Practical Examples of Proof of Mechanism Studies in Healthy Subjects

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Agenda

• Definitions
• Role of Proof of Mechanism (PoM) in Early Clinical Drug Development
• Relevant Guidelines
• Practical Examples of PoM Studies in Healthy Subjects
• Requirements for PoM Models
• Conclusions
Definitions

• Proof of Mechanism (PoM)
  ▪ Refers to Early Clinical Drug Development in Phase I, usually performed in HVs
  ▪ Showing drug exposure at the target site of action
  ▪ Showing that the drug interacts with the intended molecular receptor or enzyme
  ▪ Showing that the drug effects cell biology in the desired manner and direction

• Proof of Concept (PoC)
  ▪ Small group of patients with disease of interest, Phase II
  ▪ Showing a useful amount of desired clinical activity

• Proof of Principle (PoP)
  ▪ Relates to late clinical development in Phase III
  ▪ Showing statistically significant evidence of clinical efficacy and safety
Role of PoM in Early Clinical Drug Development
Three Pillar Theorem: PoM + PoC

Phase II Survival

Pillar 1
Exposure at the target site of action

Pillar 2
Binding to the target

Pillar 3
Expression of pharmacology

Definitions

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• **Proof of Concept (PoC)**
  - Small group of patients with disease of interest, Phase II
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• **Proof of Principle (PoP)**
  - Relates to late clinical development in Phase III
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Role of PoM in Early Clinical Drug Development

• Determination of pharmacological effect by
  ▪ Demonstrate Target engagement (e.g. receptor binding)
  ▪ Definition of a biological response after target binding

• Assessment of characteristics of target binding and response
  ▪ Time to onset
  ▪ Duration of response
  ▪ Exposure response relationship (PK/PD)
Relevant Guidelines

- Apart from describing the tolerability and PK of a drug in humans, Phase 1 and 2 studies can be used to:
  - Link animal and human findings
  - Provide evidence that the hypothesized mechanism is affected by the drug
  - Provide evidence that the effect on the mechanism leads to a desired short-term clinical outcome
  - Provide guidance for designing initial clinical endpoint trials that use a plausibly useful dose range
Practical Examples of PoM Studies in Healthy Subjects

#1 Pain
TRPV Receptor Antagonist
TRP Receptor Family

Heat
- TRPV1
- TRPV2?
- TRPV3
- TRPV4

pH
- TRPV1 (acid)
- TRPA1 (acid/base)

Reactive chemicals
- TRPA1
- TRPV1

Environmental cold
- TRPM8

Cold hyperalgesia
- TRPA1

Pain avoidance emotional reaction

Action potential

TRPV1 on nerve terminals
Other TRP channels in spinal cord?

Withdrawal in response to insult

TRP Receptors: Temperature Sensors?

- TRPM8
- TRPA1
- TRPV1
- TRPV2
- TRPV3
- TRPV4

Temperature (°C)

Sensation

- Burning Cold
- Cool
- Indifferent
- Tepid
- Warm
- Hot
- Burning Hot

Receptor type

- Nociceptors
- Cold receptors
- Warm receptors

TRP Channel Activity

-10 0 10 20 30 40 50 60
TRPV Receptor Antagonist: Early Clinical Phase Study Program

- **Study 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, Plasma PK

- **Study 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, Plasma PK

- **Study 3 (PoC):**
  - 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

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

Capsaicin

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

Heat Pain Perception Thresholds (°C)

Neurogenic Flare Area (cm²)
Practical Examples of PoM Studies in Healthy Subjects

#2 Alzheimer’s disease
Beta-secretase (BACE) 1 inhibitor
Beta-secretase (BACE) 1

beta-site Amyloid Precursor Protein cleaving enzyme

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BACE1 inhibitor:
Is the hypothesized mechanism affected by the drug?

- Continuous Cerebrospinal Fluid (CSF) Sampling
- To demonstrate changes in Beta-Amyloid and neurotransmitters
- Correlate doses with on-target mechanism of action
- Panels of 8 healthy elderly subjects
- 14 day dosing
- CSF collected for 36 hours after last dose on day 14

BACE1 inhibitor: Is the hypothesized mechanism affected by the drug?

CSF Beta-Amyloid, 14 days multiple dosing of BACE1 inhibitor

Placebo

10 mg

40 mg

Hours
BACE1 inhibitor:
Provide dose guidance for initial clinical endpoint trails

- No clinically significant laboratory findings
- 10 mg dose considered not sufficiently active on CSF biomarker (Beta-Amyloid)
- 80 mg dose considered poorly tolerated
  - No CSF sampling performed
- **Proceed to Phase 2A study with 40 mg**

<table>
<thead>
<tr>
<th>Adverse Events %</th>
<th>10 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/GI</td>
<td>14</td>
<td><strong>21</strong></td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>9</td>
<td><strong>11</strong></td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>10</td>
<td><strong>14</strong></td>
<td>18</td>
<td>7</td>
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<tr>
<td>Tremor</td>
<td>2</td>
<td><strong>3</strong></td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Increased Systolic BP</td>
<td>3</td>
<td><strong>5</strong></td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14</td>
<td><strong>16</strong></td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Vivid Dreams</td>
<td>4</td>
<td><strong>6</strong></td>
<td>10</td>
<td>2</td>
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## PoM Model Requirements

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
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<tbody>
<tr>
<td>Plausibility</td>
<td>The model should activate the relevant mechanism of the target patient population</td>
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<td>Translatability</td>
<td>The same model and the same endpoints should exist for preclinical and clinical experiments</td>
</tr>
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<td>Reproducibility</td>
<td>The model should be highly reproducible within subjects across several experiments</td>
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<tr>
<td>Robustness</td>
<td>Different investigators performing the model should get to the same results</td>
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<tr>
<td>Validity</td>
<td>Standard of care drugs should work in the model</td>
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<tr>
<td>Dynamic range</td>
<td>The model should have a wide dynamic range to allow for PK-PD relation analysis</td>
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</tbody>
</table>
Conclusions

• Proof of Mechanism (PoM)
• is an essential part of early clinical drug development
• The aim is to observe
  ▪ Drug exposure at the target site of action
  ▪ Drug interaction with the intended drug receptor
  ▪ Effect of the drug on cell biology based on biomarker
• Is an important tool for selection of appropriate dose for Proof of Concept (PoC) studies
• can often be performed already in healthy subjects (disease models or biomarkers)
Thank you

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