CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209816Orig1s000
209817Orig1s000

OTHER REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: September 7, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Deepak Aggarwal, RPM
DAIP

Subject: QT-IRT Consult to NDA 209816/ 209817 (SDN 034)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 8/21/2018 regarding the sponsor's QT related labeling changes in response to QT-IRT's previous feedback. The QT-IRT reviewed the following materials:

- Sponsor's revised proposal for labeling;
- Sponsor's response to IR dated 05/21/2018; and
- Previous QT-IRT review dated 05/16/2018 in DARRTS and associated DARS consult review.

1 QT-IRT Responses

The sponsor's revised labeling proposal is shown below.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

[redacted] (b) (4)

The following is QT-IRT's proposed language which is a suggestion only and we defer the final labeling decision to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The totality of evidence from the nonclinical and clinical data indicate a lack of clinically relevant QTc prolongation at the maximum recommended dose of omadacycline.

Reviewer's comments:

1. *We had previously conveyed to the sponsor that* [redacted] (b) (4)
2. *Furthermore, we had recommended the sponsor to propose labeling language based on the HR and QTc effects in their phase 3 studies. In the ensuing teleconference, we had asked the sponsor for the comparison of the clinical ECG data from all 3 treatments, viz. omadacycline, moxifloxacin and linezolid, used in their clinical studies. We acknowledge the submission of this information by the sponsor (described in background information below).*
3. *In line with the evolving regulatory thinking about utilizing the in vitro hERG assay results to bridge the information for informing cardiac safety risk when there is a robust safety margin in these assays and a TQT study is either not feasible or not interpretable, we are proposing the above labeling language.*
4. *The above safety margin of omadacycline (IC_{50} divided by free Cmax), which indicates the distance away from proarrhythmia risk, is 685 when calculated using free Cmax achieved with the therapeutic dose (1.696 µg/mL considering 20% protein-binding) and 484 when calculated using the free Cmax achieved by the supratherapeutic dose used in TQT study (2.4 µg/mL). These values are higher than the current thinking for cut-off value set by the FDA CiPA team for drugs without a proarrhythmia risk. DARS reviewer thus concludes that within the therapeutic exposure level, omadacycline does not block hERG channels directly and is associated with low proarrhythmia risk.*

2 BACKGROUND

2.1 Summary of sponsor's response to FDA's IR to inform QT related labeling

FDA IR:

[redacted] (b) (4) There were substantial increases in heart rate and therefore, QTc interval could not be characterized in this

TQT study. Omadacycline caused a dose-/concentration-dependent increases in heart rate that impacts the ability to interpret the ΔΔQTc effects corresponding to the administration of a single therapeutic dose (100 mg IV) as well as a single supra-therapeutic dose (300 mg IV), hence, TQT study is inconclusive regarding the QT prolongation evaluation.

We recommend that you propose labeling language based on the HR and QTc effects in the pivotal phase 3 studies.

Sponsor's response:

(b) (4)

in Paratek's continuing efforts to provide due diligence for all Agency requests, Paratek has contracted an outside vendor to attempt to transform the data obtained in Study TQTC-0803 into a more interpretable form for the Agency.

Paratek has conducted additional analyses of all electrocardiogram (ECG) data available from 1,415 patients with ABSSSI or CABP enrolled in the omadacycline randomized, Phase 3, active comparator-controlled Studies PTK0796-ABSI-1108 and PTK0796-CABP-1200. The data from these studies include ECG results obtained at the 100-mg iv dose of omadacycline, at 30 to 90 min after initial iv dosing, as well as equivalent data obtained from both positive (moxifloxacin) and negative (linezolid) controls for QT prolongation. This corresponds to the measurement of QTcF between 35 min and 90 min after initial dosing in the TQTC study. The analyses include tabular summaries, box and whisker plots, and empirical distribution function (EDF) graphs of the absolute and change from Baseline to each visit in ECG parameters and clinically notable changes in QTcF results from Baseline to each available timepoint. All analyses are provided with this response (see Appendix 1) and are selectively summarized below.

The results of these analyses confirm the conclusion of the original TQTc study, that omadacycline at the 100-mg iv dose of omadacycline does not induce QT prolongation, and importantly, extends this finding to patients with ABSSSI and CABP. The median change from Baseline in QTcF at 30 to 90 min after the first iv dose was 0.0 msec in subjects receiving omadacycline compared to 4.0 msec in subjects receiving linezolid, and 5.0 msec in subjects receiving moxifloxacin (Table 1). Results were similar when the change in QTcF was evaluated using the pre-Dose 1 (30 min prior to the first infusion) timepoint to the post-Dose 1 timepoint in the pivotal Phase 3 studies pooled (Table 14.3.5.1.4.IR3) and by study for Studies ABSI-1108 (Table 14.3.5.1.4.IR4) and CABP-1200 (Table 14.3.5.1.4.IR5). No changes in QTcF were observed in the omadacycline group in the pooled pivotal Phase 3 studies with a median change of 0.0 msec and a moxifloxacin median change of 5.0 msec after iv doses. Similar results were observed for the change in QTcF in the individual studies that included both negative (linezolid, Study ABSI-1108) and positive (moxifloxacin, Study CABP-1200) active comparator controls for QT prolongation.

The change from Baseline in QTcF in the omadacycline group is comparable or lower than the change observed in the linezolid group (negative control) in the box and whisker plot (Figure 1) and is evident in the parallel tracking of the omadacycline and linezolid groups in the EDF graph

compared to the pronounced rightward shift observed in the moxifloxacin group (positive control, Figure 2). The number of clinically notable QTcF values in the omadacycline group at 30 to 90 min after the first iv dose is comparable or lower than the number of clinically notable values observed in the linezolid and moxifloxacin groups (Table 2).

Table 1. Absolute and Change From Baseline in QTcF 30 to 90 min After the First iv Dose in Phase 3 Studies ABSS-1108 and CABP-1200 (Safety Population)

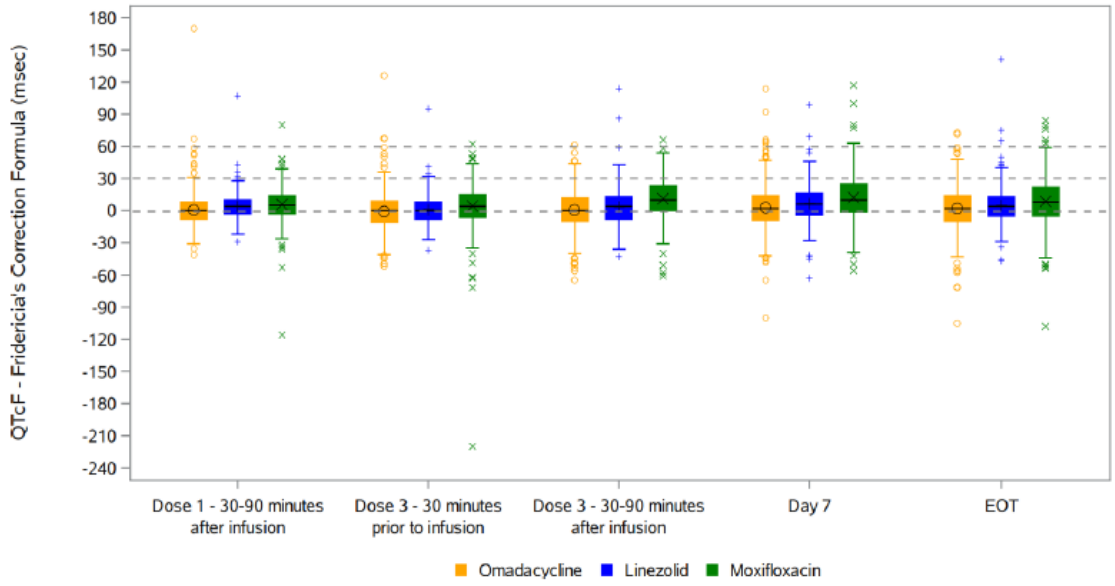
	Omadacycline (N = 705)		Linezolid (N = 322)		Moxifloxacin (N = 388)	
	Value at Baseline	Change From Baseline	Value at Baseline	Change From Baseline	Value at Baseline	Change From Baseline
QTcF (msec)						
n	660	657	316	316	355	355
Mean (SD)	417.3 (24.27)	0.7 (14.34)	418.3 (22.02)	4.0 (11.98)	422.6 (26.64)	5.8 (15.82)
Median	417.0	0.0	416.5	4.0	421.0	5.0
Min, max	355, 593	-41, 170	362, 512	-29, 107	330, 549	-116, 80

Studies included: ABSI-1108 and CABP-1200.
Baseline is defined as the value closest to but prior to the initiation of test article administration.
QTcF = QT interval corrected for heart rate using Fridericia's formula.
Source: Table 14.3.5.1.4.IR2

Table 2. Clinically Notable Values for ECG at Baseline and 30 to 90 min After Dose 1 in Phase 3 Studies ABSS-1108 and CABP-1200 (Safety Population)

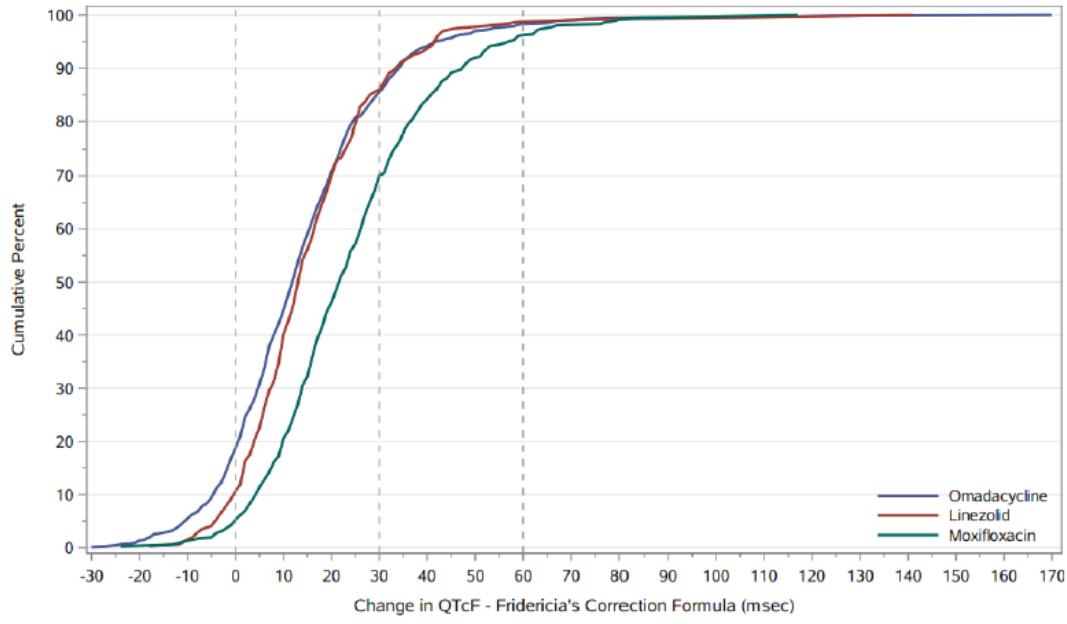
Time Point Clinically Notable Criteria	Omadacycline (N = 705) n (%)	Linezolid (N = 322) n (%)	Moxifloxacin (N = 388) n (%)
Baseline, n	673	319	362
QTcF ≤ 450 msec	635 (94.4)	302 (94.7)	331 (91.4)
QTcF > 450 to ≤ 480 msec	29 (4.3)	14 (4.4)	25 (6.9)
QTcF > 480 to ≤ 500 msec	6 (0.9)	2 (0.6)	4 (1.1)
QTcF > 500 msec	3 (0.4)	1 (.3)	2 (0.6)
Dose 1, 30 to 90 min after infusion, n	660	316	355
QTcF ≤ 450 msec	617 (93.5)	289 (91.5)	301 (84.8)
QTcF > 450 to ≤ 480 msec	35 (5.3)	25 (7.9)	48 (13.5)
QTcF > 480 to ≤ 500 msec	4 (0.6)	1 (0.3)	4 (1.1)
QTcF > 500 msec	4 (0.6)	1 (0.3)	2 (0.6)
Dose 1, 30 to 90 min after infusion, n	657	316	355
Change from Baseline ≤ 0 msec	343 (52.2)	119 (37.7)	129 (36.3)
Increase from Baseline			
> 0 to < 30 msec	301 (45.8)	192 (60.8)	207 (58.3)
≥ 30 to ≤ 60 msec	11 (1.7)	4 (1.3)	18 (5.1)
> 60 msec	2 (0.3)	1 (0.3)	1 (0.3)

Figure 1. Box and Whisker Plot of the Change from Baseline in QTcF Over Time in Studies ABSI-1108 and CABP-1200 (Safety Population)



Studies included: ABSI-1108 and CABP-1200.

Figure 2. Empirical Distribution Function of the Maximum Change from Baseline in QTcF in Studies ABSI-1108 and CABP-1200 (Safety Population)



Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

DHANANJAY D MARATHE
09/09/2018

CHRISTINE E GARNETT
09/10/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 31, 2018
Requesting Office or Division:	Division of Anti-Infective Products (DAIP)
Application Type and Number:	NDA 209816 and NDA 209817
Product Name and Strength:	Nuzyra (omadacycline) tablets, 150 mg; Nuzyra (omadacycline) for injection, 100 mg / vial
Applicant/Sponsor Name:	Paratek Pharmaceuticals
FDA Received Date:	August 21, 2018 and August 30, 2018
OSE RCM #:	2017-2607-1 and 2018-313-1
DMEPA Safety Evaluator:	Sevan Kolejian, Pharm D, MBA
DMEPA Team Leader:	Otto L. Townsend, Pharm D

1 PURPOSE OF MEMORANDUM

Division of Anti-Infective Products (DAIP) requested that we review the revised container label and carton labeling for Nuzyra (omadacycline) tablets, 150 mg, bottles of 30 tablets, Nuzyra (omadacycline) for injection, 100 mg / vial and Nuzyra tablets professional sample (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

We note Paratek Pharmaceuticals included (b) (4) labeling; however, we did not review this labeling because (b) (4) is not being considered during the review of the original application.

The revised container labels and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Kolejian, S. Label and Labeling Review for Omadacycline (NDA 209816 and NDA 209817). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 31. RCM No.: 2017-2607 and 2018-313.

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/s/

SEVAN H KOLEJIAN
08/31/2018

OTTO L TOWNSEND
08/31/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 27, 2018

To: Rama Kapoor, M.D.
Division of Anti-Infective Products (DAIP)

Jane Dean, Regulatory Project Manager, DAIP

Abimbola Adebowale, Associate Director for Labeling, DAIP

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for NUZYRA (omadacycline) for injection, for intravenous use and NUZYRA (omadacycline) tablets, for oral use

NDA: 209816 and 209817

In response to DAIP's consult request dated April 17, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for NUZYRA.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAIP on August 17, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 11 and July 2, respectively, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

48 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

DAVID F FOSS
08/27/2018

Clinical Inspection Summary

Date	June 27, 2018
From	John Lee, M.D., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Deepak Aggarwal, Regulatory Project Manager Rama Kapoor, M.D., Medical Officer Mayurika Ghosh, M.D., Clinical Team Leader Sumati Nambiar, M.D., M.P.H., Director Division of Anti-Infective Products (DAIP)
Application	NDA 209816
Applicant	Paratek Pharmaceuticals, Inc.
Drug	Omadacycline (b) (4)
NME / Original NDA	Yes
Review Status	Priority
Proposed Indication	Treatment of community-aquired bacterial pneumonia or acute bacterial skin and skin structure infections
Consultation Date	February 21, 2018
CIS Goal Date	July 15, 2018
Action Goal Date	October 2, 2018
PDUFA Due Date	October 2, 2018

I. OVERALL ASSESSMENT OF FINDINGS

Three studies (PTK-0796-ABSI-01108, PTK-0796-ABSI-16301, and PTK-0796-CABP-1200) were audited on-site at good clinical practice (**GCP**) inspections of six clinical investigator (**CI**) sites, three foreign and three domestic. A Form FDA 483 was issued at Site 606 in Study PTK-0796-ABSI-16301 (Soledad Lee; Buena Park, CA), in confirmation of the GCP deficiencies previously identified by the sponsor and reported in the NDA. For all remaining sites, no significant deficiencies were observed and a Form FDA 483 was not issued; study conduct appeared adequately GCP-compliant, including sponsor oversight of study conduct. All audited data were acceptably verifiable against source records and case report forms (**CRFs**). Except for Site 606, the data from all inspected sites appear reliable as reported in the NDA.

II. BACKGROUND

Paratek Pharmaceuticals, Inc. proposes omadacycline (b) (4) for the treatment of community-acquired bacterial pneumonia (**CABP**) or acute bacterial skin and skin structure infections (**ABSSSI**). Omadacycline is a semi-synthetic derivative of tetracycline. As an antibiotic class, tetracyclines have been used effectively for over 70 years to treat a variety of bacterial infections. The following 3 omadacycline studies supporting this NDA were identified for on-site audit at GCP inspections of six CI sites.

Study PTK-0796-ABSI-01108

A Phase 3 Randomized, Double-Blind, Multi-Center Study to Compare the Safety and Efficacy of Omadacycline IV/PO to Linezolid IV/PO for Treating Adult Subjects with Acute Bacterial Skin and Skin Structure Infection (ABSSSI)

The primary objective of this randomized (1:1), active-controlled, double-blind study was to show that omadacycline is not inferior to linezolid in treating ABSSSI due to Gram-positive bacteria. Men or women (age ≥ 18 years) with a qualifying skin and skin structure infection (**QSSSI**) were treated with omadacycline or linezolid, with QSSSI defined as ≥ 75 cm^2 of contiguous skin lesion (maximum head-toe length x maximum width) showing erythema, edema, or induration.

- Omadacycline: 100 mg intravenous (**IV**) every 12 hours (**Q12h**) for two doses, followed in 12 hours by 100 mg IV every 24 hours (**Q24h**), with the option to switch to 300 mg by mouth (**PO**) Q24h after at least 6 doses of IV treatment
- Linezolid (active control): 600 mg IV Q12h, with the option to switch to 600 mg PO Q12h after at least 6 doses of IV treatment

Co-primary Endpoints

- Early Clinical Response (**ECR**), defined for this study as survival with ≥ 20% reduced lesion size within 48 to 72 hours after starting therapy, without rescue therapy
- Investigator Assessment of Clinical Response (**IACR**) at Post-Therapy Evaluation (**PTE**), defined as survival after therapy completion with clinical improvement obviating further therapy

Study PTK-0796-ABSI-16301

A Phase 3 Randomized, Double-Blind, Multi-Center Study to Compare the Safety and Efficacy of Oral Omadacycline to Oral Linezolid for Treating Adult Subjects with Acute Bacterial Skin and Skin Structure Infection (ABSSSI)

This study was similar to Study PTK-0796-ABSI-1108: (1) randomized (equal ratio), active-controlled, double-blind study design; (2) primary study objective of showing that omadacycline is not inferior to linezolid in treating ABSSSI; (3) major subject selection criteria; (4) definition of QSSSI; and (5) efficacy assessment, including co-primary endpoints. Study medications and treatment regimens (randomization/study arms) were: (1) omadacycline 450 mg PO Q24h for two doses, followed by 300 mg PO Q24h, or (2) linezolid 600 mg PO Q12h.

Study PTK-0796-CABP-1200

A Phase 3 Randomized, Double-blind, Multi-center Study to Compare the Safety and Efficacy of Omadacycline IV/PO to Moxifloxacin IV/PO for Treating Adult Subjects with Community-acquired Bacterial Pneumonia (CABP)

The primary objective of this randomized (1:1), double-blind, active-controlled study was to show that IV omadacycline is not inferior to moxifloxacin in treating adults with CABP. The study consisted of 3 phases: subject screening and randomization to omadacycline or moxifloxacin; double-blinded treatment for at least three days (4 doses, with placebo infusions matched to omadacycline and moxifloxacin; and safety follow-up. Subjects were treated IV for at least 3 days (4 doses), with the option to switch to PO therapy. The total duration (IV and PO) was 7-14 days. The major subject selection criteria were: age $\geq$ 18 years, 3 or more of the clinical symptoms of CABP, and:

- One or more clinical signs or laboratory finding associated with CABP; radiographic findings consistent with acute bacterial pneumonia within last 24 hours; and Pneumonia Outcomes Research Team (**PORT**) Risk Class II, III, or IV
- Subject exclusion (any of): potentially effective systemic antibacterial therapy within 72 hours; CABP due to a pathogen resistant to either test article; hospital-acquired or healthcare-related pneumonia; or previous treatment with omadacycline

Primary Efficacy Evaluation

Proportions of subjects for clinical success, clinical failure, and indeterminate: at early clinical response = primary, at end-of-therapy (EOT) = non-primary

- Early clinical response (**ECR**): clinical response (**CR**) at 72 to 120 hours after treatment initiation; indeterminate = lost to follow-up or otherwise missing data
- Clinical failure (**CF**): need for rescue antibiotics, receipt of potentially effective non-study systemic antibiotics, AE requiring study medication discontinuation, unplanned major surgery for study infection, or death before study evaluation
- Clinical success (**CS**): survival with improvement by at least one level of symptom severity for at least two CABP symptoms, without worsening (at least one severity level) of the remaining CABP symptoms or meeting any criterion for CF or indeterminate

III. INSPECTION OUTCOMES

Inspected Entity		Study Site, Enrollment	Inspection Dates	Outcome
1	Carrie Cardenas, M.D. 5565 Grossmont Center Dr. La Mesa, California	PTK-0796-ABSI-1108 Site 254, 110 subjects PTK-0796-ABSI-16301 Site 608, 131 subjects	May 7 – 17, 2018	NAI
2	Soledad Lee, M.D. 6850 Lincoln Avenue Buena Park, California	PTK-0796-ABSI-16301 Site 606, 14 subjects	May 29 – June 8, 2018	VAI*
3	Tonny Tanus, M.D. 2116 17th Street Bakersfield, California	PTK-0796-ABSI-16301 Site 636, 22 subjects	May 21 – 23, 2018	NAI
4	Anca Ruxanda, M.D. 1 Tabaci Str., Dolj Craiova 200642, Romania	PTK-0796-ABSI-1108 Site140, 24 subjects	May 21 – 25, 2018	NAI*
5	Diana Mladenova, M.D. 21 Totleben Blvd. Sofia 1606, Bulgaria	PTK-0796-CABP-1200 Site 307, 36 subjects	May 14 – 18, 2018	NAI*
6	Peter Szabo, M.D. Stit 62, H-4400, N/A Nyiregyhaza 4400, Hungary	PTK-0796-CABP-1200 Site 313, 21 subjects	May 28 – 31, 2018	NAI*

Site selection: high enrollment and/or efficacy, multiple studies at same site, or sponsor notice of sub-standard GCP (Site 606)

Compliance Classification of Inspection Outcome

NAI = No Action Indicated, no significant deviations from regulations
VAI = Voluntary Action Indicated, minor deviations from regulations
OAI = Official Action Indicated, major deviations from regulations

* For these CI sites, the establishment inspection report (**EIR**) has not been received from the field office and the inspection outcome shown is based on preliminary communication with the field investigator. An addendum to this clinical inspection summary (**CIS**) will be forwarded to the review division if new significant findings are discovered at EIR review; otherwise, OSI's written letter to the inspected entity (to be copied to DAIP) indicates completion of EIR review with confirmation of the findings as reported in this CIS.

1. Carrie Cardenas, M.D.

PTK-0796-ABSI-01108: 121 subjects screened, 110 enrolled, 9 withdrawn (7 lost to follow up, 1 consent withdrawal, 1 CI discretion), and 101 completing study

PTK-0796-ABSI-16301: 138 subjects screened, 131 enrolled, 15 withdrawn (14 lost to follow up, 1 consent withdrawal), and 116 completing study

For each study, case records were reviewed in detail for a random sample of 15 subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, major efficacy endpoints, and concomitant antibiotic medication use.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared GCP-compliant. All audited NDA data were adequately verifiable against source records and CRFs.

2. Soledad Lee, M.D.

PTK-0796-ABSI-16301: 17 subjects screened, 14 enrolled, and 14 completing study

The sponsor terminated this CI site in April 2017 from further participation in Study PTK-0796-ABSI-16301 due to persistent GCP non-compliance observed at serial internal site monitoring visits, specifically for uncorrected inadequate recordkeeping (including routinely incomplete source documentation) and unreconciled investigational product (**IP**) accountability (including pill counts inconsistent with information recorded in subject diaries). The sponsor, however, did not exclude the already-collected site data from the overall study analyses. The study audit at this CI site inspection was conducted with emphasis on CI oversight. Case records were reviewed in detail for all subjects.

A Form FDA 483 was issued for two GCP deficiencies generally observed for nearly all subjects: (1) CS at EOT (non-primary endpoint) was documented late, up to 9 days after the EOT visits (23 days late for one subject, by staff not designated for this task); and (2) illegible, incomplete, internally inconsistent, or missing source records for subject sign-in logs, study medication disposition log, and study monitoring visit reports.

- This CI site had been previously inspected twice by the FDA, NON RESPONSIVE . The outcomes of both inspections were *Voluntary Action Indicated* (**VAI**) for the correction of GCP deficiencies (including recordkeeping deficiencies) unlikely to make the site data unreliable.
- The deficiencies observed at the current inspection (consistent with those seen previously) were indicative of study conduct with inadequate attention to GCP, including consistently inadequate due diligence for good recordkeeping practices (**GRP**).

The findings of the current inspection were not necessarily indicative of contrived, biased, or otherwise unreliable study data, based on: (1) no suggestive direct inspectional observations, and (2) a comparison of the site-specific outcome (this CI site) relative to the overall study outcome (all CI sites in Study PTK-0796-ABSI-16301):

- The IP and the active comparator appeared to be highly and equally effective at this site: 100% CS at ECR for both agents, with no reported AEs for either agent. For the

study overall (all sites), the efficacy appeared higher for the IP (~88%) than for the active comparator (~82%). The efficacy rates equally high for both agents as reported by this CI site do not appear to favor the IP over the active comparator.

- Protocol violations appeared to have been reported consistently by this CI site, and at a reporting rate significantly higher than by other sites (~ twice, per subject). The reporting rates were similar for the two study medications (IP and active comparator, ~4 per subject). No subjects were discontinued for either agent.

Despite the apparently unbiased data collection, inadequate attention to GCP may favor a non-inferiority study outcome (IP and active comparator). However, given the limited number of subjects enrolled at this CI site (early site termination by sponsor), the data may be sufficiently reliable to include in the overall study analyses.

3. Tonny Tanus, M.D.

PTK-0796-ABSI-16301: 34 subjects screened, 22 enrolled, 5 withdrawn (lost to follow up), and 17 completing study

Case records were reviewed in detail for all enrolled subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, major efficacy endpoints, and concomitant antibiotic medication use.

No significant deficiencies were observed and a Form FDA 483 was not issued. The following observations were verbally discussed:

- Screening urine pregnancy testing was not consistently performed per study protocol. Testing was not performed for all women, not performed for women considered (judged) to be not of child-bearing potential.
- Late recordation of calculated data as part of initial source records: Absolute neutrophil count (**ANC**) was calculated from white blood cell (**WBC**) count and neutrophil fraction, added late to initial source records without noting late data calculation and recordation
- Documentation of staff training typically lacked training dates.
- For one subject, no contact phone number was documented (not recorded on screening log), yet safety follow-up phone call was documented on source records (without documenting the number called).

These (uncited) observations appeared unlikely to be significant. Study conduct in general appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

4. Anca Ruxanda, M.D.

PTK-0796-ABSI-1108: 24 subjects screened, 24 enrolled, and 24 completing study

Case records were reviewed in detail for 12 subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, major efficacy endpoints, and concomitant antibiotic medication use.

No significant deficiencies were observed and a Form FDA 483 was not issued. Verbal discussion included: (1) participation of the unblinded pharmacist in subject screening, (2) use of post-it notes to record source data, and (3) pharmacy drug accountability log not distinguishing between scheduled and actual dispensing dates. Study conduct in general appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

5. Diana Mladenova, M.D.

PTK-0796-CABP-1200: 38 subjects screened, 36 enrolled, 7 withdrawn (6 consent withdrawal, 1 heart failure and death), and 29 completing study

Case records were reviewed in detail for 15 subjects completing study. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, major efficacy endpoints, and concomitant antibiotic medication use.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

6. Peter Szabo, M.D.

PTK-0796-CABP-1200: 23 subjects screened, 21 enrolled, 5 withdrawn (consent withdrawal), and 16 completing study

Case records were reviewed in detail for 15 subjects completing study. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, subject discontinuation, AEs, protocol deviations, major efficacy endpoints, and concomitant antibiotic medication use.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

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06/26/2018

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06/27/2018

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06/27/2018

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND	IND 75928 / 73431; NDA 209816
Brand Name	-
Generic Name	Omadacycline
Sponsor	Paretek Pharmaceuticals
Indication	ABSSSI, CABP
Dosage Form	Lyophilized powder for reconstitution and administration as IV infusion; Tablet
Drug Class	Aminomethylcyclines; antibacterial
Therapeutic Dosing Regimen	100 mg IV infusion for 30 min QD or 300 mg PO QD, with a loading dose (IV: 200 mg infusion over 60 minutes or 100 mg infusion over 30 minutes (b) (4) for the first two doses; oral: 450 mg once a day for the first 2 days) to ensure attainment of steady-state concentrations on Day 1
Duration of Therapeutic Use	Acute (7-14 days)
Maximum Tolerated Dose	400 mg IV or 600 mg oral
Submission Number and Date	SDN 153; 7/20/2016
Review Division	DAIP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

In this TQT study, omadacycline (PTK 0796) caused dose-/concentration-dependent increases in heart rate (Table 1) that impacts the ability to interpret the ΔΔQTc effects corresponding to the administration of a single therapeutic dose (100 mg IV) as well as a single supratherapeutic dose (300 mg IV). The largest upper bounds of the 2-sided 90% CI on heart rate for the mean difference between PTK 0796 IV (100 mg and 300 mg) and placebo were 18 and 23 bpm, respectively. There was rapid rise in the heart rate and the peak of heart rate increases coincided with the peak plasma concentrations for the drug. Even though the sponsor had collected pre-dose baseline data for individualized QTc correction (QTcI), the heart rate range in both the pre-dose baseline period and the placebo period did not cover the heart rate range in the treatment period. Furthermore, the sponsor has not accounted for potential QT/RR hysteresis when deriving their QTcI, which could result in a biased estimate of the individual QT/RR relationship. Thus, QTc results from neither the fixed QT correction nor individualized QT correction are

interpretable for this study. Therefore, this TQT study is inconclusive regarding the QT prolongation evaluation.

In this randomized, blinded, four-period crossover study, 64 healthy subjects received PTK 0796 100 mg IV, PTK 0796 300 mg IV, placebo, and a single oral dose of moxifloxacin 400 mg. The overall summary is presented in Table 1.

Table 1: The ΔΔHR Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for PTK 0796 IV (100 mg and 300 mg IV infusion) (FDA Analysis)

Treatment	Time (hour)	Mean ΔΔHR (bpm)	90% CI ΔΔHR (bpm)
PTK 0796 100 mg IV infusion over 0.5 h	0.583	16.9	(15.4, 18.3)
PTK 0796 300 mg IV infusion over 1 h	0.833	21.6	(20.1, 23.1)

The highest therapeutic steady state C_{max} achieved is 2120 ng/mL with 100 mg IV once daily dosing (proposed IV dosing). Majority of elimination of the drug is through feces (unabsorbed and biliary excretion) and only a minor part is with renal elimination. No substantial increase in drug exposures is observed or expected with organ impairment or DDI. Thus, the mean C_{max} of 3315 ng/mL with the supratherapeutic dose of 300 mg administered by IV infusion over 1 h in this TQT study would cover the highest clinically relevant exposures for the therapeutic dose.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

Although the QTc interval could not be characterized in the TQT study due to the confounding increases in heart rate (HR), the safety ECGs collected in Phase 3 clinical trials did not suggest that omadacycline causes large increases in the QTc interval.

An enhanced monitoring of vital signs, in particular HR around the time of dosing was instituted by the sponsor in the pivotal Phase 3 trials. Consistent with the nonclinical findings of its mechanism of action, the HR effect of omadacycline was less pronounced in patients in Phase 3 trials as compared to healthy subjects (i.e., individuals with greater vagal tone and relatively low resting HR) in the TQT study. Data from a Phase 3 Study PTK0796-CABP-1200 (Sponsor's Table 2) showed that there were no substantial increases in heart rate after the clinical dosing by IV infusion and thus the QTcF measurements in patients could be interpreted without the issue of confounding by heart rate. This study had moxifloxacin as the active comparator, which is a known QT-prolonging drug and which is used as a positive control in typical TQT studies. Even though there was a lack of placebo control in this study, the data shows that the magnitude of QTc effects (ΔQTcF) was less with therapeutic dosing of omadacycline as compared to moxifloxacin. Overall, while no supratherapeutic dosing was studied in patient population, no large increases in the QTc interval were observed with the recommended dosing of omadacycline in patients.

Table 2: ECG parameters in Phase 3 Study PTK0796-CABP-1200

			Omadacycline N = 382 Mean (SD)	Moxifloxacin N = 388 Mean (SD)
Heart rate (bpm)	ΔHR	Prior to first infusion	84.6 (16.59)	84.2 (16.59)
		30-90 minutes after first dose infusion	4.3 (10.06)	-1.5 (8.26)
		Dose 3, prior to infusion	-1.8 (13.86)	-5.4 (13.89)
		Dose 3, 30-90 minutes after infusion	-1.1 (13.34)	-6.8 (13.19)
		Day 7	-7.4 (15.95)	-8.6 (16.06)
QTcF (msec)	Δ QTcF	Prior to first infusion	415.0 (24.30)	416.5 (25.21)
		30-90 minutes after first dose infusion	0.8 (16.92)	5.8 (15.82)
		Dose 3, prior to infusion	1.4 (18.55)	4.3 (22.04)
		Dose 3, 30-90 minutes after infusion	1.8 (18.14)	11.1 (17.57)
		Day 7	5.4 (22.89)	12.2 (23.06)
PR (msec)	ΔPR	Prior to first infusion	151.4 (25.51)	155.0 (23.67)
		30-90 minutes after first dose infusion	-1.3 (11.19)	0.9 (11.14)
		Dose 3, prior to infusion	-0.4 (11.70)	0.5 (13.17)
		Dose 3, 30-90 minutes after infusion	-0.4 (13.10)	0.9 (12.33)
		Day 7	2.4 (14.72)	1.8 (15.72)
QRS (msec)	ΔQRS	Prior to first infusion	98.6 (19.55)	99.4 (19.27)
		30-90 minutes after first dose infusion	-0.2 (9.80)	-0.8 (14.49)
		Dose 3, prior to infusion	0.4 (16.73)	-0.3 (14.38)
		Dose 3, 30-90 minutes after infusion	-0.3 (10.94)	0.2 (14.93)
		Day 7	-1.2 (12.38)	-0.3 (19.32)

Source: Omadacycline Cardiac Safety Report, Table 5, Page 35 of 44

In the pooled data from pivotal Phase 3 studies, the percentage of subjects with substantial QTc outliers in the omadacycline arm was no worse than the percentage of subjects with QTc outliers in the moxifloxacin arm which is a known QT-prolonging drug: 7 (0.7%) omadacycline subjects, 2 (0.3%) linezolid subjects, and 4 (1.1%) moxifloxacin subjects had a baseline QTcF of ≤ 500 ms and any post-baseline QTcF of > 500 ms. A maximum QTcF increase from baseline of ≥ 60 ms occurred in 1.2% of omadacycline subjects, 0.8% of linezolid subjects, and 3.6% of moxifloxacin subjects.

2 PROPOSED LABEL

The sponsor's QT-related language in their current proposed label is included below.

(b) (4)

We recommend that the sponsor proposes labeling language based on the HR and QTc effects in their phase 3 studies. We defer the final labeling decision to the Division.

Sponsor's proposed label:

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Omadacycline (PTK 0796) is a novel aminomethylcycline and the newest compound in the tetracycline family, with broad-spectrum antibacterial activity that includes Gram-positive, Gram-negative, aerobes and anaerobes, and atypical pathogens. Consistent with its tetracycline-like structure, omadacycline has been shown to inhibit bacterial protein synthesis. Omadacycline is under development for clinical use by both intravenous and oral administration. It is being developed for infectious disease indications including, but not limited to, ABSSSI (Acute Bacterial Skin and Skin Structure Infections), CABP (Community-Acquired Bacterial Pneumonia) and cUTI (complicated urinary tract infection).

3.2 MARKET APPROVAL STATUS

Omadacycline (PTK 0796) is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

In vitro:

Omadacycline appeared to have minimal, if any, effect on the hERG channel, showing an IC_{25} value of 300 µM (166 µg/mL) and <50% inhibition at 1610 µM.

This provides a safety margin of >300-fold with respect to total plasma C_{max} of ~3 µg/mL (free plasma C_{max} of ~2.4 µg/mL considering ~20% protein binding) at the supratherapeutic dose used in this TQT study.

In vivo:

Anesthetized Monkey 90 mg/kg iv: decrease in contractility by 21-45%, no effect of ECG or respiratory

Conscious monkey 40 mg/kg iv: increase in BP and heart rate returned to baseline by 30 minutes after the end of infusion. Heart rate increases was not proportional to dose.

See Appendix 6.1 for more information.

3.4 PREVIOUS CLINICAL EXPERIENCE

Across 19 completed clinical trials, 747 unique subjects have received omadacycline. There were no AEs of QT prolongation, torsade de pointes, seizures, any type of ventricular arrhythmias, or sudden death. There was one case of vasovagal syncope (mild) in a 23 year-old female healthy volunteer who received a single 200 mg oral dose.

See Appendix 6.1 for more information.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of clinical pharmacology of omadacycline (PTK 0796).

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report for the study drug, including electronic datasets and waveforms to the ECG warehouse.

During the review, the following two information requests were sent to the sponsor by the review team (the link for the responses from the sponsor are provided below as well):

1. In TQT Study report PTK0796-TQTC-0803 submitted to IND75928/73431, large heart rate increases were observed in both drug treatment arms. According to your protocol, exercise treadmill testing at baseline visit (Day -1) was performed to increase the range of heart rates for heart rate correction but these data were not used in the submitted report from (b) (4). In contrast, an earlier ECG report by (b) (4) utilized the exercise data.
   Please explain the differences between the choice of QTc correction in the two reports and why the conduct of the analyses has deviated from the protocol design.
   (Response to request for information-01dec2017)

2. We acknowledge your response to our previous IR about changes to your protocol and analysis plan. However, we continue to be concerned about the interpretation of the QTc changes for omadacycline given the large mean increases in HR observed in study PTK0796-TQTC-0803. We recommend the use of QTcI in for drugs with large mean changes in HR, consistent with the description in your response to our IR. But, based on the description provided it is not clear to us if the QT/RR pairs used to generate the QTcI covers the increase in HR. In addition, it is not clear if you have accounted for QT/RR hysteresis when deriving your QTcI, and not correcting for QT/RR hysteresis could result in a biased estimate of the individual QT/RR relationship.
   We therefore request that you submit the following information to us:
   • All the QT/RR pairs used to support deriving the QTcI in the re-analysis (~80,000 beats per subject referenced on page 3 of your response). In addition, please include a history of RR values for the past 5 min for each QT/RR pair.
   • All QT/RR measurements used in the primary analysis with their corresponding 5-minute history of RR measurements.
   (Response to request for information-18dec2017)

4.2 TQT STUDY

4.2.1 Title

A Double-Blind, Double-Dummy, Randomized, Positive and Placebo Controlled, Cross-Over Study of the Effects of PTK 0796 on QT/QTc Intervals in Healthy Subjects

4.2.2 Protocol Number

PTK 0796-TQTC-0803

4.2.3 Study Dates

Initiation Date (first subject enrolled): 26 September 2008
Completion Date (last subject completed): 20 January 2009

4.2.4 Objectives

Primary objectives were to evaluate the effect of PTK 0796 compared with placebo and active control (moxifloxacin) on ventricular repolarization in healthy subjects following intravenous administration of a single therapeutic (100 mg IV) or supra-therapeutic dose (300 mg IV), and to determine the time-matched mean difference in QT/QTc interval between PTK 0796 and placebo (baseline-adjusted) and active comparator at 11 time points over the 22 hours following infusion.

Secondary objectives were to determine the pharmacokinetics of PTK 0796 at the proposed therapeutic and supra-therapeutic dose in the subjects studied, to determine if there is a pharmacodynamic relationship between the duration of the QT/QTc intervals and the plasma concentration of PTK 0796 and to evaluate the safety and tolerability of single IV doses of PTK 0796 in healthy subjects.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 4-period, 4-treatment crossover design. The washout between consecutive study periods was at least 7 days.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There are 4 treatments in this study: PTK 0796 100 mg IV, PTK 0796 300 mg IV, Placebo and Moxifloxacin 400 mg.

Treatment Code	Treatment Class	PTK 0796	Moxifloxacin
A	Therapeutic dose	100 mg IV	Placebo capsule
B	Supra-therapeutic dose	300 mg IV	Placebo capsule
C	Placebo	Placebo infusion	Placebo capsule
D	Active control	Placebo infusion	Moxifloxacin 400 mg PO

IV = intravenous, PO = per oral.

4.2.6.2 Sponsor's Justification for Doses

The dose of 100 mg IV in 100 mL over 30 min QD was the proposed therapeutic dose for the Phase 3 program in the indications of complicated skin and skin structure infections (cSSSI). This dose was well-tolerated in multiple dose Phase 1 studies and in a Phase 2 study of adults with cSSSI.

The supra-therapeutic dose was 300 mg IV in 300 mL infused over 60 minutes. In the ascending single dose Phase 1 studies in healthy young males, this dose of PTK 0796 was generally well tolerated; higher doses (400 mg and 600 mg IV over 60 min) were also well tolerated but associated with modest increases in LFTs.

The supratherapeutic dose of 300 mg IV was chosen based on the following observations from the single dose escalation studies: the C_{max} of the 300 mg intravenous dose is (a) about two-fold (2x) greater than the C_{max} of the 100 mg IV dose and (b) about nine-fold (9x) the C_{max} of the 200 mg oral dosage. At 24 h after dosing (trough), the plasma concentration for the supratherapeutic 300 mg IV dose remains 2.5x greater than for either the IV or oral therapeutic dose.

Reviewer's Comment: The proposed dosing is (i) loading dose of 200 mg IV infused over 60 minutes (or 100 mg (b) (4) *administered IV for the first two doses infused over 30 minutes) followed by 100 mg administered IV once daily or 300 mg administered orally once daily or (ii) 450 mg tablet administered orally, once a day for the first 2 days, followed by 300 mg orally once daily, for the total treatment duration of 7 to 14 days. The highest therapeutic steady state C_{max} achieved is 2120 ng/mL with 100 mg IV once daily dosing; while the therapeutic steady state C_{max} achieved is 952 ng/mL with 300 mg oral once daily dosing. Majority of elimination of the drug is through feces (unabsorbed and biliary excretion) and only a minor part is with renal elimination. No substantial increase in drug exposures is observed or expected with organ impairment or DDI. Thus, the mean C_{max} of 3315 ng/mL with the supratherapeutic dose of 300 mg by IV infusion over 1 h in this TQT study would likely cover the highest clinically relevant exposures for the therapeutic dose.*

4.2.6.3 Instructions with Regard to Meals

Not applicable since the dosing is IV infusion.

4.2.6.4 ECG and PK Assessments

For each Treatment, the ECG data time points were -1.5, -1.0, and -0.50 hours pre-dose, and 0.333, 0.583, 0.833, 1.083, 1.5, 2, 4, 6, 12, 18, and 22 hours post-dose. All times are relative to the start of infusion (t = 0). Blood samples for the determination of PTK 0796 (and moxifloxacin) plasma concentrations were collected for each Treatment at 10 min after each nominal ECG time point.

Reviewer's Comment: The ECG/PK sampling time is appropriate to capture effects near T_{max} (end of infusion times of 0.5 and 1 h for the two dose levels) and any potential delayed effects up to 22 h post-dose.

4.2.6.5 Baseline

Pre-dose baseline was used in primary analysis. Time-matched baseline on Period 1, Day-1 was used for supplementary analysis.

4.2.7 ECG Collection

The Study electrocardiograms were acquired from 12-lead, 24-hour Holter recording using the H-12 Plus ambulatory electrocardiograph recorder (Mortara Instruments, Milwaukee, WI). The Holter recorders were to be placed on the subjects on Study Day -1 and each Study Treatment Day, giving enough time to ensure that the recording was initiated 30 minutes prior to the pre-assigned subject specific dosing time on Day -1 (baseline) and on each Study Treatment Day. During each 24 hour period ECG readings were captured in triplicate electronically at approximately 14 time points.

On the day prior to the first Treatment period (Day -1, i.e., the day prior to the first administration of any study treatment) subjects were assigned a dosing time and then ECG data obtained at all of the time-points corresponding to that subject's anticipated treatment timepoints. In addition, on Day -1 each subject was to undergo a graded exercise test in the period equivalent to the anticipated "pre-dose" time of day. These data were to provide pre-treatment data for each subject covering both a range of pulse rates as well as diurnal variation strictly for purposes of computing individual correction of QT. These data were not used in any other of the analyses and do not appear in the tables and listings.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 64 subjects enrolled and were treated in the study. Two subjects discontinued from the study prior to completion of all four treatment periods.

Forty of the 64 subjects (62.5%) were male and 24 subjects (37.5%) were female. Almost 83% were Caucasian and approximately 11% were African-American. Mean age was 27.6 years and subjects ranged in age from 18 to 45 years. Weight ranged was 118 to 219 lbs., with a mean of 167 lbs. Median BMI was 25.5, ranging from 19 to 30.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

In the Sponsor's report, Cardiac Safety Report, QTcF was chosen to be the primary efficacy variable. The "by-timepoint" analysis for QTcF was based on a linear mixed-effects model with change from-baseline QTcF (ΔQTcI) as the dependent variable, period, sequence, time (categorical), treatment (PTK 0796, moxifloxacin, and placebo), time-by-treatment interaction and time-by-period as fixed effects, and baseline QTcF as a covariate. Subject was included as a random effect for the intercept. An unstructured covariance matrix was specified for the repeated measures at postdose timepoints for subject within treatment period.
The least squares (LS) mean and 2-sided 90% CIs were calculated for the contrast "PTK 0796 versus placebo" at each dose of PTK 0796 and each postdose timepoint, separately.

The upper bound of the 2-sided 90% CI (equivalent to the upper bound of 1-sided 95% CI) for the LS mean difference between PTK 0796 and placebo was <10 msec at all postdose timepoints, and thus the Sponsor concluded the study was a "negative thorough QT/QTc" study.
The Sponsor listed their primary analysis result in the following table:

Table 3: Sponsor Primary Analysis (QTcF)

Time (hrs post-dose)	ddQTcF PTK 0796 300 mg		ddQTcF PTK 0796 100 mg	
	Diff	UB	Diff	UB
0.33	-1.18	0.81	-1.03	0.95
0.58	-2.47	-0.48	-2.56	-0.57
0.83	-3.51	-1.52	-3.56	-1.57
1.08	-4.46	-2.47	-4.59	-2.61
1.5	-2.48	-0.49	-2.84	-0.86
2	-1.16	0.83	-2.08	-0.10
4	-3.23	-1.24	-1.09	0.90
6	-1.87	0.12	-0.46	1.53
12	-3.15	-1.16	-0.58	1.41
18	-5.18	-3.19	-1.88	0.10
22	-3.02	-1.04	-0.75	1.24

[Source: Section 12.6 of (b) (4)'s Cardiac Safety Report (Reissue date: February 18, 2010)]

The Sponsor also provided their secondary analysis results based on QTcI as follows:

Table 4: Sponsor Secondary Analysis (QTcI)

Time (hrs post-dose)	ddQTci PTK 0796 300 mg		ddQTci PTK 0796 100 mg	
	Diff	UB	Diff	UB
0.33	2.80	5.18	2.71	5.09
0.58	2.38	4.76	1.69	4.06
0.83	1.73	4.11	0.92	3.29
1.08	-0.38	2.00	-1.87	0.51
1.5	1.86	4.24	0.69	3.07
2	1.99	4.37	0.27	2.65
4	1.05	3.43	1.80	4.17
6	0.71	3.09	0.72	3.10
12	-1.22	1.16	0.19	2.57
18	-2.08	0.30	-1.41	0.97
22	-0.99	1.39	0.15	2.53

[Source: Section 12.7 of (b) (4)'s Cardiac Safety Report (Reissue date: February 18, 2010)]

Reviewer's comment: The subjects administered with PTK 0796 100 and 300 mg by IV infusion exhibited rapid and significant increases in heart rate (>10 bpm). Thus, the primary analysis with QTcF or QTcI may not be appropriate without accounting for QT/RR hysteresis prior to deriving the individual QT/RR relationship to avoid bias and potential lack of availability of drug-free baselines from a wide enough span of heart rates to cover on treatment changes in heart rate, within each individual.

As per the sponsor, QTci was calculated as follows: All pairs of QT and RR interval data collected on Day -1 of the first dosing period (including during graded exercise), separately for each subject, were analyzed by the following linear regression:

$log\ (QT) = log\ (a) + b_i\ log\ (RR)$

The resulting slope (b_i) for the i-th subject was used to calculate individual correction:

$QTci = QT/RR^b$ *(where* $b=b_i$*)*

However, the sponsor could not provide the data on day -1 for our review to account for possible QT/RR hysteresis and to check whether drug-free baselines from a wide enough span of heart rates to cover on treatment changes in heart rate are available, within each individual. The sponsor's response was as follows (Response to request for information-18dec2017):

"Since the sponsor does not have access to the ECG waveforms, FDA's specific requests on additional data cannot be met. In the available analysis, hysteresis was not accounted for in the derivation of correction coefficients and in the absence of data on the waveform level, further analysis that would take hysteresis into account cannot be undertaken."

4.2.8.2.2 Assay Sensitivity

Using the similar model to the primary analysis, the difference between moxifloxacin and placebo at 1.5, 2, and 4 hours postdose was tested against the 1-sided null hypothesis: ΔΔQTcF>5 msec at the 5% level.
The Sponsor found that the lower 95% confidence bound on ddQTcF exceeded 5 ms at 1.5, 2, 4, and 6 hours post-dose, hence, the assay sensitivity hypothesis is rejected in favor of moxifloxacin demonstrating an increase in ddQTcF > 5 ms.

4.2.8.2.3 Categorical Analysis

The Sponsor's report indicated that "The proportions of subjects assigned with PTK 0796 with QTcF > 450 ms ranged from 0% to 3.6%"; and that "No subject had an increase in QTcF > 30ms at any time point. Also, at most 3 subjects had increases from pre-dose in QTci > 30 ms for any of the dose groups."

4.2.8.3 Safety Analysis

No deaths nor serious adverse events occurred in this study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results for the drug are presented in Table 5. The mean C_{max} of 3315 ng/mL with the supratherapeutic dose of 300 mg by IV infusion over 1 h in this TQT study is 1.6-fold of the highest therapeutic steady state C_{max} of 2120 ng/mL with 100 mg IV infusion over 30 min once daily (proposed clinical dose).

Table 5: Pharmacokinetic Parameters for PTK 0796

				Log Transformed	
Descriptive Statistic	**AUC_{0-24} (ng.hr/mL)**	**Cmax (ng/mL)**	**Tmax (hrs)**	**AUC_{0-24} (ng.hr/mL)**	**Cmax (ng/mL)**
PTK 0796 Dose = 100 mg					
N	61	61	61	61	61
Mean	6180.02	1394.48	0.34	6092.25	1373.13
SD	1070.51	248.61	0.04		
%CV	17.32	17.83	13.14		
Median	6002.25	1350	0.33	6002.25	1350
Min	4436	908	0.33	4436	908
Max	9147.58	1940	0.58	9147.58	1940
PTK 0796 Dose = 300 mg					
N	61	61	61	61	61
Mean	17848.23	3315.08	0.8	17602.05	3215.11
SD	2916.31	918.67	0.11		
%CV	16.34	27.71	14.01		
Median	17898.75	3130	0.83	17898.75	3130
Min	9483.38	2040	0.33	9483.38	2040
Max	25315.75	7160	1.08	25315.75	7160

Source: CSR for Study PTK 0796-TQTC-0803, Table 11-2

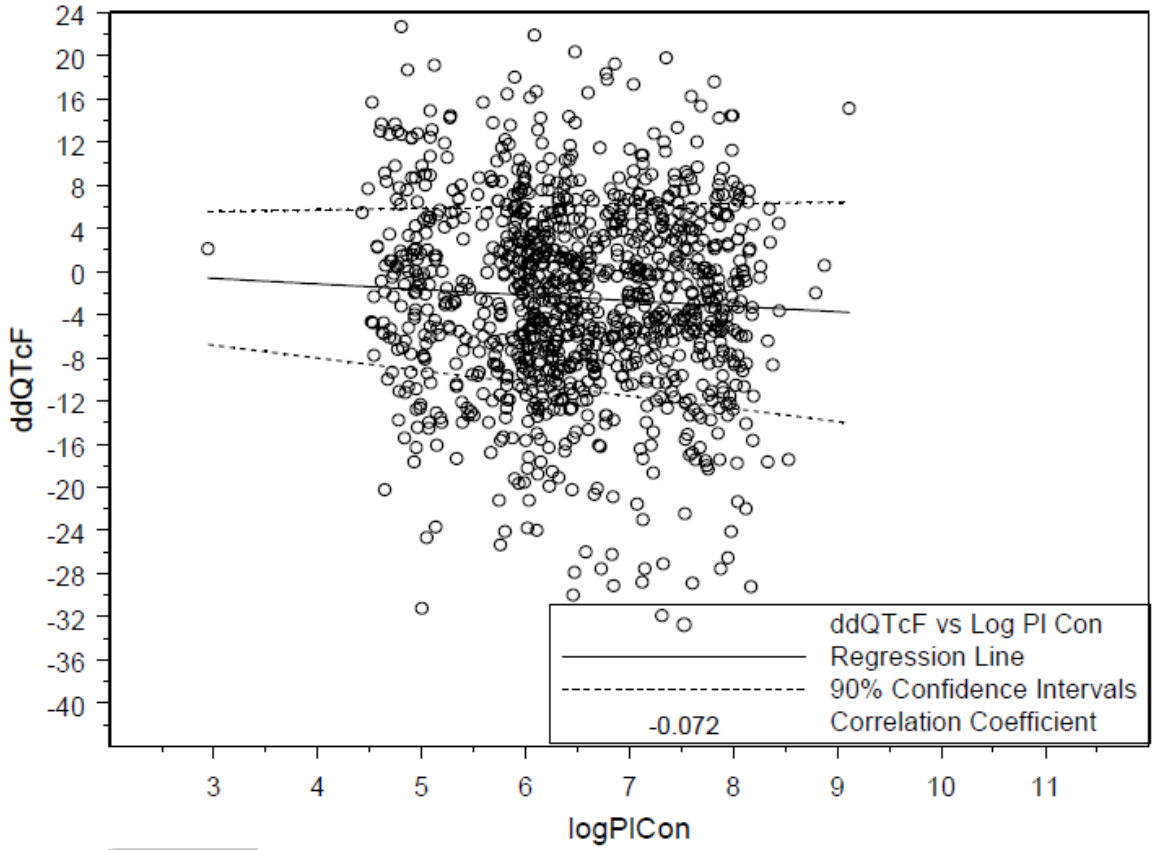
4.2.8.4.2 Exposure-Response Analysis

A linear mixed effects model was employed with the placebo-subtracted differences in pre-dose-adjusted QTc intervals (ddQTcF, ddQTci, and ddQTcB) as the independent variable and the corresponding PTK 0796 plasma concentrations as the dependent variable. The concentration data were log-transformed for this analysis. Plasma concentration values BLQ were assigned a value of 0.19 (not 0 to avoid anchoring the left side of the regression model), to ensure all values were included in the C-QT analysis, and had a finite value when log-transformed.

The figure below shows the scatter plot of ddQTcF versus PTK 0796 plasma concentration for all post-dose time points and all dose groups, and also shows the predicted linear regression line based upon the linear mixed-effects model and with a 2-sided 90% confidence interval. The correlation between ddQTc and log-transformed PTK 0796 plasma concentration was -0.72 for ddQTcF, 0.09 for ddQTci and 0.36 for ddQTcB. The width of the 90% 2-sided confidence interval not including 10 ms for PTK 0796 plasma concentrations likely to be achieved statistically indicate that ddQTcF does not

significantly increase as PTK 0796 plasma concentration increases, within the range of available data. The upper 2-sided 90% confidence interval for ddQTci suggests ddQTci values greater than 10 ms when the log plasma concentration is larger than 6.5 (ie a plasma concentration larger than 665 ng/mL). The variation in plasma concentration was large resulting in wide confidence bounds.

Figure 1: Scatter Plot for ddQTcF versus Plasma Concentration



Source: (b) (4) *ECG report for Study PTK 0796-TQTC-0803, Figure 7a*

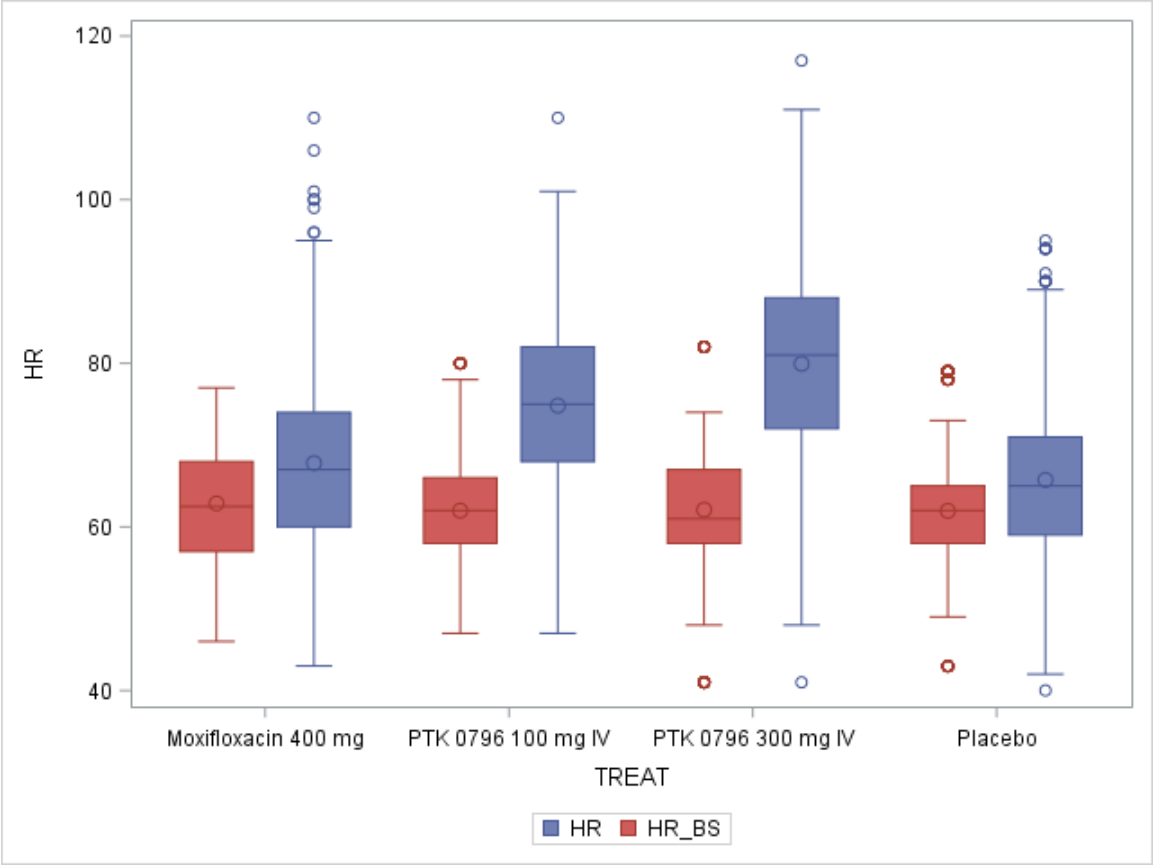
Reviewer's Analysis: Consistent with the sponsor's analysis, no statistically significant exposure-response relationship was seen in the reviewer's analysis (Section 5.3).

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

A large heart rate effect was observed in both drug doses. The heart rate range in the placebo period does not cover the range in the treatment period as shown in the box plot below. Thus, an individual QT correction method for heart rate (e.g. QTcS, QTcI, and QTcP) may not be appropriate. Nonetheless, this statistical reviewer evaluated both QTcI as primary analysis and QTcF as secondary analysis.

Figure 2: Box Plots of Heart Rate by Treatment



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

This statistical reviewer used a mixed effect model to analyze the ΔQTcI and ΔΔQTcI values. The model includes sequence, period, time, treatment, time-by-treatment and time-by-period interactions as fixed effects and subject as random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in Table 6. The largest upper bounds of the 2-sided 90% CI for the mean difference in ΔQTcF between PTK 0796 100 mg IV and placebo, and between PTK 0796 300 mg IV and placebo were 5.0 ms and 5.3 ms, respectively.

Table 6: Primary Analysis Results (QTcI as Endpoint variable)

	PTK 0796 100 mg IV			PTK 0796 300 mg IV		
	ΔQTcI LS Mean of Change from Baseline (ms)		ΔΔQTcI Difference of LS Mean and 90% CI (ms)	ΔQTcI LS Mean of Change from Baseline (ms)		ΔΔQTcI Difference of LS Mean and 90% CI (ms)
Time (Hour)	PTK 0796	Placebo	PTK 0796 vs Placebo	PTK 0796	Placebo	PTK 0796 vs Placebo
0.333	1.40	-1.40	2.8 (0.7, 5.0)	1.32	-1.40	2.7 (0.5, 4.9)

0.583	1.40	-0.69	2.1 (-0.6, 4.7)	1.92	-0.69	2.6 (-0.1, 5.3)
0.833	0.37	-1.08	1.4 (-1.0, 3.9)	1.21	-1.08	2.3 (-0.2, 4.8)
1.083	-1.16	0.18	-1.3 (-3.8, 1.1)	0.14	0.18	0.0 (-2.5, 2.5)
1.5	0.22	-0.21	0.4 (-2.2, 3.0)	1.78	-0.21	2.0 (-0.6, 4.6)
2	-2.92	-3.00	0.1 (-2.5, 2.6)	-0.92	-3.00	2.1 (-0.5, 4.7)
4	-5.12	-6.73	1.6 (-0.7, 3.9)	-5.99	-6.73	0.7 (-1.6, 3.0)
6	-3.68	-4.64	1.0 (-1.5, 3.4)	-3.89	-4.64	0.7 (-1.8, 3.3)
12	-2.64	-3.10	0.5 (-1.6, 2.5)	-4.07	-3.10	-1.0 (-3.1, 1.1)
18	1.84	3.28	-1.4 (-3.9, 1.0)	1.21	3.28	-2.1 (-4.5, 0.4)
22	-2.69	-3.53	0.8 (-1.4, 3.0)	-4.14	-3.53	-0.6 (-2.8, 1.6)

5.2.1.1.1 Secondary Analysis with QTcF as Endpoint Variable

The same model that was used in the analysis of QTcI was used for the analysis of QTcF. The results are shown in Table 7.

Table 7: Secondary Analysis Results (QTcF as Endpoint variable)

	PTK 0796 100 mg IV			**PTK 0796 300 mg IV**		
	ΔQTcF LS Mean of Change from Baseline (ms)		**ΔΔQTcF Difference of LS Mean and 90% CI (ms)**	**ΔQTcF LS Mean of Change from Baseline (ms)**		**ΔΔQTcF Difference of LS Mean and 90% CI (ms)**
Time (Hour)	**PTK 0796**	**Placebo**	**PTK 0796 vs Placebo**	**PTK 0796**	**Placebo**	**PTK 0796 vs Placebo**
0.333	-3.93	-2.81	-1.1 (-2.7, 0.5)	-4.35	-2.81	-1.5 (-3.1, 0.1)
0.583	-3.97	-1.15	-2.8 (-4.6, -1.0)	-3.99	-1.15	-2.8 (-4.7, -1.0)
0.833	-4.91	-1.19	-3.7 (-5.5, -1.9)	-4.98	-1.19	-3.8 (-5.6, -2.0)
1.083	-5.94	-1.28	-4.7 (-6.6, -2.7)	-6.01	-1.28	-4.7 (-6.7, -2.7)
1.5	-4.47	-1.59	-2.9 (-4.7, -1.0)	-4.16	-1.59	-2.6 (-4.4, -0.7)
2	-8.09	-5.96	-2.1 (-4.1, -0.2)	-7.10	-5.96	-1.1 (-3.1, 0.9)
4	-10.22	-9.02	-1.2 (-3.1, 0.7)	-12.45	-9.02	-3.4 (-5.4, -1.5)
6	-9.02	-8.74	-0.3 (-2.3, 1.8)	-10.55	-8.74	-1.8 (-3.9, 0.3)
12	-8.11	-7.20	-0.9 (-3.0, 1.2)	-10.41	-7.20	-3.2 (-5.3, -1.1)
18	0.43	2.18	-1.7 (-3.9, 0.4)	-3.24	2.18	-5.4 (-7.6, -3.3)
22	-5.79	-5.61	-0.2 (-2.3, 1.9)	-8.47	-5.61	-2.9 (-5.0, -0.7)

5.2.1.2 Assay Sensitivity Analysis

This statistical reviewer used the same statistical model that used in the primary analysis to analyze moxifloxacin and placebo QT data. The results are presented in Table 8. The largest unadjusted 90% lower confidence interval for ΔΔQTcI is 7.6. By considering

Bonferroni multiple endpoint adjustment at pre-specified three timepoints (1.5, 2.0 and 4.0 hours), the largest lower confidence interval for ΔΔQTcI is 6.9 ms (>5 ms, cutoff point suggested in ICH guidelines), indicating that appropriate assay sensitivity was demonstrated.

Table 8: Analysis Results of ΔQTcI and ΔΔQTcI for Moxifloxacin 400 mg

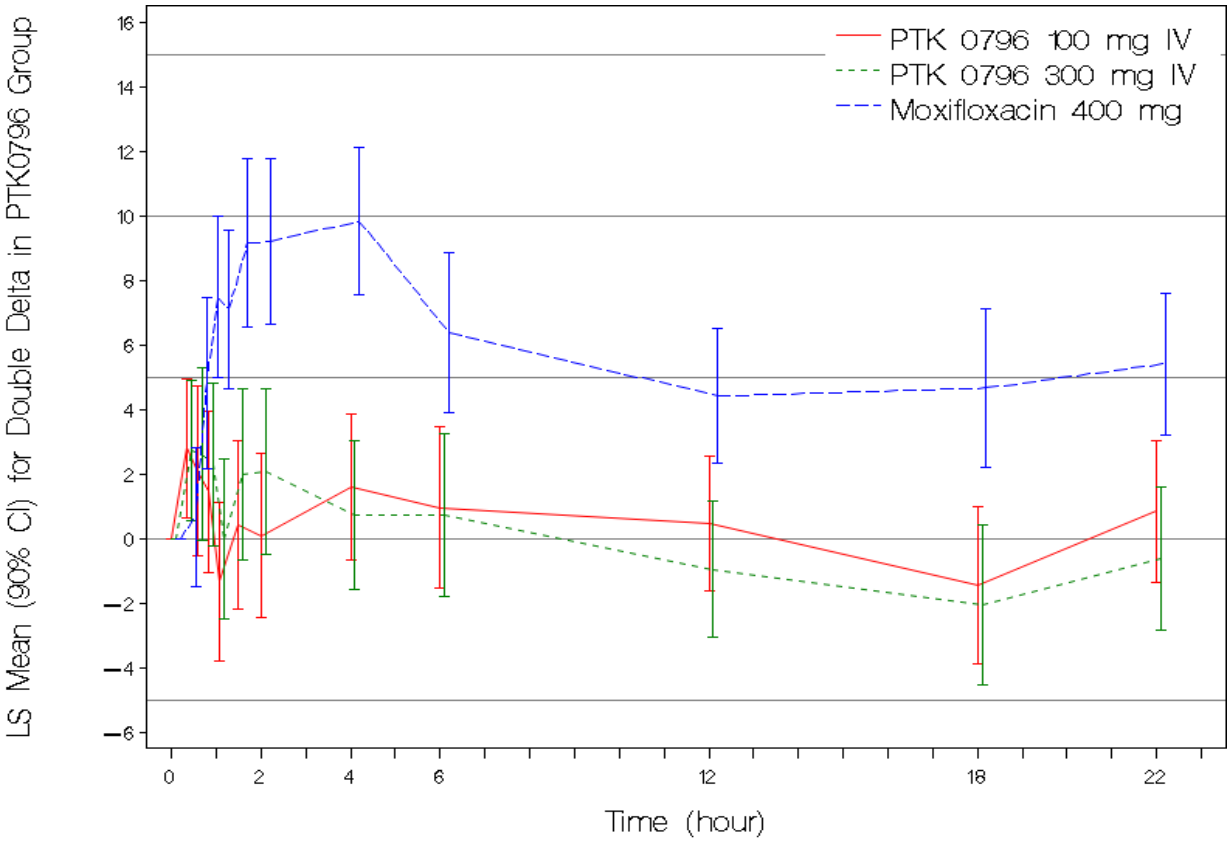
	Moxifloxacin 400 mg			
	ΔQTcI LS Mean of Change from Baseline (ms)		**ΔΔQTcI Difference of LS Mean (Unadjusted 90% CI) (ms)**	**(Adjusted* 90% CI) (ms)**
Time (Hour)	**Moxifloxacin**	**Placebo**	**Moxifloxacin vs Placebo**	
0.333	-0.74	-1.40	0.7 (-1.5, 2.8)	
0.583	4.14	-0.69	4.8 (2.2, 7.5)	
0.833	6.41	-1.08	7.5 (5.0, 10.0)	
1.083	7.28	0.18	7.1 (4.6, 9.6)	
1.5	8.95	-0.21	9.2 (6.5, 11.8)	(5.8, 12.6)
2	6.21	-3.00	9.2 (6.7, 11.8)	(5.9, 12.5)
4	3.11	-6.73	9.8 (7.6, 12.1)	(6.9, 12.8)
6	1.75	-4.64	6.4 (3.9, 8.9)	
12	1.31	-3.10	4.4 (2.3, 6.5)	
18	7.94	3.28	4.7 (2.2, 7.1)	
22	1.89	-3.53	5.4 (3.2, 7.6)	

* Bonferroni method was applied for multiple endpoint adjustment for 3 time points, Hours 1.5, 2.0 and 4.0.

5.2.1.3 Graph of ΔΔQTcI Over Time

The following figure displays the time profile of ΔΔQTcI for different treatment groups.

Figure 3: Mean and 90% CI ΔΔQTcI Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms, and >480 ms. One subject, administered with PTK0796 300 mg IV and 100 mg IV, had a value of QTcI above 480 ms at least one time point. Another subject, when administered with PTK0796 300 mg IV, had a value of QTcI above 480 ms.

Table 9: Categorical Analysis for QTcI

	Total N		QTcI <= 450 ms		450 ms < QTcI <=480 ms		QTcI >480 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**
PTK 0796 100 mg IV	63	693	59 (93.6)	662 (95.53)	3 (4.8)	30 (4.33)	1 (1.6)	1 (0.14)
PTK 0796 300 mg IV	61	671	57 (93.4)	642 (95.7)	2 (3.3)	19 (2.8)	2 (3.3)	10 (1.5)
Placebo	63	692	60 (95.2)	678 (98.0)	3 (4.8)	14 (2.0)	0 (0.0)	0 (0.0)

Table 10 lists the number of subjects as well as the number of observations whose ΔQTcI values are ≤30 ms, between 30 ms and 60 ms, and >60 ms. One subject, when

administered with PTK0796 100 mg IV and PTK0796 300 mg IV, had a value of ΔQTcI higher than 60 ms.

Table 10: Categorical Analysis of ΔQTcI

	Total N		ΔQTcI <=30 ms		30 ms< ΔQTcI <=60 ms		ΔQTcI >60 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**
PTK 0796 100 mg IV	63	693	62 (98.4)	682 (98.4)	0 (0.0)	10 (1.4)	1 (1.6)	1 (0.1)
PTK 0796 300 mg IV	61	671	58 (95.1)	648 (96.6)	2 (3.3)	12 (1.8)	1 (1.6)	11 (1.6)
Placebo	63	692	61 (96.8)	688 (99.4)	2 (3.2)	4 (0.6)	0 (0.0)	0 (0.0)

5.2.2 HR Analysis

The same statistical analysis as used in an analysis of QTcI was performed based on HR. The point estimates (ΔHR and ΔΔHR) and the 90% confidence intervals (ΔΔHR) are presented in Table 11. The largest upper limits of 90% CI for the mean differences in ΔΔHR between PTK 0796 100 mg IV and placebo and between PTK 0796 300 mg IV and placebo are 18.3 bmp and 23.1 bpm, respectively.

Table 11: Analysis Results of ΔHR and ΔΔHR

	PTK 0796 100 mg IV			PTK 0796 300 mg IV		
	ΔHR LS Mean of Change from Baseline (bpm)		**ΔΔHR Difference of LS Mean and 90% CI (bpm)**	**ΔHR LS Mean of Change from Baseline (bpm)**		**ΔΔHR Difference of LS Mean and 90% CI (bpm)**
Time (Hour)	**PTK 0796**	**Placebo**	**PTK 0796 vs Placebo**	**PTK 0796**	**Placebo**	**PTK 0796 vs Placebo**
0.333	14.02	0.64	13.4 (12.1, 14.6)	17.53	0.64	16.9 (15.6, 18.2)
0.583	17.35	0.50	16.9 (15.4, 18.3)	20.80	0.50	20.3 (18.8, 21.8)
0.833	16.79	0.47	16.3 (14.8, 17.8)	22.08	0.47	21.6 (20.1, 23.1)
1.083	16.17	2.75	13.4 (12.0, 14.8)	24.06	2.75	21.3 (19.9, 22.7)
1.5	14.99	1.70	13.3 (11.9, 14.7)	22.09	1.70	20.4 (19.0, 21.8)
2	17.19	6.13	11.1 (9.2, 12.9)	25.24	6.13	19.1 (17.3, 20.9)
4	12.77	3.82	8.9 (7.5, 10.4)	20.12	3.82	16.3 (14.8, 17.8)
6	18.08	11.42	6.7 (4.9, 8.4)	25.34	11.42	13.9 (12.1, 15.7)
12	15.35	12.52	2.8 (1.1, 4.6)	20.36	12.52	7.8 (6.1, 9.6)
18	3 35	0 82	2 5 (0 6, 4 5)	8 30	0 82	7 5 (5 5, 9 4)
22	7.52	4.09	3.4 (1.4, 5.4)	10.60	4.09	6.5 (4.5, 8.5)

Table 12 lists the number of subjects as well as the number of observations whose HR values are ≤ 100 bpm, between 100 bpm and 110 bpm, and >110 bpm. Four subjects,

administered with PTK0796 100 mg IV and 9 subjects administered with PTK0796 300 mg IV, had a value of HR above 100 bpm at least one time point.

Table 12: Categorical Analysis for HR

	Total N		HR <= 100 bpm		100 bpm < HR <=110 bpm		HR >110 bpm	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**
PTK 0796 100 mg IV	63	693	59 (93.7)	689 (99.4)	4 (6.3)	4 (0.6)	0 (0.0)	0 (0.0)
PTK 0796 300 mg IV	61	671	50 (82.0)	651 (97.0)	9 (14.8)	18 (2.7)	2 (3.3)	2 (0.3)
Placebo	63	692	63 (100.0)	692 (100.0)	0 (0.0)	0 (0.0)	2 (3.2)	0 (0.0)

Table 13 lists the number of subjects as well as the number of observations whose ΔHR values are ≤ 20 bpm, between 20 bpm and 30 bpm, and >30 bpm. Six subjects administered with PTK0796 100 mg IV, and 27 subjects administered with PTK0796 300 mg IV, had a value of ΔHR higher than 30 bpm.

Table 13: Categorical Analysis of ΔHR

	Total N		ΔHR <=20 bpm		20 bpm< ΔHR <=30 bpm		ΔHR >30 bpm	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**
PTK 0796 100 mg IV	63	693	25 (39.7)	559 (80.6)	32 (50.8)	119 (17.2)	6 (9.5)	15 (2.2)
PTK 0796 300 mg IV	61	671	6 (9.8)	362 (53.9)	28 (45.9)	234 (34.9)	27 (44.3)	75 (11.2)
Placebo	63	692	50 (79.4)	673 (97.2)	11 (17.5)	17 (2.5)	2 (3.2)	2 (0.3)

5.2.3 PR Analysis

The same statistical analysis as used in an analysis of QTcF was performed based on PR interval. The point estimates (ΔPR and ΔΔPR) and the 90% confidence intervals (ΔΔPR) are presented in Table 14. The largest upper limits of 90% CI for the mean differences in ΔΔPR between PTK 0796 100 mg IV and placebo and between PTK 0796 300 mg IV and placebo are 3.1 ms and 2.6 ms, respectively.

As shown in Table 15, in categorical analysis of PR, little differences were observed among the two drug arms and placebo.

Table 14: Analysis Results of ΔPR and ΔΔPR

	PTK 0796 100 mg IV			PTK 0796 300 mg IV		
	ΔPR LS Mean of Change from Baseline (ms)		**ΔΔPR Difference of LS Mean and 90% CI (ms)**	**ΔPR LS Mean of Change from Baseline (ms)**		**ΔΔPR Difference of LS Mean and 90% CI (ms)**
Time (Hour)	**PTK 0796**	**Placebo**	**PTK 0796 vs Placebo**	**PTK 0796**	**Placebo**	**PTK 0796 vs Placebo**

0.333	-1.87	0.55	-2.4 (-4.5, -0.4)	-1.61	0.55	-2.2 (-4.2, -0.1)
0.583	-0.86	-0.32	-0.5 (-2.5, 1.4)	-0.92	-0.32	-0.6 (-2.6, 1.4)
0.833	-0.09	0.20	-0.3 (-2.2, 1.6)	-1.39	0.20	-1.6 (-3.6, 0.4)
1.083	-1.31	0.76	-2.1 (-4.1, 0.0)	-2.59	0.76	-3.3 (-5.4, -1.3)
1.5	-0.03	0.10	-0.1 (-2.1, 1.9)	-1.60	0.10	-1.7 (-3.7, 0.3)
2	-1.49	0.60	-2.1 (-4.0, -0.1)	-2.58	0.60	-3.2 (-5.1, -1.2)
4	-3.45	-2.92	-0.5 (-2.5, 1.4)	-4.27	-2.92	-1.4 (-3.3, 0.6)
6	-6.98	-5.87	-1.1 (-3.0, 0.8)	-9.16	-5.87	-3.3 (-5.2, -1.4)
12	-2.14	-0.14	-2.0 (-4.5, 0.5)	-3.09	-0.14	-2.9 (-5.5, -0.4)
18	2.22	1.48	0.7 (-1.6, 3.1)	1.74	1.48	0.3 (-2.1, 2.6)
22	-0.61	-0.75	0.1 (-1.8, 2.1)	-1.86	-0.75	-1.1 (-3.1, 0.8)

Table 15: Categorical Analysis for PR

	Total N		**PR <= 200 ms**		**200 ms < PR <=220 ms**		**PR >220 ms**	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**
PTK 0796 100 mg IV	63	693	60 (95.2)	681 (98.3)	1 (1.6)	10 (1.4)	2 (3.2)	2 (0.3)
PTK 0796 300 mg IV	61	671	58 (95.1)	662 (98.7)	1 (1.6)	6 (0.9)	2 (3.2)	3 (0.4)
Placebo	63	692	60 (95.2)	665 (96.1)	0 (0.0)	17 (2.5)	3 (4.8)	10 (1.4)

5.2.4 QRS Analysis

The same statistical analysis as used in an analysis of QTcF was performed based on QRS interval. The point estimates (ΔQRS and ΔΔQRS) and the 90% confidence intervals (ΔΔQRS) are presented in Table 16. The largest upper limits of 90% CI for the mean differences in ΔΔQRS between PTK 0796 100 mg IV and placebo and between PTK 0796 300 mg IV and placebo are 0.9 ms and 1.0 ms, respectively.

As shown in Table 17, in categorical analysis of QRS, there was only a small difference between PTK 0796 100 mg IV and the placebo, and there were no subjects in PTK 0796 300 mg IV who had QRS > 110 ms.

Table 16: Analysis Results of ΔQRS and ΔΔQRS

	PTK 0796 100 mg IV			**PTK 0796 300 mg IV**		
	ΔQRS LS Mean of Change from Baseline (ms)		**ΔΔQRS Difference of LS Mean and 90% CI (ms)**	**ΔQRS LS Mean of Change from Baseline (ms)**		**ΔΔQRS Difference of LS Mean and 90% CI (ms)**
Time (Hour)	**PTK 0796**	**Placebo**	**PTK 0796 vs Placebo**	**PTK 0796**	**Placebo**	**PTK 0796 vs Placebo**
0.333	-0.32	-0.34	0.0 (-0.5, 0.5)	-0.46	-0.34	-0.1 (-0.6, 0.4)

0.583	-0.34	-0.03	-0.3 (-0.8, 0.2)	-0.54	-0.03	-0.5 (-1.0, 0.0)
0.833	-1.07	-0.19	-0.9 (-1.4, -0.4)	-0.53	-0.19	-0.3 (-0.8, 0.2)
1.083	-0.44	0.05	-0.5 (-1.0, 0.0)	-0.73	0.05	-0.8 (-1.3, -0.3)
1.5	-0.05	0.73	-0.8 (-1.3, -0.2)	-0.24	0.73	-1.0 (-1.5, -0.4)
2	0.48	0.72	-0.2 (-0.9, 0.4)	-0.27	0.72	-1.0 (-1.7, -0.3)
4	-0.21	-0.11	-0.1 (-0.6, 0.4)	-0.80	-0.11	-0.7 (-1.2, -0.1)
6	-0.73	-0.73	0.0 (-0.7, 0.7)	-0.62	-0.73	0.1 (-0.6, 0.8)
12	-0.22	0.00	-0.2 (-1.1, 0.6)	-0.06	0.00	-0.1 (-0.9, 0.8)
18	0.22	-0.03	0.2 (-0.4, 0.9)	0.32	-0.03	0.3 (-0.3, 1.0)
22	-0.38	-0.10	-0.3 (-1.0, 0.4)	0.01	-0.10	0.1 (-0.6, 0.8)

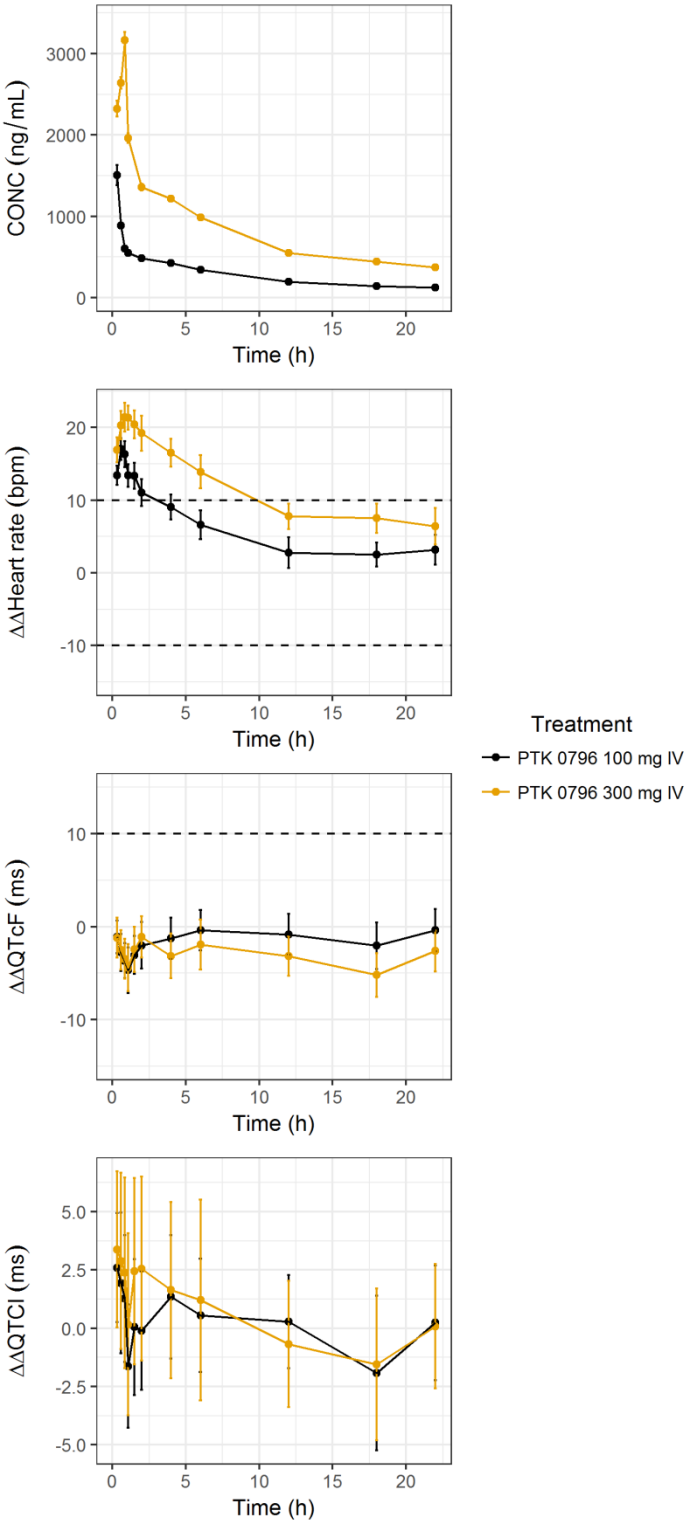
Table 17: Categorical Analysis for QRS

	Total N		QRS <= 110 ms		110 ms < QRS	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj. (%)**	**# Obs. (%)**	**# Subj. (%)**	**# Obs. (%)**
PTK 0796 100 mg IV	63	693	59 (93.7)	670 (96.7)	4 (6.3)	23 (3.3)
PTK 0796 300 mg IV	61	671	61 (100.0)	671 (100.0)	0 (0.0)	0 (0.0)
Placebo	63	692	60 (95.2)	673 (97.3)	3 (4.8)	19 (2.7)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

Figure 4 shows the comparison of drug concentration (omadacycline), ΔΔHR, ΔΔQTcF and ΔΔQTcI for each of the sampling time points. The predose baseline was used in this representation. There was a large heart rate effect (increase >10 bpm) with both the doses of omadacycline. This heart rate effect appears to be dose-/concentration-dependent (Figure 4, Figure 5).

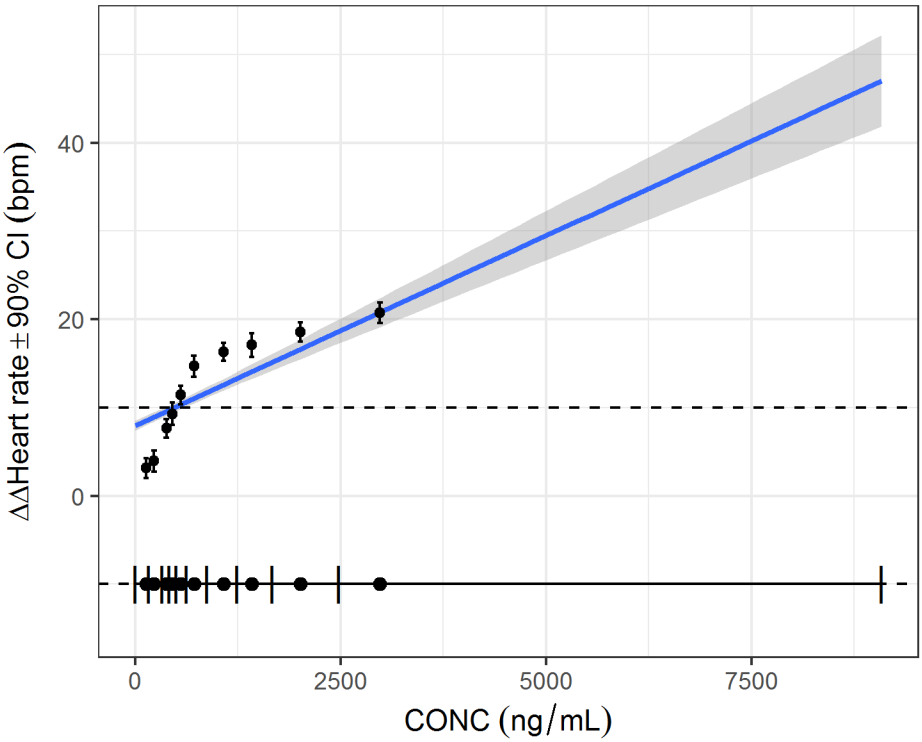
Figure 4: Time-course of mean omadacycline concentration, ΔΔHR, ΔΔQTcF, and ΔΔQTcI



Exposure-response for Omadacycline

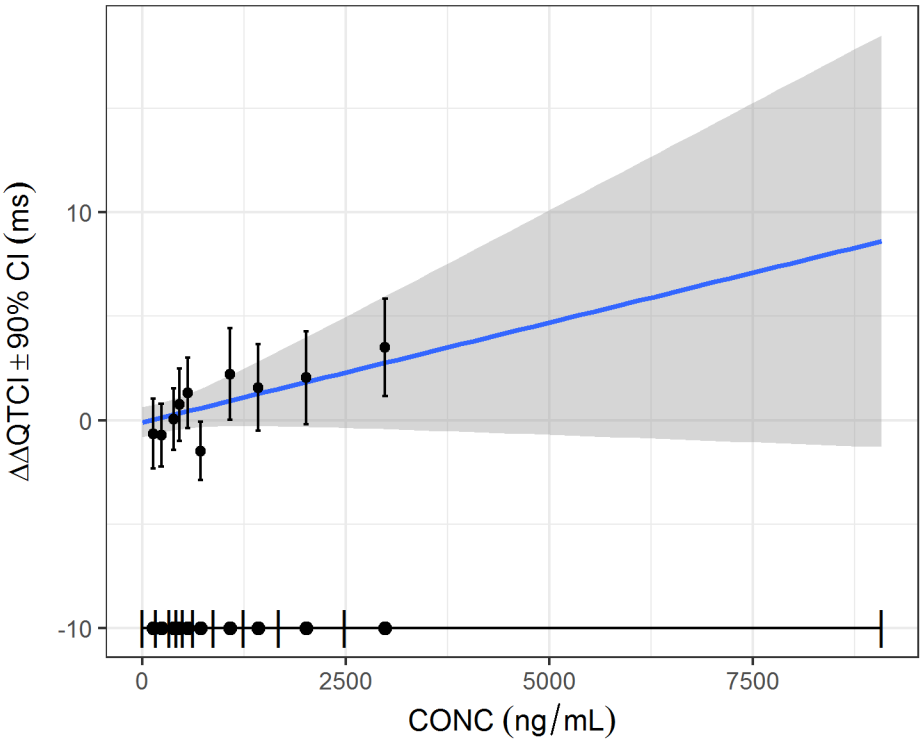
An exploratory concentration-HR relationship was visualized in Figure 5, which showed a concentration-dependent relationship for heart rate effects with possible non-linearity in the relationship.

Figure 5: ΔΔHR vs. Omadacycline Concentrations



An exploratory concentration-QTc relationship was investigated using the recommended prespecified linear mixed-effects model. The predose baseline for QTcI was used in the analysis. The slope estimate from the model was 0.96 ms per µg/mL (p-value 0.2). The relationship between ΔΔQTcI and omadacycline concentrations is visualized in Figure 6 and it was not statistically significant. Mean predicted ΔΔQTcI at the omadacycline C_{max} (3215 ng/mL) for the supratherapeutic dose (300 mg IV infusion over 1 h) is 3.0 ms with upper bound of 90% CI of 6.4 ms. This upper bound of 90% CI is below the ICH E14 threshold of 10 ms. However, this characterization could be confounded due to possibly inadequate QT/RR correction because of large heart rate effects described earlier.

Figure 6: ΔΔQTcI vs. Omadacycline Concentrations



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this TQT study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

The PR and QRS intervals are not heart rate dependent. There was no clinically relevant changes in these intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Topic	Query		Response / Comment	References
Therapeutic dose and exposure	Include maximum proposed clinical dosing regimen Mean (%CV) Cmax and AUC at the single maximum proposed clinical dose Mean (%CV) Cmax and AUC at the steady state with the maximum proposed clinical dosing regimen		Anticipated maximum single dose: IV: 200 mg Cmax 2.01 mg/L (40%) AUC 11.07 mg·h/L (23%) Oral: 600 mg Cmax 0.52 mg/L (15%) AUC 11.26 mg·h/L (13%) Maximum regimen = QD dosing for up to 14 days. At steady state; IV: 200 mg Cmax 3.55 mg/L (15%) AUC 18.00 mg·h/L (10%) Oral: 600 mg **TBD**	SDES-0501 OBAV-0502 MDES-0601
Maximum tolerated dose	Include if studied or NOAEL dose		IV: 400 mg Oral: 600 mg [based on Phase 1 studies]	SDES-0501 OBAV-0502
Principal adverse events	Include most common adverse events; dose limiting adverse events		Most common AEs (>5% incidence in combined Ph. 2 & Ph. 3 studies; combined IV & oral dosing; N=179): nausea 17%, headache 13%, constipation 6%, vomiting 6%, blood CPK increased 6% Dose-limiting AEs: IV: liver enzyme elevation at 600 mg Oral: N/A	CSSI-0702 CSSI-0804 SDES-0501
Maximum dose tested	Single Dose		IV: 600 mg Oral: 600 mg	SDES-0501 OBAV-0502

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	Multiple Dose		IV: 200 mg QD x 7d Oral: 300 mg QD x 10d	MDES-0601 MDPO-0602
Exposures Achieved at Maximum Tested Dose	Single Dose: Mean (%CV)	Mean (%CV) Cmax and AUC	IV: 600 mg Cmax 4.51 mg/L (3%) AUC 36.02 mg·h/L (7%) Oral: 600 mg Cmax 0.52 mg/L (15%) AUC 11.26 mg·h/L (13%)	SDES-0501 OBAV-0502
	Multiple Dose	Mean (%CV) Cmax and AUC	IV 200 mg QD at steady state: Cmax 3.55 mg/L (15%) AUC 18.00 mg·h/L (10%) Oral 300 mg QD at steady state: Cmax 0.88 mg/L (10%) AUC 9.27 mg·h/L (9%)	MDES-0601 MDPO-0602
Range of linear PK	Specify dosing regimen		Single doses: IV: linear from 25-600 mg Oral: linear from 50-150 mg; non-linear above 150 mg	SDES-0501 OBAV-0502
Accumulation at steady state	Mean (%CV); specify dosing regimen		Exposure increases ~50% from Day 1 to steady state with QD dosing IV 200 mg QD, AUC: Day 1 12.21 mg·h/L (9%) Day 7 18.00 mg·h/L (10%) Day 7/Day 1 = 1.47 Oral 300 mg QD, AUC: Day 1 5.88 mg·h/L (10%) Day 10 9.27 mg·h/L (9%) Day 10/Day 1 = 1.57	MDES-0601 MDPO-0602
Metabolites	Currently no active metabolites have been identified.		None identified	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)	34.5% (24%) for Phase 3 tablet formulation	CPTK796A2104

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	Tmax	Median (range) for parent	Oral under fasting conditions: Median ~2.5 h (range 1.5-4.0 h)	Multiple Phase 1 studies
Distribution	Vd	Mean (%CV)	IV single dose 25-600 mg 333 (12%) - 640 (26%) L IV 200 mg QD at steady state 414 (22%) L	SDES-0501 MDES-0601
	% bound	Mean (%CV)	Mean 21.3% Range 12.2% (50%) - 34.4% (7.0%) over a concentration range of 10-10,000 ng/mL, with no apparent concentration effect.	PTK796-Study 1000512
Elimination	Route	• Primary route; percent dose eliminated • Other routes	Oral dose Feces: 81% of the total dose (unabsorbed and biliary excretion) Urine: 14.4% of the total dose (or ~40% of the absorbed dose, assuming oral bioavailability of 35%) Recovery is as parent and degradation product (C-4 epimer); no metabolites.	CPTK796A2101
	Terminal t½	• Mean (%CV) for parent	~18 h Range 14.1 to 21 h across studies	Multiple Phase 1 studies and population PK analysis in healthy volunteers
	CL	Mean (%CV)	IV single dose 25-600 mg 15.3 (15%) - 20.9 (25%) L/h IV 200 mg QD at steady state 11.8 (16%) L/h	SDES-0501 MDES-0601

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Intrinsic Factors	Age	Specify mean changes in Cmax and AUC	Similar exposure across adult age groups. Geometric mean ratio (90% CI) for older subjects (65-80 years) / younger subjects (18-45 years): Oral 200 mg AUC: 1.13 (0.91,1.41)	WOEL-0701
	Sex	Specify mean changes in Cmax and AUC	Geometric mean ratio (90% CI) for male subjects / female subjects: IV 100 mg [WOIV-0703] Cmax 0.94 (0.72,1.22) AUC: 0.77 (0.67,0.89) Oral 200 mg [WOIV-0703] Cmax 1.15 (0.73,1.80) AUC: 1.02 (0.69,1.50) Oral 200 mg [WOEL-0701] AUC: 0.64 (0.52,0.80) In a population PK model of 8 Phase 1 studies, sex did not impact either CL or Vss. Apparent sex-related differences in individual studies may be due to confounding with body size.	WOEL-0701 WOIV-0703 Population PK analysis in healthy volunteers
	Race	Specify mean changes in Cmax and AUC	**TBD** Since OMC is not metabolized, there is unlikely to be any differences in PK due to race that cannot be accounted for by either renal function or body size.	

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	Hepatic Impairment	Specify mean changes in Cmax and AUC	Similar exposure in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, C, respectively) for both IV and oral dosing. Geometric mean ratio (90% CI) for hepatic impaired subjects / healthy subjects: <u>Mild impairment</u> IV 100 mg: Cmax: 1.37 (1.03,1.81) AUC: 0.89 (0.70,1.12) Oral 300 mg: Cmax: 0.96 (0.62,1.47) AUC:1.21 (0.91,1.60) <u>Moderate impairment:</u> IV 50 mg: Cmax: 0.98 (0.81,1.18) AUC: 0.80 (0.63,1.01) Oral 150 mg: Cmax: 1.24 (0.94,1.65) AUC: 1.01 (0.71,1.42) <u>Severe impairment</u> IV 50 mg: Cmax: 1.03 (0.86,1.24) AUC: 0.97 (0.79,1.18)	CPTK796A2201
	Renal Impairment		**TBD**	
Extrinsic Factors	Drug interactions		OMC is neither a substrate, inhibitor nor inducer of the major CYP isozymes, nor a substrate or inhibitor of the major organic ion transporters. It appears to be a substrate of P-gp, but not an inhibitor. No *in vivo* metabolic or transport DI studies have been done or are currently planned.	

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	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)	OMC exposure is decreased when administered orally with food. Compared to fasting administration, mean Cmax and AUC were decreased: • by 15-17% with a high fat meal 4 hours before dosing • by 40-42% with a high fat meal 2 hours before dosing • by 59-63% with a high fat meal with dairy 2 hours before dosing	FDEF-15101
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.		**TBD**	
Preclinical Cardiac Safety	Summarize *in vitro* and *in vivo* results per S7B guidance.		**In vitro** Ik1-no inhibition at 557 ug/mL hHERG K+-IC41-1670 ug/mL Na/K ATPase-IC50>300uM (166 ug/mL) HEK293 transfected wit hERG-IC25= 166 ug/mL Rabbit Purkinje fiber-300 ug epolarization of resting membrane potential and decrease in AP amplitude; APD were not affected. **In vivo** Anesthetized Monkey 90 mg/kg iv-decrease in contractility by 21-45%, no effect of ECG or respiratory Conscious monkey 40 mg/kg iv: increase in BP and heart rate returned to baseline by 30 minutes after the end of infusion. Heart rate increases was not proportional to dose.	

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Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	Across 19 completed clinical trials, 747 unique subjects have received OMC: IV 415 received at least one dose of IV OMC 385 received daily doses ≥100mg 113 received daily doses ≥200mg Oral 570 received at least one dose of oral OMC 273 received daily doses ≥300mg 24 received daily doses ≥400mg There were no AEs of QT prolongation, torsade de pointes, seizures, any type of ventricular arrhythmias, or sudden death. There was one case of vasovagal syncope (mild) in a 23 year-old female healthy volunteer who received a single 200 mg oral dose.	

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