Nonclinical Evaluation of Oral Antiviral Agents

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Viral Infections

- Encephalitis/meningitis
  - JC virus
  - Measles
  - LCM virus
  - Arbovirus
  - Rabies

- Pharyngitis
  - Adenovirus
  - Epstein-Barr virus
  - Cytomegalovirus

- Cardiovascular
  - Coxsackie B virus

- Hepatitis
  - Hepatitis virus
    - types A, B, C, D, E

- Skin infections
  - Varicella zoster virus
  - Human herpesvirus 6
  - Smallpox
  - Molluscum contagiosum
  - Human papillomavirus
  - Parvovirus B19
  - Rubella
  - Measles
  - Coxsackie A virus

- Common cold
  - Rhinovirus
  - Parainfluenza virus
  - Respiratory syncytial virus

- Gingivostomatitis
  - Herpes simplex type 1

- Eye infections
  - Herpes simplex virus
  - Adenovirus
  - Cytomegalovirus

- Parotitis
  - Mumps virus

- Pneumonia
  - Influenza virus, Types A and B
  - Parainfluenza virus
  - Respiratory syncytial virus
  - Adenovirus
  - SARS coronavirus

- Myelitis
  - Poliovirus
  - HTLV-1

- Gastroenteritis
  - Adenovirus
  - Rotavirus
  - Norovirus
  - Astrovirus
  - Coronavirus

- Sexually transmitted diseases
  - Herpes simplex type 2
  - Human papillomavirus
  - HIV

- Pancreatitis
  - Coxsackie B virus
Examples of Viral Targets

- **Acute infections**
  - Influenza
    - Timing issues - seasonal
  - Respiratory syncytial virus (RSV)
    - Patient population - pediatric, elderly

- **Chronic infections**
  - Human immunodeficiency virus (HIV)
    - Managed by long-term viral suppression with HAART
  - Hepatitis C (HCV)
    - Can “cure” with standard of care (pegylated interferon and ribavirin)
    - Not well tolerated, moderately efficacious (~50% in GT1)
HIV

- World’s leading infectious killer
- Each year, about 40,000 new HIV infections occur in the United States
- Globally, more than 33 million people are infected with HIV, including 2 million children
- In 2008, more than 2 million people died of AIDS-related causes. During the same year, 2.7 million new cases of HIV were reported.
- More than 25 million people have died of AIDS since the epidemic emerged in the early 1980s

Sources: Centers for Disease Control and Prevention, the World Health Organization
HIV therapeutic targets:
Multiple stages of the viral life cycle

From E. De Clercq, Nature Reviews, pp 1001-8, 2007
Between ’87 and ’95, 4 antiretrovirals were launched. Since ’95, 27 new products were introduced.

http://www.fda.gov/oashi/aids/virals.html
HIV: Global Nonclinical Program

- Phase 1 POC trials; monotherapy for 7-14 days
  - Standard IND package (14/28 day studies, genotoxicity, safety pharmacology)
- Phase 2; 48-96 wks
  - Chronic studies needed early in development
  - Drug supply adequate
  - 28 day directly to chronic studies; 13 week interim to support clinical progression
  - Teratology for EU (See M3 (R2))
  - Consider immunotoxicity study (ICH S8)
  - Carcinogenicity range-finding/planning
  - Pediatric Investigation Plan (PIP for EU)
- Phase 3
  - Fertility
- Marketing application
  - Perinatal
  - Carcinogenicity
  - Environmental assessment
Carcinogenicity Studies

- Do carcinogenicity studies need to be completed prior to submitting an NDA/MAA?
  - US: Following ICH S1A
    - “for pharmaceuticals developed to treat certain serious diseases, carcinogenicity need not be conducted before market approval…”
    - Came in effect July 2008
    - Reconsiders the need and timing for carcinogenicity studies based on “nearly all” agents exhibiting positive findings in 2 yr carcinogenicity studies and the increased life expectancy of HIV-infected patients
    - Carcinogenicity to be submitted before granting the marketing authorization except for “products intended for the treatment of patients with limited treatment options or a clearly demonstrable added value”
Juvenile Toxicity Studies

• Are juvenile toxicity studies required?
• Guidance documents
  – “Nonclinical Safety Evaluation of Pediatric Drug Products” (FDA, Feb 2006)
  – ICH M3 (R2)
• Guidelines are similar - Considerations include:
  – Tox package available, clinical data in adults
  – Pediatric population
  – Target organs relevant to developing systems
  – Case-by case decision on need for juvenile tox
Additional EU guidance

  - Recommends specific in vitro studies (cell lines, duration, endpoints)
- “Guideline on Detection of Early Signals of Drug-Induced Hepatotoxicity in Nonclinical Studies” (EU Draft EMEA/CHMP/SWP/150115/2006)
Nucleoside Reverse Transcriptase Inhibitors

• Act as alternate substrates for the RT and cause termination of the formation of the DNA chain
• Adverse effects associated with mitochondrial toxicity
  – Lactic acidosis, hepatic steatosis, neuropathy, myopathy, pancreatitis and lipodystrophy
  – Mechanisms: DNA polymerase γ inhibition, oxidative stress, mtDNA mutations
  – In vitro models
    • Kinetics of incorporation by DNA polymerase γ
    • Cell culture: e.g. HepG2, skeletal muscle, renal proximal tubule
Correlation of in vitro assays and clinical outcome

<table>
<thead>
<tr>
<th>Compound</th>
<th>Inhibition of Pol</th>
<th>Inhibition of mtDNA</th>
<th>Lipid content</th>
<th>Clinical Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>zalcitabine</td>
<td>+++</td>
<td>++++</td>
<td>ND</td>
<td>No longer used</td>
</tr>
<tr>
<td>didanosine</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>pancreatitis, peripheral nephropathy, lactic acidosis (hepatic steatosis)</td>
</tr>
<tr>
<td>stavudine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>peripheral nephropathy, lipoastryphosis, pancreatitis, lactic acidosis (hepatic steatosis), hyperlipidemia</td>
</tr>
<tr>
<td>zidovudine</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>bone marrow suppression (anemia), lactic acidosis (hepatic steatosis)</td>
</tr>
<tr>
<td>lamivudine</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>minimal toxicity</td>
</tr>
<tr>
<td>emtricitabine</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>minimal toxicity</td>
</tr>
<tr>
<td>tenofovir DF</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>renal insufficiency</td>
</tr>
<tr>
<td>abacavir</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>hypersensitivity</td>
</tr>
</tbody>
</table>

Venhoff et al, Antiviral Therapy, 2007; Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents
NonNucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- NNRTIs bind RT directly and inhibit action
- Toxicities of approved agents
  - Delavirdine: rash, incr. transaminases, headaches
  - Efavirenz: rash, incr. transaminases, CNS symptoms, teratogenic (monkeys)
  - Etravirine: rash, nausea
  - Nevirapine: rash, symptomatic hepatitis/hepatic necrosis
- Preclinical models detected liver effects
- Rash, CNS effects not detected
  - Nevirapine model in female Brown Norway rats (Uetrecht et al., U of Toronto)
Protease Inhibitors (PIs)

- PIs inactivate the HIV-1 protease and prevent cleavage of gag-pol proteins
- Common 3rd Agent
  - atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
- Due to low exposure agents generally require “boosting” with ritonavir
- Side effect profiles include:
  - Hyperglycemia and fat maldistribution – all PIs
  - Hyperlipidemia – most PIs
  - GI intolerance – most PIs
  - Hepatotoxicity – darunavir, tipranavir
  - Skin rash – darunavir, fosamprenavir, tipranavir
  - Hyperbilirubinemia, prolonged PR - atazanavir
Screening for metabolic effects: In Vitro Metabolic Toxicity in Adipocytes

• Differentiated human and mouse adipocytes

**Insulin-stimulated glucose uptake**
(Inhibition at 10 µM)

<table>
<thead>
<tr>
<th></th>
<th>% GLUT4 Inhibition at 10 µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-8374</td>
<td></td>
</tr>
<tr>
<td>DRV</td>
<td></td>
</tr>
<tr>
<td>LPV</td>
<td></td>
</tr>
<tr>
<td>ATV</td>
<td></td>
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<tr>
<td>SQV</td>
<td></td>
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<tr>
<td>RTV</td>
<td></td>
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<tr>
<td>APV</td>
<td></td>
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<tr>
<td>IDV</td>
<td></td>
</tr>
<tr>
<td>NFV</td>
<td></td>
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</table>

**Lipid accumulation**

<table>
<thead>
<tr>
<th></th>
<th>IC$_{50}$ [µM]</th>
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<tbody>
<tr>
<td>PI</td>
<td>&gt;30</td>
</tr>
<tr>
<td>ATV</td>
<td>&gt;30</td>
</tr>
<tr>
<td>DRV</td>
<td>&gt;30</td>
</tr>
<tr>
<td>APV</td>
<td>&gt;30</td>
</tr>
<tr>
<td>IDV</td>
<td>&gt;30</td>
</tr>
<tr>
<td>RTV</td>
<td>17 ± 8</td>
</tr>
<tr>
<td>SQV</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>LPV</td>
<td>16 ± 5</td>
</tr>
<tr>
<td>NFV</td>
<td>8 ± 3</td>
</tr>
</tbody>
</table>

Callebaut et al, CROI 2008
Other agents

- **Fusion inhibitors**
  - enfuvirtide: local injection site reactions (given sc), hypersensitivity

- **CCR5 antagonists**
  - maraviroc: abdominal pain, cough, dizziness, musculoskeletal symptoms, pyrexia, rash, upper respiratory tract infections, hepatotoxicity, orthostatic hypotension

- **Integrase inhibitors**
  - raltegravir: creatine kinase elevations
  - elvitegravir: being developed with a boosting agent
Combination Toxicity Studies

- HAART is based on multi-drug regimens
- Guidance documents:
  - US: “Nonclinical Safety Evaluation of Drug or Biologic combinations” (March 2006)
  - ICH M3 (R2)
- Late stage products: combination toxicity generally not needed
- Early stage products: varied guidance
  - Consider overlapping toxicities
  - Need for combination tox dependent on amount of nonclinical and clinical data with individual agents
  - 90 day combination tox in one species recommended in some cases
  - Other assessments, e.g. genotoxicity or embryo-fetal toxicity, dependent on characteristics of compounds and regional requirements
Regimen-Related Drivers of Adherence

DHHS. Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents.
Fixed Dose Combinations

• Guidance documents:
    • Encouraged the development of FDC and delineated requirements
  – “Guideline on Clinical Development of Fixed Combination Medicinal Products” (CHMP/EWP/240/95 Rev.1 Sept 2009)
  – “Guideline on the Clinical Development of Medicinal Products for the Treatment of HIV Infection” (EMEA/CHMP/EWP/633/02 June 2009)
One Pill, Once a Day, Triple Combination Regimen

- December 20, 2004: Joint venture to develop and commercialize the fixed-dose combination of Sustiva® (efavirenz) and Truvada™ (tenofovir DF and emtricitabine) in the US
  - First multi-company effort to create fixed-dose product with three HIV/AIDS medicines
  - Multiple bioequivalence studies conducted
  - FDA approved on 7/12/2006 as the first complete HIV regimen available in once-daily fixed-dose combination

\[ TDF + FTC + EFV = 1 \text{ Pill} \]
HIV: The Future

• Treatment
  – Agents with long-term safety and improved resistance profiles still needed
  – Focus on regimen simplification
  – Nucleoside-sparing regimens
  – New targets

• Prevention
  – Vaccines
  – Pre-exposure prophylaxis (PrEP)

• HIV cure?
Chronic Hepatitis C:
A Significant Unmet Medical Need

More than 20% of chronic HCV infections lead to cirrhosis
The leading cause of liver transplantation in the US
HCV accounts for 30% of end-stage liver disease and liver cancer
US: ~10,000 HCV-related deaths/year
Standard of Care (SOC) associated with numerous toxicities

- Regimen is 24 (GT2/3) to 48 (GT1) weeks
- Pegylated Interferon
  - Flu-like syndrome (fatigue, fever, headache, myalgia)
  - Neuropsychiatric events
  - Bone marrow toxicities (↓ neutrophil, platelet counts)
  - Local injection site reactions
- Ribavirin
  - Hemolytic anemia
  - Teratogenic/embryocidal
  - Mutagenic
Drug Targets in the HCV Lifecycle:

**HCV Binding/Entry**
- **Entry Inhibitors**

**Translation/Polyprotein Processing**
- **IRES Inhibitors**
- **NS2/3, NS3/4A Protease Inhibitors**

**Replication Complex**
- **Formation/RNA Replication**
  - **NS3 Helicase Inhibitors**
  - **NS4B Inhibitors**
  - **NS5A Inhibitors**
  - **NS5B Pol Nuc, Non-nuc, & Cyclophilin Inhibitors**

**Virus Assembly/Release**
- **Glucosidase Inhibitors**
Development of New HCV agents

- Regulatory path is not well established for direct acting antivirals (DAAs)
- Combination therapy will be required
  - Combination with PEG + RBV (SOC)?
  - Multiple DAAs?
- Considerations for early clinical trials
  - Limited monotherapy (rapid resistance)
  - Explore duration of therapy (differ from SOC?)
  - Which population to study
    - Naives, relapsers, partial/null responders, genotype, IL28B polymorphism?
    - Sustained virological response (SVR) data needed
- “Guideline on the clinical evaluation of direct acting antiviral agents intended for the treatment of chronic hepatitis C”
  EMEA/CHMP/EWP/30039/2008
HCV: Global Nonclinical Program

• Phase 1 POC trials; monotherapy for 3-5 days
  – Standard IND package (14/28 day studies, genotoxicity, safety pharmacology)
• Phase 2; 4/12/24 weeks
  – Duration varies with goals of Phase 2
  – Repeat dose tox to match trial design or support combination dosing
  – Combination tox considerations
  – Teratology for EU (See M3 (R2))
  – Carcinogenicity range-finding/planning
  – Pediatric Investigation Plan (PIP for EU)
• Phase 3
  – Fertility
• Marketing application
  – Perinatal
  – Carcinogenicity
  – Environmental assessment
Many Unknowns for Combination DAAs

• Clinical studies with or without PEG/RBV?
• How many agents are needed to suppress virus and produce “cure” (SVR)?
• What nonclinical combination studies are required to support combination trials?
  – US: Nonclinical combination studies not useful; 3 month repeat dose studies with individual agents needed. Combination studies with PEG/RBV not needed.
  – EU: Some countries following ICH M3(R2) which requires combination studies
  – Evaluate overlapping tox, consider trial stage and design, make an argument based on data
HCV – Agents in Development

- **VX-222**
- **ABT-072**
- **BMS791325**
- **ABT-450**
- **ANA773**
- **SCY-635**
- **ACH-1625**
- **VX-813**
- **VX-985**
- **MK-5172**
- **BMS-824393**
- **SD-101**
- **IDX375**
- **JTK-853**
- **IDX320**
- **Locteron**
- **TMC435**
- **BI201335**
- **RG7128**
- **DEBIO-025**
- **BMS790052**
- **MK-7009**
- **RG7227/ITMN-191**
- **Filibuvir/PF-868554**
- **ANA-598**
- **BI207127**
- **ABT-333**
- **NIM-811**
- **Peg-IFN lambda**
- **IDX184**
- **PSI-7977**
- **BMS650032**

*For launch dates: assumption for competitor timelines is 2 yrs for phase 2b and 2.75 yrs from start of phase 3 to NDA submission.*
HCV: The Future

• New DAAs and new combinations
• Better response rates (SVR> 60%) and fewer relapses
• Shortened duration of treatment
• Reduced toxicities