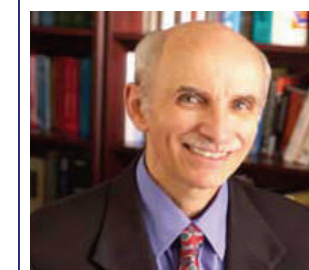




Winter 2007

Message From the President



This issue of the newsletter presents the various phase I capabilities and experience of the Clinical Research Institute (CRI) and explains how CRI can increase the efficiency of the drug development process by its studies in special populations.

As explained on pages 2 and 3, the capabilities and experience of CRI in phase I ranges from the first time in man studies through to late phase I studies in symptomatic volunteers. These later phase I studies provide opportunities to characterize the pharmacology of new molecular entities in individuals with the target illnesses. They serve as a bridge from Phase I to multi-center phase II trials. As such, the information gained from these studies can appreciably increase the confidence in "Go/No Go" decisions and appropriate dose selection for phase II and III studies.

In both normal healthy and special population studies, CRI has conducted a wide range of research designs to examine pharmacodynamic-pharmacokinetic relationships, such as QTc studies and drug-drug interaction (DDI) studies.

In collaboration with its sponsors, CRI presents the results of many of these studies at national and international meetings and publishes the full reports in prestigious clinical pharmacology journals. Such presentations and publications are a value added aspect of working with CRI. In 2006, CRI stud-

ies were presented at the following annual meetings: American Society of Clinical Pharmacology and Therapeutics, American Psychiatric Association, New Clinical Drug Evaluation Unit sponsored by the National Institute of Mental Health, and the American College of Neuropsychopharmacology. Such publications and presentations frequently represent an immediate and tangible return on investment for the sponsor.

"So Fast, Such Quality" is the title of the article on page 4. This quote comes directly from the lead clinical scientist for the sponsor on that study. CRI frequently receives such feedback from sponsors. The feedback is because of how quickly CRI can meet enrollment goals in these special population studies and the quality of our work. As is often the case with such studies, CRI was the only site involved.

This newsletter also provides a sample of the range of phase I studies CRI conducts. We would welcome the opportunity to discuss your development plans and how CRI can have you saying: "So fast, such quality". We look forward to working with you.

Sheldon Preskorn, MD
Chief Executive Officer
Clinical Research Institute

CRI has an affiliation with the University of Kansas School of Medicine (KUSOM) to further the scholarly and research activities of KUSOM faculty through their involvement as investigators on CRI clinical trials. As a result, sponsors have access to highly trained and experienced investigators in a wide range of therapeutic areas.

Newsletter

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"So Fast Such Quality"

CRI takes pride in being able to meet the challenge of recruiting special populations. Strategic recruitment campaigns have been used to develop and maintain CRI's special population databases. These databases in turn allow CRI to rapidly and cost effectively meet enrollment goals with known reliable participants.

The study that generated the above headline was a 6-way crossover study involving individuals with mildly symptomatic schizophrenia. The study was designed to estimate the effects of total calories and fat content on steady state serum concentration of a specific antipsychotic at its maximum recommended dose.

The sponsor's goal was to complete the study in 3-4 months. Diane Hilger, the study coordinator, completed the study in two months, with 100% of randomized participants completing all 6 crossovers. She provided the sponsor with excellent quality in terms of study execution, data, and completion rate.

Strategic planning and highly motivated, conscientious and competent staff is why CRI receives such feedback as well as repeat studies.



Diane Hilger, LPN, CRC

The results of this study will be presented at the 2007 American Psychiatric Association annual meeting.

Phase I studies are more to CRI than just normal volunteers.

Phase I to CRI also means conducting studies in individuals closely approximating the target population for phase II and III studies. That may mean healthy elderly volunteers but may also mean individuals with a mild and stable form of the disease process that is the anticipated indication for the new drug.

The reason for this approach is the difficulty of trying to model human psychiatric illness in animals. The reason for using participants with the illness is that the effects and/or dose-response curves in healthy volunteers may be appreciably different.

For example, individuals with schizophrenia are recognized to be more tolerant of dopamine-2 receptor blockade than are normal volunteers. In contrast, individuals with Alzheimer's Disease are more sensitive to muscarinic cholinergic receptor blockade.

These differences can be sufficiently disparate so results from studies conducted in normal volunteers may significantly over or under estimate the dose-response curve in the target populations.

It can be difficult, time-consuming, and expensive to correct these errors in large scale, phase II/III, multi-center trials. Instead, later phase I trials should include what are essentially experimental pharmacology studies aimed at better defining the effect of a new molecular CNS entity and its dose-response curve in participants with the illness. The goal of these studies are two-fold: (a) increase the validity of "Go/No Go" decisions and (b) ensure proper dose selection for the phase II studies.

In this approach, phase II and III studies become confirming studies. This strategy is consistent with the goal of enhancing efficiency in terms of both cost and time.

To ensure timely completion of these enhanced late phase I studies, CRI recruits and maintains databases of volunteers in the categories listed below and on page 3. CRI has also developed the expertise to do proof of concept studies employing these volunteers as well as including surrogate markers and experimental provocative challenges.

Healthy Young Volunteers

CRI does standard phase I studies using young healthy male and female volunteers so that a company can start its drug development with CRI and continue with us throughout the entire development process. That continuity has frequently proven useful in making adjustments in the direction of the development plan.

Healthy Elderly Volunteers

Drugs to treat dementia are used principally in an elderly population. Age alone can alter the safety, tolerability and pharmacokinetics of a drug. For this reason, CRI has a database of healthy elderly to do the interval step from young to healthy elderly volunteers. In some instances, a sponsor may wish to skip the young population and start with the elderly population.

CRI special population studies: rapid enrollment & high completion rates.

Mild Probable Alzheimer's Disease

CRI regularly conducts late phase I studies of novel CNS compounds in this population. As with the other symptomatic populations below, these individuals have the disease process which is the target of the drug treatment. Thus, late phase I studies with these individuals permit an initial assessment of efficacy as well as safety, tolerability and pharmacokinetics.

Mildly Symptomatic Schizophrenia or Schizoaffective Disorder

These participants have gone through the more floridly psychotic phase of schizophrenia. At this stage of their illness, they have more negative symptoms and cognitive deficits than positive symptoms. In addition, their positive symptoms are more stable and less bothersome. This population is ideal to assess the effect of an antipsychotic on negative and cognitive symptoms as well as positive symptoms. A recently completed study included a double-blind, randomized cross-over to six different treatment conditions (page 4).

Chronic, Stable Generalized Anxiety Disorder

These participants have typically had GAD for 10 – 20 years. Many have decided to live with the disorder rather than take medication. Others are on low doses of various anxiety medications including benzodiazepines. These individuals have well characterized patterns of symptoms over the course of a day, in response to specific situations, and from week to week. They are thus a model for the disorder and can be used to assess the effects of different drugs. CRI has done complicated cross-over studies in this population. In one such study, each participant received one of three doses of an investigational anti-anxiety agent with a novel mechanism of action versus a benzodiazepine versus placebo in a double-blind randomized fashion with a week between each dose. This study was completed in 12 weeks.

Chronic, Treatment Resistant Major Depression

A sizable percentage of patients with major depression have a chronic condition. Some can be on complicated regimens, others are on simpler regimens and can tolerate medication interruption for several weeks. CRI has worked extensively in this area and identified participants with virtually every type of major depression from recurrent to chronic persistent depression with varying levels of treatment resistance.

CRI looks forward to speaking with you about how CRI's expertise with special populations can help you increase efficiency in your drug development projects.

CRI has conducted proof of concept studies in these populations as well as efficacy trials.