Clinical trial results:
A 12-week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Once-Weekly Intra-Muscular Injections of TV-1380 (150 mg/week or 300 mg/week) as Treatment for Facilitation of Abstinence in Cocaine-Dependent Subjects

Summary

EudraCT number	2013-000208-41
Trial protocol	ES
Global end of trial date	09 June 2014

Results information

Result version number	v2 (current)
This version publication date	23 July 2016
First version publication date	09 April 2016
Version creation reason	• Correction of full data set Justification added

Trial information

Trial identification

Sponsor protocol code	TV1380-COA-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01887366
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Teva Pharmaceutical Industries Ltd.
Sponsor organisation address	5 Bazel Street, Petach Tikva, Israel,
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 01 215-591-3000, ustevatrials@tevapharm.com
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc, 01 215-591-3000, ustevatrials@tevapharm.com

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 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the efficacy and safety of TV-1380 in facilitating abstinence in cocaine-dependent subjects.

Protection of trial subjects:

Before this study starts, the protocol will be submitted to the national/local health authorities and to each IEC/IRB for review. As required, the study will not start at a given investigational center before the IEC/IRB and health authority (where applicable) for the center give written approval or a favorable opinion.
The investigator, or a qualified person designated by the investigator, should fully inform the subject of all pertinent aspects of the study, including the written information approved by the IRB/IEC. Written informed consent will be obtained from each subject before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained, according to the IRB/IEC requirements. The subject's willingness to participate in the study will be documented in writing in a consent form, which will be signed and personally dated by the subject. The investigator will keep the original consent forms, and copies will be given to the subjects. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.
Written and oral information about the study in a language understood by the subject will be given to all subjects.

Each investigator must assure that the privacy of the subjects, including their identity and all personal medical information, is maintained at all times. In CRFs and other documents/images submitted to the sponsor, subjects will be identified not by their names, but by an identification code (e.g., initials and identification number).
Personal medical information will always be treated as confidential.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	28 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United States: 196
Worldwide total number of subjects	208
EEA total number of subjects	12

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)	208
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

382 subjects were screened and 208 were stratified by: 1) alcohol dependence or non-dependence, 2) route of cocaine administration, 3) positive or negative last urine cocaine screening prior to randomization, and 4) country, and then randomized into one of the 3 treatment arms in a 1:1:1 ratio.

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	Investigator, Subject

Blinding implementation details:

- A transparent colored tape was wrapped around each TV-1380 or placebo subject syringe because the two solutions were not identical in color.
- An unblinded pharmacist or health care professional (independent of the study) prepared the study drug syringe and blinded it prior to administration.
- The injection volume of 3.0 mL was the same for all treatments. The TV-1380 150 mg treatment arm was a mix of 1.5 mL TV-1380 plus 1.5 mL placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects randomly assigned to the Placebo treatment arm were administered one intra-muscular (IM) injection of placebo over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects randomly assigned to placebo received one IM injection of 3ml QW over 12 weeks (Week 1-Week 12). The placebo injection was administered into the buttock (gluteus maximus muscle).

Arm title	TV-1380 150 mg/week

Arm description:

Subjects randomly assigned to TV-1380 150 mg/week treatment arm were administered one intra-muscular (IM) injection of 150 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).

Arm type	Experimental
Investigational medicinal product name	TV-1380
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects randomly assigned to TV-1380, 150 or 300 mg, were administered one intra-muscular (IM) injection of 150 or 300 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle). TV-1380 drug product was provided as a lyophilized cake which can deliver 100 mg of

TV-1380 in 1 mL of formulation buffer. All study injections were 3 mL. Therefore the 150 mg/week treatment consisted of 1.5 mL TV-1380 and 1.5 mL placebo.

Arm title	TV-1380 300 mg/week

Arm description:

Subjects randomly assigned to TV-1380 300 mg/week treatment arm were administered one intra-muscular (IM) injection of 300 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).

Arm type	Experimental
Investigational medicinal product name	TV-1380
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Subjects randomly assigned to TV-1380, 150 or 300 mg, were administered one intra-muscular (IM) injection of 150 or 300 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle). TV-1380 drug product was provided as a lyophilized cake which can deliver 100 mg of
TV-1380 in 1 mL of formulation buffer. All study injections were 3 mL.

Number of subjects in period 1	Placebo	TV-1380 150 mg/week	TV-1380 300 mg/week
Started	69	70	69
Safety population	67	70	68
Full analysis set (FAS)	67	70	68
Completed	55	59	57
Not completed	14	11	12
Consent withdrawn by subject	3	4	4
Not specified	4	1	-
Non-compliance	-	1	1
Lost to follow-up	5	3	6
Protocol deviation	2	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects randomly assigned to the Placebo treatment arm were administered one intra-muscular (IM) injection of placebo over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).	
Reporting group title	TV-1380 150 mg/week
Reporting group description:	
Subjects randomly assigned to TV-1380 150 mg/week treatment arm were administered one intra-muscular (IM) injection of 150 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).	
Reporting group title	TV-1380 300 mg/week
Reporting group description:	
Subjects randomly assigned to TV-1380 300 mg/week treatment arm were administered one intra-muscular (IM) injection of 300 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).	

Reporting group values	Placebo	TV-1380 150 mg/week	TV-1380 300 mg/week
Number of subjects	69	70	69
Age categorical Units: Subjects			
Adults (18-64 years)	69	70	69
Age continuous Units: years			
arithmetic mean	47.5	47.2	46.4
standard deviation	± 8.24	± 8.18	± 7.05
Gender categorical Units: Subjects			
Female	26	20	21
Male	43	50	48
Race Units: Subjects			
White	10	13	10
Black	56	55	52
Other	2	2	7
Missing	1	0	0
Ethnicity Units: Subjects			
Not Hispanic or Latino	64	64	61
Hispanic or Latino	5	6	8
Alcohol dependence			
A stratification factor			
Units: Subjects			
Yes	7	7	5
No	62	63	64
Cocaine route of administration			
A stratification factor			
Units: Subjects			
Smoking	54	54	53

Snorting	15	16	16
Last urine cocaine screen prior to randomization			
A stratification factor			
Units: Subjects			
Positive	62	62	61
Negative	7	8	8
Country			
A stratification factor			
Units: Subjects			
United States	65	65	66
Spain	4	5	3
Weight			
Units: kg			
arithmetic mean	86.7	83.6	84.7
standard deviation	± 21.74	± 14.88	± 21.68
Height			
Units: cm			
arithmetic mean	171.8	173.5	173.5
standard deviation	± 11.42	± 9.36	± 9.29
Body Mass Index			
Units: kg/m^2			
arithmetic mean	29.3	28	28.1
standard deviation	± 6.47	± 5.99	± 7.02

Reporting group values	Total		
Number of subjects	208		
Age categorical			
Units: Subjects			
Adults (18-64 years)	208		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	67		
Male	141		
Race			
Units: Subjects			
White	33		
Black	163		
Other	11		
Missing	1		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	189		
Hispanic or Latino	19		
Alcohol dependence			
A stratification factor			
Units: Subjects			

Yes	19		
No	189		
Cocaine route of administration			
A stratification factor			
Units: Subjects			
Smoking	161		
Snorting	47		
Last urine cocaine screen prior to randomization			
A stratification factor			
Units: Subjects			
Positive	185		
Negative	23		
Country			
A stratification factor			
Units: Subjects			
United States	196		
Spain	12		
Weight Units: kg arithmetic mean standard deviation	- -		
Height Units: cm arithmetic mean standard deviation	- -		
Body Mass Index Units: kg/m^2 arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects randomly assigned to the Placebo treatment arm were administered one intra-muscular (IM) injection of placebo over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).	
Reporting group title	TV-1380 150 mg/week
Reporting group description:	
Subjects randomly assigned to TV-1380 150 mg/week treatment arm were administered one intra-muscular (IM) injection of 150 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).	
Reporting group title	TV-1380 300 mg/week
Reporting group description:	
Subjects randomly assigned to TV-1380 300 mg/week treatment arm were administered one intra-muscular (IM) injection of 300 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).	
Subject analysis set title	FAS - Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects randomly assigned to the Placebo treatment arm were administered one intra-muscular (IM) injection of placebo over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle). The full analysis set (FAS) included all subjects in the ITT population who receive at least 1 dose of study drug.	
Subject analysis set title	FAS - TV-1380 150 mg/week
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects randomly assigned to TV-1380 150 mg/week treatment arm were administered one intramuscular (IM) injection of 150 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle). The full analysis set (FAS) included all subjects in the ITT population who receive at least 1 dose of study drug.	
Subject analysis set title	FAS - TV-1380 300 mg/week
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects randomly assigned to TV-1380 300 mg/week treatment arm were administered one intramuscular (IM) injection of 300 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle). The full analysis set (FAS) included all subjects in the ITT population who receive at least 1 dose of study drug.	
Subject analysis set title	Completers - Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Subjects randomly assigned to the Placebo treatment arm were administered one intra-muscular (IM) injection of placebo over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle). The completers analysis set includes all subjects in the ITT population who took the study drug according to protocol.	
Subject analysis set title	Completers - TV-1380 150 mg/week
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Subjects randomly assigned to TV-1380 150 mg/week treatment arm were administered one intramuscular (IM) injection of 150 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle). The completers analysis set included all subjects in the ITT population who took the study drug according to protocol.	
Subject analysis set title	Completers - TV-1380 300 mg/week

Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subjects randomly assigned to TV-1380 300 mg/week treatment arm were administered one intramuscular (IM) injection of 300 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).
The completers analysis set included all subjects in the ITT population who took the study drug according to protocol.

Subject analysis set title	Safety - Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects randomly assigned to the Placebo treatment arm were administered one intra-muscular (IM) injection of placebo over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).
The safety population included all randomized subjects who receive at least 1 dose of study drug. In this analysis set, treatment was assigned based upon the treatment subjects actually receive, regardless of the treatment to which they were randomized.

Subject analysis set title	Safety - TV-1380 150 mg/week
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects randomly assigned to TV-1380 150 mg/week treatment arm were administered one intramuscular (IM) injection of 150 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).
The safety population included all randomized subjects who receive at least 1 dose of study drug. In this analysis set, treatment was assigned based upon the treatment subjects actually receive, regardless of the treatment to which they were randomized.

Subject analysis set title	Safety - TV-1380 300 mg/week
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects randomly assigned to TV-1380 300 mg/week treatment arm were administered one intramuscular (IM) injection of 300 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).
The safety population included all randomized subjects who receive at least 1 dose of study drug. In this analysis set, treatment was assigned based upon the treatment subjects actually receive, regardless of the treatment to which they were randomized.

Primary: Percentage of Subjects from the Full Analysis Set (FAS) Who Abstained From Using Cocaine in the Last Three Weeks of Study

End point title	Percentage of Subjects from the Full Analysis Set (FAS) Who Abstained From Using Cocaine in the Last Three Weeks of Study

End point description:

Abstinence from cocaine during the last three weeks of the treatment phase (weeks 10-12) was based on daily self-report of no use confirmed by urine samples considered negative for cocaine metabolites.
In order to consider a subject as abstinent during weeks 10-12, the following criteria was met:
1. Self-report of no use during each whole week
2. At least one analyzable urine sample is available during each of the above weeks (usually collected thrice weekly)
3. All urine samples provided during each of the above weeks were considered negative for cocaine metabolites (BE<150 ng/ml and EME<15 ng/ml).

In case no urine sample was provided or no analyzable urine sample was available during a single week (week 10, 11 or 12), it was considered that cocaine has been used for that specific week regardless of the information from self-report.

End point type	Primary

End point timeframe:

Weeks 10-12

End point values	FAS - Placebo	FAS - TV-1380 150 mg/week	FAS - TV-1380 300 mg/week	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	67	70	68	
Units: percentage of subjects				
number (not applicable)	0	6	6	

Statistical analyses

Statistical analysis title	Abstinence Weeks 10-12: Placebo + 150mg

Statistical analysis description:

The odds ratios (active vs placebo), confidence intervals, and p-values were calculated from a logistic regression analysis stratified by country with the following effects: treatment group, alcohol dependence or non-dependence, route of cocaine administration, and positive or negative last urine cocaine screening prior to randomization. 95% CI value of 999 = infinity

Comparison groups	FAS - TV-1380 150 mg/week v FAS - Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1487 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.616
upper limit	999

Notes:

[1] - 5% significance level

Statistical analysis title	Abstinence Weeks 10-12: Placebo + 300mg

Statistical analysis description:

The odds ratios (active vs placebo), confidence intervals, and p-values were calculated from a logistic regression analysis stratified by country with the following effects: treatment group, alcohol dependence or non-dependence, route of cocaine administration, and positive or negative last urine cocaine screening prior to randomization. 95% CI value of 999 = infinity

Comparison groups	FAS - Placebo v FAS - TV-1380 300 mg/week
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1205 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	999

Notes:

[2] - 5% significance level

Primary: Percentage of Subjects from the Completers Analysis Set Who Abstained From Using Cocaine in the Last Three Weeks of Study

End point title	Percentage of Subjects from the Completers Analysis Set Who Abstained From Using Cocaine in the Last Three Weeks of Study

End point description:

Abstinence from cocaine during the last three weeks of the treatment phase (weeks 10-12) was based on daily self-report of no use confirmed by urine samples considered negative for cocaine metabolites.
In order to consider a subject as abstinent during weeks 10-12, the following criteria was met:
1. Self-report of no use during each whole week
2. At least one analyzable urine sample is available during each of the above weeks (usually collected thrice weekly)
3. All urine samples provided during each of the above weeks were considered negative for cocaine metabolites (BE<150 ng/ml and EME<15 ng/ml).
In case no urine sample was provided or no analyzable urine sample was available during a single week (week 10, 11 or 12), it was considered that cocaine has been used for that specific week regardless of the information from self-report.

End point type	Primary

End point timeframe:

Weeks 10-12

End point values	Completers - Placebo	Completers - TV-1380 150 mg/week	Completers - TV-1380 300 mg/week	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	53	57	58	
Units: percentage of subjects				
number (not applicable)	0	7	7	

Statistical analyses

Statistical analysis title	Abstinence Weeks 10-12: Placebo + 150mg

Statistical analysis description:

The odds ratios (active vs placebo), confidence intervals, and p-values were calculated from a logistic regression analysis stratified by country with the following effects: treatment group, alcohol dependence or non-dependence, route of cocaine administration, and positive or negative last urine cocaine screening prior to randomization. 95% CI value of 999 = infinity

Comparison groups	Completers - TV-1380 150 mg/week v Completers - Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.104 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.976
upper limit	999

Notes:

[3] - 5% significance level

Statistical analysis title	Abstinence Weeks 10-12: Placebo + 300mg

Statistical analysis description:

The odds ratios (active vs placebo), confidence intervals, and p-values were calculated from a logistic regression analysis stratified by country with the following effects: treatment group, alcohol dependence or non-dependence, route of cocaine administration, and positive or negative last urine cocaine screening prior to randomization. 95% CI value of 999 = infinity

Comparison groups	Completers - Placebo v Completers - TV-1380 300 mg/week
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1165 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.803
upper limit	999

Notes:

[4] - 5% significance level

Secondary: Mean Percentage of Negative Urine Samples During Weeks 5-12

End point title	Mean Percentage of Negative Urine Samples During Weeks 5-12

End point description:

The secondary efficacy endpoint for this study was defined as the percent of urine samples that were considered negative for cocaine metabolites (BE<150 ng/ml and EME<15 ng/ml) out of all planned urine samples during the last 8 weeks of the treatment phase (weeks 5-12).

End point type	Secondary

End point timeframe:

Weeks 5-12

End point values	FAS - Placebo	FAS - TV-1380 150 mg/week	FAS - TV-1380 300 mg/week	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63[5]	67[6]	66[7]	
Units: percentage of planned urine samples				
least squares mean (standard error)	12.3 (± 3.91)	15.7 (± 3.78)	20.7 (± 3.91)	

Notes:

[5] - Missing subjects discontinued prior to Week 5.

[6] - Missing subjects discontinued prior to Week 5.

[7] - Missing subjects discontinued prior to Week 5.

Statistical analyses

Statistical analysis title	% Negative Urine Samples - Placebo + TV-1380 150mg

Statistical analysis description:

An analysis of covariance (ANCOVA) model was used to compare the LS means percent of urine samples per subject that are considered negative for cocaine metabolites during week 5-week 12 (study days 29-84). The model included the following effects: treatment group, pooled center, alcohol dependence or non-dependence, route of cocaine administration, and positive or negative last urine cocaine at screening prior to randomization.

Comparison groups	FAS - Placebo v FAS - TV-1380 150 mg/week
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3607 [8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.93
upper limit	10.74
Variability estimate	Standard error of the mean
Dispersion value	3.717

Notes:

[8] - 5% significance level

Statistical analysis title	% Negative Urine Samples - Placebo + TV1380 300mg

Statistical analysis description:

An analysis of covariance (ANCOVA) model was used to compare the LS means percent of urine samples per subject that are considered negative for cocaine metabolites during week 5-week 12 (study days 29-84). The model included the following effects: treatment group, pooled center, alcohol dependence or non-dependence, route of cocaine administration, and positive or negative last urine cocaine at screening prior to randomization.

Comparison groups	FAS - Placebo v FAS - TV-1380 300 mg/week
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0268 [9]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	8.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	15.81
Variability estimate	Standard error of the mean
Dispersion value	3.759

Notes:

[9] - 5% significance level

Secondary: Subjects with Adverse Events

End point title	Subjects with Adverse Events

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment. AEs summarized are those that began or worsened after treatment with study drug. The relationship to study drug treatment and study procedures, and the severity and seriousness of each adverse event was judged by the investigator. Severity was graded as 1) Mild: No limitation of usual activities 2) Moderate: Some limitation of usual activities or 3) Severe: Inability to carry out usual activities. Relationship was considered as not related, or there was a reasonable possibility of relation to study drug. A serious AE includes death, a life-threatening AE, in-patient hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or an important medical event requiring intervention to prevent one of the aforementioned.

End point type	Secondary

End point timeframe:

Day 1 to Week 12

End point values	Safety - Placebo	Safety - TV-1380 150 mg/week	Safety - TV-1380 300 mg/week	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	67	70	68	
Units: Subjects				
Any adverse event	42	51	54	
Severe adverse event	1	0	1	
Treatment-related AE	9	15	17	
Deaths	0	0	0	
Other serious AEs	2	0	3	
Withdrawn from treatment due to AE	2	2	1	
Withdrawn from study due to AE	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with Clinically Significant Abnormal Serum Chemistry Values

End point title	Subjects with Clinically Significant Abnormal Serum Chemistry Values

End point description:

Clinically significant criteria:
Sodium: >=147 mmol/L
Potassium Low: <=3.3 mmol/L
Potassium High: >=5.4 mmol/L
Glucose Low: <=55 mmol/L
Glucose High: >=200 mmol/L
Creatinine: >=2 µmol/L
Phosphorus: <=2 mmol/L
AST: >=3x upper limit of normal
ALT: >=3x upper limit of normal
GGT: >=3x upper limit of normal
Total bilirubin: >=1.5x upper limit of normal

End point type	Secondary

End point timeframe:

Day 1 to Week 12

End point values	Safety - Placebo	Safety - TV-1380 150 mg/week	Safety - TV-1380 300 mg/week	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	64	68	66	
Units: subjects				
Sodium	0	3	0	
Potassium Low	4	4	1	
Potassium High	2	4	1	
Glucose Low	2	3	1	
Glucose High	1	2	5	
Creatinine	2	1	0	
Phosphorus	1	1	0	
AST	0	0	2	
ALT	0	0	2	
GGT	2	2	3	
Total bilirubin	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with Clinically Significant Abnormal Hematology Values

End point title	Subjects with Clinically Significant Abnormal Hematology Values

End point description:

Clinically Significant Criteria:
Hemoglobin - males: <=115 g/L
Hemoglobin - females: <=100 g/L
WBC count: <=3 * 10^9/L
Platelet count: >=600 * 10^9/L

End point type	Secondary

End point timeframe:

Day 1 to week 12

End point values	Safety - Placebo	Safety - TV-1380 150 mg/week	Safety - TV-1380 300 mg/week	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	64	68	66	
Units: subjects				
Hemoglobin	4	3	5	
WBC count	0	2	2	
PLatelet count	0	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with Clinically Significant Abnormal Vital Sign Values

End point title	Subjects with Clinically Significant Abnormal Vital Sign Values

End point description:

Clinically Significant Criteria:
Pulse High: >=120 bpm and increase >=15
Pulse Low: <=45 bpm and decrease >=1538.3
Sitting Systolic BP High: >=180 mmHg and increase >=20
Sitting Systolic BP Low: <=90 mmHg and decrease >=20
Sitting Diastolic BP High: >=100 mmHg and increase >=15
Sitting Diastolic BP Low: <=50 mmHg and decrease >=15
Body Temperature Low: <=35.5 ºC
Body Temperature High: >=38.3 ºC and increase from baseline of >=2 ºC
Respiratory rate: <=10 breaths/min
Height: <=147 cm
Weight: >=137 kg

End point type	Secondary

End point timeframe:

Day 1 to Week 12

End point values	Safety - Placebo	Safety - TV-1380 150 mg/week	Safety - TV-1380 300 mg/week	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	67	70	68	
Units: subjects				
Pulse High	1	2	1	
Pulse Low	1	0	0	
Sitting Systolic BP High	0	1	1	
Sitting Systolic BP Low	3	2	1	
Sitting Diastolic BP High	5	3	7	
Sitting Diastolic BP Low	0	1	1	
Body Temperature Low	4	2	2	
Body Temperature High	0	0	1	

Respiratory rate	0	1	1	
Height	1	0	0	
Weight	3	0	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with Newly Diagnosed Electrocardiogram Abnormalities

End point title	Subjects with Newly Diagnosed Electrocardiogram Abnormalities

End point description:

Includes only subjects with both baseline and postbaseline electrocardiograms. A subject is considered to have a newly diagnosed finding when the baseline finding is normal and there is an abnormal postbaseline finding.
For the Overall Total, the worst postbaseline finding, i.e. the abnormal finding if there are both normal and abnormal findings, are counted for each subject.
Endpoint is end of study.

End point type	Secondary

End point timeframe:

Day 1 to Week 12

End point values	Safety - Placebo	Safety - TV-1380 150 mg/week	Safety - TV-1380 300 mg/week	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	67	70	68	
Units: subjects				
Overall total	11	13	11	
Newly diagnosed -- Week 4	8	8	7	
Newly diagnosed -- Week 12	5	7	6	
Newly diagnosed -- Endpoint	8	8	9	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 12

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	PLACEBO

Reporting group description:

Subjects randomly assigned to the Placebo treatment arm were administered one intra-muscular (IM) injection of placebo over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).
The safety population included all randomized subjects who receive at least 1 dose of study drug. In this analysis set, treatment was assigned based upon the treatment subjects actually receive, regardless of the treatment to which they were randomized.

Reporting group title	TV-1380 150 mg/week

Reporting group description:

Subjects randomly assigned to TV-1380 150 mg/week treatment arm were administered one intramuscular (IM) injection of 150 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).
The safety population included all randomized subjects who receive at least 1 dose of study drug. In this analysis set, treatment was assigned based upon the treatment subjects actually receive, regardless of the treatment to which they were randomized.

Reporting group title	TV-1380 300 mg/week

Reporting group description:

Subjects randomly assigned to TV-1380 300 mg/week treatment arm were administered one intramuscular (IM) injection of 300 mg once weekly (QW) over 12 weeks (week 1-week 12) into the buttock (gluteus maximus muscle).
The safety population included all randomized subjects who receive at least 1 dose of study drug. In this analysis set, treatment was assigned based upon the treatment subjects actually receive, regardless of the treatment to which they were randomized.

Serious adverse events	PLACEBO	TV-1380 150 mg/week	TV-1380 300 mg/week
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 67 (2.99%)	0 / 70 (0.00%)	3 / 68 (4.41%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 67 (1.49%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	0 / 67 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	2 / 67 (2.99%)	0 / 70 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 67 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 67 (0.00%)	0 / 70 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	PLACEBO	TV-1380 150 mg/week	TV-1380 300 mg/week
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 67 (32.84%)	24 / 70 (34.29%)	34 / 68 (50.00%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 67 (1.49%)	3 / 70 (4.29%)	5 / 68 (7.35%)
occurrences (all)	1	4	5
Nervous system disorders			
Somnolence			
subjects affected / exposed	4 / 67 (5.97%)	2 / 70 (2.86%)	0 / 68 (0.00%)
occurrences (all)	4	3	0
Headache			
subjects affected / exposed	3 / 67 (4.48%)	2 / 70 (2.86%)	4 / 68 (5.88%)
occurrences (all)	3	2	4

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 67 (7.46%)	4 / 70 (5.71%)	6 / 68 (8.82%)
occurrences (all)	7	4	6
Diarrhoea			
subjects affected / exposed	2 / 67 (2.99%)	3 / 70 (4.29%)	4 / 68 (5.88%)
occurrences (all)	2	3	4
Vomiting			
subjects affected / exposed	1 / 67 (1.49%)	4 / 70 (5.71%)	3 / 68 (4.41%)
occurrences (all)	1	4	3
Toothache			
subjects affected / exposed	2 / 67 (2.99%)	0 / 70 (0.00%)	4 / 68 (5.88%)
occurrences (all)	2	0	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 67 (8.96%)	3 / 70 (4.29%)	2 / 68 (2.94%)
occurrences (all)	8	4	3
Back pain			
subjects affected / exposed	3 / 67 (4.48%)	1 / 70 (1.43%)	4 / 68 (5.88%)
occurrences (all)	3	1	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 67 (10.45%)	9 / 70 (12.86%)	8 / 68 (11.76%)
occurrences (all)	7	10	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2013	Amendment 01 to the protocol (dated 13 May 2013) was issued following an official response letter from the US Food and Drug Administration (FDA). No subjects were enrolled in the study at that time; the first subject enrolled in the study in June 2013. The following major procedural changes (not all-inclusive) were made to the protocol: - Certain monitoring procedures were added (prospective assessment for suicidality using the C-SSRS instrument once per week; - Inclusion of a statement that at that time, clinical studies have not demonstrated a protective effect of TV- 1380 against cocaine toxicity, and it has not been demonstrated that cocaine abusers can tolerate higher doses of cocaine after TV-1380 treatment. - Modification of the exclusion criterion regarding previous suicidal attempt or current suicidal risk; - Heart rate would be measured instead of pulse; - Clarification that the SAS-SR (short version) would be used; - INR measurement was deleted, since this was not performed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported