Clinical trial results:
RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTRE CLINICAL TRIAL TO EVALUATE THE EFFICACY OF PALLIATIVE TREATMENT WITH METHYLPHENIDATE IN ASTHENIA (IN PATIENTS WITH ADVANCED CANCER).

Summary

EudraCT number	2008-002171-27
Trial protocol	ES
Global end of trial date	07 April 2016

Results information

Result version number	v1 (current)
This version publication date	19 September 2021
First version publication date	19 September 2021
Summary attachment (see zip file)	FINAL REPORT (SPANISH) (Informe Final METILÁS09-2008.pdf)

Trial information

Trial identification

Sponsor protocol code	METILÁS09/2008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01773837
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clínica Universidad de Navarra
Sponsor organisation address	Avda. Pío XII, 36, Pamplona, Spain, 31008
Public contact	UCICEC, Clínica Universidad de Navarra, 34 948 255400 2723, ucicec@unav.es
Scientific contact	UCICEC, Clínica Universidad de Navarra, 34 948 255400 2723, ucicec@unav.es

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	01 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2016
Global end of trial reached?	Yes
Global end of trial date	07 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of methylphenidate in the treatment of asthenia in a population of patients with advanced cancer: treatment will be considered effective if in the methylphenidate group the improvement in mean asthenia intensity between baseline and day 6 is significantly greater than the improvement found in the placebo group.
The response (symptomatic improvement in asthenia) will be measured with a EVN of weakness included in the Edmonton System Assesment Scale (ESAS) (0: no weakness at all, 10: greatest weakness imaginable).

Protection of trial subjects:

This clinical trial has been carried out under conditions of respect for the fundamental rights of the individual and the ethical postulates that affect biomedical research involving human beings, following for these purposes those contained in the Declaration of Helsinki and subsequent updates. This study was conducted in accordance with the Standards of Good Clinical Practice and the standard operating procedures which outline the conduct to be followed in each of the aspects related to the organisation, conduct, data collection, documentation and verification of clinical trials. Freely given informed consent has been obtained and documented from each trial subject prior to inclusion. The confidentiality of the data and documents contained in the study file is assured.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 May 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Ethical reason
Long term follow-up duration	20 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	43
From 65 to 84 years	54
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Recruitment is carried out at the study centres, based on the clinical experience of the investigators and retrospective data. Recruitment is competitive, meaning that each centre will be able to recruit as many patients as it is able during the recruitment period of the study.

Pre-assignment

Screening details:

Patients over 18 years diagnosed with advanced cancer, including metastatic, locally advanced or relapsed cancer, with no option of radical intent treatment. Haemoglobin levels are ≥9 and on the EVN scale for "weakness" the patient should score ≥5.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental group

Arm description:

A total of 55 patients are randomly assigned to this group who are administered methylphenidate (Rubifen) in an initial dose of 10 mg at breakfast and 5 mg at lunch. The dose can be adjusted during the trial but always within the range of 10-25mg/day.

Arm type	Experimental
Investigational medicinal product name	METHYLPHENIDATE HYDROCHLORIDE
Investigational medicinal product code	N06BA04
Other name	Rubifen
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The initial dose is 10 mg at breakfast and 5 mg at lunch during the 6 days of the study. . The dose can be adjusted during the trial but always within the range of 10-25mg/day. It is supplied in blister packs of 5 mg tablets, in the form of round, white, flat tablets for oral administration.

Arm title	Control group

Arm description:

A total of 45 patients are randomly assigned to this group. For the placebo group, the manufacture of tablets without active ingredient, with the same external appearance as those containing methylphenidate, is carried out.

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:

For the placebo group, the manufacture of tablets without active ingredient, with the same external appearance as those containing methylphenidate, is carried out.

Number of subjects in period 1	Experimental group	Control group
Started	55	45
Completed	43	34
Not completed	12	11
Consent withdrawn by subject	-	3
Adverse event, non-fatal	5	3
others	3	3
Lost to follow-up	1	-
patient deterioration	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Experimental group

Reporting group description:

A total of 55 patients are randomly assigned to this group who are administered methylphenidate (Rubifen) in an initial dose of 10 mg at breakfast and 5 mg at lunch. The dose can be adjusted during the trial but always within the range of 10-25mg/day.

Reporting group title	Control group

Reporting group description:

A total of 45 patients are randomly assigned to this group. For the placebo group, the manufacture of tablets without active ingredient, with the same external appearance as those containing methylphenidate, is carried out.

Reporting group values	Experimental group	Control group	Total
Number of subjects	55	45	100
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	66	68	
full range (min-max)	38 to 87	39 to 88	-
Gender categorical Units: Subjects			
Female	26	21	47
Male	29	24	53

End points

End points reporting groups

Reporting group title	Experimental group

Reporting group description:

A total of 55 patients are randomly assigned to this group who are administered methylphenidate (Rubifen) in an initial dose of 10 mg at breakfast and 5 mg at lunch. The dose can be adjusted during the trial but always within the range of 10-25mg/day.

Reporting group title	Control group

Reporting group description:

A total of 45 patients are randomly assigned to this group. For the placebo group, the manufacture of tablets without active ingredient, with the same external appearance as those containing methylphenidate, is carried out.

Primary: Level of asthenia. ESAS scale

End point title	Level of asthenia. ESAS scale

End point description:

The main objective is to assess the level of asthenia using the Edmonton Symptom Assessment Questionnaire (ESAS). Overall, differences in effectiveness variables between methylphenidate and placebo were not statistically significant in the study population. The improvement in mean asthenia intensity between baseline and day 6 is similar in the Placebo and Methylphenidate groups. The intensity of asthenia (as assessed by ESAS) improved significantly in both groups of patients, both in the placebo-treated group and in the group receiving methylphenidate. The difference (mean) between baseline asthenia and asthenia on day 6 of treatment is statistically significant for both groups, placebo and methylphenidate (p<0,001).

End point type	Primary

End point timeframe:

The level of asthenia is asseessed on day 6.

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	34		
Units: NA				
arithmetic mean (standard deviation)				
Average improvement in asthenia (ESAS) on day 6	-2.3 (± 2.6)	-1.9 (± 2.5)		

Statistical analyses

Statistical analysis title	Mean change

Statistical analysis description:

The degree of improvement is assessed by the differences in baseline minus endpoint scores on the ESAS scale.

Comparison groups	Experimental group v Control group
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Level of asthenia. FACT-F subscale

End point title	Level of asthenia. FACT-F subscale

End point description:

As a secondary objective, the level of asthenia is assessed with the FACT-F subscale. The results of the FACT-F scale show a significant improvement of all patients at day 6, the difference between the groups receiving placebo or methylphenidate was not statistically significant (Placebo p=0,0002; Metilphenidate p=0,0004).

End point type	Secondary

End point timeframe:

The level of asthenia is asseessed on day 6.

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	30		
Units: NA				
median (confidence interval 95%)				
improvement in asthenia (FACT-F) on day 6.	4.9 (1.6 to 8.2)	6.4 (3.3 to 9.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cognitive function

End point title	Cognitive function

End point description:

Changes in cognitive level were studied with the Gagnon Test. No effects of methylphenidate on cognitive function were detected. There were no significant changes in the Gagnon Test between day 0 and day 6 in either the methylphenidate or placebo groups.

End point type	Secondary

End point timeframe:

The Gagnon Test is assessed between day 0 and day 6.

End point values	Experimental group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	34		
Units: NA				
arithmetic mean (standard deviation)				
Delayed repetition of a list of words	-0.1 (± 1.0)	-0.4 (± 0.6)		
Delayed repetition 1 of a list of words	0.2 (± 1.8)	0.4 (± 2.0)		
Delayed repetition 2 of a list of words	0.3 (± 1.8)	0.4 (± 1.7)		
Repetition of progressive series of digits forward	4.1 (± 17.1)	1.9 (± 14.5)		
Repetition of progressive series of digits backwar	1.3 (± 9.4)	-0.2 (± 6.7)		
Accuracy when copying figures	0.0 (± 2.2)	-0.1 (± 1.7)		
Writing a given sentence	0.3 (± 0.7)	-0.3 (± 1.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The investigator shall notify the principal investigator of the occurrence of an SAA within 24 hours of becoming aware of it, even if it is not related to study medication. The principal investigator shall notify the sponsor immediately.

Adverse event reporting additional description:

Adverse effects include the sensation of nausea, which is described 10 times among patients who received methylphenidate and never in the placebo group. Nausea intensity, at the beginning and at the end of the trial, shows no significant difference between the two groups.Other drug-related side effects are nervousnes sleep disturbances and headache

Assessment type	Systematic

Dictionary used

Dictionary name	ND
Dictionary version	ND

Reporting groups

Reporting group title	Experimental group

Reporting group description:

Patients in this group are administered with methylphenidate. 49% of patients had an adverse effect. 10% of these adverse events were serious.

Reporting group title	control group

Reporting group description:

Patients in this group are given placebo. 38% of patients had an adverse effect. 4% of the adverse events were serious.

Serious adverse events	Experimental group	control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 55 (7.27%)	2 / 45 (4.44%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute right hemiplegia			
subjects affected / exposed	0 / 55 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dysarthria			
subjects affected / exposed	0 / 55 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Brain haemorrhage			

subjects affected / exposed	1 / 55 (1.82%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 55 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Exitus			
subjects affected / exposed	2 / 55 (3.64%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Oppressive central thoracic pain			
subjects affected / exposed	1 / 55 (1.82%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemoptysis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 45 (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: 1 %

Non-serious adverse events	Experimental group	control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 55 (49.09%)	17 / 45 (37.78%)	
Vascular disorders			
Brain haemorrhage			
subjects affected / exposed	1 / 55 (1.82%)	1 / 45 (2.22%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	1 / 55 (1.82%)	0 / 45 (0.00%)	
occurrences (all)	1	0	

Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 55 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Nervous system disorders			
Cefalea			
subjects affected / exposed	1 / 55 (1.82%)	1 / 45 (2.22%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Deterioration of general condition			
subjects affected / exposed	3 / 55 (5.45%)	1 / 45 (2.22%)	
occurrences (all)	3	1	
Pain			
subjects affected / exposed	1 / 55 (1.82%)	1 / 45 (2.22%)	
occurrences (all)	2	2	
Discomfort			
subjects affected / exposed	1 / 55 (1.82%)	1 / 45 (2.22%)	
occurrences (all)	2	2	
Social circumstances			
Sleep disturbances			
subjects affected / exposed	3 / 55 (5.45%)	2 / 45 (4.44%)	
occurrences (all)	7	4	
Nervousness			
subjects affected / exposed	3 / 55 (5.45%)	1 / 45 (2.22%)	
occurrences (all)	6	1	
Instability			
subjects affected / exposed	1 / 55 (1.82%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 55 (7.27%)	0 / 45 (0.00%)	
occurrences (all)	10	0	
diarrhea			
subjects affected / exposed	1 / 55 (1.82%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Constipation			

subjects affected / exposed	0 / 55 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 55 (1.82%)	1 / 45 (2.22%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Redness			
subjects affected / exposed	1 / 55 (1.82%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Cellulitis			
subjects affected / exposed	0 / 55 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anorexia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 55 (3.64%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	0 / 55 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Infections and infestations			
Fever			
subjects affected / exposed	2 / 55 (3.64%)	3 / 45 (6.67%)	
occurrences (all)	3	6	
Dental phlegmon			
subjects affected / exposed	1 / 55 (1.82%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Hyponatremia			
subjects affected / exposed	1 / 55 (1.82%)	0 / 45 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2010	protocol generated version: v4. Notified to AEMPS and ethics committee.
27 September 2011	protocol generated version: v4. Notified to the ethics committee
03 April 2012	protocol generated version: v4. Notified to the ethics committee
01 August 2012	protocol generated version: v5. Notified to AEMPS and ethics committee.
01 July 2015	protocol generated version: v5. Notified to the ethics committee.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported