Lack of PK Interaction Between
the HCV Protease Inhibitor MK-5172 and
Methadone and Buprenorphine/Naloxone
in Subjects on Stable Opiate
Maintenance Therapy

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Study Rationale

• MK-5172: Potent, oral, once-daily inhibitor of the hepatitis C virus (HCV) NS3/4A protease that is being developed for the treatment of chronic HCV infection

• Intravenous (IV) drug use is a common route of HCV infection

• Treatment for substance dependence in IV drug users frequently requires oral maintenance therapy with methadone or buprenorphine/naloxone
  – Concomitant use of anti-HCV agent(s) that interfere with the ability to maintain stable opiate concentrations can lead to opiate intoxication or withdrawal symptoms

• This study evaluated the pharmacokinetic interaction of MK-5172 and methadone and buprenorphine in non-HCV-infected subjects on stable opioid maintenance therapy
MK-5172 Background

• Non-clinical antiviral activity
  – High potency against G1, G2, G4-6; activity against G3
  – Potent against RAVs detected among patients who failed 1st generation PIs†

• Phase 1b monotherapy study
  – ~5-log\textsubscript{10} mean maximal reduction from baseline in HCV G1 RNA levels with
    30 mg to 800 mg QD
  – Plasma AUC ~2-fold higher in HCV-infected patients vs healthy uninfected subjects

• Phase 2 dose-ranging trial
  – 332 treatment-naïve, non-cirrhotic, G1-infected patients
  – 4 MK-5172/PR arms: 100, 200, 400, 800 mg QD; control = standard boceprevir/PR
  – 12 weeks MK-5172/PR, followed by 12 or 36 weeks of PR based on TW4 responses
  – Across dose arms, 92% to 99% of patients achieved SVR24 or HCV RNA undetectable
    at the last follow-up visit (vs 67% for boceprevir/PR)
  – At daily doses ≥200 mg, increased ALT/AST levels to >5x upper limit of normal; ~10-fold
    exposure margin between 100 mg GM C\textsubscript{2hr} levels and threshold for ALT findings

• MK-5172 100 mg QD advanced to interferon-free studies

†boceprevir, telaprevir, simeprevir
Relevant Drug Metabolism Properties

• MK-5172
  – CYP3A4: substrate, weak inhibitor in vivo, no induction in vitro
  – CYP2C8: reversible inhibitor in vitro
  – CYP2B6: no inhibition in vitro
  – OATP1B1: Substrate in vivo
  – P-gp: no inhibition in vitro
  – UGT1A1: inhibitor in vitro

• Methadone
  – CYP3A4 and CYP2B6 substrate

• Buprenorphine
  – Undergoes glucuronidation and dealkylation
  – CYP3A4, CYP3A5, CYP2C8 substrate
  – CYP3A4 and CYP2D6 inhibitor
• Single-center, open-label, fixed-sequence, multiple-dose study in 24 adult male and female volunteers, ages 18-55 years
• Prespecified opiate comparability bounds [0.7, 1.43]
• PK parameter values for the opiates were dose-normalized for comparison purposes
• Safety assessments included electrocardiograms, vital signs, clinical laboratory tests, physical examination, and adverse event monitoring
Results - Clinical Safety

• All 24 subjects enrolled completed the trial

• No clinical manifestations of opiate toxicity or withdrawal observed

• 11 subjects reported a total of 21 clinical adverse experiences (AEs), 2 of which were considered drug-related (dry mouth and constipation) in buprenorphine/naloxone and MK-5172 panel
  – 6 AEs in methadone panel, 15 AEs in buprenorphine/naloxone panel

• All AEs were mild to moderate; most common AE was headache

• No serious AE, no drug-related laboratory AE

• No clinically significant abnormalities observed in vital signs, laboratory tests, physical examinations, ECG, and adverse event monitoring
**R-Methadone: Plasma PK Parameters and Mean Concentration Profiles**

- R-methadone AUC and $C_{\text{max}}$ slightly increased after MK-5172 coadministration, but 90% CI within prespecified bounds [0.70, 1.43]
- $T_{\text{max}}$ and half-life similar between treatments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$AUC_{0-24hr}/\text{Dose}$</td>
<td>1.09</td>
<td>(1.02, 1.17)</td>
</tr>
<tr>
<td>$C_{\text{max}}/\text{Dose}$</td>
<td>1.03</td>
<td>(0.96, 1.11)</td>
</tr>
</tbody>
</table>

*Table showing the percentage change (GMR) and 90% CI for AUC and $C_{\text{max}}$ with and without MK-5172 coadministration.*

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![Graph showing the comparison of R-methadone and R-methadone + MK-5172 concentration profiles over time.](image-url)
S-Methadone: Plasma PK Parameters and Mean Concentration Profiles

- AUC$_{0-24\text{hr}}$/Dose and C$_{\text{max}}$/Dose increased slightly after MK-5172 coadministration; appears to due to increased bioavailability
- 90% CIs within prespecified bounds [0.70, 1.43]
- T$_{\text{max}}$ decreased after coadministration. Half-life similar between treatments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR + MK-5172/-MK-5172</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-24\text{hr}}$/Dose</td>
<td>1.23</td>
<td>(1.12, 1.36)</td>
</tr>
<tr>
<td>C$_{\text{max}}$/Dose</td>
<td>1.15</td>
<td>(1.07, 1.25)</td>
</tr>
</tbody>
</table>
Buprenorphine: Plasma PK Parameters and Mean Concentration Profiles

- Buprenorphine AUC\(_{0-24\text{hr}}\) and \(C_{\text{max}}\) slightly decreased after MK-5172 coadministration
- 90% CIs within prespecified bounds of [0.70, 1.43]
- \(T_{\text{max}}\) similar between treatments. Half-life increased from ~10 hrs to ~18 hrs after coadministration with MK-5172

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AUC_{0-24\text{hr}}/\text{Dose})</td>
<td>0.98</td>
<td>(0.81, 1.20)</td>
</tr>
<tr>
<td>(C_{\text{max}}/\text{Dose})</td>
<td>0.90</td>
<td>(0.76, 1.07)</td>
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</tbody>
</table>
Norbuprenorphine: Plasma PK Parameters and Mean Concentration Profiles

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-24hr}$/Dose</td>
<td>1.13</td>
<td>(0.97, 1.32)</td>
</tr>
<tr>
<td>C$_{max}$/Dose</td>
<td>1.10</td>
<td>(0.97, 1.25)</td>
</tr>
</tbody>
</table>

- Norbuprenorphine AUC and C$_{max}$ slightly increased after MK-5172 coadministration; appears to be due to increased bioavailability
- T$_{max}$ similar between treatments. Half-life increased from ~29 hrs to ~39 hrs after coadministration with MK-5172
Naloxone: Plasma PK Parameters and Mean Concentration Profiles

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR + MK-5172/-MK-5172</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-24hr}$/Dose</td>
<td>1.10</td>
<td>(0.82, 1.46)</td>
</tr>
<tr>
<td>C$_{max}$/Dose</td>
<td>1.00</td>
<td>(0.80, 1.27)</td>
</tr>
</tbody>
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- Naloxone AUC slightly increased; C$_{max}$ unchanged after MK-5172 coadministration
- T$_{max}$ and half-life increased after coadministration with MK-5172
  - T$_{max}$: ~0.75 hours to ~1.25 hrs
  - t$_{1/2}$: ~3.5 hrs to ~6 hrs
MK-5172: Plasma PK Parameters and Mean Concentration Profiles

MK-5172 alone and with methadone

MK-5172 alone and with buprenorphine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR + meth/-meth</th>
<th>90% CI</th>
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</thead>
<tbody>
<tr>
<td>AUC_{0-24h}/Dose</td>
<td>0.85</td>
<td>(0.47, 1.53)</td>
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<tr>
<td>C_{max}/Dose</td>
<td>0.66</td>
<td>(0.30, 1.45)</td>
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<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR + bup/-bup</th>
<th>90% CI</th>
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</thead>
<tbody>
<tr>
<td>AUC_{0-24h}/Dose</td>
<td>0.84</td>
<td>(0.53, 1.33)</td>
</tr>
<tr>
<td>C_{max}/Dose</td>
<td>0.79</td>
<td>(0.39, 1.59)</td>
</tr>
</tbody>
</table>

- MK-5172 PK compared with historical control
- MK-5172 exposures decreased after coadministration with methadone and buprenorphine/naloxone
- Methadone: AUC and C_{max} decreased by 15% and 34%, respectively
- Buprenorphine/naloxone: AUC and C_{max} decreased by 16% and 21%, respectively
- T_{max} and half-life were similar between treatments
SAFETY

• Coadministration of MK-5172 with methadone and buprenorphine/naloxone was safe and well tolerated
  – No clinical manifestations of opiate toxicity or withdrawal observed
  – All 24 subjects enrolled completed the trial

METHADONE PK

• Addition of MK-5172 to stable methadone maintenance therapy did not meaningfully change the AUC_{0-24h} or C_{max} of R-methadone (active enantiomer)
  – AUC_{0-24h} GMR [90% CI] 1.09 [1.02, 1.17]
  – C_{max} GMR [90% CI] 1.03 [0.96, 1.11]

• Addition of MK-5172 to stable methadone maintenance therapy did not meaningfully change the AUC_{0-24h} or C_{max} of S-methadone
  – AUC_{0-24h} GMR [90% CI] 1.23 [1.12, 1.36]
  – C_{max} GMR [90% CI] 1.15 [1.07, 1.25]
BUPRENORPHINE/NALOXONE PK

- Addition of MK-5172 to buprenorphine/naloxone stable maintenance therapy did not meaningfully change the $\text{AUC}_{0-24h}$ or $\text{C}_{\text{max}}$ of buprenorphine
  - $\text{AUC}_{0-24h}$ GMR [90% CI] 0.98 [0.81, 1.20]
  - $\text{C}_{\text{max}}$ GMR [90% CI] 0.90 [0.76, 1.07]

- Addition of MK-5172 to buprenorphine/naloxone stable maintenance therapy did not meaningfully change the $\text{AUC}_{0-24h}$ or $\text{C}_{\text{max}}$ of norbuprenorphine
  - $\text{AUC}_{0-24h}$ GMR [90% CI] 1.13 [0.97, 1.32]
  - $\text{C}_{\text{max}}$ GMR [90% CI] 1.10 [0.97, 1.25]

- Addition of MK-5172 to buprenorphine/naloxone stable maintenance therapy did not meaningfully change the $\text{AUC}_{0-24h}$ or $\text{C}_{\text{max}}$ of with naloxone
  - $\text{AUC}_{0-24h}$ GMR [90% CI] 1.10 [0.82, 1.46]
  - $\text{C}_{\text{max}}$ GMR [90% CI] 1.00 [0.80, 1.27]

MK-5172 PK

- When coadministered with methadone, or with buprenorphine/naloxone, mean steady-state MK-5172 $\text{AUC}_{0-24h}$ and $\text{C}_{\text{max}}$ were similar compared to historical control subjects
Conclusions

• MK-5172 200 mg QD had no clinically meaningful impact on the pharmacokinetics of methadone or buprenorphine/naloxone maintenance therapy

• Maintenance therapy with methadone or buprenorphine/naloxone did not significantly impact the pharmacokinetics of co-administered MK-5172 (comparison to historical controls)

• No dose adjustments of MK-5172, methadone or buprenorphine/naloxone are needed for co-administration of methadone or buprenorphine/naloxone with MK-5172
Acknowledgments

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