Early Safety, Tolerability and Pharmacokinetic Profile of GSK2838232, a Novel 2nd Generation HIV Maturation Inhibitor, as Assessed in Healthy Subjects

1,7Johnson, M; 1Jewell RC; 2Peppercorn, A; 1Gould E; 3Xu, J; 1,4Lou, Y; 5Davies, M; 6Baldwin, S; 1,7Tenorio, A; 8Burke, M and 1Johns, B

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HIV Viral Lifecycle and Maturation Inhibitor Drug Targets

- **Protease Inhibitors**
- **RT Inhibitors**
- **Integrase Strand Inhibitors**

Attachment, entry & fusion Inhibitors

Mature HIV:
- HIV fusion with host cell membrane
- Host cell to host cell
- Migration to cell surface
- Virus assembly
- Virus budding

**Maturation Inhibitors**
GSK2838232: Preclinical Profile

- Low/moderate bioavailability; low permeability, low solubility

- CYP/transporter profile
  
  - Does not inhibit CYP1A2, 2C9, 2C19, 2D6, or 3A4 ($IC_{50} > 33 \mu M$) \textit{in vitro}
    
    - Has potential to cause metabolism-dependent inhibition of CYP3A4
  
  - No drug interaction risk was identified for co-administrated substrates of UGT1A1, 1A3, 1A6, 1A9, 2B7, and 2B15, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2
  
  - Cleared predominantly by CYP3A4 oxidative metabolism (some N-dealkylation, glucuronidation, and other minor routes)
    
    - RTV (CYP3A4 inhibitor) “boosts” GSK2838232 AUC, Cmax, and Ctau - which is then cleared via Phase II conjugation

- Preclinical Toxicology
  
  - Successful completion of reproductive toxicology studies; WOCBP can be included
  
  - NOAELs established in rat/dog chronic toxicology studies
GSK2838232: Virology Profile

Modified from Jeffrey et al 2015 CROI Poster #538

Potency, Effect of protein

<table>
<thead>
<tr>
<th></th>
<th>Potency, Effect of protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT4 wt EC$_{50}$</td>
<td>0.8 nM</td>
</tr>
<tr>
<td>MT4 V370A EC$_{50}$</td>
<td>0.7 nM</td>
</tr>
<tr>
<td>*EC$<em>{90}$ (minimum clinical C$</em>{min}$ target)</td>
<td>6.4 nM (5 ng/mL)</td>
</tr>
<tr>
<td>Protein binding</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>*Fold shift with 40% human serum</td>
<td>1 (no shift) to 5-fold</td>
</tr>
</tbody>
</table>
GSK2838232: Clinical Program

- Objectives of early clinical program
  - Safety/tolerability
  - Pharmacokinetics of single/repeat doses +/-RTV and the impact of formulation and food

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Formulation/Dose</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMI116787</td>
<td>Single escalating dose (SAD) and assessment of RTV</td>
<td>SDD, PiB 5-100 mg and 10 mg+RTV, Placebo</td>
<td>17</td>
</tr>
<tr>
<td>200912</td>
<td>Continuation of SAD (Part 1) and RBA of API then API+RTV (Part 2)</td>
<td>SDD, API, PiB 200 mg (Part 1), 100 mg API/SDD RBA then 20 mg API+RTV (Part 2)</td>
<td>20</td>
</tr>
<tr>
<td>200207</td>
<td>Multiple ascending dose (MAD)</td>
<td>SDD 20 mg, 50 mg, 10mg+RTV (single dose), Placebo</td>
<td>24</td>
</tr>
<tr>
<td>204953</td>
<td>Continuation of SAD/MAD and RBA of capsules (+food effect)</td>
<td>50-250 mg/r SAD PiB 20-50mg/r MAD PiB, 100-200 mg/r MAD Capsule 100 mg capsule/r vs PiB/r RBA +food 200mg capsule + food BID</td>
<td>63</td>
</tr>
</tbody>
</table>

PiB Powder in Bottle; API Active Pharmaceutical Ingredient; SDD Spray Dried Dispersion
GSK2838232: Safety and Tolerability

- 124 healthy subjects exposed to GSK2838232 or placebo
  - Mostly Male, 9 Female subjects
  - 18-55 yrs, Body weight ≥ 50 kg (110 lbs.) for men and ≥ 45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-31.0 kg/m² (inclusive).

- Safety
  - No study discontinuations or grade 3/4 labs related to GSK2838232
  - One SAE (NSVT) on continuous telemetry/Holter. Unlikely to be drug-related:
    - Occurred after 50 mg GSK2838232 QD dosing (39 hours after last dose) when plasma concentrations were <1 ng/mL
    - Similar event appeared on repeat Holter 17 weeks after last dose
  - No increase between GSK2838232 and placebo in frequency of CV events
  - No other clinically meaningful or significant changes in AE profile, ECG, blood pressure, heart rate, or safety labs
  - All formulations well tolerated with or without food
GSK2838232: Single Dose Pharmacokinetic Profile

Single doses up to 200 mg, from Studies HMI116787 and 200912; SDD PiB fasted

Median Plasma GSK2838232 Concentration-time Profiles

Summary of GSK2838232 PK Parameters: geometric mean (95% CI)

- Lower bioavailability than predicted from preclinical studies
- Broadly dose proportional through 100 mg
GSK2838232: Boosting with RTV

RTV administered for 12 days, GSK2838232 SDD PiB administered on Day 10

Median Plasma GSK2838232 Concentration-time Profiles

GSK2838232 PK Parameters: geometric mean (95% CI)

<table>
<thead>
<tr>
<th>Dose</th>
<th>n</th>
<th>Cmax (ng/mL)</th>
<th>tmax¹ (h)</th>
<th>AUC(0-t) (ng.h/mL)</th>
<th>AUC(0-∞) (ng.h/mL)</th>
<th>t½ (h)</th>
<th>C24¹ (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>8</td>
<td>3.49 (2.98-4.09)</td>
<td>1.76 (1.50-4.00)</td>
<td>26.8 (19.8-36.2)</td>
<td>ND</td>
<td>ND</td>
<td>0.63 (0-0.86)</td>
</tr>
<tr>
<td>(HMI116787)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/r</td>
<td>6</td>
<td>9.10 (6.85-12.1)</td>
<td>4.00 (2.48-6.00)</td>
<td>289 (213-393)</td>
<td>389 (285-531)</td>
<td>33.7</td>
<td>4.64 (3.48-8.64)</td>
</tr>
<tr>
<td>(HMI116787)</td>
<td></td>
<td></td>
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</tbody>
</table>

¹ ND = not determined

- RTV boosts GSK2838232 AUC by ~10-fold but only ~3-fold increase in Cmax
- Prolonged t½, consistent with reduced metabolic clearance
GSK2838232 + RTV: Single Dose Pharmacokinetic Profile

Study 204953: Single RTV-Boosted Doses of up to 250 mg (48 hr RTV pre-dosing)

Median Plasma GSK2838232 Concentration-time Profiles

GSK2838232 Preliminary PK Parameters: geometric mean (95% CI)

- RTV-boosted GSK2838232 API PK is generally dose proportional
- All doses provide trough concentrations above target
- $t_{1/2}$ values underestimated as a result of discontinuation of RTV dosing

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>n</th>
<th>Cmax (ng/mL)</th>
<th>tmax (h)</th>
<th>AUC(0-t) (ng.h/mL)</th>
<th>AUC(0-∞) (ng.h/mL)</th>
<th>$t_{1/2}$ (h)</th>
<th>C24 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/r</td>
<td>8</td>
<td>15.7 (10.9-23.4)</td>
<td>3 (2.5-6)</td>
<td>401 (300-558)</td>
<td>434 (334-583)</td>
<td>22.4 (19.4-26.0)</td>
<td>7.26 (3.18-9.61)</td>
</tr>
<tr>
<td>100/r</td>
<td>6</td>
<td>24.7 (19.8-30.5)</td>
<td>5 (2.5-12)</td>
<td>854 (681-1061)</td>
<td>874 (702-1079)</td>
<td>17.9 (15.3-20.7)</td>
<td>13.2 (8.64-17.4)</td>
</tr>
<tr>
<td>250/r</td>
<td>5</td>
<td>59.3 (43.7-77.6)</td>
<td>4 (2-12)</td>
<td>1658 (1101-2321)</td>
<td>1678 (1111-2352)</td>
<td>17.2 (15.9-18.6)</td>
<td>24.0 (16.0-32.0)</td>
</tr>
</tbody>
</table>

1 Median (minimum-maximum)
GSK2838232: Formulation and Food Effect, with RTV

Study 204953: API PiB vs API capsules, plus food effect (48 hr RTV pre-dosing)

Median Plasma GSK2838232 Concentration-time Profiles

Summary of GSK2838232 Preliminary PK Parameter Comparisons

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison</th>
<th>N</th>
<th>Ratio of Geometric Least Square Means</th>
<th>90% CI of Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-∞)</td>
<td>Capsule/r:PiB/r</td>
<td>12</td>
<td>1.43</td>
<td>(1.194, 1.702)</td>
</tr>
<tr>
<td>Cmax</td>
<td>Capsule/r:PiB/r</td>
<td>12</td>
<td>1.58</td>
<td>(1.312, 1.900)</td>
</tr>
</tbody>
</table>

Relative bioavailability – RTV-boosted PiB and capsule

Preliminary pharmacokinetic results:

– Geometric mean AUC(0-∞) and Cmax 43 and 58% higher after administration as capsule compared to oral suspension from powder-in-bottle and ~60% higher in the fed state versus fasted

– API [50 mg] capsules, administered with food (with RTV) suitable treatment for repeat dose
GSK2838232: Repeat Dose Pharmacokinetic Profile
Study 204953: Repeat doses +/- RTV for 11 days

Preliminary pharmacokinetic results:
- RTV-boosted GSK2838232 appeared dose proportional through 200 mg QD
- RTV-boosted GSK2838232 doses achieved IQ values between 3 and 30 (assuming 5 ng/mL target)
- GSK2838232 200 mg BID PK profile similar to RTV-boosted 50 mg QD and also achieved target (IQ ~10)
Predicted PK Profiles for Evaluation in HIV-Infected Patients

- Predicted steady-state GSK2838232 concentration-time data ± SD based on Study 204953 results

- GSK2838232/r doses achieve IQ values between 3 and 30 (assuming 5 ng/mL)
- Factoring in PK variability, GSK2838232 doses ≥50 mg/r QD are predicted to meet target exposures
  - Caveat: Cobicistat substituted for RTV in PoC
Conclusions

- GSK2838232 was generally safe and well tolerated in healthy subjects up to single doses of 250 mg + RTV and repeated daily doses of 200 mg QD + RTV or 200 mg BID for 11 days

- RTV increased AUC, Cmax, and C24 (Ctau) in single and repeated doses

- Formulation and food (normal fat content, i.e., 30%) together had a significant positive impact on overall GSK2838232 bioavailability

- PK profile is consistent with the proposed therapeutic strategy of maintaining plasma concentrations >PA-IC90 for all HIV-infected subjects

- GSK2838232, boosted with cobicistat, is currently being assessed in a Phase IIa 10-day monotherapy study in HIV patients that will support Phase IIb evaluation in 2018
Acknowledgements

Co-authors

The authors wish to sincerely thank:

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