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Applied Translational Medicine

Welcome to Celerion's Dinner and Discussion Program

Tokyo, Japan

Apr 2, 2015

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Applied Translational Medicine

Efficient Clinical Pharmacology Study Designs

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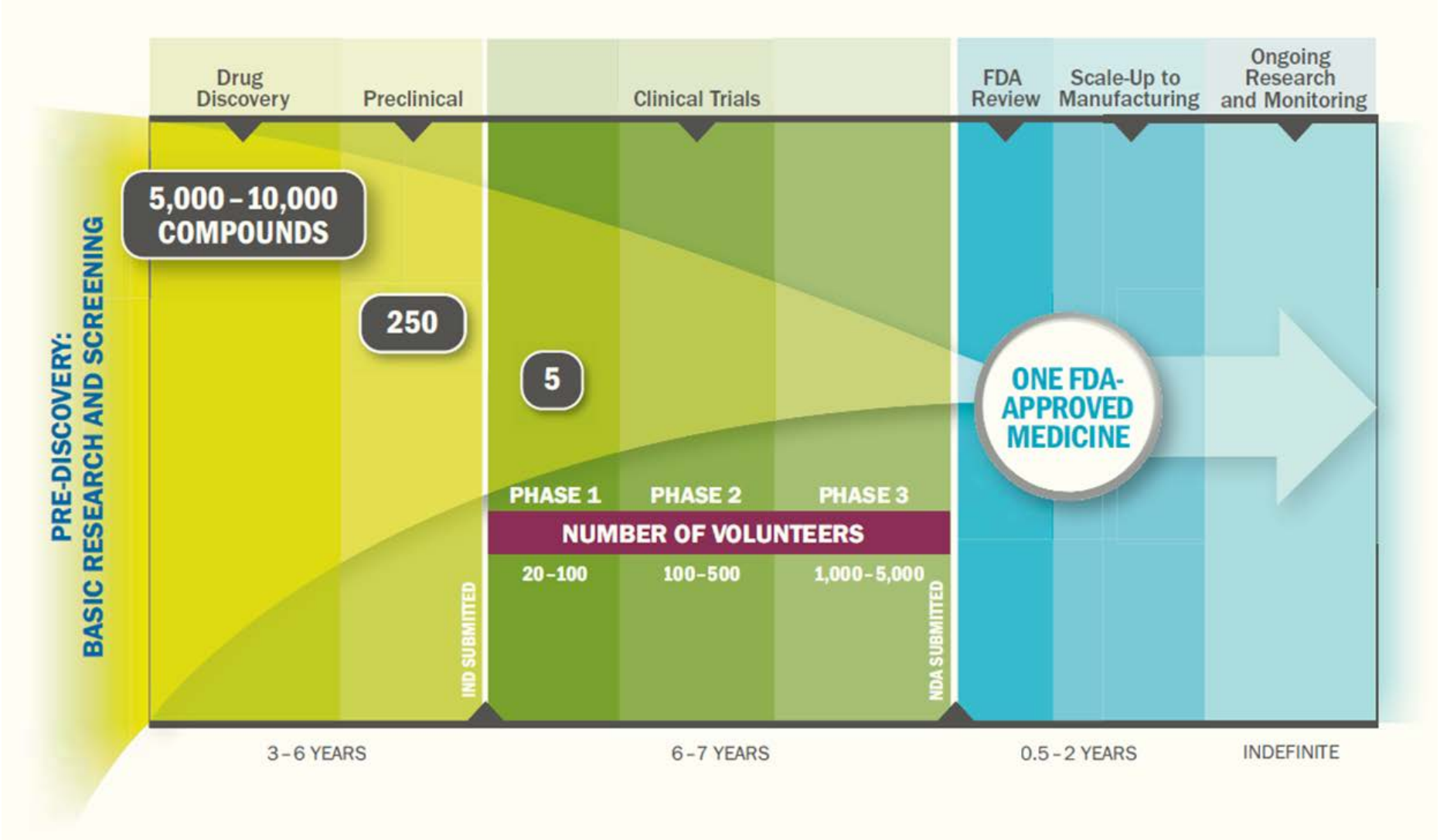
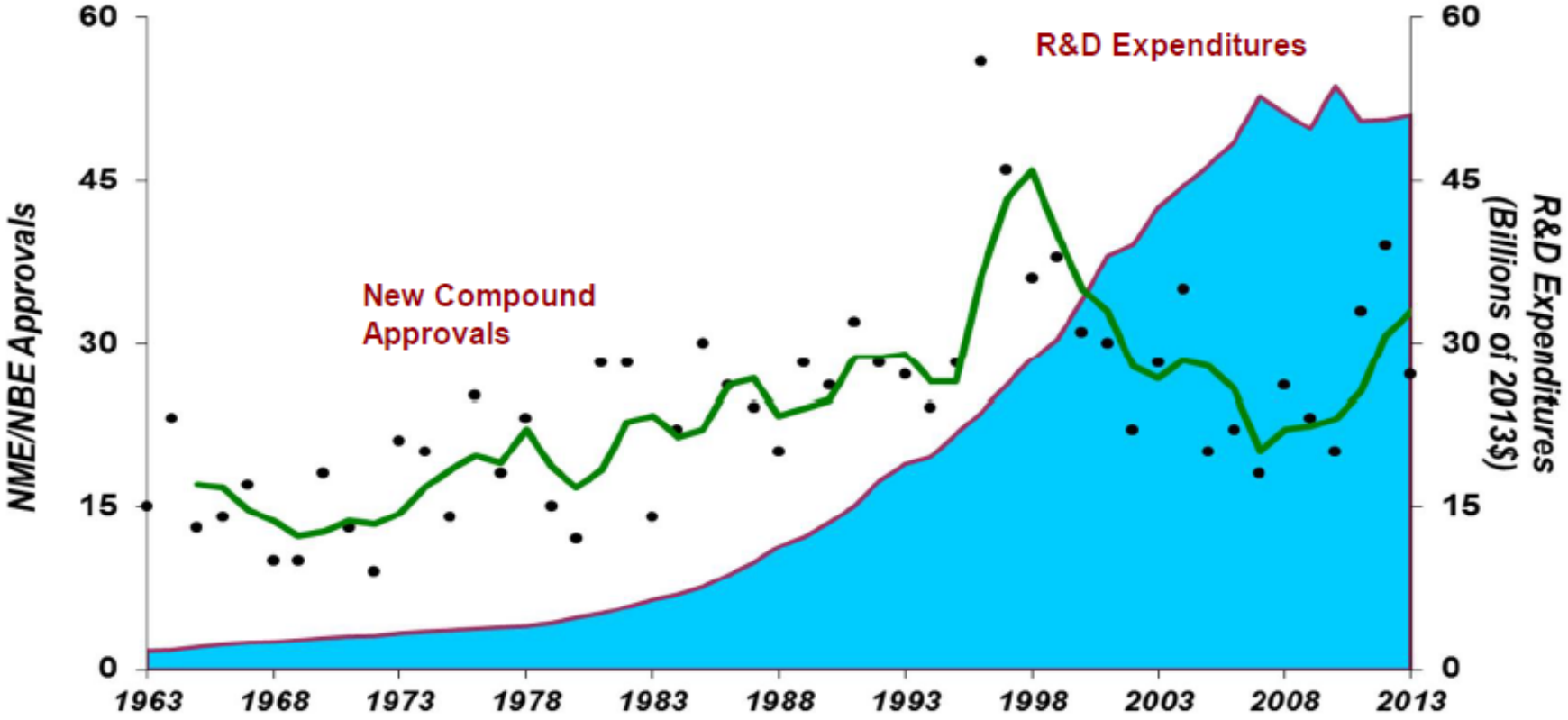
Research & Development (R&D) Process: PhRMA 2013 Profile



New Drug And Biologics Approvals/R&D Spending



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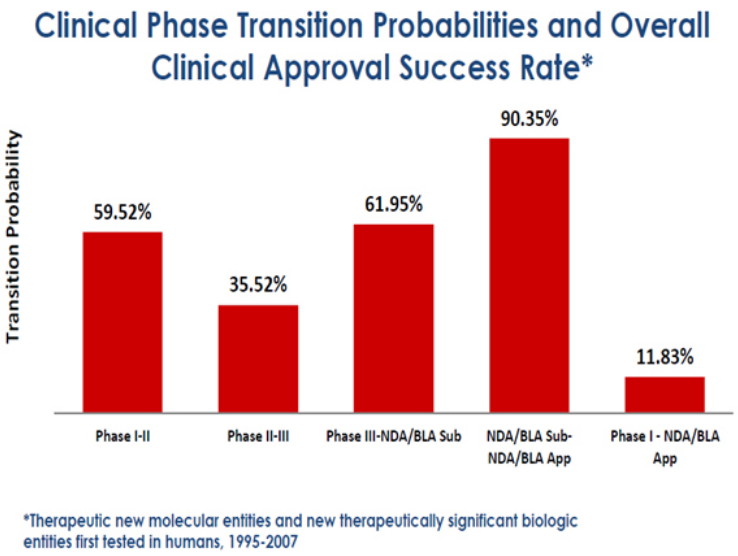
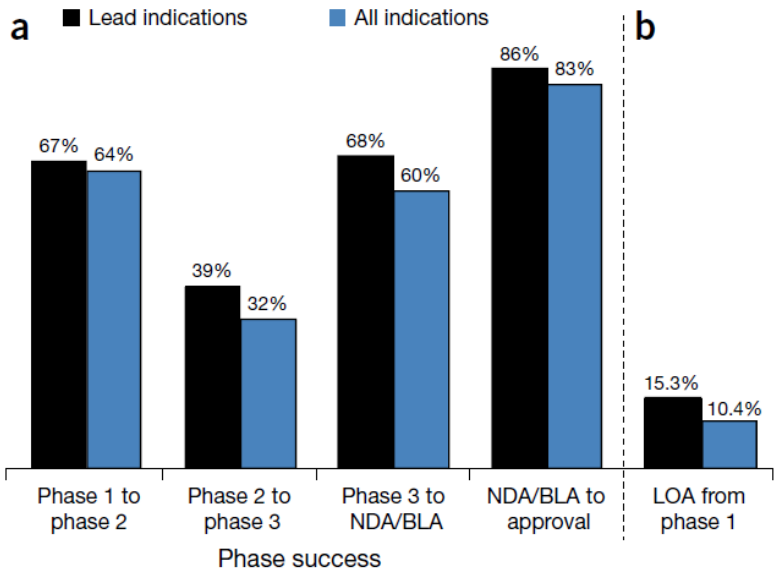
Phase Transition Rates

Tufts CDSS 2014



Hays 2014



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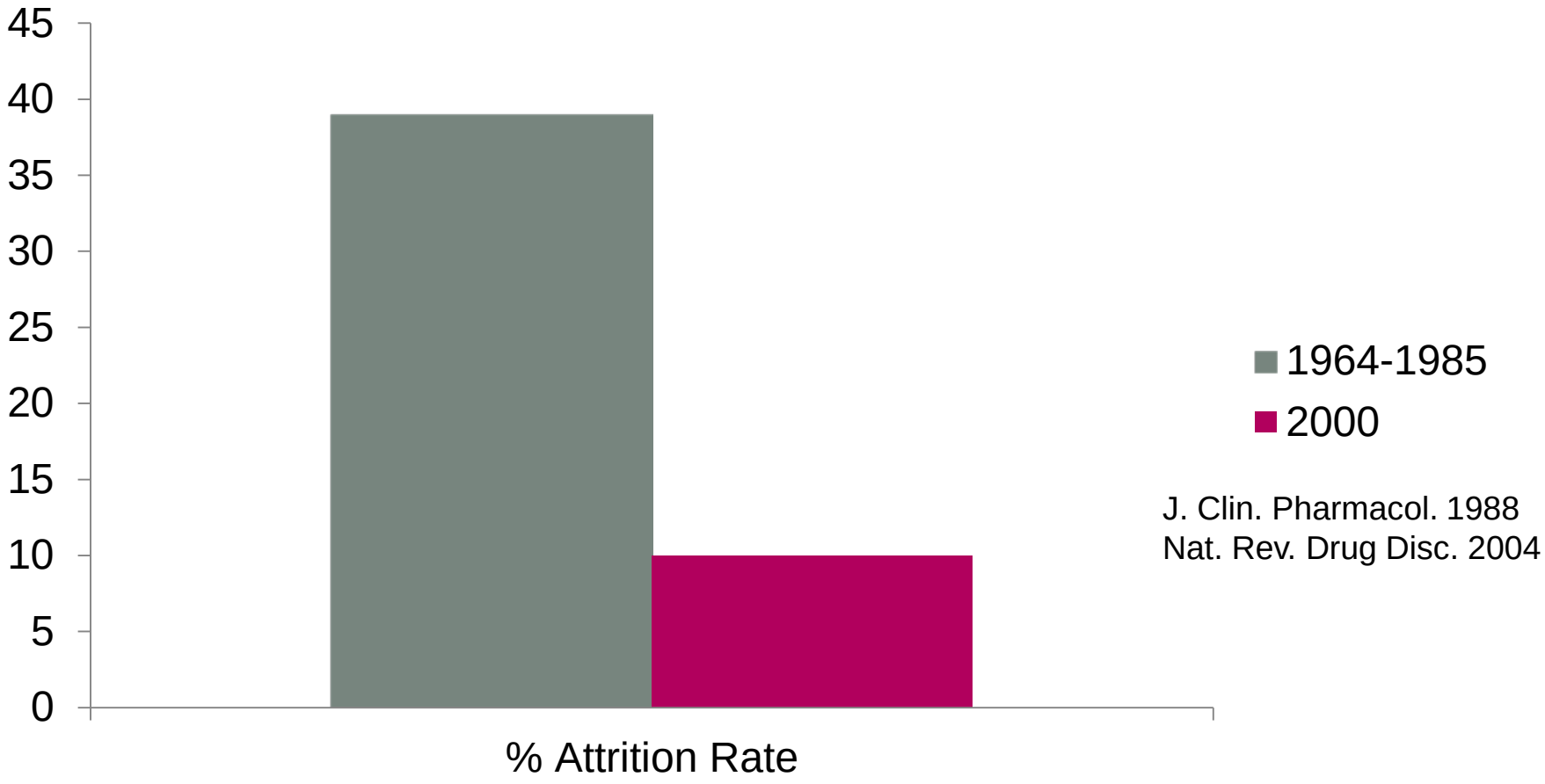
Attrition Rate of NME Due to PK/ADME



J. Clin. Pharmacol. 1988
Nat. Rev. Drug Disc. 2004

NME: New Molecular Entity
PK: Pharmacokinetic
ADME: Absorption, Distribution, Metabolism & Excretion

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Characteristics of an Efficient First-in-Human Study

- Establishes drug does not elicit acute, treatment-limiting adverse events
- Characterizes the ADME properties:
  - Peak exposure
  - Overall exposure
  - Half-life
- Identifies influences for future patient exposure
  - Effect of food for oral dosing
  - Site of administration for Subcutaneous (SC)
  - Timing of dose
- Minimizes time and cost to Proof-of-Concept (POC) step

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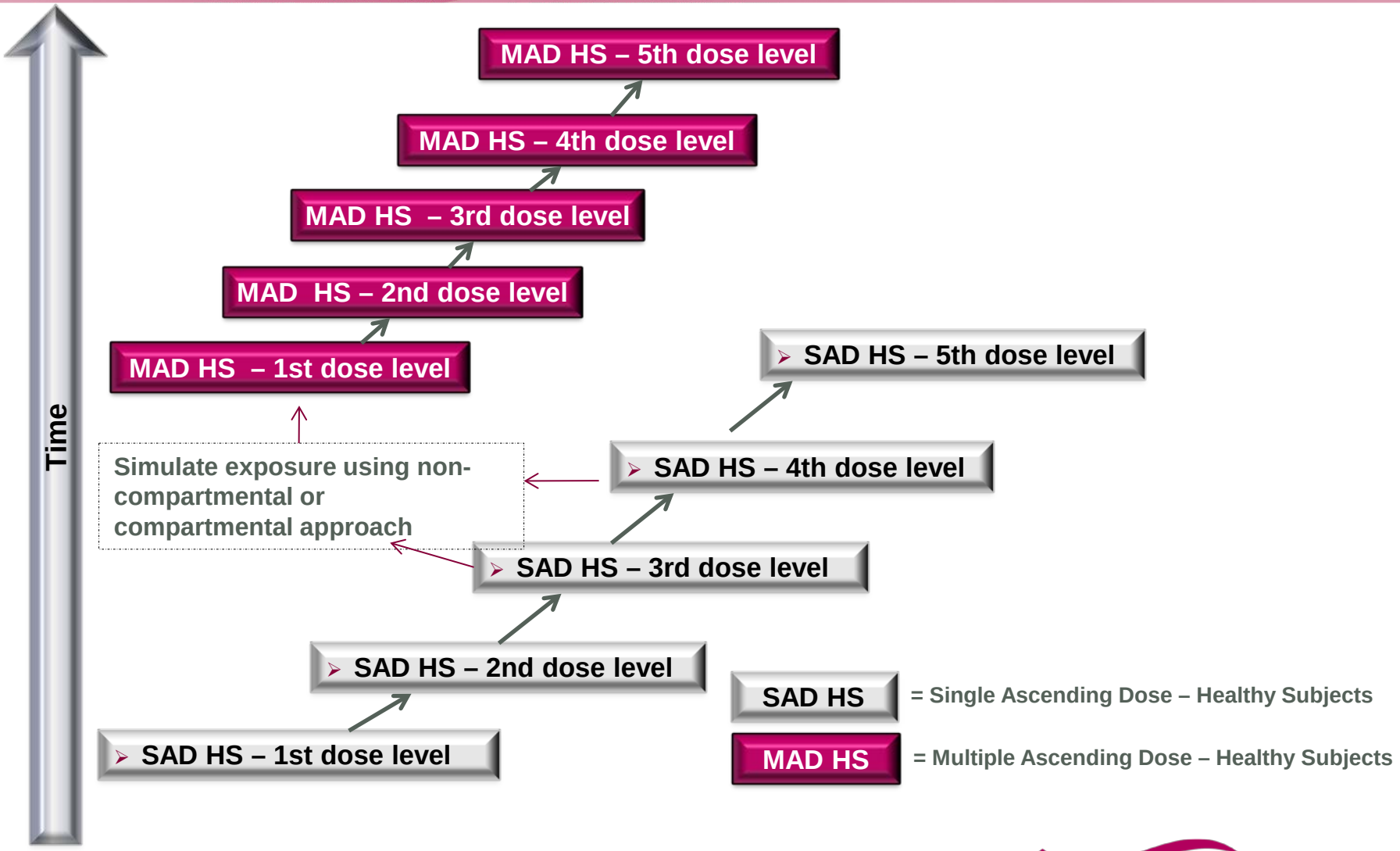
Efficient First-in-Human Designs



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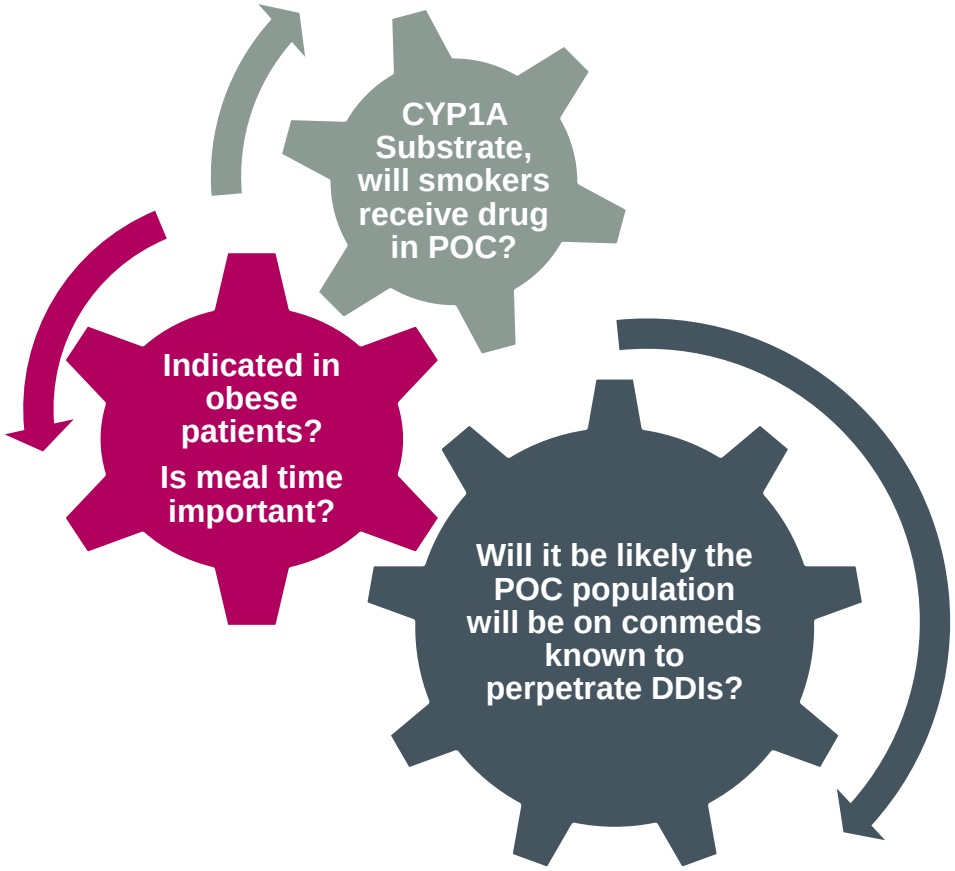
What Do We Know/Understand Regarding the Target Population?



CYP: Cytochrome P450 Enzyme
POC: Proof-of-Concept
DDI: Drug-Drug Interaction

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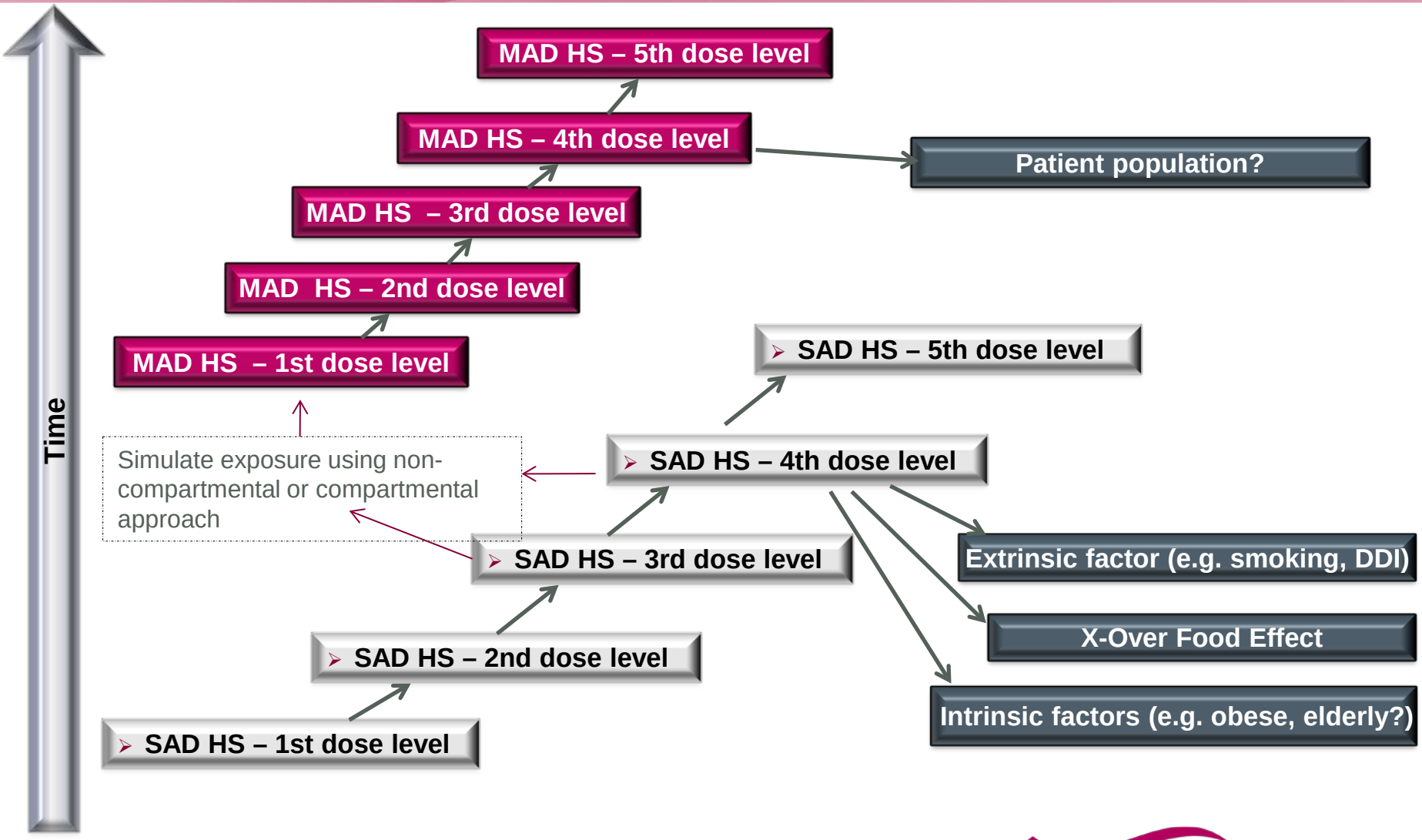
Integrate Intrinsic/Extrinsic Factors into SAD/MAD



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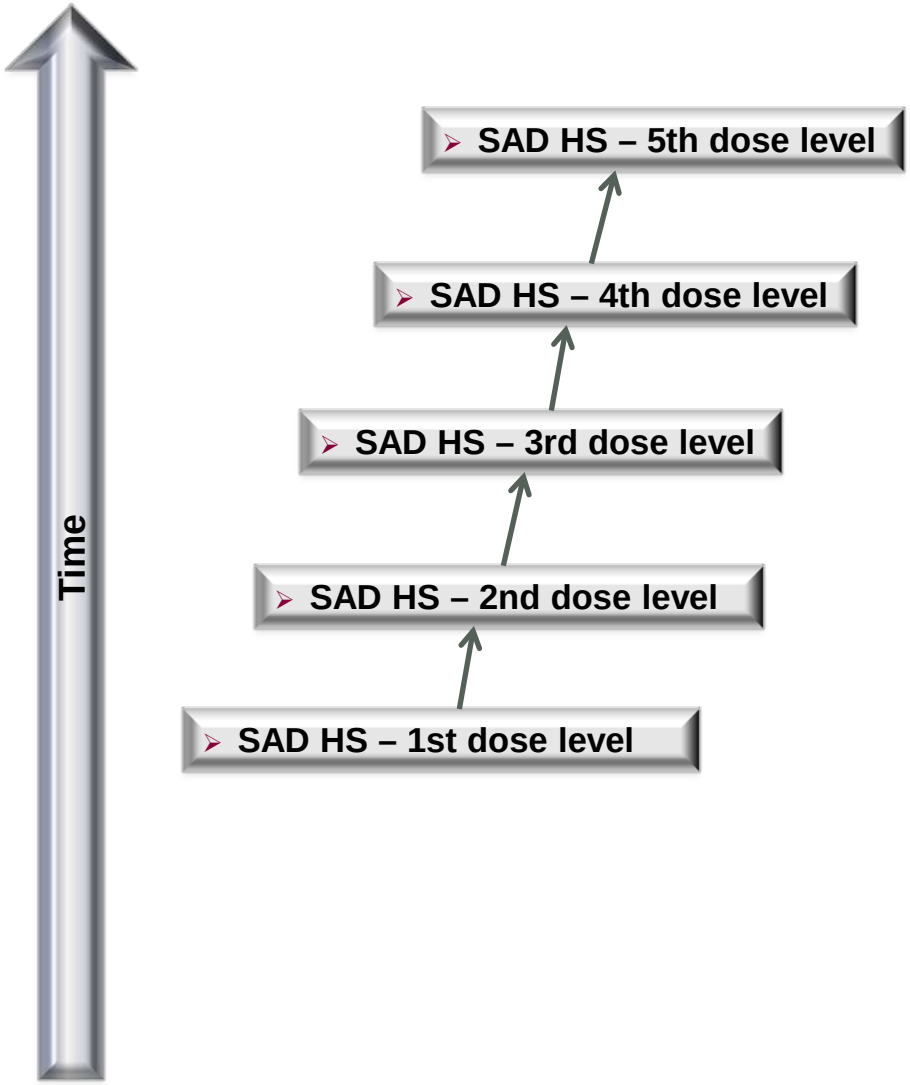
Integrate Intensive Electrocardiographic (ECG) Monitoring for Early Cardiovascular Signal



Each Cohort

- ECG Extractions
- Single 24hr Holter monitoring session
- Three triplicate baseline timepoints
- 6-9 triplicate post-dose timepoints
- Proactively plan for extended supine periods

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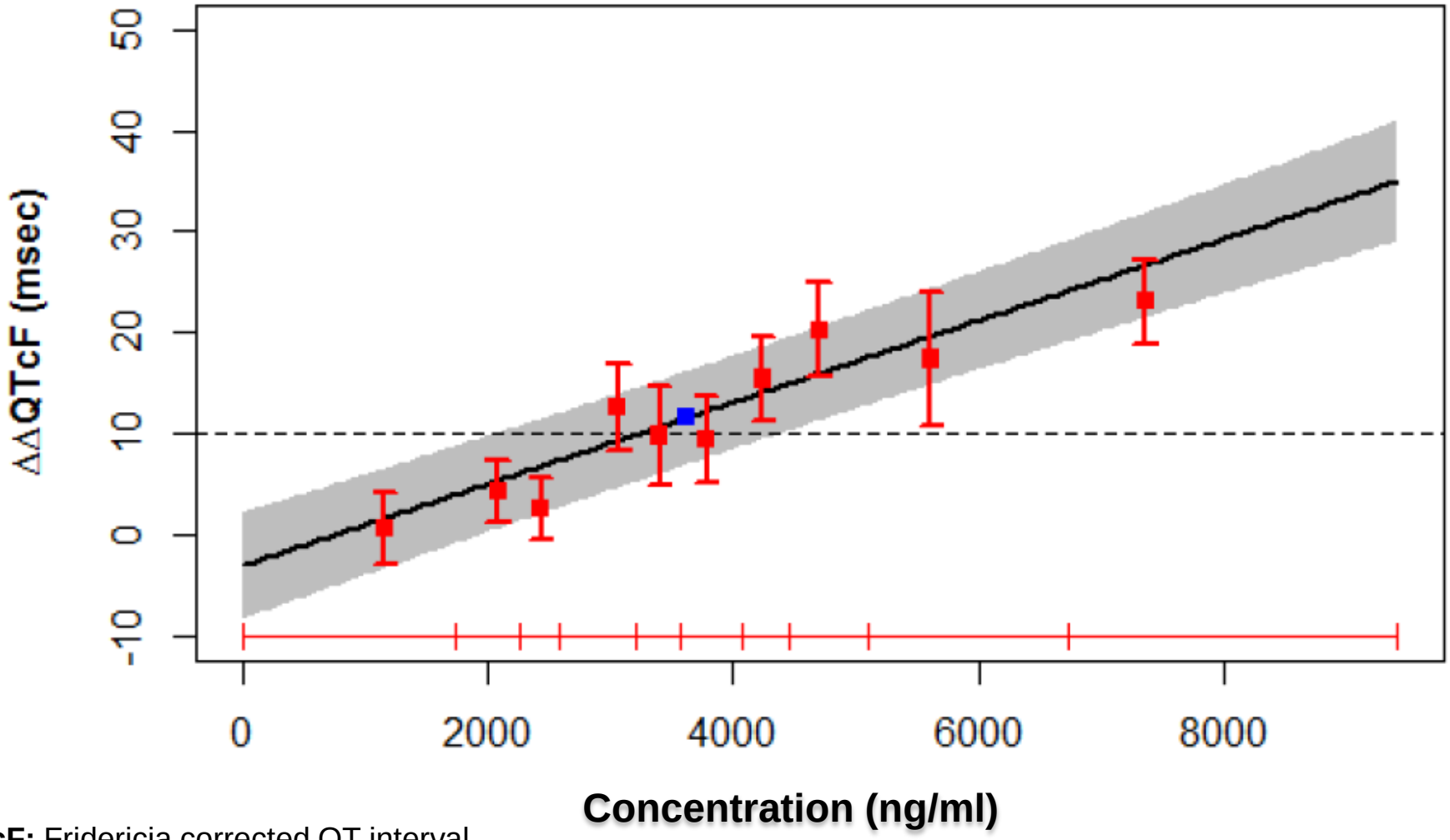
SAD Allows for Evaluation of Potentially Supra-Therapeutic Exposure



QTcF: Fridericia corrected QT interval
msec: millisecond
Δ: Greek letter 'Delta' represents change from baseline, change from placebo

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Discrete SAD & MAD Protocols with Pause Between Phases

Pros

- Low risk
- Allows for full evaluation of SAD Safety and Exposure prior to designing the MAD

Cons

- Longer duration due to not starting MAD until SAD complete
- Potentially higher cost associated with multiple protocols, CSRs, study start-up, IRB approval

CSR: Clinical Study Report
IRB: Institutional Review Board

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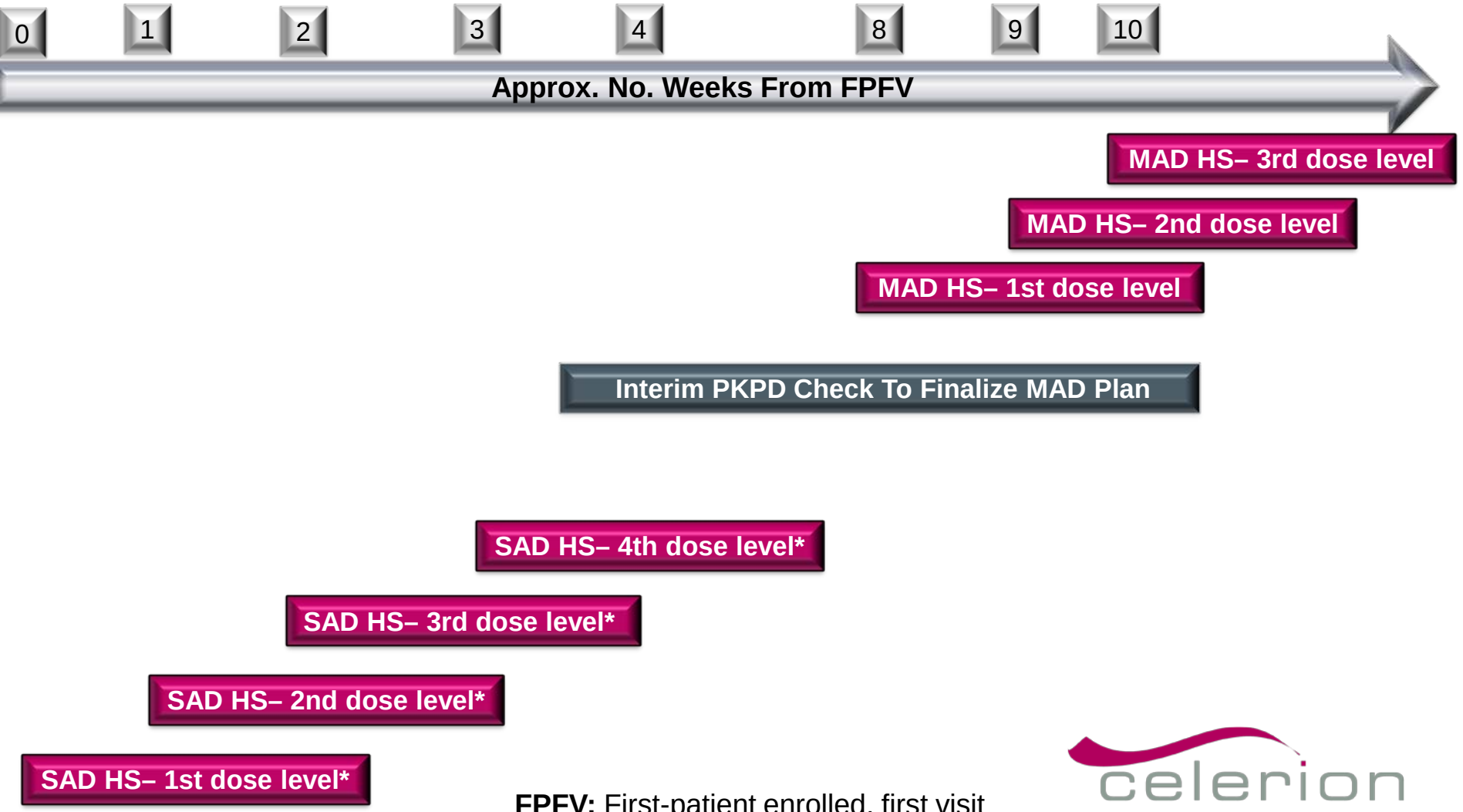
Sequential SAD/MAD Under a Single Protocol with PK Pause Between Phases



FPFV: First-patient enrolled, first visit

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Sequential SAD & MAD protocols with pause between Phases

Pros

- Cost/time savings due to single protocol, analysis plan, study start-up
- Single IRB approval
- Pause between SAD/MAD reduces risk/time/cost of amendments due to study changes based on SAD results (e.g. duration/ frequency of dosing based on exposure data)

Cons

- Longer duration than overlapping SAD/MAD
- May require additional amendments relative to sequential discrete SAD/MAD protocols

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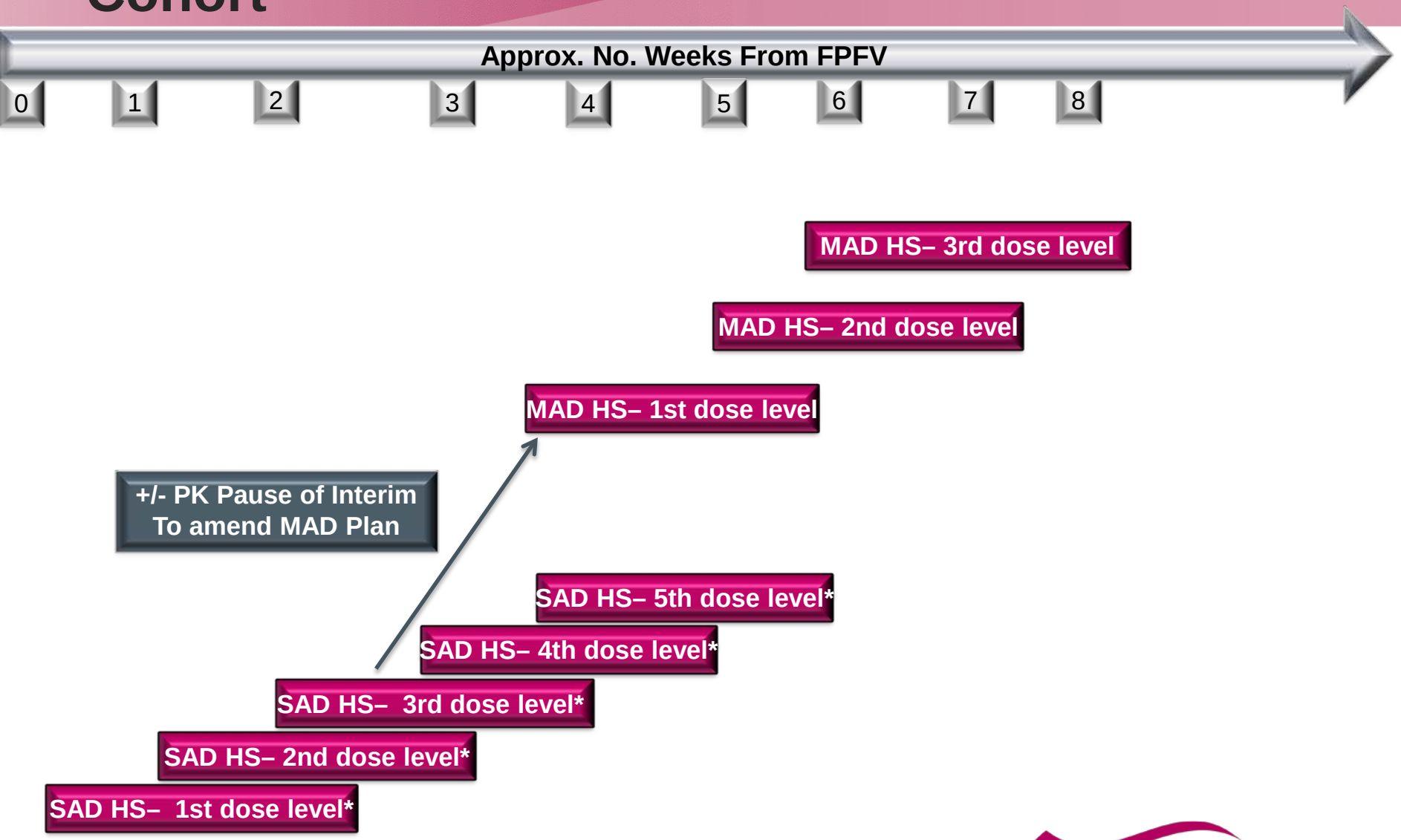
Overlap SAD MAD with Transition After 3rd SAD Cohort



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Overlap SAD MAD with Transition After 3rd SAD Cohort

Pros

- Cost/time savings due to single protocol, SAP, study start-up
- Single IRB approval
- Allows for faster transition to POC/special populations than sequential SAD/MAD
- Allows for continued exploration of single-dose evaluations while MAD on-going (intrinsic/extrinsic factor testing: elderly, obesity, smoking effects, food-effect)

Cons

- Risk is highest when little is known about exposure scaling and/or safety signals apparent in toxicology program
- Typically associated with protocol amendments (but can be mitigated by flexible/adaptive protocol construct
- Amendments may be needed for I/E, additional safety between SAD and MAD
- No true idea regarding MAD PK/Safety if transitioning without interim check

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Lessons Learned: Combined SAD/MAD

- Combining is lowest risk when more is known about the NCE
  - PK/exposure well understood and consistent across species
    - If not, definitely recommend interim PK between SAD cohort or at least one pause prior to MAD
- Failure to write protocols adaptively/flexibly results in multiple amendments & additional IRB review
    - Delay in data delivery
    - Additional costs
- Failure to confirm PK prior to MAD
    - More cohorts dosed than necessary
    - Longer duration to POC than necessary
- Desire to combine too many unrelated objectives can delay important milestones and adds risk (e.g. addition of a DDI arm adds risk to a combined SAD/MAD when PK in absence of DDI unknown and safety issues arise)

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Efficient Clinical Pharmacology Studies After FIH: Case Study

- Small molecule oncology drug being developed for several indications (including lung cancer)
- In-vitro/cell culture screening implicate CYP1A2 and CYP3A4 mediated metabolism
- IND comments from FDA specified to exclude patients on CYP 1A2 inhibitors (e.g. ciprofloxacin) & 3A4 inhibitors (e.g. clarithromycin, ketoconazole) or test before further patient studies
- Cardiac signal in dog CV study

….how can these objectives be addressed efficiently?

CYP: Cytochrome P450 Enzyme
CV: Cardiovascular

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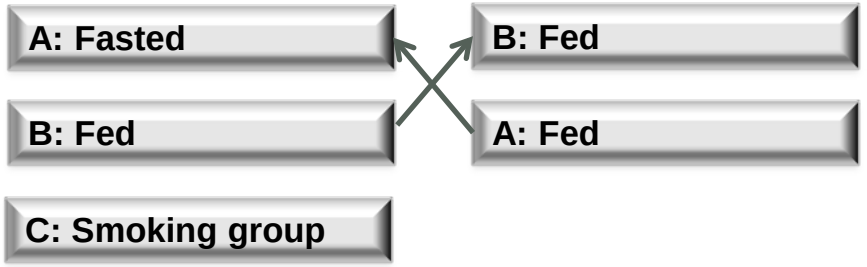
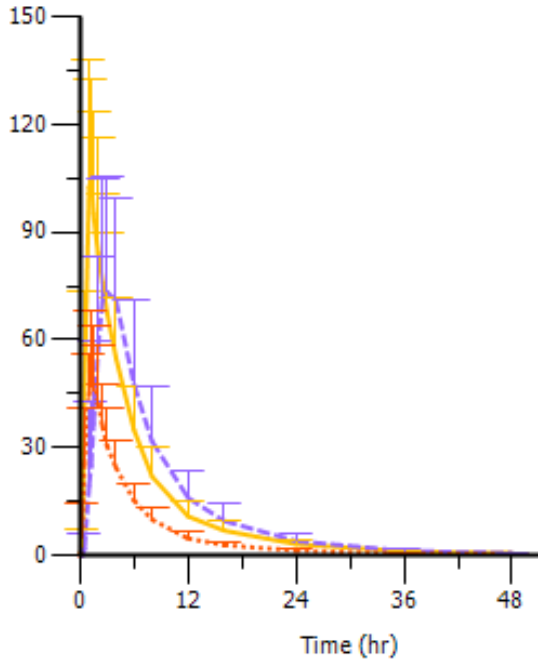
Study 1: Food-effect + Effect of Smoking (CYP1A induction)

Study 1

- 2-period single-dose x-over in HS
  - Fasted
  - Fed
- Parallel group comparison to HS moderate-heavy cigarette smokers





X-over: Crossover Design
HS: Healthy Subjects

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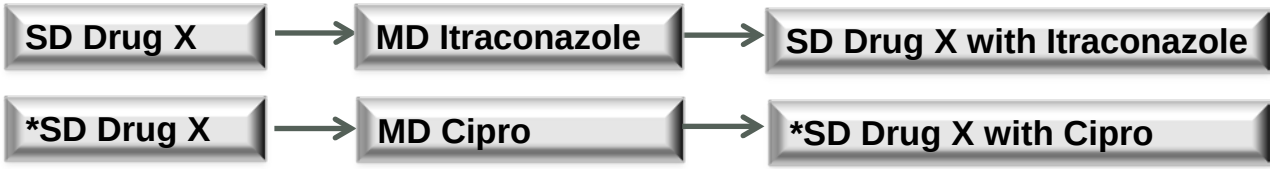
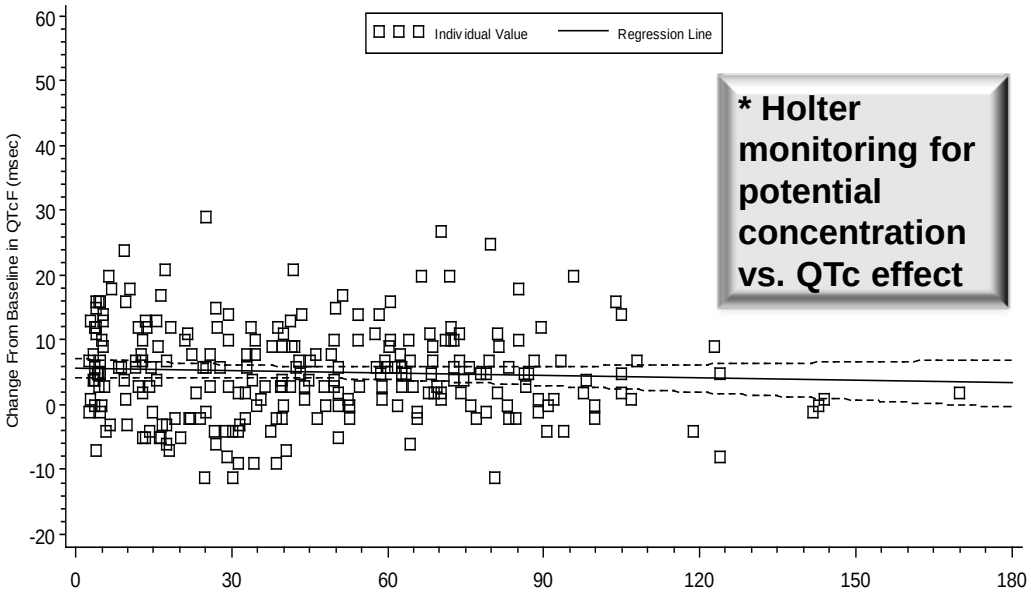
Study 2: Parallel Cohort, Fixed-Sequence DDI with Intensive ECG Monitoring



Study 2

- 2-distinct parallel cohorts
  - Fixed-sequence test of itraconazole (strong CYP3A4 inhibitor)
  - Fixed-sequence test of ciprofloxacin (strong CYP1A2 inhibitor)
  - Intensive ECG monitoring on cipro arm to test effect of higher concentrations of substrate on ΔQTcF



SD: Single-dose
MD: Multiple-dose
DDI: Drug-Drug Interaction

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Multiple DDIs Integrated into a Single Cohort

- NCE being developed for CNS indication
- In-vitro testing and PBPK simulations suggests NCE is inhibitor of MATE-2 and OCT transporters
- NCE ~7 days to achieve steady-state
- Objective to test MATE-2 and OCT probe substrates in the same study at steady-state concentrations of NCE

CNS: Central Nervous System
MATE-2/OCT: Drug Transporter

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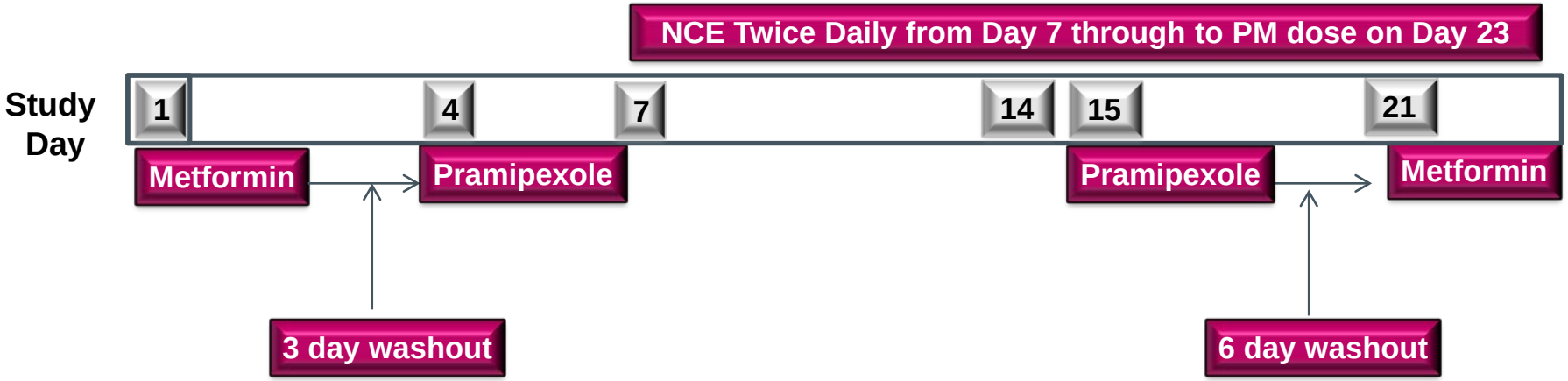
Multiple DDIs, Single Cohort



Legend

Day 1: SD Metformin 500 mg, full PK profile

Day 4: SD Pramipexole 0.25 mg, full PK profile

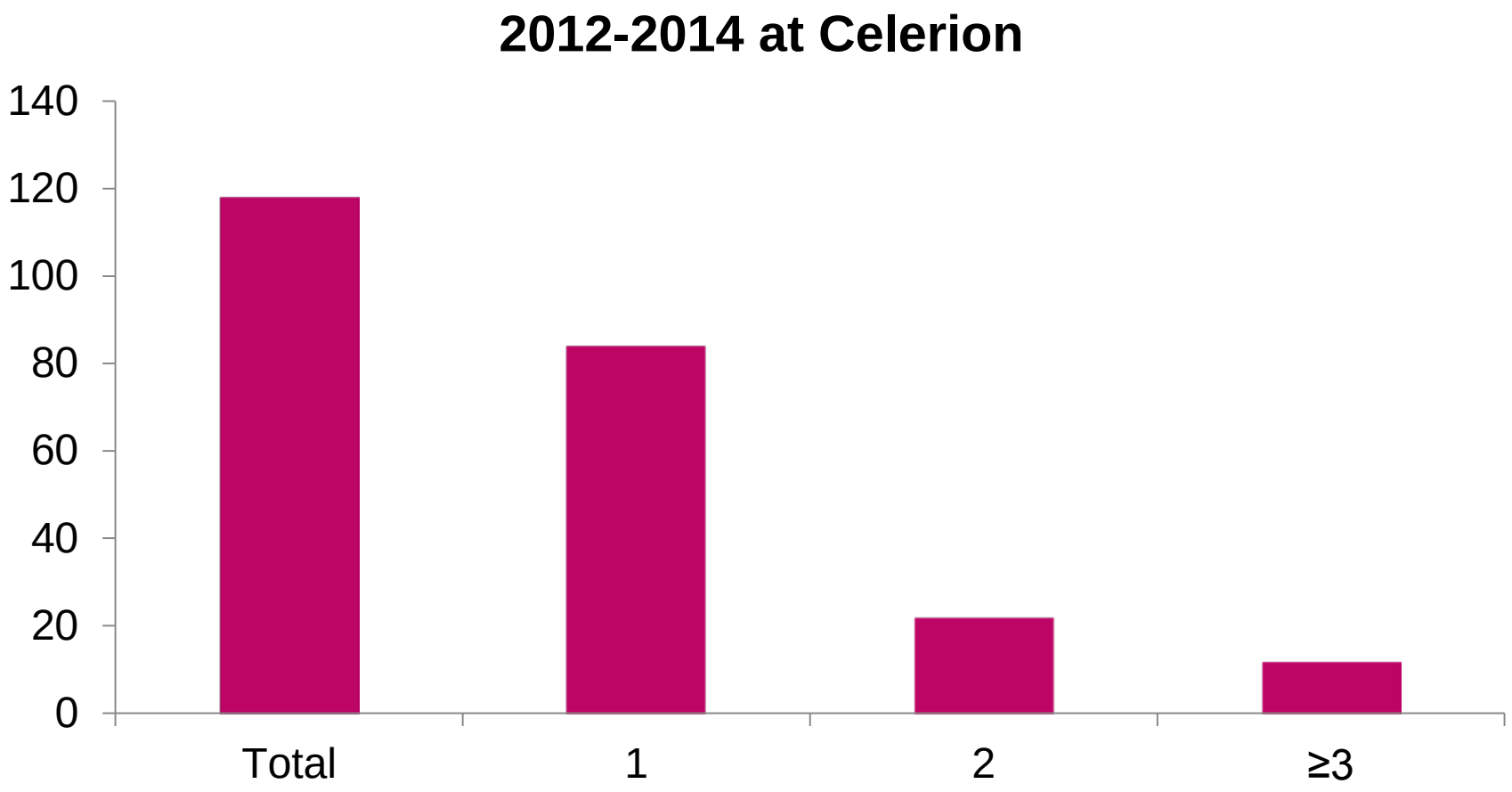
Day 7-22: NC mg twice daily (last dose is PM dose)

Day 14: PK profile of NCE over AM dosing interval

Day 15: SD Pramipexole 0.25 mg, full PK profile in presence of NCE

Day 21: SD Metformin 500 mg, full PK profile in presence of NCE

Drug-Drug Interaction Studies: Combining Objectives and Panels Under a Single Protocol



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Thank You!

ありがとうございました。