Clinical Pharmacology of the Unboosted HIV Integrase Strand Transfer Inhibitor (INSTI) Bictegravir (BIC)

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Introduction

- Bictegravir (BIC; formerly GS-9883) is a novel, once-daily, INSTI
  - High barrier to resistance and potent in vitro activity against wild-type and most INSTI-resistant variants\(^1\)\(^–\)\(^4\)

- A 10 day study of BIC monotherapy in HIV-1 infected subjects demonstrated rapid decline in HIV-1 RNA >2 log\(_{10}\)\(^5\)

- BIC single agent evaluated in Phase 2 in combination with emtricitabine (FTC) and tenofovir alafenamide (TAF)\(^6\)

- BIC is in Phase 3 clinical development as a single-tablet regimen (STR) coformulated with FTC and TAF for the treatment of HIV-1 infection

- An extensive Phase 1 program characterized the clinical pharmacology of BIC

BIC Safety Profile from Phase 1 Program

- Generally well tolerated with no dose-dependent adverse events observed
  - Evaluated BIC doses of 5 to 100 mg in HIV-infected subjects and 5 to 600 mg in healthy subjects

- No effect on QT interval based on a negative thorough QT study

- No impact on glomerular filtration as measured by iohexol clearance
BIC Absorption, Distribution, Metabolism, Elimination (ADME)

- Well absorbed (>70%)
- Highly bound to plasma proteins (>99%)
- Primarily circulates as parent drug (BIC accounted for 68% plasma radioactivity)
- Metabolism is the major clearance pathway for BIC with similar contribution by oxidation (CYP3A4) and glucuronidation (UGT1A1)
  - Moderate hepatic impairment showed no clinically significant effect on PK
- Minimal renal clearance (~1% of unchanged parent excreted in urine)
  - No clinically significant effect of severe renal impairment (eGFR_{CG} 15–30 mL/min) on PK
BIC Pharmacokinetic Profile
Healthy Subjects

- **t½:** ~18 hours
- PK profile supportive of once daily dosing
- PK profile consistent with that observed in HIV-infected subjects

BIC Pharmacokinetic Profile HIV-infected Subjects
Phase 2: BIC 75 mg + F/TAF 200/25 mg

Mean BIC Concentration, ng/mL (SD)

Time, h

IC$_{95}$

BIC PK Parameters
N=23

<table>
<thead>
<tr>
<th>BIC 75 mg</th>
<th>AUC$_{τ}$, h$\cdot$ng/mL</th>
<th>C$_{max}$, ng/mL</th>
<th>C$_{r}$, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>140,000 (27)</td>
<td>9340 (27)</td>
<td>3510 (37)</td>
</tr>
</tbody>
</table>

*Data presented as mean (%CV).
BIC Drug-Drug Interaction (DDI) Profile

- Low potential as a victim of DDIs
  - INSTIs are affected by cation-containing antacids
    - BIC administration with antacids should be staggered (± 2 hours)
    - Fasted administration 2 hours before or 2 hours after antacid resulted in a decrease in BIC exposures of 13% and 52%, respectively
  - BIC is a substrate of CYP3A4 and UGT1A1
    - Inhibition of both CYP3A4 and UGT1A1 needed for substantial increase in exposure
    - Potent induction reduces exposure to a clinically significant extent
BIC Drug-Drug Interaction Profile
Clinical Study Probing Effect of Inhibitors or Inducers

- Voriconazole;
- atazanavir;
- rifabutin;
- rifampin.

% Change in BIC AUC

CYP3A4 Inhibition*
61%

CYP3A4 + UGT1A1 inhibition†
310%

CYP3A4 + UGT1A1 Induction‡,§
-38%
-75%

*Voriconazole; †atazanavir; ‡rifabutin; §rifampin.
BIC Drug-Drug Interaction Profile

Effect of BIC on the PK of Coadministered Drugs

<table>
<thead>
<tr>
<th>CYP3A4 Probe Substrate</th>
<th>Change in AUC</th>
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<tbody>
<tr>
<td>Midazolam</td>
<td>↔</td>
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<table>
<thead>
<tr>
<th>Representative Oral Contraceptive</th>
<th>Change in AUC</th>
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<tbody>
<tr>
<td>Norelgestromin*</td>
<td>↔</td>
</tr>
<tr>
<td>Ethinyl Estradiol</td>
<td>↔</td>
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<table>
<thead>
<tr>
<th>Representative HCV DAA</th>
<th>Change in AUC</th>
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<tr>
<td>Ledipasvir</td>
<td>↔</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>↔</td>
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<tr>
<th>OCT2/MATE1 Probe Substrate</th>
<th>Change in AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>↑ 39%</td>
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</tbody>
</table>

- Low potential to perpetrate DDIs
  - Not an inhibitor or inducer of CYP3A4 or UGT1A1
    - No effect on midazolam
  - No interaction with a representative oral contraceptive
    - No effect on norgestimate/ethinyl estradiol
  - No interaction with a representative HCV DAA
    - No effect on ledipasvir/sofosbuvir
  - Limited liability for inhibition of renal transporters (OCT2 and MATE1)
    - Modest increase in metformin exposure

*Norelgestromin is circulating pharmacologically active progestin from norgestimate. 90% CI of GMR were within (↔) or extended above (↑) the predetermined protocol defined equivalence boundaries of 70–143%.
Coformulation of BIC + F/TAF into Single Tablet Regimen (STR)

- Lack of DDI between BIC and FTC/TAF established
  - FTC/TAF 200/25 mg dose

- STR formulation development
  - Improved BIC bioavailability vs single agent Phase 2 formulation
  - Reduced food effect vs single agent Phase 2 formulation
  - STR with 50 mg BIC dose selected for Phase 3; administered with or without food
Conclusions

- Bictegravir is an INSTI with pharmacokinetics supportive of once daily dosing and a favorable DDI profile.
- Coformulated BIC/FTC/TAF 50/200/25 mg STR under evaluation in Phase 3 studies.
Acknowledgements

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