European Journal of Drug Metabolism and Pharmacokinetics

The Effect of Verapamil, a P-gp Inhibitor, on the Pharmacokinetics, Safety, and Tolerability of Omadacycline in Healthy Adults: A Phase I, Open-Label, Single-Sequence Study

Supplementary Information

Thomas L. Hunt[1], Evan Tzanis[2], Stephen Bai[2], Amy Manley[2,*], Surya Chitra[2], Paul C. McGovern[2]

[1]PPD Phase 1 Clinic, 7551 Metro Center Drive, Suite 200, Austin, TX 78744, USA
[2]Paratek Pharmaceuticals, Inc., 1000 First Avenue, Suite 200, King of Prussia, PA 19406, USA

***Corresponding author:**
Amy Manley
Amy.Manley@ParatekPharma.com

Inclusion Criteria

Each participant met all of the following criteria at screening and baseline period 1 (day –1 of period 1) to be enrolled in this study:

- Written and signed informed consent must have been obtained before any protocol-specific assessment was performed.
- Male and female participants between 18 and 55 years of age, inclusive, and in good health as determined by past medical history, clinical laboratory test results (no clinically significant abnormalities in the opinion of the investigator), vital sign measurements, 12-lead ECG results, and physical examination findings at screening.
- Vital signs (oral body temperature, systolic blood pressure [BP], diastolic BP, and heart rate) must have been assessed in the sitting position after the participant had rested for at least 3 minutes. Sitting vital signs should have been within the following ranges:
    - Oral body temperature, 35.0–37.5°C (95.0–99.5°F)
    - Systolic BP, 100–140 mmHg
    - Diastolic BP, 50–90 mmHg
    - Heart rate, 55–90 beats/minute
- At screening only, BP and heart rate were assessed again after 3 minutes in a standing position. There should have been no more than a 20 mmHg decrease in systolic BP or a 10 mmHg decrease in diastolic BP, each combined with an increase in heart rate (> 20 beats/minute) and any symptoms associated with postural hypotension. Out-of-range vital signs may have been repeated once at the discretion of the investigator, if necessary.
- Weight must have been ≥ 50 kg and body mass index ≥ 18 and ≤ 30 kg/m^2.
- Females must have had a negative serum pregnancy test and agreed to use a highly effective form of birth control (e.g., post-menopausal [defined as amenorrhea 12 consecutive months and documented serum follicle-stimulating hormone level > 40 IU/mL], abstinence, intrauterine device, tubal ligation, hysterectomy, or bilateral oophorectomy) from screening through to the study completion visit. Males must have agreed to use a highly effective method of birth control with female partner(s) and must not have donated sperm for 90 days following the last dose of study drug.
- Participants must have been able to swallow one capsule or up to two tablets in succession.
- Participants must have been able to communicate well with the investigator and understand and comply with the requirements of the study.

Exclusion Criteria

Participants meeting any of the following criteria at screening and/or baseline period 1 (day –1 of period 1) were excluded from the study:

- Use of other investigational drugs within five half-lives or 30 days prior to screening, whichever was longer.
- History of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening or baseline period 1:
    - PR > 200 msec
    - QRS complex ≥ 120 msec
    - Long QT syndrome
    - Corrected QT interval (QTc) for heart rate using Fridericia's formula (QTcF) > 450 msec (males) or > 470 msec (females)

  Out-of-range ECGs may have been repeated once at the discretion of the investigator, if necessary.
- History of sick sinus syndrome, arrhythmia, ventricular tachycardia, unexplained syncope, or bradycardia.
- History of aortic stenosis, cardiogenic shock, symptomatic hypotension, cardiomyopathy, or congestive heart failure.
- History of second- or third-degree atrioventricular block, atrial flutter or fibrillation, or an accessory bypass tract (e.g., Wolff-Parkinson-White or Lown-Ganong-Levine syndromes).
- History of malignancy of any organ system (other than localized squamous and basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases.
- Inability to tolerate oral medication (e.g., nausea, vomiting, diarrhea, or any other condition that might impair ingestion or absorption of oral medication).
- Inability to tolerate drinking orange juice.
- Pregnant or nursing (breastfeeding) women.
- Use of tobacco products in the 3 months prior to screening.
- Use of any prescription drugs or herbal supplements within 4 weeks prior to baseline period 1, and/or over-the-counter medications including dietary and fitness/body-building supplements (vitamins included) within 2 weeks prior to baseline period 1.
- Intake of xanthine-containing (e.g., caffeine) food or beverages within 48 hours before baseline period 1.
- Intake of grapefruit-containing food or beverages within 48 hours before baseline period 1.
- Donation or loss of 400 mL or more of blood within 8 weeks before baseline period 1, or longer if required by local regulation.
- Hemoglobin level < 12.5 g/dL for males or < 11.0 g/dL for females at screening or baseline period 1.
- Significant illness within 2 weeks before baseline period 1.

- History of autonomic dysfunction (e.g., recurrent episodes of fainting or palpitations) within 3 years prior to screening.
- History of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated) within 3 years prior to screening.
- History of hypersensitivity or allergic reaction (e.g., anaphylaxis, urticaria, or other significant reaction) to any tetracycline (e.g., minocycline, doxycycline, or tigecycline).
- History of hypersensitivity to verapamil hydrochloride.
- Any surgical or medical condition that, in the opinion of the investigator, might have significantly altered the absorption, distribution, metabolism, or excretion of drugs, or that may have jeopardized the participant in case of participation in the study.
- History of or active inflammatory bowel disease, ulcers, GI or rectal bleeding, or pancreatitis.
- Liver disease or liver injury as indicated by abnormal serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), or serum bilirubin. The investigator was guided by the following criteria:
    - Serum bilirubin may not have exceeded 1.2 × upper limit of normal (ULN).
    - Any other single parameter listed above may not have exceeded 1.5 × ULN.
    - More than one parameter listed above may not have exceeded ULN.

  A single parameter elevated up to and including 1.5 × ULN (or 1.2 × ULN for serum bilirubin) may have been repeated once at the discretion of the investigator as soon as possible. Rechecked results must have been within normal limits in order for a participant to qualify.

- Serum creatinine or blood urea nitrogen exceeding 1.2 × ULN. Testing may have been repeated once at the discretion of the investigator as soon as possible.
- Evidence of urinary obstruction or difficulty in voiding at screening.
- History or evidence of immunodeficiency or a positive human immunodeficiency virus (chemiluminescence assay and Multispot analyses) test result regardless of immune status.
- Positive hepatitis B surface antigen or hepatitis C antibody test result.
- Positive alcohol test or positive drug screen (including cotinine).
- Had been treated with omadacycline or verapamil within 30 days of baseline period 1 or had previously enrolled in this study.
- Had any planned medical intervention that might have interfered with the ability to comply with study requirements.
- No additional exclusions may have been applied by the investigator, in order to ensure that the study population was representative of all eligible participants.

Pharmacokinetic Variables

The following pharmacokinetic parameters were estimated and reported by treatment after omadacycline dosing on day 1 of each period and verapamil dosing on day 1 of period 2:

$AUC_{0–24}$	Area under the plasma concentration versus time curve from time 0 to 24 hours after dosing calculated by the linear trapezoidal linear interpolation method.
$AUC_{0–t}$	Area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration calculated by the linear trapezoidal rule: $AUC_{0–t} = \sum_{i=1}^{n} \frac{(C_i + C_{i-1})}{2}(t_i - t_{i-1})$, where C_i and C_{i-1} was the plasma concentration at t_i and t_{i-1}, respectively, and t_i-t_{i-1} was the time interval.
$AUC_{0–inf}$	Area under the plasma concentration versus time curve from time 0 extrapolated to infinity, calculated as $AUC_{0–inf} = AUC_{0–t} + C_{last}/\lambda_z$, where C_{last} was the last quantifiable plasma drug concentration.
C_{max}	Maximum (peak) observed plasma concentration.
t_{max}	Time to reach C_{max}.
$t_{1/2}$	Terminal elimination half-life, calculated as $t_{1/2} = \ln(2)/\lambda_z$.
λ_z	Terminal phase rate constant, calculated using linear regression on the terminal portion of the ln-concentration versus time curve. At least three time points (excluding C_{max}) and $r^2 \geq 0.80$ were required to calculate and retain λ_Z and its associated parameters [$AUC_{(0–inf)}$].