Rapid Drug Development from First-in-Human to Proof-of-Concept: New Strategies

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University of Hong Kong

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EARLY PHASE

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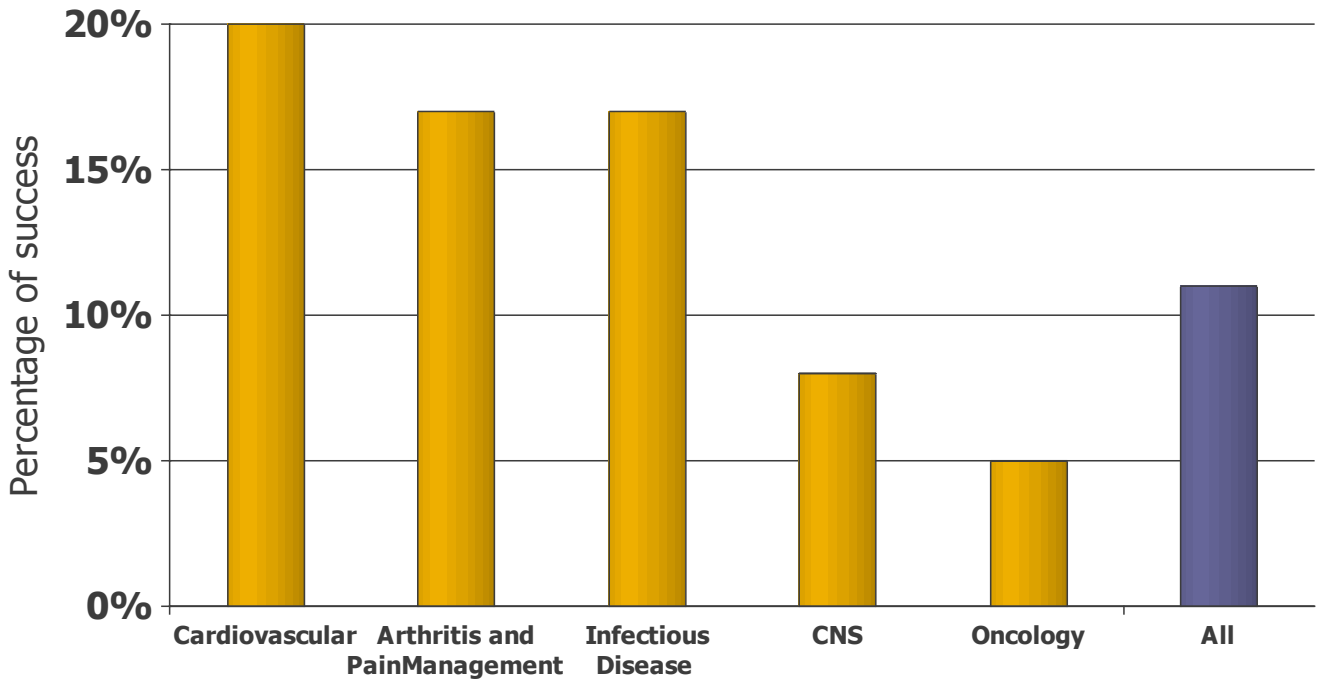
Agenda

- Background
- Requirements to Accelerate Drug Development
- Case Studies - complex combination protocol
  - proof of mechanism using disease models
  - CNS biomarkers
- Lessons learnt
- The future

Success Rates 1991-2000



- 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

Source: Kola & Landis. Nat Rev Drug Discov, 2004

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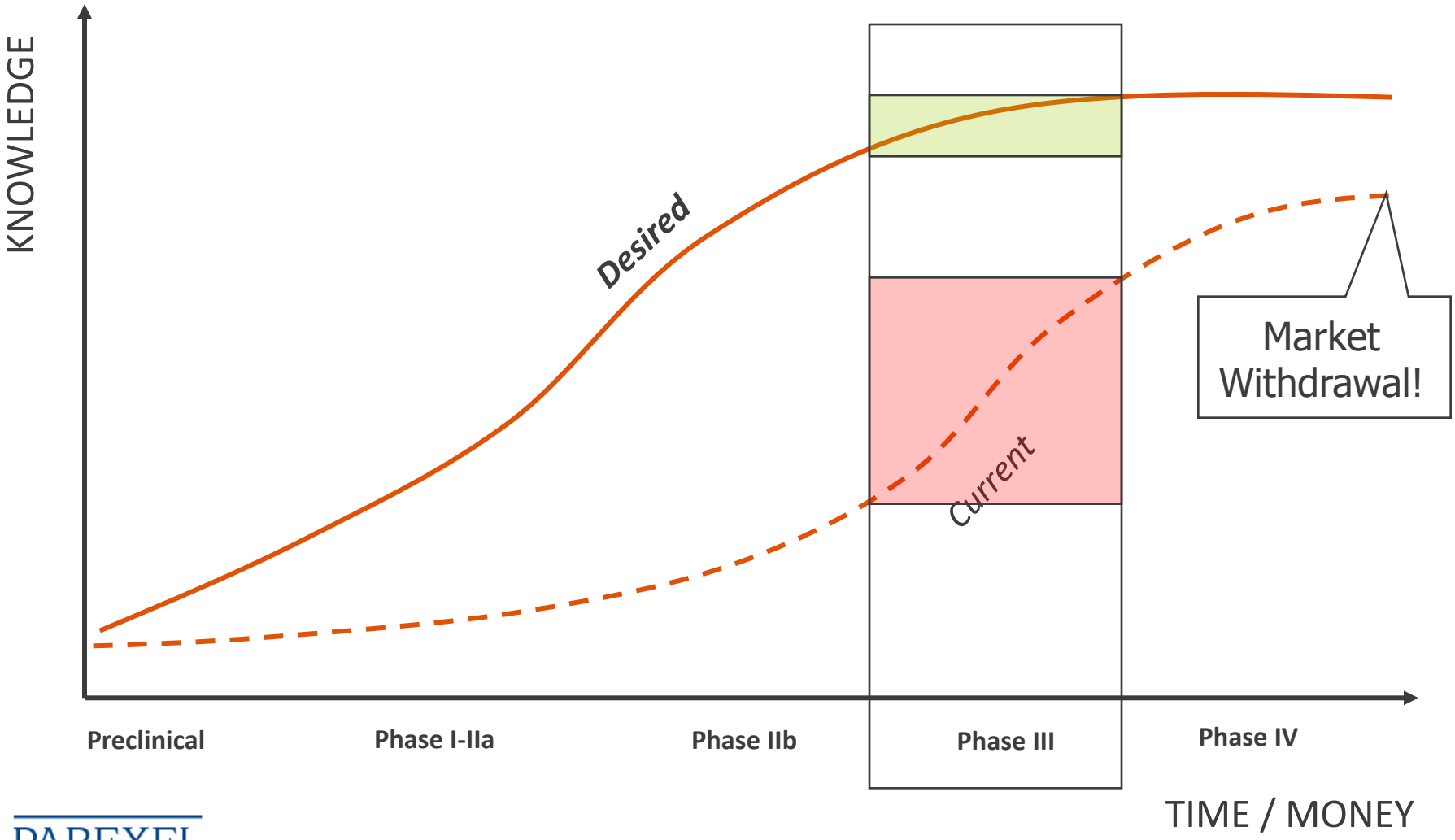
Learning Too Little Too Late



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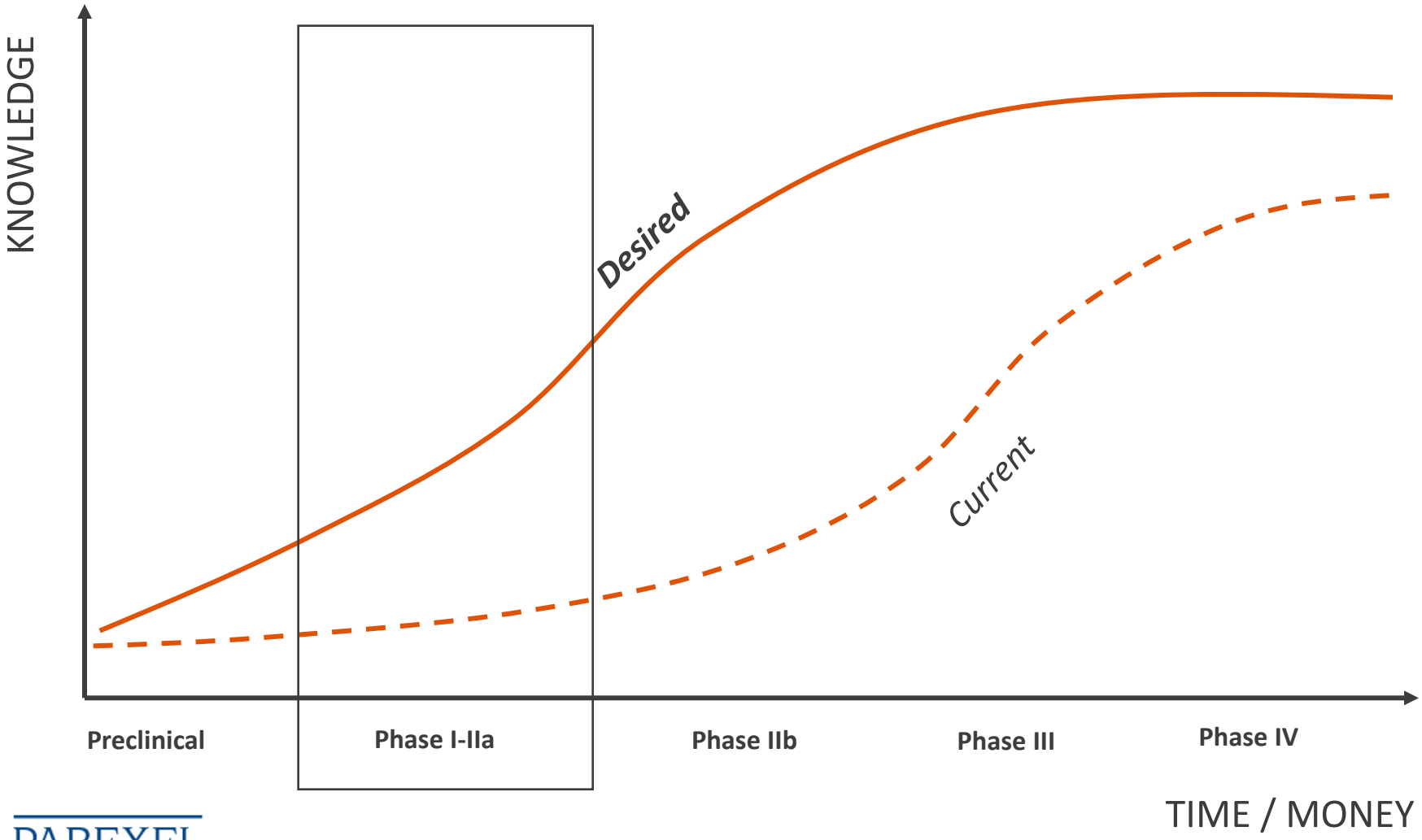
Learning Too Little Too Late



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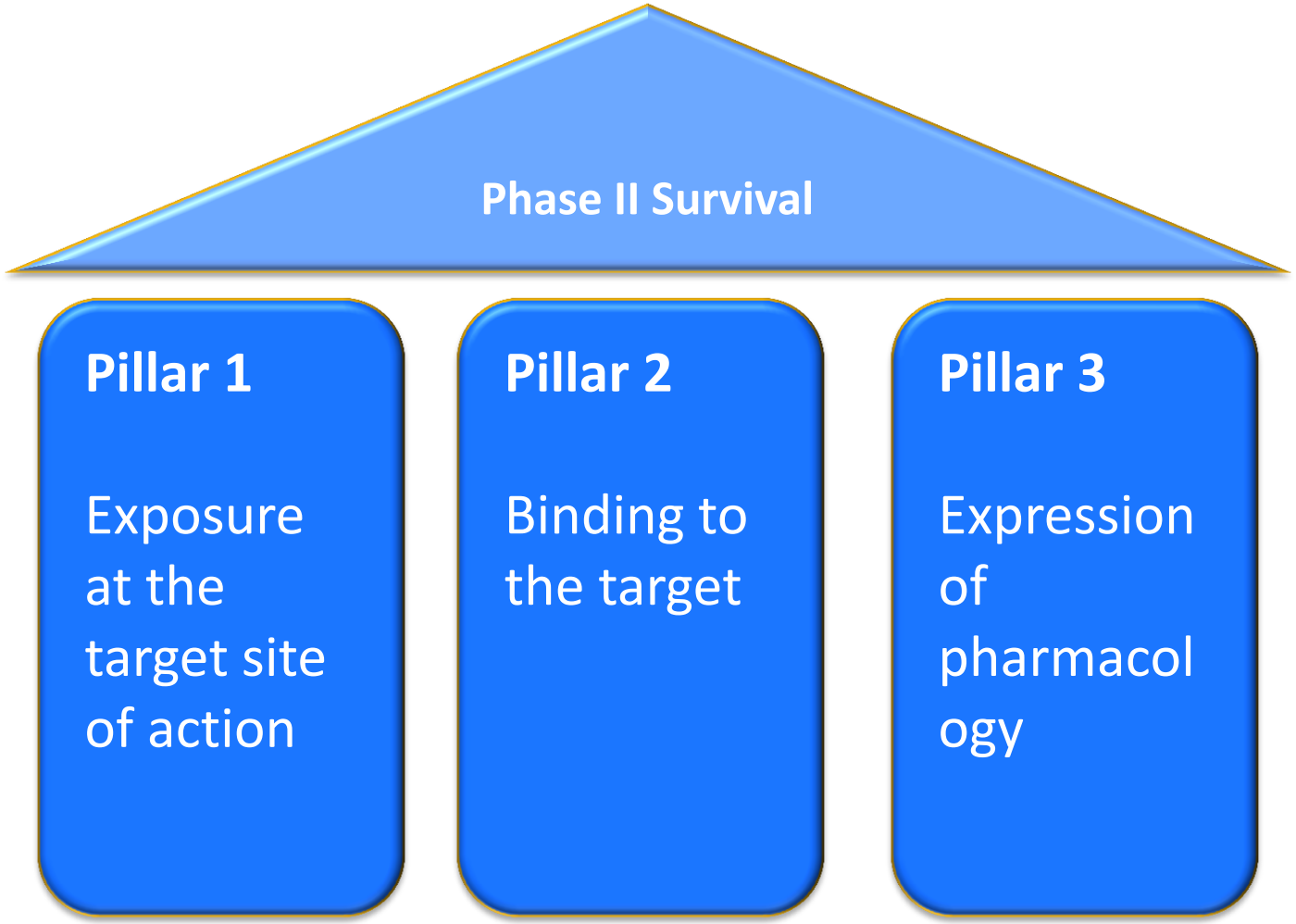
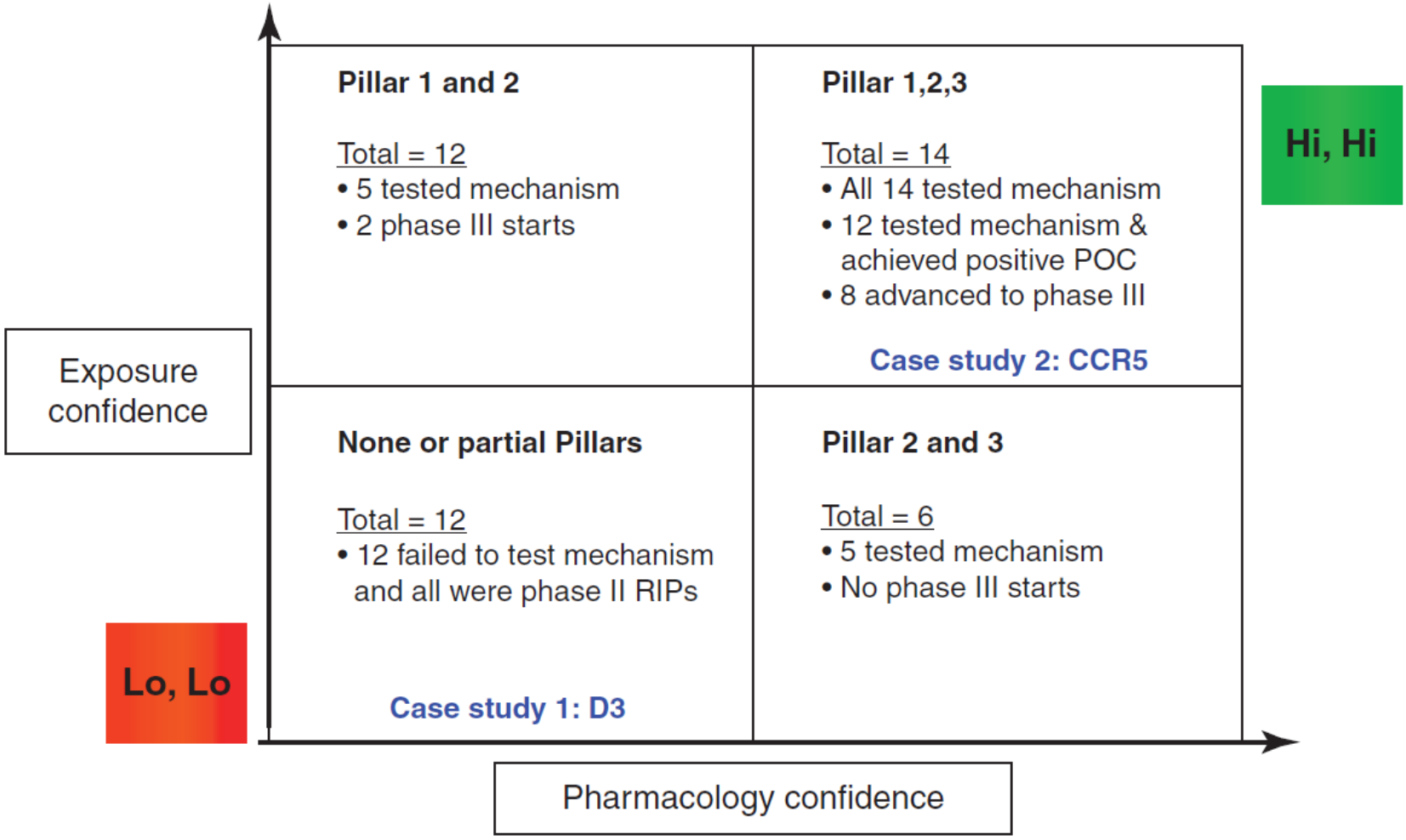
Phase I-IIa Success - Three Pillar Theorem: Proof of Mechanism + Proof of Concept



Morgan P. Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival., Drug Discov Today. 2011 Dec.

Pfizer Analysis of 44 Studies (2005-2009)



Drug Discovery Today

7

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

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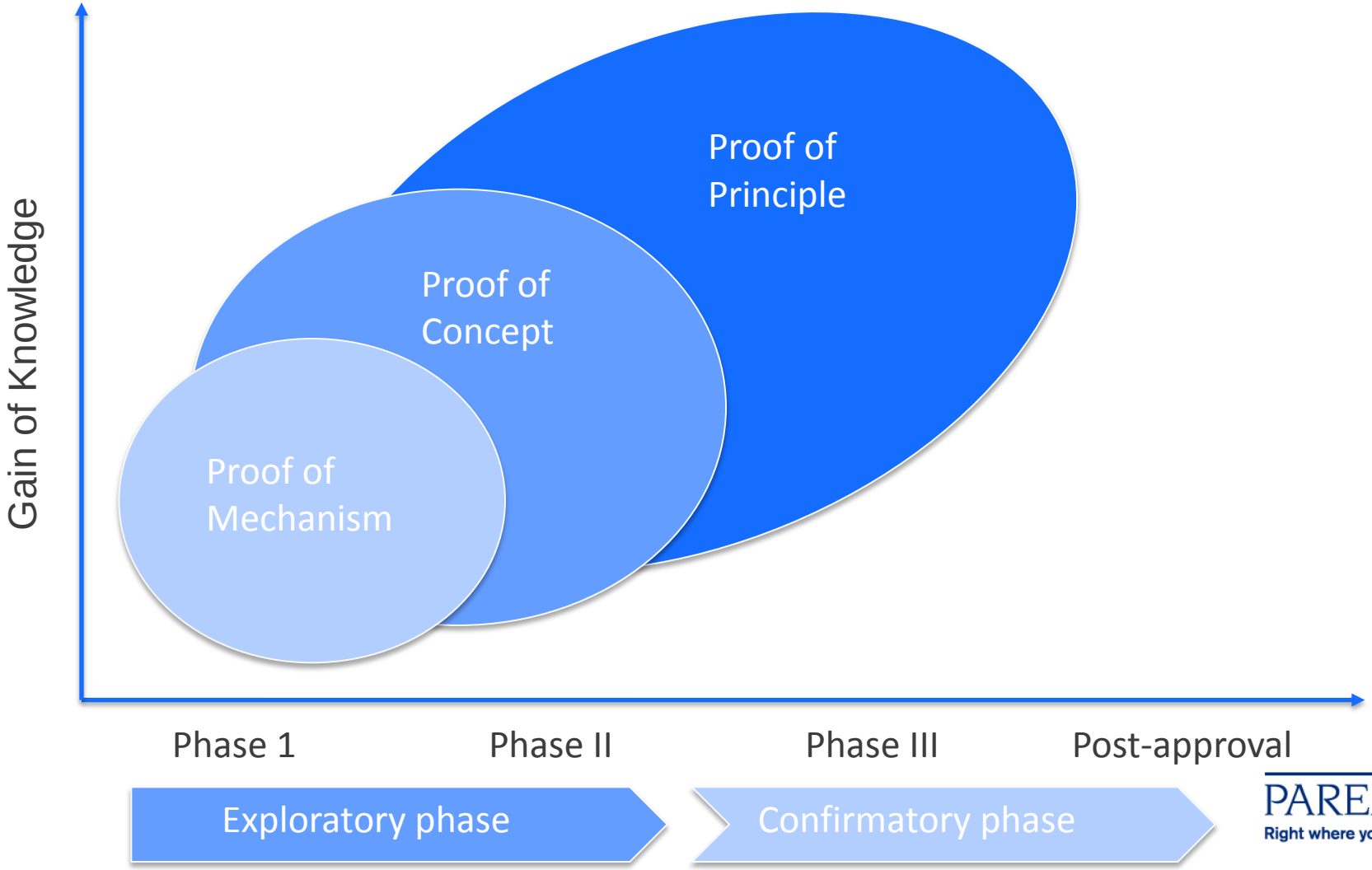
Early Acquisition of Knowledge



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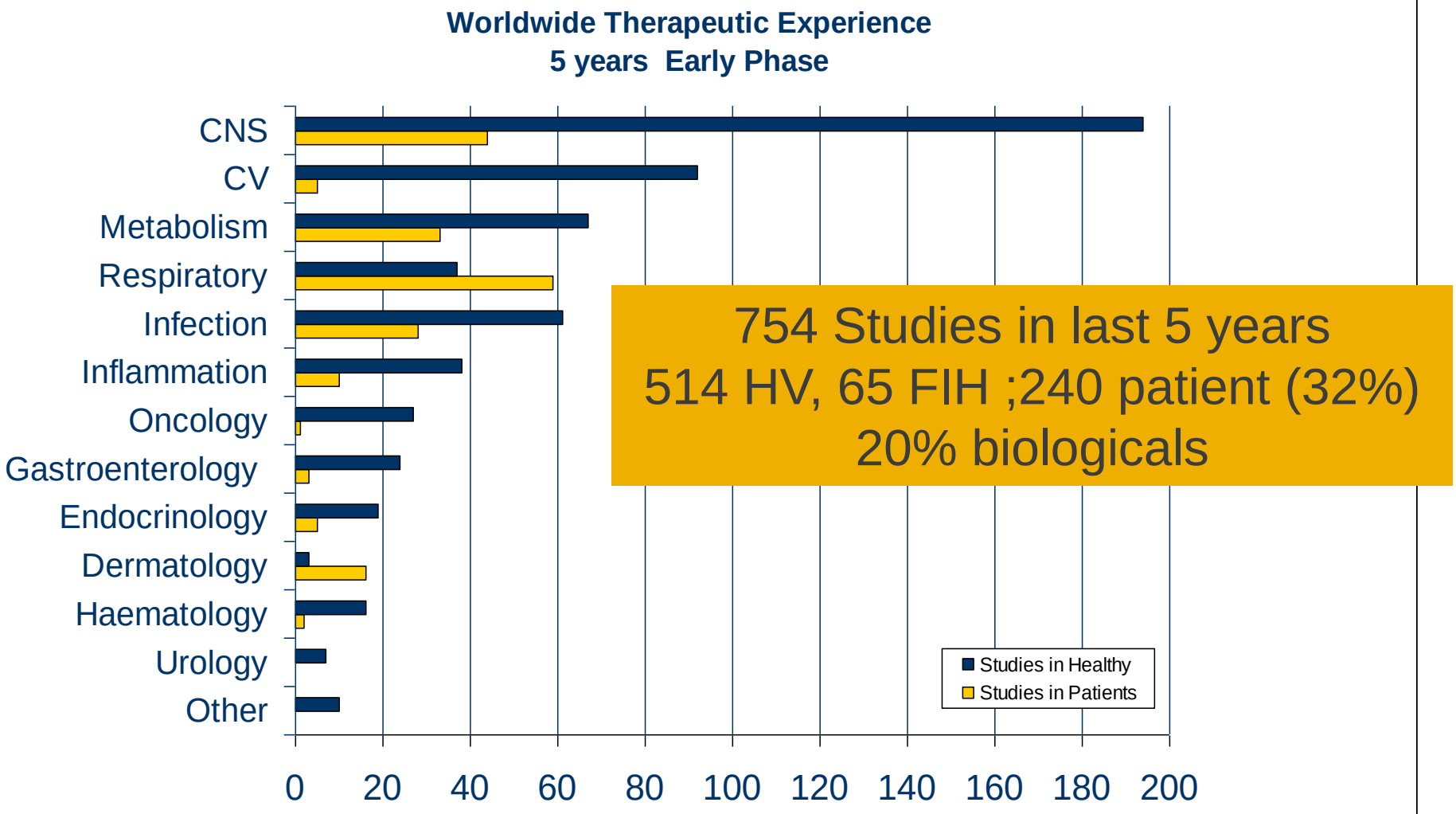
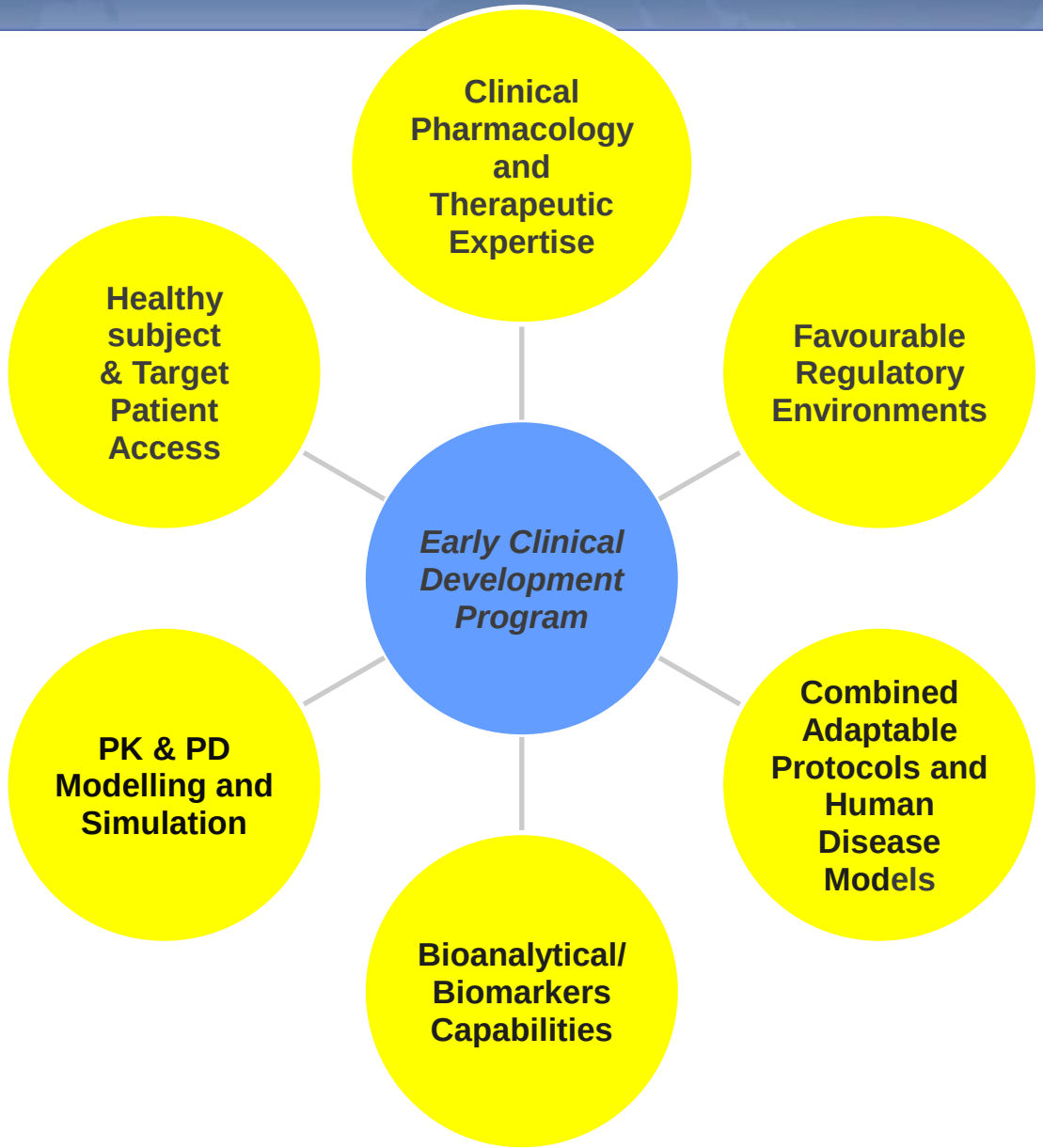
PAREXEL Therapeutic Early Clinical Experience Phase I/IIa



Key Requirements for Rapid Development



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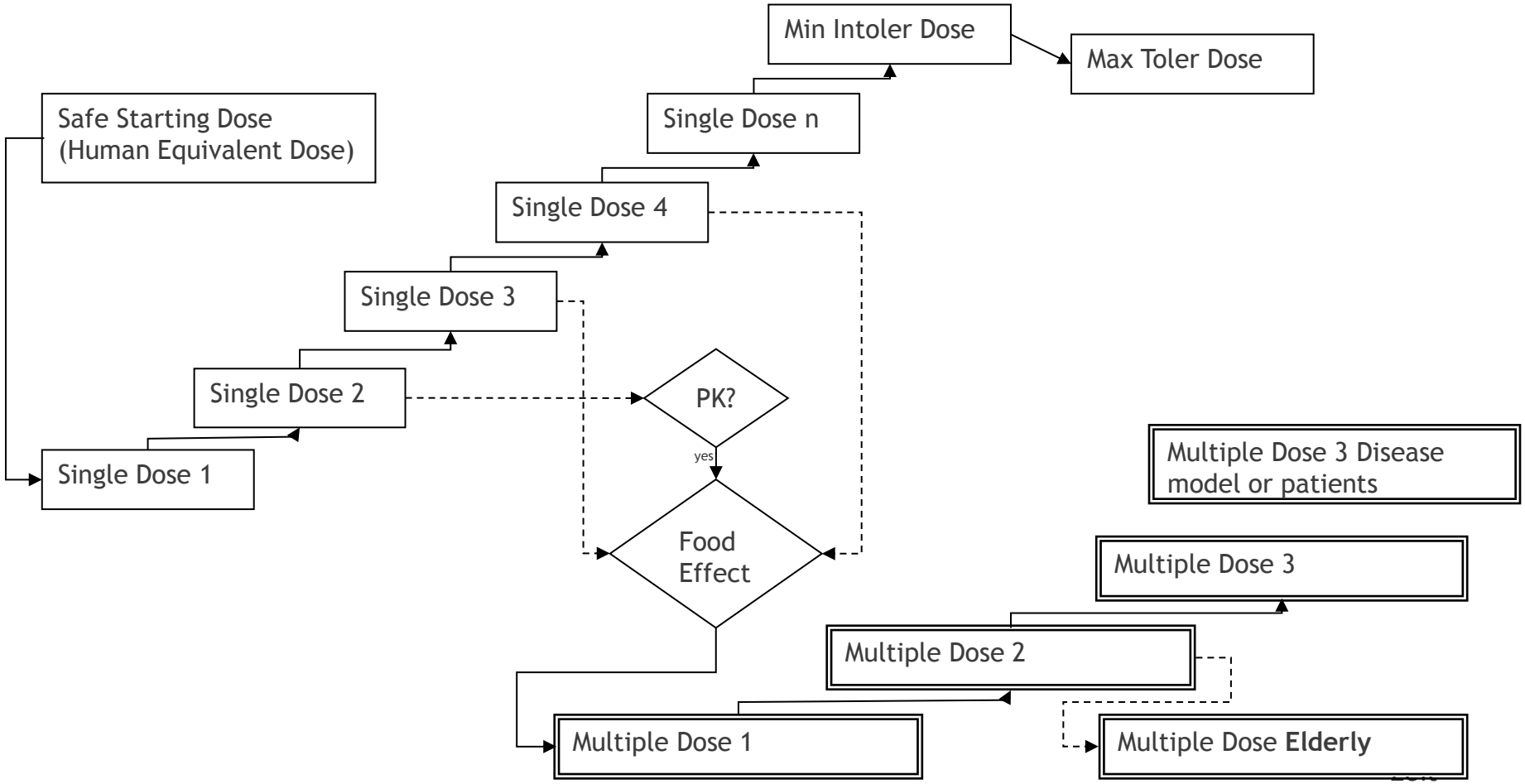
Time Saving in Early Phase

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



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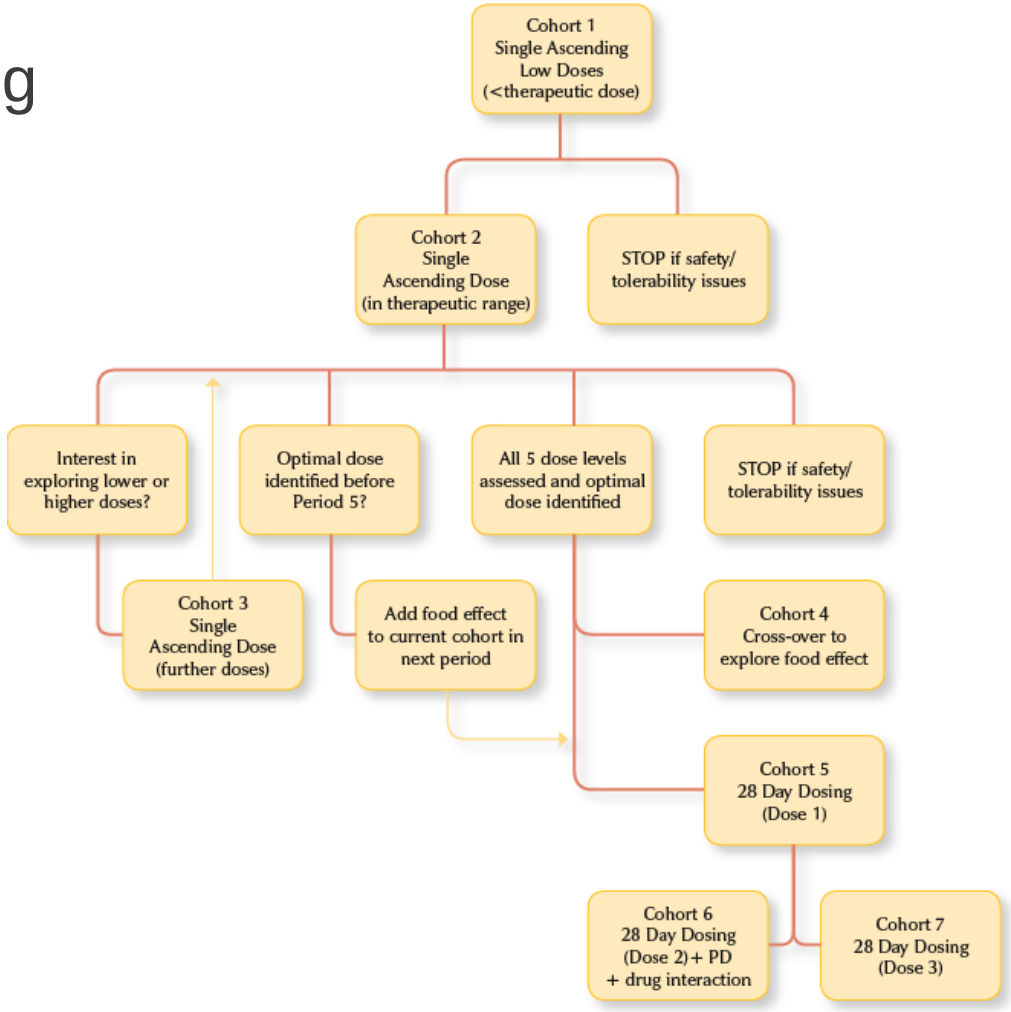
Combination Flexible Study Designs

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



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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

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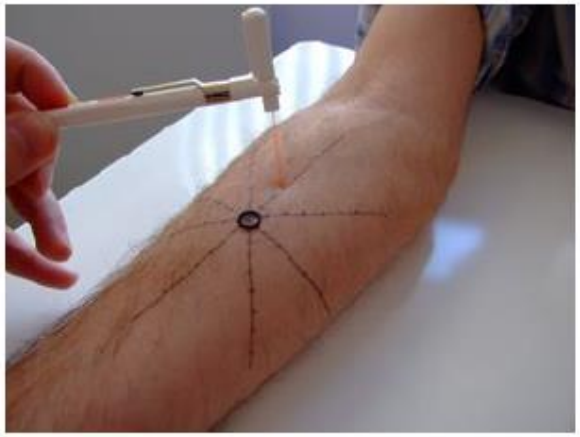
If Patients cannot be recruited easily?

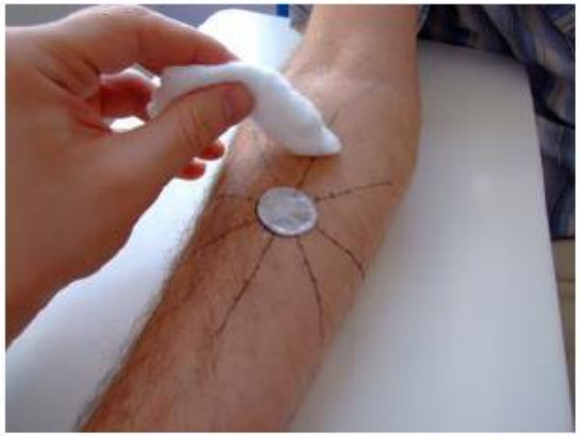
Use Human Disease Models in healthy subjects or other patient populations with similar target

Example 1: Experimental Pain Models

Numerous validated models

- Capsaicin
- UVB Sunburn
- Electrical Hyperalgesia





Various assessments e.g:

- Hyperalgesia / Allodynia
- Temperature perception
- Erythema (LDF)

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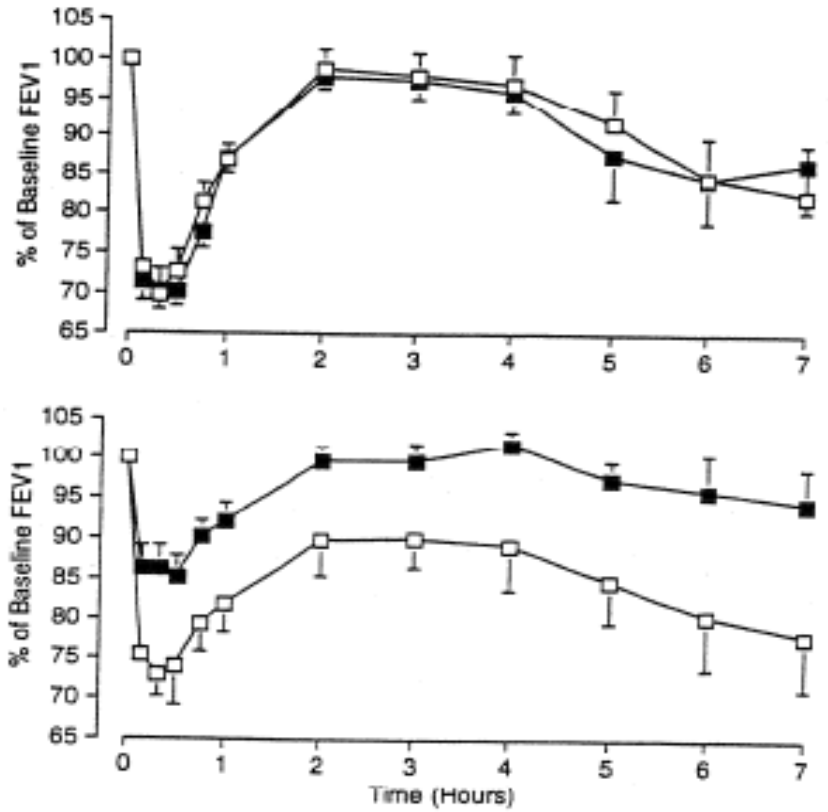
Example 2: Inhaled Allergen Challenge



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

Source: Fahy et al. Am J Resp. Crit. Care Med. 1997; 155:1828-1834

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

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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

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TRPV Receptor Antagonist:
Link animal to human findings

Hot Plate Tail Flick Test

BIOSEB In Vivo Research Instruments

Heat Pain Tolerance Test

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TRPV Receptor Antagonist:
Link animal to human findings

Hindpaw Pinch Test

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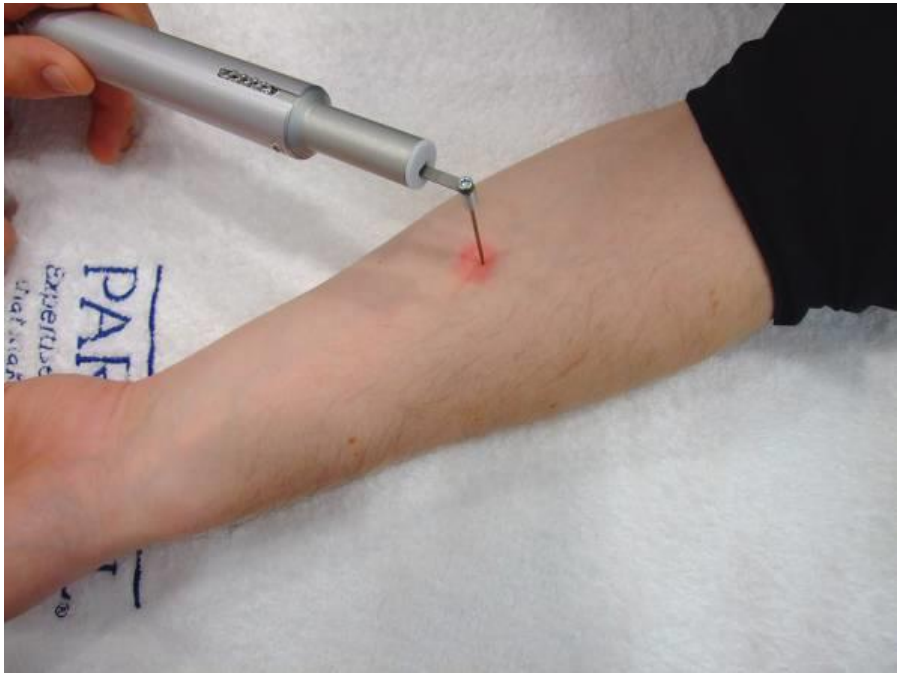

Pin Prick Test

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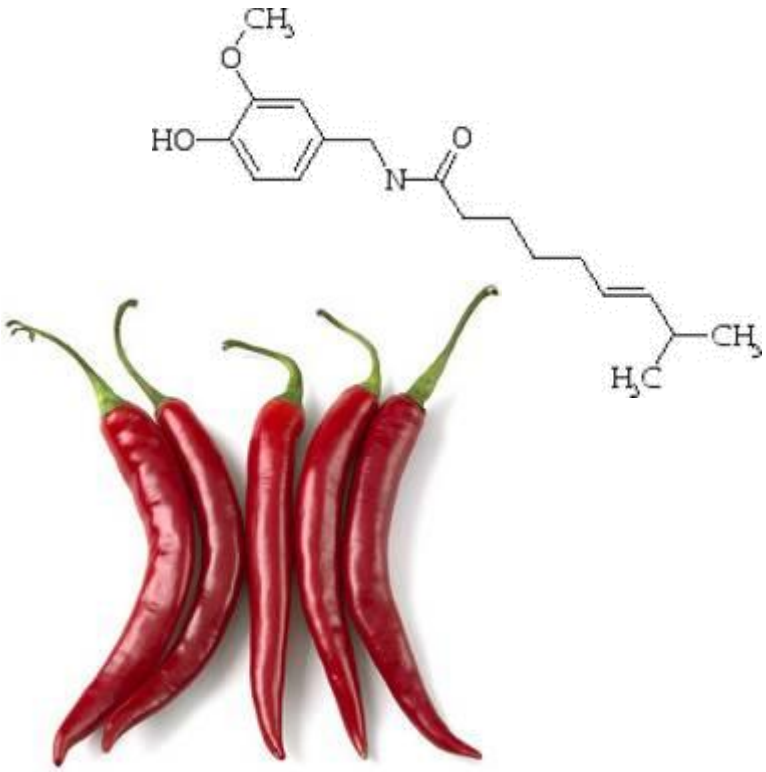
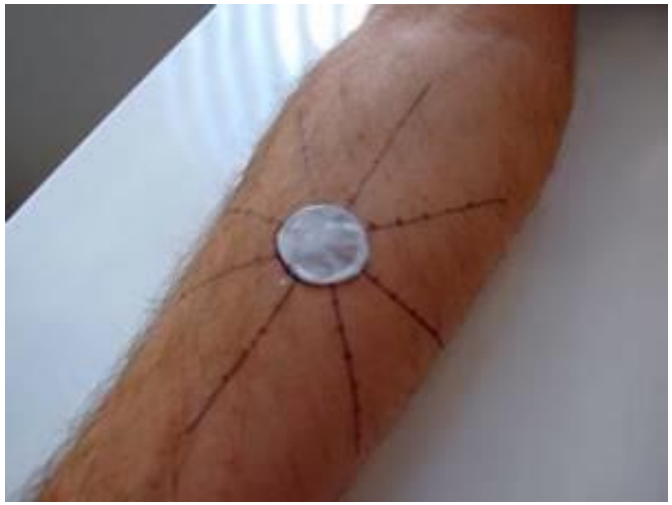
TRPV Receptor Antagonist:
Is the hypothesized mechanism affected by the drug?



Capsaicin



Capsaicin Cream Application

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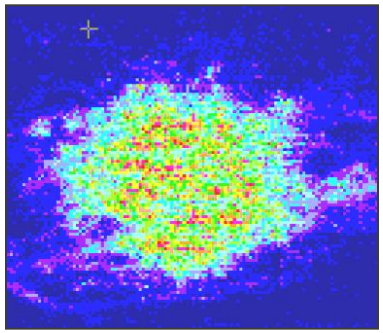
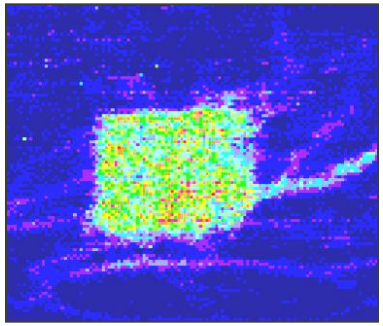
Practical Examples: TRPV Receptor Antagonist

Is the hypothesized mechanism affected by the drug?
Is there a dose response?

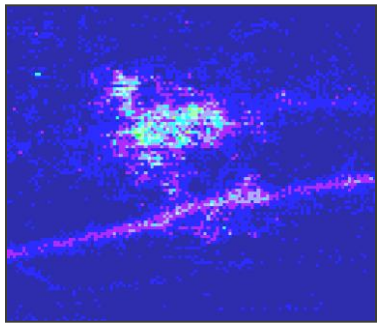
Placebo

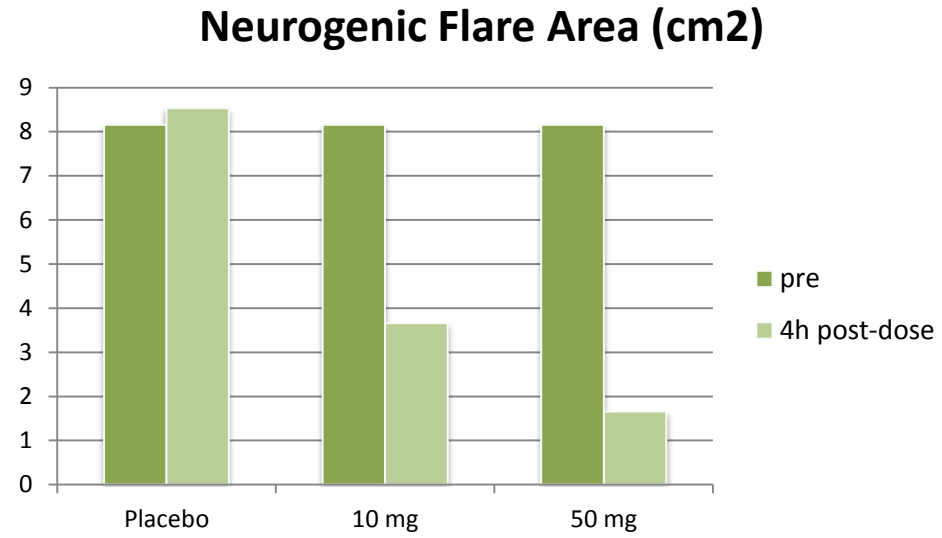


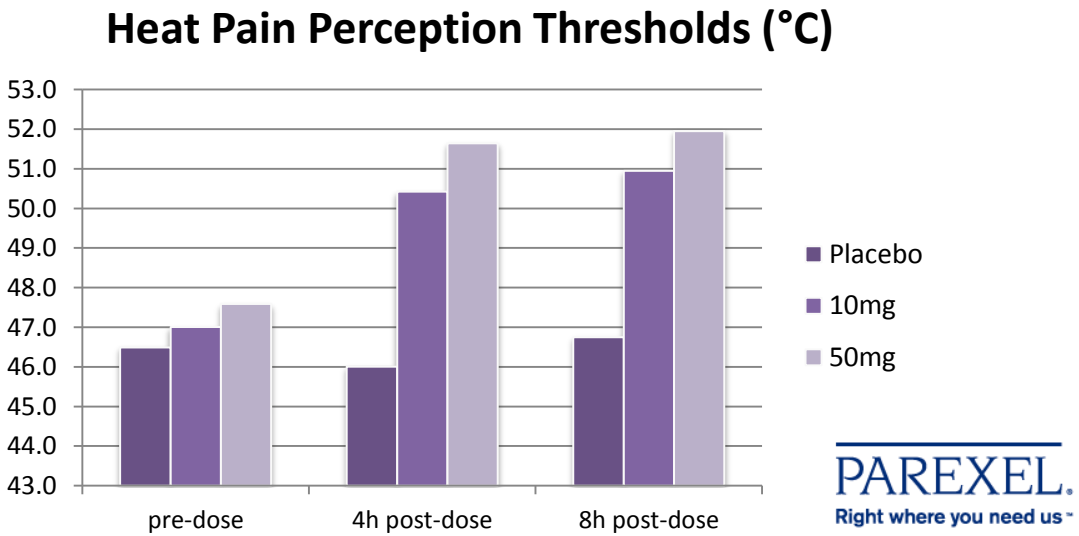
10 mg



50 mg







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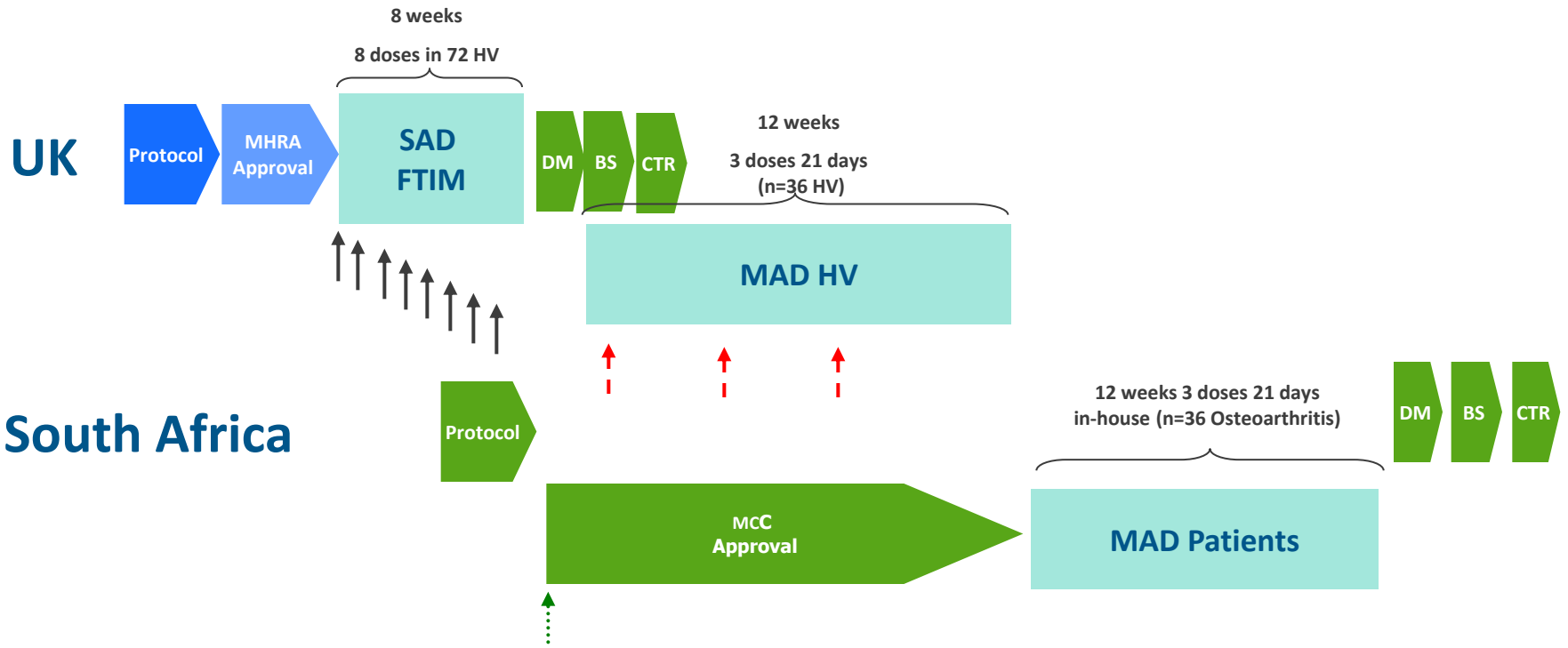
TRPV1 Receptor Antagonist:
44 weeks from FIH to PoC



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

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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

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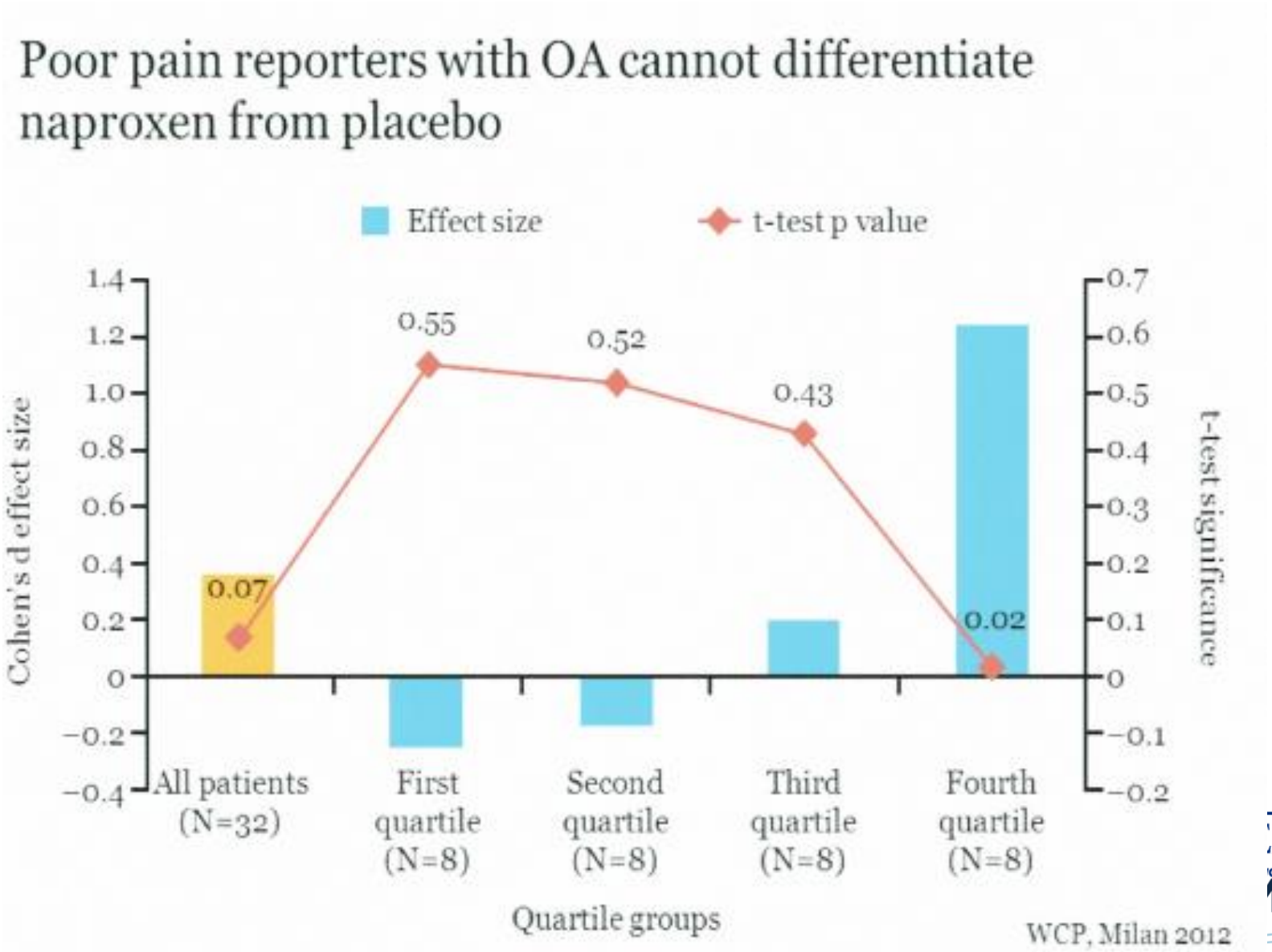
Optimise Pain Response by Enhancement of OA patients - FAST Score Quartiles



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

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Illustrative Case Studies

#2 Alzheimer's disease
Histamine 3 Receptor Antagonist
NXE-00X1

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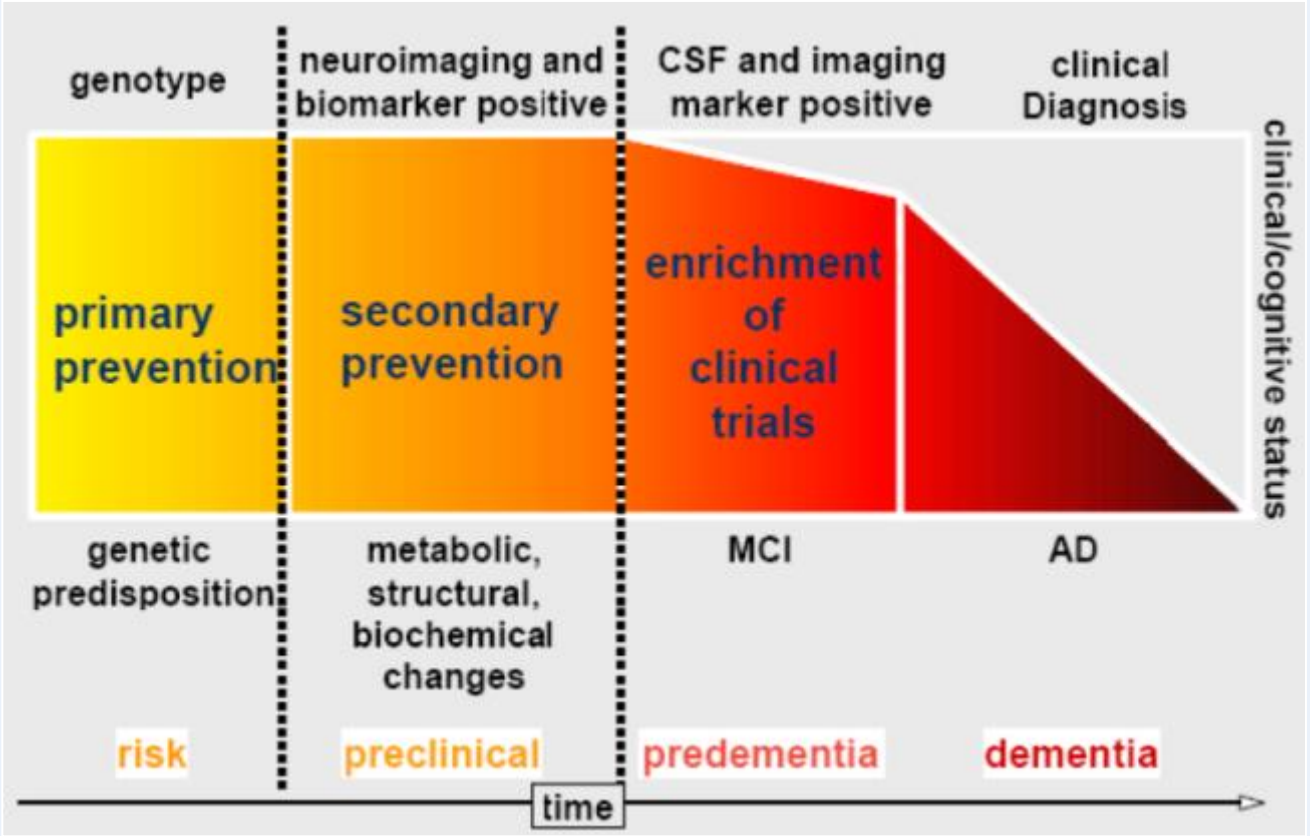
Changes in our Conceptualization of Alzheimer's Disease: Implications for Early Drug Development



Mild Cognitive Impairment Patients' Diagnosed by:

- Amyloid PET
- CSF lumbar puncture using modified amyloid ADNI cutoff

From: Hampel & Broich 2009

ISCTM Winter Meeting, Washington, Feb. 2010.

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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

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

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

Go No-Go Decision

Phase IIa

Safety, exploratory, efficacy

12-week

Mild cognitive impairment

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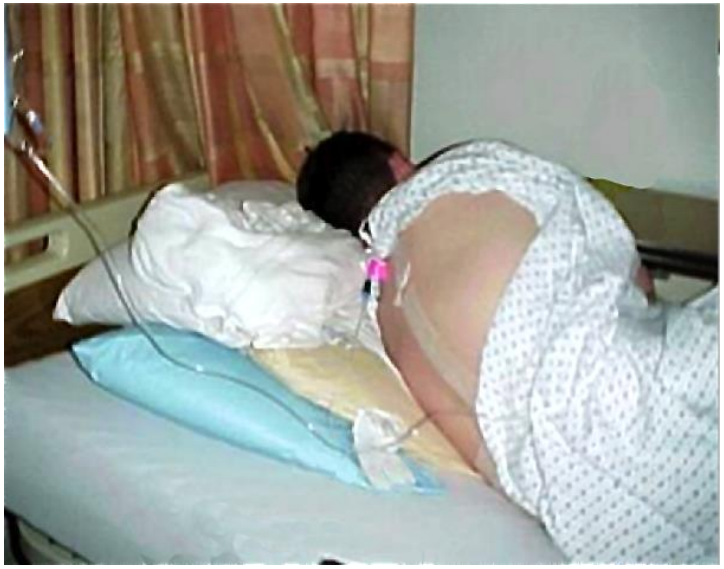
NCE-00X1:
Is the hypothesized mechanism affected by the drug?

- 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



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Ereshefsky L, et al. *Biomark Med*. 2009;3:711-721.

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

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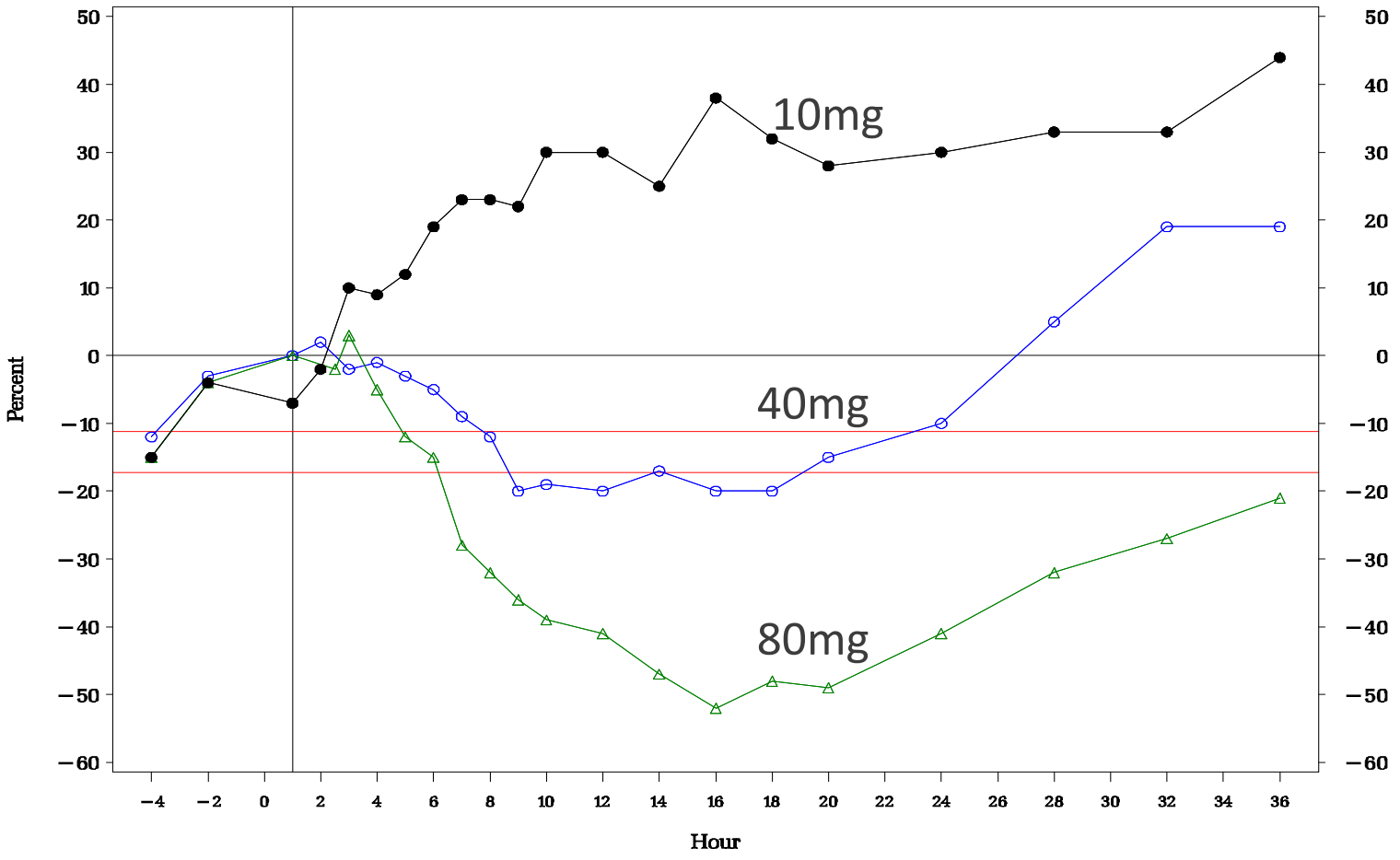
CSF Amyloid beta 42 on Day 14



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NCE-00X1:
Provide guidance for initial clinical endpoint trials

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

- 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**

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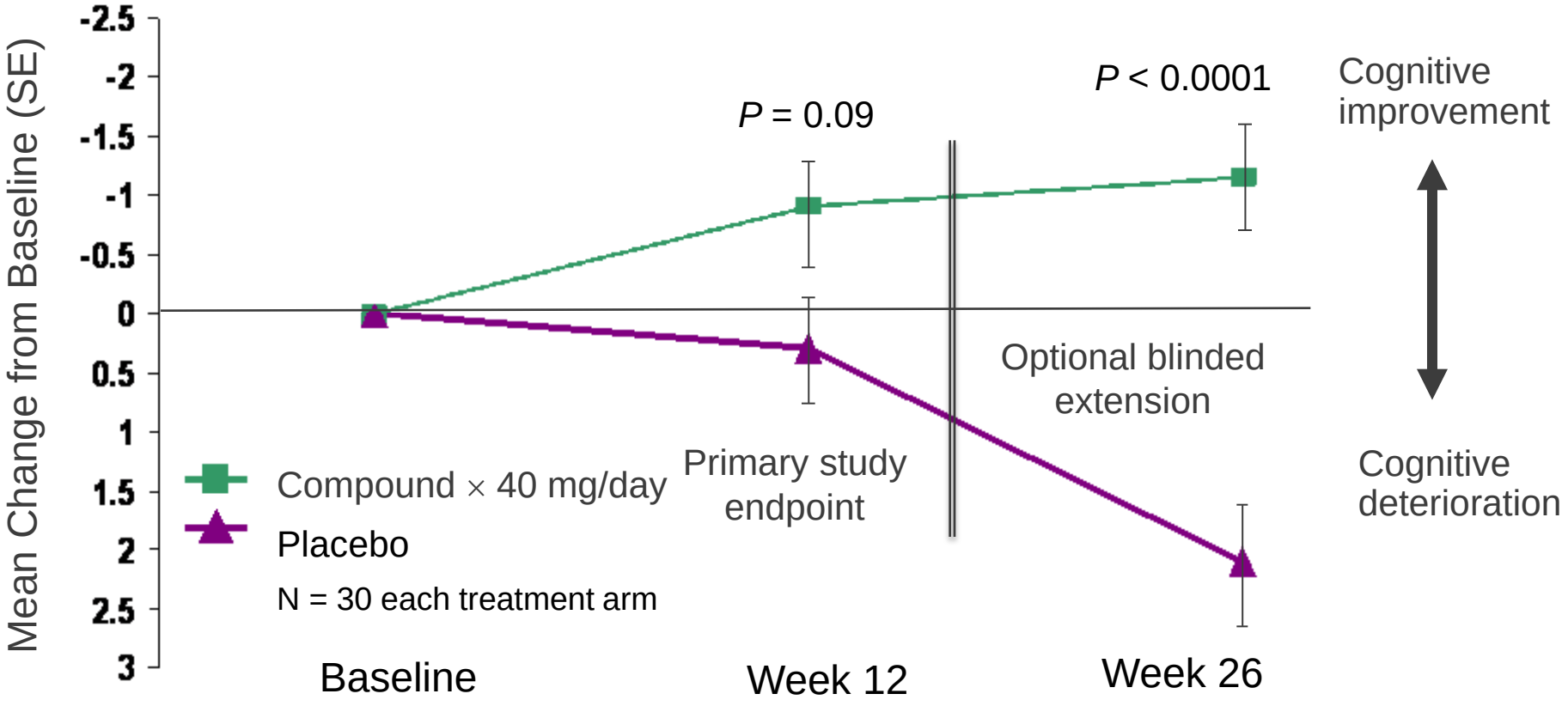
Phase IIa Safety Study at Target Dose
Efficacy: Alzheimer's Disease Assessment Scale (ADAS-Cog)



ITT/LOCF analysis.

Simulation of response.

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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

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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”

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Thank you

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