PROPOSED STUDY TITLE
The Magnitude and Duration of the Central Nervous System Effects following Intravenous Infusion of Diphenhydramine using Pharmacokinetic and Pharmacodynamic Modeling

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NCT NUMBER
NCT05219604

DOCUMENT DATE
2022-FEB-09

SECTION 1.0: STUDY RATIONALE AND SIGNIFICANCE

This study seeks to explore the magnitude and duration of central nervous system (CNS) effects after intravenous (IV) infusion of diphenhydramine. IV diphenhydramine is an antihistamine commonly used in clinical practice as prophylaxis for infusion-related reactions of monoclonal antibodies. Differences in CNS effects between adults aged 35 to 50 and elderly aged 65+ will be explored. This study aims to construct a pharmacokinetic/pharmacodynamic (PK/PD) model describing the magnitude and time course of CNS effects when variables such as dose, rate of infusion, etc. are adjusted. To the knowledge of the investigators, there are no other studies exploring the CNS effects of diphenhydramine with such a wide variety of cognitive tests and as in-depth PK/PD analysis as the present study.

SECTION 2.0: PURPOSE

Objectives:

- To assess the magnitude and duration of CNS impairment produced by intravenous doses of diphenhydramine 50 mg as measured using objective neuropsychometric endpoints.
- To construct a PK/PD model statistically fitted to the individual serum concentrations and CNS impairment data to produce estimates of PK endpoints including area under the curve (AUC), half-life and total clearance as well as PD endpoints including Emax (the maximal effect of a drug) and EC50 (blood concentrations for 50% of maximum effect).

The PK/PD model will be used to explore the effects on estimates of maximal effect and time course of CNS effect when variables such as dose, rate of infusion, etc. are adjusted.

SECTION 3.0: BACKGROUND

In recent years, the introduction of monoclonal antibodies has significantly increased the number of chronic conditions treated in infusion suites. The reported overall incidence of hypersensitivity reactions to some monoclonal antibodies can be significant. For example, the overall incidence of hypersensitivity reactions to rituximab is reported to be as high as 77% with the first infusion. Fortunately, prophylactic pre-infusion medications can reduce this to less than 10%.[1]

Common medications used alone or in combination with corticosteroids are H1 antihistamines. Until recently this was limited to intravenous diphenhydramine. While intravenous diphenhydramine is effective, it carries with it significant adverse effects. Diphenhydramine readily crosses the blood brain barrier producing both H1 receptor-mediated and cholinergic receptor-mediated effects in the CNS. These CNS effects become more frequent and severe in older patients.

A recently published work found that diphenhydramine was effective in relieving urticarial symptoms but produced subjective "sedation".[2] Sedation is a depressed state of CNS activity, generally considered a decrease in alertness. However, the effects of diphenhydramine go beyond sedation. There is sufficient published data to suggest that diphenhydramine can have negative effects on several specific domains of cognition including reaction time, recognition and recall, working memory processing speed and ability to perform divided attention tasks. These are many of the same domains of cognition involved in skills related to driving an automobile, etc.[3-7]

We propose this study to specifically explore the effects of intravenous diphenhydramine on specific domains of cognition. We propose a formal pharmacokinetic/pharmacodynamic (PK/PD) analysis so that models can be developed that allow estimates of these effects when variables such as dose are varied.

SECTION 4.0: OUTCOME MEASURES

The primary outcome will be the difference in the results of the battery of cognitive function tests (Appendix A) after diphenhydramine administration compared to baseline.

The secondary outcomes will be:

1. The difference in the results of the battery of cognitive function tests in elderly subjects (Group B) vs. adult subjects (Group A)
2. The difference in diphenhydramine area under the curve (AUC) in elderly subjects (Group B) vs. adult subjects (Group A)
3. The difference in the results of the battery of cognitive function tests (Appendix A) after diphenhydramine administration compared to baseline in elderly subjects (Group B) vs. adult subjects (Group A)

SECTION 5.0: INCLUSION CRITERIA

The following are required for inclusion in this study:

1) Medically-stable volunteers of either gender between 35 and 50 years old (Group A) or over the age of 65 (Group B)
2) No medication changes anticipated for the duration of the study except as defined in section 9.4

SECTION 6.0: EXCLUSION CRITERIA

The following will be considered exclusionary for participation in this study:

1) Insulin-dependent diabetes
2) Psychiatric or neurologic disease affecting cognition in a way that may interfere with study outcomes in the opinion of the investigator
3) Unstable Coronary Artery Disease (active angina, MI within 6 months, stent placement within 6 months, cardiac surgery within 6 months)
4) Estimated CrCl < 30 mL/min using the Cockroft-Gault equation based on ideal body weight or total body weight
5) Any malignancy actively being treated or not in remission
6) Currently taking any CNS stimulant or depressant medications that may interfere with study outcomes in the opinion of the investigator unless using as defined in section 9.4
7) Positive toxicology test for marijuana at screening visit or visit 2 or using marijuana not as defined in section 9.4
8) Active or recent history of a substance use disorder within one year
9) Any medical condition that in the opinion of the investigator would disqualify the subject from participation in the study
10) Female subjects who are pregnant, planning to become pregnant, or breastfeeding on any study day
11) Female subjects of childbearing potential unwilling to use acceptable method of contraception during the study as defined in section 9.3
12) Contraindication, known allergy, or suspected intolerability to study medication
13) Receipt of an antihistamine (details in section 9.4) within 5 half-lives prior to the start of study visit 1 or study visit 2, as determined by the investigator

14) Positive toxicology test for a drug that is inconsistent with permitted medication use (defined in section 9.4) as interpreted by the investigator
15) Participation in any other investigational drug study during the study or within 4 weeks prior to screening

SECTION 7.0: METHODS

Section 7.1: Overview

Table 1. Schedule of study assessments.

Assessment	Screening Visit (V0) (Day 0)	Study Visit 1 (V1) (Day 7 +/- 3)	Study Visit 2 (V2) (Day 14 + 7)
Demographics	X		
Medical history	X		
Prior/concomitant medications	X		X
Review health and any changes in health	X	X	X
Vital signs	X		X
Weight	X		X
Height	X		
CBC and CMP	X		
Diphenhydramine PK			X
Urine pregnancy test[a]	X		X
Urine toxicology test	X	X	X
Alcohol breath test	X	X	X
Physical exam	X		
Cognitive tests		X	X
Infusion with diphenhydramine			X

CBC = complete blood count, CMP = comprehensive metabolic panel, PK = pharmacokinetics
[a]Women of child-bearing potential only.

At the screening visit, following provision of informed consent, subjects will provide information regarding their demographics, medical history, concomitant medications and medications taken in the last 4 weeks. Subjects will have their vitals/height/weight measured and undergo a physical exam,

routine clinical blood work (comprehensive metabolic panel and complete blood count), urine toxicology screening, alcohol breath test, and a pregnancy test (women of child-bearing potential as defined in section 9.3).

Subjects meeting all inclusion and exclusion criteria will arrive at the study center for study visit 1 (V1).

During V1, practice cognitive function testing will be conducted to assure each subject has overlearned the test. This is accomplished by having subjects perform each test three times at V1. Prior to cognitive testing, subjects will undergo a urine toxicology screening and alcohol breath test.

Subjects will then return within 7 to 14 days after V1 for study visit 2 (V2). V2 is a treatment day. Subjects will have their vitals and weight measured and will undergo urine toxicology screening, alcohol breath test, and a pregnancy test if indicated. Subjects will then receive treatment with IV diphenhydramine 50 mg at V2. Blood will be drawn for PK samples and cognitive testing will be completed by subjects at predetermined intervals throughout V2. At the end of V2, subjects will have completed the study.

Section 7.2: Study Drug

The study drug will be intravenous diphenhydramine, which will be purchased commercially. Diphenhydramine will be maintained by the study staff and will be administered as per Dent Policy & Procedure INF-024 for intravenous infusion of diphenhydramine (Appendix B), with the exception that diphenhydramine (50 mg) will be administered intravenously by diluting with 5 mL of sterile normal saline and administering as a single bolus injection over 5 minutes.

Section 7.3: Psychometric Testing Study Schedule/Design (Study Visit 2)

Start of Psychometric Testing Time (min from end of administration)	**Group A**	**Group B**
0, 30, 210, 450	Subjects 1 – 8	Subjects 1 – 8
0, 60, 240, 480	Subjects 9 – 16	Subjects 9 – 16

Time 0 for conducting psychometric testing will be completed 0 – 60 minutes prior to start of intravenous push. Remaining times represent when the subject will begin psychometric testing. All psychometric tests will begin in a window of +/- 10 minutes.

Measurements will be taken pre-treatment, just after infusion (30-60 min post-infusion), half-way (210-240 min post-infusion), and at the end (450-480 min post-infusion) of the experiment. This design was selected to generate a robust set of richly collected psychometric testing data that can be analyzed over the full-time course of the experiment. In addition, the population PK/PD analysis method to be implemented (see below) will permit a "sharing" of information between subjects. This strategy will permit robust sampling of the psychological effects of each drug after a single dose, and relate these effects to the concentration of diphenhydramine.

Section 7.4: Pharmacokinetic Sampling Schedule/Design (Study Day 2)

All subjects will have PK samples drawn at the following time points from end of study drug administration:

PK Sample Time (min from end of administration)	Acceptable Range (min)
15	+/- 5
30	+/- 5
60	+/- 5
90	+/- 5
120	+/- 5
180	+/- 10
210	+/- 10
360	+/- 10
420	+/- 10
480	+/- 10

Additionally, a sample will be drawn at time 0 at 0-60 minutes prior to start of drug administration.

At time points where both PK samples are taken and psychometric testing is completed, the PK sample will be taken prior to the start of psychometric testing.

Given the limited population of PK data in the literature for diphenhydramine, a rich sampling scheme will be implemented for each subject. The frequent samples after the end of administration at 15, 30, and 60 min will capture the distributional phase of diphenhydramine. Furthermore, by richly sampling all 32 subjects, this will allow for adequate description of PK fixed effects (clearance, volume of distribution, etc.) and the corresponding inter-individual variabilities on each of those terms.

Section 7.5: Adverse Events (AEs)

Subjects will be under continuous observation at the study site. Both medical and nursing staff will be at the study site for the entire study day. Any subject reporting AEs during the study day will be medically evaluated as appropriate. All AEs and treatments will be recorded in the subject's study file. Serious adverse effects will be reported to the IRB according to IRB reporting policy. Subjects will be given direct phone numbers to report any adverse event after discharge from the study site.

SECTION 8.0: ASSESSMENTS

Section 8.1: Battery of Cognitive Function Tests

The domains of cognitive function that will be measured will be reaction time, movement time, sustained attention, response latency, working memory, visual memory, short-term memory, and new learning. These domains of cognition will be measured before and serially after study drug administration as outlined in the protocol. The specific neuropsychometric tests that subjects will complete are Reaction Time, Rapid Visual Information Processing, Paired Associates Learning, Spatial Working Memory, and Digit Span (Appendix A). These tests have been developed for use in clinical trials by Cambridge Cognition Inc. to assess cognition as a drug safety measure. They have been shown to be sensitive to cognitive decline by pharmacological interventions, confirming their suitability for use in clinical trials to characterize negative effects on various domains of cognitive function.[8] A Visual Analog Scale will also be used to assess sedation (Appendix A).

SECTION 9.0: ENROLLMENT AND CRITERIA FOR SUBJECT SELECTION

The study will consist of 32 healthy volunteers of any race or ethnicity. Sixteen subjects will be between the ages of 35 and 50 (Group A) and 16 subjects will be aged 65+ (Group B).

Section 9.1: Sample Size Calculation

The expected magnitude of the effect size for impairment and drowsiness is based on our previous work.(7) Taking into consideration the number of subjects that can be reasonably expected to complete the battery of psychometric exams, 32 subjects can be sampled at each of the given time points. Power was calculated using the pwr package in R (version 4.0.2). Using previously published information on cognitive effects of diphenhydramine, this design will result in a power > 0.8 to detect impairing effects of diphenhydramine, and > 0.9 to detect drowsiness effects from diphenhydramine.(7) For impairment, power was calculated at the type I error level of alpha = 0.05 for four sample groups (0, 30-60, 210-240, and 450-480 min) each with 32 subjects/samples and the previously established effect z-score of 0.45. The exact same procedure was used to calculate the power to observe changes in drowsiness scores, but using the previously observed effect z-score of 0.82.

Section 9.2: Females of Childbearing Potential

Females are considered to be of childbearing potential unless they meet one of the following criteria as documented by the investigator:

1. Post-menopausal for at least 1 year
2. Hysterectomy, bilateral oophorectomy, or salpingectomy
3. Congenital sterility

Section 9.3: Contraceptive Methods for Females of Childbearing Potential

Female subjects of childbearing potential must be willing and able to practice birth control for the duration of the study. Female subjects must be willing to use a highly effective method of birth control (i.e. contraceptive measure with a failure rate of <1% per year). Highly effective methods of contraception include:

1. Placement of an intrauterine device or intrauterine system.
2. Established use of oral, injected, or implanted hormonal methods of contraception associated with inhibition of ovulation.
3. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
4. Bilateral tubal ligation.
5. True abstinence: when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

Females must not donate ova for the duration of the study.

In addition to the list of highly effective contraception methods above, other acceptable methods of contraception include:

1. Progesterone-only oral contraception, where inhibition of ovulation is not the primary mode of action

2. Cap, diaphragm, or sponge with spermicide
3. Condom

Section 9.4: Concomitant and Prior Medications

The following may not be used within 5 half-lives prior to the start of study visit 1 or study visit 2, as determined by the investigator:

- Antihistamines (including but not limited to: diphenhydramine, chlorpheniramine, dimenhydrinate, cetirizine, levocetirizine, desloratadine, loratadine, fexofenadine, azelastine, olopatadine, doxylamine, brompheniramine, ranitidine, cimetidine, famotidine, cyproheptadine, acrivastine, clemastine)

The following CNS depressant or stimulant medications may not be taken by subjects more frequently than two doses per week in the 3 months prior to screening and may not be taken within 5 half-lives prior to study visit 1 or study visit 2, as determined by the investigator:

- Narcotic analgesics (including but not limited to: hydrocodone, oxycodone, tramadol, codeine, morphine, fentanyl, hydromorphone, propoxyphene)
- Marijuana (recreational or medical)
- Anxiolytics (including but not limited to: chlordiazepoxide, clonazepam, diazepam, flurazepam, meprobamate, triazolam, alprazolam, buspirone, lorazepam, oxazepam, quazepam, chloral hydrate, temazepam, zolpidem, eszopiclone, ramelteon, zaleplon, tasimelteon)
- Antidepressants with strong anticholinergic properties (including but not limited to: doxepin, mirtazapine)
- CNS Stimulants (including but not limited to: methylphenidate, amphetamine salts, dextroamphetamine, lisdexamfetamine)
- Anticholinergic agents (including but not limited to: meclizine, hydroxyzine, diphenoxylate with atropine, hyoscyamine)

The following medications are permitted if dose is stable for 4 weeks prior to screening and throughout the study period:

- Antidepressant medications (including but not limited to: selective serotonin reuptake inhibitors [excluding paroxetine], selective norepinephrine reuptake inhibitors)
- Antipsychotic medications (including but not limited to: lurasidone, haloperidol)

The following medications may not be taken within 4 weeks prior to screening or during the study period:

- Antidepressants with strong anticholinergic properties (including but not limited to: amitriptyline, amoxapine, clomipramine, desipramine, imipramine, isocarboxazide, lithium, maprotiline, nortriptyline, phenelzine, protriptyline, tranylcypromine, trimipramine, paroxetine)
- Antipsychotic medications with strong anticholinergic properties (including but not limited to: molindone, iloperidone)
- Antipsychotic medications with known histamine receptor affinity (including but not limited to: aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, lumateperone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone)
- Antiparkinsonian medications (including but not limited to: bromocriptine, selegiline, levodopa, pergolide, ropinirole, pramipexole, entacapone, chlorpromazine, prochlorperazine, fluphenazine, loxapine, perphenazine, thioridazine, thiothixene, trifluoperazine)

- Anticholinergic agents (including but not limited to: oxybutynin, promethazine, flavoxate, belladonna, tolterodine, bethanechol, amantadine, benztropine, dicyclomine, trihexyphenidyl, trimethobenzamide)
- Cognitive enhancing agents (including but not limited to: physostigmine, pyridostigmine, tacrine, donepezil, rivastigmine, galantamine, memantine, over-the-counter "cognition-enhancing" nutraceuticals/foods/supplements)

SECTION 10.0: STATISTICAL ANALYSIS PLAN

Section 10.1: Statistical Plan

The PD endpoints, cognitive test result differences between Groups A and B and between baseline and post-diphenhydramine time points, will be assessed via one-way ANOVA with contrast. The PK endpoint will be assessed via one-way ANOVA with contrast of noncompartmental PK analysis. Patient AUCs will be numerically calculated based on patient-specific parameter estimates (i.e, the empiric Bayesian estimates) and compared between Groups A and B.

Section 10.2: Pharmacokinetic/Pharmacodynamic Modeling Strategy

The population PK modeling approach will be implemented using S-ADAPT. In order to utilize available information in the literature, priors will be obtained for key PK parameters for diphenhydramine in order to leverage a maximum *a posteriori* estimation method. Previous PK studies will be used to supply prior information of the anticipated PK parameters expected from this study. A full step-wise covariate analysis will be done using log-ratio testing with a pre-defined significance level of alpha < 0.05 for forward selection and alpha < 0.01 for backward elimination. Concentrations below the limit of quantification will be handled using the Beal M3 method.

PK data from both Group A (subjects aged 35-50 years) and Group B (subjects aged $\geq$ 65 years) will be analyzed simultaneously. Patient age will be explored as a possible covariate on the disposition of diphenhydramine.

Intravenous data generated from this study and absorption data following intramuscular administration from literature data will be used to perform model estimates for intramuscular administration.

Continuous PD biomarkers (cognitive test results) will be handled accordingly, which will entail estimation of maximum effect (Emax) and corresponding blood concentrations for 50% of maximum effect (EC50). Categorical PD biomarkers (cognitive test results) will be handled using a hidden Markov method. This method will provide the probability of a patient being at a certain level given the concentration of the drug in the body. This approach has been used extensively to jointly model PK/PD for psychoactive substances.

Subsequent simulation-based studies will be utilized to simulate the likely performance on psychometric testing given a dose, dosing interval, and infusion time. Clinical trial simulations, incorporating the inter-individual variability observed in this study, will provide recommendations for optimal dosing regimens given the desired psychometric outcomes for the majority of patients.

SECTION 11.0: ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted according to good clinical practice guidelines, the Declaration of Helsinki, and the U.S. 21 CFR parts 50 and 56. Written informed consent for the study must be received from all participants.

SECTION 12.0: PARTICIPANT CONFIDENTIALITY

All information obtained during the conduct of the study with respect to the patient's state of health will be regarded as confidential in accordance with national data legislations. In order to maintain anonymity, patients will be identified by a special patient number in lieu of the patient's name in all patient data handling outside the study site. The patient log connecting the patient numbers to the identity of the patients will be kept by the Investigator, and will only be disclosed to external parties for the purpose of quality control, quality assurance, and at the request of the IRB. The participant code number and identifying information will be kept [redacted]

The results of the research may be published; however, the identifying information of subjects will be kept confidential.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify subjects. At most, the website will include a summary of the results.

A detailed study report with results and data generated from this research may be provided to [redacted] in a format which protects the confidentiality of study participants.

Laboratory specimens (CBC and CMP) will be sent to [redacted] for processing. Coded laboratory specimens (PK samples) will be sent to [redacted] for processing.

Coded data or specimens collected in this research might be used for future research or distributed to another investigator for future research without the consent of research subjects.

SECTION 13.0: RISKS

There will be risk associated with this study.

A total of 13 tubes (about 4 tablespoons) of blood will be drawn over the course of the study. As a reference point, when donating blood to an organization such as the Red Cross, approximately 16 ounces or 32 tablespoons of blood are taken. The blood draws may be painful and cause redness, bruising, or infection at the site of needle entry. Sometimes, people experience dizziness and faint or feel nauseous. Experienced medical personnel will be responsible for blood draws to minimize these risks.

Participants will receive diphenhydramine on study visit 2. Diphenhydramine is FDA approved for use and has demonstrated safety. However, diphenhydramine may cause side effects, many of which are more common in the elderly. Possible side effects of diphenhydramine include drowsiness, confusion, lack of concentration, memory impairment, blurry vision, dry mouth, urinary retention, nausea, constipation, agitation, and delirium. Rare but serious side effects of diphenhydramine include allergic reaction and fainting. In addition, the use of diphenhydramine has been linked to accidental injury. Subjects may feel some of the effects of diphenhydramine on the day following the infusion.

Diphenhydramine will be infused intravenously once on study day 2. Intravenous (IV) infusion involves placement of a needle into the vein. For most people, needle sticks for IV injections do not cause any serious problems. Sometimes they may cause bleeding or bruising. They may also cause infections and/or pain at the needle site. Sometimes, people experience dizziness and faint or feel nauseous. Placing the IV line will be done with sterile equipment, but germs on the skin may enter through the skin around the IV, causing swelling, redness, and fever. Phlebitis is irritation of a vein. Subjects may feel swelling, pain, and redness around the vein. A blood clot or an air bubble can be delivered into the circulation through an IV and end up blocking a vessel; this is called embolism. There is a low risk of this. Extravasation is accidentally putting the drugs into the surrounding tissue instead of the vein. Experienced medical personnel will be responsible for infusing diphenhydramine to minimize these risks.

Subjects will be asked to perform an alcohol breath test. This involves forcefully blowing air into a breathalyzer device. Subjects may experience some lightheadedness, fatigue, or shortness of breath after this test.

A urine toxicology test is a test of the urine. The test checks for recent drug use. Subjects will be asked to urinate or "pee" into a small cup. The test involves only normal urination. There is usually no discomfort.

Subjects will be asked to perform cognitive tests on an electronic device during this study. Subjects will also be asked to complete some surveys on paper. Subjects may experience some fatigue, frustration, boredom, or eye strain from these tests.

The investigators will collect subjects' personal information including health-related information for this study. Although there are many safeguards protecting subject information, there is always a risk that the confidentiality of information is breached.

Subjects will be asked to come to the study site for several hours to complete this study. It is estimated that V0 will take around 3 hours, V1 will take around 2 hours, and V2 will take around 9 hours. This may result in financial loss for subjects if they must take time off work to attend study visits.

Subjects will be counseled on the symptoms associated with adverse events so that they may monitor for them. Additionally, subjects will be asked for the presence of any adverse events at every visit specifically including side effects associated with diphenhydramine use.

SECTION 14.0: BENEFITS

Participation in this study will not provide direct benefit to the population. It may, however, provide insight into CNS effects of diphenhydramine which may impact patient care in the future.

SECTION 15.0: COMPENSATION FOR STUDY PARTICIPANTS

For taking part in this research, subjects may be paid up to a total of $200. Compensation will be broken down as follows:

- $75 at screening visit, $25 at study visit 1, $100 at study visit 2
- Payments will be initiated following the final study visit
- Subjects will not be paid for any visits that they do not complete

SECTION 16.0: ALTERNATIVE TO PARTICIPATION

The alternative to be involved in this study is to not participate.

SECTION 17.0: STUDY START AND END DATES

Section 17.1: Enrollment Start Date

Upon IRB approval via central IRB. IRB review is anticipated within 30 days of Submission.

Section 17.2: Screening and Data Collection

To begin immediately following IRB approval. Data collection is expected to be complete within 6 months of IRB approval.

Section 17.3: Anticipated Manuscript Submission

Within 6 months of completion of data collection.

SECTION 18.0: INFORMED CONSENT PROCESS

Please refer to Appendix C.

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Appendix A: Battery of Cognitive Tests

See attached Paired Associates Learning (PAL), Digit Span (DGS), Reaction Time (RTI), Rapid Visual Information Processing (RVP), Spatial Working Memory (SWM), and Visual Analog Scales for Sedation Assessment.

Appendix B: Dent Policy & Procedure INF-024 for Intravenous Infusion of Diphenhydramine

See attached.

Appendix C: Informed Consent Process

See attached.