



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 | v1 |
| This version publication date | 09 April 2016 |
| First version publication date | 09 April 2016 |

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 - Placebo v FAS - TV-1380 150 mg/week |
| 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 μ mol/L

Phosphorus: ≤ 2 mmol/L

AST: ≥ 3 x upper limit of normal

ALT: ≥ 3 x upper limit of normal

GGT: ≥ 3 x upper limit of normal

Total bilirubin: ≥ 1.5 x 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: $\leq 3 \times 10^9$ /L

Platelet count: $\geq 600 \times 10^9$ /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 °C

Body Temperature High: ≥ 38.3 °C and increase from baseline of ≥ 2 °C

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 | <p>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:</p> <ul style="list-style-type: none">- 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