Agenda

- Robert A. Fromtling, PhD
  - Introduction
- Bach-Yen Nguyen, MD
  - Raltegravir Background
  - Clinical Development Program Overview
  - Clinical Trials Results
    - Efficacy
    - Resistance
    - Safety
- Robin Isaacs, MD
  - Drug-Drug Interactions
  - Risk Management Plan
  - Conclusions

Clinical Bounds to Assess Significance of Drug-Drug Interactions

- Doses studied in Phase II are likely on plateau of dose-response curve
- Phase III studies confirm the efficacy and safety of the raltegravir 400 mg BID dose
- Key question
  - Does this dose provide the expected margin for safety and efficacy when raltegravir is co-administered with drugs that are inhibitors or inducers of UGT1A1?
- Drug-drug interaction studies were undertaken to inform
  - Clinically significant changes in raltegravir pharmacokinetics were based on clinical experience
    - Lower bound (efficacy): $C_{12hr}\downarrow$ >60%
    - Upper bound (safety): AUC $\uparrow$ >100%

Drug-Drug Interactions

- Limited propensity for raltegravir to be involved in drug-drug interactions based on its route of metabolism and excretion
  - Major mechanism of raltegravir clearance is glucuronidation mediated by UGT1A1
  - Raltegravir has a low propensity for causing drug interactions with substrates of cytochrome P450 enyzmes
    - Not a substrate, an inhibitor, or an inducer of cytochrome P450 enzymes
- Phase I studies were undertaken to assess impact of inhibitors and inducers of UGT1A1 on raltegravir levels
  - Possible to bracket the likely effects of other agents on raltegravir

Drug-Drug Interactions

Mean Effect on Raltegravir

	C_{12hr}	AUC†	C_{max}

† $AUC_{0-\infty}$ for single dose raltegravir; AUC_{0-12hr} for multiple dose raltegravir.

Drug-Drug Interactions
Mean Effect on Raltegravir

	C_{12hr}	AUC†	C_{max}
Inhibition of UGT1A1			
Atazanavir/Ritonavir‡‡	↑ 77%	↑ 41%	↑ 24%

† $AUC_{0-\infty}$ for single dose raltegravir; AUC_{0-12hr} for multiple dose raltegravir.
‡‡ Multiple doses of concomitant medication plus multiple doses of raltegravir.

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Atazanavir/Ritonavir‡‡	↑ 77%	↑ 41%	↑ 24%
Induction of UGT1A1			
Rifampin‡	↓ 61%	↓ 40%	↓ 38%

† $AUC_{0-\infty}$ for single dose raltegravir; AUC_{0-12hr} for multiple dose raltegravir.
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Induction of UGT1A1			
Rifampin‡	↓ 61%	↓ 40%	↓ 38%
Tipranavir/Ritonavir‡‡	↓ 55%	↓ 24%	↓18%
Efavirenz‡	↓ 21%	↓ 36%	↓ 36%
Ritonavir‡	↓ 1%	↓ 16%	↓ 24%

† $AUC_{0-\infty}$ for single dose raltegravir; AUC_{0-12hr} for multiple dose raltegravir.
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Ritonavir‡	↓ 1%	↓ 16%	↓ 24%
Mechanism unknown			
Tenofovir‡‡	↑ 3%	↑ 49%	↑ 64%

† $AUC_{0-\infty}$ for single dose raltegravir; AUC_{0-12hr} for multiple dose raltegravir.
‡ Multiple doses of concomitant medication plus single dose of raltegravir.
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Drug-Drug Interactions

Mean Effect of Raltegravir on Other Agents

	C_{24h}	C_{max}	AUC†
CYP3A4 probe study			
Midazolam	--	↑ 3%	↓ 8%
Mechanism unknown			
Tenofovir	↓ 13%	↓ 33%	↓ 10%

† $AUC_{0-\infty}$ for midazolam; AUC_{0-24hr} for tenofovir.

Dose Recommendation

- Proposed dosing statement
  - The recommended dosage of raltegravir is 400 mg administered orally, twice daily with or without food
- Rationale
  - Raltegravir 400 mg BID was highly efficacious and generally well tolerated in Phase III studies
    - Dosed without regard to food in all clinical studies
  - Drug-drug interaction studies demonstrate only modest impact on raltegravir PK parameters except for strong inducers
  - In combination with other antiretroviral drugs, clinical experience indicates no dose adjustment is required

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Risk Management Plan Summary

Potential, Identified Risks & Missing Information	PVP†	Ongoing Clinical Trials	Pregnancy Registry	Active Surveillance

† PVP = pharmacovigilance.

Risk Management Plan Summary

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General safety data	X	X		X
Malignancies	X	X		X

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General safety data	X	X		X
Malignancies	X	X		X
Immune reconstitution syndrome	X	X		
Drug resistance	X	X		
Pregnancy exposure	X	X	X	

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Planned and Ongoing Clinical Trials

Protocol	Type of Study	Type of Patient	Additional Raltegravir Exposure (Person-Years)
005, 018, 019	Comparative	Adult, experienced	1,382 post NDA†
004, 021, 032, 033	Comparative	Adult, naïve and experienced-controlled	1,210 post NDA†

† NDA = new drug application.

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004, 021, 032, 033	Comparative	Adult, naïve and experienced-controlled	1,210 post NDA†
Expanded access	Non-comparative	Adult, experienced	–‡
Pediatric	Non-comparative	Pediatric, experienced	~120

† NDA = new drug application.
‡ Additional patient-years of raltegravir exposure cannot be predicted. There are >5,000 patients enrolled.

Active Post-licensure Safety Surveillance

- Aim
  - Monitor general safety of raltegravir in “real world” usage, including surveillance for malignancies
- Key elements
  - Assess the incidence of medical conditions of interest in subjects treated with raltegravir post-licensure
  - For comparison purposes, determine background incidence rates of these clinical events in 2 control cohorts
    - Pre-licensure historical cohort
    - Post-licensure non-raltegravir users concurrent cohort

Large-Scale Post-licensure Active Surveillance Proposed Design for Prospective Study

Design:	Observational prospective cohort surveillance
Study setting:	Large databases with links between prescriptions and medical outcomes
Study population:	Treatment-experienced HIV-infected patients
Outcomes:	Malignancies and general safety outcomes resulting in hospitalizations or emergency room visits
Monitoring:	Ongoing monitoring every 6 months
Follow-up period:	All exposure-time after raltegravir prescription
Duration:	At least three years post-launch
Committee:	External independent Safety Monitoring Committee
Drug use setting:	Routine use of raltegravir post-launch

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Raltegravir Provides a Significant New Option for Treatment-Experienced Patients

- Novel mechanism of action
  - First-in-class HIV integrase inhibitor with no cross-resistance to currently licensed antiretroviral agents
  - Active against multi-drug resistant HIV-1
- Low pill burden and convenience in dosing
  - Dosed one tablet twice daily without regard to food
  - No dose adjustment with other antiretroviral agents
- Favorable benefit/risk assessment
  - Raltegravir has rapid, potent and sustained antiretroviral activity
    - Efficacy maximized when combined with other potent active agents
    - Undetectable viral load demonstrated in treatment-experienced patients
  - Excellent safety profile and tolerability based on available data
    - Additional follow-up planned

Raltegravir Provides a Significant New Option for Treatment-Experienced Patients

Raltegravir is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.