Age and Gender Effects on the Pharmacokinetics of Multiple Oral Doses of MK-5172

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Background

• **MK-5172**: A 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

• **Study Rationale:**
  – HCV-infected patients >65 years are an understudied and difficult-to-treat population
  – Burden of chronic HCV infection in the elderly is expected to increase significantly in the USA over the next 2 decades
  – Early clinical program and PK characterization in predominantly young (<45 years), male, healthy population

• **Study Objectives:**
  – To assess the safety and tolerability of multiple oral doses of MK-5172 when administered to elderly male and female subjects
  – To assess the MK-5172 multiple-dose PK between healthy elderly males and females and between healthy elderly and young subjects
MK-5172: Drug Metabolism and Pharmacokinetics

Metabolism/Transporters
- 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

Clinical PK
- AUC & C\text{max}: Dose-proportional <200 mg; > dose-proportional >200 mg
- Steady state achieved within 7 days of QD dosing
- Average apparent terminal t\text{1/2} ~15-35 hr
- No circulating metabolites
- Minimal renal excretion (<1%)
- Minor food effect: Fed/fasted GMR: AUC\text{0-∞} = 0.7, C\text{max} = 1.2
- ~2-fold higher AUC in HCV patients vs healthy young males
  - Exposure at 200 mg in NHV similar to 100 mg (clinical dose) in HCV-infected patients
Methods

• Double-blind, randomized, placebo-controlled, parallel-group, multiple-dose study in HCV-uninfected subjects
  – Panel A: 8 healthy males aged 65 to 78 years
  – Panel B: 8 healthy females aged 65 to 79 years
  – Active: Placebo = 3:1

• **Dose:** 400 mg MK-5172 or matching placebo QD (fasted) PO X 7 days

• **Clinical Safety Evaluation**
  – Safety and tolerability: assessed by physical examination, vital signs, ECGs, and laboratory safety tests (CBC, chemistry panel, and urinalysis)

• **MK-5172 PK**
  – Blood samples:
    • Day 1: Predose and at specified time points over 24 hours postdose
    • Day 3: Predose
    • Day 6: Predose
    • Day 7: Predose and specified time points over 120 hours postdose
  – Plasma PK parameters \( (AUC_{0-24}, C_{\text{max}}, T_{\text{max}} \text{ and } C_{24}) \) were calculated on Day 1 and Day 7; Day 3 and 6 were used for steady-state analysis
Results - Safety and Tolerability

- No serious clinical or laboratory experiences were reported and no subjects discontinued.
- Eight (8) subjects reported a total of 26 clinical adverse experiences, of which 14 were considered drug-related. 1 of these AEs was reported after receiving placebo.
- The most frequently reported clinical adverse experiences considered related to study drug were headache and diarrhea.
Day 7 Elderly Males vs Females

- AUC$_{0-24hr}$: 76% higher in females than males
- C$_{\text{max}}$: 90% higher in females than males
- T$_{\text{max}}$ was the same between elderly males and females

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR Female/Male</th>
<th>90% CI</th>
</tr>
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<tbody>
<tr>
<td>AUC$_{0-24hr}$</td>
<td>1.76</td>
<td>(0.82, 3.81)</td>
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<tr>
<td>C$_{\text{max}}$</td>
<td>1.90</td>
<td>(0.82, 4.41)</td>
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**Individual Ratio**

**Geometric Ratio**

**Mean MK-5172 Plasma Concentration, nM**

- Elderly Males on Day 7
- Elderly Females on Day 7
Day 7 Elderly Males vs Young Males

- **AUC\textsubscript{0-24hr}:** 118% higher in elderly males than young males
- **C\textsubscript{max}:** 68% higher in elderly males than young males
- **T\textsubscript{max}** was the same between elderly males and young males

### Table

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<tr>
<th>Parameter</th>
<th>GMR Elderly/Young</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC\textsubscript{0-24hr}</td>
<td>2.18</td>
<td>(1.01, 4.71)</td>
</tr>
<tr>
<td>C\textsubscript{max}</td>
<td>1.68</td>
<td>(0.73, 3.90)</td>
</tr>
</tbody>
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Results Summary

• Elderly/Young PK Comparison
  – Following 7-day dosing of 400 mg MK-5172, the steady-state AUC₀-2₄ geometric mean ratio (GMR) (90% confidence interval [CI]) for elderly males/young males was 2.18 (1.01, 4.71)
  – Using historical PK data for young males, Cₘₐₓ and C₂₄ values were 68% and 107% greater in elderly males than young males, respectively
  – A direct comparison between elderly females and healthy young females could not be made as there were no MK-5172 PK data available in young females

• Elderly Female/Elderly Male PK Comparison
  – Following 7-day dosing of 400 mg MK-5172, the steady-state AUC₀-2₄ GMR (90% CI) for elderly females/elderly males was 1.76 (0.82, 3.81)
  – Cₘₐₓ and C₂₄ values were 90% and 29% greater in elderly females than elderly males, respectively
Discussion

- Multiple oral dosing of MK-5172 400 mg for 7 days is generally well tolerated in healthy elderly male and female subjects
- Gender and age effects on PK were observed
- Gender effect (increase in $AUC_{0-24}$, $C_{\text{max}}$ and $C_{24}$):
  - The body weight of the elderly males was 31% higher than elderly females
- Potential explanations for age effect (increase in $AUC_{0-24}$, $C_{\text{max}}$ and $C_{24}$)
  - Age-related loss of renal function
    - Given the minimal renal elimination of MK-5172, a substantial change due to renal impairment is not expected
  - Increase in body fat composition = reduced volume of distribution for drugs with low lipophilicity (e.g., MK-5172)
  - Increase in bioavailability (e.g., reduced P-glycoprotein-mediated intestinal efflux or decreased pre-systemic metabolism)
    - Effects of aging are inconsistent
  - Decrease in CYP3A4-mediated clearance
    - For high-clearance drugs, decreased liver blood flow may explain a decrease in hepatic clearance
Conclusions

• Multiple oral dosing of 400 mg MK-5172 for seven days was generally well tolerated in healthy elderly male and female subjects

• An age effect on MK-5172 PK was observed with an $\text{AUC}_{0-24} \text{ GMR}$ for elderly males/young males of 2.18

• A gender effect on MK-5172 PK in elderly subjects was observed with an $\text{AUC}_{0-24} \text{ GMR}$ for elderly females/elderly males of 1.76

• No dose adjustments for age or gender are anticipated given the overall safety and efficacy margins of the expected clinical dose
Acknowledgments

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  – Clinical research unit staff
Disclosures

Christina Reitmann, Luzelena Caro, Iain Fraser, and Deborah Panebianco are current employees of Merck Sharp & Dohme Corp.