

Innovation in CNS Experimental Medicine



P1vital[®]
and

Hammersmith Medicines Research

Collaboration

Hammersmith Medicines Research



P1vital and Hammersmith Medicines Research (HMR) collaboration

P1vital and Hammersmith Medicines Research (HMR) collaborate on early phase clinical studies. The unique CNS experimental medicine expertise and capabilities of P1vital together with the outstanding Phase 1 experience and facilities of HMR provide a comprehensive solution for early assessment of the safety and potential efficacy of novel CNS compounds.

P1vital is an innovative Clinical Research Organisation specialising in experimental medicine for Central Nervous System (CNS) disorders and obesity that:

- **Provides** CNS experimental medicine biomarkers in anxiety, depression, schizophrenia, cognitive disorders and obesity
- **Collaborates** with internationally renowned opinion leaders in psychiatry, neuroscience and obesity, linked through University hospitals and UK clinical research facilities
- **Enables** clients to make more rapid and effective decisions in the Phase 1 and Phase 2 clinical development of drugs for CNS disorders and obesity
- **Creates** synergy through combining our CNS drug discovery and development expertise with the strong clinical science base in the UK

Unique CNS Translational Solutions for Pharma & Biotech

P1vital provides a unique range of products and services in CNS experimental medicine. Our highly experienced team has extensive expertise in all aspects of CNS drug discovery and development.

This enables P1vital to offer their clients customised experimental medicine solutions including:

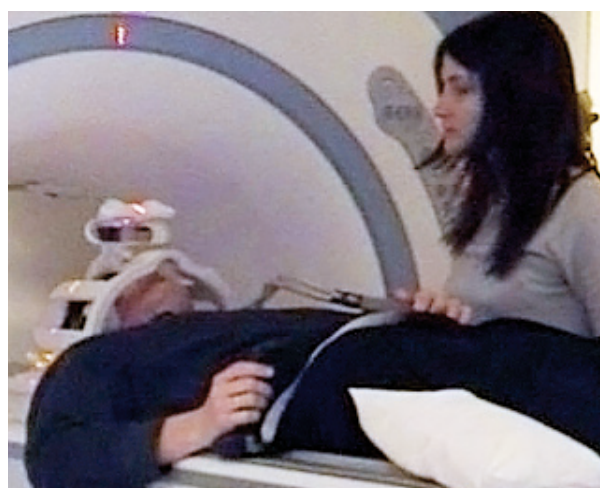
- Consultancy and study delivery services to enable you to assess the clinical efficacy of your early phase CNS development compounds
- P1vital® Oxford Emotional Test Battery (ETB), a product that can be used to assess antidepressant efficacy in your clinical trials

Our objective is to enable you to more effectively manage your risk and investment in CNS drug development.

Expanding Portfolio of Biomarkers

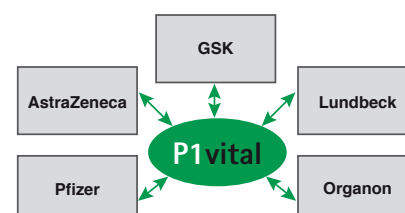
P1vital provides CNS experimental medicine models for anxiety, depression, schizophrenia, cognitive disorders and obesity including:

- Depression: P1vital® Oxford ETB
- Depression: Pharmacological fMRI
- Anxiety: CO₂ inhalation
- Schizophrenia: Pharmacological fMRI
- Schizophrenia: Bi-conditional learning
- Schizophrenia: Eye tracking
- Cognitive disorders: Arena & Platform tasks
- Obesity: Universal eating monitor



P1vital Pre-Competitive Consortium in Psychiatry

P1vital is expanding its portfolio of validated CNS experimental medicine models through a pre-competitive consortium agreement with AstraZeneca, GlaxoSmithKline, Lundbeck, Organon (a subsidiary of Merck) and Pfizer.



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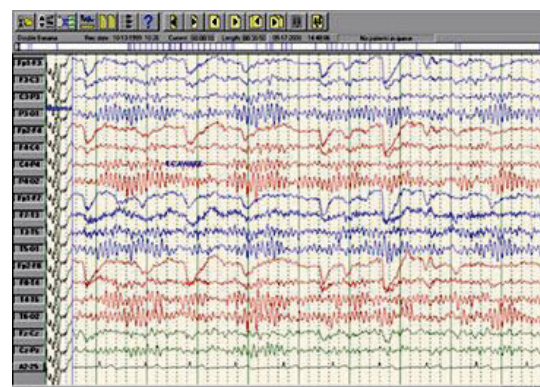
Since 1993, HMR has done 550 Phase 1 studies, 154 (28%) of which involved compounds with central nervous system (CNS) activity. Many of the studies were first-in-man.

HMR has experience of a wide range of procedures to assess novel CNS compounds, such as:

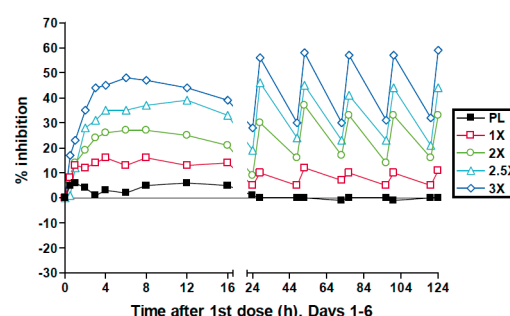
- psychomotor tests
- coordination tests
- ataxiometer
- body sway
- erythrocyte cholinesterase activity
- cognitive function assessment, using a computerised system, such as CDR and Cogstate
- scopolamine model of dementia
- saliva flow rate
- pain models
- saccadic eye movements
- critical flicker fusion frequency threshold
- digit span
- EEG, with interpretation by consultant neurologist
- PET, with GE Imanet, Hammersmith Hospital
- SPECT, with UC Hospital
- MRI, with GE Imanet, Hammersmith Hospital
- clinical questionnaires, e.g. POMS, CSSRS, AIMS, Simpson-Angus, Barnes ARS, TFEQIII, BDI and HRS
- simple and choice reaction times
- visual analogue rating scales
- tyramine challenge tests, to assess MAO-B inhibition
- 5-HT_{1A}-receptor mediated function tests.



EEG electrodes



EEG trace



Dose-related inhibition of red-cell cholinesterase in healthy men (Reference 10).

Types of molecule that HMR has studied include:

- dopamine receptor antagonists
- cannabinoid-1 receptor inverse agonists
- MAO-B inhibitors
- anti-convulsants
- anti-psychotics
- anti-depressants
- cholinesterase inhibitors
- histamine H₃-receptor antagonists
- histamine H₁-receptor antagonists
- 5-HT_{1A} receptor agonists
- benzodiazepine analogues
- GABA inverse agonists.

Recent P1vital and HMR Publications

1. Harmer CJ, Cowen PJ, Goodwin GM.
Efficacy markers in depression.
J Psychopharmacol 2010; Jun 8. [Epub ahead of print].
2. Harmer CJ, de Bodinat C, Dawson GR, Dourish CT, Waldenmaier L, Adams S, Cowen PJ, Goodwin GM.
Agomelatine facilitates positive vs negative affective processing in healthy volunteer models.
J Psychopharmacol 2010; Jul 21. [Epub ahead of print].
3. Harmer CJ, O'Sullivan U, Favaron E, Massey-Chase R, Ayres R, Reinecke A, Goodwin GM, Cowen PJ.
Effect of acute antidepressant administration on negative affective bias in depressed patients.
Am J Psychiatry 2009; 166: 1178–1184.
4. Dourish, C.T., Wilding J.P.H. and Halford, J.C.G.
Anti-obesity Drugs: From Animal Models to Clinical Efficacy. In: Animal and Translational Models for CNS Drug Discovery. Volume 3 – Reward Deficit Disorders, 2008 (Edited by R. A. McArthur and F. Borsini), Academic Press, pp. 271–315.
5. Halford JCG, Boyland EJ, Cooper SJ, Dovey TM, Huda MSB, Dourish CT, Dawson GR, Wilding, JPH.
The effects of sibutramine on the microstructure of eating behaviour and energy expenditure in obese women.
J Psychopharmacol 2010; 24: 99–109.
6. Antonova E, Parslow D, Brammer M, Simmons A, Williams S, Dawson GR, Morris RG. *Scopolamine disrupts hippocampal activity during allocentric spatial memory in humans: an fMRI study using a virtual reality analogue of the Morris Water Maze.*
J Psychopharmacol 2010; Sep 7. [Epub ahead of print].
7. Addy C, Li S, Warrington S et al.
Safety, tolerability, pharmacokinetics and pharmacodynamic properties of taranabant, a novel selective cannabinoid-1 receptor inverse agonist, for the treatment of obesity: results from a double-blind, placebo-controlled, single oral dose study in healthy volunteers.
J Clin Pharm 2008; 48: 418–427.
8. Norris V, Baisley KJ, Calder N, van Troostenburg AR, Warrington SJ.
Assessment of the Accusway Plus system in measuring the effect of lorazepam on body sway in healthy volunteers.
Int J Pharm Med 2005; 19: 233–238.
9. Clarke A, Johnson ES, Mallard N, Corn TH, Johnston A, Boyce M, Warrington S, MacMahon DG.
A new low-dose formulation of selegiline: clinical efficacy, patient preference and selectivity for MAO-B inhibition.
J Neural Transmission 2003; 110: 1257–1271.
10. Johnson N, Cattoni M, Warrington S, Boyce M.
Tolerability and pharmacodynamic effects of repeated doses of ganstigmine, a new cholinesterase inhibitor, in healthy men.
British Journal of Clinical Pharmacology 2000; 49: 492P–493P.

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