PAIN STUDIES AT PRA EARLY DEVELOPMENT SERVICES

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EXECUTIVE SUMMARY

PRA Health Sciences offers a range of pain models to assess pain perception and the efficacy of experimental analgesics in healthy subjects and patient populations. PRA has been involved in conducting Phase I-IV studies in healthy subjects and patients with various types of acute and chronic pain, including migraine, arthritis, back, radiculopathy, post-herpetic neuralgia, post-traumatic neuralgia, and post-operative dental.

PRA’s in-house scientific experts in neuroscience and pain have international experience as academic researchers and clinicians, advisory board members, strategic consultants, principal investigators, and medical monitors.

In our Early Development Services (EDS) group, we have state-of-the-art Phase I facilities and equipment combined with a broad expertise in pain studies and availability of a large network of pain specialists. We have experience with validated experimental pain models encompassing a unique and novel neuropathic pain model. We apply pain models successfully in the setting of studies in healthy subjects and in clinical proof-of-concept work in patients.
PAIN STUDY EXPERIENCE

Our Phase I indications include acute and chronic pain in migraine, arthritis, back pain, radiculopathy, post-herpetic neuralgia, post-traumatic neuralgia, and post-operative dental pain. Study designs include medical device, single and multiple ascending dosing, bioavailability, pharmacodynamics, pharmacokinetic, first-in-human, and registration studies. Dosing methods include topical patches, intravenous, oral, inhaler, and implanted devices.

During the last several years, we have performed 100+ clinical trials in 12 subtypes of pain across all phases. The patients in these trials suffered from a variety of pain-related disorders, including osteoarthritis, rheumatoid arthritis, and migraines.

We have also conducted several multicenter studies and provided consulting services on 40 development programs.

Our global facilities offer specialized capabilities and expertise in experimental human pain models, both acute and chronic. Using a variety of stimuli, we activate the mechanisms of specific nociceptive pathways, enabling us to study pain physiology that resembles the manifestations of chronic pain types as well as acute pain. Pharmacological and non-pharmacological treatments are administered to assess their effects.

EARLY PHASE PAIN EXPERTISE & EXPERIENCE

Pain is one of our key areas of expertise and we offer a broad variety of experimental pain models to study the pharmacodynamics of pain compounds in healthy volunteers. In the last five years, EDS has conducted more than 100 pain-related studies and 35 studies with new treatments for pain. A variety of compounds have been studied, among them opioids, calcium channel blockers, cannabinoids, serotonin uptake inhibitors, CGRP antagonists, NOP-agonists, and a TRPA1 antagonist. We study opioids in the presence or absence of an opioid blocker or active comparator. Our clinical pharmacology units (CPUs) are licensed to manage controlled substances.

Our Netherlands CPU has state-of-the-art equipment available for our pain studies in healthy volunteers, and for characterizing patients with chronic pain using Quantitative Sensory Testing (QST). The QST protocol provides parameters such as sensory loss, allodynia, hyperalgesia, and paresthesias. It enables us to characterize the somato-sensory profile of patients in an objective and standardized way. We are also able to study the potential effects of the investigational compound on a specific somato-sensory aspect; this is a valuable step in gathering information on the
potential of a compound prior to investing in large Phase II/III patient studies. PRA has participated in the creation of a local QST database of more than 200 neuropathic pain patients and approximately 300 healthy volunteers with a full QST profile.

We have dedicated test rooms available with temperature control, as well as Medoc PATHWAY pain and sensory evaluation systems (Medoc Ltd and temperature-controlled water baths for cold pressor testing) and state-of-the-art equipment for laser Doppler imaging for measuring flare responses. For acute pain studies with antinociceptive compounds, we use a range of thermal and mechanical pain tests.

For studies with anti-neuropathic pain compounds, we use these sensitization models:

- Intradermal capsaicin model
- UV-B burn model
- Heat-capsaicin sensitization model
- Heat-capsaicin-warmth model
- Mustard oil model

For specific assessments and specialized support in Phase I/IIa pain studies, we have expertise available at various levels of the organization. In addition, well-established collaborations exist with experts from various departments of the University Medical Center Groningen (UMCG) in the Department of Anesthesiology NeuroImaging Center and the Department of Nuclear Medicine and Molecular Imaging (PET center). Our director of Scientific Affairs, Dr Johan A den Boer, serves as Professor of Psychopharmacology and Neuroscience.
Somato-Sensory Profiling of Patients with Chronic (Neuropathic) Pain

The QST protocol to classify patients, developed by the German Research Network on Neuropathic Pain (DFNS), is operational at our CRU in the Netherlands.

The QST protocol includes 13 tests:

- Cold and warm detection thresholds (CDT and WDT)
- Number of paradoxical heat sensations (PHS) during the thermal sensory limen (TSL) procedure
- Cold and heat pain thresholds (CPT and HPT)
- Mechanical detection thresholds (MDT)
- Mechanical pain thresholds (MPT)
- Mechanical pain sensitivity (MPS)
- Dynamic mechanical allodynia (DMA)
- Pain summation to repetitive stimuli; wind up ratio (WUR)
- Vibration detection thresholds (VDT)
- Pressure pain thresholds (PPT)

UV-B Burn Model for Chronic Pain

This pain model uses UV-B radiation administered in a series of 6 standardized fields of increasing UV-irradiation. This provides a degree of inflammation and erythema that represents inflammatory pain with a strong component of peripheral sensitization. We can measure 3 components of sensory testing as primary outcomes: mechanical allodynia, mechanical hyperalgesia, and thermal heat hyperalgesia of the sensitized area of skin. We use laser Doppler to measure blood flow as a measure of inflammation. For UVB, we follow a 2-step procedure: first we determine what degree of inflammation is produced by the minimum UV-B erythema dose (MED) and whether the subject is able to participate in the necessary sensory testing for intensity of allodynia and hyperalgesia; next, following a 24-hour wait, we conduct analgesic drug administration and sensory testing. We perform Numeric Pain Rating (NPR) assessments using brush; monofilament; NeuroPen; and warm (38°C), cool (24°C), cold (0°C) and hot (50°C) thermal stimulus using our Medoc machines. Mechanical allodynia is assessed with a brush and cotton tip across irradiated areas.
Mechanical hyperalgesia assessed using monofilaments determines threshold and supra-threshold. Thermal hyperalgesia determines threshold and supra-threshold (an increasing stimulus starting at 32°C and increasing until subject experiences pain and a warm stimulus at 50°C).

**Capsaicin Model For Chronic Pain**

The capsaicin test consists of applying capsaicin topically or by intradermal injection using a fine needle (usually 30 gauge). There are 2 components to this test: initial pain (usually lasting minutes) due to activation of C-fibers with lingering milder pain (up to 30-45 minutes) and associated central pathways, which is followed by steady pain and manifestations of central sensitization (alldynia and hyperalgesia, usually lasting up to 60 minutes). The primary outcome is the area and intensity rating of alldynia and hyperalgesia. Both components (area and intensity) are responsive to analgesic drug and non-drug treatments. Prior to the analgesic study, we familiarize the subject with all aspects of testing.

**Advanced Heat Capsaicin Warmth (HCW) Model - A New Neuropathic Pain Model**

Working with experts from the UMCG, PRA has improved the topical heat-capsaicin model, resulting in a new neuropathic pain model that mimics hyperalgesia and alldynia as typical features of neuropathic pain in combination with a stable level of continuous pain. In a pharmacological validation study performed at PRA with the advanced heat capsaicin warmth (HCW) model, gabapentin and remifentanil showed differential analgesic effects on continuous pain and secondary hyperalgesia and alldynia in strong agreement with their clinical profile. This new topical capsaicin model for neuropathic pain offers a unique opportunity to investigate the potential of new compounds.

**Micro-Incision Model for Chronic Pain**

This model consists of micro-incisions with micro-needles resulting in inflammatory pain, with manifestations of peripheral and central sensitization. The primary outcomes are mechanical alldynia, mechanical hyperalgesia, and thermal heat hyperalgesia of the sensitized area of skin. On Day 1, micro-incisions are made and the subject is familiarized with sensory testing. On Day 2, approximately 24 hours later, analgesic drug administration and sensory testing are performed.
Acute Pain Models - General

An ideal acute pain model exhibits several desirable characteristics (see Figure 1).

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<tr>
<th>DESIRABLE CHARACTERISTICS OF AN IDEAL ACUTE PAIN MODEL</th>
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<tr>
<td>Small between- and within-patient availability</td>
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<td>High assay sensitivity</td>
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<td>Reproducibility</td>
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<td>Predictable development of immediate postoperative pain</td>
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<td>Understandable pathophysiology</td>
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<td>Few competing postoperative therapies</td>
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<td>Response to prototype analgesics</td>
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<td>Minimized placebo response</td>
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<td>Interpretable dose response and time effect curves</td>
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<td>Amenability to evaluations of various dosing regimens</td>
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Figure 1: Desirable Characteristics of an Ideal Acute Pain Model

Two acute pain models with which PRA has extensive experience—the postsurgical bunionectomy model and dental extraction model—demonstrate the importance of these advantages. Having trained staff is an important component of the acute pain models, and we have expertise executing pre- and post-dose designs. Compounds studied in our acute pain models include opioid combinations, cannabinoids, TRPV1 antagonists, NSAIDs, and p38 MAP kinase inhibitors.

Bunionectomy Model for Acute Pain

This elective surgery involves osteotomy to correct a hallux valgus, or bunion, and is performed in generally healthy patients who normally require postoperative analgesics for more than 7 days (see Figure 2). The bunionectomy model provides for critical upside sensitivity evaluation, standardized surgical and anesthetic protocols, flexible dosing regimens, standardized pain data collection, and close monitoring during an in-house period of at least 48 hours after surgery. We have conducted 12 post-surgical bunionectomy pain studies, enrolling 990+ subjects for an average enrollment of 82 per study.

Figure 2: Bunionectomy Model for Acute Pain
WHY PERFORM HUMAN PAIN MODELS DURING EARLY DRUG DEVELOPMENT?

When a battery of human pain models is applied during early drug development, specifically in clinical Phase I, it is possible to obtain critical information that will likely serve as first-human-derived data that would lead to Phase II and indirectly to Phase III clinical studies.

It is recommended to do a battery since the models and testing modalities are more relevant to a specific type of pain and pain mechanisms. Furthermore, a battery of studies provides a more complete picture of pain as a clinical phenomenon and assures that a potentially effective investigational drug is not deemed ineffective solely because the appropriate test is not done. When the results of testing an investigational drug are compared to an established drug, the investigational drug is given an opportunity to manifest its analgesia in relation to the established drug.

Dental (Third Molar) Extraction Model for Acute Pain

PRA’s EDS-US Salt Lake City team has performed 6 postsurgical dental pain studies in the past 3 years, enrolling 800+ subjects with an average of 136 per study, lasting approximately 2 months. The screen-to-enroll ratio was 71% (see Figure 3). Utah is home to a large population of patients awaiting molar extraction due to a younger-than-national-average demographic and a requirement to excise third molars before serving a mission for the Church of Jesus Christ of Latter-Day Saints. Due to this accessibility, 3,653 subjects are currently in our database awaiting dental extraction studies.

Figure 3: Dental (Third Molar) Extraction Model for Acute Pain
THERAPEUTIC EXPERTS IN PAIN

Therapeutic Expertise, a specialized unit within PRA, is home to a respected group of experts. Their backgrounds cover a broad range of therapeutic areas and functional responsibilities. At PRA, our in-house scientific experts in neuroscience and pain have international experience as advisory board members, strategic consultants, principal investigators, medical monitors, and NDA managers for numerous pain treatments. They offer decades of experience in project team training and support. PRA leverages our global presence to resource projects with professionals who are knowledgeable in the indication. Our experts have built strong relationships with key opinion leaders worldwide and know where to find study-specific target populations. By using in-depth feasibility assessments, we increase the likelihood for study/program success.

CONCLUSION

At PRA EDS we have excellent Phase I facilities and state-of-the-art equipment combined with a broad expertise in pain studies and availability of a large network of pain specialists. We have experience with validated experimental pain models including a unique and novel neuropathic model. We apply these pain models in studies in healthy subjects and clinical proof-of-concept work in patients. With this variety of testing models and options available, EDS is extremely comfortable offering these services to you for rapidly exploring the clinical potential for new treatment modalities in pain.
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ABOUT PRA HEALTH SCIENCES

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 75+ 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.