

Pharmacokinetics of Oral Maribavir, a Novel Anti-Cytomegalovirus Agent, in Subjects with Renal Impairment

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INTRODUCTION

Maribavir (5,6-dichloro-2-(isopropylamino)-1-β-L-ribofuranosylbenzimidazole) is an orally bioavailable antiviral drug with a novel mechanism of action against cytomegalovirus (CMV).¹ Unlike currently available anti-CMV agents that inhibit CMV DNA polymerase, the dominant phenotypic inhibitory effect of maribavir is on viral DNA assembly and egress of viral capsids from the nucleus of infected cells.² In addition, maribavir is active *in vitro* against strains of CMV that are resistant to ganciclovir, acyclovir, cidofovir, and foscarnet.³ In clinical studies, maribavir demonstrated encouraging anti-CMV activity *in vivo* and was generally well tolerated across a wide range of doses.⁴

Maribavir is being developed for the prevention of CMV disease in transplant recipients. Subjects who have undergone solid organ or stem cell transplantations may have multiple factors contributing to the possible development of renal impairment. Thus, characterization of the pharmacokinetic profile of maribavir in subjects with renal impairment was needed to determine if dose adjustment would be required in these patients.

METHODS

Eligible subjects had to be nonsmoking adults, 18 to 70 years old, with a body mass index between 18 and 35, and with renal function expected to be stable for study duration. Subjects with renal impairment who required peritoneal dialysis or hemodialysis were not eligible. The Institutional Review Board of each participating site approved the protocol.

Subjects were classified according to measured creatinine clearance (CrCl) as follows:

| Renal Function Group | Measured CrCl (mL/min) |
|----------------------|------------------------|
| Normal | > 80 |
| Mild | 50-80 |
| Moderate | 30-49 |
| Severe | < 30 |

Study Design

In this open-label study, subjects were confined to the study unit from Day -1 (the day before dosing) through Day 3 for dosing, pharmacokinetic sampling, and safety evaluations. An outpatient visit was also required on Day 8 to assess for adverse events.

Following an overnight fast, a single 400-mg oral dose of maribavir (4 x 100-mg tablets) was administered on Day 1; subjects continued to fast for 4 hours after the dose. Blood samples were collected before maribavir administration through 36-hours post dose.

Safety was monitored through the recording of adverse events and changes in the results of physical examinations, vital signs (blood pressure and heart rate), 12-lead electrocardiograms (ECGs), and clinical safety laboratory tests (hematology, clinical chemistry, and urinalysis).

Drug Assays

MDS Pharma Services (Montreal, Quebec, Canada) determined the concentrations of maribavir and its N-dealkylated metabolite (VP 44469) in plasma (EDTA) using the reverse-phase high-performance liquid chromatography with mass spectrometry (LC/MS/MS) method of detection. The minimum detectable concentration using this method was 5 ng/mL for both maribavir and VP 44469.

Quest Pharmaceutical Services (Newark, DE) determined the free fraction of maribavir in plasma (f_u) using equilibrium dialysis and LC/MS/MS. Where samples were available, the f_u for maribavir was measured from the 0- (after addition of 5 mg/mL of maribavir), 2-, and 12-hour samples.

Pharmacokinetic Analyses

Pharmacokinetic parameters for maribavir and VP 44469 were estimated using noncompartmental methods. Nominal sampling times were used in calculations. WinNonlin® Pro (Version 2.1; Pharsight® Corporation, Cary, NC) was used for pharmacokinetic analyses. Summary statistics were prepared for vital signs, clinical laboratory evaluations, and ECG intervals.

The natural logarithmic transformation was applied to area under the plasma concentration-time curve (AUC), maximum plasma concentration (C_{max}), oral clearance (Cl/F), and terminal-phase volume of distribution/bioavailability (V_z/F ; total and unbound) prior to statistical analysis. The actual values of the terminal half-life ($T_{1/2}$) and time to maximum plasma concentration (T_{max}) were analyzed.

The pharmacokinetic parameter estimates were analyzed using one-way analysis of variance (ANOVA) comparing the 3 groups. Slope estimates were calculated from a simple linear regression of the pharmacokinetic parameter estimates on the measured CrCl.

RESULTS

Subject Disposition and Characteristics

- The study population is presented in [Table I](#).
- No subject with normal renal function and 95% (18/19) of subjects with renal impairment took concomitant medications.
- The most common medications taken during the study were diuretics (12 subjects) and medications for diabetes mellitus (12 subjects).

Table I. Demographic and clinical characteristics of the study population.

| Characteristic | Renal Function Group (CrCl, mL/min) | | | All (N=31) |
|---------------------------------|-------------------------------------|---|--------------------------------|------------|
| | Normal Function (> 80) (n=12) | Mild/Moderate Impairment (30-80) (n=10) | Severe Impairment (< 30) (n=9) | |
| Age (y), mean (SD) | 58 (5.7) | 59 (7.8) | 54 (11.4) | 57 (8.3) |
| Gender (n) | | | | |
| Female/Male | 4/8 | 8/2 | 4/5 | 16/15 |
| Body weight (kg), mean (SD) | | | | |
| Females | 75 (4.6) | 77 (10.6) | 71 (11.1) | 75 (9.4) |
| Males | 81 (8.6) | 105 (4.7) | 84 (18.6) | 85 (14.2) |
| Race, n (%) | | | | |
| Black/African American | 6 (50) | 4 (40) | 5 (56) | 15 (48) |
| White | 5 (42) | 6 (60) | 3 (33) | 14 (45) |
| American Indian/Alaskan | 1 (8) | 0 | 1 (11) | 2 (6) |
| Relevant medical history, n (%) | | | | |
| Diabetes | 0 | 6 (60) | 8 (89) | 14 (45) |
| Hypertension | 1 (8) | 8 (80) | 9 (100) | 18 (58) |
| Measured CrCl, (mL/min) | | | | |
| Mean | 105.5 | 51.8 | 21.8 | - |
| Min, max | 82, 127 | 30, 70 | 12, 28 | |

Pharmacokinetic Results

Figure 1. Mean maribavir plasma concentration-time profiles for subjects with normal renal function, mild/moderate renal impairment, and severe renal impairment following oral administration of a single 400-mg dose of maribavir.

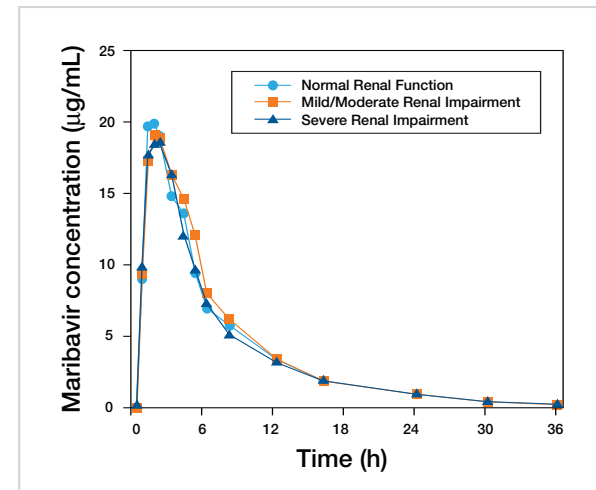


Table II. Maribavir pharmacokinetic parameters (mean ± SD) following oral administration of a single 400-mg maribavir dose.*

| Parameters | Unit | Renal Function Group (CrCl, mL/min) | | | P-Value |
|--------------------------|-----------|-------------------------------------|---|--------------------------------|---------|
| | | Normal Function (> 80) (n=12) | Mild/Moderate Impairment (30-80) (n=10) | Severe Impairment (< 30) (n=8) | |
| Parameter | | | | | |
| T_{max} | h | 1.8 (0.7) | 2.2 (1.1) | 1.8 (0.8) | 0.559 |
| C_{max} | µg/mL | 22.56 (5.98) | 21.97 (6.89) | 21.5 (7.7) | 0.869 |
| Kel | 1/h | 0.132 (0.03) | 0.125 (0.015) | 0.136 (0.029) | NC |
| $T_{1/2}$ | h | 5.31 (1.16) | 5.61 (0.65) | 5.28 (1.05) | 0.780 |
| AUC _{0-t} | µg · h/mL | 136.6 (59.5) | 143.6 (44.5) | 133.8 (70.6) | 0.804 |
| AUC _{0-∞} | µg · h/mL | 138.6 (61.9) | 145.3 (45.4) | 135.7 (72.6) | 0.810 |
| Extrap. | % | 1.04 (0.98) | 1.09 (0.57) | 1.16 (0.99) | NC |
| V_z/F | L | 25.5 (8.7) | 24.7 (9.8) | 26.8 (11.1) | 0.950 |
| Cl/F | L/h | 3.38 (1.29) | 3.05 (1.12) | 3.56 (1.53) | 0.808 |
| $V_z/F/kg$ | L/kg | 0.327 (0.131) | 0.297 (0.096) | 0.336 (0.116) | NC |
| Cl/F/kg | L/h/kg | 0.0434 (0.0185) | 0.037 (0.0114) | 0.0445 (0.0132) | NC |
| Unbound Parameter | | | | | |
| f_u | % | 1.1 (0.2) | 1.2 (0.5) | 1.5 (0.6) | 0.124 |
| $C_{max,u}$ | µg/mL | 0.248 (0.082) | 0.269 (0.117) | 0.308 (0.109) | 0.542 |
| AUC _{0-∞,u} | µg · h/mL | 1.52 (0.49) | 1.68 (0.47) | 1.96 (1.04) | 0.623 |
| V_z/F_{u} | L | 2230 (506) | 2152 (913) | 1916 (921) | 0.430 |
| Cl/F _u | L/h | 288 (90) | 260 (93) | 259 (139) | 0.616 |
| $V_z/F/kg_{u}$ | L/kg | 28.1 (6.0) | 25.7 (7.6) | 23.5 (7.7) | 0.318 |
| Cl/F/kg _u | L/h/kg | 3.66 (1.21) | 3.14 (0.76) | 3.17 (1.09) | 0.558 |

*P-values from analysis of variance comparing renal function groups for maribavir pharmacokinetic parameter estimates.

AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time of last measurable concentration (t); AUC_{0-∞} = AUC from time 0 to infinity; AUC_{0-∞,u} = AUC_{0-∞} based on unbound plasma concentration; Cl/F = oral clearance; Cl/F/kg = weight-normalized Cl/F; Cl/F_u = unbound oral clearance; Cl/F/kg_u = weight-normalized Cl/F/kg; C_{max} = maximum plasma concentration; $C_{max,u}$ = maximum unbound plasma concentration; f_u = unbound fraction of maribavir in plasma; Kel (λ_z) = elimination rate constant; NC = not calculated; $T_{1/2}$ = terminal half-life; T_{max} = time to C_{max} ; V_z/F = terminal-phase volume of distribution/bioavailability; $V_z/F/kg$ = weight-normalized V_z/F ; V_z/F_{u} = terminal-phase volume of distribution/bioavailability based on unbound concentrations; $V_z/F/kg_{u}$ = weight-normalized V_z/F_{u} .

- Except for f_u ($P = 0.022$), slopes of lines of linear regression of pharmacokinetic parameters compared with measured CrCl were not different from zero.

Figure 2. Mean VP 44469 plasma concentration-time profiles for subjects with normal renal function, mild/moderate renal impairment, and severe renal impairment following oral administration of a single 400-mg dose of maribavir.

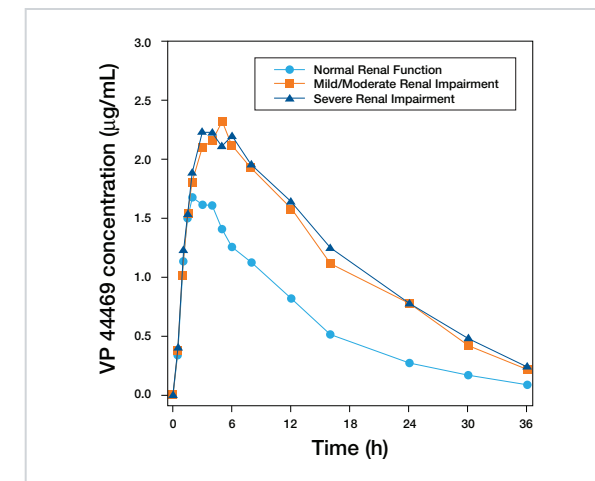
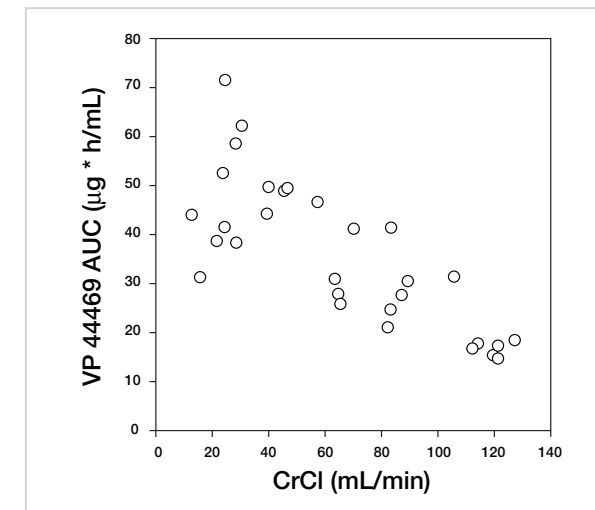


Figure 3. VP 44469 AUC_{0-∞} vs measured creatinine clearance.



- Maribavir metabolite VP 44469 AUC values for the mild/moderate and severe groups were roughly 2 times higher, whereas CrCl values were roughly 2 times lower compared with the normal group ([Figure 3](#)). Pharmacokinetic parameters for the mild/moderate and severe groups were similar. This finding indicates that non-renal pathways of VP 44469 elimination prevent exponential increases in VP 44469 AUC_{0-∞} with decreasing renal function.

Clinical Observations and Tolerability

- No serious adverse events occurred during this study.
- No subject was withdrawn from the study due to an adverse event.
- Taste disturbance was the only adverse event reported in > 1 subject: 6 (50%) subjects with normal function, 5 (50%) with mild/moderate impairment, and 2 (22%) with severe impairment.
- No subject experienced any adverse event related to abnormal laboratory findings, vital signs, or ECG results.

CONCLUSIONS

- Renal impairment does not affect the pharmacokinetics of maribavir.
- Mean maribavir plasma concentration-time profiles for all 3 groups were similar.
- Mean VP 44469 concentrations and AUC values for subjects with renal impairment increased with decreasing CrCl values.
- A single oral dose of maribavir 400 mg was well tolerated by subjects in all 3 groups. Taste difference was the only adverse event reported for > 1 subject.

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