PK/PD Modeling and Simulation for Compound Progression of Antiretroviral Agents

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NEDMDG Meeting, June 8, 2006
Outline

• Background
  • HIV-1 and AIDS: Drug Development Environment
  • Pharmacologic and Clinical Determinants of Pharmacotherapeutic Success with Antiretroviral Therapy

• Modeling and Simulation
  • Objectives and Goals
  • Approach, Process and Methods
  • M&S Overlay on the Compound Progression of ARV Agents
  • Drill down to actual analyses

• Examples
  • Dose selection
  • Regimen comparison / rescue
  • Pop-PK and Clinical Trial Design

• Plan for NK1 Receptor Antagonists
  • U Penn / CHOP IPCP Grant

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**Background**

**HIV-1 and AIDS: Drug development Environment**

- 4 unique drug classes of antiretroviral agents: PIs, NRTIs, NNRTIs and entry or fusion inhibitors.
- Antiretroviral therapy with multiple agents is used to suppress viral replication reducing morbidity and mortality in HIV-1-infected patients.
- The three most commonly prescribed initial multidrug HAART regimens are a PI plus two NRTIs; a NNRTI plus two NRTIs; and NRTIs.
- HIV-infected patients usually receive a wide variety of drug in addition to their antiretroviral drug regimen.

HIV-1 life cycle and sites action of antiretroviral drugs from Pomerantz et. al.

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Background: Progression of PK/PD knowledge through the drug development process

- **Drug Molecule Characterization**
  - Physiochemical Properties
  - In vitro ADME Screening
  - Toxicology Profiling
  - Activity Screen: Drug Potency

- **Initial PK (and PK/PD) Relationships**
  - Healthy Volunteer and Patient PK: SD, MD, Food, etc
  - Human Safety: MTD, Tolerability, AE / ADR Profile
  - Drug Interactions: CYPs, genotyping / phenotyping
  - Dose-finding: Activity targets by dose group

- **Clinical Guidance Derived from PK/PD**
  - Dosing guidance in mainstream patients indicated
  - Potential for drug interactions
  - Drug monitoring strategy / guidance
  - Guidance in special populations: renal / hepatic impairment, obesity, pregnancy, pediatrics, etc.

- **Move to Clinic**
  - Pre-IND – Phase 1

- **Larger Patient Trials**
  - Phase 1 – 2B

- **Phase 2B – Approval**
Background: Progression of PK/PD knowledge through the drug development process


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Background
HIV-1 and AIDS: Drug development Environment

KEY DEVELOPMENT ISSUES

• When would we normally generate the most relevant information/data on a new agent to assess whether it offered any benefit to the existing HAART regimens?

• Can we accelerate the timing of the experiments to facilitate earlier assessment or reduce the number of assessments in order to accelerate development?

• If so, what are the risks to such a shift in the timing or number of these experiments? Is the risk acceptable?

• Are there tools to alleviate or reduce such risks?
Background
HIV-1 and AIDS: Drug development Environment

**KEY CLINICAL ISSUES**

- How potent is the agent? What is the potential for monotherapy or as an adjunctive therapy in a HAART regimen?
- How safe is the compound? Is the toxicity profile acceptable?
- Can it be administered once a day?
- What is the interaction potential?
- What is the potential / likelihood / timeline for resistance development?
**Background**

**Determinants of Pharmacotherapeutic Success**

- Active as assessed by viral RNA suppression
- Once daily, oral administration
- Low drug interaction potential
- Low or “acceptable” side effect profile
- Low or “acceptable” resistance potential
- Minimal lifestyle requirements: food, time of day administration, etc
- Formulation features (small oral dosage form; 1 tablet/capsule per dose)
- Formulation options (easy to swallow formulations for late-stage patients, non-bitter, oral suspensions for pediatrics, etc)
# Background

**HIV-1 and AIDS: Example of Dose-exposure Diversity**

<table>
<thead>
<tr>
<th>Class</th>
<th>Naming Conventions</th>
<th>PK Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Brand</strong></td>
<td><strong>Generic (Abbreviations)</strong></td>
</tr>
<tr>
<td><strong>Protease Inhibitors</strong> (PI)</td>
<td>Agenerase</td>
<td>Amprenavir</td>
</tr>
<tr>
<td></td>
<td>Crixivan</td>
<td>Indinavir sulfate</td>
</tr>
<tr>
<td></td>
<td>Kaletra</td>
<td>Lopinavir + ritonavir</td>
</tr>
<tr>
<td></td>
<td>Viracept</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td></td>
<td>Norvir</td>
<td>Ritonavir</td>
</tr>
<tr>
<td></td>
<td>Fortovase</td>
<td>Saquinavir</td>
</tr>
<tr>
<td></td>
<td>Invirase</td>
<td>Saquinavir mesylate</td>
</tr>
</tbody>
</table>
## Background

### Approach of the Past . . .

<table>
<thead>
<tr>
<th>Bioavailability</th>
<th>&lt;10%</th>
<th>10 – 50%</th>
<th>&gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>QD</td>
<td>BID</td>
<td>TID</td>
</tr>
<tr>
<td>Activity</td>
<td>YES</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>3A4</td>
<td>2D6</td>
<td>2C19</td>
</tr>
<tr>
<td>Safety</td>
<td>NO</td>
<td>YES</td>
<td></td>
</tr>
</tbody>
</table>

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**M&S: Objectives and Goals**

To define the continuity of processes which project the relevant clinical outcomes predictive of therapeutic success.

- **Activity assumptions**
  - In vitro signal / in vivo models
    - Characterization of both drug substance and drug target
  - Exposure vs Dose Correlation
  - Concentration/Dose vs Activity Correlation
- **Outcomes**
**M&S: Objectives and Goals**

- **Model validation and/or refinement**
- **Conduct trial & data analysis**
- **Optimize study design through simulation work**
- **Forecast exposure or response at target doses**
- **Simulate alternative what-if scenarios:**
  - Quantify risk in patients
  - Design additional in vitro and/or clinical work as needed for development
- **Develop dose-exposure & exposure-response models**
  - Identify model uncertainties
- **New Drug**
  - Generate in vitro data in microsomes, hepatocytes or S9 fraction:
    - Metabolic stability
    - Enzyme identification
    - Inhibition potential
    - Induction potential
  - Determine physico-chemical properties:
    - pKa, LogD
    - Lipophilicity
    - Solubility
    - Protein binding
    - Tissue partitioning
    - Caco2 perm & P-gp
  - In vivo bioavailability
  - In vivo biomarker data

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Modeling and Simulation Approach

Dose-Exposure Model
- Variation in systemic and peripheral (organ) exposure with dose and time
  - Correlation of systemic and peripheral exposure
  - Dose proportionality
  - Interaction potential
  - Body-size / age dependency

Concentration-Effect Model
- Correlation between exposure and toxicity occurrence and severity
- Covariance of patient factors with exposure variation
Modeling and Simulation Approach

Clinical Trial Model
• Early projection of a drug molecule’s expected clinical performance, trial design testing, specific scenarios (altered PK, PD, adherence, etc)
  • Trial Design Scenarios
  • Population Properties
  • Treatment Properties
  • Observation Properties
  • Protocol Deviation Scenarios
Models are not static. They evolve with the development phase (i.e., as new and more informative data is generated)

**EXAMPLE: PK Model Evolution**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Available Data</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>Structure-activity, physiochemical data</td>
<td>“Druggability” estimate, screening based on absorption potential, PB or half-life; Tox correlation</td>
</tr>
<tr>
<td>Pre-clinical</td>
<td>Animal PK, <em>in vitro</em> metabolism, formulation info.</td>
<td>Project human doses; verify animal scaling potential; IVIVE; assessment of drug delivery</td>
</tr>
<tr>
<td>Clinical</td>
<td>Healthy volunteer / patient PK across dose and regimen</td>
<td>Assessment of <em>in vivo</em> performance potential – optimal input profile</td>
</tr>
</tbody>
</table>
Modeling and Simulation
Methods

EXAMPLE: PK Model Evolution – Discovery-stage Model

Tools: In silico ADME algorithms (e.g., Pre-ADME, KnowItAll® ADME/Tox; SimCYP; GastroPLUS)

Inputs: Chemical structure, molecular descriptors

Outputs: Molecular descriptors, ADME properties (permeability for Caco-2 cell, MDCK cell and BBB, HIA, plasma protein binding and skin permeability)

Methodologies: Neural Net (Bayesian and back propagation), logistic regression, NLMEM, Monte Carlo Simulation, etc

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Modeling and Simulation Methods

KnowItAll® ADME/Tox
Both GSK and Pfizer report good performance with \textit{in silico} ADME prediction with respect to HTS.
Modeling and Simulation
Methods – Does this work

Still a work in progress
Modeling and Simulation Methods

APPLICATION – Discovery-stage Model

- Obtain absorption potential, PB, CYP potential from *in silico* ADME software
- Estimate CL and Vd in various animal species and man – *Note: physiological-based models easiest to extrapolate.*
- Construct simple PK (1, 2 CPMs w/ and w/o nonlinear elimination if suspect) or PBPK models
- Examine dose and regimen effects on systemic profiles using Excel, WinNonlin or NONMEM
Modeling and Simulation
Methods

EXAMPLE: PK Model Evolution – Preclinical Model

\[ P = A w^k. \]

Next we take logarithms to obtain:

\[ \ln(P) = \ln(A) + k \ln(w). \]

As noted above, this is a straight line in \( \ln(P) \) and \( \ln(w) \) with slope of \( k \) and intercept of \( \ln(A) \). From the data,

<table>
<thead>
<tr>
<th>Animal</th>
<th>Weight (kg)</th>
<th>( \ln(w) )</th>
<th>Pulse (beats/min)</th>
<th>( \ln(P) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>0.017</td>
<td>-4.075</td>
<td>500</td>
<td>6.215</td>
</tr>
<tr>
<td>Human</td>
<td>68</td>
<td>4.220</td>
<td>65</td>
<td>4.174</td>
</tr>
</tbody>
</table>

The slope \( k \) is given by:

\[ k = \frac{4.174 - 6.215}{4.220 + 4.075} = -0.246 \]
EXAMPLE: PK Model Evolution – Preclinical Model

We can use this slope with one of the points to find $\ln(A)$ as follows:

$$\ln(A) = -k \ln(w_0) + \ln(P_0) = 0.246 \times 4.220 + 4.174 = 5.212$$

Thus,

$$\ln(P) = -0.246 \ln(w) + 5.212$$

$$P = 183.5w^{-0.246}$$

If we use the first equation with a 1.34 kg rabbit, then it gives $P = 171$. 
**Modeling and Simulation Methods**

**EXAMPLE:** PK Model Evolution – Clinical Model

**Tools:** Population-based PK/PD models and adherence models: NONMEM, NLME, NPEM, etc

**Inputs:** Concentration-time, dose, patient covariates, biomarkers (CD4, viral RNA), safety and PK parameters, etc.

**Outputs:** PK, PD, outcome parameters

**Methodologies:** Nonlinear regression, NLMEM, ANOVA, ANCOVA, etc
Modeling and Simulation

Methods

APPLICATIONS

• Variation partition: identification of factors which explain variability (patient/lifestyle factors)
• Exposure-response correlation (viral dynamics)
• Correlates of therapeutic success (adherence modeling)
• Simulations to explore optimal conditions (dosing, population, combinations, etc)
Examples
Dose–response relationship of emtricitabine was analyzed using a simple $E_{\text{max}}$ model as:

$$E = \frac{E_{\text{max}} \times \text{dose}}{\text{ED}_{50} + \text{dose}},$$

where $E_{\text{max}}$ is the maximal antiviral activity, $\text{ED}_{50}$ is the dose required to produce 50% of the maximal antiviral activity. The effect parameter used for antiviral activity was median AAUCMB (average area under the viral load–time curve minus baseline) to day 15 and the dose parameter was the total daily dose of emtricitabine.
Examples
Dose Selection


• Based on Pop-PK model from HIV-1 Infected patients
• Underpinning assumptions were as follows:
  • (i) Time _ Threshold (EC90) is the pharmacodynamically linked variable for NNRTIs;
  • (ii) Protein binding needs to be taken into account;
  • (iii) the free drug needs to exceed the EC90, not just the EC50, to develop full antiviral effect; and
  • (iv) steady-state pharmacokinetics in volunteers is an accurate reflector of steady-state pharmacokinetics in patients.
Examples
Dose Selection


- Simulations guide dose selection
- Percentage of subjects with trough free concentration > 10x the EC50 for HIV activity.
Examples
Rescue Therapy – Regimen Comparison

Based on Pop-PK model from HIV-1 Infected patients
Exploration of time course above IC90 for QD, BID and TID regimens
Examples
Rescue Therapy – Regimen Comparison

Figure 2. Simulated Efavirenze Patient Plasma Profiles following 300 mg q12h (Mean and Percentiles) from Monte Carlo Simulation (n=100) of Population Parameter Estimates
Examples
Adherence Modeling

• Hierarchical Markov used to model to describe adherence patterns of patients with TID zidovudine treatment. Adherence behavior is illustrated in Figures 1 and 2. Sequences of dose times transformed into ‘data’ vectors and observed dose times modeled for a specific patient in terms of three components:
(i) Nominal times that the patient takes his medication;
(ii) Number of doses he takes at each of these times denoted \( n \); and
(iii) The differences between actual dose-taking times and the nominal times with which they are associated, denoted \( \Delta \).

• Analysis strategy was, for computational convenience, to estimate individual-specific nominal times in a first stage, condition on these to create observed data \( \Delta \) and \( n \), define a population model for these data using the decomposition
\[
p(n, \Delta) = p(n)p(\Delta | n)
\]
and then in a second stage fit this model to the data by maximum likelihood.

Examples
Population PK/PD

- Ritonavir inhibits the hepatic metabolism of indinavir, prolonging the half-life
- With combination, indinavir can be given BID instead of TID and with food.

### Pharmacokinetics and pharmacodynamics of indinavir

**Table 1. Demographics of the patients**

<table>
<thead>
<tr>
<th></th>
<th>Indinavir 800 mg every 8 h</th>
<th>Indinavir 800 mg + ritonavir 100 mg every 12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>13/6</td>
<td>12/5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34 (30–36)</td>
<td>36 (32–41)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>60.5 (52.7–67.5)</td>
<td>59.2 (54.2–73.6)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.68 (1.62–1.73)</td>
<td>1.63 (1.55–1.79)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.69 (1.53–1.78)</td>
<td>1.63 (1.55–1.79)</td>
</tr>
<tr>
<td>CD4 cell count (mm³)</td>
<td>84 (16–315)</td>
<td>207 (69–265)</td>
</tr>
<tr>
<td>Viral load (log₁₀ copies/mL)</td>
<td>4.1 (3.4–4.5)</td>
<td>4.0 (3.6–4.3)</td>
</tr>
</tbody>
</table>

Data are medians with interquartile ranges in parentheses.

**Figure 1.** Indinavir plasma concentration versus time curves of both regimens. Data are median values.

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Examples
Population PK/PD

- Noncompartmental PK calculated in Excel
- Correlation of PK metrics with bodyweight explored by least squares regression analysis

Figure 2. (a) Correlation between body weight and indinavir AUC in both regimens; (b) correlation between body weight and indinavir $C_{max}$ in both regimens.
Examples
Population PK/PD

- Virologic and safety/toxicity calculated by ROC analysis
- Mann-Whitney U and Pearson chi-square tests used for subgroup analysis

**Table 3. Pharmacokinetic-pharmacodynamic relationships between indinavir and virological failure or nephrotoxicity**

<table>
<thead>
<tr>
<th></th>
<th>Virological failure</th>
<th>Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>breakpoint (mg/L)</td>
<td>N</td>
</tr>
<tr>
<td><strong>Indinavir 800 mg every 8 h</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (mg·h/L)</td>
<td>&lt;14</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>&gt;14</td>
<td>13</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>&lt;7.0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>&gt;7.0</td>
<td>13</td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (mg/L)</td>
<td>&lt;0.10</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>&gt;0.10</td>
<td>13</td>
</tr>
<tr>
<td><strong>Indinavir 800 mg + ritonavir 100 mg every 12 h</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (mg·h/L)</td>
<td>&lt;42</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&gt;42</td>
<td>13</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;min&lt;/sub&gt; (mg/L)</td>
<td>&lt;0.25</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;0.25</td>
<td>15</td>
</tr>
</tbody>
</table>
**NK1 Receptor Antagonism**
*A New Mechanism for HAART?*

**Neurokinin-1R (SP Receptor) Antagonists for HIV Therapy**

Overall goal of Integrated Preclinical/Clinical Program (IPCP) is to identify a neurokinin-1 receptor (substance P preferring receptor) antagonist that is:

1. **Active as an anti-HIV agent through interaction with chemokine/cytokine receptors** *(Project 1)*;
2. **Specific for chemokine and G-protein coupled receptors** *(Project 2)*;
3. **Safe for use in SIV-infected non-human primates and provides proof of concept related to antiviral, immunomodulatory, and neurobehavioral effects** *(Project 3)*; and,
4. **Safe in HIV-infected humans and provides positive immunomodulatory effects, in particular through innate immunity and natural killer cells** *(Project 4)*.
**NK1 Receptor Antagonism**

**A New Mechanism for HAART?**

**Grant Goals**

- Demonstrate the safety, pharmacokinetics and therapeutic potential of an NK-1R antagonist (aprepitant or alternative) in SIV infection in the Rhesus macaque (Project 3).

- Determine safety of an NK-1R antagonist (aprepitant or alternative) in relation to toxicity and effects on HIV viral load in a Phase I study of adults with HIV infection (Project 4).

- All projects contribute to understanding the basic virologic, molecular and cellular immunologic mechanisms of SP, NK-1R antagonists, and HIV/SIV infection.
NK1 Receptor Antagonism
M&S Drivers

A key component of this IPCP is the linkage between the translational science coupled with modeling and simulation techniques to aid in . . .

1. Ranking of various preclinical candidates,

2. Criteria for advancement to animal pharmacologic testing (proof-of-principle / proof-of-mechanism),

3. Evaluation of drug properties which constitute suitable criteria for advancement to human testing, and

4. Specific experimental and study design features which will permit specific, hypothesis-driven evaluation of the clinical utility of neurokinin-1 receptor antagonism as a treatment modality in patients infected with HIV-1.
NK1 Receptor Antagonism
M&S Drivers: Target Drug Exposure

Empirical Dose Calculation

\[
Dose_{\text{target}} = \frac{EC_{\text{target}} \times 24(\text{hr}/\tau) \times CL}{F}
\]

\[
Dose_{\text{load}} = EC_{\text{effective}} \times V_{ss}
\]

Required information:

- PK parameters
  - CL
  - V
  - F

- Target concentrations
  - EC\text{50}, C_{\text{effective}}
Aprepitant inhibits HIV-1 infection of MDM by down regulating CCR5 expression.
NK1 Receptor Antagonism
Defining Target Exposure for Aprepitant

Preclinical data support single agent activity and demonstration of synergistic effects when given in combination with clinically relevant agents (including HAART agents).

Inhibition of HIV (Bal) Infection of MDM by NK-1R Antagonists (10-6 M)
NK1 Receptor Antagonism
M&S Drivers – Preliminary Data

Allometric modeling with aprepitant
• Interpolation of monkey PK for SIV dosing strategy
• Human Phase 1B dose selection

Table 1. Interspecies Pharmacokinetic Data with Aprepitant

<table>
<thead>
<tr>
<th>Species</th>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat(^a)</td>
<td>CL (mL/min/kg)</td>
<td>13.4 ± 2.6</td>
<td>Huskey et. al., Drug Metab Disposit, 1999 [31]</td>
</tr>
<tr>
<td></td>
<td>Vdss (L/kg)</td>
<td>2.8 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Dog(^a)</td>
<td>CL (mL/min/kg)</td>
<td>0.9 ± 0.2</td>
<td>Huskey et. al., Drug Metab Disposit, 1999 [31]</td>
</tr>
<tr>
<td></td>
<td>Vdss (L/kg)</td>
<td>0.9 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Ferret</td>
<td>CL (mL/min/kg)</td>
<td>1.5 ± 0.1</td>
<td>Huskey et. al., Drug Metab Disposit, 2003 [32]</td>
</tr>
<tr>
<td></td>
<td>Vdss (L/kg)</td>
<td>1.3 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Human(^b)</td>
<td>AUC(_{0-24h})</td>
<td>19455</td>
<td>Aprepitant NDA (# 21-549) [33]</td>
</tr>
<tr>
<td></td>
<td>(ng*h/mL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NK1 Receptor Antagonism
M&S Drivers – Preliminary Data

Direct Comparison: Monkey vs Human Exposure

Aprepitant Exposure in Healthy Volunteers (N=12)
Following Standard CINV Dosing

Cynomologous Monkeys (n=3)
80 mg Aprepitant p.o. QD over 14 days

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**NK1 Receptor Antagonism**
**M&S Drivers – Preliminary Data**

Projecting Doses in HIV Patients – Current Projection

Aprepitant Exposure in Healthy Volunteers (N=12) Following Standard CINV Dosing

Prior Information:
- Inhibition of HIV Bal strain in MDM by Aprepitant (10-6 M) is 79.5 %
- Assuming that the human exposure target is similar to the *in vitro* activity yields a target trough free drug concentration of ~ 500 ng/mL.
- Aprepitant is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. Seven metabolites of aprepitant (only weakly active) identified in human plasma.
- Enzyme induction reduces the exposure of aprepitant following chronic administration (not published).
- Protein binding ~ 95%
- F ~ 60-65%
- Half-life: 9-13 hours
- Elimination by metabolism; no renal
**NK1 Receptor Antagonism**

**M&S Drivers – Preliminary Data**

**Projecting Doses in HIV Patients – Current Projection**

Model Assumptions / Features:
- Induction reduces exposure by 50% at SS (↑ CL by 2-fold)
- Moderate variability in CL and V
- Staged first-order input explains absorption

Monte Carlo Simulations from Pop-PK
Simulation Model: Exposure from 375 mg QD
Administration of Aprepitant
**NK1 Receptor Antagonism**

**Compound Progression**

**PK/PD in SIV**
- Define target profile and ITW in the cynomologous monkey
- Scale doses to obtain human equivalent exposures

**PK/PD in HIV**
- Project exposure-response profile in HIV-1 infected patients
- Simulate Phase 1B exposure-response
- Conduct trial
- Evaluate Pop-PK/PD in patients
- Simulate Phase IIB Proof-of-concept trial outcomes

**COMPOUND SCREENING / SELECTION / RANKING**
- Create mol file for chemical structures under consideration
- Model NK1 and immunomodulatory activity (Projects 1 and 2)
- Project criteria for advancement based on “druggability”
- Conduct tox and pharmacology studies on viable candidates
Development Strategy for IPCP:
NK1rA Compound Progression

**In vitro**
(MDM, patient isolates, etc)
Assays
- Early screening of compounds based on IC_{50} value.
- In silico ADME screening to assess candidates based on druggability
- Based on prior experience, candidates will be selected for the next phase
- Synergy with other agents assessed; ranking of agents

Preclinical (SIV)
- In vitro IC_{50} as a guide for preclinical dose selection
- SIV PK/PD models to assess all biomarkers e.g. RNA, SP, behavioral changes and Drug conc.

**PK/PD Simulation**
- In vitro and preclinical data for clinical dose and regimen selection – integration into Phase IB protocol
- Clinical development plan

Dose optimization in HIV patients
- Pilot study - PoC and dose optimization
- E-R and ITW for HIV patients

Clinical Trial Simulation Phase IIB

Quantitative analysis

Projections about follow-on compounds

PKPD data

IC_{50}

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References


