Clinical trial results:
Treatment of multi-organ bodily distress syndrome.
A double-blinded placebo controlled trial of the effect of Imipramine (STreSS-3)

Summary

EudraCT number	2011-004294-87
Trial protocol	DK
Global end of trial date	01 May 2015

Results information

Result version number	v1 (current)
This version publication date	28 June 2017
First version publication date	28 June 2017
Summary attachment (see zip file)	Eudract 2011-004294-87 Imipramine versus placebo (Eudract 2011-004294-87.pdf)

Trial information

Trial identification

Sponsor protocol code	1,2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01518634
WHO universal trial number (UTN)	-
Other trial identifiers	The Danish Health Authority: 2011100742, The Ethics Committee of the Central Denmark Region: 20110210, The Danish Data Protection Agency: 2007-58-0010

Notes:

Sponsors

Sponsor organisation name	Research Clinic for Functional Disorders and Psychosomatics, Per Fink
Sponsor organisation address	Noerrebrogde 33, Aarhus, Denmark, 8000
Public contact	Clinical Trial Information, Research Clinic for Functional Disorders and Psychosomatics, +45 89494310, aarhus.ffl@rm.dk
Scientific contact	Clinical Trial Information, Research Clinic for Functional Disorders and Psychosomatics, +45 89494310, aarhus.ffl@rm.dk

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 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2015
Global end of trial reached?	Yes
Global end of trial date	01 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to test the effect of Imipramine in patients with multi-organ Bodily Distress Syndrome (BDS). BDS is a unifying diagnosis that encompasses a group of closely related conditions such as somatisation disorder, fibromyalgia, irritable bowel syndrome and chronic fatigue syndrome. The project consists of a double-blinded placebo controlled trial of treatment with the tricyclic antidepressant Imipramine in dosages of 25-75 mg. Primary outcome is patient-rated improvement measured by Clinical Global Improvement Scale (CGI-I). Secondary outcome is functional level (physical, mental and social) measured by the SF-36.

Protection of trial subjects:

The diagnosis was established by an MD after a thorough physical and psychological assessment including diagnostic interview (Schedules for Clinical Assessment in Neuropsychiatry), physical examination, blood test, ECG, and a close review of all medical records.
Up to eight tablets of 500 mg paracetamol were available daily as escape medication.

Background therapy:

Up to eight tablets of 500 mg paracetamol were available daily as escape medication

Evidence for comparator:

placebo

Actual start date of recruitment	30 January 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 138
Worldwide total number of subjects	138
EEA total number of subjects	138

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)	138
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From January 30, 2012 to November 24, 2014, consecutively referred patients with multiple, long-lasting symptoms were screened for inclusion in a university hospital setting at The Research Clinic for Functional Disorders, Aarhus University Hospital, Denmark.

Pre-assignment

Screening details:

A total of 551 consecutively referred patients were screened. 418 patients fulfilled diagnostic criteria for multi-organ BDS. 161 excluded. Primary reasons for exclusion hereafter were psychiatric disorders demanding treatment or ongoing pain medication. 118 declined to participate.

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, Data analyst, Carer, Assessor

Blinding implementation details:

Coded (numbered) packs of study drug and matched placebo were produced according to the randomisation schedule by the hospital pharmacy. Capsules of 10 mg and 25 mg imipramine and matched placebo for 25 mg were provided by Takeda Pharma A/S; placebo for 10 mg was produced by the hospital pharmacy. The capsules of 10 mg imipramine along with pharmacy-produced 10 mg placebos were both over-encapsulated by the hospital pharmacy to ensure identical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Imipramine

Arm description:

After wash-out, the patients started treatment with 10 mg imipramine or matched placebo, increasing to 25 mg after one week. Drugs and placebos were hereafter titrated to a maximum of 75 mg once daily. Depending on tolerance, dosages were maintained at this level during the remaining part of the study, or reduced if required. Total enrolment time was 19 weeks from inclusion until two weeks after the final dose of study drug.

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

Dosage and administration details:

No study drugs were administered during the pre-intervention period.

Arm title	Placebo

Arm description:

After wash-out, the patients started treatment with 10 mg imipramine or matched placebo, increasing to 25 mg after one week. Drugs and placebos were hereafter titrated to a maximum of 75 mg once daily. Depending on tolerance, dosages were maintained at this level during the remaining part of the study, or reduced if required. Total enrolment time was 19 weeks from inclusion until two weeks after the final dose of study drug.

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:

No study drugs were administered during the pre-intervention period.

Number of subjects in period 1[1]	Imipramine	Placebo
Started	65	60
Completed	57	53
Not completed	8	7
Adverse event, non-fatal	4	3
practical issues	-	1
regret participation	2	-
Protocol deviation	2	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The patients included in the analysis are the ones who received at least one dose of study drug

Baseline characteristics

Reporting groups	
Reporting group title	Imipramine

Reporting group description:

After wash-out, the patients started treatment with 10 mg imipramine or matched placebo, increasing to 25 mg after one week. Drugs and placebos were hereafter titrated to a maximum of 75 mg once daily. Depending on tolerance, dosages were maintained at this level during the remaining part of the study, or reduced if required. Total enrolment time was 19 weeks from inclusion until two weeks after the final dose of study drug.

Reporting group title	Placebo

Reporting group description:

After wash-out, the patients started treatment with 10 mg imipramine or matched placebo, increasing to 25 mg after one week. Drugs and placebos were hereafter titrated to a maximum of 75 mg once daily. Depending on tolerance, dosages were maintained at this level during the remaining part of the study, or reduced if required. Total enrolment time was 19 weeks from inclusion until two weeks after the final dose of study drug.

Reporting group values	Imipramine	Placebo	Total
Number of subjects	65	60	125
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)	65	60	125
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	53	41	94
Male	12	19	31

End points

End points reporting groups

Reporting group title	Imipramine

Reporting group description:

After wash-out, the patients started treatment with 10 mg imipramine or matched placebo, increasing to 25 mg after one week. Drugs and placebos were hereafter titrated to a maximum of 75 mg once daily. Depending on tolerance, dosages were maintained at this level during the remaining part of the study, or reduced if required. Total enrolment time was 19 weeks from inclusion until two weeks after the final dose of study drug.

Reporting group title	Placebo

Reporting group description:

After wash-out, the patients started treatment with 10 mg imipramine or matched placebo, increasing to 25 mg after one week. Drugs and placebos were hereafter titrated to a maximum of 75 mg once daily. Depending on tolerance, dosages were maintained at this level during the remaining part of the study, or reduced if required. Total enrolment time was 19 weeks from inclusion until two weeks after the final dose of study drug.

Primary: Clinical global improvement scale CGI

End point title	Clinical global improvement scale CGI

End point description:

Response to "How do you consider your health status now compared with when you first came to the clinic?" with 5 respons categories

End point type	Primary

End point timeframe:

from baseline to after 10 weeks of minimum 25 mg study drug

End point values	Imipramine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	57		
Units: points				
much worse	1	1		
worse	4	11		
unchanged	25	31		
better	22	14		
much better	11	0		

Statistical analyses

Statistical analysis title	Porportional odds model

Statistical analysis description:

Analysis of the main outcome, CGI score, was based on the three outcome groupings comparing imipramine with placebo using an unadjusted proportional odds model. We reported as the main result the analysis based on data available in the ITT population.

Comparison groups	Imipramine v Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	6.8
Variability estimate	Standard deviation
Dispersion value	0.001

Secondary: SF-36 PCS

End point title	SF-36 PCS
End point description:	
Physical component summary SF-36	
End point type	Secondary
End point timeframe:	
from baseline to after 10 weeks of minimum 25 mg study drug	

End point values	Imipramine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	57		
Units: points	63	57		

Statistical analyses

Statistical analysis title	Differnces between groups at endpoint
Comparison groups	Placebo v Imipramine
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	7.2

Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from the first dose of study drug until 2 weeks after the last dose of study drug	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1

Reporting groups	
Reporting group title	imipramine
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

Serious adverse events	imipramine	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	imipramine	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 65 (55.38%)	12 / 60 (20.00%)	
Nervous system disorders			
moderate adverse events			
subjects affected / exposed	36 / 65 (55.38%)	12 / 60 (20.00%)	
occurrences (all)	36	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28408193