Industry Academic Collaboration: A Key to Successful Involvement of Patients Early in Clinical Development

Aernout van Haarst PhD
Director, European Corporate Corporate Development
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Industry Academic Collaboration - Trends

- Pharma and academia: from separate worlds to team approach
  - Academia leveraging IP ("valorization")
  - Knowledge exchange
  - Combined resources
- Expanding role for CROs in setup and conduct of studies
- Increased patient involvement in early stage
Clinical Development is Evolving

Traditional Paradigm: Phased Approach

- Scarcity of molecules from discovery
- Pre-Clinical
- Phase I
- Phase II
- Phase IIb
- Phase III

Emerging Paradigm: Proof-of-Concept (POC) / Confirmation Approach

- Abundance of molecules from discovery
- Pre-Clinical
- Hypothesis Generating (Proof-of-Concept)
- Hypothesis Confirmation

Test each scarce molecule thoroughly

Shift attrition earlier

Adapted from: William Blair & Company, (Bain and Company) Covance Investors Overview June 16, 2010
What’s Driving Evolution of New Paradigm?

- Increase in novel new drugs from discovery research
- More difficult disease states to study and treat
- Greater regulatory expectations on clinical studies
- Need for more informed decisions at clinical Proof-of-Concept
- Increased cost of clinical research
- Expanding universe of new technology applications

**Clinical Proof-of Concept (CPoC) is where a new drug acquires real value**

- Regulatory acceptance of adaptive-like study designs

Innovation
Does the Drug Work in Humans?

- **Proof-of-Presence**
  - Does the drug get to its site of action?
  - Value Add: $

- **Proof-of-Mechanism**
  - Does the drug affect the biological target as it was designed?
  - Value Add: $$$

- **Proof-of-Concept**
  - Is there a sufficient signal that the drug favorably impacts the disease with an acceptable risk of toxicity that would stimulate further investment in the drug?
  - Value Add: $$$$$

**Pharmacokinetics**
- Tissue concentrations
- Healthy subjects (HS) or patients

**Biomarkers reflecting target engagement**
- Biomarkers of toxicity (liver, kidney effects)
- Healthy subjects or patients

**Biomarkers reflecting impact on disease**
- Biomarkers of toxicity (liver, kidney effects)
- Patients
Bridging Strategy to CPoC

- Start design of CPoC study first
  - What is “Proof”? Endpoints?
  - What patients? How many?

- How to get to CPoC?
  - What can I do in healthy subjects?
  - Are biomarkers available?
  - Develop novel biomarkers?
    - Biochemical assays
    - Imaging and imaging agents
    - MicroRNA panels
  - Can PK/PD modeling be applied?

- What preclinical work is needed to support the early clinical program?
Early Signals of Clinical Safety and Efficacy are the Key to Applied Translational Medicine

To get an early sense that a drug is working in humans as it was designed, you need:

Patients
- Small number
- Stable disease
- Minimal confounding treatments
- Appropriately motivated

Investigators / Clinical Trial Units
- Small number of sites
- Scientifically / medically robust
- Controlled study setting
- Follow global GCP standards
- Ethical
The Challenge of Involving Patients in Early Clinical Studies

- Not a single disease
- Non-therapeutic
- Treatment withdrawal
- Disease prevalence
- Study criteria
- Specialist involvement
- Co-medication
- Willingness patient
- Alternative treatment
Collaboration with Queen’s University, Belfast

- Partnership with Prof. Elborn at Queen’s University Belfast (QUB)
  - Focused on Respiratory – asthmatics, COPD and Cystic Fibrosis

- Collaboration
  - Queens University provides scientific expertise, specialized procedures and access to patient populations
  - Celerion provides access to a high level of clinical recruitment, conduct and ability to analyze large amounts of data to high standards

- Expansion
  - Based on the success of respiratory, expanded to other areas, most recently Ophthalmology
Expertise and Skills In-house

- Lung Clearance Index
- Bronchoalveolar Lavage
- Challenge Models
- Fractional Exhaled Nitric Oxide Testing
- Spirometry
- Body Plethysmography
Partnering with Queen’s University: A Case Study

- **Background**
  - Biotech company
  - First-in-Patient study in *cystic fibrosis* patients
  - Aim to assess safety and tolerability
  - Explore pharmacodynamics

- **Study design**
  - Multiple ascending dose
  - 15 day treatment
  - Parallel RCT (double-blind & placebo)
Case Study: Challenges

- Cystic Fibrosis (CF) patients are very difficult to recruit
  - Rare disease
  - Willingness
  - Eligibility criteria?
- End point selection may be cumbersome
  - Reliable outcomes?
  - Feasibility in CF patients?
- Complex methodologies
- Patient management
  - Infection risk
  - Variable health status
Case Study: Approach

- Leveraged Queen’s University expertise throughout study design, recruitment, conduct and reporting
- Specialized methodologies transferred to Phase I setting
  - Lung function tests, LCI
  - Sputum collection
- Patients in a controlled research environment
  - Minimize risk of cross-infection
- Flexible schedule to accommodate variable health status
Case Study: Outcomes

- Inclusion of 17 Cystic Fibrosis patients
- Fast turn-around of results allowing rapid dose-escalation
- First Patient In – Last Patient Out: 14 months
- Drug in general well tolerated (adverse events mostly mild)
- Changes in biomarkers reflected drug’s Mechanism-of-Action
Five Key Elements in Translational Medicine

- **Expertise**: Scientific and medical staff with study skills
- **Experience**: Operational know-how (e.g. high density sampling)
- **Facilities and Equipment**: Modern confinement clinics and labs equipped with innovative technologies
- **Access to Patients**: Effective subject recruitment
- **Access to Biomarkers**: Capabilities to ascertain drug effect in humans

1 + 1 = 3
Global Clinical Pharmacology Unit Networks

- Most patient needs in early clinical research cannot be met by a single center
- Increasing the number of sites has its own challenges
- Need to evolve similar partnering and alliance models among groups of clinical pharmacology units
  - Work to same quality standards (undergo common systems Quality Assurance audits)
  - Coordinate through a group which also brings in other study services such as protocol preparation, bioanalysis, pharmacokinetics, data management and statistics, and clinical study report preparation
Celerion’s Strategic Expansion of Patient Access by Leveraging Qualified Sites

- **Offices in South Korea and Singapore**
  - Modern clinical trial centers at major academic medical centers
    - Patient access in controlled clinical research settings
    - Supporting biomarker assays and imaging capabilities
  - Highly qualified investigators and well-trained, motivated staff
  - Superb access to patients
    - Various cancers, RA, infectious diseases, liver and brain disorders.

- **Acquisition of Assign Clinical Research, Vienna Austria**
  - Based throughout Europe (strong academic-CRO collaborations)
  - European and global Phase I-III studies
  - Strong expertise in multi-site patient studies
  - Key: new oncology treatments, immunology drugs and vaccines
  - Complements Celerion’s early clinical research expertise in respiratory and metabolic diseases.
Conclusion

- Earlier engagement of patients in studies (PoC)
- Need to implement operational setting near clinician
- Multiple centers may be required in early clinical research
- Replication of “Belfast model” and alliance model of clinical pharmacology units preferred approach
Thank You!