

**CLINICAL PROTOCOL**

PharmacokinetIcS of allopregnanolone after multiple dose administration of progesterone

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| **Compounds:** | Pregnanolone |
| **Investigators:** | A/Prof Yoram BarakProf Paul GlueA/Prof Natalie Medlicott  |
| **Phase:** | 1 |
| **Date:** | 3/10/19 |
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1. PROTOCOL SYNOPSIS

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| **Title** | Pharmacokinetics of allopregnanolone after multiple dose administration of progesterone |
| **Investigators** | A/Prof Yoram Barak and Prof Paul Glue, Psychological MedicineA/Prof Natalie Medlicott, School of PharmacyUniversity of Otago |
| **Study Timeline** | Enrolment should commence in 2Q  2020 and be complete by end 4Q 2020 |
| **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. |
| **Study Design** | Multiple rising dose study to measure plasma ALLO concentrations after multiple doses of extended release progesterone tablets |
| **Study Objective(s)** | * To measure plasma ALLO concentrations after 3 days dosing with ascending doses of extended release progesterone tablets
* To assess the safety and tolerability of extended release progesterone tablets in healthy volunteers
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| **Number of Participants**  | n=8/dose cohort; n=24 total |
| **Inclusion/exclusion criteria** | In: Healthy females; aged 20-60; post-menopausal; weight at least 50kg, with a minimum BMI of 18Ex: Severe or unstable medical conditions; regular use of alcohol/ recreational drugs.  |
| **Duration of Study** | 1.5 days for individual participants  |
| **Dosage and regimen**  | Dosing with progesterone 300mg tablets as follows:

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| Cohort | Day 1 dosing | Day 2 |
| 1 | 300mg AM, 300mg PM | 600mg AM |
| 2 | 300mg AM, 600mg PM | 900mg AM |
| 3 | 300mg AM, 900mg PM | 1200mg AM |

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| **Blood Sampling/ Assay/Analysis** | Plasma samples to measure plasma progesterone and ALLO concentrations, predose and 2, 4, 6 and 8 hours post Day 2 morning dose. Plasma samples will be assayed using a validated ELISA method. Pharmacokinetics will be analysed using standard noncompartmental methods. The primary endpoint will be peak ALLO concentrations on Day 2, along with an assessment of dose-proportionality. The dose of progesterone required to achieve plasma ALLO concentrations of 50ng/mL will be modelled based on these pharmacokinetic data, |
|  **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.  |