30	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: FACIT-Fatigue score				
arithmetic mean (standard deviation)	23.9 (± 11.8)	28.3 (± 18.1)		

Statistical analyses

Statistical analysis title	Adjusted between-group difference
Statistical analysis description:	
Mean difference between arms at week 30; difference adjusted for baseline fatigue (FAS) score	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence[18]
Parameter estimate	Mean difference (net)
Point estimate	-6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	1
Variability estimate	Standard deviation

Notes:

[18] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Anxiety (HADS-A) Week 12

End point title	Anxiety (HADS-A) Week 12
End point description:	
HADS-A score	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Units (HADS-A)				
arithmetic mean (standard deviation)	6.8 (± 3.9)	4.3 (± 4.3)		

Statistical analyses

Statistical analysis title	Mean group difference (adjusted)
Statistical analysis description:	
Adjusted between-group difference (adjusted for baseline fatigue/FAS score)	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[19]
Parameter estimate	Mean difference (net)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	5
Variability estimate	Standard deviation

Notes:

[19] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Anxiety (HADS-A) Week 24

End point title	Anxiety (HADS-A) Week 24
End point description:	
HADS-A Anxiety level score	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: HADS-A score				
arithmetic mean (standard deviation)	5.6 (± 1.8)	2.2 (± 2.7)		

Statistical analyses

Statistical analysis title	Between-group analysis

Statistical analysis description:

Between-group difference adjusted for baseline fatigue (FAS) scores.

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[20]
Parameter estimate	Mean difference (net)
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	5.3
Variability estimate	Standard deviation

Notes:

[20] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Anxiety (HADS-A) Week 30

End point title	Anxiety (HADS-A) Week 30

End point description:

End point type	Secondary

End point timeframe:

Week 30 (6 weeks after completing medications)

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: HADS-A score				
arithmetic mean (standard deviation)	6.9 (± 3.7)	2.5 (± 2.5)		

Statistical analyses

Statistical analysis title	Adjusted between-group difference

Statistical analysis description:

Adjusted between-group difference (adjusted for baseline fatigue (FAS) score)

Comparison groups	Active treatment v Placebo

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence[21]
Parameter estimate	Mean difference (net)
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	6.5
Variability estimate	Standard deviation

Notes:

[21] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Depression (HADS-D) score week 12

End point title	Depression (HADS-D) score week 12
End point description:	
HADS-D (depression symptoms) score	
End point type	Secondary
End point timeframe:	
Week 12 - depression score	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: HADS-D score				
arithmetic mean (standard deviation)	6.9 (± 4.3)	7.6 (± 6.6)		

Statistical analyses

Statistical analysis title	Adjusted between-group mean difference
Statistical analysis description:	
Between-group difference adjusted for baseline fatigue score	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[22]
Parameter estimate	Mean difference (net)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	3.3

Variability estimate	Standard deviation

Notes:

[22] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Depression (HADS-D) Week 24

End point title	Depression (HADS-D) Week 24

End point description:

Depressive symptoms on HADS-D score

End point type	Secondary

End point timeframe:

Week 24 HADS-D score

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: HADS-D score				
arithmetic mean (standard deviation)	6.4 (± 2.5)	3.2 (± 5.0)		

Statistical analyses

Statistical analysis title	Adjusted between-group difference

Statistical analysis description:

Between-group difference adjusted for baseline fatigue score (by group)

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[23]
Parameter estimate	Mean difference (net)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	6.7
Variability estimate	Standard deviation

Notes:

[23] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Depression symptoms (HADS-D) week 30

End point title	Depression symptoms (HADS-D) week 30

End point description:

Depressive symptoms (measured by HADS-D) at week 30, 6 weeks after completing trial medications

End point type	Secondary
End point timeframe:	
Week 30	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: HADS-D score				
arithmetic mean (standard deviation)	8.1 (± 3.8)	3.8 (± 4.6)		

Statistical analyses

Statistical analysis title	Adjusted between-group difference
Statistical analysis description:	
Mean between-group difference adjusted for baseline fatigue score	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence[24]
Parameter estimate	Mean difference (net)
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	7.1
Variability estimate	Standard deviation

Notes:

[24] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-GHS Week 12

End point title	KSQ-GHS Week 12
End point description:	
Kings Sarcoidosis Questionnaire - General Health Status	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: points				
arithmetic mean (standard deviation)	55.8 (± 14.7)	64.0 (± 26.2)		

Statistical analyses

Statistical analysis title	Adjusted mean difference
Statistical analysis description:	
Between-group adjusted mean difference (adjusted for baseline fatigue severity)	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[25]
Parameter estimate	Mean difference (net)
Point estimate	-10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.7
upper limit	-6.2
Variability estimate	Standard deviation

Notes:

[25] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-GHS Week 24

End point title	KSQ-GHS Week 24
End point description:	
Kings Sarcoidosis Questionnaire - General health status questionnaire	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: points				
arithmetic mean (standard deviation)	59.0 (± 14.4)	71.2 (± 13.1)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Mean difference between groups adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[26]
Parameter estimate	Mean difference (net)
Point estimate	-14.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.7
upper limit	-6.2
Variability estimate	Standard deviation

Notes:

[26] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-GHS Week 30

End point title	KSQ-GHS Week 30
End point description:	
Kings Sarcoidosis Questionnaire General Health Score	
End point type	Secondary
End point timeframe:	
Week 30	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: points				
arithmetic mean (standard deviation)	53.9 (± 13.1)	57.1 (± 28.8)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue score	
Comparison groups	Active treatment v Placebo

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence[27]
Parameter estimate	Mean difference (net)
Point estimate	-8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.6
upper limit	3.1
Variability estimate	Standard deviation

Notes:

[27] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Lung Week 12

End point title	KSQ-Lung Week 12
End point description:	
Kings Sarcoidosis Questionnaire - Lung symptoms score	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: points				
arithmetic mean (standard deviation)	58.4 (± 18.0)	53.7 (± 30.5)		

Statistical analyses

Statistical analysis title	Adjusted between-group difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue score	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[28]
Parameter estimate	Mean difference (net)
Point estimate	-11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.7
upper limit	3.7

Variability estimate	Standard deviation

Notes:

[28] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Lung Week 24

End point title	KSQ-Lung Week 24

End point description:

Kings sarcoidosis questionnaire - lung symptoms

End point type	Secondary

End point timeframe:

Week 24

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Points				
arithmetic mean (standard deviation)	64.5 (± 20.8)	70.8 (± 15.9)		

Statistical analyses

Statistical analysis title	Adjusted between-group mean difference

Statistical analysis description:

Between-group mean difference

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[29]
Parameter estimate	Mean difference (net)
Point estimate	-16.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.7
upper limit	0.2
Variability estimate	Standard deviation

Notes:

[29] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Lung Week 30

End point title	KSQ-Lung Week 30

End point description:

Kings sarcoidosis questionnaire - lung symptoms week 30

End point type	Secondary

End point timeframe:

Week 30

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: points				
arithmetic mean (standard deviation)	64.0 (± 24.1)	61.8 (± 24.0)		

Statistical analyses

Statistical analysis title	Between-group mean difference
Statistical analysis description:	
Mean between-group difference adjusted for baseline fatigue score	
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence[30]
Parameter estimate	Mean difference (net)
Point estimate	-11.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.6
upper limit	7.8
Variability estimate	Standard deviation

Notes:

[30] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Skin Week 12

End point title	KSQ-Skin Week 12
End point description:	
Kings sarcoidosis questionnaire - skin symptoms	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: points				
arithmetic mean (standard deviation)	85.8 (± 17.1)	85.7 (± 17.2)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue score	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[31]
Parameter estimate	Mean difference (net)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.9
upper limit	16.9
Variability estimate	Standard deviation

Notes:

[31] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Skin Week 24

End point title	KSQ-Skin Week 24
End point description:	
Kings Sarcoidosis Questionnaire - skin symptoms	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: points				
arithmetic mean (standard deviation)	94.6 (± 9.3)	100.0 (± 0.0)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group adjusted mean difference (adjusted for baseline fatigue)	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[32]
Parameter estimate	Mean difference (net)
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.4
upper limit	3.7
Variability estimate	Standard deviation

Notes:

[32] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Skin Week 30

End point title	KSQ-Skin Week 30
End point description:	
Kings sarcoidosis questionnaire - skin symptoms	
End point type	Secondary
End point timeframe:	
Week 30 (6 weeks after completing medications)	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: points				
arithmetic mean (standard deviation)	90.3 (± 15.4)	81.8 (± 25.4)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue scores	
Comparison groups	Active treatment v Placebo

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence[33]
Parameter estimate	Mean difference (net)
Point estimate	7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	24.7
Variability estimate	Standard deviation

Notes:

[33] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Medications Week 12

End point title	KSQ-Medications Week 12
End point description:	
Kings sarcoidosis questionnaire - medications symptoms	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Points				
arithmetic mean (standard deviation)	88.5 (± 18.0)	77.3 (± 38.9)		

Statistical analyses

Statistical analysis title	Adjusted between-group mean difference
Statistical analysis description:	
Between-group mean difference, adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[34]
Parameter estimate	Mean difference (net)
Point estimate	11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.4
upper limit	32.7

Variability estimate	Standard deviation

Notes:

[34] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Medications Week 24

End point title	KSQ-Medications Week 24

End point description:

Kings sarcoidosis questionnaire - medication score

End point type	Secondary

End point timeframe:

Week 24

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: points				
arithmetic mean (standard deviation)	94.3 (± 9.2)	90.5 (± 10.5)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference

Statistical analysis description:

Between-group difference adjusted for baseline fatigue score

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[35]
Parameter estimate	Mean difference (net)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	15.1
Variability estimate	Standard deviation

Notes:

[35] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Medications Week 30

End point title	KSQ-Medications Week 30

End point description:

Kings sarcoidosis questionnaire - medication symptoms

End point type	Secondary

End point timeframe: Week 30

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: points				
arithmetic mean (standard deviation)	81.4 (± 27.0)	78.3 (± 36.9)		

Statistical analyses

Statistical analysis title	Between-group adjusted difference
Statistical analysis description: Between-group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[36]
Parameter estimate	Mean difference (net)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.8
upper limit	26
Variability estimate	Standard deviation

Notes:

[36] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Eye Week 12

End point title	KSQ-Eye Week 12
End point description: Kings sarcoidosis questionnaire - eye symptoms	
End point type	Secondary
End point timeframe: Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Points				
arithmetic mean (standard deviation)	67.0 (± 13.5)	62.1 (± 33.9)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[37]
Parameter estimate	Mean difference (net)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.4
upper limit	22.4
Variability estimate	Standard deviation

Notes:

[37] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Eye Week 24

End point title	KSQ-Eye Week 24
End point description:	
Kings sarcoidosis questionnaire - eye symptoms	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Points				
arithmetic mean (standard deviation)	68.4 (± 17.5)	73.3 (± 21.9)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[38]
Parameter estimate	Mean difference (net)
Point estimate	-6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.3
upper limit	16.7
Variability estimate	Standard deviation

Notes:

[38] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Eye Week 30

End point title	KSQ-Eye Week 30
End point description:	
Kings sarcoidosis questionnaire eye symptoms	
End point type	Secondary
End point timeframe:	
Week 30	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: Points				
arithmetic mean (standard deviation)	66.6 (± 14.7)	71.2 (± 23.3)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence[39]
Parameter estimate	Mean difference (net)
Point estimate	-6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.4
upper limit	5.6
Variability estimate	Standard deviation

Notes:

[39] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Composite score Week 12

End point title	KSQ-Composite score Week 12
End point description:	
Kings sarcoidosis questionnaire - Composite score	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Points				
arithmetic mean (standard deviation)	55.8 (± 8.6)	61.0 (± 21.0)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[40]
Parameter estimate	Mean difference (net)
Point estimate	-11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20
upper limit	-2.2

Variability estimate	Standard deviation

Notes:

[40] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Composite score Week 24

End point title	KSQ-Composite score Week 24

End point description:

Kings sarcoidosis questionnaire composite output

End point type	Secondary

End point timeframe:

Week 24

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: points				
arithmetic mean (standard deviation)	59.5 (± 11.9)	66.3 (± 10.6)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference

Statistical analysis description:

Between group mean difference adjusted for baseline fatigue severity

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[41]
Parameter estimate	Mean difference (net)
Point estimate	-12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.6
upper limit	-4.2
Variability estimate	Standard deviation

Notes:

[41] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: KSQ-Composite score Week 30

End point title	KSQ-Composite score Week 30

End point description:

Kings sarcoidosis questionnaire composite outcome

End point type	Secondary

End point timeframe: Week 30

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: points				
arithmetic mean (standard deviation)	56.4 (± 10.5)	59.3 (± 19.1)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description: Between-group mean difference adjusted by baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence[42]
Parameter estimate	Mean difference (net)
Point estimate	-9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18
upper limit	-1.2
Variability estimate	Standard deviation

Notes:

[42] - Mean difference is equivalent to the methylphenidate group value minus the placebo group value. Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: EQ5D Utility Week 12

End point title	EQ5D Utility Week 12
End point description: EQ5D health utility score	
End point type	Secondary
End point timeframe: Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Points				
arithmetic mean (standard deviation)	0.733 (± 0.249)	0.725 (± 0.378)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[43]
Parameter estimate	Mean difference (net)
Point estimate	-0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.121
upper limit	0.111
Variability estimate	Standard deviation

Notes:

[43] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: EQ5D Utility Week 24

End point title	EQ5D Utility Week 24
End point description:	
EQ5D-derived health utility value	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: points				
arithmetic mean (standard deviation)	0.817 (± 0.133)	0.947 (± 0.066)		

Statistical analyses

Statistical analysis title	Between-group mean adjusted difference
Statistical analysis description:	
Between group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[44]
Parameter estimate	Mean difference (net)
Point estimate	-0.139
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.214
upper limit	-0.065
Variability estimate	Standard deviation

Notes:

[44] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: EQ5D Utility Week 30

End point title	EQ5D Utility Week 30
End point description:	
EQ5D-derived health utility value	
End point type	Secondary
End point timeframe:	
Week 30 (6 weeks after completing medications)	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Points				
arithmetic mean (standard deviation)	0.817 (± 0.133)	0.947 (± 0.061)		

Statistical analyses

Statistical analysis title	Between-group mean adjusted difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[45]
Parameter estimate	Mean difference (net)
Point estimate	-0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.209
upper limit	0.104
Variability estimate	Standard deviation

Notes:

[45] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: SF6D Health Utility Week 12

End point title	SF6D Health Utility Week 12
End point description:	
SF6D-derived health utility score	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Points				
arithmetic mean (standard deviation)	0.617 (± 0.120)	0.657 (± 0.204)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[46]
Parameter estimate	Mean difference (net)
Point estimate	-0.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.173
upper limit	-0.021
Variability estimate	Standard deviation

Notes:

[46] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: SF6D Health Utility Week 24

End point title	SF6D Health Utility Week 24
End point description:	
SF6D-derived health utility score	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Points				
arithmetic mean (standard deviation)	0.631 (± 0.085)	0.764 (± 0.153)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[47]
Parameter estimate	Mean difference (net)
Point estimate	-0.161

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.266
upper limit	-0.056
Variability estimate	Standard deviation

Notes:

[47] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: SF6D Health Utility Week 30

End point title	SF6D Health Utility Week 30

End point description:

SF6D-derived health utility value

End point type	Secondary

End point timeframe:

Week 30 (6 weeks after medication completion)

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: Points				
arithmetic mean (standard deviation)	0.597 (± 0.108)	0.677 (± 0.204)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference

Statistical analysis description:

Between-group mean difference adjusted for baseline fatigue severity

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence[48]
Parameter estimate	Mean difference (net)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.217
upper limit	-0.043
Variability estimate	Standard deviation

Notes:

[48] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group,

negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: EQ-VAS Health Utility Week 12	
End point title	EQ-VAS Health Utility Week 12
End point description: EQ-VAS derived health utility	
End point type	Secondary
End point timeframe: Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	7		
Units: Units				
arithmetic mean (standard deviation)	62.1 (± 19.9)	66.0 (± 21.4)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description: Between-group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	equivalence[49]
Parameter estimate	Mean difference (net)
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.9
upper limit	13.6
Variability estimate	Standard deviation

Notes:

[49] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: EQ-VAS Health Utility Week 24	
End point title	EQ-VAS Health Utility Week 24
End point description: EQ-VAS derived health utility score	
End point type	Secondary

End point timeframe:

Week 24

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Points				
arithmetic mean (standard deviation)	65.5 (± 24.4)	72.5 (± 22.9)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[50]
Parameter estimate	Mean difference (net)
Point estimate	-7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.4
upper limit	17.2
Variability estimate	Standard deviation

Notes:

[50] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: EQ-VAS Health Utility Week 30

End point title	EQ-VAS Health Utility Week 30
End point description:	
Health utility score derived from EQ-VAS questionnaire	
End point type	Secondary
End point timeframe:	
Week 30 (6 weeks after completing medications)	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: Units				
arithmetic mean (standard deviation)	64.3 (± 20.9)	57.6 (± 24.6)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence[51]
Parameter estimate	Mean difference (net)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	19.6
Variability estimate	Standard deviation

Notes:

[51] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Sleep Quality - PSQI score

End point title	Sleep Quality - PSQI score
End point description:	
Pittsburgh Sleep Quality Index Questionnaire sleep quality	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	4		
Units: Units				
arithmetic mean (standard deviation)	8.4 (± 4.0)	10.5 (± 6.5)		

Statistical analyses

Statistical analysis title	Between-group mean adjusted difference

Statistical analysis description:

Between group mean difference adjusted for baseline fatigue severity

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	equivalence[52]
Parameter estimate	Mean difference (net)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	11.9
Variability estimate	Standard deviation

Notes:

[52] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Sleep Quality - PSQI score (Week 24)

End point title	Sleep Quality - PSQI score (Week 24)

End point description:

Pittsburgh Sleep Quality Index questionnaire score

End point type	Secondary

End point timeframe:

Week 24

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: Units				
arithmetic mean (standard deviation)	9.8 (± 2.5)	10.8 (± 5.8)		

Statistical analyses

Statistical analysis title	Between-group mean adjusted difference

Statistical analysis description:

Between-group mean difference adjusted for baseline fatigue severity

Comparison groups	Active treatment v Placebo

Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	equivalence[53]
Parameter estimate	Mean difference (net)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.3
upper limit	25.1
Variability estimate	Standard deviation

Notes:

[53] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Sleep efficiency

End point title	Sleep efficiency

End point description:

Sleep efficiency, Higher values indicate better sleep efficiency (higher percentage of the time in bed spent asleep)

End point type	Secondary

End point timeframe:

Week 12

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	4		
Units: Percentage points				
arithmetic mean (standard deviation)	81.4 (± 15.4)	67.0 (± 18.8)		

Statistical analyses

Statistical analysis title	Between-group mean adjusted difference

Statistical analysis description:

Between group mean difference adjusted for baseline fatigue severity

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	equivalence[54]
Parameter estimate	Mean difference (net)
Point estimate	-12.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.3
upper limit	68
Variability estimate	Standard deviation

Notes:

[54] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Sleep efficiency - week 24

End point title	Sleep efficiency - week 24

End point description:

Sleep efficiency (time asleep as a percentage of time in bed)

End point type	Secondary

End point timeframe:

Week 24

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: Percentage points				
arithmetic mean (standard deviation)	76.5 (± 12.4)	65.6 (± 22.4)		

Statistical analyses

Statistical analysis title	Between group adjusted mean difference

Statistical analysis description:

Between group mean difference adjusted for baseline fatigue severity

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	equivalence[55]
Parameter estimate	Mean difference (net)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64.7
upper limit	68
Variability estimate	Standard deviation

Notes:

[55] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: FEV1 percentage predicted - week 12

End point title	FEV1 percentage predicted - week 12
End point description:	
Forced expiratory volume in 1 second percentage predicted value	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Percentage points				
arithmetic mean (standard deviation)	98.4 (± 14.6)	78.3 (± 20.7)		

Statistical analyses

Statistical analysis title	Adjusted mean difference
Statistical analysis description:	
Between group adjusted mean difference	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[56]
Parameter estimate	Mean difference (net)
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	18.6
Variability estimate	Standard deviation

Notes:

[56] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: FEV1 percentage predicted - week 24

End point title	FEV1 percentage predicted - week 24
End point description:	
Forced expiratory volume in 1 second percentage predicted value	
End point type	Secondary

End point timeframe:

Week 24

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Percentage points				
arithmetic mean (standard deviation)	94.5 (± 19.6)	80.0 (± 20.8)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between-group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[57]
Parameter estimate	Mean difference (net)
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	19.3
Variability estimate	Standard deviation

Notes:

[57] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Forced vital capacity percentage predicted - week 12

End point title	Forced vital capacity percentage predicted - week 12
End point description:	
Forced vital capacity percentage predicted value	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Percentage points				
arithmetic mean (standard deviation)	106.1 (± 13.0)	88.0 (± 20.8)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference
Statistical analysis description:	
Between group adjusted mean difference	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[58]
Parameter estimate	Mean difference (net)
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	23.3
Variability estimate	Standard deviation

Notes:

[58] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: MSWT Week 12

End point title	MSWT Week 12
End point description:	
Modified shuttle walk test distance (metres)	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: metres				
arithmetic mean (standard deviation)	658.0 (± 397.7)	515.0 (± 252.4)		

Statistical analyses

Statistical analysis title	Between group adjusted mean difference
Statistical analysis description:	
Between group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	equivalence[59]
Parameter estimate	Mean difference (net)
Point estimate	56.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-73.9
upper limit	186.6
Variability estimate	Standard deviation

Notes:

[59] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: MSWT Week 24

End point title	MSWT Week 24
End point description:	
Modified shuttle walk test distance (metres)	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: metres				
arithmetic mean (standard deviation)	624.3 (± 430.3)	432.5 (± 235.4)		

Statistical analyses

Statistical analysis title	Between group adjusted mean difference
Statistical analysis description:	
Between-group difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo

Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	equivalence[60]
Parameter estimate	Mean difference (net)
Point estimate	43.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-216.3
upper limit	304.1
Variability estimate	Standard deviation

Notes:

[60] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: MVPA minutes per day

End point title	MVPA minutes per day

End point description:

Time in moderate or vigorous physical activity per day

End point type	Secondary

End point timeframe:

Week 12

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: minutes				
arithmetic mean (standard deviation)	116.8 (± 76.6)	76.6 (± 47.7)		

Statistical analyses

Statistical analysis title	Between-group adjusted mean difference

Statistical analysis description:

Between group mean difference adjusted for baseline fatigue severity

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	equivalence[61]
Parameter estimate	Mean difference (net)
Point estimate	14.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.1
upper limit	58.6

Variability estimate	Standard deviation

Notes:

[61] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: MVPA minutes per day (week 24)

End point title	MVPA minutes per day (week 24)

End point description:

Time in moderate or vigorous activity per day (minutes)

End point type	Secondary

End point timeframe:

Week 24

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	6		
Units: Minutes				
arithmetic mean (standard deviation)	108.1 (± 62.9)	86.4 (± 48.7)		

Statistical analyses

Statistical analysis title	Between group adjusted mean difference

Statistical analysis description:

Between group mean difference adjusted for baseline fatigue severity

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence[62]
Parameter estimate	Mean difference (net)
Point estimate	24.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.8
upper limit	65.9
Variability estimate	Standard deviation

Notes:

[62] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: MVPA10 Week 12

End point title	MVPA10 Week 12

End point description:

Time in moderate or vigorous physical activity (10 minute bout criteria)

End point type	Secondary

End point timeframe:

Week 12

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: Minutes				
arithmetic mean (standard deviation)	19.4 (± 32.8)	3.8 (± 3.4)		

Statistical analyses

Statistical analysis title	Between group adjusted mean difference

Statistical analysis description:

Between group mean difference adjusted for baseline fatigue severity

Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	equivalence[63]
Parameter estimate	Mean difference (net)
Point estimate	-6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.2
upper limit	13.8
Variability estimate	Standard deviation

Notes:

[63] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: MVPA10 - Week 24

End point title	MVPA10 - Week 24

End point description:

Time in moderate or vigorous physical activity (ten minute bout criteria) in minutes per day.

End point type	Secondary

End point timeframe:

Week 24

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	6		
Units: Minutes				
arithmetic mean (standard deviation)	15.0 (± 20.3)	12.0 (± 15.4)		

Statistical analyses

Statistical analysis title	Between group adjusted mean difference
Statistical analysis description:	
Between group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence[64]
Parameter estimate	Mean difference (net)
Point estimate	-6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.2
upper limit	13.8
Variability estimate	Standard deviation

Notes:

[64] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: Sedentary time per day - week 12

End point title	Sedentary time per day - week 12
End point description:	
Time in sedentary behaviours per day	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: Minutes				
arithmetic mean (standard deviation)	565.9 (± 156.6)	700.2 (± 123.2)		

Statistical analyses

Statistical analysis title	Between group adjusted mean difference
Statistical analysis description:	
Between group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	equivalence[65]
Parameter estimate	Mean difference (net)
Point estimate	-167.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-320.9
upper limit	-13.8
Variability estimate	Standard deviation

Notes:

[65] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Secondary: sedentary time per day - week 24

End point title	sedentary time per day - week 24
End point description:	
Time spent in sedentary behaviours per day	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	6		
Units: Minutes				
arithmetic mean (standard deviation)	567.9 (± 96.7)	656.5 (± 126.1)		

Statistical analyses

Statistical analysis title	Between group adjusted mean difference
Statistical analysis description:	
Between group mean difference adjusted for baseline fatigue severity	
Comparison groups	Active treatment v Placebo

Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence[66]
Parameter estimate	Mean difference (net)
Point estimate	-139.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-341.4
upper limit	63
Variability estimate	Standard deviation

Notes:

[66] - 1Mean difference is equivalent to the methylphenidate group value minus the placebo group value.
Positive values indicate the methylphenidate group value was higher than the placebo group, negative values indicate the methylphenidate group value was lower than the placebo group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs assessed at week 1,2,3,4,5,6,8,10,12,14,16,18,20,22,24

Adverse event reporting additional description:

Weeks 2,4,6,12,18 and 24 were face-to-face visits with assessment of patients in person. This included blood tests, ECGs, physical observations.
Weeks 1,3,5,8,10,14,16,20 and 22 were telephone calls to record any AEs.
Participants could also contact the trial team if any problems occurred between visits.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Methylphenidate

Reporting group description:

Fifteen participants receiving methylphenidate

Reporting group title	Placebo

Reporting group description:

Seven participants receiving placebo

Serious adverse events	Methylphenidate	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Syncope	Additional description: Bradycardia with syncope thought to be unrelated to the medication (occurred after afternoon in the pub and then suddenly standing up), brief hospital admission meant that it was classified as an SAE.		
subjects affected / exposed	1 / 15 (6.67%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.1 %

Non-serious adverse events	Methylphenidate	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)	7 / 7 (100.00%)	
Vascular disorders			

Hypertension	Additional description: 1x grade 1 and 1x grade 2 AE in methylphenidate group		
subjects affected / exposed	2 / 15 (13.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Unknown	Additional description: Multiple non-specific disorders 2x grade 1, 2x grade 2 in methylphenidate 1x grade 1, 1x grade 2 in placebo		
subjects affected / exposed	4 / 15 (26.67%)	2 / 7 (28.57%)	
occurrences (all)	4	2	
Reproductive system and breast disorders			
Testicular pain	Additional description: 2x grade 1 AEs in methylphenidate group only		
subjects affected / exposed	2 / 15 (13.33%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertionalasia	Additional description: 9x grade 1 and 4x grade 2 AEs in methylphenidate group 6x grade 1 and 1x grade 2 AEs in placebo group		
subjects affected / exposed	13 / 15 (86.67%)	7 / 7 (100.00%)	
occurrences (all)	13	7	
Psychiatric disorders			
Mood altered	Additional description: 2x grade 1 and 3x grade 2 AE in methylphenidate group 2x grade 1 and 2x grade 2 AE in placebo group		
subjects affected / exposed	5 / 15 (33.33%)	4 / 7 (57.14%)	
occurrences (all)	5	4	
Investigations			
Liver function test abnormal	Additional description: One patient with deranged LFTs in methylphenidate group who had an intercurrent viral illness		
subjects affected / exposed	1 / 15 (6.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache	Additional description: 14x grade 1 AEs in methylphenidate group 1x grade 2 AE in methylphenidate group 3x grade AE in placebo group		
subjects affected / exposed	14 / 15 (93.33%)	3 / 7 (42.86%)	
occurrences (all)	15	3	
Ear and labyrinth disorders			
Dizziness	Additional description: Grade 1 severity only		
subjects affected / exposed	2 / 15 (13.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 15 (6.67%)	3 / 7 (42.86%)	
occurrences (all)	0	0	

Gastrointestinal disorders			
Diarrhoea	Additional description: Diarrhoea, also abdominal pains; reported AEs were reported by class in final results		
subjects affected / exposed	14 / 15 (93.33%)	1 / 7 (14.29%)	
occurrences (all)	15	1	
Skin and subcutaneous tissue disorders			
Rash	Additional description: 2x grade 1 and 2x grade 2 AEs in methylphenidate group 1x grade 2 AE in placebo group		
subjects affected / exposed	4 / 15 (26.67%)	1 / 7 (14.29%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
Muscle discomfort	Additional description: 3x grade 1 and 2x grade 2 AE in methylphenidate group 1x grade 2 AE in placebo group All AEs myopathy/muscle pain		
subjects affected / exposed	5 / 15 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	5	1	
Infections and infestations			
Respiratory tract infectionratory	Additional description: 1x grade 1 infection in methylphenidate group 1x grade 2 infection in placebo group		
subjects affected / exposed	1 / 15 (6.67%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Appetite disorderite	Additional description: 1x grade 1 AE in methylphenidate group only.		
subjects affected / exposed	1 / 15 (6.67%)	0 / 7 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2017	After four months of recruitment it became apparent that the recruitment rate was below that expected. In order to increase the recruitment period, two amendments were made. Firstly, the ability to recruit participants from PIC sites in the eastern region was added, with Royal Papworth Hospital and Addenbrooke's hospital operating in this capacity. Secondly, in order to increase the recruitment phase (and maximise the time participants could enter the study without reducing the overall study duration), follow-up for participants recruited between December 2017 and March 2018 was truncated. Participants randomised between 01/12/2017 and 01/02/2018 received study medication for 18 weeks, plus an additional two weeks if a down-titration period at the end of the study was required; participants randomised between 02/02/2018 and 02/03/2018 received study medication for 12 weeks, plus an additional two weeks if down-titration was required. The last date of follow-up was fixed at 06/07/2018. As part of this substantial amendment, two additional outcome measures were added. The PSQI and Exit questionnaires were administered to patients entering the study after 23/05/2017 according to the questionnaire schedule in table 1; participants who had already commenced the study were administered the additional questionnaires if they consented to completing these additional measurements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The individual AEs are archived and not immediately available, the overall data results are presented and entered here.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29208618

http://www.ncbi.nlm.nih.gov/pubmed/34020962