Economics, Genetics and Clinical Development

NAS Enabling Precision Medicine
Session III Reaction
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Successful Clinical Development Requires Extensive Preclinical Effort

Genetics Driven development must begin as early as Exploratory Development (Merck/EMD Serono experience)

- Is the preclinical Proof of Principle (pPoP) established with the proposed pre-candidate drug(s)?
- Are relevant safety species identified based on target expression, metabolite pattern, drug exposure and immunogenicity?
- Are “fit for purpose” biomarker assays available for preclinical models and safety species? Which assays are translatable for clinical use?

<table>
<thead>
<tr>
<th>Target</th>
<th>Dose &amp; Drug</th>
<th>Patient</th>
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<tr>
<td>Is the preclinical Proof of Principle (pPoP) established with the proposed pre-candidate drug(s)?</td>
<td>Has at least one pre-candidate drug been identified with the desired exposure-response relationship and translatable pharmacodynamic biomarker(s)?</td>
<td>What efficacy and benefit/risk can be anticipated based on the Merck Serono-generated evidence with the pre-candidate drugs?</td>
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<tr>
<td>Are relevant safety species identified based on target expression, metabolite pattern, drug exposure and immunogenicity?</td>
<td>What is the expected therapeutic window based on preliminary non-clinical safety data (e.g., <em>in vitro</em> selectivity, limited <em>in vivo</em> toxicology study)?</td>
<td>Is the range of target and pathway variability in the intended indication(s) potentially suitable for a stratified medicine approach? Is this information incorporated into the biomarker and early clinical strategy?</td>
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Center for Biomedical Innovation 3/8/2017
Biomarker and Companion Diagnostic Strategy Must Evolve Systematically Throughout Early Development

Developing evidence to address critical science questions and capabilities is proving a key to success

| Target | Is a biomarker strategy established? | Are “fit for purpose” biomarker assays available for preclinical models and safety species? Which assays are translatable for clinical use? | Are translatable pharmacodynamic biomarkers measurable in the Phase I population through analytically validated methods? | Dose & Drug | Has at least one pre-candidate drug been identified with the desired exposure-response relationship with translatable pharmacodynamic biomarker(s)? | Patient | Is the range of target and pathway variability in the intended indication(s) potentially suitable for a stratified medicine approach? Is this information incorporated into the biomarker and early clinical strategy? | What is the preliminary clinical development strategy (as supported by the biomarker strategy), including the outline for first in human trial(s)? | What is the design of the initial clinical trials, as supported by the biomarker strategy? | What is the evidence to support population selection for the Phase I program? | What is the anticipated distribution (variance) of the candidate stratification biomarker in the intended population? | If a stratification biomarker will be deployed for efficacy (or safety), which analytically or clinically accepted methods are proposed? Is a companion diagnostic development strategy included? |

Genetics Driven Development Requires Economies of Scale that Linked Platform Trials (PIPELINEs) Can Deliver

**117 month Development Time for Individual Product Indication**

- Classic
  - Phase II: 44.5 mos
    - Plan: 8 mos
    - IRB: 12 mos
    - Train: 12 mos
    - Recruit: 2 mos
    - Treat: 6 mos
    - Result: 67 mos
  - Phase III: 8 mos
    - Plan: 32 mos
    - IRB: 24 mos
    - Train: 3 mos

- PIPELINE
  - I-SPY2: 29 mos
    - Plan: 4 mos
    - IRB: 14 mos
    - Train: 12 mos
    - Recruit: 1 mos
    - Treat: 24 mos
    - Result: 1 mos
  - I-SPY3: 42 mos
    - Plan: 4 mos
    - IRB: 12 mos
    - Train: 12 mos
    - Recruit: 4 mos
    - Treat: 24 mos
    - Result: 2 mos

**Time Savings**

- 8 mos 22.5 mos 12 mos 2 mos
- 6 mos
- 67 mos

- 8 mos 32 mos 24 mos 3 mos

- 117 month Development Time for Individual Product Indication

- 71 month Development Time

- Time savings from:
  - Master protocol & standard informed consent
  - Standard entry criteria, regimens, endpoints
  - Reduced site training, mgmt, & auditing
  - Faster recruitment

(Modified from Trusheim et al, PIPELINES/CP&T December 2016)