

**Clinical trial results:****The Efficacy of Ibogaine in the Treatment of Addiction; an open label, single fixed dose pilot-study of the efficacy of ibogaine in opioid-dependent subjects****Summary**

| | |
|--------------------------|-----------------|
| EudraCT number | 2014-000354-11 |
| Trial protocol | NL |
| Global end of trial date | 30 October 2019 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 24 December 2022 |
| First version publication date | 07 May 2022 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set Data has been published and will now be added to the register. |
| Summary attachment (see zip file) | Safety of ibogaine administration~1 Knuijver et.al. (Addiction - 2021 - Knuijver - Safety of ibogaine administration in detoxification of opioiddependent individuals a.pdf) ASI results (ASI.pdf) QTc measurement per subject (QTc.pdf) Summary of HR and BP measurements (RR HR.pdf) All SARA measurements (SARA.pdf) Lab results pre and during treatment (Lab results.pdf) Summary of QTc measurements (QTc Summary.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|----------|
| Sponsor protocol code | ABR47613 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Dept Psychiatry, Radboudumc, Nijmegen |
| Sponsor organisation address | Reinier Postlaan 10, Nijmegen, Netherlands, 6525 GC |
| Public contact | Dept Psychiatry 966, Radboud UMC, 31 243613490, robbert-jan.verkes@radboudumc.nl |
| Scientific contact | Dept Psychiatry 966, Dept Psychiatry, Radboudumc, 31 243613490, robbert-jan.verkes@radboudumc.nl |

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 | 30 November 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 November 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 October 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

1. To investigate, in patients with opioid dependence, the short and long term effects of a single administration of ibogaine on cardiac, cerebellar and psychomimetic safety, craving and substance use during immediately after detoxification and during a six month follow up period.

Protection of trial subjects:

During the 24 hours after administration of the drug, participants are in calm, single hospital room with a bed and with continuous monitoring.

Electrocardiographic monitoring (ECG) is performed every half hour for the first 12 hours. Thereafter, ECG measurements will be performed every hour in case of persistent QTc prolongation (> 450 ms for men; > 470 ms for women) or every 4 hours if automatic QTc time is shortening and below 500 ms. ECG measurements will be continued for 24 hours after administration. After 24 hours a cardiologist will assess the ECG if monitoring needed to continue. If, after administration of the ibogaine, QTc exceeds 500 ms, participants will receive a magnesium bolus infusion of 2 g in 10 minutes, followed by 2 g of magnesium over the next 10 hours for myocardial stabilization. If necessary, subjects can be transferred to the coronary care unit (CCU) for continuous cardiac monitoring.

Symptoms of ataxia, delirium, and withdrawal symptoms will be monitored and scored 1,6,10 and 24 hours after drug administration.

Background therapy:

Before ibogaine administration subjects will be given 20 mg of metoclopramide to prevent nausea for comfort and to ensure full ingestion.

Evidence for comparator:

not applicable

| | |
|---|------------------|
| Actual start date of recruitment | 01 April 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 6 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 14 |
| Worldwide total number of subjects | 14 |
| EEA total number of subjects | 14 |

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) | 14 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at two outpatient addiction clinics (IrisZorg: Arnhem and Nijmegen). 36 patients deemed eligible were approached to participate; 29 patients were willing and were screened, 14 actually participated. Inclusion took place between October 2015 and November 2017.

Pre-assignment

Screening details:

Inclusion criteria: 20–60 yrs of age, a wish for detoxification of opioids and prior treatment failure.

Exclusion criteria: a history of clinically significant cardiac disease, serum potassium > 5.0 or < 3.5 mmol/l, severe liver or renal dysfunction or pregnancy, (a history of) psychotic symptoms, severe major depressive disorder or suicidality.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

not blinded

Arms

| | |
|-----------|--------------|
| Arm title | study cohort |
|-----------|--------------|

Arm description:

There is only one arm

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | ibogaine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral powder |
| Routes of administration | Oral use |

Dosage and administration details:

ibogaine-HCl 10mg/kg orally
administered in a yoghurt mixture

| | |
|--------------------------------|--------------|
| Number of subjects in period 1 | study cohort |
| Started | 14 |
| Completed | 14 |

Baseline characteristics

Reporting groups

| Reporting group title | overall trial |
|---|---------------|
| Reporting group description: | |
| 14 subjects entered the study, 12 men, 2 women. | |
| Besides opioids there was other drug use 1 month prior to detoxification: | |
| Alcohol 2/14 | |
| Amphetamine 0/14 | |
| Benzodiazepines 3/14 | |
| Cannabis 4/14 | |
| Cocaine 7/14 | |
| Heroin 8/14 | |
| Tobacco 13/14 | |

| Reporting group values | overall trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 14 | 14 | |
| Age categorical | | | |
| Age (median; 25th and 75th percentile) 48 (44–51) | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 14 | 14 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| median: 48 ; 25th and 75th percentile: 44–51 | | | |
| Units: years | | | |
| median | 48 | | |
| inter-quartile range (Q1-Q3) | 44 to 51 | - | |
| Gender categorical | | | |
| 12 men, 2 women | | | |
| Units: Subjects | | | |
| Female | 2 | 2 | |
| Male | 12 | 12 | |

End points

End points reporting groups

| | |
|---|--------------------------|
| Reporting group title | study cohort |
| Reporting group description: There is only one arm | |
| Subject analysis set title | baseline data |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Baseline QTc | |
| Subject analysis set title | QTc after administration |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All QTc measurements of the 24 hour period after ibogaine administration | |

Primary: difference between the QTc (ECG) before administration and the maximum QTc during the observation period

| | |
|--|---|
| End point title | difference between the QTc (ECG) before administration and the maximum QTc during the observation period ^[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: until 24 hours after drug administration | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics have been used, no analysis was performed.

| | | | | |
|-----------------------------|-------------------|--|--|--|
| End point values | study cohort | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 ^[2] | | | |
| Units: msec | | | | |
| median (standard deviation) | 102 (± 40) | | | |

Notes:

[2] - all subjects were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: SARA

| | |
|--|-----------|
| End point title | SARA |
| End point description: Measurement of the severity of ataxia | |
| End point type | Secondary |
| End point timeframe: During the first 24 hours (0, 2, 6, 10 and 24) | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | study cohort | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: Score | | | | |
| number (not applicable) | 14 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: DOS

| | |
|-------------------------------|-----------|
| End point title | DOS |
| End point description: | |
| Delerium observation scale | |
| End point type | Secondary |
| End point timeframe: | |
| 24 hours after administration | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | study cohort | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 | | | |
| Units: Score | | | | |
| number (not applicable) | 14 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First 24 hours after drug administration

Adverse event reporting additional description:

ECGs every half hour for the first 12 hours, then the second 12 hours every hour in case of persistent QTc prolongation
or every 4 hours if automatic QTc time was shortening and below
500 ms.

Ataxia and and psychomimetic (delirium) were assessed at 2, 6, 10 and
24 hours after administration of ibogaine.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------------------|
| Dictionary name | no dictionary used |
|-----------------|--------------------|

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|--------------------|---|
| Dictionary version | 0 |
|--------------------|---|

Reporting groups

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|-----------------------|--------------|
| Reporting group title | study sample |
|-----------------------|--------------|

Reporting group description:

study sample

| Serious adverse events | study sample | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | study sample | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 14 (50.00%) | | |
| Cardiac disorders | | | |
| prolonged QTc time | Additional description: Half the participants reached a QTc of >500 msec ECG abnormalities, including QTc > 450 ms for men and > 470 ms for women, were reason for exclusion to enter the trial. | | |
| subjects affected / exposed | 7 / 14 (50.00%) | | |
| occurrences (all) | 7 | | |
| Nervous system disorders | | | |
| Ataxia | Additional description: All subjects developed clinical signs of cerebellar ataxia, with full remission within 24 hours after ibogaine administration. | | |

| | | | |
|-----------------------------|---|--|--|
| subjects affected / exposed | 4 / 14 (28.57%) | | |
| occurrences (all) | 1 | | |
| Psychomimetic effects | Additional description: In two subjects delirious signs were observed, in full remission after 24 hours | | |
| subjects affected / exposed | 2 / 14 (14.29%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 11 November 2014 | Due to financial constraints, fMRI research was dropped from this protocol |
| 15 June 2016 | On the 15th of June a request was made to allow a 61-year old subject to enter the study |
| 14 December 2016 | Intent to increase from 12 to 15 subjects (14 were eventually included) Ibogaine INIRI monitorrapport 2 2016-12-14_draft1 |
| 06 May 2019 | Retrospective monitoring report, these are minor adjustments made to accomodate the intent of measuring depression, ataxia and delirium, aswell as bloodwithdrawals. - Addition of: Becks Depression Inventory, SARA, SOWS and OOWS. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33620733>