



# Clinical Pharmacology 2: Clinical Pharmacology Considerations During Phase 2 and Phase 3 of Drug Development

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Food and Drug Administration



## ■■■ Objectives

- Describe information needed to interpret clinical significance of factors that alter drug exposure
- Discuss the need to evaluate specific populations
- Discuss Phase 2 and Phase 3 drug development decisions that are affected by drug interaction information
- Understand the impact of complete and incomplete clinical pharmacology programs on information available to health care providers

## ■ ■ ■ Outline

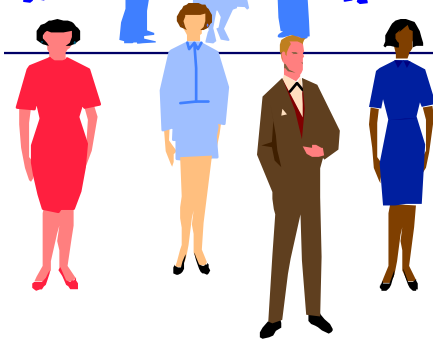
- **The goals of a clinical pharmacology program throughout drug development**
- **The value of exposure-response information**
  - **specific situations when the information is valuable**
- **Barriers to informative exposure-response evaluation**
- **Case studies (drug interactions)**
- **Conclusions- relevance and impact**

# ■ ■ ■ The Ultimate Goal



**RIGHT  
DRUG**

**RIGHT  
PATIENT**



**RIGHT  
DOSE**

**RIGHT  
TIME**



# ■ ■ ■ Phases 2 & 3 of Drug Development

## Phase 2 studies

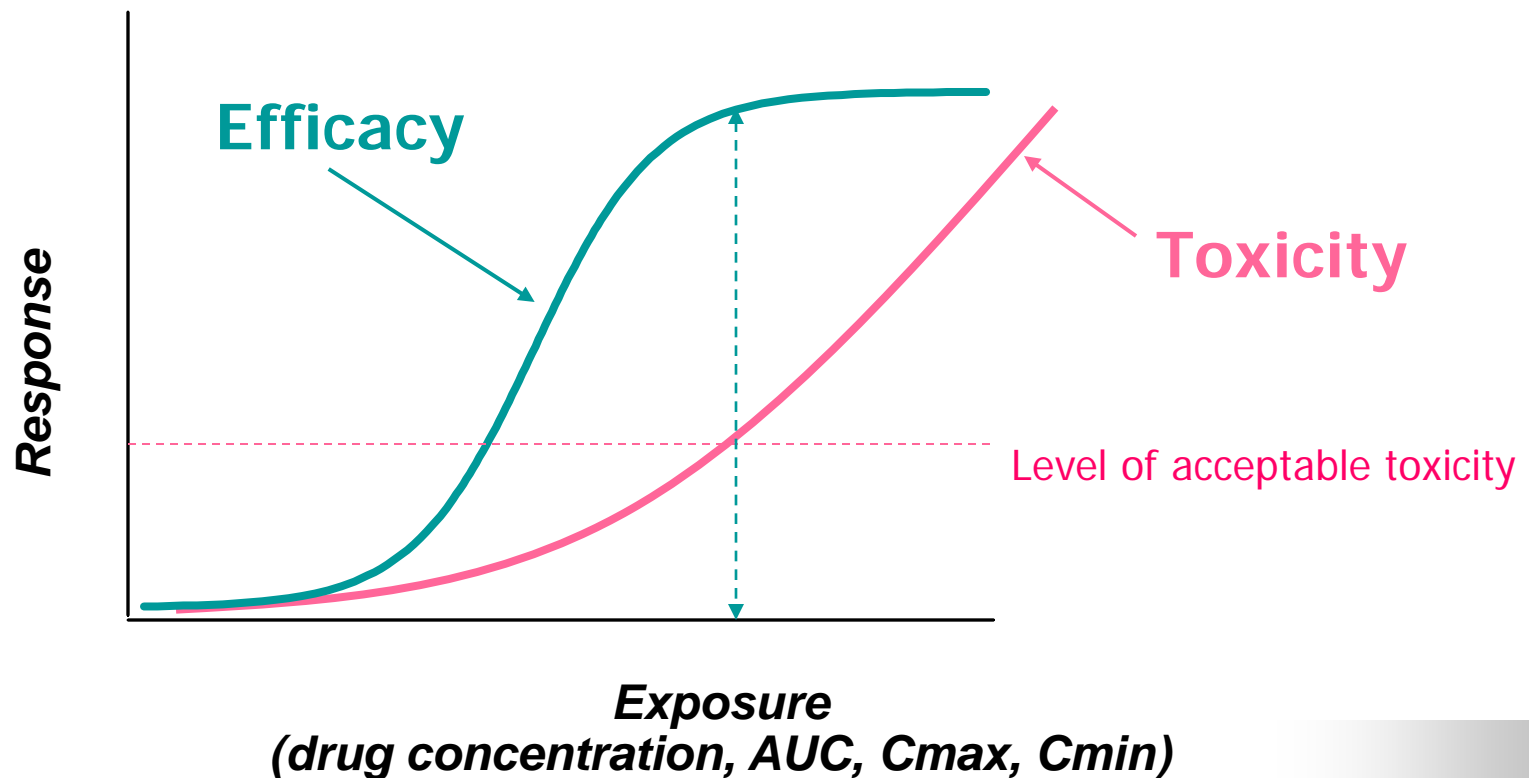
- provide preliminary data on the effectiveness of the drug
- allow selection of appropriate dose range for evaluation in Phase 3

## Phase 3 studies

- provide pivotal information about effectiveness and safety
- allow evaluation of the overall benefit-risk relationship of the drug

# ■ ■ ■ Exposure-response relationship

- Determine relationships for safety and efficacy in phase 2 and phase 3





# The value of exposure-response information



# **Add to weight of evidence supporting efficacy and safety**

- **Allow better understanding of clinical trial data**
- **Explain results based on concentration data and knowledge of exposure-response relationship**
  - **Resolve safety concerns**
  - **Understand or support evidence of subgroup differences**



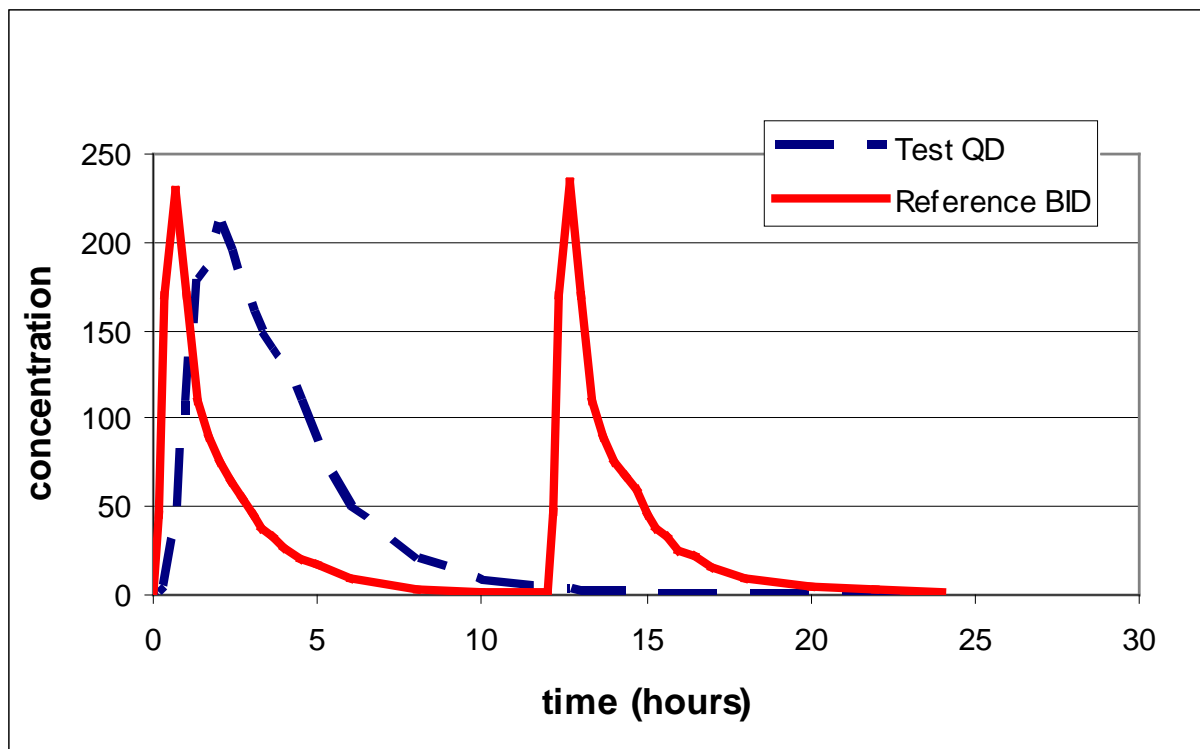


## **New drug administration scenarios**

- **New dosing regimen (e.g., BID to QD)**
- **New dosage form or formulation**
- **New route of administration**

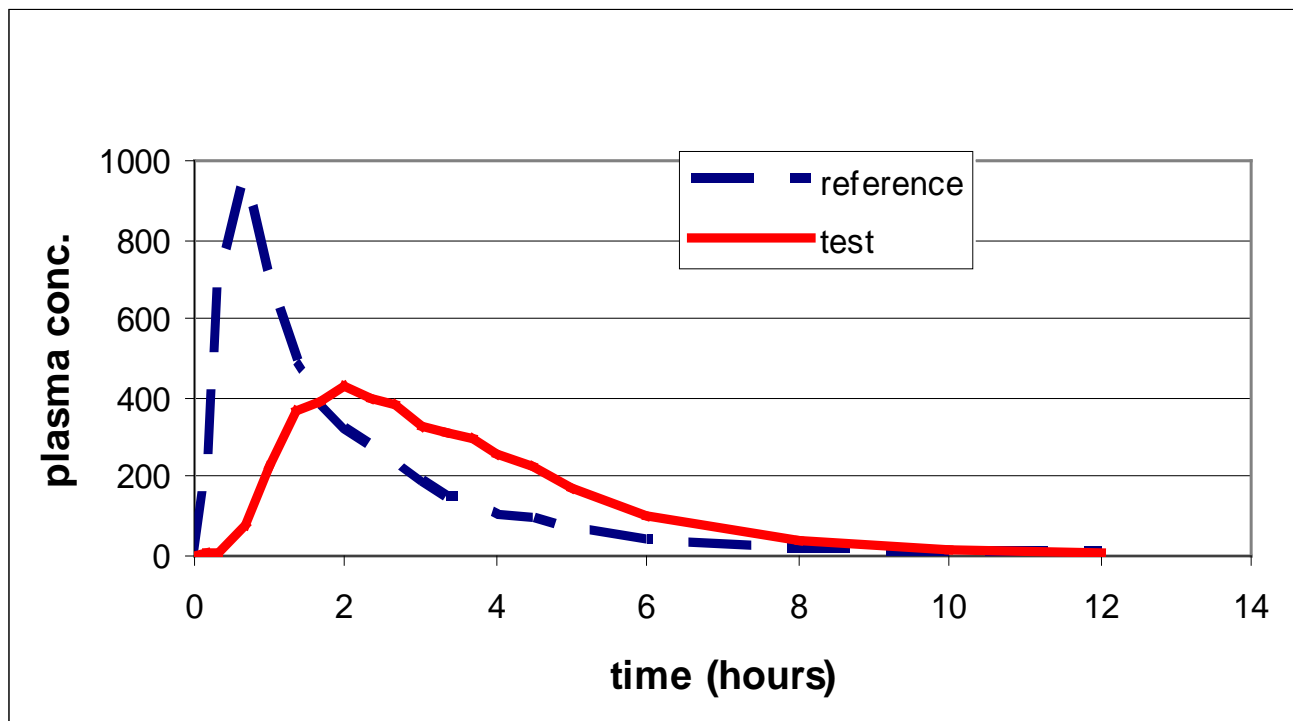


# New Dosing Regimen





# New Formulations



# New Populations or Specific Populations

## EXAMPLES-

- **Age groups**
  - Elderly
  - **Pediatric (decision tree)**
- **Renal or Hepatic Impairment**
  - consider phase 1 results
  - can collect exposure data in Phases 2 and 3
- **Women**
- **May not be possible to adjust the dose to achieve similar AUC, C<sub>max</sub> and C<sub>min</sub> as in previous population**

# Pediatric Study Decision Tree



Reasonable to assume (pediatrics vs adults)  
-- similar disease progression?  
-- similar response to intervention?

NO

-- Conduct PK studies  
-- Conduct safety/efficacy trials

YES TO BOTH

Reasonable to assume similar concentration-response (C-R) in pediatrics and adults?

NO

Is there a PD measurement that can be used to predict efficacy?

NO

-- Conduct PK studies to achieve levels similar to adults  
-- Conduct safety trials

YES

YES

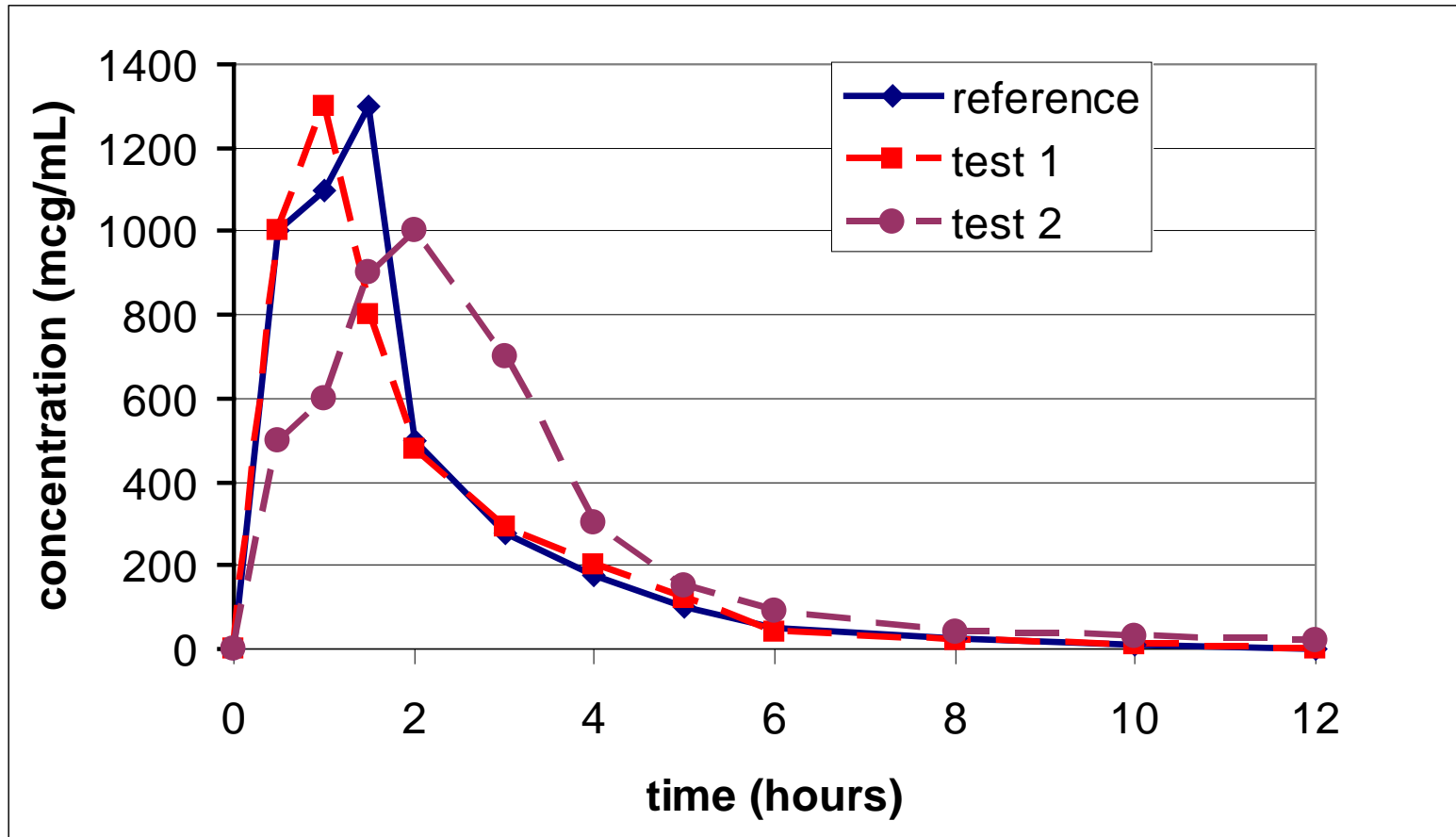
-- Conduct PK/PD studies to get C-R for PD measurement  
-- Conduct PK studies to achieve target conc. based on C-R  
-- Conduct safety trials



# ■■■ Bioequivalence (BE) Studies

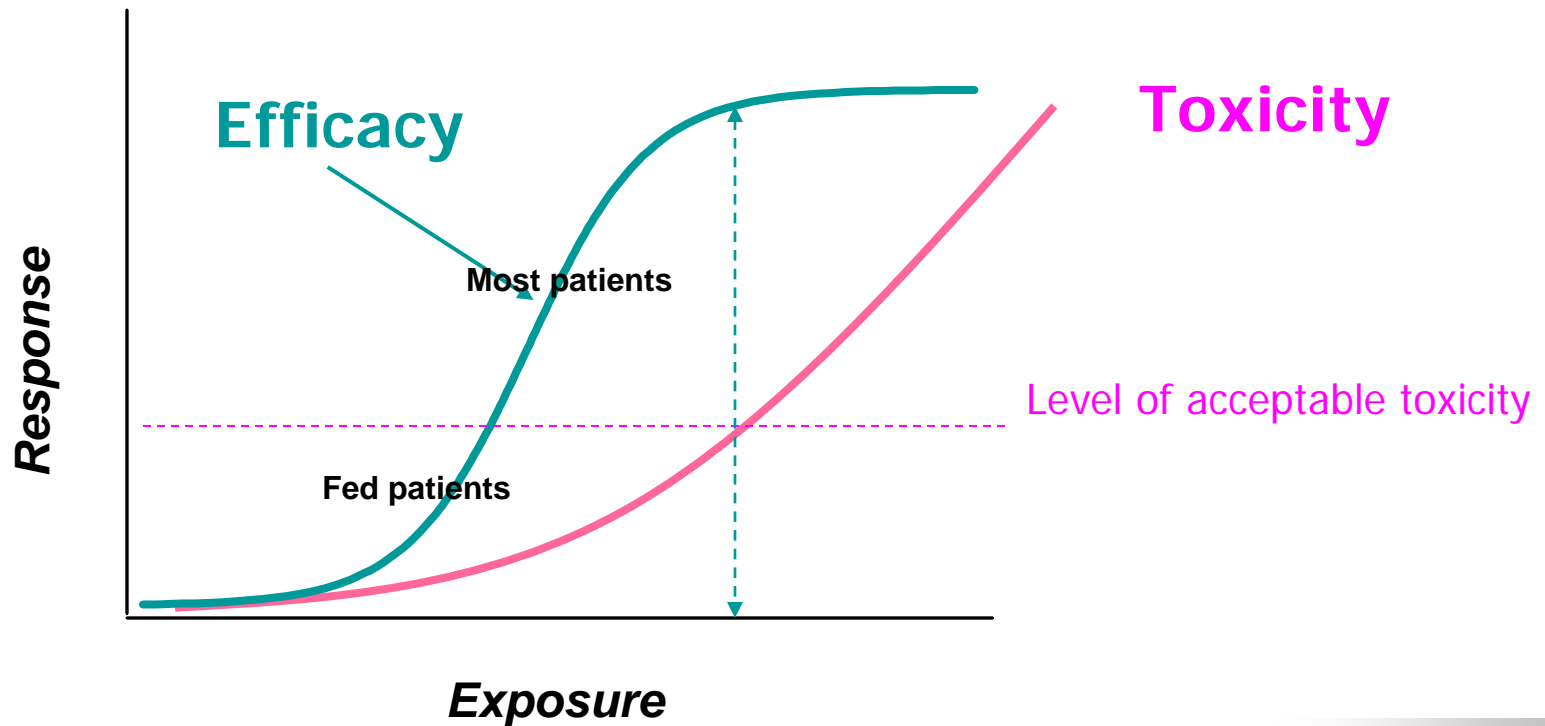
- **(Pivotal BE) Formulation change after phase 3 studies are complete**
- **Alter formulation of active control (blinding)**
- **For valid phase 3 results**
  - **need to determine whether the formulation change alters exposure**
  - **if exposure changes, are the changes clinically relevant?**

# ■■■ Bioequivalence



# ■ ■ ■ Impact of food effect

- Administration of drugs with food may....
  - Alter drug concentrations (increase or decrease)
  - Alter efficacy and safety
- A possible scenario.....







# Impact of food effect

## Possible sequence of events...

- **First food effect study: no effect of food**
- **Phase 2 studies allow administration with or without food; evaluate a range of doses**
- **Formulation change prior to Phase 3**
  - **New formulation is not bioequivalent to old formulation, but it is possible to select a dose for Phase 3**
- **New formulation is administered without food restrictions in Phase 3**



# Impact of food effect

## Possible sequence of events...

- **Food effect study conducted in parallel with Phase 3 trials**
  - Food decreases AUC and C<sub>max</sub> by 30%
- **The results of the Phase 3 study (conducted with no food restrictions) are positive: the drug is safe and effective**
  - Can we conclude that the food effect is not clinically significant?



# Impact of food effect

## Possible sequence of events...

- ..... Can we conclude that the food effect is not clinically significant?
- To answer the question, consider-
  - How often was drug given with food/without food
  - Exposure-response relationship



# Barriers to informative exposure-response evaluation



# Barriers to informative exposure-response evaluation

- **Exposure data are not collected in late phase 2 or phase 3**
- **Study design flaws**
- **Study conduct flaws**

# ■■■ Study Design Flaws

- **Under-powered for study objectives**
- **Doses**
  - too few
  - doses too close together
- **Plasma samples**
  - inappropriate timing
  - insufficient number
  - sample for only one drug in multidrug therapy

# ■■■ Flaws in Conduct of Study

- **Poor record-keeping**
  - dosing times
  - plasma sample times
- **Analytical methods**
  - bioanalytical method for PK unacceptable



# Two case studies



# ■ ■ ■ Case 1- Maraviroc

- **HIV CCR5 inhibitor**
- **Indication: treatment of HIV infection in patients infected with CCR5-tropic HIV-1 virus**

# ■ ■ ■ Maraviroc

## Phase 2b/3 Dose Selection

- Phase 2a conclusion (Viral dynamic modeling; **exposure-response evaluation**)
  - Evaluate maraviroc 300 mg qd and 300 mg bid in Phase 2b/3
- Drug interaction data
  - Maraviroc is a CYP3A substrate
  - **Other drugs in antiretroviral regimen may increase or decrease maraviroc concentrations**
  - Maraviroc does not affect concentrations of other drugs

# ■ ■ ■ Maraviroc

## Phase 2b/3 Dose Selection

### Drug interaction results

- **Effect of other drugs on maraviroc**
  - CYP3A inhibitors- **↑maraviroc concentrations 3-11 x**
  - CYP3A inducer (efavirenz)- **↓maraviroc concentrations by 50%**
  - CYP3A inducer (nevirapine)- little effect on maraviroc concentrations
  - CYP3A inhibitor and inducer- **↑maraviroc concentrations**

# ■■■ Maraviroc Phase 2b/3 Doses

**Doses were selected based on exposure-response information and drug interaction study results**

<b>Concomitant medications</b>	<b>Maraviroc Phase 2/3 dose (q.d or b.i.d.)</b>
<b><u>CYP3A inhibitor</u> (with or without CYP3A inducer), including Protease inhibitor (except tipranavir/rtv)</b>	<b>150 mg</b>
<b><u>CYP3A inducers</u> (efavirenz)</b>	<b>600 mg</b>
<b><u>Other</u> concomitant medications</b>	<b>300 mg</b>

## ■ ■ ■ Case 2 - Etravirine

- **Non-nucleoside reverse transcriptase inhibitor for treatment of HIV (part of combination therapy)**
- **Two identical phase 3 studies**
  - **Etravirine 200 mg b.i.d. + optimized therapy that included darunavir/ritonavir 600/100 mg b.i.d.**
  - **Vs. optimized therapy that included darunavir/ritonavir 600/100 mg b.i.d.**



# Drug interaction: etravirine and darunavir/ritonavir

- **Phase 1 drug interaction study results**
  - **coadministration of darunavir/ritonavir decreases etravirine plasma concentrations by 30 to 50%**
- **No efficacy concern- the etravirine efficacy data were collected in the presence of darunavir/ritonavir**

## ■ ■ ■ Potential safety concern

- Etravirine may be administered without darunavir/ritonavir.
- Etravirine may be administered with drugs that increase its concentrations.
- Thus, etravirine plasma concentrations may be higher than observed in Phase 3 studies.
  - How much higher?
  - Are the higher concentrations safe?
  - What is the risk/benefit for specific populations?

# ■ ■ ■ Etravirine + lopinavir/ritonavir (How much higher?)

- ↑ mean etravirine AUC by 17%
- (↑ mean etravirine AUC by ~85% compared to etravirine + darunavir/ritonavir)
- No effect on lopinavir concentrations



# Etravirine + Lopinavir/Ritonavir

## Are higher concentrations safe?

	Observation from Phase 3 data	Multiply each AUC by 1.85 to account for administration of lopinavir/rtv rather than darunavir/rtv
<b>AUC12 (ng*hr/mL) range</b>	<b>145 to 69,997</b>	<b>268 to 129,495</b>
% subjects with AUC > 70,000	0	0.51%
% subjects with AUC 50,000 to 70,000	0.34%	0.51%
% subjects with AUC 30,000 to 50,000	0.69%	4.47%
% subjects with AUC 10,000 to 30,000	<b>16.67%</b>	<b>48.97%</b>



# Etravirine + Lopinavir/Ritonavir Risk/benefit

## Considerations

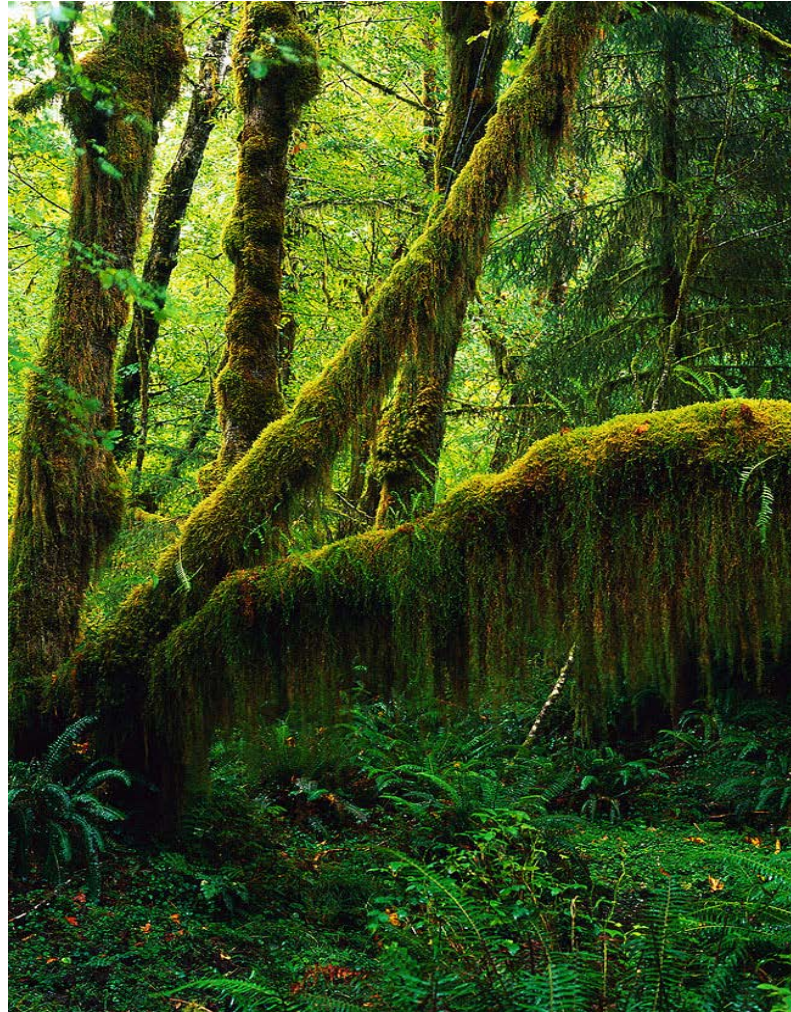
- etravirine concentration data from Phase 3
- anticipated etravirine concentrations when etravirine is given with LPV/RTV
- the population that would receive lopinavir/ritonavir instead of darunavir/ritonavir
- safety risks of etravirine



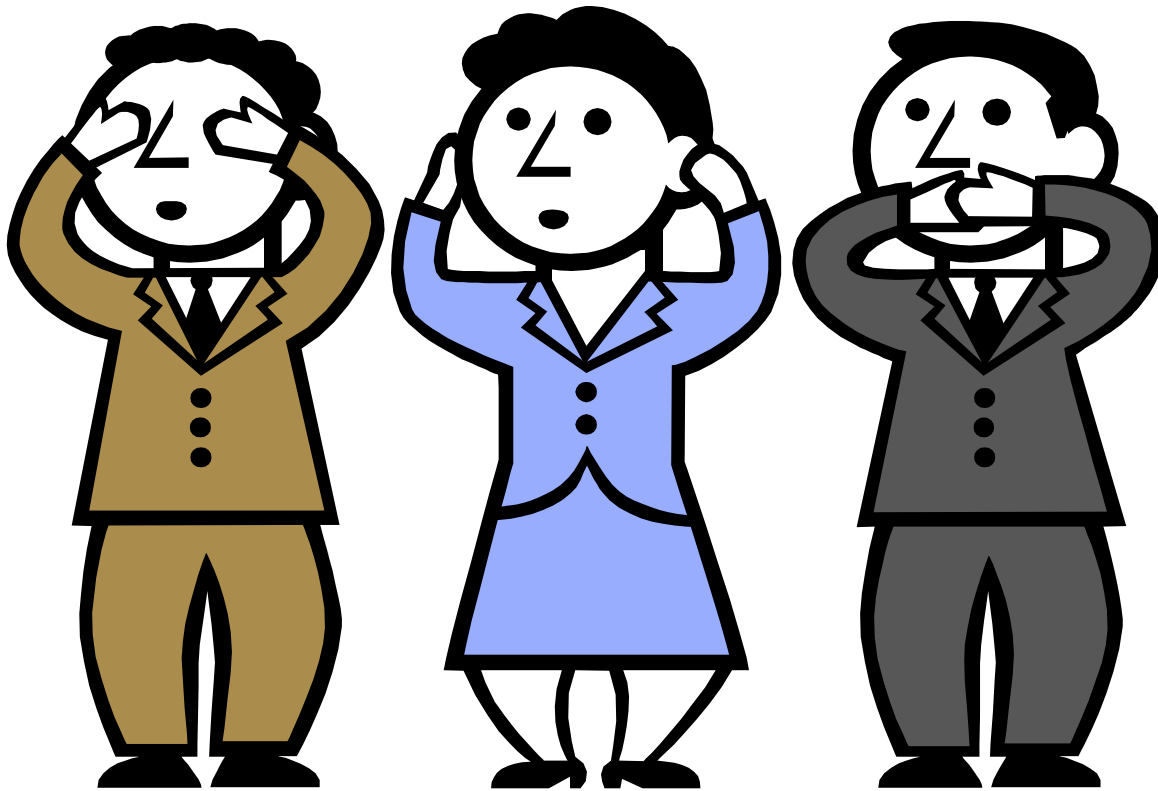
# Conclusions: Relevance and impact

■ ■ ■

**If a tree falls in the forest and no one hears it, does it make a sound?**



- ■ ■ If an exposure-response relationship exists for a drug, but drug concentrations are not determined during phase 2 or phase 3, can we optimize therapy for all patient populations?



# ■■■ Answer: NO!!

**Other versions of the answer:**

- **You don't know what you don't know**
- **Ignorance is not bliss**

## ■■■ Conclusions (relevance and impact)

- **Without exposure-response information**
  - Dose selection may not be optimal
  - We cannot interpret significance of exposure changes
- **Result: Lack of dosing instructions for certain groups**
  - They are deprived of therapy
  - Or, they risk suboptimal safety and efficacy