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University of Hong Kong

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Agenda

- Background
- Requirements to Accelerate Drug Development
- Case Studies  - complex combination protocol  
  - proof of mechanism using disease models  
  - CNS biomarkers
- Lessons learnt
- The future
In general, most IMP’s fail in clinical development
the chance to become a medicine is 11% of all IMP’s entering Phase I
some therapeutic areas have even lower success rates

Learning Too Little Too Late

KNOWLEDGE vs. TIME / MONEY

Preclinical  Phase I-IIa  Phase IIb

Desired

Phase III  Phase IV

Current

Market Withdrawal!
Learning Too Little Too Late

KNOWLEDGE

TIME / MONEY

Preclinical  Phase I-IIa  Phase IIb  Phase III  Phase IV

Desired  Current

PAREXEL.  Right where you need us
Phase I-IIa Success - Three Pillar Theorem: Proof of Mechanism + Proof of Concept

Pillar 1
Exposure at the target site of action

Pillar 2
Binding to the target

Pillar 3
Expression of pharmacology

Pfizer Analysis of 44 Studies (2005-2009)

- **Pillar 1 and 2**
  - Total = 12
    - 5 tested mechanism
    - 2 phase III starts

- **Pillar 1,2,3**
  - Total = 14
    - All 14 tested mechanism
    - 12 tested mechanism & achieved positive POC
    - 8 advanced to phase III

- **None or partial Pillars**
  - Total = 12
    - 12 failed to test mechanism and all were phase II RIPS

- **Pillar 2 and 3**
  - Total = 6
    - 5 tested mechanism
    - No phase III starts

**Case study 1: D3**

**Case study 2: CCR5**

**Exposure confidence**

**Pharmacology confidence**

Sources:

- *Drug Discovery Today*
Role Proof of Mechanism - Early Drug Development

• Assess pharmacological response to a drug

• Assess characteristics of the response:
  ▪ Time to onset
  ▪ Duration of response
  ▪ Dose response relationship
Early Acquisition of Knowledge

- **Phase 1**: Proof of Mechanism
- **Phase II**: Proof of Concept
- **Phase III**: Proof of Principle
- **Post-approval**: Gain of Knowledge

**Exploratory phase**

**Confirmatory phase**
PAREXEL  Therapeutic Early Clinical Experience
Phase I/IIa

Worldwide Therapeutic Experience
5 years  Early Phase

- CNS
- CV
- Metabolism
- Respiratory
- Infection
- Inflammation
- Oncology
- Gastroenterology
- Endocrinology
- Dermatology
- Haematology
- Urology
- Other

Studies in Healthy
Studies in Patients

754 Studies in last 5 years
514 HV, 65 FIH ;240 patient (32%)
20% biologicals
Key Requirements for Rapid Development

- Clinical Pharmacology and Therapeutic Expertise
- Favourable Regulatory Environments
- Combined Adaptable Protocols and Human Disease Models
- Bioanalytical/ Biomarkers Capabilities
- PK & PD Modelling and Simulation
- Healthy subject & Target Patient Access

Early Clinical Development Program
Time Saving in Early Phase

Combined Adaptive Flexible designs

- Single and multiple dose
- Inclusion of special populations – elderly, females, ethnic groups
- Food effect, drug interactions
- Small patient cohorts, disease models

Aim is to obtain necessary data to move to next stage of development as quickly as possible
Adaptive Combination Protocol

Safe Starting Dose (Human Equivalent Dose)

- Single Dose 1
- Single Dose 2
- Single Dose 3
- Single Dose 4

PK?

- yes

Food Effect

Min Intoler Dose

Max Toler Dose

Single Dose n

Multiple Dose 1

Multiple Dose 2

Multiple Dose 3

Multiple Dose 3 Disease model or patients

Multiple Dose Elderly

Safe Starting Dose (Human Equivalent Dose)
Combination Flexible Study Designs

- Requires careful planning
- PK/PD modelling simulation at different stages
- Must be flexible
- Very clear rules for decision making
  - stopping
  - dose escalation
  - dose selection
Patients in Early Clinical Development

- Patients cohorts in multiple dose when drug has specific effects; minimal off target effects; predictable PK; limited drug-drug interactions

- Common patient groups – obesity, diabetes, COPD, asthma, mild cognitive impaired, hypertension, hyperlipidemia, psoriasis

- Dedicated patient recruitment group

- Develop database of well documented patient groups and use pre evaluated external sites/investigators

- Dedicated team of staff – project managers, CRAs, medical monitors for phase Ib (Oncology) & IIa studies
If Patients cannot be recruited easily?

Use Human Disease Models in healthy subjects or other patient populations with similar target.
Example 1: Experimental Pain Models

Numerous validated models

- Capsaicin
- UVB Sunburn
- Electrical Hyperalgesia

Various assessments e.g.:
- Hyperalgesia / Allodynia
- Temperature perception
- Erythema (LDF)
Example 2: Inhaled Allergen Challenge

- Model of Asthmatic response (in atopic volunteers)
- Early and late phase response
- Good negative correlation with efficacy

Caveats of Disease Models

• Must not obscure primary purpose – Safety

• Must not add significantly to timeline

• Should not substitute for later phase evaluation

• Confidence in clinical pharmacology models varies by disease area

• Use of patients with similar target eg mild psoriasis patients developing immunomodulators for Crohn’s disease
Illustrative Case Studies

#1 Pain
TRPV Receptor Antagonist
TRPV Receptor Antagonist: 
Early Phase Study Program

**Combination Protocol – SAD/MAD UK**

- **Part 1 (FIH, SAD):**
  - Single ascending dose, parallel group design (8 dose levels, n=9 HVs per cohort)
  - **PoM:** Heat pain perception test, warm water bath hand immersion test

- **Part 2 (MAD):**
  - Multiple dose, parallel group design (3 dose levels, n=12 HVs per cohort), 14 days treatment
  - **PoM:** Capsaicin flare test, Heat pain and mechanical pain perception on naive skin and UVB-Sunburn

**PoC Study**

- Osteoarthritis patients
- Multiple dose, parallel group design (3 dose levels, n=12 per cohort), 14 days treatment
- **PoC:** Pain VAS, WOMAC Scale
TRPV Receptor Antagonist:
Link animal to human findings

Hot Plate Tail Flick Test

Heat Pain Tolerance Test
TRPV Receptor Antagonist:
Link animal to human findings

Hindpaw Pinch Test

Pin Prick Test
TRPV Receptor Antagonist:
Is the hypothesized mechanism affected by the drug?

Capsaicin

Capsaicin Cream Application
Practical Examples: TRPV Receptor Antagonist
Is the hypothesized mechanism affected by the drug? Is there a dose response?

**Neurogenic Flare Area (cm²)**

- Placebo
- 10 mg
- 50 mg

**Heat Pain Perception Thresholds (°C)**

- Placebo
- 10 mg
- 50 mg

Graphs showing changes in neurogenic flare area and heat pain perception thresholds before and after drug administration.
TRPV1 Receptor Antagonist:
44 weeks from FIH to PoC

Key
- Capsaicin Flare Reaction and UVB Pain model
- PD assessments: Warmth and Heat Pain Thresholds, Heat Pain Latency, Mechanical Pain Threshold
- Only need SAD healthy volunteer data to submit to MCC in MAD patient studies
OA Patient Enrichment Strategies for Pain compounds - FAST Assessments

- Prescreen OA patients
  **Psychophysical response** to induced **thermal pain**
- Various pre-defined thermal stimulus intensities delivered in a random order
- Subjects provide **pain ratings** using a computerized visual analogue scale (coVAS)
- A **psychophysical function score (FAST)** is derived from subjects’ responses to reflect pain reporting ability
Optimise Pain Response by Enhancement of OA patients - FAST Score Quartiles

Poor pain reporters with OA cannot differentiate naproxen from placebo

Cohen's effect size

<table>
<thead>
<tr>
<th>Quartile groups</th>
<th>Effect size</th>
<th>t-test p value</th>
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</thead>
<tbody>
<tr>
<td>All patients (N=32)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>First quartile (N=8)</td>
<td>0.55</td>
<td>0.02</td>
</tr>
<tr>
<td>Second quartile (N=8)</td>
<td>0.52</td>
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<tr>
<td>Third quartile (N=8)</td>
<td>0.43</td>
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<tr>
<td>Fourth quartile (N=8)</td>
<td>0.02</td>
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Key Messages

• Combination adaptive protocol - provides time savings of up to 30% and cost savings up to 20%.

• Advantageous use of 2 different regulatory environments – UK and South Africa

• Validated sensory assessments and human disease models of pain to support PoM

• Access to patient populations using enhancement strategies if feasible
#2 Alzheimer’s disease
Histamine 3 Receptor Antagonist
NXE-00X1
Mild Cognitive Impairment Patients’ Diagnosed by:
• Amyloid PET
• CSF lumbar puncture using modified amyloid ADNI cutoff

From: Hampel & Broich 2009
Histamine 3 Receptor Antagonist:
Early Phase Study Program

Preclinical package; renal safety signal

First in man, healthy volunteers
Part A: Single ascending dose
1. N = 8 volunteers × 6 cohorts
   Japanese + Caucasian subjects
   • PK/PD renal markers
   • Safety: ECG; vital signs; renal markers; cognition, sleep
2. Food Effect panel
3. Elderly panel

Part B: Multiple ascending dose in healthy elderly for 14 days;
N = 8 volunteers × 4 cohorts
• PK
• Safety; renal markers
• Biomarkers: quantitative EEG evoked potentials; cognition; plasma sAPP and ABeta

Part C: CSF Study
N = 12 × 2 cohorts
healthy Mild Cognitive Impaired
• CNS PK
• amyloid/sAPP Cognition/EEG
• PK/PD modeling

• Joint Review of Data
• Go/No-Go Decision – How to proceed forward?

Phase IIa
Safety, exploratory, efficacy
12-week Mild cognitive impairment

Go No-Go Decision
NCE-00X1: Is the hypothesized mechanism affected by the drug?

- Continuous Cerebrospinal Fluid (CSF) Sampling
- To demonstrate changes in amyloid beta and neurotransmitters
- Correlate doses with on-target mechanism of action
- 2 Panels of 12 MCI
- 14 day dosing
- CSF is collected for 36 hours after last dose on day 14

NCE-00X1: Is the hypothesized mechanism affected by the drug?

CSF Amyloid beta 42 on Day 14

- 10mg
- 40mg
- 80mg
NCE-00X1:
Provide guidance for initial clinical endpoint trials

<table>
<thead>
<tr>
<th>Adverse Event (%)</th>
<th>10 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Nausea/GI</td>
<td>14</td>
<td>21</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td>11</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>10</td>
<td>14</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Tremor</td>
<td>2</td>
<td>3</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Increased Systolic BP (&gt;10 mm Hg)</td>
<td>3</td>
<td>5</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14</td>
<td>16</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Intense Dreams (Awakening)</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

- No clinically significant laboratory findings
- 10-mg dose considered not sufficiently active on CSF biomarker
- 80-mg dose considered poorly tolerated
- **Proceed to Phase IIa study with 40 mg**
**Phase IIa Safety Study at Target Dose**

**Efficacy: Alzheimer’s Disease Assessment Scale (ADAS-Cog)**

- **Baseline**
- **Week 12**
- **Week 26**

- **Mean Change from Baseline (SE)**
  - **Compound × 40 mg/day**
  - **Placebo**

**N = 30 each treatment arm**

- ITT/LOCF analysis.
- Simulation of response.

- **P** = 0.09
- **P** < 0.0001

**Optional blinded extension**

**Cognitive improvement**

**Cognitive deterioration**
Key Messages

• Combination adaptive protocol

• Validated CSF markers with known variability to assist sample size calculations

• Appropriate targeted renal safety markers

• Access to target patient populations – mild cognitive impaired/Alzheimer’s
Summary

• Early drug development complex

• Expand knowledge base early using disease models, biomarkers, PK/PD modelling and simulation

• Early access to special populations – elderly, ethnic groups, others – and target patient populations; use of enhancement strategies

• Better use of historic internal data to optimise study design, biomarkers, safety measures and disease models – electronic data capture and “data mining”
Thank you

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