PRAHEALTHSCIENCES

GLOBAL CAPABILITIES IN NEUROSCIENCE & PAIN RESEARCH

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EXECUTIVE SUMMARY:
Our Neuroscience & Pain Capabilities in Brief

PRA Health Sciences' Early Development Services (EDS) group has a long-standing record of early clinical development work in various neuroscience and pain indications in our global clinical facilities. In the last decade, PRA EDS in the Netherlands (Groningen) has gained extensive experience in neuroactive drug development through 160+ Phase I and Phase IIa clinical studies with neuroactive agents. The Groningen clinic has dedicated and well-established collaborations with various departments at the University Medical Center Groningen (UMCG), and with other external partners for specialized clinical assessments in neuroimaging, including positron emission tomography and functional- or pharmaco-MRI.

PRA's US Clinical Research Centers at Marlton, NJ; Salt Lake City, UT; and Lenexa, KS offer additional expertise in neuroscience and pain early phase trials. These sites supported 160 Phase I studies and enrolled 3,000+ subjects from 2009 to 2013.

Approximately 520 studies for later-phase neuroscience studies have been conducted across our US sites since 2004.

At PRA's US sites, several studies have been performed on experimental drugs for Alzheimer's disease. A full spectrum of clinical tests is available for the measurement of efficacy in psychiatric disorders, addiction, human abuse liability, and acute and chronic pain. The Salt Lake City clinic collaborates with several neuroimaging providers located within 20 minutes of the facility: The Brain Institute at the University of Utah, Neuroimaging Institute, US-MRI, and King's Open Imaging.

This document summarizes our experience assessing the clinical efficacy and safety of neuroscience active agents.

PRA Health Sciences offers neuroscience and pain capabilities at 3 locations run by Early Development Services:

- *Groningen (Netherlands)*
- *Salt Lake City Research Center (UT)*
- *Marlton Research Center (NJ)*

GENERAL PRINCIPLES

Regardless of location, the PRA team involved in testing neuroactive agents is knowledgeable in the general concepts of early clinical development. Clinical studies executed at any location will comply with all applicable national and international rules, regulations, and guidelines, and will address the development questions identified in the clinical development program. This paper provides a comprehensive picture of the pharmacodynamic assessments that create value in the clinical development of compounds active in the central nervous system.

PET & SPECT Studies

Our Groningen clinic performs positron emission tomography (PET) and single proton emission computerized tomography (SPECT) studies in collaboration with the Department of Nuclear Medicine and Molecular Imaging (NMMI) at the UMCG. The Department of NMMI has a clinical research focus on neuroscience and pain, oncology, and cardiology, and has state-of-the-art equipment consisting of 2 PET cameras, 3 SPECT systems, 2 cyclotrons, and a fully equipped radiochemistry laboratory. Because of the extensive experience of the unit in neuroimaging, many tracers are available for use. Furthermore, the unit is experienced developing new tracers in collaboration with pharmaceutical industry partners. The Department of NMMI is ISO certified and is fully GMP compliant.

The PRA office at UMCG is within walking distance of the Department of Nuclear Imaging, so PET/SPECT studies are logistically easy to perform.

The Utah Cancer Specialists, located on the first floor of our Salt Lake City facility, offers PET scans for research using a GE discovery scanner that yields high-definition images.

Siemans Biograph mCT 4-64 (time-of-flight, HD, 64-slice CT; one of the state-of-the-art machinery at the Department of Nuclear Medicine & Molecular Imaging)

(f)MRI Studies

The Groningen clinic performs functional and structural magnetic resonance imaging (f)MRI studies with the NeuroImaging Center (NIC), a joint research center of the UMCG and University of Groningen. The NIC has a 3-Tesla MRI scanner and state-of-the-art analyzing systems and capabilities for spectroscopy. Equipment and expertise are dedicated to clinical research purposes and the unit operates independent of routine patient care. This operational model implies that a substantial part of the available scanning time is reserved for contract research in collaboration with PRA's clients.

EEG, qEEG, ERP & PST

For electroencephalogram (EEG), event-related potentials (ERPs), and polysomnography (PSG) studies, the Groningen clinic has relationships with a number of external experts and departments who are involved depending on the study requirements

We have the ability to conduct PSGs, maintenance wakefulness tests (MWTs), and actigraphy on subjects to characterize the pharmacodynamics of wake-promoting and sedating molecules.

EEGs are performed as part of eligibility screening. For pharmacodynamic (quantitative EEG [qEEG] and ERPs) and safety EEG registrations during the clinical phase of studies, we collaborate with EEG providers. All providers have state-of-the-art equipment including up to 32-channel portable devices. If required, expert personnel are available for consulting, training, and performing EEG recordings.

The technologies mentioned above have been applied to a variety of development programs with anti-depressants, anxiolytics, anti-psychotics, and cognition enhancers. They were also used to characterize the side effect potential of neurology and non-neurology compounds.

Anxiety Studies

At PRA-NL, we have extensive experience with human experimental anxiety models using cholecystokinin (CCK4) and pentagastrin as challenge agents. These challenges induce a well-defined, short-lasting anxiety, thus providing an excellent paradigm for early proof-of-concept testing of novel anxiolytic agents after single and multiple dosing in healthy subjects. Assessments in the frame-work of this paradigm typically comprise physiological and psychological measures before, during, and after the challenge in combination with blood sampling for the assay of the parent compound and active metabolites, if any. The resulting dataset allows for extensive analysis including PK-PD modeling.

Cognitive Function

In-house laboratory

Cognitive function testing of healthy volunteers and patients is performed in many of PRA's Phase I and IIa clinical studies at both our NL and US facilities. Our trusted partners for standardized cognition testing use the CDR system; CogState Ltd and Cambridge Cognition Ltd use the CANTAB system. These companies provide expertise, equipment, training, and data analysis.

We also have experience with a variety of other psychometric tests including sleep questionnaires:

- ARCI49
- POMS
- MMSE
- DSST CSSR
- Specific VAS scales

Studies with cognitive testing are performed in the healthy young and elderly population, as well as in special populations, such as Alzheimer's disease/age-associated memory impairment, ADHD, schizophrenia, and major depression.

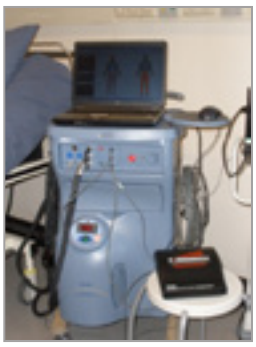
Pupillometry

Pupillometry is a routine assay in many pain studies performed at our NL and US locations. It is performed in a variety of clinical trials to study the potential effects of investigational drugs on the autonomous nervous system.

Body Sway

As a typical element of the battery of pharmacodynamics assessments in neuroscience and pain, body sway is routinely assessed as a surrogate measure of sedation.

Pain Assessments



PRA has state-of-the-art equipment: Medoc Pathway Sensory systems

At PRA, we have a well-validated battery of experimental pain tests available for pain modeling; these provide study sponsors with early insight into the mechanism of action for their compound, including the determination of central or peripheral effects (Figure 1).

We have state-of-the-art equipment, including two PATHWAY systems (Medoc Ltd), available for pain studies. For specific assessments and specialized support, the Groningen clinic has a collaboration with the Department of Anesthesiology at the UMCG.

Our site conducts pain studies using established models to assess the analgesic properties of experimental compounds.

Human Pain Models - Recognized by FDA	
Bunionectomy model	Dental extraction model
Experimental Pain Models	
Cold pressor test	Ultraviolet burn model
Micro-surgical incision model	Topical capsaicin challenge model
Intradermal capsaicin challenge model	Intramuscular capsaicin challenge model

Figure 1: Salt Lake City Pain Studies

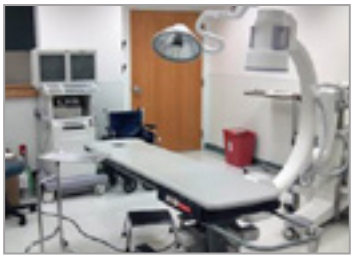
We understand the importance of detecting the pharmacological signal produced by the investigational drug or intervention. Our clinical research staff understands the importance of minimizing intra-subject and inter- and intra-examiner variability. Our team members have the training, demonstrated skills, and expertise to minimize variability with the goal of eliminating noise and detect a signal.

For a detailed description of pain studies and different models used at our worldwide locations, please see our white paper on pain.

Cerebrospinal Fluid Sampling

Cerebrospinal fluid (CSF) sampling enables us to answer key development questions, and has evolved into an often used method in the study protocols executed by PRA. For single and repeated CSF sampling, the Groningen clinic works with the Department of Anesthesiology at the UMCG. This assures that experienced anesthesiologists are routinely available to perform punctures and sampling, and that adequate procedures for safety monitoring are in place. The Salt Lake City clinic has an on-site procedure room for obtaining samples under fluoroscopy using C-Arm.

The Salt Lake City clinic also has extensive experience in CSF collection with both single and continuous aspirations for up to 72 hours through spinal catheters in both healthy and elderly populations.



This is the actual procedure room (OR) in SLC where surgeries are performed and CSF is collected. The machine is the C-arm, used for fluoroscopy (for imaging of needle placement for clean CSF samples).

PATIENT STUDIES

Our EDS clinics have executed clinical studies in Parkinson's disease and in Alzheimer's/AAMI elderly.

Our Marlton clinic has significant experience supporting inpatient studies in schizophrenia, major depression, and anxiety disorders. This experience is not limited to early-stage clinical development, but extends to all stages including participation in large, pivotal clinical Phase III programs.

The Salt Lake City region is a major hub in genetics research. In this established setting, the Salt Lake City team is able to provide the genetics expertise to support clinical development programs in neuroscience and pain.

Using an elaborate Quantitative Sensory Testing (QST) protocol, we have established a large database of information on the somato-sensory profile of individual patients. This database is open to studies evaluating efficacy and safety of novel agents in chronic pain, including neuropathic pain.

CONCLUSION

PRA has long-standing experience in neuroscience and pain Phase I and IIa studies, with a proven record of transitioning early clinical development in neuroscience into confirmative late-stage development. By anticipating novel questions and needs in neuroscience and pain research, we have established a large network of neuroscience specialists who support the design and execution of your programs.

Our expertise and existing collaborations in neuroscience and pain are a great asset that complement PRA's extensive experience in clinical drug development in a broad range of therapeutic areas.

CONTACT INFORMATION

For further information or to discuss any aspect of PRA's services offered in the field of neuroscience and pain, please contact your Business Development Manager or the employee listed below:

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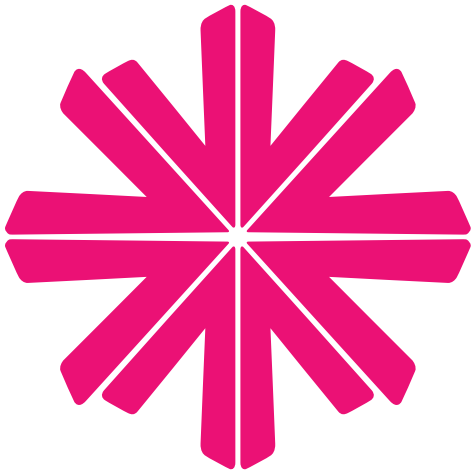

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ABOUT PRAHEALTHSCIENCES

PRA Health Sciences delivers innovative drug development solutions that improve patients' lives. Our people are passionate about clinical research, working tirelessly to provide quality results for clients. We offer exceptional experience across all phases, therapeutic areas, and a broad spectrum of solutions, ranging from full-service clinical development to our pioneering embedded model.

With 13,000+ employees covering 85+ countries, we reinforce an impressive global presence with keen local insights. Our project teams apply their understanding of local regulations, standards of care, and cultural customs to effectively align our approaches with each study's unique goals.

At PRA, we love what we do because we are making a difference in the lives of patients and their family members worldwide. Over the years, we have contributed to the development of 70+ drugs now available to countless patients. From our scientific and medical experts to therapeutically aligned project managers and monitors, we provide the commitment and expertise needed for today's complex studies.

To learn more about PRA, please visit www.prahs.com or email us at prahealthsciences@prahs.com.

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