CLINICAL TRIAL SUMMARY REPORT

Phase III, multicenter, open-label, study to evaluate the efficacy and safety of different regimens of lofexidine hydrochloride 0.2 mg (DIMATEX®), in the treatment of withdrawal symptoms in the course of detoxification from opioids

Administrative information	**Protocol number:** DETOX-11 **EudraCT number:** 2011-004775-36 **Date of trial report:** October 20th, 2015 Is the trial part of a Paediatric Investigation Plan? YES☐ NO ☒
Trial design	phase III, multicenter, open-label study on three toxicological groups
Background for conducting the trial	It is estimated that in Italy the prevalence of heroin use, defined as at least one use in the last 12 months, in the age group between 15 and 64 years, is 0,25 %. According to the same source, about 216,000 heroin users (5.5 per 1,000 inhabitants) would benefit from therapeutic treatment, while in 2009 only 19,075 new users relied on a Service for Drug Addiction (Ser.T.) for treatment. The number of subjects currently treated in a Ser.T. for heroin related disorders, is about 170,000, and less than half of them are receiving a specific pharmacological treatment. In particular, there are about 60,000 people in treatment with methadone, about 15,000 with buprenorphine or buprenorphine/naloxone, about 1,000 with naltrexone and other 1,000 treated with clonidine. Quite different is the situation in other countries, like the UK, where a different health policy for addiction is implemented. In 2008/09, 210,815 people entered in contact with the National Treatment Agency for Substance Misuse and over 94% of them received a therapeutic treatment for a minimum of 12 weeks. Considering that 161.494 subjects, i.e. 83%, were heroin users or Problem Drug User (PDU) for opiates and that almost 74% of prescribed treatments was pharmacological one(one type of medication alone in 47% of cases and an association of medications in the rest), it must be concluded that, unlike Italy, in the United Kingdom (UK) the pharmacological approach is a tool indeed available to the physician and that such conduct is reflected in the necessary health policies of that country. Analyzing the types of interventions implemented, it is in fact found that the number of subjects undertaking a program of detoxification is 9,392 (3.0%), compared to a percentage of maintenance pharmacological treatments of 50%. While every year in Italy there is little less than twenty thousand new Ser.T. users, in the UK in 2008/09 there were over sixty thousand new users and, in about 85% of these, an effective treatment was established. In a clinical setting like the Italian one, it should be a priority for the healthcare structure on the territory and for the scientific community in general, to create the conditions for an increasing number of heroin users to go towards a controlled therapeutic treatment. It appears equally clear that, if a different health policy on addiction was implemented, would significant benefits would arise from the enlargement of the therapeutic offer. It is well known that the treatment for heroin addiction should be a combined one, providing a drug treatment associated with a psycho-social support. The pharmacological intervention, which consists in detoxification with agonists such as methadone and buprenorphine or symptomatic drugs such as clonidine and lofexidine, or in a maintenance therapy with substitute drugs such as methadone or buprenorphine or antagonists such as naltrexone, is in many cases the first step of a wider plan of care and rehabilitation. In these cases, the following steps will be expected to be a drug treatment with agonists or antagonists and/or a program of psychosocial support for relapse prevention. In other cases, the detox treatment can be a useful tool to halve the maintenance therapy with methadone or buprenorphine in patients who have achieved abstinence from substance use and want to discontinue agonist support therapy. In any case, detoxification from opiates is always an essential phase of the rehabilitation program and treatment of heroin addiction. From a clinical point of view it is often a severe withdrawal syndrome , that can lead to relapse, and to the failure of the process of treatment and rehabilitation. Therefore, "acute detoxification" can be an important

	clinical goal in order to allow the continuation of the therapeutic and rehabilitative project set forth. Within the programs for opiate detox therapy, α2 adrenergic agonists have proved to be particularly effective, even for subjects in therapy with methadone or buprenorphine who wish to discontinue the agonist therapy. Other evidence have recently shown that α2 agonist therapy may be particularly effective co-administered with methadone to improve the treatment outcome and facilitate, in the course of a maintenance therapy with methadone, the switch to buprenorphine. Lofexidine, 2- [1-(2,6 dichlorophenoxy) -ethyl] -4,5-dihydro-1H-imidazoline monohydrochloride is an imidazoline derivative with α2 adrenergic agonist activity, with high affinity for the subtype a2A, and with inhibitory activity on the post-gangliar muscarininc receptors. Developed in the seventies , it was marketed for a short period by Nattermann GmbH with the name of Lofetensin® with the indication of essential hypertension. In October 1990, lofexidine was approved in the UK for the treatment of opiate withdrawal syndrome, and Britannia Pharmaceuticals obtained the marketing authorization as Britlofex ™ in 1992. Based on data from the Periodic Safety Update Report (PSUR) drawn up by the manufacturer, lofexidine was used from April 1997 to August 2000, by more than 78,000 subjects, from August 2000 to August 2005 by 96,500 subjects and from August 2005 to August 2008 by more than 47.400 subjects, always showing a favorable risk benefit profile. In February 2011, Laboratorio Farmaceutico C.T. srl obtained the Marketing Authorization (MA) for lofexidine (Dimatex®, AIC 037323019) in Italy with the indication of treatment of withdrawal symptoms in the course of detoxification from opiates. Lofexidine is pharmacologically similar to clonidine, despite having a much smaller antihypertensive activity with respect to clonidine and to other imidazole derivatives. This feature explains lofexidine lack of induction of the strong orthostatic hypotension, rather typical for clonidine. The mechanism of action of lofexidine in the treatment of opioid detoxification is common to that of other α2-adrenergic agonists. The prolonged suppression of noradrenergic activity in the locus coeruleus, caused by the inhibitory effect of opiates, causes an increase of α2-adrenergic receptors and a diminished synthesis of endorphins. Moreover, upon chronic consumption of opiates, the locus coeruleus develops tolerance: therefore, abstinence from opiates is followed by an increased release and turnover of noradrenaline. This adrenergic hyperactivity, commonly referred to as “Adrenergic Storm”, explains the most frequent withdrawal symptoms (sweating, hypertension, tachycardia, tremor, lacrimation, drowsiness, nausea, vomiting, cramps and muscle spasms). Lofexidine, by binding pre-synaptically to α2-adrenergic receptors, causes a decreased release of central noradrenaline and, consequently, reduces the signs and symptoms of opioid withdrawal. Lofexidine is readily absorbed after oral administration, reaching a peak after about 3 hours from its intake; It has a half-life of 11-12 hours and is metabolized primarily by the liver. The main side effects are closely linked to its mechanism of action and consist of dry mouth, drowsiness, dizziness and slight hypotension. For this reason, even without inducing the strong orthostatic hypotension that characterizes its analogue clonidine, lofexidine is contraindicated subjects treated with antihypertensive medications and in hypotensive subjects. Moreover, lofexidine can increase the depressive effects of substances such as alcohol, benzodiazepines and barbiturates, while its association with tricyclic antidepressants may minimize its effectiveness. Since a case-report showed a lengthening of the QT interval in a subject being treated with lofexidine and methadone, electrocardiographic monitoring is recommended when the drug is combined with other drugs that may prolong the QT interval. Data from Post Marketing Surveillance (PMS) of lofexidine, both when it was marketed as antihypertensive (Lofetensin®), and with the indication for the reduction of opioid withdrawal (Britlofex ™), never show any toxicity for pregnant women and lactating mothers. This information is not sufficient, however, to confirm the safety of lofexidine in these subjects.

Participants of the trial

Eligibility criteria for participants

Inclusion Criteria

- Men and women aged between 18 and 60 years
- Subjects diagnosed as heroin addicts according to DSM-IV criteria, whoser inclusion in a program of rapid detoxification is already planned; or subjects diagnosed as heroin addicts according to DSM-IV criteria and in course of maintenance treatment with methadone (<40 mg / day) or buprenorphine (<8 mg / day) or buprenorphine / naloxone (<8 mg / day) , whose inclusion in a program of detoxification from opiates is already planned.
- Subjets urine toxicological screening is positive for heroin and synthetic opiates (methadone, buprenorphine) and negative for other substances
- Subjects with no clinically significant abnormalities in the lab tests, that could interfere with the conduct and evaluation of the study
- Subjects willing and able to understand and sign a written informed consent.

Exclusion Criteria

- Women of childbearing age not using an acceptable contraception method or complete from sexual abstinence for the entire period of the study
- Women who are pregnant or breast-feeding or intend to conceive a child during the study period
- Subjects with blood pressure <90/60 mm / Hg and/or in treatment with antihypertensive medications
- Subjects with heart failure (NYHA class II) or heart rate <55 bpm at rest, or a severe cardiac condition in medical history
- Subjects affected by diabetes mellitus.
- Subjects affected by significant liver disease (AST and / or ALT> 3N).
- Subjects positive to HBV and/or HCV and undergoing a pharmacological treatment.
- Subjects affected by gastric disorders which might significantly alter the absorption of the study drug.
- Asthmatic subjects in chronic treatment.
- Subjects affected by severe psychiatric disorders including psychosis, bipolar disorders, schizophrenia, major depression
- Subjects who took part in other clinical trials within 3 months from enrollment.
- Subjects affected by epilepsy or who have been treated with anticonvulsants in the last 3 years.
- HIV positive subjects
- Subjects with obvious clinical history of renal disease (CL creatinine <55 mL / min).
- Subjects testing positive for alcohol concentration (at breath test) with values higher than 0.8 g /L
- Subjects potentially uncooperative during the study, in the opinion of the Investigator.

Settings and locations where the data were collected

The study was conducted at 23 clinical sites in Italy.
The Investigators and their address and roles are listed below:

Site no. 1 Sert Bergamo 2 – ASL Bergamo Dipartimento delle dipendenze P.zza Maggiore, 11 4057, Martinengo (BG) - Italia	*Site no. 8* Azienda Sanitaria Provinciale di Catanzaro Ser.T Soverato Via Trento e Trieste, 98 88068 Soverato (Cz)

	Site no. 2 A.S.L. Torino 2 Dipartimento Dipendenze 1 Corso Lombardia 187 10149 TORINO *Site no.3* A.S.L. della Provincia di Milano 2 Dipartimento delle Dipendenze Via Turati, 4 Cernusco sul Naviglio (Mi) *Site no.4* Ser.T di Lodi A.S.L. di Lodi Via Pallavicino 57/A 26900 Lodi *Site no.5* SERD AZ ULSS 21 Servizio Dipendenze Via Chiarenzi, 3 37059 Zevio (Vr) *Site no. 6* AZ ULSS 13 del Veneto Dipertimento per le Dipendenze Via Arino, 4 30031 Dolo (Ve) *Site no. 7* SOC Tossicodipendenze A.U.L.S.S. 18 Rovigo Viale Gramsci, 27 45100 Rovigo *Site no. 14* Dipartimento Dipendenze ASP Cosenza Via Fiume, 1 87100 Cosenza *Site no. 15* Ser T Catanzaro Azienda Sanitaria Provinciale Catanzaro Viale Pio X, 91/C 88100 Catanzaro *Site no. 16* Ser T Pescara AUSL Pescara Via Renato Paolini, 68 65124 Pescara	*Site no. 9* Dipartimento Dipendenze Sostanze d'Abuso c/o SerT area Azienda Ospedaliera Terni (ASL 4) Via Tristano di Joannuccio, 1 Terni *Site no. 10* Struttura Semplice SERT MVT AUSL2 dell' UMBRIA Via Piccolotti, 1 06055 Marsciano (Pg) *Site no. 11* Dipartimento Dipendenze Sostanze d'Abuso c/o SerT area Azienda Ospedaliera Terni (ASL 4) Via Tristano di Joannuccio, 1 Terni *Site no.12* U.O.C. Prevenzione e Cura Tossicodipendenze ed Alcolismo D11 ASL RMC Via Appia Antica, 220V 00178 Roma *Site no.13* Dipartimento Dipendenze Caserta ASL Caserta Via S. Lucia 81031 Aversa (Ce) *Site no. 19* ASL della Provincia di Bergamo Dipartimento delle Dipendenze Via Borgo Palazzo, 130 24121 – Bergamo *Site no. 20* ASL Omegna V.C.O Dipartimento delle Dipendenze – SOC. Ser. T Via Realini, 36 28883 Gravellona Toce-Vb *Site no. 21* Ser.T - Poliambulatorio di Cossato ASL di Biella Via Marconi, 166/A - 1° Piano 13836 Cossato (Bi)

	Site no. 17 DH di Psichiatria al Policlinico Gemelli Largo F. Vito, 1 00168 Roma *Site no. 18* ASL di Trapani Ser T Alcamo Via Cernaia, 8 91011 Alcamo (Tp)	*Site no. 22* Sert Treviglio ASL di Bergamo Via XXV Aprile, 6 24047 Treviglio (Bg) *Site no. 23* Sert Chieti ASL 2 Lanciano Vasto Chieti Via Discesa delle Carceri, 4 66100 Chieti

Interventions	A total number of 74 subjects were enrolled and analysed: - *6 subjects enrolled in the toxicological group A (Heroin)* - *22 subjects enrolled in the toxicological group B (Methadone < 40 mg/day)* - *46 subjects enrolled in the toxicological group C (Buprenorphine or Buprenorphine/Naloxone < 8 mg/day).* The administration and the daily dosage of the trial drug varied depending on the toxicological group. a) Patients addicted to heroin followed the treatment stages as described below: • Treatment start: within 24 hours from the last use of heroin • Duration of treatment: 10 days • Induction phase: 2 days (Day 1 0.8 mg/day, Day2 1.6 mg/day) • Maintenance phase: 3 days (2.4 mg/day) • Reduction phase: 5 days (Day 6 1.6 mg/day with subsequent daily reduction of 0.4 mg until reaching 0.2 mg/day on Day 10) b) Patients on methadone treatment (in abstinence from substance) with a dose <40 mg/day followed the treatment stages as described below: • Treatment initiation: 24 h after the last dose of methadone • Duration of treatment: 12 days • Induction phase: 2 days (Day 1 0.8 mg/day, Day21.6 mg/day) • Maintenance phase: 5 days (2.4 mg/day) • Reduction phase: 5 days (Day 8 1.6 mg/day with subsequent daily reduction of 0.4 mg until reaching 0.2 mg/day on Day 12). c) Patients treated with buprenorphine or buprenorphine/naloxone (in abstinence from substance use) with a dosage <8 mg/day followed the treatment stages as described below: • Treatment initiation: 24 h after the last dose of buprenorphine or buprenorphine/naloxone; • Duration of treatment: 11 days • Induction phase: 2 days (Day 1 0.8 mg/day, Day21.2 mg/day) • Maintenance phase: 5 days (1.6 mg/day) • Reduction phase: 4 days (Day 8 1.2 mg/day with subsequent reduction of 0.4 mg/day until reaching 0.2 mg/day to Day 11).
Objective(s) of the Trial	***Primary Objectives*** 1. Confirm the profile of tolerability and safety of use of lofexidine for the duration of the treatment 2. Evaluate the effectiveness of lofexidine in the process of drug-free *detoxification* ***Secondary Objectives*** 1. To assess whether the standard dosage schedule of lofexidine used in the English clinical practice can be used satisfactorily also in the Italian services for drug addiction for the drug-free detoxification program from heroin, methadone or buprenorphine, buprenorphine / naloxone.
Outcome measures	*Primary outcomes:* - Frequency and type of adverse events. - Quantification of withdrawal symptoms by SOWS (Subjective Opiate Withdrawal Scale) and assessment of craving by VAS (Visual Analogic Scale). Adverse events reported during the study will be coded as MedDRA preferred term and summarized using frequency and percentage by type and location. *Secondary outcomes:* - Number of patients who have completed the treatment. - Number of patients relapsed to opiate use during follow-up.
Randomisation implementation	Not applicable, this study was a single arm study.

Blinding	Not applicable, the study was an open label study.
Statistical methods	The number of subjects enrolled for each toxicological group (drug treatment for heroin, methadone detoxification subjects and buprenorphine or buprenorphine/ naloxone detoxification subjects) was reported. The demographics and patient characteristics at baseline were analyzed by toxicological group. Continuous variables were summarized by the number of patients, mean, standard deviation, median, minimum, maximum. Categorical variables were summarized by the number and the proportion of patients. The significance level of the statistical test was 0.05 and the confidence intervals of the indicators estimated at 95%. Adverse events reported during the study were coded according to the MedDRA coding and described using frequency and percentage. The number and percentage of subjects with at least one adverse event were reported. The frequency of AE by SOC (System Organ Class) and PT (Preferred Term) and characteristics of the events of the subjects (severity, duration, outcome, etc.) were also investigated. Withdrawal symptoms were quantified using SOWS. The values obtained at the peak of SOWS (typically, a few days after the start of treatment) and at the end of the treatment were compared using T-test for repeated measures. The craving was assessed using a VAS scale with values from 0 to 100. Values obtained at different time point were compared to baseline using t-test for repeated measures. The proportion of subjects who completed the treatment according to the prescribed schedule and the percentage of patients who relapsed to opiates use during follow-up were assessed.
Participant flow	A total of 85 subjects were screened for the study. The first subject signed the informed consent and performed the Visit 1 (Day 1) on September 17th, 2012 and the last subject on June 26th, 2014. A total of 74 subjects matched the inclusion/exclusion criteria outlined in the protocol and accepted to be enrolled in the study at the baseline visit (Day 1). They started the assigned treatment on treatment day 1. The last subject completed the study on October 21st, 2014. The following figure shows the patients' disposition at each visit.
Recruitment	First subject enrolled: September 17th, 2012 Last subject completed: October 21st, 2014

Baseline data

Characteristic	Category		Treatment group		
			HEROIN	METHADONE	BUPRENORPHINE
Gender	Men	N	5	17	41
		%	83.33	77.27	89.13
	Women	N	1	5	5
		%	16.67	22.73	10.87
Race	Caucasian	N	6	22	46
		%	100.00	100.00	100.00
SOWS at Day 1		Mean	15.00	7.30	6.52
		SD	15.90	7.36	7.43
VAS for craving at Day 1		Mean	2.83	0.97	0.82
		SD	2.88	1.71	2.00

Trial interruption	The trial was not interrupted

Outcomes and estimation	**Efficacy results:** *Primary endpoints* The occurrence and intensity of withdrawal symptoms was assessed each treatment day through the SOWS. In the Heroin group, the SOWS increased between day 1 and day 2 and then it starts to decline. Despite the low number of subjects, a statically significant decrease was observed at day 4 and from day 6 to day 10 (i.e., the end of treatment day – Mean difference = -10.50, *p=0.0303*). In the methadone group, the SOWS significantly increased between Day 1 and Day 3, then it started to decrease considerably, but the decrease was not constant over time and not significant at end of treatment (day 12 – Mean difference = -5.2). The only statically significant decrease was observed at day 9 (Mean difference = -5.07, *p=0.0271*). In the Buprenorpfhine group, the SOWS significantly increased between day 1 and day 2 and then it started to decline constantly over time. A statically significant decrease was observed from day 6 to day 11 (i.e., the end of treatment day – Mean difference = -5.69, *p=0.0093*). The intensity of craving for drug was assessed at each treatment day through a VAS ranging between 0 and 100 mm. In the Heroin group, only very few patient filled in the VAS and no statistical analysis could be reliably performed. In the methadone group, the SOWS significantly increased between Day 1 and Day 3, then it started to decrease, but the decrease was not constant over time and not significant at end of treatment (day 12 – Mean difference = -1.51, *p=0.0846*). The only statically significant decrease was observed at day 11 (Mean difference = -1.61, *p=0.0397*). In the buprenorphine group, the VAS score for craving increased between day 1 and day 2 (peak day) and the increase was statistically significant (0.0093). After day 2, the VAS score started to decrease and the decrease was quite constant over time. The decrease was statistically significant at day 6 and followings. At end of treatment the maximum decrease was observed (-1.79) and it was statistically significant (p=0.0093). *Secondary endpoints* The study was correctly completed by 2 subjects in the heroin group (33.33%), 9 patients in the methadone group (40.91%) and 31 patients in the buprenorphine group (67.39%). The percentage of patients that relapsed to opiates (heroin, methadone or buprenorphine) at end of treatment or during follow-up was not easily assessable, due to the large number of subjects that did not perform the toxicological tests. No patient relapsed to any opiate (i.e., no patient was positive to at least one toxicological test for opiate) in the heroine group, 3 subjects relapsed to opiates in the methadone group out of 14 tested (22.22%) and 14 subjects in the buprenorphine group out of the 35 tested (40.00%).
Ancillary analysis	Not Applicable

Adverse events	Twenty-three patients experienced at least one Adverse Event (AE): 1 (16.67%) in the Heroin group, 10 (45.45%) in the Methadone group and 12 (26.09%) in the Buprenorphine group. They globally reported forty-three AEs: 2, 12, and 15 in the Heroin, Methadone and Buprenorphine group, respectively. Thirty-three AEs were considered possibly, probably or definitely related to the study treatment. Only ten AEs were considered not or unlikely related to the study treatment (7 in the methadone and 3 in the buprenorphine group, respectively). Twenty adverse events were mild, 19 moderate and only 4 were severe or very severe. Six AEs lead to permanent drug discontinuation and ten to other actions. Most of the AEs were completely resolved before the end of the study (36 out of 43), six were ongoing and one was experienced by a subject that was lost to follow-up. No SAE were observed.
Trial termination	Study terminated prematurely YES☐ NO ☒
Discussion and interpretation of study results	An increase both in the SOWS and in the VAS in the first days of treatment was observed. This was expected as there was a sudden "stop" in the opioid assumption. Lofexidine treatment is of help in the control of the withdrawal symptoms and the parameters above (SOWS and VAS scores) tend to decrease after the first 3-5 days. In virtually all patients, the control of abstinence seems satisfactory, precisely because, after the initial increase, the values tend to stabilize or decrease. This obviously would not happen without a treatment with Lofexidine: the situation would worsen rather than stabilize or improve. It seems, on average, a better answer in the buprenorphine group. The compliance to treatment is very good (over 80% in the group buprenorphine and very close to 80% in the other groups). It's important to underline the generally good tolerability and safety of the treatment, no SAE were observed, only a minority (10/43) of AEs needed intervention measures, the majority (> 80%) has recovered before the end of the study, only 6 cases had to discontinue the treatment for an AE. Also for safety, the situation looks better in the buprenorphine group.