Clinical trial results:
Methylphenidate versus placebo for fatigue in advanced cancer (MePFAC)

Summary

EudraCT number	2017-001950-33
Trial protocol	GB
Global end of trial date	03 July 2023

Results information

Result version number	v1 (current)
This version publication date	16 July 2024
First version publication date	16 July 2024

Trial information

Trial identification

Sponsor protocol code	15/0592

Additional study identifiers

ISRCTN number	ISRCTN79478762
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Priment CTU, Marie Curie Palliative Care Research Department, UCL, priment@ucl.ac.uk
Scientific contact	Paddy Stone, Marie Curie Palliative Care Research Department, UCL, p.stone@ucl.ac.uk

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	04 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 July 2023
Global end of trial reached?	Yes
Global end of trial date	03 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

What is the clinical effectiveness of methylphenidate versus placebo for cancer-related fatigue in patients receiving palliative care?

Protection of trial subjects:

During the trial participants were treated in accordance with routine clinical care and under supervision of a consultatant in palliative medicine (Principal Investigators at each site). Participants were contacted on a weekly basis to elicit adverse effects. Non-serious adverse events were recorded weekly and assessed for severity. Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARS) were additionally assessed for causality and expectedness and were reported to the sponsor within 24 hours.

Background therapy:

Participants received usual care in both study arms in addition to the trial intervention

Evidence for comparator:

Methylphenidate is a psychostimulant drug that is widely used as part of the management of people with Attention Deficit Hyperactivity Disorder. It has also been evaluated as a potential treatment for cancer-related fatigue. Some trials and meta-analyses have suggested that this medication may also be effective for relief of cancer related fatigue, but the evidence is mixed with many trials showing no benefit. In the context of ongoing uncertainty about its role, this research was conducted in response to a commissioned call by the NIHR, and placebo was considered to be a suitable comparator.

Actual start date of recruitment	29 June 2018
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: 159
Worldwide total number of subjects	159
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	81
From 65 to 84 years	76
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Across 17 active sites (hopsices, hosptial and community palliative care teams), 162 participants were randomised (73 men; mean 65.8 [SD 10.3] years). The first patient was enrolled on 29th June 2018 and the last patient randomised on 27th April 2023. The last visit for the last patient was 3rd July 2023, which is when the trial ended.

Pre-assignment

Screening details:

297 patients were screened
54 did not meet the inclusion criteria
78 met an exclusion criterion
3 died before consent/randomisation

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

Identical appearance between methyphenidate and placebo

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

Methylphenidate arm

Arm type	Experimental
Investigational medicinal product name	Methylphenidate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Initially participants were prescribed 1 tablet twice daily (=methylphenidate 10mgs/day) or matching placebo. Participants were contacted every week and the dose of medication was adjusted (either up or down) over the course of the first six weeks of the study (dose titration phase), up to a maximum of 12 tablets/day (=60mgs/day). Thereafter, for the next two weeks (dose maintenance phase), the dose of medication was not increased any further (although it could be reduced in response to adverse effects). During the next week (dose tapering phase) the dose was reduced and then the medication was stopped completely for the last week of the trial.

Arm title	Placebo

Arm description:

Placebo tablets individually dose-titrated in same manner as in active arm

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

Dosage and administration details:

Initially participants were prescribed 1 tablet twice daily. Participants were contacted every week and

the dose of medication was adjusted (either up or down) over the course of the first six weeks of the study (dose titration phase), up to a maximum of 12 tablets/day. Thereafter, for the next two weeks (dose maintenance phase), the dose of medication was not increased any further (although it could be reduced in response to adverse effects). During the next week (dose tapering phase) the dose was reduced and then the medication was stopped completely for the last week of the trial.

Number of subjects in period 1	Intervention	Placebo
Started	82	77
Completed	82	77

Period 2	
Period 2 title	Week 6
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

Identical appearance to methylphenidate and placebo

Arms	
Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

Methylphenidate arm

Arm type	Experimental
Investigational medicinal product name	Methylphenidate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Initially participants were prescribed 1 tablet twice daily (=methylphenidate 10mgs/day) or matching placebo. Participants were contacted every week and the dose of medication was adjusted (either up or down) over the course of the first six weeks of the study (dose titration phase), up to a maximum of 12 tablets/day (=60mgs/day). Thereafter, for the next two weeks (dose maintenance phase), the dose of medication was not increased any further (although it could be reduced in response to adverse effects). During the next week (dose tapering phase) the dose was reduced and then the medication was stopped completely for the last week of the trial.

Arm title	Placebo

Arm description:

Placebo tablets individually dose-titrated in same manner as in active arm

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Initially participants were prescribed 1 tablet twice daily. Participants were contacted every week and the dose of medication was adjusted (either up or down) over the course of the first six weeks of the study (dose titration phase), up to a maximum of 12 tablets/day. Thereafter, for the next two weeks (dose maintenance phase), the dose of medication was not increased any further (although it could be reduced in response to adverse effects). During the next week (dose tapering phase) the dose was reduced and then the medication was stopped completely for the last week of the trial.

Number of subjects in period 2	Intervention	Placebo
Started	82	77
Completed	72	67
Not completed	10	10
Adverse event, serious fatal	2	-
Lost to follow-up	8	10

Baseline characteristics

Reporting groups	
Reporting group title	Intervention
Reporting group description:	
Methylphenidate arm	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets individually dose-titrated in same manner as in active arm	

Reporting group values	Intervention	Placebo	Total
Number of subjects	82	77	159
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	43	38	81
From 65-84 years	37	39	76
85 years and over	2	0	2
Age continuous			
Units: years			
arithmetic mean	64.7	62.6	
standard deviation	± 11.9	± 11.8	-
Gender categorical			
Units: Subjects			
Female	44	42	86
Male	38	35	73
FACIT-Fatigue score			
Units: FACIT-F fatigue score			
arithmetic mean	20	22	
standard deviation	± 9	± 10	-
EORTC QLQc15 - Pain score			
Units: EORTC QLQc15-Pain score			
arithmetic mean	52	53	
standard deviation	± 19	± 20	-
EORTC QLQc15 - Physical functioning			
Units: EORTC QLQc15-Physical functioning score			
arithmetic mean	50	50	
standard deviation	± 18	± 17	-
EORTC QLQc15 - Emotional Functioning			
Note that only 81/82 in methylphenidate group provided a baseline score			
Units: EORTC QLQc15-Emotional Functioning score			

arithmetic mean	44	42	
standard deviation	± 17	± 17	-
EORTC QLQc15 - Quality of life			
Units: EORTC-QLQc15 Quality of life score			
arithmetic mean	30	31	
standard deviation	± 13	± 14	-
EORTC QLQc15 - Nausea			
Units: EORTC QLQc15 - Nausea			
arithmetic mean	44	39	
standard deviation	± 22	± 22	-
EORTC QLQc15 - Anorexia			
Units: EORTC QLQc15 - anorexia			
arithmetic mean	52	52	
standard deviation	± 25	± 26	-
EORTC QLQc15 - Dyspnoea			
Units: EORTC QLQc15 - Dyspnoea			
arithmetic mean	52	53	
standard deviation	± 21	± 24	-
EORTC QLQc15 - Constipation			
Units: EORTC QLQc15 - Constipation			
arithmetic mean	47	41	
standard deviation	± 24	± 21	-
EORTC QLQc15 - Insomnia			
Units: EORTC QLQc15 - insomnia			
arithmetic mean	56	51	
standard deviation	± 25	± 27	-
Utility score			
Units: EQ-5D-5L			
arithmetic mean	0.62	0.65	
standard deviation	± 0.21	± 0.18	-
Depression score			
Hospital Anxiety and Depression Scale (HADS) - Depression (D) subscale score Note that baseline HADS-D score was only available for n=81 in the intervention group			
Units: HADS-D			
median	7	6	
inter-quartile range (Q1-Q3)	5 to 11	4 to 9	-
Anxiety score			
Hospital Anxiety and Depression Scale (HADS) - Anxiety (A) subscale scores			
Units: HADS-A			
median	6	4	
inter-quartile range (Q1-Q3)	3 to 9	2 to 9	-
EORTC QLQc15 - Fatigue			
This is a fatigue subscale of the EORTC QLQc15 and was used only as a secondary fatigue outcome measure in this study			
Units: EORTC QLQc15 - Fatigue			
arithmetic mean	74	72	
standard deviation	± 15	± 18	-

End points

End points reporting groups	
Reporting group title	Intervention
Reporting group description: Methylphenidate arm	
Reporting group title	Placebo
Reporting group description: Placebo tablets individually dose-titrated in same manner as in active arm	
Reporting group title	Intervention
Reporting group description: Methylphenidate arm	
Reporting group title	Placebo
Reporting group description: Placebo tablets individually dose-titrated in same manner as in active arm	

Primary: FACIT-Fatigue at 6 +/- 2 weeks	
End point title	FACIT-Fatigue at 6 +/- 2 weeks
End point description: FACIT-F Fatigue score	
End point type	Primary
End point timeframe: 6 weeks - but if fatigue data were missing at 6 weeks then data from week 7, 8, 5 or 4 (in that order) could be used.	

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[1]	77[2]	75[3]	72[4]
Units: FACIT-F fatigue score				
arithmetic mean (standard deviation)	20 (± 9)	22 (± 10)	32 (± 11)	31 (± 12)

Notes:

[1] - Baseline fatigue

[2] - Baseline fatigue

[3] - Week 6 +/- 2 weeks fatigue

[4] - Week 6 +/- 2 weeks fatigue

Statistical analyses

Statistical analysis title	Baseline to week 6 +/- 2
Statistical analysis description: Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).	
Comparison groups	Intervention v Placebo

Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	4.9

Secondary: EORTC QLQ-C15-PAL Pain scores at 6 weeks

End point title	EORTC QLQ-C15-PAL Pain scores at 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 Weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[5]	77[6]	72[7]	66[8]
Units: EORTC QLQc15-PAL Pain scores				
arithmetic mean (standard deviation)	52 (± 19)	53 (± 20)	46 (± 18)	45 (± 18)

Notes:

[5] - Baseline pain

[6] - Baseline pain

[7] - Week 6 pain

[8] - Weeks 6 pain

Statistical analyses

Statistical analysis title	Baseline to 6 weeks

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	1.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.66
upper limit	6.93

Secondary: EORTC QLQ-C15-PAL Physical functioning scores at 6 weeks

End point title	EORTC QLQ-C15-PAL Physical functioning scores at 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[9]	77[10]	72[11]	66[12]
Units: EORTC QLQc15 Physical functioning score				
arithmetic mean (standard deviation)	50 (± 18)	50 (± 17)	41 (± 16)	44 (± 17)

Notes:

[9] - Baseline physical functioning

[10] - Baseline physical functioning

[11] - Week 6 physical functioning

[12] - Week 6 physical functioning

Statistical analyses

Statistical analysis title	Baseline to 6 weeks

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	-2.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.28
upper limit	1.94

Secondary: EORTC QLQ-C15-PAL Emotional functioning scores at 6 weeks

End point title	EORTC QLQ-C15-PAL Emotional functioning scores at 6 weeks

End point description:

End point type	Secondary

End point timeframe:

6 weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81[13]	77[14]	72[15]	66[16]
Units: EORTC QLQ-C15-PAL Emotional functioning				
arithmetic mean (standard deviation)	44 (± 17)	42 (± 17)	38 (± 17)	35 (± 17)

Notes:

[13] - Baseline Emotional functioning

[14] - Baseline Emotional functioning

[15] - Week 6 Emotional functioning

[16] - Week 6 Emotional functioning

Statistical analyses

Statistical analysis title	Baseline to 6 weeks

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.18
upper limit	6.59

Secondary: EORTC QLQc15 - Quality of Life

End point title	EORTC QLQc15 - Quality of Life

End point description:

End point type	Secondary

End point timeframe:

6 weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[17]	77[18]	72[19]	66[20]
Units: EORTC QLQc15 Quality of life score				
arithmetic mean (standard deviation)	30 (± 13)	31 (± 14)	26 (± 11)	28 (± 14)

Notes:

[17] - Baseline QoL

[18] - Baseline QoL

[19] - Week 6 QoL

[20] - Week 6 QoL

Statistical analyses

Statistical analysis title	Baseline to week 6

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	-2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.91
upper limit	1.74

Secondary: EORTC QLQc15 - Fatigue

End point title	EORTC QLQc15 - Fatigue

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[21]	77[22]	72[23]	66[24]
Units: EORTC QLQc15 - Fatigue scores				
arithmetic mean (standard deviation)	74 (± 15)	72 (± 18)	54 (± 17)	55 (± 19)

Notes:

[21] - Baseline intervention

[22] - Baseline placebo

[23] - Week 6 intervention

[24] - Week 6 placebo

Statistical analyses

Statistical analysis title	Baseline to 6 weeks

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.79
upper limit	2.8

Secondary: EORTC QLQc15 - Nausea

End point title	EORTC QLQc15 - Nausea

End point description:

End point type	Secondary

End point timeframe:

Baseline to 6 weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[25]	77[26]	72[27]	66[28]
Units: EORTC QLQc15 - Nausea score				
arithmetic mean (standard deviation)	44 (± 22)	39 (± 22)	41 (± 19)	35 (± 19)

Notes:
[25] - Baseline
[26] - Baseline
[27] - Week 6
[28] - Week 6

Statistical analyses

Statistical analysis title	Baseline to 6 weeks

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.07
upper limit	10.66

Secondary: EORTC QLQc15 - Anorexia

End point title	EORTC QLQc15 - Anorexia

End point description:

End point type	Secondary

End point timeframe:

Baseline to six weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[29]	77[30]	72[31]	66[32]
Units: EORTC QLQc15 - Anorexia scores				
arithmetic mean (standard deviation)	52 (± 25)	52 (± 77)	47 (± 26)	41 (± 23)

Notes:
[29] - Baseline
[30] - Baseline
[31] - Week 6
[32] - Week 6

Statistical analyses

Statistical analysis title	Baseline to week 6

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	6.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	14

Secondary: EORTC QLQc15 - Dyspnoea

End point title	EORTC QLQc15 - Dyspnoea

End point description:

End point type	Secondary

End point timeframe:

Baseline to six weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[33]	77[34]	72[35]	66[36]
Units: EORTC QLQc15 - Dyspnoea scores				
arithmetic mean (standard deviation)	52 (± 21)	53 (± 24)	45 (± 23)	51 (± 26)

Notes:

[33] - Baseline

[34] - Baseline

[35] - Week 6

[36] - Week 6

Statistical analyses

Statistical analysis title	Baseline to week 6

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo

Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	-6.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.78
upper limit	0.44

Secondary: EORTC QLQc15 - Constipation

End point title	EORTC QLQc15 - Constipation

End point description:

End point type	Secondary

End point timeframe:

Baseline to six weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81[37]	77[38]	72[39]	66[40]
Units: EORTC QLQc15 - Constipation				
arithmetic mean (standard deviation)	47 (± 24)	41 (± 21)	43 (± 22)	36 (± 19)

Notes:

[37] - Baseline

[38] - Baseline

[39] - Week 6

[40] - Week 6

Statistical analyses

Statistical analysis title	Baseline to 6 weeks

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Coefficient
Point estimate	4.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.02
upper limit	11.29

Secondary: EORTC QLQc15 - Insomnia

End point title	EORTC QLQc15 - Insomnia

End point description:

End point type	Secondary

End point timeframe:

Baseline to six weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[41]	77[42]	72[43]	66[44]
Units: EORTC QLQc15 - Insomnia scores				
arithmetic mean (standard deviation)	56 (± 25)	51 (± 27)	44 (± 24)	47 (± 25)

Notes:

[41] - Baseline

[42] - Baseline

[43] - Week 6

[44] - Week 6

Statistical analyses

Statistical analysis title	Baseline to 6 weeks

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	-5.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.96
upper limit	1.98

Secondary: FACIT-F Fatigue at 6 weeks only

End point title	FACIT-F Fatigue at 6 weeks only

End point description:

End point type	Secondary

End point timeframe:

Baseline to six weeks only
Note that this is different to the primary outcome for the study, which was FACIT-F scores at 6+/-2 weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[45]	77[46]	72[47]	67[48]
Units: FACIT-F Fatigue scores				
arithmetic mean (standard deviation)	20 (± 9)	22 (± 10)	33 (± 11)	31 (± 12)

Notes:

[45] - Baseline

[46] - Baseline

[47] - Week 6

[48] - Week 6

Statistical analyses

Statistical analysis title	Baseline to 6 weeks

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	3.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	6.05

Secondary: Utility Score

End point title	Utility Score

End point description:

End point type	Secondary

End point timeframe:
Baseline to 6 weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[49]	77[50]	72[51]	66[52]
Units: EQ-5D-5L scores				
arithmetic mean (standard deviation)	0.62 (± 0.21)	0.65 (± 0.18)	0.71 (± 0.23)	0.70 (± 0.22)

Notes:
[49] - Baseline
[50] - Baseline
[51] - Week 6
[52] - Week 6

Statistical analyses

Statistical analysis title	Baseline to 6 weeks

Statistical analysis description:
Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.086

Secondary: Anxiety Score

End point title	Anxiety Score

End point description:

End point type	Secondary

End point timeframe:
Baseline to six weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[53]	77[54]	72[55]	66[56]
Units: HADS-A score				
median (inter-quartile range (Q1-Q3))	6 (3 to 9)	4 (2 to 9)	4 (2 to 6)	4 (2 to 6)

Notes:

[53] - Baseline

[54] - Baseline

[55] - Week 6

[56] - Week 6

Statistical analyses

Statistical analysis title	Baseline to 6 weeks

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	-0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	0.62

Secondary: Depression score

End point title	Depression score

End point description:

End point type	Secondary

End point timeframe:

Baseline to six weeks

End point values	Intervention	Placebo	Intervention	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81[57]	77[58]	72[59]	66[60]
Units: HADS-D score				
median (inter-quartile range (Q1-Q3))	7 (5 to 11)	6 (4 to 9)	4 (2 to 8)	5 (3 to 9)

Notes:

[57] - Baseline

[58] - Baseline

[59] - Week 6

[60] - Week 6

Statistical analyses

Statistical analysis title	Baseline to 6 weeks

Statistical analysis description:

Analysis of the outcome used a mixed effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow up), randomized treatment, and the stratification factors (except site and fatigue severity).

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Coefficient
Point estimate	-1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	-0.3

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events are reported across the 10-weeks of the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	Study specific
Dictionary version	1

Reporting groups	
Reporting group title	Methylphenidate arm
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Methylphenidate arm	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 82 (23.17%)	16 / 77 (20.78%)	
number of deaths (all causes)	6	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Progression of underlying cancer			
subjects affected / exposed	5 / 82 (6.10%)	4 / 77 (5.19%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 82 (3.66%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Worsening of heart failure			
subjects affected / exposed	0 / 82 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Facial droop			

subjects affected / exposed	0 / 82 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cord compression			
subjects affected / exposed	1 / 82 (1.22%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient loss of consciousness			
subjects affected / exposed	0 / 82 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 82 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Bleeding or clotting			
subjects affected / exposed	0 / 82 (0.00%)	3 / 77 (3.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	2 / 82 (2.44%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 82 (1.22%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 82 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mucositis / diarrhoea			
subjects affected / exposed	2 / 82 (2.44%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 82 (1.22%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Impaired liver function			
subjects affected / exposed	2 / 82 (2.44%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney injury, haematuria, kidney pain			
subjects affected / exposed	1 / 82 (1.22%)	2 / 77 (2.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	5 / 82 (6.10%)	3 / 77 (3.90%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Methylphenidate arm	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 82 (100.00%)	77 / 77 (100.00%)	
Cardiac disorders			
Palpitations	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	26 / 82 (31.71%)	25 / 77 (32.47%)	
occurrences (all)	57	65	
Feeling of abnormal heart rhythms	Additional description: Self-reported as "mild, moderate or severe" at any time		

	over the 10-week period		
subjects affected / exposed	11 / 82 (13.41%)	12 / 77 (15.58%)	
occurrences (all)	15	31	
Nervous system disorders			
Headache	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	46 / 82 (56.10%)	46 / 77 (59.74%)	
occurrences (all)	203	171	
Feeling dizzy	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	52 / 82 (63.41%)	42 / 77 (54.55%)	
occurrences (all)	219	203	
Feeling drowsy	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	62 / 82 (75.61%)	61 / 77 (79.22%)	
occurrences (all)	307	321	
General disorders and administration site conditions			
Insomnia	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	60 / 82 (73.17%)	58 / 77 (75.32%)	
occurrences (all)	269	293	
Feeling abnormally active	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	8 / 82 (9.76%)	10 / 77 (12.99%)	
occurrences (all)	13	17	
Fever	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	19 / 82 (23.17%)	14 / 77 (18.18%)	
occurrences (all)	33	20	
Flu-like symptoms	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	41 / 82 (50.00%)	34 / 77 (44.16%)	
occurrences (all)	126	70	
Gastrointestinal disorders			
Abdominal pain	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	47 / 82 (57.32%)	45 / 77 (58.44%)	
occurrences (all)	257	217	
Diarrhoea	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	40 / 82 (48.78%)	41 / 77 (53.25%)	
occurrences (all)	113	148	
Nausea	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		

subjects affected / exposed	57 / 82 (69.51%)	43 / 77 (55.84%)	
occurrences (all)	228	167	
Vomiting	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	31 / 82 (37.80%)	21 / 77 (27.27%)	
occurrences (all)	74	56	
Dry mouth	Additional description: Self-reported as "severe" at any time over the 10-week period		
subjects affected / exposed	60 / 82 (73.17%)	53 / 77 (68.83%)	
occurrences (all)	359	300	
Other GI symptoms	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	43 / 82 (52.44%)	42 / 77 (54.55%)	
occurrences (all)	101	92	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	49 / 82 (59.76%)	41 / 77 (53.25%)	
occurrences (all)	189	145	
Sore throat	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	35 / 82 (42.68%)	33 / 77 (42.86%)	
occurrences (all)	82	76	
Other respiratory AEs	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	44 / 82 (53.66%)	37 / 77 (48.05%)	
occurrences (all)	117	121	
Skin and subcutaneous tissue disorders			
Hair loss	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	25 / 82 (30.49%)	18 / 77 (23.38%)	
occurrences (all)	76	67	
Itch	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	40 / 82 (48.78%)	32 / 77 (41.56%)	
occurrences (all)	126	108	
Skin rashes	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	27 / 82 (32.93%)	22 / 77 (28.57%)	
occurrences (all)	65	46	
Other skin or hair symptoms	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		

subjects affected / exposed	11 / 82 (13.41%)	16 / 77 (20.78%)	
occurrences (all)	16	29	
Psychiatric disorders			
Anxiety	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	50 / 82 (60.98%)	42 / 77 (54.55%)	
occurrences (all)	178	175	
Depression	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	42 / 82 (51.22%)	29 / 77 (37.66%)	
occurrences (all)	149	102	
Irritability	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	51 / 82 (62.20%)	50 / 77 (64.94%)	
occurrences (all)	211	186	
Aggression	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	11 / 82 (13.41%)	16 / 77 (20.78%)	
occurrences (all)	28	32	
Mood swings	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	10 / 82 (12.20%)	10 / 77 (12.99%)	
occurrences (all)	93	87	
Abnormal beviour	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	6 / 82 (7.32%)	5 / 77 (6.49%)	
occurrences (all)	6	5	
Other mood or mental state symptoms	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	10 / 82 (12.20%)	10 / 77 (12.99%)	
occurrences (all)	12	14	
Musculoskeletal and connective tissue disorders			
Abnormal muscle movements (twitches)	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	36 / 82 (43.90%)	37 / 77 (48.05%)	
occurrences (all)	138	131	
Joint pain	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	53 / 82 (64.63%)	52 / 77 (67.53%)	
occurrences (all)	251	243	
Metabolism and nutrition disorders			

Anorexia	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	63 / 82 (76.83%)	55 / 77 (71.43%)	
occurrences (all)	279	231	
Weight loss	Additional description: Self-reported as "mild, moderate or severe" at any time over the 10-week period		
subjects affected / exposed	38 / 82 (46.34%)	43 / 77 (55.84%)	
occurrences (all)	125	99	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2018	CHANGES TO INCLUSION CRITERIA Prognosis of 2-12 months removed as an inclusion criterion Requirement to be under care of Specialist Palliative Care team changed to requirement to be receiving generalist or specialist palliative care CHANGES TO EXCLUSION CRITERIA Cardiovascular exclusions modified so that it was only uncontrolled heart failure, uncontrolled angina or myocardial infarction in the last one year that were regarded as exclusions Cerebrovascular exclusions modified so that it was only stroke in the last one year that was regarded as an exclusion Alcohol or drug dependency exclusion criterion was modified so that it was only dependency within last one year that was regarded as an exclusion Estimated Glomerular Filtration Rate (eGFR) exclusion was reduced from <60mls/hr to <45mls/hr Alkaline Phosphatase (ALP) levels no longer regarded as an exclusion Exclusion of inpatient hospital or hospice patients was removed
20 May 2019	CHANGES TO EXCLUSION CRITERIA Exclusion of patients who are currently in another Clinical Trial of an Investigational Medicinal Product (CTIMP) expanded to include patients who have been on a CTIMP within last four weeks CHANGES TO TRIAL PROCEDURES Window for dose titration increased from ±3 days to ±4 days
22 August 2019	CHANGES TO TRIAL PROCEDURES Collection of cancer diagnosis and Eastern Cooperative Oncology Group Performance Status from participants at screening/baseline Collection of baseline Adverse Event data
17 March 2020	CHANGES MADE IN RESPONSE TO COVID PANDEMIC Emergency action to stop new recruitment, taper the dose of methylphenidate for patients already on trial and then withdrawal of medication. Enrolled participants remained on follow-up but did not take investigational medicinal product or placebo.
06 July 2020	CHANGES MADE IN RESPONSE TO COVID PANDEMIC Telephone assessments permitted to replace face-to-face visits at weeks 3, 6 and 10 Home delivery of IMP permitted Need for separate face-to-face screening visit (with written informed consent) was removed. Consent for screening tests (blood tests, blood pressure and pulse) could now be verbal rather than written Screening and enrolment visits could be merged CHANGES TO SAMPLE SIZE Sample size for randomised participants changed from 230 to 215-230

09 January 2023	CHANGES TO SECONDARY OUTCOMES References to carer satisfaction as an outcome were removed from the protocol - Inclusion of carer satisfaction in the original protocol was an error, no data were collected on this outcome. Anxiety and depression were specified as secondary outcomes - Data on anxiety and depression had not previously been explicitly specified as secondary outcomes. CHANGES TO SAMPLE SIZE Sample size reduced from 215-230 randomised participants to 162-230 randomised participants. Estimated number of evaluable participants changed from 172 to 130-172: In light of below expected recruitment rates, funder agreed to extend trial to achieve at least 130 evaluable participants (estimated to require at least 162 randomised participants).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 March 2020	Recruitment suspended nationally due to COVID pandemic	31 October 2020

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38757263