Clinical trial results:
New pharmacotherapeutic treatment options for crack-cocaine dependent people in the Netherlands: A double-blind, placebo-controlled randomized feasibility study of sustained release dexamphetamine

Summary

EudraCT number	2013-004024-11
Trial protocol	NL
Global end of trial date	30 June 2015

Results information

Result version number	v1 (current)
This version publication date	20 August 2022
First version publication date	20 August 2022

Trial information

Trial identification

Sponsor protocol code	60-60600-97-103

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Academic Psychiatric Centre; AMC-UvA
Sponsor organisation address	Meibergdreef 5, Amsterdam, Netherlands, 1105 AZ
Public contact	Dr. Vincent M. Hendriks, Parnassia Addiction Research Centre (PARC), Brijder Addiction Treatment, Parnassia Groep, +31 0883852034, Vincent.Hendriks@Brijder.nl
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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 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2015
Global end of trial reached?	Yes
Global end of trial date	30 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This double-blind, placebo-controlled RCT aims to evaluate, in crack-cocaine dependent patients with comorbid heroin dependence, the response to medically prescribed oral dexamphetamine SR (60 mg/day) as an add-on to heroin-assisted treatment, in terms of cocaine use.

Protection of trial subjects:

The study was approved by the medical ethics committee of the Academic Medical Centre of the University of Amsterdam.
Health assessments included: blood sampling and electrocardiography (at baseline/screening and week 12); weekly medical monitoring of heart rate, blood pressure, and bodyweight; weekly standardised registration of (serious) adverse events and co-medication; monthly pregnancy testing (female patients).

Background therapy:

co-prescription of inhalable or injectable diacetylmorphine and oral methadone

Evidence for comparator:

placebo

Actual start date of recruitment	08 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 73
Worldwide total number of subjects	73
EEA total number of subjects	73

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	72
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study participants were recruited from the population of patients currently receiving oral methadone plus inhalable or injectable diacetylmorphine for their concurrent heroin dependence in supervised heroin assisted treatment programmes in two treatment centres in Amsterdam, one in Rotterdam, and one in The Hague.

Pre-assignment

Screening details:

Inclusion criteria: (1) meeting inclusion criteria for heroin assisted treatment; (2) cocaine dependence (DSM-IV); (3) regular cocaine use; (4) primarily by means of basing (smoking crack-cocaine); (5) at least two earlier failed treatments for cocaine; (6) able and willing to participate in the 12-week study; and (7) written informed consent.

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, Data analyst

Blinding implementation details:

Eligible patients were randomly assigned (1:1) to receive either 12 weeks oral sustained-release dexamfetamine or identical placebo. Randomisation was conducted by the collaborating pharmacist, using a computer-generated random number sequence with stratification by treatment centre (four centres) in blocks of four per stratum. Randomisation was concealed for patients, staff , and researchers throughout the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	dexamfetamine-SR

Arm description:

dexamfetamine (in sustained-release formulation): supervised, single oral dose of 60 mg/day (2 tablets of 30 mg)

Arm type	Experimental
Investigational medicinal product name	Dexamfetamine sulphate 30 mg controlled release tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Supervised, daily intake of two tablets in the morning

Arm title	placebo

Arm description:

placebo: supervised, single oral dose of 60 mg/day (2 tablets of 30 mg)

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:

Supervised, daily intake of two tablets in the morning

Number of subjects in period 1	dexamfetamine-SR	placebo
Started	38	35
Completed	34	31
Not completed	4	4
incarceration	2	1
Adverse event, non-fatal	2	2
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	dexamfetamine-SR
Reporting group description:	
dexamfetamine (in sustained-release formulation): supervised, single oral dose of 60 mg/day (2 tablets of 30 mg)	
Reporting group title	placebo
Reporting group description:	
placebo: supervised, single oral dose of 60 mg/day (2 tablets of 30 mg)	

Reporting group values	dexamfetamine-SR	placebo	Total
Number of subjects	38	35	73
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			
arithmetic mean	48.4	49.0	
standard deviation	± 6.6	± 5.3	-
Gender categorical			
Units: Subjects			
Female	3	4	7
Male	35	31	66
Years cocaine use			
Units: years			
arithmetic mean	19.1	19.9	
standard deviation	± 7.7	± 7.1	-
years heroin use			
Units: years			
arithmetic mean	21.1	23.0	
standard deviation	± 8.4	± 8.5	-
previous number addiction treatments			
Units: number			
arithmetic mean	6.2	8.4	
standard deviation	± 3.2	± 7.2	-
duration heroin assisted treatment			
Units: months			
arithmetic mean	46.2	57.5	
standard deviation	± 34.3	± 35.1	-

Days cocaine use (past month) Units: days			
arithmetic mean	23.5	23.7	
standard deviation	± 7.6	± 7.6	-

End points

End points reporting groups	
Reporting group title	dexamfetamine-SR
Reporting group description:	
dexamfetamine (in sustained-release formulation): supervised, single oral dose of 60 mg/day (2 tablets of 30 mg)	
Reporting group title	placebo
Reporting group description:	
placebo: supervised, single oral dose of 60 mg/day (2 tablets of 30 mg)	

Primary: days cocaine use during 12 week study period	
End point title	days cocaine use during 12 week study period
End point description:	
days cocaine use during 12 week study period	
End point type	Primary
End point timeframe:	
12 week study period	

End point values	dexamfetamine-SR	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: days				
arithmetic mean (standard deviation)	44.9 (± 29.4)	60.6 (± 24.3)		

Statistical analyses

Statistical analysis title	Primary outcome days cocaine use
Statistical analysis description:	
The primary outcome—ie, number of self-reported days of cocaine use during the 12-week study—was analysed with negative binomial regression analyses with treatment group as the only independent variable and the interaction of treatment group with treatment centre as the only effect modifier. To fit the negative binomial regression model, a reflection transformation was done on the negatively skewed data of the primary outcome (ie, 84 days minus cocaine use days).	
Comparison groups	dexamfetamine-SR v placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.1 [1]
Method	negative binomial regression analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	2.67

Notes:

[1] - For this proof-of-principle study, a lenient alpha of 0·10 was chosen to minimise the risk of a false negative outcome (type 2 error).

Secondary: Consecutive cocaine abstinence for ≥21 days

End point title	Consecutive cocaine abstinence for ≥21 days

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	dexamfetamine -SR	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: patients	11	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Days of cocaine abstinence in fi nal 4 weeks

End point title	Days of cocaine abstinence in fi nal 4 weeks

End point description:

End point type	Secondary

End point timeframe:

4 weeks

End point values	dexamfetamine -SR	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: days				
arithmetic mean (standard deviation)	15.2 (± 10.8)	7.5 (± 9.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: cocaine-negative urine samples in final 4 weeks

End point title	cocaine-negative urine samples in final 4 weeks

End point description:

End point type	Secondary

End point timeframe:

4 weeks

End point values	dexamfetamine -SR	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35		
Units: Proportion				
arithmetic mean (standard deviation)	10.6 (± 25.1)	3.9 (± 17.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
12 week study period	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	non-specific
Dictionary version	1

Reporting groups	
Reporting group title	dexamfetamine

Reporting group description:

Twenty-eight patients in the dexamfetamine group reported 69 adverse events, of which 58 (84%) events were possibly, probably, or certainly related to the study medication. Most of these adverse events (51 events; 74%) were resolved before the end of the study treatment. Sleeping problems was the adverse event reported by most patients (n=13; 34%).
In four patients, adverse events resulted in (temporary) discontinuation of study treatment. Two patients resumed treatment with a dose of 30 mg/day sustained-release dexamfetamine, one patient discontinued medication intake due to psychotic symptoms, and one patient due to concurrent adverse events of mild to moderate severity.

Reporting group title	placebo

Reporting group description:

Sixteen patients in the placebo group reported 26 adverse events, of which 18 (69%) were possibly, probably, or certainly related to the study medication.

Serious adverse events	dexamfetamine	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
COPD assessment test	Additional description: One serious adverse event occurred: a patient in the placebo group was admitted to hospital during the study period due to an exacerbation of chronic obstructive pulmonary disease, which was not related to the study drug.		
subjects affected / exposed	0 / 38 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2.7 %

Non-serious adverse events	dexamfetamine	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 38 (73.68%)	16 / 35 (45.71%)	
Nervous system disorders			
Agitation / irritability			
subjects affected / exposed	6 / 38 (15.79%)	2 / 35 (5.71%)	
occurrences (all)	6	2	
Physical arousal			
subjects affected / exposed	5 / 38 (13.16%)	2 / 35 (5.71%)	
occurrences (all)	5	2	
General disorders and administration site conditions			
Influenza			
subjects affected / exposed	3 / 38 (7.89%)	3 / 35 (8.57%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Changes in appetite			
subjects affected / exposed	6 / 38 (15.79%)	2 / 35 (5.71%)	
occurrences (all)	6	2	
Changes in weight			
subjects affected / exposed	5 / 38 (13.16%)	2 / 35 (5.71%)	
occurrences (all)	5	2	
Diarrhoea			
subjects affected / exposed	5 / 38 (13.16%)	3 / 35 (8.57%)	
occurrences (all)	5	3	
Psychiatric disorders			
Sleeping problems			
subjects affected / exposed	13 / 38 (34.21%)	3 / 35 (8.57%)	
occurrences (all)	13	3	

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/27015909

http://www.ncbi.nlm.nih.gov/pubmed/31908066