November 15, 2026

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Comments on Early Clinical Trials of Ibogaine

Docket FDA-2026-N-10429
Design and Safety Considerations for Clinical Trials Involving Ibogaine Drug Products
91 Fed. Reg. 63563–63569 (October 6, 2026)

Dear Dockets Management Staff:

I appreciate the FDA's proposal to begin with small, sequential inpatient cohorts, with one participant dosed at a time (Food and Drug Administration [FDA], 2026b). I would limit the initial cohorts to one administration per participant. This is a complicated medicine, and we still have much to learn about it.

I became involved in ibogaine treatment through my work in medicine and addiction recovery in 2019 after serving as a U.S. Navy Fleet Marine Force Corpsman. My responsibilities in ibogaine settings have included screening and preparation, medical oversight during administration and observation, and post-discharge care. I am a neurobehavioral researcher and serve as a lead research assistant at Texas A&M University–Central Texas. My recommendations draw on what I have observed in ibogaine care and the published research cited in this comment. I am submitting this comment in my personal capacity, and I have received no compensation for preparing or submitting this comment. My interest is leaving this world in a better state than I found it in.

This comment focuses on what I consider to be the major points that need attention, aspects I think may be overlooked, and some of my own theory.

1 General Study Design

Who Should Enroll

RFI III.1.a and preliminary considerations II.G and II.H

For these initial studies, I believe the most appropriate participants are adults with moderate or severe OUD and adults with persistent moderate to severe PTSD in separate cohorts. Two observational studies of opioid dependence have reported a reduction in acute withdrawal scores (Brown & Alper, 2018; Noller et al., 2018). In Brown and Alper (2018), 15 of the 30 enrolled participants reported no opioid use in the 30 days prior to their one-month assessment. In an uncontrolled study of 30 male special operations veterans (the majority of whom had mild TBI), disability and clinician-assessed PTSD symptom scores improved on average following a program that included magnesium, ibogaine, and complementary care (Cherian et al., 2024). These findings are sufficient to justify the study of acute withdrawal, subsequent opioid use, PTSD symptoms, and daily functioning as separate outcomes.

Document exactly what past treatments each participant has received, how long they lasted, and why they stopped. For OUD, document which of the approved medications the person had access to, which they actually tried, and whether they were able to complete an adequate course. For PTSD, document whether the person had an adequate course of medication and trauma-focused psychotherapy and any clinical reasons why they were unable to complete it. I would replace the 12-month interval after the most recent course of PTSD treatment in the FDA's example (FDA, 2026b) with 4 weeks of documented observation prior to dosing in the initial cohorts. Confirm current PTSD at screening with the past-month CAPS-5 and then use the past-week version at each weekly visit to track symptoms (National Center for PTSD, n.d.; Weathers et al., 2018). At each visit, record daily functioning and any changes to medication or psychotherapy. Extend the observation period if symptoms or functioning are still significantly changing. On the day of dosing, the study psychiatrist should confirm that the PTSD remains moderate to severe, that any required supervised taper and washout is complete, and that the participant still meets all the psychiatric eligibility criteria.

Suicidal ideation is common among people with PTSD or OUD (Akbar et al., 2023; Na et al., 2022). At screening, document the person's normal pattern of thought, any current intent or plan, and the time of any suicidal behavior. I would be prepared to consider people with stable passive thoughts of death after a full psychiatric assessment. People with current suicidal intent or a plan, with a history of suicidal behavior within the period stipulated in the protocol, or with acute risk requiring crisis care, should be excluded. Prior to the single planned dose, review any change from the person's documented baseline. If there is any emergence or worsening of suicidal thoughts, reassess the risk and defer the dose until the study psychiatrist has confirmed that the individual still meets the eligibility criteria.

Assess and record each participant's stage of readiness to reduce or stop opioid use at screening (prior to study preparation or any medication transition). Record baseline opioid use, withdrawal, craving, mood, confidence in making a change, and access to continuing care and rewarding activities post-discharge. Use the stages of change to inform the preparation process (Prochaska et al., 1992). For someone in precontemplation, start by asking them what the opioid use does for them and whether they have any concerns at all about it. For someone in the contemplation stage, explore what draws them toward change and what makes change so difficult. For someone who is already in the preparation or action stage, develop a concrete plan for dealing with cravings and accessing support post-discharge. Reassess readiness at the end of the preparation phase, prior to the therapeutic dose and again during follow-up. This gives the study a record of changes that occurred before ibogaine administration. Report on the degree of acute withdrawal relief and look at whether longer-term opioid use, daily functioning, and engagement in care differ by stage at entry (taking into account the actual preparation and continuing care that the participant received).

Medication Transitions

RFI III.1.b and preliminary considerations II.C and II.G

Start the medication reconciliation at screening, prior to asking the participant to make any changes to their current care. The study physician and clinical pharmacist should go through all prescribed medications (including OTC), all non-prescribed substances, supplements, and relevant food and beverage exposures. For each exposure, record the dose, formulation, and timing of recent use. For each exposure, assess the potential for QTc effects, effects on heart rate, effects on drug metabolism, serotonergic activity, sedation, and respiratory depression. Apply the

same assessment to any medications the protocol allows for withdrawal for reasons such as nausea, insomnia, or other symptoms (including rescue medications) (FDA, 2026b).

Review CYP2D6 inhibition as a separate interaction risk. CYP2D6 is the primary enzyme that metabolizes ibogaine to noribogaine. In a small study of healthy volunteers, co-administering paroxetine before a single low dose of ibogaine increased ibogaine exposure and prolonged its plasma half-life. Total noribogaine exposure was similar in both groups (Glue et al., 2015). In patients with opioid use disorder, CYP2D6 genotype was found to be associated with ibogaine clearance, and the study's model estimated that QTc prolongation approached a plateau as ibogaine concentrations rose (Knuijver et al., 2024). Genotype should be interpreted in the context of current and recently discontinued medications. Some inhibitors will continue to affect the enzyme after the last dose, and this effect is likely to last longer with fluoxetine, for example, than with paroxetine or sertraline (Deodhar et al., 2021; Liston et al., 2002). Justify each washout based on the medication's formulation, active metabolites, and expected duration of inhibition. The timing of these exposures should be recorded so that the investigators can interpret the ibogaine and noribogaine concentrations in the context of the serial ECGs.

An addiction medicine physician should be in charge of the transition from methadone or buprenorphine. If an inpatient bridge is appropriate, then the protocol should provide for a short-acting opioid such as immediate-release oral morphine. A published inpatient ibogaine study used oral morphine to standardize opioid therapy prior to ibogaine administration and to reduce the methadone contribution to QT prolongation (Knuijver et al., 2022). Transition and reassessment criteria for each maintenance medication and formulation should be specified. Monitor withdrawal, sedation, and respiratory status, and document the time of the last maintenance and bridge dose.

At screening, ask specifically about fentanyl, fentanyl analogs, other synthetic opioids, kratom leaf and extracts, and products marketed as concentrated 7-hydroxymitragynine (7-OH). A participant who reports using kratom may be referring to a concentrated 7-OH product. Clinically significant opioid withdrawal has been reported following cessation of concentrated 7-OH (Held & Varicat, 2026). Concentrated 7-OH also carries a risk of sedation and respiratory depression (American College of Medical Toxicology, 2026). Record the product name, formulation (if known), the labeled strength (if known), route, frequency, time of last use, and whether it was used to treat withdrawal. Ask about alcohol, benzodiazepines, and any other sedatives taken concomitantly. Use the exposure history and the observed course of withdrawal or sedation to determine what monitoring and treatment are required. Include the specific product in the interaction review. In 12 healthy adults, a single 2 g dose of kratom leaf tea increased exposure to oral midazolam (a CYP3A probe) and produced no measurable change in exposure to dextromethorphan (a CYP2D6 probe) (Tanna et al., 2023). Mitragynine has inhibited the hERG current in laboratory studies. Given ibogaine's effects on repolarization, I would treat recent use as a cardiac safety concern. The magnitude of the combined cardiac risk, particularly for concentrated 7-OH products, remains undetermined (Koenig et al., 2013; Leong Bin Abdullah & Singh, 2021).

Before interrupting medication for OUD, identify who is going to treat the worsening of withdrawal, who is going to provide the naloxone and overdose education, and who is going to be the one to get you back into approved treatment. Predetermine who is going to be in charge of participants who withdraw or become ineligible. It will also be important to account for the loss

of opioid tolerance and the risk of overdose during the transition and after discharge (Sordo et al., 2017; Weimer et al., 2023). A psychiatric prescriber should be in charge of any change to psychiatric medication and should be monitoring for discontinuation symptoms, any worsening of the underlying condition, and any change in suicide risk. Document who will restart treatment and when. The study team should remain responsible until the receiving prescriber has accepted the handoff. You should defer enrolment if the interruption or handoff cannot be managed safely.

After the transition, obtain a new baseline ECG before the ibogaine dose. Carry out appropriate checks of electrolytes and renal and hepatic function, and repeat the relevant assessments after vomiting, poor intake, or a new exposure. Give participants the opportunity to have a private chat about any recent use before administration. Routine opiate immunoassays will typically be for morphine and codeine. To detect fentanyl, the fentanyl analogs, and kratom alkaloids, you will need assays that will cover those substances (Stolbach et al., 2022). Specify which substances the trial will be testing for and when targeted testing will be appropriate. Interpret the results in the context of the exposure history and clinical picture. At the time of consent, explain who will be able to see the results and how they will inform care and eligibility. Postpone administration if a material interaction or safety issue remains unresolved.

Start safety tracking with the first treatment change required by the trial. Report how many participants started the transition, how many completed it, and how many received ibogaine. Record the timing of withdrawal, sedation or respiratory events, psychiatric deterioration, rescue treatment, return to opioid use, overdose, and resumption of established care. Include those who didn't receive ibogaine so the safety record captures any harm resulting from the transition.

2 Dose Selection and Escalation

Starting Dose and Measured Exposure

RFI III.2.a and preliminary consideration II.A

Retain 10 mg/kg as the upper bound for the starting dose in section II.A (FDA, 2026b). Sponsors should justify the actual starting dose for the formulation using the available human and non-clinical exposure and safety data. If the initial dose-finding trial also uses 10 mg/kg as the ceiling under section III.2.a, explain why that ceiling is appropriate for the protocol. A trial can identify a minimum pharmacologically active dose without necessarily reaching a maximum tolerated dose. Report either of these as undetermined if the trial is unable to determine it within the allowed range. Prior to dosing the next subject or escalating to the next cohort, review the measured exposure, adverse events, ECG findings, and neurologic recovery.

In my field experience, an initial 9 mg/kg of ibogaine HCl was, more often than not, enough for people to start to experience the subjective effects of ibogaine. Some people should be expected to report very little or no effect. I believe that a separate trial offering a booster dose would be worthwhile. I would consider the two-hour mark a candidate time to reassess clinical condition, rhythm, and QT interval before any booster, with the timing justified by the single-administration data. Those who requested and received a boost later told me they were glad they'd taken it. Brown and Alper (2018) also reported that participants sometimes requested a further dose to intensify the acute experience.

In the first trial, define how and when the acute subjective effect is going to be measured and what we would consider to be little or no effect. Report how often that happens and look at its relationship to clinical outcomes (degree of withdrawal, subsequent opioid use, PTSD symptoms, daily functioning, etc., as appropriate). Assess the prespecified measures of pharmacological activity separately. If many participants report little or no subjective effect and then have clinically worse outcomes, I would favor a separate trial of one optional booster during the same session. The trial would test whether offering the booster improves clinical outcomes and would measure its effect on the experience. The booster will alter both drug exposure and potentially the subjective experience, so improvement would leave open the question of which is responsible for the benefit. Subjective report, exposure data, and the evolution of ECG findings should justify the booster dose, timing, cumulative dose limit, and criteria for withholding the booster. ECG morphology will also be especially important to track for participants receiving a booster or participating in any kind of fractional or tiered style of dosing.

Record the exact product (including salt form, formulation, potency, purity, lot number, and certificate of analysis), dose basis, and amount administered. Record whether participants were fed or fasted, when and what they were fed, and any poor intake or vomiting. Use the data from the specific formulation to assess any food effect. If there is repeated administration on later days (including courses at lower doses), I would use a separate protocol supported by data from the single-administration study. That protocol would need to address residual exposure, food and fluid intake between administrations, any electrolyte changes, and potential for cumulative cardiac and neurologic injury (FDA, 2026a; Henstra et al., 2017; Knuijver et al., 2024).

Cerebellar Risk and Exposure Margins

RFI III.2.a.i through III.2.a.iii

Xu et al. (2000) found cerebellar abnormalities in two of six rats after a single intraperitoneal injection of 50 mg/kg, predominantly patchy astrocytosis, with a few degenerating neurons. All 6 rats in each group (at 75 and 100mg/kg) had Purkinje cell degeneration. At 25 mg/kg, the findings were comparable to saline controls on the measures examined. Molinari et al. (1996) also saw degeneration following one 100mg/kg injection and following 100mg/kg daily for 3 days. The single 40mg/kg group showed no excess degeneration over saline. Cerebellar injury is therefore a risk to be assessed in the proposed human trials.

Two points limit what we can learn from those studies as they relate to the oral trial. First, the injury is localized. Helsley et al. (1997) found no significant difference in total Purkinje cell numbers following six rats receiving 10 mg/kg IP every other day for 60 days. O'Hearn and Molliver (1997) found cell loss in very narrow bands of the cerebellum following a single 100 mg/kg injection. A total cell count can miss focal injury. Second, the 40 mg/kg concentrations come from a separate rat study. Baumann et al. (2001) reported mean peak whole blood concentrations of 3,859 ng/mL for ibogaine and 7,265 ng/mL for noribogaine following a 40 mg/kg IP dose. The concentrations associated with the tissue findings across the doses tested by Xu et al. are unknown, as is the size of the safety margin for the proposed oral trial. Xu et al. did not measure the concentrations associated with their tissue findings.

For section III.2.a, each proposed human trial protocol should state the evidence for the starting dose and how the uncertainty around cerebellar injury will constrain the ability to

escalate, not just QT. Ibogaine and noribogaine should be measured in the participants at the doses that are justified in the protocol. The sampling schedule should be such that it will capture both compounds. Following a single oral dose of 10 mg/kg ibogaine hydrochloride, Knuijver et al. (2024) estimated median times to peak plasma concentration of approximately 37 minutes for ibogaine and 7.6 hours for noribogaine in the same 14 participants described in the safety report. This would support sampling prior to dosing, within the first hour, around 6-10 hours, at 24 hours, and then at further time points as needed to characterize residual exposure. The timing of the samples would, of course, be adjusted for the formulation being tested. Before any dose escalation, review peak and total exposure in the context of the timing, severity, and duration of neurological changes and cardiac findings.

For section III.3.b: use the Scale for the Assessment and Rating of Ataxia prior to dosing and at 2, 6, 10, and 24 hours. Knuijver et al. (2022) used that protocol following a single oral dose of 10 mg/kg. All 14 subjects developed ataxia; scores peaked between 2 and 6 hours, and five subjects still had scores of 1 or 2 points at 24 hours. These findings resolved by reassessment at 48 hours. Compare each subject to their own baseline and record if they require any new or additional assistance with standing or walking. Repeat the exam on discharge and at 48 hours if findings remain above baseline at 24 hours. A seizure or new focal deficit warrants immediate assessment. I would recommend pausing escalation if new ataxia is still present at 48 hours (pending safety committee review). Reassess neurology on discharge and continue with the proposed cognitive testing for up to 12 months. Use MRI to look at any new focal findings or for any persistent unexplained deficits as clinically appropriate. Normal cognitive testing and routine MRI still leave the question of microscopic Purkinje cell injury unanswered.

3 Safety Considerations

Cardiac Safety

RFI III.3.a.i through III.3.a.vi and preliminary considerations II.B and II.D through II.G

I support inpatient monitoring for the initial single-dose trials. An ICU or hospital telemetry unit is appropriate, provided the team can respond to life-threatening arrhythmia at the bedside 24/7. The room should be as naturalistic and comfortable as possible. Adjustable lighting is a must; minimize noise and interruptions, and allow participants to bring in their own meaningful familiar items where possible. Where equipment and staffing permit, route alarms so staff can hear and respond immediately, and the participant is not subjected to the sound. Keep access to the participant and emergency equipment clear. Continuous telemetry, a physician who can respond immediately, staff trained in ACLS, and immediate access to defibrillation, pacing, ventilation, and emergency drugs are all required. Before enrolment, you should confirm with the team who will respond to an alarm, who will lead resuscitation, and how monitoring will continue through the transfer. Verify the plan works overnight and through shift changes. Arrange emergency transport and receiving care in advance, and at consent, explain who will pay for transport and treatment for a study-related injury (FDA, 2026b; Wigginton et al., 2025).

Participant waveform morphology should be treated as a phenotype. Get a screening 12-lead ECG prior to any trial medication changes and a comparable tracing immediately prior to dosing. The first establishes the participant's baseline rhythm, conduction, and repolarization prior to the transition. The second shows what changed during the transition and serves as the reference for changes after ibogaine. Keep both tracings (the baseline and the one taken immediately prior to dosing), any baseline rhythm recording, the original serial ECGs, and the

telemetry strips around any significant events. In Knuijver et al. (2022), ECGs were obtained every 30 minutes during the first 12 hours, and 7 of the 14 participants had a QTcF above 500 ms after a single oral dose of 10 mg/kg. Use that protocol as the benchmark for the first cohorts (with continuous telemetry and additional diagnostic ECGs as appropriate when symptoms or rhythm changes occur). There are published reports of serious arrhythmias and deaths following ibogaine. A meaningful event rate in a screened trial population is still unknown (Alper et al., 2012; Knuijver et al., 2022).

For the first cohorts, I support excluding those with a confirmed screening QTcF of 430 ms or greater (as per section II.G, with section III.3.a.iv using > 430 ms as an example). An adjudicated value of exactly 430 ms would meet the exclusion criterion, and borderline tracings would be repeated at a stable resting rate. Eligibility would be reassessed if the immediate pre-dose ECG worsened. Resting rate and BP, structural heart disease, medication and substance exposure, and personal and family history of arrhythmia, or SCD would all be reviewed. Any potassium, calcium, or magnesium abnormalities would be corrected before dosing, and the ECG would be repeated after any vomiting or other circumstances expected to affect electrolytes. I consider 430 ms a conservative precaution. Published ibogaine screening has used QTc exclusion thresholds above 450 ms for men and above 470 ms for women (Knuijver et al., 2022). The ability of the 430 ms cutoff to predict who would go on to cross 500 ms is not known. Individual risk would be assessed, and screening exclusions and cardiac findings would be reported by sex, age, and baseline risk (FDA, 2026b; Knuijver et al., 2022).

Ibogaine can have a bradycardic effect and can delay ventricular repolarization. QTcF should be used for trial comparisons, and the measured QT, RR interval, QRS duration, recent rate history, lead, and method of measurement should all be preserved. Bazett can undercorrect at slow rates, and the QT can fall behind the rate. A 500ms QT at 46 or 47 bpm would require bedside assessment and confirmation of the trace. A qualified manual review of all scheduled ECGs is required, and review should be prompt if there is any discrepancy between the monitor and the trace or if the end of the T wave is difficult to identify. Use a lead with a clearly identifiable end to the T wave; exclude a distinct U wave from the QT measurement, and document uncertainty if fusion makes the endpoint unidentifiable. Device readings should be compared with an independent review at both slow and changing rates. The retained tracings would also allow an exploratory comparison with a correction based on each participant's baseline QT and most recent RR history. The clinical use of that estimate would, of course, require prospective validation (Andršová et al., 2022; Drew et al., 2010; FDA, 2026c; Vandenberk et al., 2018).

In my work on ibogaine ECG morphology, I've been very much in the habit of comparing the tracing to the participant's earlier recordings. A prolonged QT can occur with a regular rhythm and a fairly consistent waveform. If the T wave is flattening or notching, then you need to check whether the interval can still be measured and whether the change is beat-to-beat stable. An increase in distortion after a pause, beat-to-beat alternation, new ventricular ectopy, or couplets all warrant prompt review, even if the displayed QTc has not changed significantly. Record the lead, the change from baseline, and the relationship to any pauses or ectopy (Drew et al., 2010).

Following the single dose, require an immediate bedside assessment for a verified QTcF above 500 ms or an increase of at least 60 ms from the immediate pre-dose ECG. These QTc

thresholds come from hospital guidance on drug-induced QT prolongation. I would apply them using the trial's prespecified Fridericia correction. In the AUD pilot, one participant's QTc rose from 413 to 496 ms using the Framingham correction, an increase of 83 ms. Report the absolute value and the change from baseline using the same correction method. State who verifies the ECG, who assesses the symptoms and perfusion, who looks for reversible contributors, and who escalates care. The bedside physician should act as soon as they see anything of concern (Drew et al., 2010; Rocha et al., 2026; Wigginton et al., 2025).

Retain the FDA's proposed study holds for sustained ventricular arrhythmia, seizure, death, or serious adverse event possibly related to ibogaine, QTc above 500 ms that persists for more than two days, new suicidal ideation or behavior post-acute effects, a lasting perceptual disturbance, or severe adverse events in at least two participants within a cohort (FDA, 2026b). The two-day criterion will govern further dosing. Assess a participant with a concerning finding as and when it arises. Give the Safety Review Committee the power to halt further dosing earlier if a serious finding remains unexplained or if events start to form a pattern.

The independent Data & Safety Monitoring Board should review any event that leads to a study hold. They should receive the full clinical course, the relevant ECGs and telemetry, the participant's outcome, and any proposed changes before dosing resumes. Send the FDA a summary of the hold and the proposed restart plan and submit any required IND safety reports on the timelines in 21 CFR § 312.32. For a protocol hold, the IND holder should authorize dosing to recommence only after the independent board has recommended it in writing and any FDA-requested review is complete. If the FDA imposes a formal clinical hold, dosing may resume after FDA notifies the sponsor that the investigation may proceed under 21 CFR § 312.42(e).

Once the monitoring and rescue plan has proven effective in the initial trial, consider a randomized comparison of elective magnesium pretreatment to assess its effect on QTc and arrhythmia risk where this is both medically and ethically appropriate. Obtain an ECG prior to the assigned pretreatment and again immediately prior to ibogaine so that any change during the pretreatment period is visible. Use the same ibogaine formulation, dosing conditions, ECG schedule, and rescue criteria in both groups. Have ECGS read in a blinded fashion and pre-specify how the analysis will handle rescue treatment. Report QTc change and arrhythmia separately. Magnesium was given as part of a broader regimen in the veterans cohort, so its effect on QTc and arrhythmia risk in ibogaine therapy remains unclear (Cherian et al., 2024; FDA, 2026b).

If the protocol uses a 48-hour ECG to assess readiness for discharge, it may be worth continuing telemetry through that period. Use a wearable wireless inpatient telemetry transmitter that transmits the ECG in real time to staff. It must be a system with limited or no delay in the readout. In the area under observation, the participants should be able to change position and get up to walk once safe. Keeping someone on a bedside monitor for a significant length of time can be frustrating and may, in fact, affect the outcomes the trial is trying to measure.

Extend the observation period for any unresolved QTc prolongation, new rhythm abnormalities or pauses, electrolyte abnormalities, or other concerning symptoms. Henstra et al. (2017) described a case of QTc prolongation which persisted for 12 days in a patient who had taken several capsules of ibogaine obtained via the internet. That case supports having a plan in place for delayed recovery. Before discharge, review serial ECGs, rhythm events, electrolytes,

symptoms, the medication plan, and access to reassessment. Document cardiac recovery separately from the point at which the participant says the acute experience is over (FDA, 2026b; Henstra et al., 2017).

Myocardial Injury and Heart Rate

Koenig et al. (2013) showed that ibogaine inhibits the hERG potassium current, which is involved in ventricular repolarization. In the single-dose study by Knuijver et al. (2022), 7 of the 14 participants had a heart rate below 60 bpm after receiving 10mg/kg orally. Slowing and pauses matter in this context because they can increase arrhythmia risk if repolarization is already delayed (Drew et al., 2010). It is not known whether ibogaine slows the heart via a direct effect on pacemaker activity, via autonomic input, or via the heart's own network of neurons. Put the ECG and telemetry, blood pressure, symptoms, ibogaine, and noribogaine concentrations all on the same timeline. Record the times of vomiting, withdrawal symptoms, and rescue meds. That would let the trial see whether the slowing or pauses occur before any change in repolarization or ventricular ectopy. To identify the source of any neural contribution would require a study designed to test that.

Another issue is whether the myocardium itself is damaged and what happens once the ECG recovers. Vidonja Uzelac et al. (2024) examined part of the left ventricular wall in rats at 6 or 24 hours after a single oral dose. They reported focal necrosis at 1 mg/kg and diffuse necrosis at 20 mg/kg. Those two time points don't tell us whether there's scarring, whether ventricular function recovers, or whether repeated dosing causes cumulative damage. I think it would be worth following up with paired tissue and cardiac function assessments, plus ibogaine and noribogaine exposure measurements. In the human trial, if there's any chest pain, sustained arrhythmia, persistent hypotension, or new ischemic ECG changes, assess the potential for myocardial injury with serial high-sensitivity cardiac troponin and imaging, as appropriate (Kontos et al., 2022). If you're going to take troponin as an exploratory measure, then take a pre-dose baseline and justify the sampling during the acute observation period and the following day. A QTc that comes back to baseline still doesn't rule out myocardial injury.

Neurologic Recovery and Continuing Care

RFI III.3.b.i and III.3.b.ii and preliminary considerations II.B and II.F

Prior to dosing, record gait, balance, coordination, alertness, and cognition, as well as the walking aids or assistance the participant normally uses. In Knuijver et al. (2022), all 14 participants developed ataxia following a single oral dose of 10 mg/kg. The authors describe participants needing a nurse’s help to get to the bathroom. Assign the bedside nurse to assess mobility and to arrange for trained assistance for transfers and toileting. Use a bedside commode or nearby bathroom if the participant can transfer safely with assistance, and a bedpan or urinal if they cannot. Discuss the need for physical assistance before dosing, maintain privacy, and keep telemetry on during transfers. Repeat any part of the neurological examination that can be safely performed and record why any part was not tested. Keep suction and oxygen at the bedside. If a drowsy participant vomits, help them to turn onto their side when safe and assess their airway and breathing. If a participant has a seizure, collapses, or unexpectedly loses responsiveness, activate the hospital response immediately. Assess airway, breathing, pulse, glucose, and rhythm, and preserve the ECG from the event to help determine what occurred. On discharge, confirm cardiac clearance, adequate alertness, safe swallowing, and safe mobility with the aids and

assistance the participant will actually have on discharge (FDA, 2026b; Hewett Brumberg et al., 2024).

Contact participants in the first week after discharge, then repeat the neurologic and cognitive assessments at 1, 3, 6, and 12 months. Compare the results to the participant's baseline and note whether any new deficits either resolve, persist, or are actually seen for the first time post-discharge. Where possible, use alternate forms of the cognitive tests and account for practice effects when interpreting changes (Calamia et al., 2012). Record any missed visits and the reason, if known. Obtain clinically indicated imaging for a new focal deficit or for a persistent unexplained finding. For the research imaging substudy, state what the scan is intended to measure. The structural MRI and the subjective experience data both come from the original observational cohort of veterans with TBI. Geoly et al. (2026) had structural scans from 25 participants at baseline and 22 at one month and measured cortical thickness, subcortical volumes, and estimated brain age. It remains unclear whether these changes reflect actual cellular repair (Cherian et al., 2024; Geoly et al., 2026; Olash et al., 2026).

For OUD: assess acute withdrawal, subsequent opioid use, overdose, and return to treatment. With consent, where possible, corroborate self-report via toxicology or treatment records. For PTSD: assess symptoms and functioning. At 3 and 6 months, ask what the participant can do now that they couldn't do prior to treatment and what has become harder or what remains difficult. In both cohorts, record any changes in sleep, behavior, suicidal ideation or behavior, manic or psychotic symptoms, and distressing perceptual changes. Ask what happened when they faced a familiar stressor again, how they coped, and who was available to help. Record the timing of any other treatments, any further substance exposures, and any major changes at home in relation to any improvement or recurrence. A number of veterans had a recurrence of their psychiatric symptoms by the one-month visit, and at least two encountered a significant stressor upon returning home (Cherian et al., 2024). At 12 months, 25 of 30 had completed the assessment, and group outcomes remained better than baseline. Of those 25, 23 used at least one psychedelic between the one-month and 12-month assessments (Faerman et al., 2026). These details will be important in assessing how much of the change over the year can be attributed to the initial intervention.

If a participant requests to leave before meeting discharge criteria, determine why. In some cases, a change in the environment may be all that is required; be prepared to accommodate this need. A qualified clinician should assess the participant's capacity to make that decision and explain the remaining risks. If the participant decides to leave, arrange the safest possible transport, confirm who will receive them, and provide written instructions on when and where to access urgent care. If capacity is impaired or there is an immediate safety risk, then the hospital's emergency procedure and relevant law will apply. Seek permission before involving family or other support. Provide a named clinician or service, an after-hours number, and a backup contact. The routes to care and to adverse event reporting should remain open after early departure, and you should separately confirm what further research contact the participant is happy to have.

4 Ethics and Oversight

Preparation and Informed Consent

RFI III.4.a and preliminary considerations II.B and II.I

Integration starts in the preparation phase. Get the participants to become aware of how they normally react to distress and to practice what they'll do if it arises during the session or when they get back home. Breathwork is one of the most useful tools for this. Proper self-inquiry is another. Before dosing, teach them how to signal for help and whom to call if distress or cravings return at home. If further practice is required after the scheduled preparation sessions, then provide it and re-assess prior to dosing. Note what staff provided, what participants practiced, and which follow-up contacts took place so you can account for differences in support when reviewing outcomes.

Prior to any trial requiring a medication interruption, ask the participant to articulate in their own words the risks of that interruption, the risk of fatal arrhythmia, and what is still uncertain regarding the long-term neurologic effects. Confirm their decision again prior to dosing. Tell them who will be in charge of their care should they elect to defer or withdraw. The trial should cover study-related emergency transport and treatment. Prior to dosing, discuss what physical assistance may be required and agree on how the participant can refuse or withdraw from optional touch. Ask again when optional touch is proposed and respect any refusal. Prohibit staff from engaging in any sexual contact or sexualized behavior with the participant, with a private route for reporting outside of the session team. Obtain separate consent for any optional recording or for the secondary use of personal narratives (FDA, 2023, 2025, 2026d).

Staffing and Independent Review

RFI III.4.b and preliminary considerations II.B, II.E and II.I

Keep at least two staff members assigned to each participant throughout the acute effects phase (including a licensed mental health professional) as part of the inpatient medical team. Confirm who can identify deterioration, provide psychological support within their scope of practice, safely assist an ataxic participant, and call for emergency care. Test these competencies in drills and ensure staff roles and authorities are clearly defined. Designate a clinical lead with the authority to step in and replace a staff member who cannot safely carry out their role. Provide trained relief for breaks and shift changes, and assign someone to confirm coverage and receive a structured handover. The staffing plan must work for long sessions and when a staff member needs to step away (FDA, 2026b, 2026d).

Have a cardiologist on the cohort safety review committee. Maintain an independent Data and Safety Monitoring Board with cardiac, neuro, psychiatric, and statistical expertise, and include Addiction Medicine on both the DSMB and the cohort safety review committee. The DSMB should have access to the source ECGs and individual timelines from the time of medication transition through to follow-up. Specify who has the authority to defer a participant, who has the authority to pause study dosing, who has the authority to approve escalation, and who has the authority to notify the FDA. The investigator's brochure should link the risks and uncertainties of the product and its metabolites to the proposed population, dose, monitoring, and stopping criteria, and should be updated as evidence accrues (FDA, 2025, 2026b).

Ask the IRB to review deferrals, early discharge, coercion, conflicts of interest, payments, touch and recording policies, and how staff handles reports about colleagues. Provide a confidential reporting route separate from the administering team that is available after discharge. Make it clear to participants who will receive the report, how urgent concerns will be dealt with, and what the limits of confidentiality are. A participant should be able to request a deferral, report an adverse event, or raise a concern about staff without losing care or the reimbursement they have already earned.

Early Relief and Testimonials

People can feel much better right after ibogaine. You will often hear people call it the pink cloud phase. The relief can be very real and significant, and people may want to tell the world about it while they're still processing what happened. If the treatment team asks for a testimonial while a participant still depends on them for medication adjustments, managing distress, or follow-up care, the participant may worry that saying no could affect the care they receive. There's also the issue of what lasts. In the veterans' study, a few participants reported some return of psychiatric symptoms between the first assessment after treatment and the one-month assessment. At least two faced significant stressors when they got home (Cherian et al., 2024). A testimonial recorded in the first few days captures how someone felt at the time, before they've had a chance to see what holds up in their normal life.

The REBUS model proposes that under psychedelics, existing beliefs may have less influence, and people may become more responsive to their experiences and surroundings (Carhart-Harris & Friston, 2019). Nardou et al. (2023) found that adult male mice could still learn a preference for cues associated with social contact four weeks after an ibogaine injection. Whether people become unusually receptive to influence after ibogaine, and for how long, remains unknown. I would suggest at least 30 days as a minimum ethical safeguard. That gives participants time to return to their normal lives, attend an early follow-up visit, and consider what, if anything, they want to say publicly.

From preparation through at least 30 days after dosing, trial sponsors, investigators, and affiliated providers should refrain from asking for, recording, commissioning, or using testimonials or identifiable material to promote the program or the drug. This includes asking for permission to post something later and reposting a participant's own story. Participants remain free to tell their stories as they see fit, give private feedback, and report adverse events. After the waiting period, when a request is otherwise permissible, have someone outside the participant's care teams speak with them privately. This gives them room to decline without feeling it may affect their care or follow-up. Defer the request if the participant still relies on the team for care, feels pressure to agree, or has unresolved distress. Obtain a current, dated account and fresh written consent that identifies the material and where it will appear. Use clinical and research recordings only for the purposes for which they were obtained. Professional ethics rules and the restrictions on promotion of investigational drugs under 21 CFR § 312.7 continue to apply after the waiting period.

Evidence From Outside the United States

RFI III.4.c

For question III.4.c, records from treatment settings outside the US should allow a reviewer to reconstruct what happened to each individual. Use a participant code to link the product, formulation, lot, available identity and purity testing, dose, and time administered. Put the ibogaine and noribogaine sampling times and concentrations on the same timeline as the original ECGs and rhythm strips, the QT correction method, the lab results, the medication changes, the other interventions, the rescue care, the transfers, the discharge, and the follow-up. Show where monitoring was interrupted or a measurement was missed. Distinguish between what the participant reported, what the staff observed, and what an independent reviewer could confirm from the original records.

Use the same event definitions and follow-up intervals at each site. Report the number screened, the number who stopped prior to receiving ibogaine, the number who received it, and the number who completed each follow-up assessment. Record the reason for missing assessments where known. A single documented arrhythmia can inform the next trial about what it is monitoring and what rescue care it may need. To estimate how often it occurs, you need to know who received the product, how long they were monitored and followed, and whose outcomes are missing. Keep the original records and maintain a traceable history of any corrections. For foreign clinical studies conducted outside of an IND and submitted in support of an IND or marketing application, you must document GCP, including independent ethics review and informed consent, and retain the required records and make the data available for FDA validation if requested under 21 CFR § 312.120 (FDA, 2012, 2025). Keep the personal narratives and any optional recordings that participants agreed to have recorded.

Where a trial uses plant-derived material, I recommend documenting the species, where it was grown or harvested, and how it was traced to the finished lot. I recommend documenting lawful sourcing, and you must involve the relevant Indigenous communities in the sourcing and stewardship decisions. Where the research draws on community-held knowledge, I recommend documenting the permission of the relevant knowledge holders and any agreed terms around use and benefit sharing. If possible, an analysis of the soil it grew in would also be quite useful.

Questions for Later Studies

Neurotensin interacts with dopamine in the reward/reinforcement circuits. Binder et al. (2001) describe a rat study in which ibogaine increased neurotensin content in the striatum, substantia nigra, and nucleus accumbens. Ibogaine pretreatment also blunted the cocaine-induced increase in neurotensin content in the caudate putamen and substantia nigra pars reticulata. The study examined neurotensin immunoreactivity in tissue samples. How much was released and whether receptor activity changed remains unknown.

Bugni et al. (2012) looked at a different question. Following five weekly injections of the carcinogen azoxymethane at 10 mg/kg, mice expressing the neurotensin receptor 1 developed more than twice as many colon tumors per mouse as mice that lacked the receptor. For the proposed single-dose study, the question is whether ibogaine or noribogaine alters neurotensin signaling in the colon at human-relevant levels and whether any such alteration is sustained. If you're measuring circulating proneurotensin, then you'd need to keep meal timing and fat content

the same across the blood samples, as dietary fat can increase it (Fawad et al., 2020). A change in blood would require further evidence to link it to activity at the receptor in the colon. I'd re-evaluate the need for carcinogenicity testing if evidence showed sustained activity in the colon or if a regimen involving repeated administration were proposed. That decision would need to consider the intended frequency and duration of use, the measured exposure, and the rest of the toxicology data under ICH S1A and S1B(R1) (FDA, 1996, 2022).

Oulton et al. (2026) found that mitochondrial respiration was lower after four hours of ibogaine exposure in cultured mouse cortical neurons and then increased above control levels 20 hours after washout. That course supports sampling during both exposure and recovery. If you're measuring C-reactive protein, GDF15, or FGF21, then you need to be very clear as to what each of those samples is intended to tell you. C-reactive protein can mark systemic inflammation. GDF15 and FGF21 can both be elevated in a number of different forms of metabolic stress. Take a sample prior to any required medication transition and another immediately prior to dosing so that the changes that occur during the transition are visible. Record withdrawal severity, recent food intake, illness, and rescue meds at the time of sampling. If the question is whether mitochondrial respiration changed, then measure oxygen consumption in peripheral blood mononuclear cells and use standardized collection tubes and time to process. Interpret that result as a measure of respiration in the blood cells that you've sampled (Pepys & Hirschfield, 2003; Tsygankova et al., 2019; Werner et al., 2022).

Before you increase exposure or broaden eligibility, review every individual who started a medication transition as part of the trial. How many completed it? How many stopped prior to dosing and why? Were those who stopped able to return to their usual care? For those who received ibogaine, review the rhythm events, QTc changes, and any neurologic findings alongside measured ibogaine and noribogaine levels. When did each finding resolve, and what was still present at the last assessment? Include any adverse events that occurred post-discharge or on early exit. If someone with a significant finding missed their follow-up, what remains unknown about their recovery, and how does that affect the decision to proceed?

Respectfully submitted,

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