Project Title: A Phase 2 Clinical Trial of Intranasal Oxytocin for Frontotemporal Dementia

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Statistical Analysis Plan

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FOXY Statistical Analysis Plan

Contributions

Kristy Coleman developed the statistical analysis plan (SAP) based on the analyses set out in the trial protocol by Berry Consultants and Dr. Elizabeth Finger. Kristy Coleman is the junior statistician and data coordinator and helped answer questions related to trial data and management relevant to the development of the SAP. Dr Elizabeth Finger and Dr. Scott Berry contributed, reviewed, and approved the SAP.

Abbreviations and Definitions

AD – Alzheimer's Disease
bvFTD – behavioural variant Frontotemporal Dementia
CNS – Central Nervous System
CSF – Cerebral Spinal Fluid
DSMB – Data and Safety Monitoring Board
ECG - Electrocardiogram
ED - Everyday
EOD – Every Other Day
EOT – End of Treatment
ET – Early Termination
ETD – Every Third Day
FTD – Frontotemporal Dementia
IP – Investigational Product
IRI – Interpersonal Reactivity Index
ITT – Intention to Treat
IU – International Units
LOCF – Last Observation Carried Forward
MAR – Missing at Random
m-CGIC – modified – Clinicians Global Impression of Change
MITT – Modified Intention to Treat
MMSE – Mini Mental State Exam
NPI – Neuropsychiatric Inventory
OXTR – Oxytocin Receptor Gene
OXY - Oxytocin
PBO - Placebo
PI – Principal Investigator
PK - Pharmacokinetics
PPP – Per Protocol Population
QTcF – QT Interval Fridericia's correction
RSMS – Revised Social Monitoring Scale
SAP – Statistical Analysis Plan
SOI – Social Observation Inventory

Section 2: Introduction

Background and Rationale

Frontotemporal dementia (FTD) is a progressive neurodegenerative disease for which there is presently not available cure, and only a few symptomatic treatments that are marginally effective. Hallmark symptoms of FTD include social apathy and indifference, including the loss of empathy for others. Although these are among the most burdensome for caregivers of patients with FTD, presently there are no approved or off-label treatments for the apathy, lack of empathy and decline in related social behaviours. The lack of treatments targeting these deficits renders physicians unable to

manage the most emotionally challenging and destructive symptoms for families and caregivers. Our group has identified oxytocin as a candidate treatment for the social apathy and indifference patients with FTD develop towards others. Growing evidence indicates that the neuropeptide oxytocin is an important mediator of social behaviour across species. Our early studies of intranasal oxytocin in patients with FTD have demonstrated improvements in neuropsychiatric behaviours, specifically in social apathy and empathy. We propose a novel proof-of-concept phase 2 adaptive design trial, repurposing the hormone and neuropeptide oxytocin as a potential symptomatic treatment for apathy/indifference and related empathy deficits in patients with FTD. We will examine different dose schedules of oxytocin (intermittent and daily) given concerns in animal models of potential habituation of effects when oxytocin is chronically administered. If effective, oxytocin would be the first symptomatic treatment for patients with FTD specifically targeting the core deficits in social apathy so devastating in this disorder.

Objectives

Research Question:
Is intranasal oxytocin an effective symptomatic treatment for improving social apathy/indifference deficits and related behaviour in patients with FTD?

Primary Efficacy Objective
Change in Neuropsychiatric Inventory (NPI) apathy/indifference domain score

Secondary objectives:
- Change in emotional facial expression recognition performance
- Change in the Interpersonal Reactivity Index (IRI) empathic concern scale and IRI total score
- Change in the Revised Self-Monitoring Scale (RSMS) score
- Change in modified Clinicians Global Impression of Change (m-CGIC) scores (directed to apathy)
- Change in Caregiver Distress Scores on NPI apathy/indifference scale and Caregiver Distress Scores on Total NPI
- Change in total NPI scores
- Difference in CSF oxytocin levels (oxytocin vs. placebo treatment periods) (optional substudy)

Safety Measures:
- Adverse symptoms
- Changes in serum sodium levels, heart rate and blood pressure
- Change in QTcF as measured by ECG
- Compliance with treatment (based on daily logs and measurement of residual volumes)

Exploratory Measures:
- Change in social behaviours based on videotaped segments of naturalistic behaviour
- Examination of impact of oxytocin receptor (OXTR) polymorphisms on behavioural outcome measures.

Section 3: Study Methods

3.1 Trial Design

This is a multi-centre double blind, placebo-controlled randomized cross-over study comparing 6 weeks of oxytocin treatment to 6 weeks of placebo with a 6-week washout between periods. A phase II adaptive design will be used to efficiently identify promising dose schedules and obtain meaningful efficacy data. In Stage 1 of the study, we will evaluate three dosing schedules compared to placebo: daily dosing, alternate day dosing, and every 3rd day dosing. At the end of Stage 1, Bayesian analysis will be conducted to identify the most promising dose schedule, termed the “target dose”. In Stage 2, additional patients will be enrolled at the target dose schedule. In both stages the primary outcome measure is change on the NPI apathy/indifference domain score from baseline. At the end of Stage 2, data from patients receiving the target dose (from Stage 1 and Stage 2) are combined in the efficacy analysis. An optional CSF sub-study

measuring oxytocin levels during oxytocin vs. Placebo periods will confirm CSF oxytocin level rises in FTD and determine whether changes in CSF oxytocin levels correlate with behavioural measures.
The study is double blinded, participants and all study staff aside from central drug coordinator and unblinded DSMB members will be blinded to dose and arm. In Stage 2 of the study, the study staff and participants will be blinded to dose (at the suggestion of the DSMB and TSC) and arm. Randomization occurs after screening data is accessed and the participant deemed eligible but prior to baseline appointment. In some instances, this meant that participants were randomized into the trial without ever attending a baseline appointment.

3.2 Randomization
Randomization for stage 1 and 2 will be stratified across the treatment groups listed above according to sex and disease severity (CDR score of 0-1 mild vs. CDR score of 2 moderate). Given the number of centres required for a trial in FTD, the study will not be powered to stratify randomization according to centre. Participants will be randomized using variable block sizes concealed from participating sites. Central randomization will occur with web-based Guide 98 and 21CFR11 compliant technology. Central drug coordinator is responsible for randomization and identification of blinded kit assignment. Site coordinators will be provided with kit receipts to provide to local blinded pharmacy for dispensing of appropriate kit on baseline visit days. Only compounding pharmacy and central drug coordinator have access to kit treatment allocation. Central drug coordinator was sequestered and had no contributions to the study other than ordering and tracking kits, and kit assignment.

3.3 Sample Size

The details on the operating characteristics of the adaptive design, including sample size calculation and justification can be found in section 6.1 of the protocol.

3.4 Statistical Interim analyses and stopping guidance (if applicable)

An interim analysis was conducted to select a dose during Stage 1 of the trial design for Stage 2. Details on the interim analysis can be found in protocol Section 6.0 and 6.1.

A futility analysis was not originally planned as part of the original protocol. Due funding and enrolment challenges an administrative analysis took place in October of 2022. Details of this analysis are available in the “Administrative Analysis of FOXY Trial for Frontotemporal Dementia 04 October 2022” document. This administrative analysis does not impact the sample size nor analytic plan.

3.5 Timing of final analysis

The final end of treatment visit occurred in June 2023. Following this, the data will be cleaned, verified, and locked. Collection of SOI and biosamples back to central coordinating site will commence as each site finalizes their individual participation. Analysis of primary outcome measure will commence once the relevant data set has been locked, and the statistical analysis plan is finalized by blinded statisticians and investigators.

3.6 Timing of outcome assessment
Screening window is 0–28-days followed immediately by Baseline 1 assessments. Initial dose of treatment occurs at baseline appointment but after baseline visit outcome assessments have occurred. Baseline 1 treatment window is 42 days +/- 3 days and then End of Treatment visit 1 assessments occur. The final dose of treatment occurs at the beginning of treatment visit prior to End of Treatment 1 outcome assessments. Then a 42 day +/- 3 days washout. Baseline 2 treatment window is 42 days +/- 3 days and then End of Treatment visit 2 assessments occur. The final dose of treatment occurs at the end of treatment visit 2 prior to outcome assessments.

Section 4: Statistical Principles
The trial has a 2-stage design:

In Stage 1 the trial will compare three dosing schedules of 72 IU intranasal oxytocin (daily, alternate day, or every 3rd day dosing) for patients with FTD compared to placebo. Twenty participants per arm will be randomized to each of the three dose arms and order of the cross-over (order of oxytocin and placebo). All dose schedules will use sprays bid (morning and afternoon, with placebo on non-oxytocin Rx days) to maintain blinding to schedule across all of the cohorts. After 6 weeks, patients will have a 6-week washout period and then cross-over to the other treatment arm (placebo to oxytocin; oxytocin to placebo). After 60 participants have completed their participation, interim Bayesian analysis will determine which of the dosing schedules appears most promising. For Stage 2, the most promising dose schedule, designated the "target dose," will be carried forward for the remainder of participants n=40 who will complete the exact same procedures as participants in Stage 1. Data from the target dose group from stage 1 and 2 will be combined for the final analysis.

4.1 Confidence Intervals and P-values

Stage 1 and Stage 2 for the target selected treatment arm will be used to test superiority using a nominal 2.5% one-sided test for the primary outcome of change in NPI.

All secondary, safety and exploratory outcomes will be reported as two-sided tests with statistical significance set at a two-sided 0.05 level.

4.2 Adherence and protocol deviations

Adherence to treatment is assessed by participant drug diary. Caregivers completed the diary with doses completed and missed. These notes were confirmed by study coordinators at EOT visits and are used to assess compliance. The compliance notes are cross-referenced with bottle weights to confirm medication dispensed.

For safety ECG data, per-protocol analysis will include ECGs obtained within the 0–25-minute window following IP treatment. Sensitivity analysis will also include those obtained outside the window of 15-25 min post-treatment. Sensitivity analysis of primary and secondary outcomes will exclude patients who had the addition of a new medication targeting behaviour or cognition during either of the treatment periods.

For assessments completed by caregiver, the data must be collected within 30 days of last dose of IP.
For cognitive outcomes completed by patient, data must be collected within 3 days of last dose of IP.
Data for which there are clear validation errors or where administration errors are clear and unreconcilable for neuropsychological testing will also be excluded from PPP. Exclusion for validation errors will only be possible for IRI and RSMS where such validation errors are apparent.

Protocol deviations were identified throughout the administration of the trial by CRO and central data coordinator.

4.3 Analysis populations

Intent-to-Treat Population (ITT) - All participants who were randomized and completed at least one baseline assessment.

Modified Intent-to-Treat Population (MITT) - The modified intent-to-treat population is defined as all participants in the ITT Population, but excluding those that did not complete at least one treatment period. Analysis will compare relative period effects for PBO and OXY periods on change in scores from Baseline to End of Treatment.

Per protocol Population (PPP) - All participants who completed each protocol specified study visit and who were at least 70% compliant in study drug administration for both treatment periods. For assessments completed by caregiver, the data must be collected within 30 days of last dose of IP. For cognitive outcomes completed by patient, data must be collected within 3 days of last dose of IP. Data for which there are clear validation errors or where administration errors are clear and unreconcilable for neuropsychological testing will also be excluded from PPP. Exclusion for validation errors will only be possible for IRI and RSMS where such validation errors are apparent.

A CONSORT diagram, detailing the participants excluded from each subsequent population restriction will be presented for the study.

Section 5 – Trial Population
5.1 Eligibility

There were no changes to eligibility criteria from the initiation of participant recruitment to end of study.
1. Diagnosis of probable FTD (behavioural variant FTD, FTD-semantic subtype or FTD-Progressive Nonfluent Aphasia) with supportive brain imaging (centrally rated frontotemporal atrophy score of 2 or greater on brain MRI or CT) or known FTD causing genetic mutation.
2. Current symptoms of social apathy/indifference as measured by NPI apathy/indifference severity subscale score >= 2 indicating the presence of moderate to marked levels of apathy/indifference.
3. Study partner who consents to study participation and who cares for/visits the patient daily for at least3 hours/day and who can administer all trial medications.
4. FTLD-CDR score 0-2.5.
5. MMSE >10.
6. Stable baseline medications related to cognition or behaviour for >=30 days such as acetylcholinesterase inhibitors, memantine, anti-depressants, antipsychotic agents, other mood stabilizers, benzodiazepines.
7. Written informed consent must be obtained and documented (from the patient or, where jurisdictions allow it, from their substitute decision maker).
8. Participant age at screening between 30 and 80 inclusive.

5.2 Withdrawal/Follow-up

For participants who withdraw from the study for reasons other than death or participant or study partner consent withdrawn, a visit should be scheduled as soon as possible after the last dose of study drug and identified end of treatment safety evaluations performed. For participants who withdraw consent or when a study partner withdraws consent without available alternate study partner, the investigator should request that the reason be specified, and the participant have any clinically indicated safety assessments performed.
Participants in whom treatment is discontinued or who are lost to follow-up should be encouraged to return for a post-treatment visit as soon after the last dose of study drug possible. Participants withdrawn from the study will not be replaced nor can they be re-enrolled.
If a participant is unable to complete the EOT visit, acquired data will be included in the analysis. For patients withdrawing from the study, if they cannot complete an in-person visit, outcome measures that can be acquired via a telephone interview with the study partner/caregiver will be obtained whenever possible.

5.3 Baseline Participant Characteristics

Table 1

Demo	**Overall Total**	**Placebo - Oxytocin Total (stage 1 and 2 combined)**	**Oxytocin_Placebo Total(stage 1 and 2 combined)**	**Stage 1 Every Day - Placebo**	**Stage 1 Placebo –Every Day**	**Stage 1 Every Other Day- Placebo**	**Stage 1 Placebo -Every Other Day**	**Stage 1 Every Third Day- Placebo**	**Stage 1 Placebo -Every Third Day**	**Stage 2 Every Third Day- Placebo**	**Stage 2 Placebo -Every Third Day**
Sex											
Age											
FTD Subtype											
Severity											
MMSE											
Ethnicity											
Handedness											
FBI											
NPI-Apathy											
Weight											
Years of Education											
FTD genetic mutation											

Section 6 – Analysis
6.1 Outcome Definition

Primary Efficacy Objective

• Change in Neuropsychiatric Inventory (NPI) apathy/indifference domain score

Rationale: Pilot data from our two prior studies of oxytocin in FTD have driven the selection of the NPI as the primary outcome measure. The NPI was developed by Dr. Jeffery Cummings and is the most commonly used rating tool for neuropsychiatric behaviours in clinical trials in dementia. The NPI assesses 12 domains of behaviour via study partner interview and also includes validated, integrated caregiver distress measure to demonstrate the effect of each domain of behaviour on caregivers. We previously identified a 3-point change relative to placebo on the NPI apathy/indifference domain score in response to oxytocin treatment. The NPI apathy/indifference domain captures changes in affection and

emotional responses towards others and interest in others, core deficits in FTD that we hypothesize will improve with extended oxytocin treatment.

Secondary Efficacy Objective

• Change in emotional facial expression recognition performance

Rationale: Patients are presented with a standardized set of emotional facial expressions (Ekman faces) and multiple-choice labels (angry, happy, fear, disgusted, sad, neutral, surprised) and asked to designate via pointing or verbal response which expression is displayed. This task is included as an objective measure of pharmacodynamic effect (i.e. independent of study partner ratings) as oxytocin administration has been demonstrated to improve recognition of positive facial expressions in healthy adults, and to reduce recognition of threat related expressions (anger, fear) in FTD and controls. Total scores on OXY vs PBO. Facial expression labels will be grouped into three categories "neutral, positive or negative".

• Change in the Interpersonal Reactivity Index (IRI) empathic concern scale and IRI total score

Rationale: The IRI is a 28-item study partner questionnaire answered on a 5-point Likert scale that ranges from "Does not describe me well" to "Describes me very well". The measure has 4 subscales, including an empathic concern scale which looks at feelings of sympathy and concern for others. FTD patients demonstrate deficits in the Empathic concern and Perspective taking subscales. Based on our dose- finding study which demonstrated improvements in empathic concern on the IRI following oxytocin in FTD, we predict that empathic concern scores will be improved following oxytocin administration, demonstrating the efficacy of oxytocin to improve core empathy deficits in patients with FTD.

• Change in the Revised Self-Monitoring Scale (RSMS) score

Rationale: The RSMS is a 13-item study partner completed scale to assess patient's changes in self-presentation to fit the social setting. The RSMS was added to the new FTLD National Alzheimer's Coordinating Centers module and will serve as a secondary measure of sensitivity to other's emotions and the ability of patients to adapt their behaviour accordingly.

• Change in modified Clinicians Global Impression of Change (apathy) (m-CGIC) scores

Rationale: The Clinical Global Impression scale is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response. This modified version includes items directed towards apathy. The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (most severely ill patients). CGI-C scores range from 1 (very much improved) through to 7 (very much worse). Treatment response ratings take account of both therapeutic efficacy and treatment-related adverse events and range from 0 (marked improvement and no side-effects) to 4 (unchanged or worse and side-effects outweigh the therapeutic effects).

• Change in modified Clinicians Global Impression of Change (overall) (m-CGIC) scores

Rationale: The Clinical Global Impression scale is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response. CGI-C scores range from 1 (very much improved) through to 7 (very much worse). Treatment response ratings take account of both therapeutic efficacy and treatment-related adverse events and range from 0 (marked improvement and no side-effects) to 4 (unchanged or worse and side-effects outweigh the therapeutic effects).

• Change in Caregiver Distress Scores on NPI apathy/indifference scale and Caregiver Distress Scores and Total NPI

Rationale: Assessment of changes in caregiver distress related to the main target symptoms of interest and impact on global neuropsychiatric symptoms will identify whether any improvements in social apathy translate to improvements in caregiver burden and therefore inform estimations of the impact and value of oxytocin as a clinical treatment

• Change in total NPI scores

Rationale: Examination of the total NPI scores will allow integration of the large range of caregiver-rated neuropsychiatric behaviours over the course of the study, permitting net assessments of improvements or worsening

across behavioural domains.

Safety Outcomes:

• Adverse symptoms

Nature, frequency, severity and timing of adverse events and serious adverse events.

• Changes in QTcF interval as measured by ECG

• Changes in serum sodium level, heart rate and blood pressure

Rationale: Intravenous oxytocin administration has been associated with changes in heart rate, QTcF interval and blood pressure, and with serum sodium levels in participants concomitantly receiving intravenous fluids.

• Compliance with treatment (based on daily logs and measurement of residual volumes)

Withdrawal rates per dose schedule arm

Exploratory outcome measures:

• Change in social behaviours based on videotaped segments of naturalistic behaviour

Rationale: It is recognized that naturalistic and qualitative behavioural observations are very informative in the diagnosis of FTD beyond the information provided by traditional assessments. Recent work has demonstrated the power of objective quantitative ratings of patient behaviours from in-home video assessments during mealtime by blinded trained reviewers using the Social Observation Checklist to distinguish between patients with bvFTD, AD and study partners. The Social Observation checklist includes numerous verbal and nonverbal items that we predict may be improved by oxytocin including:

1) spontaneous verbal behaviour,
2) verbal responsiveness to others' comments (i.e. reflective comments),
3) elaboration of verbal responses (more than minimal answers),
4) "others" references ("you" statements or references to family),
5) joint attention,
6) gaze/eye contact during the interaction,
7) facial responses appropriate to the interaction,
8) social tact

To obtain a naturalistic behavioural assessment independent from study partner ratings, using procedures similar to those in Mendez et al. we will obtain 1 hour videotape sessions during a meal via a non-intrusive camera placed by study personnel for the treatment and placebo arms of the study. Videotape sessions will be conducted at the study visits during a meal break with study partners in a private setting. Central raters will be trained to rate behaviours using the Social Observation Checklist blinded to treatment and visit status.

Other measures:

• Change in Serum Estradiol and Testosterone Levels

Rationale: Estrogen is known to modulate oxytocin binding in regions of the limbic system. Interactions between testosterone and oxytocin have also been suggested in human studies. We will obtain estradiol and free testosterone and total testosterone measurements at each baseline and the end of treatment periods to examine potential interactions of these hormone levels with the effects of oxytocin administration.

• Genetic Testing for Oxytocin Polymorphisms

Rationale: Polymorphisms in the oxytocin receptor may account for some of the heterogeneity of response to intranasal oxytocin observed across studies. We will examine genetic polymorphisms related to oxytocin function including the most common rs53576 SNP, for which GG homozygosity has been linked to increased empathic responses, and greater response to intranasal oxytocin compared to AA allele carriers.

Pharmacokinetic Objective

• Difference in CSF oxytocin levels following oxytocin vs. placebo treatment periods

Rationale: Studies of intranasal oxytocin administered to non-human primates consistently show increases of CSF oxytocin levels of >=50% in 30-60 minutes. A similar increase was observed in the single study conducted in humans. Whether the neuropathophysiology of FTD or aging may affect uptake and distribution of oxytocin in the CNS is unknown. We will measure CSF levels in consenting participants during the oxytocin and placebo phases to confirm intranasal oxytocin and CSF oxytocin PK findings from healthy adults in patients with FTD. In the event that the clinical outcomes are positive, these data may help to refine dose selection for the next trial. In the event that there is no efficacy signal, the data would confirm that sufficient drug reached the CNS, and therefore support a negative (as opposed to inconclusive) result. CSF levels of oxytocin will be measured by the Biomarkers Core at Emory University which has extensive experience in oxytocin analysis in human and nonhuman primates using the Liquid chromatography-mass spectrometry (LC-MS) All submitted samples are run in duplicate in batches including in house controls and % coefficients of variation are calculated and reported for all analyses.

6.2 Analysis Methods

The primary analysis of the change from baseline NPI apathy domain is based on a linear model with covariates for sex and order of treatment in the crossover including data from both Stage 1 and Stage 2 for the target selected treatment arm (ETD) will be used to demonstrate superiority using a nominal 2.5% one-sided test using the PPP. Estimated mean effect of the treatment compared to placebo and 95% confidence intervals will be reported. Analysis will compare relative period effects for PBO and OXY periods via change in scores from Baseline to End of Treatment visit.

Supportive primary analysis will be conducted on the MITT population. Given the crossover design, the ITT analysis excludes those that did not take any study medications in their second treatment period.

Sensitivity analysis combining all dose groups for OXY vs. PBO will be conducted for all primary, secondary, and exploratory outcome measures.

Covariates:
Order of treatment (End of treatment 2: Oxytocin versus End of Treatment 2: Placebo)
Sex (male vs female)

Subgroup analyses:
By sex
By severity
Age (median split : young <67 years; older 67+ years)
Oxytocin Genetic polymorphism (GG vs AG vs AA)
FTD subtype (bvFTD vs PNFA vs SD)

ALL other outcomes as listed above, will be analysed using the same methods as for the primary outcome using 5% 2-sided test. Subject is modeled as a random effect, the others are all fixed effects.

To explore whether hormonal levels or imaging atrophy patterns predict behavioural response to OXY, we will conduct a linear regression with NPI apathy domain change scores for OXY-PBO as the dependent measure and predictors of regional MRI atrophy ratings (scores from the Harper et al. visual rating scale for each of the following regions: orbitofrontal, rostral anterior cingulate, fronto-insula, medial temporal, and posterior), baseline serum estrogen level (continuous), baseline serum testosterone level (continuous), sex, and treatment order.

The following endpoints are included in the prospective analysis plan:

Table 6.1A. Endpoints for Analysis

#	Endpoint	Role	Endpoint Type	Pop	Model
1	NPI – Apathy Domain Change Score	Primary Efficacy Endpoint	Continuous Outcome. Higher scores represent worse apathy values.	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + subject + period2 + female + OXY The intercept covers the reference group of placebo, period #1, and male. The "OXY" is an indicator of treatment — OXY. The Period2 is an indicator of it being the second period. The 'female' is an indicator of female patient. Y_period represents the NPIA domain score at End of Treatment for that period – score at Baseline for that period
2	NPI – Apathy Domain Change Score	Primary Efficacy Endpoint Supportive Analysis	Continuous Outcome. Higher scores represent worse apathy values.	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
3	NPI – Apathy Domain Change Score	Primary Endpoint Sensitivity Analysis	Continuous Outcome. Higher scores represent worse apathy values.	PPP– all dose groups combined	Y_period = Intercept + period2 + subject + female + OXY
4	NPI – Apathy Domain Change Score	Primary Efficacy Endpoint Sensitivity Analysis	Continuous Outcome. Higher scores represent worse apathy values.	PPP exclude all new behaviour meds Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
5	NPI – Apathy	Efficacy Endpoint	Continuous Outcome.	PPP	Y_period = Intercept + period2 + subject + female + OXY

	Doman Change Score	SUBGROUP	Higher scores represent worse apathy values.	Most promising dose group (Q3D) from stage 1 and stage 2	BY SEX (M/F)
6	NPI – Apathy Doman Change Score	Efficacy Endpoint SUBGROUP	Continuous Outcome. Higher scores represent worse apathy values.	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY BY SEVERITY (CDR 0-1 vs 2)
7	NPI – Apathy Doman Change Score	Efficacy Endpoint SUBGROUP	Continuous Outcome. Higher scores represent worse apathy values.	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY BY AGE (0-65 vs >65)
8	NPI – Apathy Doman Change Score	Primary Efficacy Endpoint SUBGROUP	Continuous Outcome. Higher scores represent worse apathy values.	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY OXYTOCIN GENE rs53576 AA vs GG vs AG
9	NPI – Apathy Doman Change Score	Primary Efficacy Endpoint SUBGROUP	Continuous Outcome. Higher scores represent worse apathy values.	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY By FTD clinical subtype: bvFTD vs. svPPA vs. nfPPA
[Publish Date] 10	EFER	Secondary Efficacy Endpoint	Categorical	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
11	EFER	Secondary Efficacy Endpoint Sensitivity	Categorical	PPP All doses combined	Y_period = Intercept + period2 + subject + female + OXY
12	EFER	Secondary Efficacy Endpoint Sensitivity	Categorical	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY

13	IRI – Empathic Concern	Secondary Efficacy Endpoint	Continuous outcome. Higher scores represent better values.	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
14	IRI – Empathic Concern	Secondary Efficacy Endpoint Sensitivity	Continuous outcome. Higher scores represent better values.	PPP – all doses	Y_period = Intercept + period2 + subject + female + OXY
15	IRI – Empathic Concern	Secondary Efficacy Endpoint Sensitivity	Continuous outcome. Higher scores represent better values.	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
16	IRI - Total Score	Secondary Efficacy Endpoint	Continuous outcome. Higher scores represent better values.	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
17	IRI - Total Score	Secondary Efficacy Endpoint	Continuous outcome. Higher scores represent better values.	PPP– all dose groups	Y_period = Intercept + period2 + subject + female + OXY
18	IRI - Total Score	Secondary Efficacy Endpoint sensitivity	Continuous outcome. Higher scores represent better values.	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
19	RSMS Total	Secondary Efficacy Endpoint	Continuous outcome. Higher scores represent better values.	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
20	RSMS Total	Secondary Efficacy Endpoint	Continuous outcome. Higher scores represent better values.	PPP– all dose groups	Y_period = Intercept + period2 + subject + female + OXY
21	RSMS Total	Secondary Efficacy Endpoint Sensitivity	Continuous outcome. Higher scores	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY

			represent better values.		
22	RSMS Total	Secondary Efficacy Endpoint sensitivity	Continuous outcome. Higher scores represent better values.	PPP – excluding those with obvious validity issues	Y_period = Intercept + period2 + subject + female + OXY
23	CGIC – Apathy score	Secondary Efficacy Endpoint	Ordinal Outcome (1,2,3,4,5,6,7). 1 (marked improvement) to 7 (marked worsening)	PPP Most promising dose group (Q3D) from stage 1 and stage 2	General Estimating Equation
24	CGIC – Apathy score	Secondary Efficacy Endpoint sensitivity	Ordinal Outcome (1,2,3,4,5,6,7). 1 (marked improvement) to 7 (marked worsening)	PPP– all dose groups	Y_period = Intercept + period2 + subject + female + OXY
25	CGIC – Apathy score	Secondary Efficacy Endpoint sensitivity	Ordinal Outcome (1,2,3,4,5,6,7). 1 (marked improvement) to 7 (marked worsening)	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
26	NPI Apathy – Caregiver distress Score	Secondary Efficacy Endpoint	Continuous Outcome. Higher scores represent worse values.	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
27	NPI Apathy – Caregiver distress Score	Secondary Efficacy Endpoint	Continuous Outcome. Higher scores represent worse values.	PPP – all dose groups	Y_period = Intercept + period2 + subject + female + OXY
28	NPI Apathy – Caregiver distress Score	Secondary Efficacy Endpoint sensitivity	Continuous Outcome. Higher scores represent worse values.	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY

29	NPI – Total Caregiver Distress Score	Secondary Efficacy Endpoint	Continuous Outcome. Higher scores represent worse values.	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
30	NPI – Total Caregiver Distress Score	Secondary Efficacy Endpoint	Continuous Outcome. Higher scores represent worse values.	PPP– all dose groups	Y_period = Intercept + period2 + subject + female + OXY
31	NPI – Total Caregiver Distress Score	Secondary Efficacy Endpoint sensitivity	Continuous Outcome. Higher scores represent worse values.	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
32	Total NPI Score	Secondary Efficacy Endpoint	Continuous Outcome. Higher scores represent worse values.	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
33	Total NPI Score	Secondary Efficacy Endpoint	Continuous Outcome. Higher scores represent worse values.	PPP – all dose groups	Y_period = Intercept + period2 + subject + female + OXY
34	Total NPI Score	Secondary Efficacy Endpoint sensitivity	Continuous Outcome. Higher scores represent worse values.	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
35	Social Observation Outcome	Exploratory Outcome	Continuous Outcome. Higher score represents better values	PPP All dose groups	Y_period = Intercept + period2 + subject + female + OXY
36	CGIC - Overall	Secondary Outcome	Ordinal Outcome (1,2,3,4,5,6,7). 1 (marked improvement) to 7 (marked worsening)	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
37	CGIC - Overall	Secondary Outcome	Ordinal Outcome	PPP – all dose groups	Y_period = Intercept + period2 + subject + female + OXY

			(1,2,3,4,5,6,7). 1 (marked improvement) to 7 (marked worsening)		
38	CGIC - Overall	Secondary Outcome sensitivity	Ordinal Outcome (1,2,3,4,5,6,7). 1 (marked improvement) to 7 (marked worsening)	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
39	CGIC - Overall	Secondary Outcome sensitivity	Ordinal Outcome (1,2,3,4,5,6,7). 1 (marked improvement) to 7 (marked worsening)	MITT all combined	Y_period = Intercept + period2 + subject + female + OXY
40	Cambridge Behavioural Inventory-Revised Motivation scale	Secondary Outcome	Continuous (sum of 5 symptom scores that can range from 0,1,2,3,4). Higher scores represent worse outcome	PPP – all dose groups	Y_period = Intercept + period2 + subject + female + OXY
41	Cambridge Behavioural Inventory-Revised Motivation scale	Secondary Outcome Sensitivity	Continuous (sum of 5 symptom scores that can range from 0,1,2,3,4). Higher scores represent worse outcome	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
42	Cambridge Behavioural Inventory-Revised Total Score	Secondary Outcome	Continuous (0-180) Higher scores represent worse outcome	PPP – all dose groups	Y_period = Intercept + period2 + subject + female + OXY
43	Cambridge Behavioural Inventory-Revised	Secondary Outcome	Continuous (sum of 5 symptom scores that can range	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY

	Total Score		from 0,1,2,3,4). Higher scores represent worse outcome		
44	NPI – Apathy Doman Change Score	Exploratory biomarker predictors of response	Continuous Outcome. Higher scores represent worse apathy values.	PPP all dose groups combined	Y_period = Intercept + period2 + subject + female + OXY Linear regression model: Dependent variable: change in NPI Apathy domain scores during OXY – PLC period. Predictor variables: OXT receptor genotype, serum estrogen (baseline), serum testosterone (baseline), change in CSF_oxy, MRI regional atrophy ratings, age, sex, treatment order. -OXYTOCIN GENE rs2254298 AA vs GG vs AG -MRI atrophy ratings (frontal right, frontal left, temporal right, temporal left, etc.)
45	ACE-III	Exploratory Analysis	Continuous Outcome. Higher scores represent better cognition	PPP Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
46	ACE-III	Exploratory Analysis Supportive	Continuous Outcome. Higher scores represent better cognition	MITT Most promising dose group (Q3D) from stage 1 and stage 2	Y_period = Intercept + period2 + subject + female + OXY
47	ACE-III	Exploratory Analysis	Continuous Outcome. Higher scores represent better cognition	PPP– all dose groups combined	Y_period = Intercept + period2 + subject + female + OXY
48	QTcF interval as measured by ECG	Safety Outcome	Continuous < change	mITT	ECG = Y_period = Intercept + period2 + subject + female + OXY Y_period is QTcF interval as measured by EVG, change from baseline in each period.

49	QTcF interval as measured by ECG	Safety Outcome sensitivity	Continuous < change	mITT removing participants outside of >25 minutes post dose	Y_period = Intercept + period2 + subject + female + OXY Y_period is QTcF interval as measured by ECG, change from baseline in each period.
50	serum sodium level	Safety Outcome	Continuous < change	mITT	Y_period = Intercept + period2 + subject + female + OXY Y_period is serum sodium level, change from baseline in each period.
51	heart rate	Safety Outcome	Continuous < change	mITT	Y_period = Intercept + period2 + subject + female + OXY For following periods: Y_period is HR, change from baseline in each period.
52	Systolic blood pressure	Safety Outcome	Continuous < change	mITT	Y_period = Intercept + period2 + subject + female + OXY Y_period is SBP, change from baseline in each period.
53	Diastolic blood pressure	Safety Outcome	Continuous < change	mITT	Y_period = Intercept + period2 + subject + female + OXY Y_period is DBP, change from baseline in each period.
54	Change in CSF Oxytocin Levels	Exploratory	Continuous	PPP	Y_period = Intercept + period2 + subject + female + OXY Y_period is HR, change from baseline in each period.
55	Adverse Events	Safety Outcome		ITT all dose groups	Counts per OXY and PLC periods, McNemar's test (see below)

56	Serious Adverse Events	Safety Outcome		ITT all dose groups	Counts per OXY and PLC periods McNemar's test (see below)
57	Withdrawal Rate	Safety		ITT all dose groups	Withdrawal counts= ED, EOD, ETD, P
58	Compliance	Safety		ITT all dose groups	Percentage of treatments taken for each dose schedule and period, t-tests

6.3 Missing Data

NPI apathy is assessed at screening and then at each baseline visit *before study drug administration and at end of treatment visits *after study drug administration.

Schedule: Baseline 1 Visit: 6 weeks on treatment then End of Treatment 1 visit, then 6 weeks washout to Baseline 2 then 6 weeks on treatment and then End of treatment 2 visit.
Missing data will be approached with the assumption that it is Missing at Random. The statistical models incorporate each observed observation and sensors unobserved observations.

6.4 Harms

Investigators will assess the occurrence of adverse events and serious adverse events at all patient evaluation time points during the study. All adverse events and serious adverse events, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be recorded in the patient's medical record and on the appropriate adverse event or serious adverse event eCRF. Each recorded adverse event or serious adverse event will include a description of its duration (i.e., start and end dates), severity, seriousness according to regulatory criteria, if applicable, and suspected relationship to the investigational product, as well as any actions taken. All AEs will be recoded into terms using MEDdra. Type and overall frequency of adverse events under each intervention will be described and analyzed using McNemar's test. Concordant and discordant pairs of adverse events and where appropriate, estimates of effect and precision will help to inform the relative safety of the intervention.

Adverse event		No of adverse events
	Zero adverse events under either OXY or placebo	
	Adverse event observed under placebo but not under OXY	
	Adverse event observed under OXY but not under placebo	
	Adverse event observed under both OXY and placebo	

November 23, 2023

Signature: PI Elizabeth Finger, MD

Date