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**CLINICAL PROTOCOL**

PharmacokinetIcS of allopregnanolone after multiple dose administration of progesterone (2); confirmation of MODELLED DATA

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| **Compounds:** | Progesterone |
| **Investigators:** | A/Prof Yoram Barak  Prof Paul Glue  Prof Natalie Medlicott  Dr Charlotte Mentzel  Dr Shona Neehoff |
| **Phase:** | 1 |
| **Date:** | V1.0 20/11/21 |
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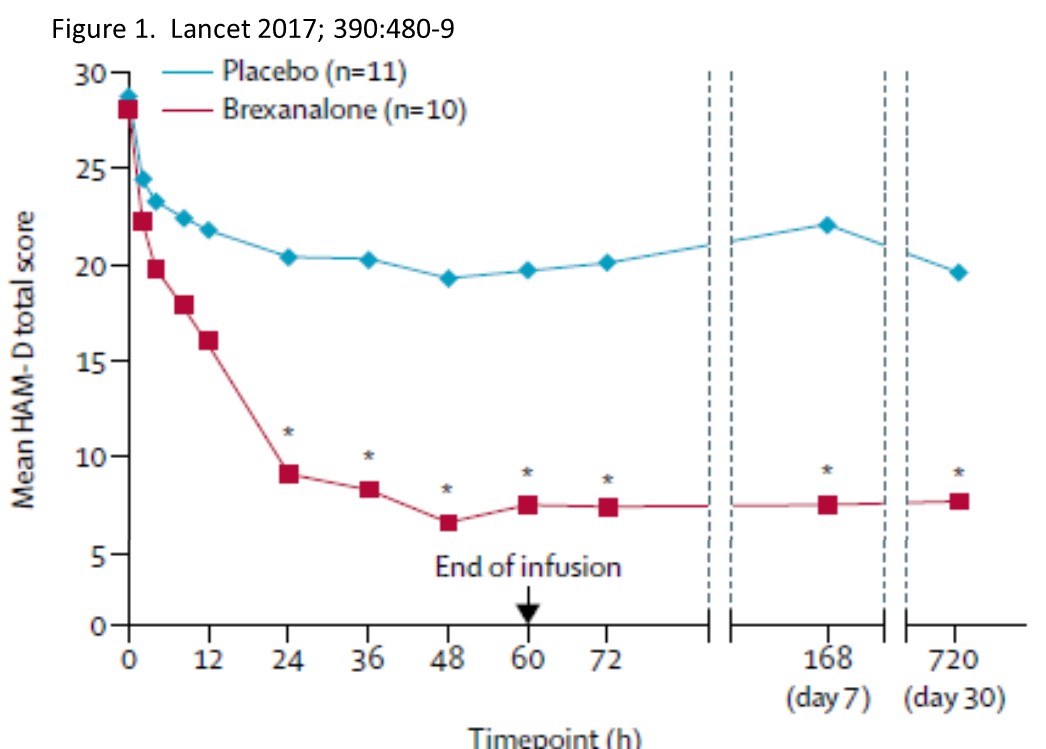
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1. PROTOCOL SYNOPSIS

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| **Title** | Pharmacokinetics of allopregnanolone after multiple dose administration of progesterone (2): Confirmation of modelled data |
| **Investigators** | A/Prof Yoram Barak, Prof Paul Glue, Dr Charlotte Mentzel, Dr Shona Neehoff, Psychological Medicine  A/Prof Natalie Medlicott, School of Pharmacy  University of Otago |
| **Study Timeline** | Enrolment should commence in 1Q 2022 and be complete by end 4Q 2022 |
| **Background** | Postpartum depression (PPD) is a severe disorder that adversely impacts both mothers and infants and is associated with significant morbidity and mortality. PPD’s pathophysiology may involve changes in perinatal hormones such as allopregnanolone (ALLO, an endogenous progesterone metabolite). Brexanolone (BREX) is a small molecule, neuroactive steroid GABAA receptor allosteric modulator consisting of synthetic ALLO and a solubilizing agent. In early 2019 BREX received FDA approval for the treatment of PPD. BREX is only available through a restricted program and is expensive. We explored whether ALLO concentrations could be increased via oral progesterone loading.  We have now completed a Phase 1 pharmacokinetic study to evaluate plasma ALLO concentration-time profiles after oral dosing of progesterone (20/CEN/205), and have modelled this to identify a dosage regimen which will give plasma ALLO concentrations similar to those seen at the end of pregnancy (~50ng/mL). The objective of this study is to collect and analyze plasma ALLO samples in healthy volunteers on this dosage regimen, to confirm accuracy of this model. |
| **Study Design** | Open label multiple dose pharmacokinetic and safety study to measure plasma ALLO concentrations after repeat doses of extended release progesterone capsules given 8 hourly, over 40 hours. |
| **Study Objective(s)** | * To measure plasma ALLO concentrations between 0-48 hours after 8-hourly dosing with extended release progesterone capsules. * To assess the safety and tolerability of extended release progesterone capsules in healthy volunteers |
| **Number of Participants** | Up to 12 healthy volunteers |
| **Inclusion/exclusion criteria** | In: Healthy females; 50-65; post-menopausal; and/or healthy males, aged 18-65; weight at least 50kg, with a minimum BMI of 18.  Ex: Severe or unstable medical conditions; regular use of alcohol/ recreational drugs. |
| **Duration of Study** | 2 days for individual participants |
| **Dosage and regimen** | Dosing with progesterone 100mg capsules every 8 hours as follows:  8AM 0 hours: 200mg  4PM 8 hours: 100mg  12MN 16 hours: 100mg  8AM 24 hours: 100mg  4PM 32 hours: 100mg  12MN 40 hours: 100mg |
| **Pharmacokinetic assessments** | Trough (end of dose) plasma samples to measure plasma progesterone and ALLO concentrations, predose and 8, 24, 32, and 48 hours. Because ALLO has a half-life of 9 hours, we predict ALLO will be at steady state prior to the last blood sampling time (4x half-life). Plasma samples will be assayed using a validated ELISA method. Pharmacokinetics will be analysed using standard noncompartmental methods. |
| **Safety and Tolerability Assessments** | Vital signs and adverse events will be used to assess safety and tolerability throughout the study.  Tolerability: reported adverse events throughout study. |

1. Background

Postpartum depression (PPD) is a severe disorder that adversely impacts both mothers and infants and is associated with significant morbidity and mortality. Clinical research in the treatment of PPD supports a role for a neuroactive steroid GABAA receptor (GABAAR)–positive allosteric modulator, such as allopregnanolone (ALLO, an endogenous progesterone metabolite). Brexanolone (BREX) is a small molecule, neuroactive steroid GABAA receptor allosteric modulator consisting of synthetic ALLO and a solubilizing agent. Figure 1 shows the rapid onset and durable mood response in patients with PPD treated with a 60-hour BREX infusion (red symbols) compared with placebo (blue symbols). In early 2019 BREX received FDA approval for the treatment of PPD. However BREX is only available through a restricted access program and is expensive. We explored whether ALLO concentrations could be increased via oral progesterone loading (progesterone is metabolized to ALLO).



We have now completed a Phase 1 pharmacokinetic study to evaluate plasma ALLO concentration-time profiles after oral dosing of progesterone (20/CEN/205), and have modelled these data to identify a dosage regimen which will give steady-state plasma ALLO concentrations similar to those seen at the end of pregnancy (~50ng/mL). The objective of this study is to collect and analyze plasma ALLO samples in healthy volunteers on this dosage regimen, to confirm accuracy of this model.

2.1 Benefit / Risk Assessment

We do not anticipate there will be any benefit to participants in this study. In the longer term, if we can identify a progesterone dosing regimen that provides plasma ALLO levels similar to those reported for brexanolone, we would then set up a clinical trial using progesterone in women with PPD. If confirmed, this could be a quick and inexpensive treatment for PPD.

The risks of participation include the possibility of increased sedation. After oral 200mg doses of progesterone, participants report a mild increase in sedation (score increase from 5/100 to 20/100, with 0 representing no sedation, and 100 the most sedated ever), peaking at 1-2 hours after dosing. We will manage this by ensuring participants are directly observed for the first 2 hours after dosing on Day 1, and that they do not drive cars for the duration of the study.

**3. STUDY DESIGN AND TREATMENT PLAN**

**3.1. Overall Design**

After participants complete screening, they will be given a visit schedule for clinic attendance, blood sampling, and dosing.

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| --- | --- | --- | --- |
| Clock time | Study time (h) | Dosing | Blood sampling |
| 8AM | 0 | 200mg | x |
| 4PM | 8 | 100mg | x |
| 12 midnight | 16 | 100mg |  |
| 8AM | 24 | 100mg | x |
| 4PM | 32 | 100mg | x |
| 12 midnight | 40 | 100mg |  |
| 8AM | 48 | - | x |

Safety will be monitored throughout the study, by vital signs and reported adverse events. Sedation will be assessed at each blood draw using a 100mm visual analog scale, where 0 represents no sedation, and 100 the most sedated ever.

**3.1.1. Medications**

* 700mg of micronized progesterone capsules (Utrogestan®) given over 40 hours (see Table for dose schedule).

Dose justification: The dosing schedule is based on modelling of single dose 0-8 hour ALLO pharmacokinetic data from study 20/CEN/205, to achieve steady-state serum ALLO concentrations of 50ng/mL. This is the reported ALLO concentration at the end of pregnancy (Luisi et al 2000). Furthermore, much higher progesterone doses (10 g/24 hr, or approximately 25x higher doses) have been reported to be safe and well tolerated (Aebi et al., 1999; Christen et al., 1993).

**3.1.3. Pre-dose preparation**

Participants will be instructed not to drive to the clinic, as drowsiness from progesterone could affect their ability to drive post-dosing. Progesterone bioavailability is increased if it is dosed with food, and we will provide a standard snack (e.g. muesli bar plus 200mL orange juice with each dose. Participants will be advised not to drive until the morning after dosing.

**3.2 Food & Fluid Intake**

No restrictions on food or fluid intake.

**3.4 Safety Precautions**

Participants will only be permitted to participate if they are in good general health and meet all the inclusion criteria and no exclusion criteria. Safety laboratory tests (CBC, electrolytes) and urine drug screen will be obtained at screening.

Throughout the study, the general well-being of the participants will be sought and any adverse events will be recorded and investigated.

Safety data will be monitored for at least 2 hours after the first dose of progesterone. Adverse events will be monitored throughout the study. Safety data will consist of a baseline assessment of general well-being, including systems enquiry, vital signs (blood pressure, heart rate, and temperature). Tolerability assessments include reported adverse events throughout study.

Study personnel with CPR training at Level 4 or greater will be immediately available if subjects report any symptoms during the study. Apart from midnight dosing (at 16 and 40 hours), all other dosing will take place in the Fraser Building, with resuscitation facilities on hand.

There will be regular contact with subjects either in person or by telephone. All participants will have Prof Glue’s cell phone number in case of adverse events that occur outside of these times.

**3.5 Endpoints**

The following will be collected predose (0h) and at visits over the next 48h:

* 100mm visual analog scale (0mm=no sedation, 100mm=most sedation ever)
* Vital signs, adverse events
* 5mL blood samples at 0, 8, 24, 32 and 48h.

**4. Participants**

**4.1 Number of Participants**

Up to 12 male or female participants will be enrolled in this study.

**4.2 Inclusion Criteria**

To be included in the study, participants must meet all of the following inclusion criteria:

1. Capable of understanding and signing an informed consent
2. Males: aged 18-65 years
3. Females: post-menopausal, aged 50-65 years.
4. Weight at least 50kg, with a minimum BMI of 18.

**4.3 Exclusion Criteria**

To be included in the study, participants must meet none of the following exclusion criteria:

1. Female participants who are not post-menopausal
2. Participants who, in the opinion of the investigator, do not understand the information and procedures of the study, or would not be compliant with them (in particular the study restrictions and risks involved).
3. Any participant for whom the investigator believes, for any reason, that participation would not be an acceptable risk.
4. Participants with severe acute or chronic medical illnesses.
5. Participants who regularly use alcohol or recreational drugs.
6. Participants using HRT

**4.4 Stopping Rules**

1. Participants may withdraw from the study at any time at their request.
2. Participants may be withdrawn from the study if they report severe side effects during the study which make it impossible to continue participation, or if they are not able to adhere to study procedures.

**5. SCREENING EVALUATION**

5.1. Process

The screening evaluation consists of a complete medical history and systems review. Screening evaluations will consist of the following components:

* Demographic/Medical History: A complete medical history will be taken from each participant as part of the Screening Evaluation.
* Physical Examination and Vital signs: The physical examination will consist of a review of major body systems plus height and weight (with indoor clothing). Vital signs will include blood pressure, heart rate, respiratory rate and temperature measurements.
* Drug/Alcohol Tests: Drugs of abuse testing will be carried out on urine samples on all participants at screening

**6. METHODS USED TO MINIMISE BIAS**

The following are incorporated into the conduct of the study to minimise bias:

* Participant enrolment is dependent on satisfactory fulfilment of a prescribed list of entry criteria
* The circumstances in which individual participants will discontinue treatment prior to planned completion of the study are specified.

**8. STATISTICAL PLAN**

**8.1 Participant Population**

The Evaluable Participant Population (EPP) will be defined as all participants who receive at least one dose of progesterone. The primary population for the evaluation of study objectives in this trial will be the EPP population.

**8.2 Observational Period**

The observational period for the study will be from participant entry until 48 hours

**8.3 Statistical Analyses**

Participant demographics, background characteristics and trial data (safety, vital signs, pharmacokinetics) will be descriptively summarized for all subjects. The relationship between sedation VAS ratings and ALLO concentrations will be explored using regression methods.

**8.3.1. Statistical Power Calculation**

The sample size is chosen pragmatically and not based on any statistical power considerations.

**8.4. Data Collection**

The Case Report Form (CRF) will be used to collect all participant data assessments that will be used for evaluation of specified analyses. The CRF should be completed in a timely fashion. When this database is locked the data will be exported into Excel for statistical analyses.

**9. MONITORING ADVERSE EVENTS AND PARTICIPANT WITHDRAWAL**

**9.1. Monitoring Adverse Events**

Adverse events will be recorded from when each participant provides written consent until the final visit. All adverse events observed or reported will be recorded on the CRF, specifying the verbatim description of the event, time of onset, time of resolution, severity, causality, duration, seriousness, treatment and resolution of each episode. All Participants will be advised that they are to contact the PI or other senior clinicians at any time if they feel unwell or have any concerns while they are in the study. Participants who experience an adverse event will be carefully followed up to determine the outcome. An internal Data and Safety Monitoring Committee (DSMC) will be established to review safety and efficacy. The composition of DSMC members and its processes will be established in a separate charter. DSMC meetings will be held at least once every 3 months, or more frequently based on rate of recruitment.

**9.1.1. Reporting Adverse Events**

Each adverse event (AE) will be classified by the Clinical Investigator as SERIOUS or NON-SERIOUS.

A SERIOUS adverse event (SAE) is defined as any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

A NON-SERIOUS adverse event is all other adverse events.

The Investigator will also use the adjectives mild, moderate, or severe to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

* MILD Does not interfere with participant's usual function
* MODERATE Interferes to some extent with participant's usual function
* SEVERE Interferes significantly with participant's usual function.

Note the distinction between the gravity and the intensity of an adverse event. Severe is a measure of intensity. Thus, a severe reaction is not necessarily a serious adverse event. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events.

**9.1.2. Notification**

If an SAE occurs, Medsafe will be notified by telephone within 24 hours of the PI becoming aware of the occurrence. The telephone report is to be followed by submission of a written report within 3 working days of the event. All such reportable events must be monitored until the condition subsides and the cause is identified, or the PI considers the event resolved even if no cause is identified. Clinical, diagnostic and laboratory measures employed to identify the cause of the reaction in question will be performed and the results reported. In all cases of serious adverse events, appropriate supportive and definitive therapy will be given. Study evaluations may also be suspended until a full evaluation has been completed.

**9.1.3. Ethics Committee Notification**

SAEs are also to be reported to the approving Ethics Committee within 7-15 days of the event, if they are unexpected, and not defined study endpoints.

**9.1.4. Regulatory Authority Notification**

The adverse event reporting requirements in New Zealand differ from those set out in the CPMP GCP Guideline. Only expedited reports of serious adverse events occurring in New Zealand trial participants must be sent to Medsafe (NZ’s Ministry of Health) within 7 days.

**9.1.5. Causal Relationship**

The Clinical Investigator will also provide the possible relationship between the adverse event and study treatment as highly probable, probable, possible, remotely or not related to the study medication.

Causal Relationship definitions

**Not related:** An AE which is not related to the use of the investigational product.

**Remotely related:** An AE for which an alternative explanation is more likely - e.g. concomitant medication(s), concomitant or progressive disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

**Possibly related:** An AE that might be due to the use of the investigational product. An alternative explanation - e.g. concomitant medication(s), concomitant or progressive disease(s) is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

**Probably related:** An AE that might be caused by the use of the investigational product. The relationship in time is suggestive. An alternative explanation is less likely, e.g. concomitant medication(s), concomitant or progressive disease(s).

**Highly Probably Related:** An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant medication(s), concomitant or progressive disease(s). The relationship in time is very suggestive.

**9.2. Participant Withdrawal**

Participants who withdraw from the study are encouraged to advise the PI of the reason for discontinuing. However, they will be informed that they have the right to withdraw from the study at any time without giving an explanation. They will be advised that for their own safety they should undergo a final examination including all observations scheduled for the study end visit.

If any participant withdraws or is removed from the study by the Clinical Investigator, a case report, including an explanation for withdrawal, will be provided. All efforts will be made to contact participants who do not wish to continue with the study. Participants who withdraw for medical reasons will be carefully monitored until their condition has resolved or the investigator has determined that it has stabilized.

**9.3. Premature End of Treatment/End of Study Participation**

The primary reason for the premature discontinuation of study participation, including follow-up, should be selected from the following:

• Adverse Event

• Protocol Violation

• Withdrawal of Consent

• Lost to Follow-Up

• Death

The primary reason for the premature discontinuation of the study may be one of the following:

* Unexpected Adverse Events
* Other Unexpected Events
* PI request

**10. DATA CONTROL**

## 10.1 Data management plan

* A Case Report Form (CRF) will be used for the purposes of recording participant specific data. The CRF will contain all study data. Data will be collected by investigators named on the protocol. Any change(s) of information made on the CRF will be initialled and dated by the Principal Investigator or study staff.
* The health data collected for this study will be used for the purposes of this study only.
* When participants enter the study we will maintain with each paper CRF a one page document containing demographic details, for the purposes of being able to contact participants throughout the duration of the study, contact their GP if necessary. On completion of the study this page will be destroyed. We will retain the NHI in case participants need to be contacted in the future.
* At the beginning of the study participants will be allocated a unique identifier (study number) and throughout the CRF only their study number and initials will be used.
* Electronic data is stored on password protected databases via password protected computers in locked rooms. The identifiers on electronic data are the participants’ study number, age and gender.
* Data is only able to be accessed by named researchers working directly in the study.
* Research participants will provide informed consent prior to any activities being undertaken in the study. Informed consent requires participants to consent to research staff collecting and processing their information, including health information.
* All data related to this study will be stored securely in Dept of Psychological Medicine. All data will be kept for a minimum of 10 years and then destroyed.
* The paper CRFs will be stored in locked filing cabinets in locked rooms, throughout the study. On completion of the study, the CRFs will be archived in sealed file boxes and locked in archive cupboards.
* Any breaches of privacy would constitute a major breach of protocol and would be reported to HDEC. The breach would be discussed with any affected participants and they would be given an opportunity to withdraw consent for their data to be used. The PI has overall responsibility for data privacy and confidentiality.
* We will advise participants of any incidental findings.
* There will be no commercial use of the data collected in this study. Health data collected in this study will not be transferred outside of New Zealand or to other institutions.
* Participants have the right to access and correct their data.
* When participants provide informed consent they either agree/disagree to their data continue to being used if they withdraw or are withdrawn from the study. If they do not provide consent, all data collected up to that point in the study would be destroyed.

**10.2 Auditing**

Medsafe and other Regulatory Authorities may also audit the PI during or after the study. The PI must fully cooperate with regulatory authority audits conducted at a reasonable time in a reasonable manner.

**11. PROTOCOL CHANGES & DEVIATIONS**

**11.1. Protocol Changes**

Any amendments to the Protocol will only proceed with the written consent of the Ethics Committee.

**11.2. Protocol Deviations and Violations**

Any deviations and violations from the approved Protocol must be documented and included in the final report of the study.

**12. ETHICAL AND LEGAL REQUIREMENTS**

**12.1. Benefit/Risk Assessment**

Based on the available clinical information relating to the intervention and the design of the study, the PI considers this study to be ethically acceptable.

**12.2. General Regulations**

The study will be conducted in accordance with the following directives and guidelines:

* ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95).
* The Declaration of Helsinki
* The Nuremberg Code

**12.3 Ethical Approval**

This protocol, any amendments and the written informed consent form shall be submitted to an HDEC Ethics Committee. Notification in writing of approval must come from the EC chairman or secretary, to the PI, as a letter. The investigator will not participate in the decision. The investigator will submit status reports to the EC upon request. The EC must be notified by the investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the EC all protocol amendments and will not make such changes without EC approval except where necessary to eliminate apparent immediate hazards to human participants. In these cases, the EC must be notified within 5 days of the change. The investigator will promptly report to the EC all SAEs and unanticipated problems involving risk to participants or others. The investigator is required to maintain an accurate and complete record of all written correspondence to and received from the EC and must agree to share all such documents and reports with the sponsor.

**13. INFORMED CONSENT**

The Participant Information Sheet (PIS) and Informed Consent Form (ICF) explaining the procedures of the study will be given and explained to potential Participants. This will take place up to 3 weeks before their screening visit to allow Participants time to consider their involvement.

The risks of participating in the study will be explained to all potential Participants. Prospective Participants will be invited to ask any questions about the study and seek independent advice if they wish. The PIS will include the elements required by ICH GCP Guidelines such as a statement that the study has been reviewed and approved by an Ethics Committee; a fair explanation of the procedures to be followed, and their purposes, description in lay language of any possible side effects; an offer to answer any inquiries concerning the procedures, and an instruction that the participant is free to withdraw their consent and discontinue participation at any time and without prejudice against them. The PIS and ICF must be approved by the Ethics Committee prior to the start of the trial.

If any protocol amendment is to be made, the PIS and ICF may need to be revised in order to reflect the changes to the protocol. It is the responsibility of the Principal Investigator to ensure that an amended written informed consent form is approved by the Ethics Committee, and that it is signed by all Participants subsequently entered in the trial and those currently enrolled in the trial if they are affected by the amendment.

An initialled PIS and signed ICF will be obtained from each potential participant before screening them for participation in the study. Receipt of the PIS and ICF will be recorded in each participant’s case notes, and the signed forms retained by thestudy site. The participant will be provided with a copy of the PIS and their ICF.

**14. CONFIDENTIALITY**

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study. However, authorized regulatory officials and sponsor personnel will be allowed full access to the records. All medications provided and participant bodily fluids and/or other materials collected shall be used solely in accordance with this protocol.

Only participant initials and unique participant study numbers will identify participants on CRFs. However, participants’ full names may be made known to a regulatory agency or other authorized official if necessary.

**15. SPONSORSHIP**

This study has no commercial sponsorship, and is being funded by funds from the Kinsman Foundation.

**16. REPORTING**

**16.1 Final Report**

The PI will prepare a study report used for publication in a peer reviewed journal comprising all participant data, adverse reactions, and statistical aspects. All data will be de-identified.

**17. REFERENCES**

Aebi, S et al. A phase II/pharmacokinetic trial of high-dose progesterone in combination with paclitaxel. Cancer Chemotherapy and Pharmacology 1999, 44(3), 259–265.

Christen, RD et al. Phase I/pharmacokinetic study of high-dose progesterone and doxorubicin. Journal of Clinical Oncology 1993, 11(12), 2417–2426.

Luisi, S et al. Serum allopregnanolone levels in pregnant women: Changes during pregnancy, at delivery, and in hypertensive patients. Journal of Clinical Endocrinology and Metabolism 2000, 85(7), 2429–2433.

SIGNATURE PAGE

**Principal Investigator Statement**

I hereby declare that I have read and understood the Information contained in this Protocol and I agree to adhere to it in full. I have read and understand the protocol and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, registered nurses, and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the study drug, the efficacy and safety parameters and the conduct of the study in general. I am aware that this protocol must be approved by the Ethics Committee prior to commencement of this study. I agree to make all reasonable efforts to adhere to the attached protocol. I agree to allow auditors full access to all medical records at the research facility for participants screened or randomized in the study.

I agree to provide all participants with informed consent forms, as required by government and ICH regulations.

Date: ………. A/Prof Yoram Barak

Principal Investigator

University of Otago