Clinical trial results:
A Phase III, multicenter, open-label study, to evaluate the efficacy and safety of different dosage regimens of 0.2 mg lofexidine hydrochloride (DIMATEX) in the treatment of withdrawal symptoms during opioid detoxification

Summary

EudraCT number	2011-004775-36
Trial protocol	IT
Global end of trial date	21 October 2014
Results information	
Result version number	v1 (current)
This version publication date	10 August 2016
First version publication date	10 August 2016
Summary attachment (see zip file)	Clinical Trial Summary Report (DETOX-Clinical Trial Summary Report 20Oct2015.pdf)

Trial information

Trial identification	
Sponsor protocol code	DETOX-11
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	GET srl
Sponsor organisation address	Via Dante Alighieri, 73, Sanremo, Italy, 18038
Public contact	SEGRETERIA ORGANIZZATIVA, FEDERSERD, +39 031748814, federserd@expopoint.it
Scientific contact	SEGRETERIA ORGANIZZATIVA, FEDERSERD, +39 031748814, federserd@expopoint.it

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	20 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 October 2014
Global end of trial reached?	Yes
Global end of trial date	21 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

a) To confirm the tollerability and safety profile with the use of Lofexidine during the entire time of treatment. b) To evaluate Lofexidine efficacy undergoing drug free detoxification.

Protection of trial subjects:

The informed consent form was written in accordance to the current legislation, the GCPs and the ethical principles of the Declaration of Helsinki. The informed consent form was reviewed and approved by the Ethics Committee of both the coordinating site and the participating sites, before being submitted to any patient.
The written informed consent form had to be personally signed and dated by the patient or his/her legally authorized representative (LAR) prior to his/her participation in the study. The study doctor or the person who discussed the informed consent with the patient had to sign the form, too. The patient, or the patient's LAR, received a copy of the signed and dated informed consent form and any other intended written information.
Informed Consent form and any other document provided to each patient was updated during the study, when there was any new information relevant to the patients. The updated documents were reviewed and approved by the Ethics Committee before being given to the patients. The patient, besides receiving a copy of the updated document, had to confirm his/her willingness to continue to participate in the study, signing and dating the updated Informed Consent form. The subject (or the subject's LAR) also received a signed and dated copy of the updated Informed Consent form and a copy of any amended or new written information.

Background therapy:

None

Evidence for comparator:

No comparator was used

Actual start date of recruitment	01 January 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 74
Worldwide total number of subjects	74
EEA total number of subjects	74

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)	74
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening visit (day -21 -7):
• Signing of the Informed Consent
• Clinical history and physical examination
• Vital signs
• ECG
• Body weight
• Criteria for inclusion and exclusion
• Blood chemistry tests
• Pregnancy test (urine)
• Test alcohol concentration (expired)
• urine toxicology tests
• Concomitant therapies

Pre-assignment period milestones

Number of subjects started	85[1]
Number of subjects completed	74

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Physician decision: 2
Reason: Number of subjects	Screening Failure: 3
Reason: Number of subjects	Synus bradycardia: 1
Reason: Number of subjects	Screening not completed: 1
Reason: Number of subjects	Unknown: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Only the subjects that had passed the pre-assignment period (screening) have been considered enrolled in the trial

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	HEROIN

Arm description:

Subjects dependent on heroin

Arm type	Toxicological group

Investigational medicinal product name	Lofexidine hydrochloride 0.2 mg
Investigational medicinal product code	037 323 019
Other name	DIMATEX
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

• Start of treatment: within 24 h from the last use of heroin;
• Duration of treatment: 10 days;
• Induction Step: 2 days (Day 1 0.8 mg / day, 2nd day 1.6 mg / day);
• Maintenance phase: 3 days (2.4 mg / day);
• Reduction Step: 5 days (Day 6 1.6 mg / day with subsequent reduction of 0.4 mg / day up to the achievement of 0.2 mg / day to 10 th day).

Arm title	METHADONE

Arm description:

Subject currently treated with methadone with a daily dose lower than 40 mg/die and abstinent about other drugs

Arm type	Toxicological group
Investigational medicinal product name	Lofexidine hydrochloride 0.2 mg
Investigational medicinal product code	037 323 019
Other name	DIMATEX
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

• Start of treatment : after 24 h last used methadone ;
• Duration of treatment : 12 days ;
• Induction phase : 2 days (Day 1 0.8 mg / day , 2nd day 1.6 mg / day) ;
• Maintenance phase : 5 days (2.4 mg / day) ;
• Reduction phase : 5 days (Day 8 1.6 mg / day with subsequent reduction of 0.4 mg / day up to the achievement of 0.2 mg / day to 12 days) .

Arm title	BUPRENORPHINE

Arm description:

Subjects treated with buprenorphine and buprenorphine/naloxone with dosing <8 mg/day and abstinent from substance use

Arm type	Toxicological group
Investigational medicinal product name	Lofexidine hydrochloride 0.2 mg
Investigational medicinal product code	037 323 019
Other name	DIMATEX
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

• Start of treatment: after 24 h the last dose of buprenorphine or buprenorphine / naloxone;
• Duration of treatment: 11 days;
• Induction Step: 2 days (Day 1 0.8 mg / day, 2nd day 1.2 mg / day);
• Maintenance phase: 5 days (1.6 mg / day);
• Reduction Step: 4 days (Day 8 1.2 mg / day with subsequent reduction of 0.4 mg / day up to the achievement of 0.2 mg / day to 11 th day).

Number of subjects in period 1	HEROIN	METHADONE	BUPRENORPHINE
Started	6	22	46
Completed	6	22	46

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

None

Arms

Are arms mutually exclusive?	Yes
Arm title	HEROIN

Arm description:

Subjects dependent on heroin

Arm type	Toxicological group
Investigational medicinal product name	Lofexidine hydrochloride 0.2 mg
Investigational medicinal product code	037 323 019
Other name	DIMATEX
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

• Start of treatment: within 24 h from the last use of heroin;
• Duration of treatment: 10 days;
• Induction Step: 2 days (Day 1 0.8 mg / day, 2nd day 1.6 mg / day);
• Maintenance phase: 3 days (2.4 mg / day);
• Reduction Step: 5 days (Day 6 1.6 mg / day with subsequent reduction of 0.4 mg / day up to the achievement of 0.2 mg / day to 10 th day).

Arm title	METHADONE

Arm description:

Subject currently treated with methadone with a daily dose lower than 40 mg/die and abstinent about other drugs

Arm type	Toxicological group
Investigational medicinal product name	Lofexidine hydrochloride 0.2 mg
Investigational medicinal product code	037 323 019
Other name	DIMATEX
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

• Start of treatment : after 24 h last used methadone ;
• Duration of treatment : 12 days ;
• Induction phase : 2 days (Day 1 0.8 mg / day , 2nd day 1.6 mg / day) ;
• Maintenance phase : 5 days (2.4 mg / day) ;
• Reduction phase : 5 days (Day 8 1.6 mg / day with subsequent reduction of 0.4 mg / day up to the achievement of 0.2 mg / day to 12 days) .

Arm title	BUPRENORPHINE

Arm description:

Subjects treated with buprenorphine and buprenorphine/naloxone with dosing <8 mg/day and abstinent from substance use

Arm type	Toxicological group
Investigational medicinal product name	Lofexidine hydrochloride 0.2 mg
Investigational medicinal product code	037 323 019
Other name	DIMATEX
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

• Start of treatment: after 24 h the last dose of buprenorphine or buprenorphine / naloxone;
• Duration of treatment: 11 days;
• Induction Step: 2 days (Day 1 0.8 mg / day, 2nd day 1.2 mg / day);
• Maintenance phase: 5 days (1.6 mg / day);
• Reduction Step: 4 days (Day 8 1.2 mg / day with subsequent reduction of 0.4 mg / day up to the achievement of 0.2 mg / day to 11 th day).

Number of subjects in period 2	HEROIN	METHADONE	BUPRENORPHINE
Started	6	22	46
Completed	2	12	32
Not completed	4	10	14
Consent withdrawn by subject	3	2	2
Adverse event, non-fatal	-	2	3
Non adherence to protocol procedures	-	-	2
Unknown	1	3	1
Lost to follow-up	-	2	4
Lack of efficacy	-	1	2

Period 3

Period 3 title	Follow-up
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	HEROIN
Arm description:	
Subjects dependent on heroin	
Arm type	Toxicological group
No investigational medicinal product assigned in this arm	

Arm title	METHADONE
Arm description:	
Subject currently treated with methadone with a daily dose lower than 40 mg/die and abstinent about other drugs	
Arm type	Toxicological group
No investigational medicinal product assigned in this arm	

Arm title	BUPRENORPHINE
Arm description:	
Subjects treated with buprenorphine and buprenorphine/naloxone with dosing <8 mg/day and abstinent from substance use	
Arm type	Toxicological group
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	HEROIN	METHADONE	BUPRENORPHINE
Started	2	12	32
Completed	2	9	32
Not completed	0	3	0
End of treatment visit not attended	-	2	-
Started treatment with methadone	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	HEROIN
Reporting group description:	
Subjects dependent on heroin	
Reporting group title	METHADONE
Reporting group description:	
Subject currently treated with methadone with a daily dose lower than 40 mg/die and abstinent about other drugs	
Reporting group title	BUPRENORPHINE
Reporting group description:	
Subjects treated with buprenorphine and buprenorphine/naloxone with dosing <8 mg/day and abstinent from substance use	

Reporting group values	HEROIN	METHADONE	BUPRENORPHINE
Number of subjects	6	22	46
Age categorical			
Age was not categorized. Only adults (age 18-60 years old) were enrolled.			
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)	6	22	46
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
the age was estimated as a difference in years between birth date and informed consent date.			
Units: years			
arithmetic mean	33.3	36.35	34.9
standard deviation	± 9.23	± 8.09	± 7.49
Gender categorical			
Units: Subjects			
Female	1	5	5
Male	5	17	41

Reporting group values	Total		
Number of subjects	74		
Age categorical			
Age was not categorized. Only adults (age 18-60 years old) were enrolled.			
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)	74		
From 65-84 years	0		
85 years and over	0		
Age continuous			
the age was estimated as a difference in years between birth date and informed consent date.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	11		
Male	63		

End points

End points reporting groups

Reporting group title	HEROIN

Reporting group description:

Subjects dependent on heroin

Reporting group title	METHADONE

Reporting group description:

Subject currently treated with methadone with a daily dose lower than 40 mg/die and abstinent about other drugs

Reporting group title	BUPRENORPHINE

Reporting group description:

Subjects treated with buprenorphine and buprenorphine/naloxone with dosing <8 mg/day and abstinent from substance use

Reporting group title	HEROIN

Reporting group description:

Subjects dependent on heroin

Reporting group title	METHADONE

Reporting group description:

Subject currently treated with methadone with a daily dose lower than 40 mg/die and abstinent about other drugs

Reporting group title	BUPRENORPHINE

Reporting group description:

Subjects treated with buprenorphine and buprenorphine/naloxone with dosing <8 mg/day and abstinent from substance use

Reporting group title	HEROIN

Reporting group description:

Subjects dependent on heroin

Reporting group title	METHADONE

Reporting group description:

Subject currently treated with methadone with a daily dose lower than 40 mg/die and abstinent about other drugs

Reporting group title	BUPRENORPHINE

Reporting group description:

Subjects treated with buprenorphine and buprenorphine/naloxone with dosing <8 mg/day and abstinent from substance use

Subject analysis set title	Full Analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

According to the protocol, data obtained from the trial have been analyzed using an intention to treat (ITT) approach. Each patient enrolled in the study and randomized has been included in the statistical analysis, even those with minor protocol violations.

Primary: Adverse Events

End point title	Adverse Events[1]

End point description:

End point type	Primary

End point timeframe:

During the study, since informed consent signing to completion of or withdrawal form the study

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The endpoint was the number of adverse events within each toxicological group. No statistical analysis was needed.

End point values	HEROIN	METHADONE	BUPRENORPHINE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	22	46	
Units: Adverse events				
No Adverse Events	5	10	32	
At Least an Adverse Event	1	10	12	

Statistical analyses

No statistical analyses for this end point

Primary: First significant difference in SOWS Score from peak

End point title	First significant difference in SOWS Score from peak[2]

End point description:

The occurence and intensity of withdrawal symptoms was collected on each treatment day through the SOWS. The difference between the peak day, occurring 2-3 days after the treatment start, and each of the following days was calculated and the first statistically significant difference within each toxicological group is reported here.

End point type	Primary

End point timeframe:

Between Day 1 and end of treatment (Day 10 for Heroin group, Day 11 for Buprenorphine group and Day 12 for Methadone group)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was not a comparison between toxicologial group, the comparison was between two time points within each toxicological group, but this kind of statistical analysis
is not accepted by the clinical trials database. The statistical analysis is reported on the attached summary report.

End point values	HEROIN	METHADONE	BUPRENORPHINE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	14	33	
Units: points				
arithmetic mean (standard deviation)	-9.33 (± 2.52)	-5.07 (± 7.62)	-5.19 (± 8.88)	

Attachments (see zip file)	SOWS Score difference with peak day by group/DETOX-11 -

Statistical analyses

No statistical analyses for this end point

Primary: First significant difference in craving for drug from day 1

End point title	First significant difference in craving for drug from day 1[3]

End point description:

End point type	Primary

End point timeframe:

Between Day 1 and end of treatment (Day 10 for Heroin group, Day 11 for Buprenorphine group and Day 12 for Methadone group)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was not a comparison between toxicologial group, the comparison was between two time points within each toxicological group, but this kind of statistical analysis
is not accepted by the clinical trials database. The statistical analysis is reported on the attached summary report.

End point values	HEROIN	METHADONE	BUPRENORPHINE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	12	21	
Units: points				
arithmetic mean (standard deviation)	-0.2 (± 0.28)	-1.61 (± 2.39)	-1.08 (± 1.79)	

Attachments (see zip file)	VAS Craving difference with day 1 by group/DETOX-11 -

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients who completed the treatment

End point title	Number of patients who completed the treatment

End point description:

End point type	Secondary

End point timeframe:

Between Day 1 and end of treatment (Day 10 for Heroin group, Day 11 for Buprenorphine group and Day 12 for Methadone group)

End point values	HEROIN	METHADONE	BUPRENORPHINE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	22	46	
Units: Number of patients				
Not completed	4	13	15	
Completed	2	9	31	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients who relapsed to opiate

End point title	Number of patients who relapsed to opiate

End point description:

End point type	Secondary

End point timeframe:

During the study, from Day 1 to end of study

End point values	HEROIN	METHADONE	BUPRENORPHINE	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[4]	14[5]	35[6]	
Units: Number of patients				
Not relapsed	2	11	21	
Relapsed	0	3	14	

Notes:

[4] - Some subjects did not perform the toxicological tests

[5] - Some subjects did not perform the toxicological tests

[6] - Some subjects did not perform the toxicological tests

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Between informed consent given and end of study	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	HEROIN
Reporting group description:	
Subjects dependent on heroin	
Reporting group title	METHADONE
Reporting group description:	
Subject currently treated with methadone with a daily dose lower than 40 mg/die and astinent about other drugs	
Reporting group title	BUPRENORPHINE
Reporting group description:	
Subjects treated with buprenorphine and buprenorphine/naloxone with dosing <8 mg/day and abstinent from substance use	

Serious adverse events	HEROIN	METHADONE	BUPRENORPHINE
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 22 (0.00%)	0 / 46 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	HEROIN	METHADONE	BUPRENORPHINE
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)	10 / 22 (45.45%)	12 / 46 (26.09%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 6 (16.67%)	5 / 22 (22.73%)	2 / 46 (4.35%)
occurrences (all)	2	5	3
Cardiac disorders			
Bradycardia			

subjects affected / exposed	0 / 6 (0.00%)	3 / 22 (13.64%)	1 / 46 (2.17%)
occurrences (all)	0	3	1
Sinus tachycardia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 22 (4.55%)	0 / 46 (0.00%)
occurrences (all)	0	2	0
Bundle branch block right, Left axis deviation			
subjects affected / exposed	0 / 6 (0.00%)	1 / 22 (4.55%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 6 (0.00%)	1 / 22 (4.55%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram repolarization abnormality			
subjects affected / exposed	0 / 6 (0.00%)	1 / 22 (4.55%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
Palpitations			
subjects affected / exposed	0 / 6 (0.00%)	0 / 22 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 22 (4.55%)	1 / 46 (2.17%)
occurrences (all)	0	1	1
Drowsiness			
subjects affected / exposed	0 / 6 (0.00%)	2 / 22 (9.09%)	0 / 46 (0.00%)
occurrences (all)	0	2	0
Sedation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 22 (0.00%)	2 / 46 (4.35%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 22 (4.55%)	0 / 46 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 22 (4.55%)	2 / 46 (4.35%)
occurrences (all)	0	1	2
Pyrexia			

subjects affected / exposed	0 / 6 (0.00%)	1 / 22 (4.55%)	1 / 46 (2.17%)
occurrences (all)	0	1	1
Malaise	Additional description: General disorders and administration site conditions, Musculoskeletal and connective tissue disorders		
subjects affected / exposed	0 / 6 (0.00%)	0 / 22 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Muscular weakness, Bradycardia	Additional description: General disorders and administration site conditions, Cardiac disorders		
subjects affected / exposed	0 / 6 (0.00%)	0 / 22 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	2 / 22 (9.09%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Heartburn			
subjects affected / exposed	0 / 6 (0.00%)	1 / 22 (4.55%)	0 / 46 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 22 (4.55%)	1 / 46 (2.17%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Knee pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 22 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Infections and infestations			
Epididymis infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 22 (4.55%)	0 / 46 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2012	Reasons and aims of the amendment: A) An exclusion criterion, according to which, if a subject have an alcohol concentration of more than 0.8 g/L, he/she is not eligible, is added to the study protocol. In addition, the intake of alcohol during the study will cause the discontinuation of the treatment and the study. Therefore, it is introduced an evaluation by breathalyzer at screening visit and at all subsequent visits. B) According to the protocol, during the treatment phase (10 or 12 days, depending on the detox group), the patient undergo to daily visits at the clinical center, to monitor health status, evaluate abstinence and to dispense daily lofexidine treatment. Recently, it was found that many centers cannot offer assistance on holidays; therefore, they are not able to maintain the schedule of visits planned on weekends or during holidays. This amendment has the aim to adapt the protocol of the study to the real possibility of drug-addicted patient management at the centers. After this amendment, one/two visits during the active treatment could be considered as "optional" rather than "mandatory". The study drug needed to cover these days will dispensed to the patient, with appropriate indications and dosage recommendations. C) To specify in more detail the management of concomitant therapies during the study. To ensure the quality of the results obtained from the treatment with lofexidine and for safety reasons the study protocol excluded the administration of any type of drug during the active treatment phase. Should it be necessary, however, to give the patient a concomitant therapy, the Investigator should consult the Study Coordinator and the Sponsor, to evaluate the need to stop treatment with lofexidine and the participation of the patient in the study. D) To give more guidance on drug management at the end of the study. E) On this occasion, some typos correct were corrected.
10 September 2012	Change of principal investigator in a clinical center: The Principal Investigator Laura Tidone was replaced By Paolo Donadoni at the clinical center "A.S.L. Bergamo - Dipartimento delle Dipendenze", Bergamo (Italy)

01 October 2013	Reasons and aims of the amendment: A) The chest radiological examination planned during the Screening visit (day -21 -7) is eliminated. The decision to remove it is mainly motivated by the fact that this type of examination is not required to assess patient's eligibility and, in any case, it is not part of the normal clinical practice in the treatment of the target subjects of the study protocol. In addition, most of Investigators complained the major difficulties to perform the radiological examination at their center and, inevitably, this difficulty has, in many cases, lowered the enrollment rate. Finally, please note that the decision has been shared with the Study Coordinator and is taken having given due consideration to the safety of patients in the study. B) The enrollment period is extended by further 9 months, from 12 to 21 months. Consequently, the total duration of the study, which includes the enrollment period and the successive steps of pre-treatment, treatment and follow-up, will be approximately 25 months. The extension of this period was needed in order to achieve the sample size of 200 patients planned in the protocol, having regard to the recruitment difficulty encountered in most of the centers involved. The term of the enrollment period is now extended to June 30th 2014, therefore it is estimated that the study will be completed by the end of October 2014. C) On this occasion the name and references of the CRO "Opera" will be replaced in the Study Protocol with the name and references of the CRO "Latis", the CRO currently authorized by the Promoter, as already communicated with the "Substantial Amendment Notification No. 3 06.02.2013 - Change in practice management." D) Finally, to communicate the details of the new Dimatex® batch: Batch No. 021810, which expires on September 2014. The new batch certificate was issued on 12.09.2013 by the Laboratorio Farmaceutico CT Srl.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

According to the protocol, 200 patients would have been enrolled, but only 74 were. The lower number of patients enrolled prevented to observe some significant result in the methadone group. Too few patients were enrolled in the heroin group.

Notes: