# Interdisciplinary Review Team for QT Studies Consultation: Multiple Ascending Dose (MAD) Study Review

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|---|---|
| **IND** | 70462 |
| **Brand Name** | Darvon, Darvon-N, Darvocet-N-50/100 |
| **Generic Name** | Propoxyphene |
| **Sponsor** | Xanodyne Pharmaceuticals, Inc |
| **Indication** | Relief of mild to moderate pain when pain is present alone or when accompanied by fever |
| **Dosage Form** | Oral tablets |
| **Drug Class** | Opioid analgesic |
| **Therapeutic Dosing Regimen** | 100 mg q4h<br>Maximum dose is 6 tablets per day |
| **Duration of Therapeutic Use** | Acute or chronic |
| **Maximum Tolerated Dose** | Not known |
| **Submission Number and Date** | SDN 039/040, September 3, 2010 |
| **Clinical Division** | DAAP/HFD 170 |

## 1 SUMMARY

### 1.1 OVERALL SUMMARY OF FINDINGS

A significant QTc interval prolongation was observed at two dose levels (i.e., 600 mg and 900 mg) of propoxyphene.

In this randomized, double-blind, placebo-controlled, sequential multiple-ascending dose, parallel study, 18 healthy subjects were randomized to received propoxyphene 600 mg and 900 mg for 11 days. The results are summarized in Table 1.

**Table 1: The Point Estimates and 90% Confidence Interval Corresponding to the Largest Mean ΔΔQTcF Interval for Propoxyphene (600 mg, 600 mg repeated, and 900 mg)**

| Treatment | Outcome | Time (hour) | Mean and 90% CI (ms) |
|---|---|---|---|
| Dose Level 1: 600 mg | ΔΔQTcF | 7 | 29.8 ( 11.7, 47.9) |
| Dose Level 1R: 600 mg | ΔΔQTcF | 2 | 18.8 ( -0.2, 37.9) |
| Dose Level 2: 900 mg | ΔΔQTcF | 2 | 38.2 ( 19.0, 57.4) |

Exposure-response analysis demonstrated a significant linear relationship between norpropoxyphene concentration and ΔΔQTcF. The ΔΔQTcF for 600 mg was 16.8 ms with an upper 90% CI of 21.8 ms. It is recognized in the E14 Guidelines that hERG

channel blockers with mean QT/QTc interval prolongation > 20 ms have a substantially increased likelihood of being proarrhythmic. Several examples are presented in 1.2.1.

The maximum concentrations of propoxyphene and norpropoxyphene following 900-mg dose at steady state were 2.6- and 1.5-fold higher than those observed following 600-mg/day dose at steady state (399 ng/mL for propoxyphene and 1290 ng/mL for norpropoxyphene). At the 900-mg dose, model predicted ΔΔQTcF was 27.9 ms (90% CI: 20.3; 35.4). The norpropoxyphene exposures achieved with the 900-mg dose in normal young volunteers is similar to those observed in elderly patients taking 300 mg. In Flanagan *et al.* (Br. J. Clin. Pharm. 1989), mean steady state norpropoxyphene $C_{max}$ in 12 patients age 70-79 years (creatinine clearance 45-95 mL/min) administered 300 mg was 1100 ng/mL. Based on our exposure response analysis, the model predicted ΔΔQTcF at 1100 ng/mL is 22.9 ms (90% CI: 16.5; 29.4).

The exposure from the 900-mg dose is not sufficient to address the high exposure scenario, that is, patients with severe renal impairment. Based on the linear pharmacokinetics of the metabolite, patients with severe renal impairment (e.g. creatinine clearance of 20 mL/min) administered 600 mg are expected to have a steady-state $C_{max}$ of 3397 ng/mL. This is 2.6-fold higher than the $C_{max}$ at 900 mg and will result in greater QT prolongation.

In addition, dose-dependent prolongation of PR and QRS intervals was also observed in the trial. The results are summarized in Table 2

**Table 2: The Point Estimates and 90% Confidence Interval Corresponding to the largest ΔΔPR, and ΔΔQRS Interval for Propoxyphene (600 mg, 600 mg repeated, and 900 mg)**

| Treatment | Outcome | Time (hour) | Mean and 90% CI (ms) |
|---|---|---|---|
| Dose Level 1: 600 mg | ΔΔPR | 4 | 28.3( 4.3, 52.3) |
| Dose Level 1R: 600 mg | ΔΔPR | 2 | 17.7 ( -4.2, 39.6) |
| Dose Level 2: 900 mg | ΔΔPR | 2 | 25.1 ( 4.4, 45.7) |
| Dose Level 1: 600 mg | ΔΔQRS | 7 | 15.4 ( 5.7, 25.0) |
| Dose Level 1R: 600 mg | ΔΔQRS | 2 | 7.2 ( -1.0, 15.3) |
| Dose Level 2: 900 mg | ΔΔQRS | 2 | 17.9 ( 8.9, 27.0) |

### 1.2 QT-IRT EXPERIENCE REGARDING PREVIOUS REGULATORY ACTION WITH SOME $QT_C$, PR AND QRS PROLONGERS WITH SIMILAR EFFECT SIZE.

The QT-IRT was asked to provide a summary of some regulatory actions for known QTc prolongers with similar effect size. It is to be noted that anti-arrhythmic drugs associated with torsade de pointes (TdP) e.g. sotalol at a dose of 160 to 640 mg/day shows a dose-related mean increase of QTc of 10-40 ms (sotalol PI). Similarly dofetilide (TIKOSYN) at a therapeutic dose increased QTc by 15 ms to 87 ms (dofetilide PI). This summary will

focus on regulatory actions of some non-antiarrhythmic drugs that were known QT or PR prolongers, for which the QT-IRT was consulted.
We would like to emphasize that regulatory actions are a balance of efficacy vs. risk assessments which we defer to the review division.

### 1.2.1 QT-prolongers

Sertindole (NDA 20644) is an atypical antipsychotic agent, the original NDA for which was submitted in September 1995. An "Approvable" Action Letter was issued on June 16, 1997, with the greatest issues of concern being (1) a dose dependent QTc prolongation in phase II/III studies (with effect size over 20 ms with the therapeutic dose), and (2) a seemingly disproportionate incidence of sudden and unexpected deaths (SUDS) among schizophrenics treated with sertindole as compared to those treated with other recently developed anti-psychotic drugs.

The sponsor withdrew the NDA in January 1998 and resubmitted the NDA in 2008 after conducting a randomized, active-controlled, open-label, prospective use study (SCoP Study; n=9858) comparing the safety of sertindole and risperidone. The sponsor reported that sertindole and risperidone had comparable all-cause mortality. Based on this study, the sponsor proposed that although sertindole has the potential to prolong the QT interval, this does not appear to translate into an increased safety risk. Although all cause mortality was similar, the estimated hazard ratio (sertindole versus risperidone) of documented sudden death (including cases with cardiac origin probable), adjusting for age and sex, was 5.0 (95% CI: 1.4 to 17.5), showing a statistically significant (p=0.01) higher risk of sudden death in the sertindole group than in the risperidone group. Specifically, 8/13 cases were young females with no pre-existing cardiac conditions. These findings were presented at an advisory committee who concurred that the concern over a potential proarrhythmic effect of sertindole raised by the substantial QT-prolonging effect was well-founded. (refer to NDA 20-644, (b) (4) for further details).

ANZEMET (dolasetron mesylate, NDA 20623) is approved since 1997 for the following indications as an IV and oral formulations:
1) the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin (CINV);
2) the prevention and treatment of postoperative nausea and vomiting (PONV).
In April 2006, the sponsor (Sanofi-Aventis) submitted to the FDA supplemental labeling changes to contraindicate Anzemet (dolasetron) use in pediatrics. Their action was prompted following the UK Medicines and Healthcare Products Regulatory Agency's (MHRA) initial drug application review and decision to contraindicate Anzemet (dolasetron) in children and adolescents due to cardiovascular safety concerns (January 2006) observed in pediatric trials. The Agency's review of the submitted pediatric cases from the pediatric trials found the information inconclusive and the sponsor was asked to conduct a TQT study. The sponsor submitted the TQT study, QT-IRT's findings were discussed in a regulatory briefing held in July 16, 2010.

In the TQT (refer to QT-IRT review under NDA 20623 & 20624, March 12, 2010), dolasetron prolonged the QT PR and QRS intervals in a dose and concentration-dependent fashion. The effect size (upper bound of 2-sided 90% CI) on QTc for the 100 mg therapeutic dose and 300 mg IV supra-therapeutic dose was over16 and 38 ms. Based on concentration-QTc modeling, it was determined that mean effect sizes in adult and pediatric cancer patients could be over 20 ms. DGP has withdrawn the CINV indication for the IV formulation and the contraindications and warning & precautions section of the PI has been updated to describe the ECG effects and populations at risk. With the oral formulation, the upper bounds of the derived QTc intervals based on the established concentration-QT relationship were below 20 ms for elderly patients and patients with compromised renal function. Additional language in the warning and precautions section was added for these special patient populations.

Chloroquine and hydroxychloroquine (PLAQUENIL) are indicated for the treatment of malaria. Hydroxychloroquine is also indicated for the treatment of discoid and systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) on a long-term basis at a dose of 400mg to 600 mg/day. (b) (4)

[redacted]

INVIRASE [Saquinavir (SQV)1000 mg/ritonavir (RTV)100 mg, NDA 21785 & NDA 20628] is an inhibitor of human immunodeficiency virus (HIV- 1) viral protease. Ritonavir (NORVIR, RTV), a protease inhibitor (PI) with antiviral activity against HIV-1 and HIV-2, is a potent inhibitor of CYP3A4 and P-glycoprotein (P-gp). Low dose RTV is administered in combination with SQV (and other antiretroviral agents) to increase SQV exposure due to CYP-3A4 inhibition. In a TQT study, significant QT prolongation (largest upper bound of 90% CI over 20 ms) with the therapeutic dose was noted on Day 3. Due to auto induction of metabolism higher exposures are expected around this time compared to steady-state. In a previous TQT study, the QT effect (upper bound of 90% CI) for ritonavir 400 mg was 5.2 ms (7.5 ms). Our estimated QT effect for ritonavir 100 mg based on concentration-QT analysis is 1~2 ms, indicating that the QT effect size observed in this study is likely due to SQV alone. Dose dependent PR prolongation was also noted which will be discussed in the next section. There was only one report of TdP which was confounded due to co-morbidities and concomitant medications. However, the division indicated that utilization of this protease inhibitor in the US is very low. DAVP is updating the PI with a contraindication and warning & precaution statement related to ECG effects. A drug safety letter was sent to health providers to communicate major changes in the label.

Some marketed oncology products that are known QTc prolongers with mean effect size over 20 ms include arsenic trioxide, for acute pro-myelocytic leukemia, nilotinib for imatinib resistant and newly diagnosed CML, sunitib for advanced renal cell cancer or GIST tumors and toremifene for advanced breast cancer in post-menopausal women (NDA 20-497) or prevention of bone fractures in men with prostate cancer on androgen deprivation therapy (NDA 22-477). Arsenic trioxide and sunitinib have been associated with documented cases of TdP. There were sudden deaths in the nilotinib clinical development program Arsenic trioxide and nilotinib have a boxed warning statement in the PI. A boxed warning has also been recommended for toremifene based on effect size (26 ms) with therapeutic dose even in the absence of events in the clinical trial or post-marketing (b) (4). Sunitinib only has a warning and precautions statement about QT prolongation effects.

#### 1.2.1.1 QT-IRT reviews for opiate agonists

Other than propoxyphene, the QT-IRT has been consulted regarding opiate agonists on limited occasions:

- We have reviewed a TQT study for transdermal buprenorphine (NDA 21-306). The maximum mean ΔΔQTcF exceeded the 10 ms threshold at the supra-therapeutic dose which was sufficient to cover the increased exposure for patients with severe renal impairment. Review of AEs in the clinical program did not suggest significant arrhythmogenic potential at the doses studied. Higher exposures can be expected with oral buprenorphine and we have no information regarding the same.
- (b) (4)
- We have not received consults or reviewed information regarding QT or ECG effects of morphine sulphate, tramadol, codeine, hydrocodone or oxycodone.

### 1.2.2 PR prolongation

- We have noted dose dependent PR prolongation of similar effect size to propoxyphene in the following TQT studies for the following products:
    - Lopinavir (LPV NDA 21906) is an antiviral protease inhibitor co-formulated with ritonavir (RTV) to boost exposure due to CYP-3A4 inhibition. In the TQT study LPV 400 mg/RTV 100 mg BID (KALETRA) and RTV 400 mg bid (NORVIR, NDA 20945) and had a maximum mean effect size on the PR interval greater than 20 ms. There have been reports of second and third degree heart block post-marketing. Both these drugs have a warning and precaution statement in the PI related to PR interval effects and patients at risk.

- SQV 1000 mg/RTV 100 mg (discussed earlier) also had a maximum mean effect size on the PR interval over 28 ms with reports of second and third-degree AV block post-marketing. DAVP has proposed a labeling update with a contraindication statement for patients with/high risk for complete heart block without implanted pacemakers, and a warning and precautions statement related to PR effects.
- Dolasetron (discussed in section 1.2.1) had an effect size of 10 ms on the PR interval with the therapeutic dose and 33 ms with the supra-therapeutic dose. A warning and precautions statement is being included in the updated PI regarding PR effects.

- In the literature PR prolongation is reported to be associated with increased risk of atrial fibrillation, pacemaker implantation and all cause mortality[1]

### 1.2.3 QRS prolongation

We have had very limited experience with regulatory action related to QRS prolongation. All the drugs discussed in section 1.2.2 had dose dependent QRS prolongation but the mean effect size was less than 4 ms with the therapeutic dose. With dolasetron the 300 mg IV dose had a mean effect size of 13 ms. QRS prolongation effects were included in the PI update.
With the local anesthetic type Class Ic anti-arrhythmic (flecainide) the mean effect size reported in the PI is 25% change from baseline (approximately 20- to 25- ms change from baseline), but mean effect size as low as 8 ms have been reported in the literature[2] Flecainide at therapeutic dose increases mortality in post- MI patients[3].

## 2 BACKGROUND

Propoxyphene is a centrally acting opiate analgesic that is structurally related to methadone. Propoxyphene hydrochloride was initially approved and marketed in 1957. The napsylate salt was subsequently approved. In addition, various other combination drugs, predominantly with acetaminophen, have been approved. Propoxyphene containing products have come under scrutiny at various times during their marketing history. One of the issues that have been raised is possible cardiotoxicity at labeled, therapeutic doses and adverse cardiac AEs high plasma concentrations.

The sponsor is conducting this study as a PMR in response to recommendations from an Advisory Committee Meeting was held in January 2009. This was related to a Citizens Petition in 2006 requesting the phased withdrawal of propoxyphene-containing products from the market. Cardiotoxicity, QRS prolongation, and cardiac depressant effects are reported in the literature and AERs database for propoxyphene over-doses. There is no clear evidence for these adverse events at therapeutic doses.

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[1] Long-term outcomes in individuals with prolonged PR interval or First-Degree Atrioventricular block: *JAMA.* 2009;301(24):2571-2577

[2] Oral flecainide acetate for the treatment of ventricular arrhythmias; N Engl J Med.1981; 305:473-7)

3 Preliminary Report: Effect of Encainide and Flecainide on Mortality in a Randomized Trial of Arrhythmia Suppression after Myocardial Infarction The Cardiac Arrhythmia Suppression Trial (CAST) Investigators N Engl J Med 1989; 321:406-412, August 10, 1989

The QT-IRT has been consulted on numerous occasions regarding this study (refer to QT-IRT reviews to IND 70462 dated November 18, 2009, February 2, 2010, April 9, 2010 and September 1, 2010 for further details). The initial plan was to conduct an MAD study to establish the maximum tolerated dose and then proceed with a TQT study. However, based on preliminary review of the data (600- and 900-mg dose cohort), the QT-IRT and DAAP inferred that the effects on all ECG intervals (QTc, PR and QRS) observed were of significant magnitude and therefore the TQT study was not necessary. The QT-IRT was advised to conduct a detailed review of preliminary results from the MAD study to decide on further regulatory action.

### 2.1 CLINICAL PHARMACOLOGY

Appendix 5.2 summarizes the key features of propoxyphene's clinical pharmacology.

## 3 SPONSOR'S SUBMISSION

### 3.1 OVERVIEW

The sponsor has submitted the study report for data up to dose level 2 (900 mg) from the MAD study (XP20C-101) including electronic datasets, Waveforms were not submitted to the ECG warehouse for review.

### 3.2 MAD STUDY

#### 3.2.1 Title

A randomized, multiple-dose, double-blind, placebo-controlled study of sequential ascending dose levels to assess the safety, tolerability, and electrocardiographic effects of propoxyphene napsylate capsules (and its metabolite norpropoxyphene) when administered orally to healthy adult subjects.

#### 3.2.2 Protocol Number

XP20C-101

#### 3.2.3 Study Dates

July, 2010 --August, 2010

#### 3.2.4 Objectives

The primary objective of the study is to determine the daily maximum tolerated dose (MTD) of propoxyphene napsylate in healthy subjects which will then be used as the supratherapeutic dose in a subsequent thorough QTc study.
The secondary objectives of the study are:

1. To determine the relationship between the AUC and Cmax of propoxyphene and norpropoxyphene to the change in QTc observed from baseline produced from multiple dose levels of propoxyphene napsylate when administered under steady-state conditions.

2. To evaluate the pharmacokinetic (PK) profile of propoxyphene and norpropoxyphene produced from multiple dose levels of propoxyphene napsylate when administered under steady-state conditions.

### 3.2.5 Study Description

#### 3.2.5.1 Design

The study utilizes a randomized, multiple-dose, double-blind, placebo-controlled, sequential ascending dose parallel design.

#### 3.2.5.2 Controls

The Sponsor used placebo but no positive (moxifloxacin) controls.

#### 3.2.5.3 Blinding

All treatment groups were double blinded.

### 3.2.6 Treatment Regimen

#### 3.2.6.1 Treatment Arms

- Dose Level 1: Daily dose titrated to 600 mg propoxyphene napsylate per day
- Dose Level 1R: Daily dose titrated to 600 mg propoxyphene napsylate per day.
- Dose Level 2: Daily dose titrated to 900 mg propoxyphene napsylate per day.
- Placebo

#### 3.2.6.2 Sponsor's Justification for Doses

The first proposed dose level (600 mg day) is considered the therapeutic level based on current maximum clinical recommendations for dosing and has been shown to be safe and well-tolerated in a clinical trial (Xanodyne Study XP20B-102) studying the 600-mg daily dose to steady-state conditions (Study XP20B-102). Per FDA recommendations, 2400 mg per day has been chosen to be the highest dose level for this study to evaluated equivalent propoxyphene exposures to that observed in the elderly or patients with hepatic impairment. Other dose levels that have been designated for the study (i.e., 900, 1200, 1500, 1800, and 2100 mg) are reasonable incremental doses for a dose ranging study.

Peak plasma concentrations of propoxyphene are reached in 2 to 2.5 hours. Repeat dosing of propoxyphene at 6-hour intervals lead to increasing plasma concentrations, with a plateau after the ninth dose at 48 hours. Effective plasma concentrations vary widely and are of no practical use for treating pain syndromes. Propoxyphene has a half-life of 6 to 12 hours. Linear PK is anticipated following administration of 100 mg, 200 mg, and 300 mg doses of propoxyphene napsylate.

*Reviewer's Comments:*

- *A 900-mg dose provides1.5-fold and 2.6-fold higher exposure in norpropoxyphene and propoxyphene as compared to 600-mg dose.*

- *The 900-mg dose is adequate to cover the anticipated exposure increase in an elderly patient receiving a 300-mg dose.*
- *The recommended supratherapeutic dose of 2400 mg is designed to cover the exposure increase in patients with severe renal impairment or patients with compromised hepatic functions (Please refer to IRT review dated on February 2, 2010).*
- *Additional information for the pharmacokinetics of propoxyphene and norpropoxyphene was summarized as the following:*
    - *Pharmacokinetics of propoxyphene and norpropoxyphene have been shown to change in elderly subjects after single or multiple doses. Steady state AUC of propoxyphene increases approximately 1.6-fold in elderly subjects (731 vs. 1155 μg. h/L) while steady state $C_{max}$ increases 2-fold for propoxyphene (116 vs. 239 μg/L) and 1.6-fold for norpropoxyphene (673 vs. 1100 μg/L), respectively (Flanagan et al. (1989) Br. J. Clin. Pharmac.). No formal propoxyphene PK study has been conducted in patients with mild, moderate, or severe hepatic impairment, but the PK of propoxyphene and norpropoxyphene has been evaluated in patients with hepatic cirrhosis (Giacomini et al. (1980), Clin Pharmacol Ther). Single dose PK indicated a 3-fold and 2-fold increase in $C_{max}$ and AUC, respectively, for propoxyphene. Production of norpropoxyphene was reduced in patients with hepatic cirrhosis with a 3-fold and 3.5-fold decrease in $C_{max}$ and AUC of norpropoxyphene relative to patients without hepatic impairment. The AUC ratio of norpropoxyphene: propoxyphene was significantly lower in patients with cirrhosis (0.5 to 0.9) than in controls (2.5 to 4). Finally, no formal study of propoxyphene has been conducted in patients with mild, moderate, or severe renal impairment. However, the pharmacokinetics of propoxyphene and norpropoxyphene has been evaluated in anephric patients after a single dose of propoxyphene. AUC and $C_{max}$ increased 1.8- and 1.9-fold, respectively, for propoxyphene, and 1.3- and 1.6-fold, respectively, for norpropoxyphene.*

- *This report covers the initial 600-mg dose level, a second analysis at the 600-mg dose level that was repeated due to dosing errors, and a reduced second dose level of 900 mg due to observed QT prolongation from the 600-mg dose. Patients are administered 1/3 of the dose on day 1 (1/6 of the dose every 12 hours),1/2 the dose on day 2 (1/6 every 8 hours), the full dose on day 3 through 11 (1/6 every 4 hours). This dose schedule is sufficient to attain steady state exposures for propoxyphene on day 11 of the study.*

#### 3.2.6.3 Instructions with Regard to Meals

Meals and snacks were provided as appropriate on Day -2. The menus on Days -1, 1, 4, and 11 were to be identical. Standard meals were provided uniformly to all subjects and dose levels for all other study days. Standard clinic meals were served at convenient times from dinner on Day 11 through the meal provided prior to release on from the

clinic on Day 13. Foods and beverages containing alcohol, caffeine, or grapefruit were not served in the clinic.

*Reviewer's Comments: The proposed schedule for meal intake with regards to propoxyphene dosing is acceptable. Previous food effect studies with propoxyphene demonstrated negligible impact on pharmacokinetics following a high-fat or high-protein meal and a 40% increase in propoxyphene $C_{max}$ with a high-carbohydrate meal. Changes in AUC were less than 10% for all meals.*

#### 3.2.6.4 ECG and PK Assessments

**Table 3. PK and ECG Sampling Schedule on Days -1, 1, 4, and 11.**

| Study Day | -1 | 1 | 4 | 11 |
|---|---|---|---|---|
| **12-Lead ECGs** | Predose (Hour 0) and Hour 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12 | Predose (Hour 0) and Hour 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12 | Predose (Hour 0) and Hour 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12 | Predose (Hour 0) and Hour 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12 |
| **PK Samples for propoxyphene and norpropoxyphene** | None collected | Days 1, 4, and 11 at Hour 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12. | Days 1, 4, and 11 at Hour 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12. | Days 1, 4, and 11 at Hour 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 9, 12, 24, 36, 48, 60. |

*Reviewer's Comments: The ECG sampling on Day 11 was acceptable for assessing QT prolongation at steady state propoxyphene and norpropoxyphene exposure.*

#### 3.2.6.5 Baseline

Time-matched baseline ECG measures on Day -1 were used as baseline.

### 3.2.7 ECG Collection

Each subject was connected to a Mortara H12+ ambulatory, continuous 12-lead recorder for a minimum of 12 hours on Days -1, 1, 4, and 11. Data was recorded on flashcards and sent to [redacted] (b) (4) for review. Triplicate twelve-lead electrocardiograms records of 10 seconds in length were extracted from the flashcard within a 5-minute time window around each nominal time point specified in Table 3 and averaged for a single value for each time point. The same evaluator (cardiologist), blinded to time and treatment, evaluated all cardiodynamic ECGs for a given subject, by applying the superimposed representative complex method. Continuous 12-lead Holter recordings were evaluated by a Cardiologist for detection of any arrhythmic event.

### 3.2.8 Sponsor's Results

Data for the current analysis was collected over three separate studies. Dose 1 consisted of 8 subjects (6 on active treatment, 2 on placebo) at 600-mg propoxyphene napsylate. Due to contamination of the placebo arm the 600-mg treatment arm was repeated (6 on

active treatment, 2 on placebo) as Dose 1R. Dose 2 consisted of 8 subjects (6 on active treatment, 2 on placebo) at 900 mg of propoxyphene napsylate. The four placebo subjects from the original Dose Level 1 and the repeat, Dose Level 1R were also included in these analyses. Therefore, 6 placebo subjects were used in these analyses (where data was available). All changes were noted as compared to baseline (Day -1) or changes from placebo and baseline.

#### 3.2.8.1 Study Subjects

All subjects enrolled in Dose 1 and Dose 1R completed the study. At Dose Level 2, excluding subjects (b) (6) and (b) (6) (1 placebo, 1 active) all other subjects received all doses of the study medication and completed all ECG extractions on Day 11. However, three subjects had episodes of emesis that closely followed study drug administration: subjects (b) (6), and (b) (6). 11 episodes of emesis occurred among the 3 subjects. Of the 11 episodes, 6 episodes occurred in ≤ 1 hour post-dosing (2 for each subject). None of these episodes occurred on Day 11.

#### 3.2.8.2 Statistical Analyses

See Appendix (Section 5.1)

#### 3.2.8.3 Safety Analysis

There were no deaths or serious AEs in the study. Most of the AEs were minor like dizziness, light-headedness, emesis and nausea, headache and mood changes.
At dose level 2, two subjects discontinued due to AEs:

- Subjec (b) (6)-048 randomization #20 [last dose of study medication on Day 6 Hour 0, withdrew due to confinement anxiety].
- Subject (b) (6)-049 randomization #21 [last dose of study medication on Day 5 Hour 20, withdrew due to nausea, emesis, and malaise].

#### 3.2.8.4 Clinical Pharmacology

##### *3.2.8.4.1 Pharmacokinetic Analysis*

*The sponsor did not provide a summary of PK results for the either propoxyphene dose. A summary of $C_{max}$ values for both propoxyphene and norpropoxyphene on day 11 can be found in the reviewer's analysis.*

##### *3.2.8.4.2 Exposure-Response Analysis*

<u>See Appendix (Section 5.1.2)</u>
*Reviewer's Comments: The sponsor only performed individual dose concentration-ΔΔQTcF analyses for norpropoxyphene instead of pooling all available data. The selection of only norpropoxyphene is acceptable even though both propoxyphene and norpropoxyphene inhibit hERG channels as concentrations of norpropoxyphene are 4- to 6-fold greater than propoxyphene. A major deficiency in the analysis concerns not including concentration-ΔΔQTcF observations across all three studies and is addressed*

*in the reviewer's analysis. The individual analyses are one reason why a concentration-ΔΔQTcF relationship may not have been identified by the sponsor for the Dose 1R cohort. The slopes identified by the sponsor in the individual analyses agrees with the estimated slope by the reviewer (0.0255 ms per ng/mL norpropoxyphene).*

# 4 REVIEWERS' ASSESSMENT

## 4.1 STATISTICAL ASSESSMENTS

### 4.1.1 QTc Analysis

Linear regression model was used to obtain the difference between treatment and placebo of ΔΔQTcF on Day 11 with targeted dose. Gender, treatment and baseline QTcF were included as covariates in the model. There are 6 subjects in each treatment group.

**Table 4:Analysis Results of ΔΔQTcF for Treatment Group of Dose Level 1: 600 mg on Day 11**

| | Dose Level 1: 600 mg ΔQTcF | Placebo ΔQTcF | ΔΔQTcF | |
|---|---|---|---|---|
| Time/(hr) | Mean ms | Mean ms | Diff LS Mean ms | 90% CI ms |
| 0 | 18.5 | 0.5 | 18.0 | ( -6.3, 42.3) |
| 0.5 | 16.9 | -2.8 | 19.7 | ( 0.2, 39.2) |
| 1 | 11.1 | -2.8 | 13.9 | (-14.4, 42.3) |
| 2 | 23.0 | -4.2 | 27.2 | ( 6.2, 48.3) |
| 3 | 21.7 | 6.9 | 14.8 | (-13.7, 43.2) |
| 4 | 24.9 | 4.8 | 20.1 | ( 0.7, 39.5) |
| 5 | 19.8 | 3.9 | 15.9 | ( -5.7, 37.4) |
| 6 | 15.1 | -3.7 | 18.8 | ( -1.4, 39.0) |
| 7 | 24.7 | -5.1 | 29.8 | ( 11.7, 47.9) |
| 9 | 27.0 | -0.0 | 27.0 | ( 8.2, 45.8) |
| 12 | 9.2 | 9.0 | 0.2 | (-37.6, 38.1) |

**Table 5: Analysis Results of ΔΔQTcF for Treatment Group of Dose Level 1R: 600 mg on Day 11**

| | Dose Level 1R: 600 mg ΔQTcF | Placebo ΔQTcF | ΔΔQTcF | |
|---|---|---|---|---|
| Time/(hr) | Mean ms | Mean ms | Diff LS Mean ms | 90% CI ms |
| 0 | 6.2 | 0.5 | 5.6 | (-17.3, 28.6) |
| 0.5 | 4.7 | -2.8 | 7.5 | (-10.7, 25.7) |
| 1 | 6.2 | -2.8 | 9.0 | (-16.4, 34.5) |
| 2 | 14.6 | -4.2 | 18.8 | ( -0.2, 37.9) |
| 3 | 12.6 | 6.9 | 5.7 | (-19.7, 31.1) |
| 4 | 10.8 | 4.8 | 6.0 | (-11.6, 23.6) |
| 5 | 9.0 | 3.9 | 5.1 | (-14.0, 24.2) |
| 6 | 7.3 | -3.7 | 11.1 | ( -7.5, 29.6) |
| 7 | 8.4 | -5.1 | 13.5 | ( -2.8, 29.9) |
| 9 | 10.8 | -0.0 | 10.8 | ( -5.0, 26.6) |
| 12 | 6.7 | 9.0 | -2.2 | (-36.4, 31.9) |

**Table 6**: Analysis Results of ΔΔQTcF for Treatment Group of Dose Level 2: 900 mg on Day 11

| | **Dose Level 2: 900 mg ΔQTcF** | **Placebo ΔQTcF** | **ΔΔQTcF** | |
|---|---|---|---|---|
| **Time/(hr)** | **Mean ms** | **Mean ms** | **Diff LS Mean ms** | **90% CI ms** |
| 0 | 23.3 | 0.5 | 22.8 | ( 0.3, 45.3) |
| 0.5 | 17.3 | -2.8 | 20.1 | ( 1.9, 38.3) |
| 1 | 24.5 | -2.8 | 27.3 | ( 1.1, 53.5) |
| 2 | 34.0 | -4.2 | 38.2 | ( 19.0, 57.4) |
| 3 | 23.3 | 6.9 | 16.4 | (-10.3, 43.0) |
| 4 | 22.8 | 4.8 | 18.0 | ( 0.0, 36.0) |
| 5 | 28.1 | 3.9 | 24.1 | ( 3.1, 45.2) |
| 6 | 28.0 | -3.7 | 31.8 | ( 12.5, 51.0) |
| 7 | 29.7 | -5.1 | 34.8 | ( 18.1, 51.5) |
| 9 | 22.4 | -0.0 | 22.4 | ( 5.3, 39.5) |
| 12 | 7.2 | 9.0 | -1.8 | (-36.0, 32.4) |

The following table lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 7: Categorical Analysis for QTcF**

| | Total N | | Value<=450 ms | | 450 ms<Value<=480 ms | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **# Subj.** | **# Obs.** | **# Subj.** | **# Obs.** | **# Subj.** | **# Obs.** |
| Baseline | 24 | 239 | 23 (95.8%) | 237 (99.2%) | 1 (4.2%) | 2 (0.8%) |
| Dose Level 1: 600 mg | 6 | 56 | 5 (83.3%) | 50 (89.3%) | 1 (16.7%) | 6 (10.7%) |
| Dose Level 1R: 600 m | 6 | 60 | 6 (100%) | 60 (100%) | 0 (0.0%) | 0 (0.0%) |
| Dose Level 2: 900 mg | 5 | 46 | 4 (80.0%) | 45 (97.8%) | 1 (20.0%) | 1 (2.2%) |
| Placebo | 5 | 41 | 5 (100%) | 41 (100%) | 0 (0.0%) | 0 (0.0%) |

The following table lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

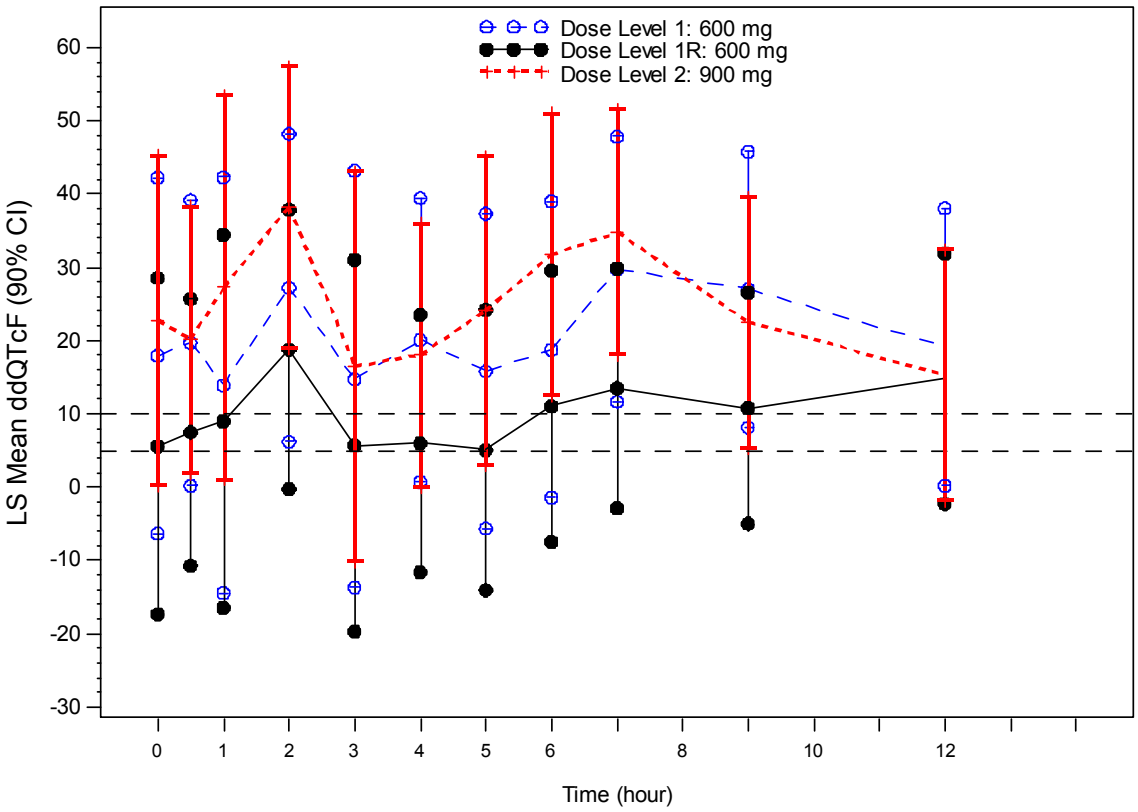
**Table 8: Categorical Analysis of ΔQTcF**

| | Total N | | Value<=30 ms | | 30 ms<Value<=60 ms | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **# Subj.** | **# Obs.** | **# Subj.** | **# Obs.** | **# Subj.** | **# Obs.** |
| Dose Level 1: 600 mg | 6 | 56 | 2 (33.3%) | 42 (75.0%) | 4 (66.7%) | 14 (25.0%) |
| Dose Level 1R: 600 m | 6 | 60 | 5 (83.3%) | 58 (96.7%) | 1 (16.7%) | 2 (3.3%) |
| Dose Level 2: 900 mg | 5 | 46 | 2 (40.0%) | 34 (73.9%) | 3 (60.0%) | 12 (26.1%) |
| Placebo | 5 | 41 | 5 (100%) | 41 (100%) | 0 (0.0%) | 0 (0.0%) |

#### 4.1.1.1 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups on Day 11.

**Figure 1: Mean and 90% CI ΔΔQTcF Time course**

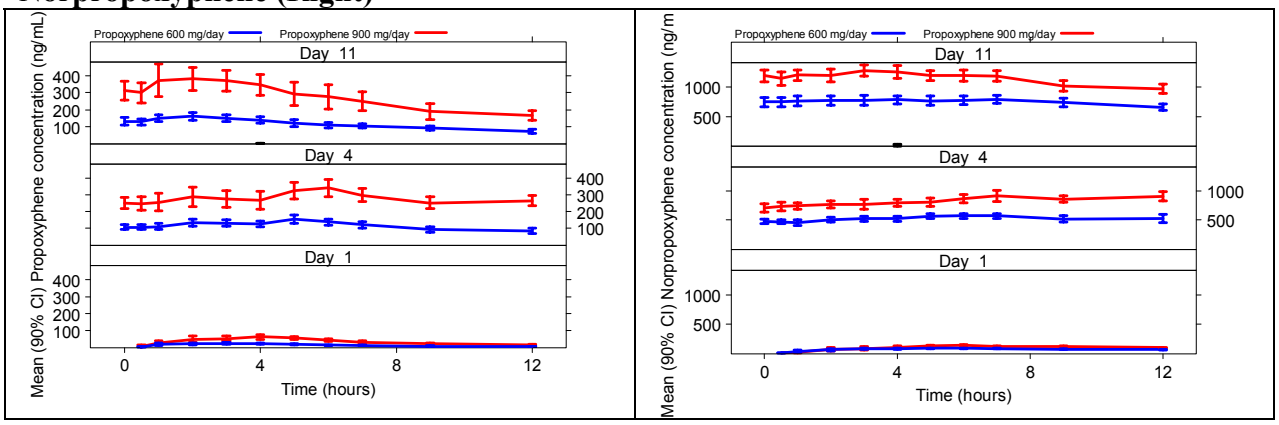



*Reviewer's comments: The analysis results indicate propoxyphene has some QTc prolongation potential.*

### 4.2 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean (90% CI) PK-time profiles for propoxyphene and norpropoxyphene are shown below in Figure 2.

**Figure 2: Day 1, 4, and 11 Pharmacokinetics for Propoxyphene (Left) and Norpropoxyphene (Right)**




A summary of propoxyphene and norpropoxyphene $C_{max}$ on day 11 for both 600 mg/day and 900 mg/day is shown in Table 9. The maximum concentrations of propoxyphene and norpropoxyphene following 900-mg dose at steady state were 2.6- and 1.5-fold higher than those observed following 600-mg dose at steady state.

**Table 9:Propoxyphene and Norpropoxyphene $C_{max}$ on Day 11**

| Treatment | Analyte | Conc |
|---|---|---|
| Propoxyphene 600 mg/day | Propoxyphene | 155 ng/mL |
| | Norpropoxyphe | 855 ng/mL |
| Propoxyphene 900 mg/day | Propoxyphene | 399 ng/mL |
| | Norpropoxyphe | 1290 ng/mL |

The relationship between ΔΔQTcF and either propoxyphene and norpropoxyphene concentrations were investigated by linear mixed-effects modeling. As both drugs are anticipated to interact with hERG channels, an additional model exploring the relationship between ΔΔQTcF and total propoxyphene and norpropoxyphene was also investigated by linear mixed-effects modeling.

The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

The final model was established by using the concentration of norpropoxyphene, because at steady state, the mean peak concentration for norpropoxyphene (600 mg) are 5.5-fold greater than propoxyphene. Based on the exposure difference, norpropoxyphene is likely the main contributor for the overall QTc interval change, unless propoxyphene is much more potent hERG blocker. A linear concentration-ΔΔQTcF relationship was identified for norpropoxyphene with results of the analyses summarized in Table 10. Model 1 was used for further analysis since the model with intercept was found to fit the data best.

**Table 10: Exposure-response Analysis of Norpropoxyphene Associated ΔΔQTcF Prolongation**

| Parameter | Estimate | P-value | IIV |
|---|---|---|---|
| Model 1: ΔΔQTcF = Intercept + Slope * Norpropoxyphene Concentration | | | |
| Intercept (ms) | -5.02 (-6.82; -3.22) | 0.0001 | 2.38 |
| Slope (ms per ng/mL) | 0.0255 (0.0194; | <.0001 | 13.39 |
| Residual Variability (ms) | 10.62 | | |
| Model 2: ΔΔQTcF = Intercept + Slope * Norpropoxyphene Concentration (Fixed Intercept) | | | |
| Intercept (ms) | 0 | | 5.52 |
| Slope (ms per ng/mL) | 0.0218 (0.0154; | <.0001 | 13.43 |
| Residual Variability (ms) | 10.64 | | |
| Model 3: ΔΔQTcF = slope * Norpropoxyphene Concentration (No Intercept) | | | |
| Slope (ms per ng/mL) | 0.0183 (0.0124; | <.0001 | 13.92 |
| Residual Variability (ms) | 11.04 | | |

The relationship between norpropoxyphene concentrations and ΔΔQTcF is visualized in Figure 3 (top). The goodness-of-fit plot in Figure 3 (bottom left) shows the observed median-quantile norpropoxyphene concentrations and associated mean (90% CI) ΔΔQTcF (90% CI) together with the mean (90% CI) predicted ΔΔQTcF. The predicted ΔΔQTcF at the geometric mean peak norpropoxyphene concentrations can be found in Table 11 and visualized in Figure 4 (bottom, right). Predicted ΔΔQTcF at the 600-mg/day and 900-mg/day norpropoxyphene peak concentration was 16.8 ms (90% CI: 11.8; 21.8) and 27.9 ms (90% CI: 20.3; 35.4). Peak steady state norpropoxyphene in elderly subjects administered 300 mg/day was 1100 ng/mL, which is between peak concentrations observed for 600 mg/day and 900 mg/day in healthy subjects and has a model predicted ΔΔQTcF of 22.9 ms (90% CI: 16.5; 29.4).

**Figure 3: Observed ΔΔQTcF Versus Norpropoxyphene Concentrations Together with the Population Predictions (Red Line, Top). Observed Median-Quantile Norpropoxyphene Concentrations and Associated Mean (90% CI) ΔΔQTcF (Colored Dots) Together with the Mean (90% CI) Predicted ΔΔQTcF (Black Line with Shaded Grey Area, Bottom Left). Mean (90% CI) Predicted ΔΔQTcF at Geometric Mean $C_{max}$ (Bottom Right).**

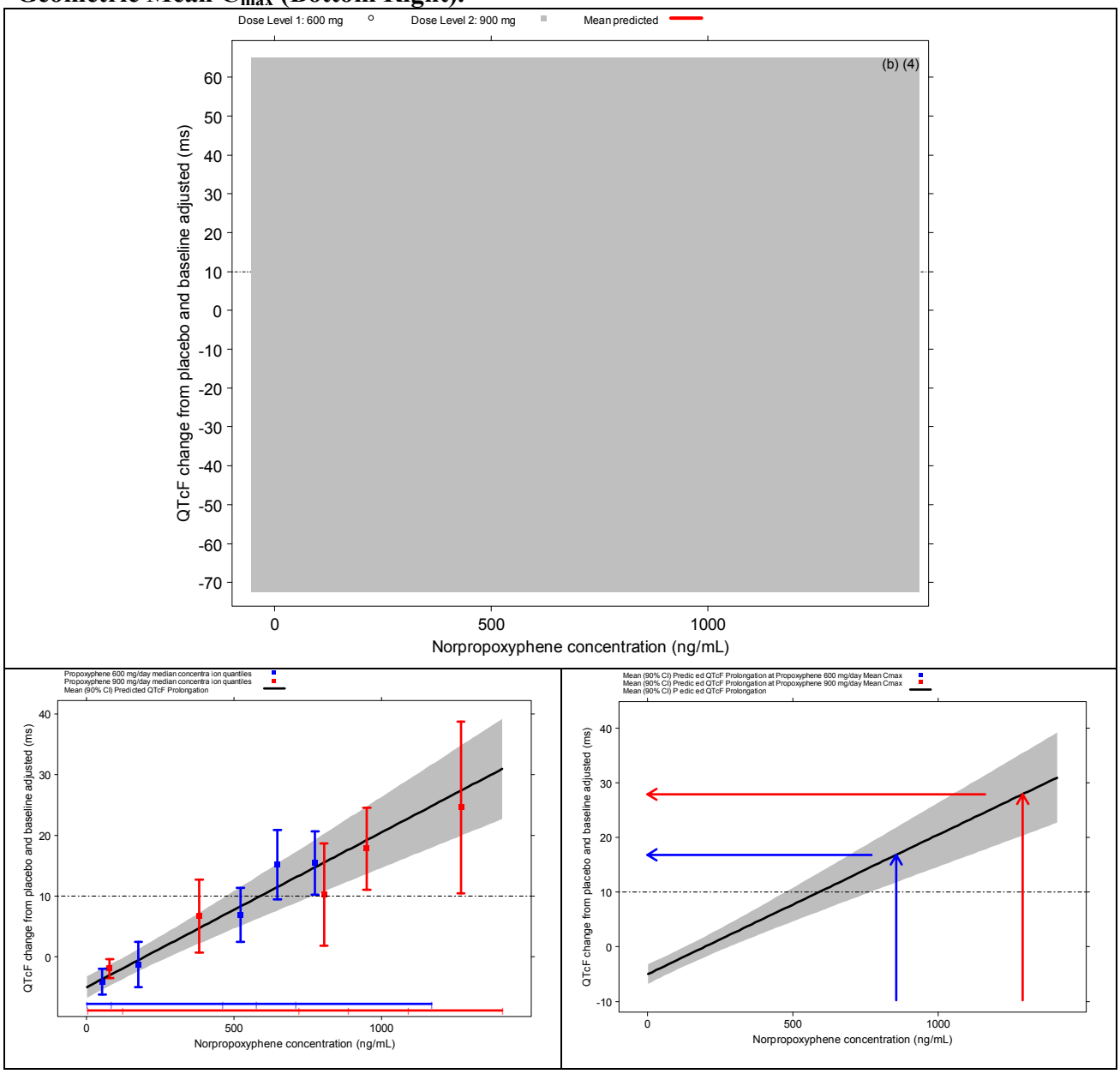


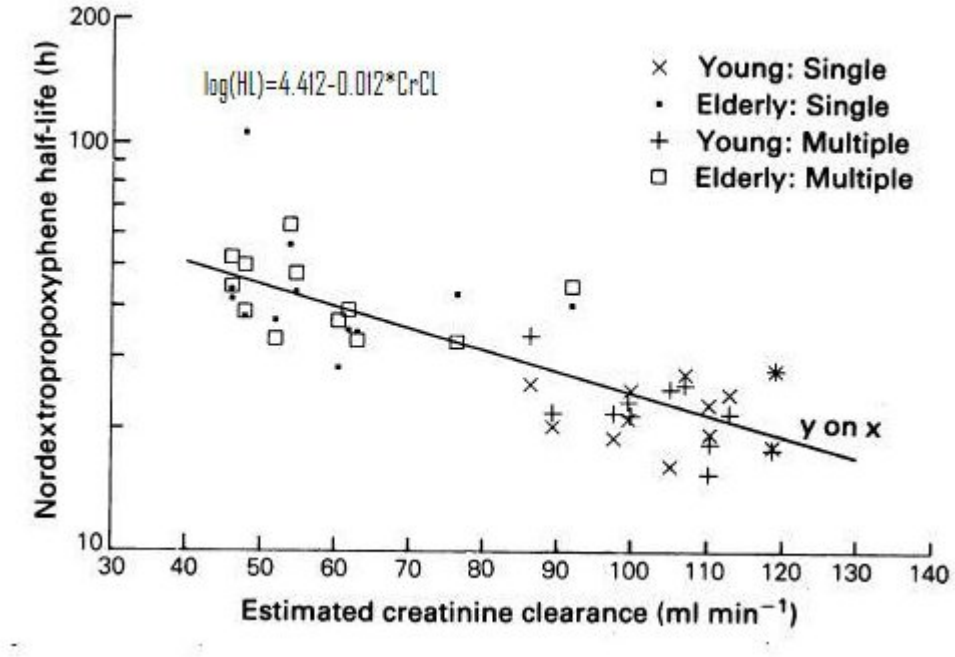
**Table 11:Predicted ΔΔQTcF Interval at Geometric Mean Peak Norpropoxyphene Concentration Using Model 1**

| Treatment | Conc | Pred | CI |
|---|---|---|---|
| Propoxyphene 600 mg/day | 855 ng/mL | 16.8 | (11.8; 21.8) |
| Propoxyphene 900 mg/day | 1290 ng/mL | 27.9 | (20.3; 35.4) |

*High Exposure Scenario*

The high exposure scenario will involve patients with severe renal impairment taking 600-mg/day. Flanagan *et al.* (1989) estimated a relationship between norpropoxyphene half-life and subject estimated creatinine clearance developed from 12 healthy and 12 elderly subjects over single and multiple propoxyphene doses. All of the elderly subjects had moderate or better renal function, but the relationship can be extended to predict the half-life of norpropoxyphene in a subject with a creatinine clearance of 20 mL/min. For the equation shown in Figure 4, a subject with creatinine clearance 20 mL/min has a predicted norpropoxyphene half-life of 64 h. From this half-life, a dosing frequency of every 4 h, total propoxyphene daily dose of 600-mg, and single dose $C_{max}$ of norpropoxyphene in anephric patients receiving 200-mg [Gibson (1980)], the expected norpropoxyphene steady-state $C_{max}$ can be calculated. This steady-state $C_{max}$ of 3397 ng/mL exceeds peak exposures for 900-mg in healthy volunteers by 2.6-fold and would likely result in even greater QT prolongation.

**Figure 4: Norpropoxyphene Half-life Versus Estimated Creatinine Clearance Relationship from Flanagan (1989).**




## 4.3 ADDITIONAL ECG INTERVAL ASSESSMENTS

### 4.3.1 PR Analysis

The same linear regression model was used to obtain the difference between treatment and placebo of ΔΔPR on Day 11 with targeted doses. Gender, treatment and baseline PR were included as covariates in the model.

**Table 12: Analysis Results of ΔΔPR for Treatment Group of Dose Level 1: 600 mg on Day 11**

| | Dose Level 1: 600 mg ΔPR | Placebo ΔPR | ΔΔPR | |
|---|---|---|---|---|
| Time/(hr) | Mean ms | Mean ms | Diff LS Mean ms | 90% CI ms |
| 0 | 18.3 | 14.2 | 4.1 | (-15.5, 23.8) |
| 0.5 | 19.3 | 12.9 | 6.4 | (-15.4, 28.2) |
| 1 | 21.7 | 12.3 | 9.4 | (-14.7, 33.6) |
| 2 | 30.4 | 7.4 | 23.1 | ( 0.7, 45.4) |
| 3 | 29.5 | 6.7 | 22.8 | ( -4.1, 49.6) |
| 4 | 28.7 | 0.4 | 28.3 | ( 4.3, 52.3) |
| 5 | 18.2 | 6.9 | 11.2 | ( -9.6, 32.1) |
| 6 | 24.7 | 5.3 | 19.4 | ( 0.9, 37.8) |
| 7 | 17.1 | 13.8 | 3.3 | (-20.9, 27.6) |
| 9 | 21.3 | -0.1 | 21.4 | ( -6.2, 48.9) |
| 12 | 19.6 | 9.0 | 10.5 | ( -9.5, 30.6) |

**Table 13: Analysis Results of ΔΔPR for Treatment Group of Dose Level 1R: 600 mg on Day 11**

| | Dose Level 1R: 600 mg ΔPR | Placebo ΔPR | ΔΔPR | |
|---|---|---|---|---|
| Time/(hr) | Mean ms | Mean ms | Diff LS Mean ms | 90% CI ms |
| 0 | 13.7 | 14.2 | -0.5 | (-19.3, 18.3) |
| 0.5 | 13.8 | 12.9 | 0.9 | (-20.4, 22.2) |
| 1 | 16.0 | 12.3 | 3.7 | (-19.8, 27.1) |
| 2 | 25.1 | 7.4 | 17.7 | ( -4.2, 39.6) |
| 3 | 12.6 | 6.7 | 5.9 | (-19.4, 31.2) |
| 4 | 17.8 | 0.4 | 17.4 | ( -5.8, 40.6) |
| 5 | 17.8 | 6.9 | 10.9 | (-10.9, 32.7) |
| 6 | 12.9 | 5.3 | 7.6 | (-10.7, 25.9) |
| 7 | 6.8 | 13.8 | -7.0 | (-29.7, 15.7) |
| 9 | 13.3 | -0.1 | 13.4 | (-13.0, 39.8) |
| 12 | 11.4 | 9.0 | 2.3 | (-17.0, 21.7) |

**Table 14: Analysis Results of ΔΔPR for Treatment Group of Dose Level 2: 900 mg on Day 11**

| | Dose Level 2: 900 mg ΔPR | Placebo ΔPR | ΔΔPR | |
|---|---|---|---|---|
| Time/(hr) | Mean ms | Mean ms | Diff LS Mean ms | 90% CI ms |
| 0 | 21.1 | 14.2 | 6.9 | (-11.6, 25.5) |
| 0.5 | 26.6 | 12.9 | 13.7 | ( -6.9, 34.3) |
| 1 | 27.6 | 12.3 | 15.3 | ( -7.2, 37.9) |
| 2 | 32.4 | 7.4 | 25.1 | ( 4.4, 45.7) |
| 3 | 27.0 | 6.7 | 20.3 | ( -3.3, 43.8) |
| 4 | 20.0 | 0.4 | 19.6 | ( -1.3, 40.6) |
| 5 | 23.8 | 6.9 | 16.9 | ( -4.0, 37.8) |
| 6 | 16.3 | 5.3 | 11.0 | ( -6.1, 28.1) |
| 7 | 18.4 | 13.8 | 4.6 | (-17.9, 27.2) |
| 9 | 18.4 | -0.1 | 18.4 | ( -4.8, 41.7) |
| 12 | 16.3 | 9.0 | 7.3 | ( -9.6, 24.2) |

The outlier analysis results for PR are presented in following table. There was one subject in dose Level 1R and one subject in dose level 2 had one observation of PR > 200 ms.

**Table 15: Outlier Analysis for PR**

| Treatment | SUBJID | time | PR | Baseline |
|---|---|---|---|---|
| Dose Level 1R: 600 mg | 001028 | 2 hrs | 202 | 165 |
| Dose Level 2: 900 mg | 001054 | 2 hrs | 202 | 156 |

### 4.3.2 QRS Analysis

The same linear regression model was used to obtain the difference between treatment and placebo of ΔΔQRS on Day 11 with targeted doses. Gender, treatment and baseline QRS were included as covariates in the model.

**Table 16: Analysis Results of ΔΔQRS for Treatment Group of Dose Level 1: 600 mg on Day 11**

| | Dose Level 1: 600 mg ΔQRS | Placebo ΔQRS | ΔΔQRS | |
|---|---|---|---|---|
| Time/(hr) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0 | 6.7 | 1.0 | 5.7 | ( -0.3, 11.7) |
| 0.5 | 8.5 | -1.0 | 9.5 | ( 0.9, 18.1) |
| 1 | 9.5 | -0.1 | 9.6 | ( 0.0, 19.2) |
| 2 | 9.9 | -4.5 | 14.4 | ( 5.1, 23.6) |
| 3 | 8.8 | -1.7 | 10.5 | ( 2.0, 18.9) |
| 4 | 10.3 | -2.6 | 13.0 | ( 3.7, 22.2) |
| 5 | 12.3 | -0.6 | 12.9 | ( 4.4, 21.4) |
| 6 | 9.5 | -1.3 | 10.8 | ( 2.7, 18.9) |
| 7 | 12.8 | -2.6 | 15.4 | ( 5.7, 25.0) |
| 9 | 6.2 | -2.8 | 9.0 | ( -1.5, 19.5) |
| 12 | 6.4 | -0.7 | 7.1 | ( -2.8, 17.1) |

**Table 17: Analysis Results of ΔΔQRS for Treatment Group of Dose Level 1R: 600 mg on Day 11**

| | Dose Level 1R: 900 mg ΔQRS | Placebo ΔQRS | ΔΔQRS | |
|---|---|---|---|---|
| Time/(hr) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0 | 3.6 | 1.0 | 2.6 | ( -2.8, 8.0) |
| 0.5 | 1.3 | -1.0 | 2.3 | ( -5.5, 10.2) |
| 1 | 1.6 | -0.1 | 1.8 | ( -6.8, 10.3) |
| 2 | 2.6 | -4.5 | 7.2 | ( -1.0, 15.3) |
| 3 | 3.4 | -1.7 | 5.0 | ( -2.5, 12.6) |
| 4 | 1.9 | -2.6 | 4.5 | ( -3.7, 12.7) |
| 5 | 2.8 | -0.6 | 3.4 | ( -4.1, 11.0) |
| 6 | 0.7 | -1.3 | 2.0 | ( -5.2, 9.2) |
| 7 | 0.8 | -2.6 | 3.4 | ( -4.9, 11.7) |
| 9 | -1.5 | -2.8 | 1.3 | ( -6.5, 9.1) |
| 12 | 0.8 | -0.7 | 1.5 | ( -7.1, 10.2) |

**Table 18: Analysis Results of ΔΔQRS for Treatment Group of Dose Level 2: 900 mg on Day 11**

| | Dose Level 2: 900 mg ΔQRS | Placebo ΔQRS | ΔΔQRS | |
|---|---|---|---|---|
| Time/(hr) | Mean (ms) | Mean (ms) | Diff LS Mean (ms) | 90% CI (ms) |
| 0 | 10.8 | 1.0 | 9.8 | ( 4.2, 15.4) |
| 0.5 | 8.7 | -1.0 | 9.7 | ( 1.6, 17.8) |
| 1 | 10.7 | -0.1 | 10.9 | ( 2.1, 19.7) |
| 2 | 13.4 | -4.5 | 17.9 | ( 8.9, 27.0) |
| 3 | 12.2 | -1.7 | 13.8 | ( 6.0, 21.6) |
| 4 | 9.9 | -2.6 | 12.5 | ( 3.9, 21.1) |
| 5 | 13.2 | -0.6 | 13.8 | ( 5.4, 22.1) |
| 6 | 11.4 | -1.3 | 12.7 | ( 4.7, 20.6) |
| 7 | 10.3 | -2.6 | 12.8 | ( 3.6, 22.0) |
| 9 | 7.5 | -2.8 | 10.4 | ( 1.8, 19.0) |
| 12 | 6.9 | -0.7 | 7.6 | ( -1.2, 16.4) |

The outlier analysis results for QRS are presented in the following table:

**Table 19: Outlier Analysis for QRS**

| Treatment | SUBJID | _NAME_ | time0 | time0_5 | time1 | time2 | time3 | time4 | time5 | time6 | time7 | time9 | time12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Level 1: 600 mg | 001002 | QRS | | | | | | | | 110 | | | |
| Level 1: 600 mg | 001002 | Baseline | | | | | | | | 99 | | | |
| Level 1: 600 mg | 001003 | QRS | 114 | 116 | 116 | 116 | 116 | 116 | 115 | 115 | 117 | 114 | 116 |
| Level 1: 600 mg | 001003 | Baseline | 107 | 103 | 104 | 102 | 109 | 103 | 106 | 103 | 98 | 107 | 102 |
| Level 1: 600 mg | 001007 | QRS | 116 | 114 | 114 | 112 | 116 | 111 | 116 | | 115 | 112 | |
| Level 1: 600 mg | 001007 | Baseline | 103 | 105 | 107 | 105 | 105 | 102 | 103 | | 102 | 106 | |
| Level 2: 900 mg | 001053 | QRS | 114 | 112 | 114 | 113 | 115 | 111 | 115 | 113 | 111 | | |
| Level 2: 900 mg | 001053 | Baseline | 99 | 97 | 98 | 95 | 97 | 97 | 97 | 98 | 95 | | |
| Level 2: 900 mg | 001054 | QRS | 113 | 111 | 112 | 116 | 115 | 113 | 116 | 112 | 114 | 111 | 111 |
| Level 2: 900 mg | 001054 | Baseline | 95 | 94 | 91 | 94 | 95 | 95 | 97 | 96 | 98 | 96 | 96 |

## 4.4 CLINICAL ASSESSMENTS

### 4.4.1 Safety Assessments

The sponsor reported that none of the mandatory criteria under section 11.2.1 of the protocol, "Mandatory ECG Determination of Defining Dose Level as Not Tolerable" were met.

### 4.4.2 ECG Acquisition and Interpretation

Waveforms from this study were not submitted to the ECG warehouse for review. However, based on review of previous TQT studies from [redacted] (b) (4), including waveforms and report from the Division of Scientific Investigation (DSI), it was decided that review of this study can proceed especially since dose dependent prolongation of QTcF and other intervals was observed.

### 4.4.3 PR and QRS Interpretation

As indicated in the statistical assessments, there were increases in the mean PR and QRS in all 3 groups (Dose1 -600 mg, Dose 1R -600 mg and Dose 2-900 mg). One subject each in the Dose 1R and 900 mg groups had an absolute PR of over 200 ms with a change from baseline of about 20%. Two subjects in the Dose1 and Dose 2 groups had an absolute QRS of over 110 ms. At dose level 2 the change from baseline was 15-20%.

# 5 APPENDIX

## 5.1 SPONSOR'S RESULTS

### 5.1.1 Statistical Analyses

#### 5.1.1.1 Primary Analysis

For dose level 1, baseline adjusted mean QTcF changes from placebo are greater than 10 ms and it occurred at 3 time points on Day 4 and at every time point on Day 11, with the largest mean change of ΔΔQTcF to be 30.5 ms on hour 7. The 95% upper bound CIs were exceeded 10 ms on Day 1 (2 time points), Day 4 (9 time points) and Day 11 (all time points). The highest value of ΔΔQTcF was 43.5 ms.

The sponsor reported analysis results of ΔΔQTcF for dose level 1 (600 mg) are provided below:

| QTcF Duration | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
| 1 | 0.0 h | 6 | -5.3(12.1) | -9.2 | -16.0:18.0 | -12.0:-3.7 | -15.3:4.7 |
| | 0.5 h | 6 | -10.9(4.5) | -11.7 | -15.3:-3.3 | -14.3:-9.3 | -14.7:-7.2 |
| | 1.0 h | 6 | -10.0(7.1) | -8.2 | -18.8:-2.5 | -18.5:-3.8 | -15.8:-4.2 |
| | 2.0 h | 6 | -3.0(11.4) | -0.5 | -22.7:10.0 | -7.7:3.3 | -12.4:6.4 |
| | 3.0 h | 6 | -10.8(5.4) | -10.5 | -19.0:-4.7 | -14.3:-5.7 | -15.2:-6.4 |
| | 4.0 h | 5 | -4.6(7.4) | -6.0 | -13.0:5.3 | -9.7:0.3 | -11.7:2.5 |
| | 5.0 h | 6 | 3.0(10.3) | 2.8 | -8.4:14.9 | -7.1:13.3 | -5.5:11.5 |
| | 6.0 h | 6 | 8.4(10.6) | 9.3 | -10.0:19.7 | 5.0:17.3 | -0.3:17.2 |
| | 7.0 h | 6 | -4.7(8.8) | -1.8 | -18.5:3.8 | -12.2:2.2 | -12.0:2.5 |
| | 9.0 h | 6 | 0.5(7.5) | 2.8 | -13.0:6.0 | -1.7:6.0 | -5.6:6.6 |
| | 12.0 h | 6 | -6.8(8.3) | -9.7 | -14:4.0 | -14.0:2.7 | -13.6:0.0 |
| 4 | 0.0 h | 6 | 2.1(14.8) | -4.0 | -8.8:29.8 | -8.2:7.8 | -10.1:14.3 |
| | 0.5 h | 6 | -4.4(9.4) | -4.5 | -19.3:7.3 | -8.7:3.0 | -12.2:3.3 |
| | 1.0 h | 6 | -8.1(18.3) | -3.3 | -34.8:12.5 | -25.2:5.8 | -23.1:7.0 |
| | 2.0 h | 6 | 8.1(13.6) | 4.5 | -8.0:25.7 | -1.0:23.0 | -3.1:19.3 |
| | 3.0 h | 6 | 4.0(8.1) | 5.2 | -6.7:16.3 | -3.0:7.0 | -2.6:10.6 |
| | 4.0 h | 6 | 3.9(10.5) | 5.8 | -13.7:15.7 | -2.0:11.7 | -4.7:12.5 |
| | 5.0 h | 6 | 5.1(9.6) | 4.4 | -5.8:20.6 | -2.8:9.6 | -2.8:13.0 |
| | 6.0 h | 6 | 13.9(13.2) | 13.3 | -4.5:33.2 | 7.2:21.2 | 3.1:24.8 |
| | 7.0 h | 6 | 11.8(12.5) | 13.8 | -7.0:28.3 | 3.7:18.3 | 1.5:22.1 |
| | 9.0 h | 6 | 13.2(7.0) | 11.5 | 7.5:26.8 | 9.2:12.5 | 7.4:18.9 |
| | 12.0 h | 6 | 1.8(13.1) | 4.2 | -20.2:18.2 | -4.2:8.8 | -8.9:12.6 |
| 11 | 0.0 h | 6 | 19.9(19.6) | 16.1 | 0.3:55.6 | 6.3:25.3 | 3.8:36.0 |
| | 0.5 h | 6 | 19.3(12.9) | 17.5 | 4.2:36.2 | 8.5:32.2 | 8.7:29.9 |
| | 1.0 h | 6 | 10.6(23.6) | 10.0 | -27.7:39.3 | 1.3:30.7 | -8.8:30.0 |
| | 2.0 h | 6 | 26.8(17.3) | 25.2 | 4.0:51.3 | 14.0:41.3 | 12.6:41.1 |
| | 3.0 h | 6 | 25.1(10.9) | 21.7 | 13.3:43.0 | 18.3:32.8 | 16.1:34.1 |
| | 4.0 h | 6 | 12.2(12.0) | 14.3 | -5.0:25.7 | 2.3:21.3 | 2.3:22.0 |
| | 5.0 h | 6 | 19.8(17.3) | 21.5 | -1.0:42.0 | 3.3:31.7 | 5.6:34.1 |
| | 6.0 h | 6 | 18.3(17.5) | 16.2 | -3.7:49.7 | 11.0:20.7 | 3.9:32.8 |
| | 7.0 h | 5 | 30.5(12.4) | 26.3 | 20.0:49.7 | 20.7:35.7 | 18.6:42.3 |
| | 9.0 h | 4 | 22.8(17.6) | 21.8 | 2.3:45.3 | 11.8:33.8 | 2.1:43.5 |
| | 12.0 h | 5 | 11.9(23.0) | 17.7 | -24.3:37.0 | 6.7:22.3 | -10.0:33.8 |

For dose level 1R, baseline adjusted mean QTcF changes from placebo are greater than 10 ms and it occurred at 5 time points on Day 4 and 4 times on Day 11, with the largest mean change of ΔΔQTcF to be 18.4 ms at hour 6 on Day 4. The 95% upper bound CIs were exceeded 10 ms on Day 1 (1 time point), Day 4 (all time points) and Day 11 (all time points). The highest value of ΔΔQTcF was 29 ms on Day 4, at hour 6.

The sponsor reported analysis results of ΔΔQTcF for dose level 1R (600 mg) are provided below:

QTcF Duration

| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
|---|---|---|---|---|---|---|---|
| 1 | 0.0 h | 6 | -0.5(8.2) | -3.3 | -9.3:11.7 | -6.0:7.3 | -7.2:6.2 |
| | 0.5 h | 6 | -3.7(12.2) | -7.8 | -16.5:15.0 | -12.3:7.3 | -13.7:6.3 |
| | 1.0 h | 6 | -7.9(8.9) | -5.7 | -22.5:2.5 | -13.8:-2.2 | -15.2:-0.5 |
| | 2.0 h | 6 | -8.1(8.8) | -7.8 | -23.3:2.7 | -10.0:-2.3 | -15.3:-0.9 |
| | 3.0 h | 6 | -1.8(5.4) | -1.8 | -10.6:5.4 | -3.6:1.4 | -6.2:2.6 |
| | 4.0 h | 6 | -4.6(9.2) | -5.5 | -19.0:7.3 | -7.7:3.0 | -12.1:3.0 |
| | 5.0 h | 6 | -4.2(5.4) | -4.3 | -10.1:3.9 | -9.8:-0.8 | -8.7:0.2 |
| | 6.0 h | 6 | 7.9(8.4) | 9.8 | -2.3:19.1 | -1.6:12.8 | 1.0:14.8 |
| | 7.0 h | 6 | -0.7(7.5) | -2.5 | -9.0:9.3 | -7.0:7.3 | -6.9:5.5 |
| | 9.0 h | 6 | -4.7(6.6) | -6.4 | -13.1:4.6 | -8.4:1.6 | -10.1:0.7 |
| | 12.0 h | 6 | -5.1(7.5) | -4.3 | -16.4:5.9 | -9.4:-2.1 | -11.2:1.1 |
| 4 | 0.0 h | 6 | 5.8(10.5) | 5.3 | -6.9:18.8 | -4.3:16.4 | -2.8:14.3 |
| | 0.5 h | 6 | 3.5(11.0) | 4.1 | -14.4:18.4 | -0.6:9.4 | -5.5:12.5 |
| | 1.0 h | 6 | 9.8(6.7) | 8.5 | 1.0:19.3 | 5.7:16.0 | 4.3:15.4 |
| | 2.0 h | 6 | 8.4(6.1) | 8.6 | 1.9:17.6 | 1.9:12.2 | 3.5:13.4 |
| | 3.0 h | 6 | 12.4(3.8) | 12.4 | 8.3:18.9 | 8.9:13.3 | 9.2:15.5 |
| | 4.0 h | 6 | 10.4(9.5) | 9.3 | -2.6:24.8 | 5.5:16.5 | 2.7:18.2 |
| | 5.0 h | 6 | 8.2(9.3) | 6.8 | -5.2:22.5 | 4.8:13.8 | 0.6:15.9 |
| | 6.0 h | 6 | 18.4(12.9) | 20.6 | -2.9:32.8 | 11.1:28.4 | 7.8:29.0 |
| | 7.0 h | 6 | 17.1(8.1) | 17.1 | 8.3:29.3 | 9.3:21.9 | 10.4:23.8 |
| | 9.0 h | 6 | 11.4(7.3) | 13.0 | 1.2:20.5 | 4.5:16.5 | 5.4:17.5 |
| | 12.0 h | 6 | 8.4(4.7) | 8.9 | 0.4:14.4 | 6.8:11.1 | 4.5:12.3 |
| 11 | 0.0 h | 6 | 6.2(14.0) | 0.5 | -6.2:30.8 | -2.8:14.2 | -5.3:17.7 |
| | 0.5 h | 6 | 8.5(12.5) | 5.5 | -6.7:26.5 | 0.5:19.5 | -1.8:18.7 |
| | 1.0 h | 6 | 10.7(11.1) | 9.2 | -2.0:28.0 | 1.3:18.3 | 1.5:19.8 |
| | 2.0 h | 6 | 14.7(6.9) | 15.6 | 3.1:24.4 | 13.1:16.4 | 9.1:20.4 |
| | 3.0 h | 6 | 8.7(13.5) | 10.4 | -11.2:25.1 | -1.9:19.4 | -2.3:19.8 |
| | 4.0 h | 6 | 0.2(12.7) | -1.2 | -13.0:16.3 | -11.3:11.3 | -10.3:10.6 |
| | 5.0 h | 6 | 4.3(11.2) | 9.3 | -13.6:16.1 | -5.2:10.1 | -4.9:13.6 |
| | 6.0 h | 6 | 11.3(7.2) | 11.6 | 0.9:21.2 | 7.6:15.2 | 5.4:17.2 |
| | 7.0 h | 6 | 14.5(12.4) | 10.4 | 4.8:36.8 | 5.1:19.4 | 4.3:24.7 |
| | 9.0 h | 6 | 7.9(12.0) | 4.8 | -3.9:24.1 | -2.2:19.8 | -2.0:17.8 |
| | 12.0 h | 6 | 4.5(11.5) | 6.4 | -12.4:14.9 | -2.8:14.6 | -4.9:13.9 |

For dose level 2 (900 mg), baseline adjusted mean QTcF changes from placebo is greater than 10 ms at 8 time points on Day 4 and 10 time points on Day 11, with the largest mean change of ΔΔQTcF to be 30.5 ms on hour 2 on Day 11. The 95% upper bound CIs were exceeded 10 ms on Day 1 (3 time points), Day 4 (all time points) and on Day 11 (all time points). The highest value of ΔΔQTcF was 50.3 ms on Day 11, at hour 7.

The sponsor reported analysis results of ΔΔQTcF for dose level 2 (900 mg) are provided below:

| QTcF Duration | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
| 1 | 0.0 h | 6 | -1.3(12.9) | -3.7 | -18.7:16.7 | -8.3:9.7 | -11.9:9.3 |
| | 0.5 h | 6 | 3.4(9.6) | 4.8 | -10.9:18.4 | -1.6:5.1 | -4.5:11.4 |
| | 1.0 h | 6 | -4.8(8.6) | -5.6 | -14.1:7.3 | -12.7:1.6 | -11.9:2.3 |
| | 2.0 h | 6 | -0.4(12.1) | -1.8 | -16.3:15.7 | -8.7:10.3 | -10.4:9.5 |
| | 3.0 h | 6 | -2.8(7.6) | -2.7 | -15.2:7.8 | -4.6:0.8 | -9.0:3.5 |
| | 4.0 h | 6 | -2.7(13.1) | -2.1 | -18.8:16.6 | -15.1:5.6 | -13.4:8.1 |
| | 5.0 h | 6 | 5.1(6.8) | 5.5 | -7.1:12.5 | 3.9:10.2 | -0.5:10.7 |
| | 6.0 h | 6 | 5.9(4.1) | 5.3 | 1.8:11.5 | 2.2:9.2 | 2.5:9.2 |
| | 7.0 h | 6 | 8.6(8.3) | 8.3 | -2.2:19.8 | 1.8:15.4 | 1.7:15.4 |
| | 9.0 h | 6 | 0.4(5.3) | 1.4 | -8.6:6.7 | -2.3:3.7 | -4.0:4.8 |
| | 12.0 h | 6 | -3.2(10.3) | -1.1 | -20.9:6.4 | -7.9:5.7 | -11.6:5.3 |
| 4 | 0.0 h | 6 | 12.4(21.0) | 11.1 | -12.6:38.8 | -7.6:33.8 | -4.8:29.7 |
| | 0.5 h | 6 | 9.8(15.3) | 12.3 | -14.7:31.6 | 2.9:14.6 | -2.7:22.4 |
| | 1.0 h | 6 | 12.4(17.9) | 11.2 | -10.0:37.0 | -0.7:26.0 | -2.3:27.2 |
| | 2.0 h | 6 | 20.3(18.7) | 26.1 | -8.4:38.3 | 4.6:34.9 | 4.9:35.6 |
| | 3.0 h | 6 | 8.4(10.6) | 8.4 | -5.2:25.4 | 0.4:12.8 | -0.3:17.1 |
| | 4.0 h | 6 | 0.4(18.8) | 5.7 | -30.1:20.2 | -12.8:13.9 | -15.0:15.9 |
| | 5.0 h | 6 | 15.7(10.4) | 16.4 | 4.4:27.4 | 4.7:25.0 | 7.2:24.2 |
| | 6.0 h | 6 | 18.7(14.9) | 17.8 | -2.2:42.5 | 12.2:23.8 | 6.4:31.0 |
| | 7.0 h | 6 | 24.1(12.4) | 25.2 | 4.4:39.7 | 16.7:33.1 | 13.8:34.3 |
| | 9.0 h | 6 | 13.3(11.8) | 17.8 | -10.7:20.3 | 15.3:19.0 | 3.5:23.0 |
| | 12.0 h | 6 | 10.2(10.6) | 13.3 | -8.9:22.4 | 6.4:14.4 | 1.4:18.9 |
| 11 | 0.0 h | 5 | 22.7(16.9) | 17.5 | 7.1:41.8 | 7.8:39.5 | 6.7:38.8 |
| | 0.5 h | 5 | 18.9(22.7) | 25.3 | -9.1:43.3 | -0.4:35.3 | -2.8:40.5 |
| | 1.0 h | 5 | 23.5(25.7) | 19.8 | -11.9:51.1 | 12.8:45.8 | -1.0:48.0 |
| | 2.0 h | 5 | 35.0(14.6) | 39.1 | 14.4:50.4 | 26.1:44.8 | 21.0:48.9 |
| | 3.0 h | 5 | 10.8(31.0) | 14.3 | -39.3:37.3 | 6.3:35.3 | -18.8:40.4 |
| | 4.0 h | 5 | 10.5(14.9) | 17.0 | -11.7:26.3 | 3.0:17.7 | -3.8:24.7 |
| | 5.0 h | 4 | 20.0(15.3) | 17.3 | 6.7:38.7 | 7.5:32.5 | 2.0:38.0 |
| | 6.0 h | 4 | 31.4(7.5) | 32.1 | 21.6:39.9 | 26.8:36.1 | 22.6:40.3 |
| | 7.0 h | 4 | 33.6(14.2) | 35.9 | 15.8:46.8 | 22.3:44.9 | 16.9:50.3 |
| | 9.0 h | 4 | 16.3(11.6) | 18.1 | 1.3:27.9 | 7.6:25.1 | 2.7:30.0 |
| | 12.0 h | 5 | -5.9(35.9) | 10.8 | -67.2:21.8 | -7.5:12.5 | -40.1:28.3 |

#### 5.1.1.2 Additional Analyses

**PR, QRS and Heart Rate Analysis**

The sponsor reported analysis results of ΔΔPR for dose level 1 (600 mg) are provided below:

| PR Interval | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
| 1 | 0.0 h | 6 | -3.9(9.7) | -2.5 | -20.7:5.3 | -8.0:5.0 | -11.8:4.1 |
| | 0.5 h | 6 | -1.0(6.0) | -1.7 | -9.2:9.5 | -2.8:-0.2 | -6.0:4.0 |
| | 1.0 h | 6 | -0.6(8.4) | 0.3 | -10.2:12.8 | -9.2:2.5 | -7.5:6.4 |
| | 2.0 h | 6 | -4.8(14.9) | 0.2 | -34.0:5.0 | -4.7:4.7 | -17.0:7.5 |
| | 3.0 h | 6 | 14.0(9.3) | 14.5 | 3.3:29.8 | 6.0:16.0 | 6.4:21.7 |
| | 4.0 h | 5 | 5.2(12.3) | 5.0 | -11.3:23.0 | 1.7:7.7 | -6.6:17.0 |
| | 5.0 h | 6 | -3.0(8.5) | 0.6 | -14.8:5.6 | -12.4:2.6 | -10.0:4.0 |
| | 6.0 h | 6 | 12.0(11.1) | 12.3 | -3.2:29.2 | 4.5:16.8 | 2.8:21.2 |
| | 7.0 h | 6 | -0.4(8.9) | -3.2 | -10.0:11.3 | -7.0:9.3 | -7.7:6.8 |
| | 9.0 h | 6 | -3.3(12.0) | -3.3 | -20.3:17.0 | -7.0:-3.0 | -13.2:6.5 |
| | 12.0 h | 6 | 4.3(7.2) | 2.7 | -2.7:14.3 | -2.3:11.0 | -1.6:10.2 |
| 4 | 0.0 h | 6 | 19.6(15.5) | 18.2 | 1.2:42.8 | 6.2:30.8 | 6.8:32.3 |
| | 0.5 h | 6 | 16.1(6.2) | 15.2 | 8.3:24.3 | 11.5:22.3 | 11.0:21.2 |
| | 1.0 h | 6 | 15.9(8.5) | 14.0 | 5.3:27.7 | 10.0:24.3 | 8.9:22.9 |
| | 2.0 h | 6 | 16.7(10.8) | 16.5 | 0.0:29.3 | 11.0:27.0 | 7.9:25.6 |
| | 3.0 h | 6 | 29.7(13.2) | 27.5 | 14.3:46.7 | 18.3:44.0 | 18.9:40.6 |
| | 4.0 h | 6 | 23.2(12.8) | 20.5 | 10.3:41.0 | 12.3:34.3 | 12.6:33.7 |
| | 5.0 h | 6 | 3.0(8.2) | 1.6 | -6.9:13.8 | -2.9:11.1 | -3.7:9.8 |
| | 6.0 h | 6 | 27.2(7.2) | 25.3 | 20.2:39.2 | 21.8:31.2 | 21.3:33.1 |
| | 7.0 h | 6 | 13.2(14.2) | 13.0 | -10.5:30.2 | 8.5:24.8 | 1.5:24.8 |
| | 9.0 h | 6 | 26.3(13.4) | 24.3 | 9.7:48.7 | 18.0:32.7 | 15.2:37.3 |
| | 12.0 h | 6 | 19.9(14.2) | 17.2 | 5.8:46.5 | 10.5:22.2 | 8.2:31.6 |
| 11 | 0.0 h | 6 | 14.8(24.9) | 6.8 | -7.5:60.5 | -2.2:24.2 | -5.7:35.2 |
| | 0.5 h | 6 | 11.3(24.4) | 3.2 | -7.3:59.3 | -1.3:11.0 | -8.7:31.4 |
| | 1.0 h | 6 | 17.3(21.5) | 15.5 | -13.7:51.3 | 9.0:26.3 | -0.4:35.0 |
| | 2.0 h | 6 | 29.8(21.2) | 20.5 | 10.0:67.3 | 18.7:42.0 | 12.4:47.3 |
| | 3.0 h | 6 | 47.7(24.3) | 39.7 | 25.3:84.5 | 28.3:68.7 | 27.7:67.7 |
| | 4.0 h | 6 | 45.0(17.8) | 41.7 | 28.0:77.3 | 32.7:48.7 | 30.4:59.6 |
| | 5.0 h | 6 | 21.6(13.3) | 24.7 | -4.0:34.3 | 21.7:28.0 | 10.6:32.5 |
| | 6.0 h | 6 | 42.6(12.1) | 39.0 | 32.3:65.7 | 35.0:44.7 | 32.7:52.5 |
| | 7.0 h | 5 | 19.5(26.6) | 22.3 | -16.0:55.0 | 6.0:30.3 | -5.8:44.9 |
| | 9.0 h | 4 | 48.3(24.5) | 37.7 | 33.0:85.0 | 35.2:61.5 | 19.5:77.2 |
| | 12.0 h | 5 | 30.1(14.6) | 24.7 | 19.7:55.7 | 23.3:27.0 | 16.2:43.9 |

The sponsor reported analysis results of ΔΔQRS for dose level 1 (600 mg) are provided below:

| QRS Duration | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
| 1 | 0.0 h | 6 | 0.4(3.3) | 0.3 | -3.2:5.5 | -2.8:2.5 | -2.3:3.1 |
| | 0.5 h | 6 | -0.7(2.9) | -1.2 | -3.7:4.7 | -2.7:-0.3 | -3.1:1.7 |
| | 1.0 h | 6 | -3.7(2.2) | -3.2 | -7.5:-1.5 | -4.8:-2.2 | -5.5:-1.9 |
| | 2.0 h | 6 | 4.1(2.8) | 4.2 | 1.0:7.0 | 1.7:6.7 | 1.8:6.4 |
| | 3.0 h | 6 | -2.7(3.2) | -2.3 | -6.7:2.0 | -5.7:-1.0 | -5.3:-0.1 |
| | 4.0 h | 5 | -1.1(3.9) | 1.2 | -5.8:2.2 | -4.8:1.8 | -4.8:2.6 |
| | 5.0 h | 6 | 5.9(2.7) | 5.0 | 3.5:10.2 | 3.5:8.2 | 3.7:8.1 |
| | 6.0 h | 6 | 2.4(2.6) | 3.0 | -1.0:5.0 | 0.0:4.7 | 0.3:4.6 |
| | 7.0 h | 6 | 1.4(4.4) | 3.2 | -6.5:4.8 | -0.5:4.5 | -2.2:5.0 |
| | 9.0 h | 6 | -2.8(3.8) | -2.8 | -9.3:1.3 | -3.7:0.3 | -5.9:0.3 |
| | 12.0 h | 6 | 5.7(2.1) | 5.5 | 3.3:8.7 | 3.7:7.7 | 4.0:7.5 |
| 4 | 0.0 h | 6 | 1.7(4.9) | 0.7 | -4.0:10.0 | -1.3:4.3 | -2.3:5.8 |
| | 0.5 h | 6 | 2.3(5.2) | 3.2 | -6.3:7.3 | -0.7:7.2 | -2.0:6.6 |
| | 1.0 h | 6 | -0.1(5.2) | 0.2 | -6.2:8.2 | -4.8:1.8 | -4.4:4.2 |
| | 2.0 h | 6 | 9.9(5.6) | 9.7 | 1.3:18.0 | 8:12.7 | 5.3:14.5 |
| | 3.0 h | 6 | 3.1(4.4) | 5.0 | -3.7:7.3 | -1.0:6.0 | -0.5:6.8 |
| | 4.0 h | 6 | 3.2(4.9) | 4.5 | -5.7:7.7 | 2.0:6.3 | -0.8:7.2 |
| | 5.0 h | 6 | 8.3(4.4) | 10.5 | -0.3:11.0 | 7.7:10.7 | 4.7:12.0 |
| | 6.0 h | 6 | 6.3(4.0) | 7.2 | 0.3:10.7 | 3.0:9.7 | 3.1:9.6 |
| | 7.0 h | 6 | 7.9(4.2) | 8.7 | 0.7:12.3 | 6.3:10.7 | 4.4:11.4 |
| | 9.0 h | 6 | 0.5(2.6) | 0.8 | -3.5:3.2 | -0.8:2.5 | -1.6:2.6 |
| | 12.0 h | 6 | 7.6(2.9) | 8.7 | 2.0:9.7 | 7.0:9.3 | 5.2:9.9 |
| 11 | 0.0 h | 6 | 5.9(4.3) | 6.2 | -1.3:12 | 5.7:7.0 | 2.4:9.5 |
| | 0.5 h | 6 | 7.2(6.8) | 7.7 | -4.8:15.5 | 5.8:11.5 | 1.6:12.9 |
| | 1.0 h | 6 | 8.3(5.1) | 7.8 | 1.3:15.0 | 4.7:13.0 | 4.1:12.5 |
| | 2.0 h | 6 | 11.4(4.7) | 11.3 | 4.0:17.0 | 9.3:15.7 | 7.5:15.3 |
| | 3.0 h | 6 | 10.2(4.8) | 11.3 | 1.7:14.7 | 8.0:14.0 | 6.2:14.1 |
| | 4.0 h | 6 | 8.4(6.5) | 10.2 | -4.3:14.0 | 8.3:12.0 | 3.0:13.8 |
| | 5.0 h | 6 | 12.8(4.3) | 13.8 | 4.7:17.3 | 12.3:14.7 | 9.2:16.3 |
| | 6.0 h | 6 | 8.6(4.6) | 10.3 | 1.0:13.0 | 5.0:12.0 | 4.8:12.4 |
| | 7.0 h | 5 | 13.3(6.1) | 14.3 | 6.7:21.0 | 7.7:17.0 | 7.5:19.2 |
| | 9.0 h | 4 | 3.8(2.9) | 4.7 | -0.3:6.3 | 2.2:5.5 | 0.4:7.2 |
| | 12.0 h | 5 | 6.9(7.4) | 7.7 | -4.3:16 | 5.7:9.3 | -0.2:13.9 |

The sponsor reported analysis results of ΔΔHR for dose level 1 (600 mg) are provided below:

| Heart Rate | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
| 1 | 0.0 h | 6 | 3.0(7.3) | 3.8 | -6.8:14.5 | -2.5:5.2 | -3.0:9.0 |
| | 0.5 h | 6 | 2.6(5.2) | 1.3 | -2.5:12.2 | -0.5:3.8 | -1.7:6.9 |
| | 1.0 h | 6 | 5.6(5.8) | 5.7 | -2.7:14.3 | 2.3:8.3 | 0.8:10.4 |
| | 2.0 h | 6 | -3.9(6.8) | -3.3 | -15.3:5.3 | -5.7:-1.0 | -9.5:1.7 |
| | 3.0 h | 6 | -1.8(9.3) | 0.0 | -13.3:10.8 | -11.7:3.7 | -9.4:5.9 |
| | 4.0 h | 5 | -7.6(16.8) | -1.2 | -37.5:1.5 | -1.2:0.5 | -23.6:8.4 |
| | 5.0 h | 6 | -0.9(5.7) | -1.9 | -7.1:7.9 | -5.8:3.6 | -5.5:3.8 |
| | 6.0 h | 6 | -1.8(7.2) | -1.5 | -9.5:9.5 | -8.8:1.2 | -7.7:4.1 |
| | 7.0 h | 6 | -1.9(8.1) | -1.2 | -15.8:7.8 | -4.5:3.5 | -8.5:4.8 |
| | 9.0 h | 6 | -0.9(8.7) | -4.3 | -9.7:13.0 | -6.3:6.3 | -8.0:6.2 |
| | 12.0 h | 6 | -10.7(8.0) | -10.2 | -20.0:1.7 | -18.7:-7.0 | -17.3:-4.1 |
| 4 | 0.0 h | 6 | 4.6(4.1) | 5.2 | -2.3:8.3 | 3.0:8.3 | 1.2:8.0 |
| | 0.5 h | 6 | -3.4(3.6) | -4.3 | -6.8:1.8 | -6.8:0.2 | -6.4:-0.4 |
| | 1.0 h | 6 | -3.4(3.5) | -3.7 | -6.7:3.0 | -6.7:-3.0 | -6.4:-0.5 |
| | 2.0 h | 6 | -9.3(6.4) | -8.3 | -21.0:-3.3 | -10.7:-4.3 | -14.6:-4.1 |
| | 3.0 h | 6 | -4.9(5.7) | -4.0 | -12.7:2.3 | -10.3:-0.7 | -9.6:-0.2 |
| | 4.0 h | 6 | -3.7(15.5) | 3.2 | -28.8:8.8 | -16.5:8.2 | -16.4:9.1 |
| | 5.0 h | 6 | -2.8(9.6) | -4.1 | -12.6:11.4 | -10.6:3.4 | -10.6:5.1 |
| | 6.0 h | 6 | -1.8(4.9) | -1.3 | -9.8:3.5 | -4.5:2.5 | -5.9:2.2 |
| | 7.0 h | 6 | -4.9(9.7) | -6.7 | -14.8:12.5 | -11.5:-2.2 | -12.9:3.1 |
| | 9.0 h | 6 | 4.7(5.3) | 5.0 | -1.3:12.3 | -0.3:7.7 | 0.4:9.1 |
| | 12.0 h | 6 | -9.9(7.8) | -13.7 | -16.2:3.8 | -14.8:-5.2 | -16.4:-3.5 |
| 11 | 0.0 h | 6 | 3.1(7.0) | 4.3 | -4.8:13.8 | -4.5:5.5 | -2.6:8.9 |
| | 0.5 h | 6 | -0.7(6.3) | 0.3 | -11.2:5.5 | -4.2:4.8 | -5.9:4.5 |
| | 1.0 h | 6 | -1.4(7.4) | -1.0 | -14.0:7.0 | -3.7:4.3 | -7.4:4.7 |
| | 2.0 h | 6 | -1.9(5.0) | -1.8 | -7.7:4.0 | -7.3:3.3 | -6.0:2.2 |
| | 3.0 h | 6 | -9.8(6.2) | -9.4 | -19.3:-2.0 | -13.3:-5.0 | -14.8:-4.7 |
| | 4.0 h | 6 | -18.1(19.4) | -13.2 | -51.3:6.0 | -27.0:-9.7 | -34.0:-2.1 |
| | 5.0 h | 6 | -6.8(13.7) | -5.8 | -26.7:9.7 | -16.7:4.3 | -18.1:4.5 |
| | 6.0 h | 6 | -2.1(9.9) | -4.2 | -14.3:13.7 | -8.0:4.3 | -10.3:6.1 |
| | 7.0 h | 5 | -7.7(11.5) | -11.0 | -16.7:12.3 | -13.3:-9.7 | -18.6:3.3 |
| | 9.0 h | 4 | -10.7(8.5) | -8.0 | -23.0:-3.7 | -16.0:-5.3 | -20.7:-0.7 |
| | 12.0 h | 5 | -6.5(6.5) | -11.0 | -11.7:0.7 | -11.0:0.7 | -12.7:-0.3 |

The sponsor reported analysis results of ΔΔPR for dose level 1R (600 mg) are provided below:

| PR Interval | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
| 1 | 0.0 h | 6 | -2.2(10.4) | -2.2 | -19.2:11.2 | -6.2:5.5 | -10.7:6.4 |
| | 0.5 h | 6 | 0.1(9.6) | 1.1 | -11.9:15.1 | -6.6:3.8 | -7.8:8.0 |
| | 1.0 h | 6 | -2.2(14.7) | -1.0 | -22.8:17.8 | -14.2:8.2 | -14.3:9.9 |
| | 2.0 h | 6 | 5.6(9.6) | 8.4 | -9.8:15.6 | -1.1:11.9 | -2.3:13.4 |
| | 3.0 h | 6 | 2.8(10.9) | 6.3 | -17.5:12.2 | -0.8:10.2 | -6.2:11.7 |
| | 4.0 h | 6 | 1.7(6.6) | 2.2 | -6.7:12.3 | -3.7:4.0 | -3.7:7.2 |
| | 5.0 h | 6 | -1.9(7.5) | 0.4 | -14.5:6.2 | -6.8:2.9 | -8.1:4.3 |
| | 6.0 h | 6 | 6.0(4.8) | 5.4 | -1.6:11.4 | 4.4:11.1 | 2.1:10.0 |
| | 7.0 h | 6 | 0.1(7.7) | 1.1 | -12.6:9.8 | -3.3:4.8 | -6.2:6.5 |
| | 9.0 h | 6 | 8.3(9.6) | 6.8 | -3.3:25.7 | 4.0:10.0 | 0.4:16.3 |
| | 12.0 h | 6 | 2.1(4.8) | 1.8 | -6.0:7.7 | 1.0:6.3 | -1.9:6.1 |
| 4 | 0.0 h | 6 | 12.6(4.9) | 13.4 | 5.8:17.4 | 8.8:17.1 | 8.6:16.7 |
| | 0.5 h | 6 | 13.0(12.3) | 15.3 | -5.5:30.5 | 4.5:17.8 | 2.8:23.2 |
| | 1.0 h | 6 | 11.3(11.8) | 11.4 | -7.8:25.3 | 6.6:20.6 | 1.5:21.0 |
| | 2.0 h | 6 | 17.6(12.9) | 19.5 | -4.0:32.0 | 11.7:27.0 | 7.0:28.2 |
| | 3.0 h | 6 | 14.9(14.5) | 18.9 | -12.4:28.3 | 11.6:23.9 | 2.9:26.8 |
| | 4.0 h | 6 | 11.5(12.1) | 18.6 | -7.4:20.3 | -0.4:19.3 | 1.5:21.5 |
| | 5.0 h | 6 | 10.6(9.2) | 13.4 | -5.1:19.9 | 5.2:16.9 | 3.0:18.2 |
| | 6.0 h | 6 | 17.3(11.6) | 20.5 | -2.7:31.0 | 11.3:23.0 | 7.7:26.8 |
| | 7.0 h | 6 | 13.7(11.6) | 17.2 | -8:23.3 | 10.7:21.7 | 4.1:23.2 |
| | 9.0 h | 6 | 19.4(4.5) | 19.9 | 13.6:26.3 | 15.3:21.3 | 15.6:23.1 |
| | 12.0 h | 6 | 19.6(2.9) | 20.1 | 15.9:23.6 | 16.9:21.3 | 17.2:22.0 |
| 11 | 0.0 h | 6 | 13.0(6.6) | 12.9 | 4.1:21.1 | 7.8:19.1 | 7.6:18.4 |
| | 0.5 h | 6 | 13.0(10.2) | 9.9 | 2.6:30.3 | 6.6:18.9 | 4.6:21.4 |
| | 1.0 h | 6 | 13.8(16.6) | 9.5 | -3.0:43.3 | 3.0:20.3 | 0.1:27.4 |
| | 2.0 h | 6 | 24.1(9.2) | 22.8 | 12.8:34.8 | 17.4:34.1 | 16.6:31.7 |
| | 3.0 h | 6 | 23.0(8.8) | 22.7 | 8.6:33.6 | 19.9:30.6 | 15.8:30.2 |
| | 4.0 h | 6 | 26.1(13.8) | 23.7 | 12.2:49.2 | 16.6:30.9 | 14.7:37.4 |
| | 5.0 h | 6 | 13.0(7.7) | 12.7 | 4.7:25.7 | 5.7:16.7 | 6.7:19.3 |
| | 6.0 h | 6 | 16.1(6.7) | 15.7 | 5.2:25.9 | 14.6:19.2 | 10.5:21.6 |
| | 7.0 h | 6 | 7.2(8.3) | 8.1 | -7.1:18.6 | 5.6:10.2 | 0.4:14.1 |
| | 9.0 h | 6 | 24.8(4.2) | 23.8 | 20.1:31.1 | 21.8:28.4 | 21.3:28.3 |
| | 12.0 h | 6 | 10.1(8.1) | 11.6 | -1.9:19.8 | 3.8:15.8 | 3.4:16.8 |

The sponsor reported analysis results of ΔΔQRS for dose level 1R (600 mg) are provided below:

| QRS Duration | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
| 1 | 0.0 h | 6 | 2.1(1.9) | 2.0 | -0.3:4.7 | 0.3:3.7 | 0.5:3.6 |
| | 0.5 h | 6 | -0.2(2.9) | -0.3 | -4.7:3.5 | -1.7:2.3 | -2.6:2.2 |
| | 1.0 h | 6 | -3.8(2.6) | -3.3 | -7.6:-0.9 | -5.9:-1.6 | -5.9:-1.6 |
| | 2.0 h | 6 | 1.9(2.9) | 1.6 | -2.1:5.6 | 0.2:4.6 | -0.5:4.3 |
| | 3.0 h | 6 | 0.4(3.9) | 0.2 | -4.2:7.5 | -1.8:0.8 | -2.8:3.7 |
| | 4.0 h | 6 | -1.0(2.3) | -0.5 | -4.0:2.0 | -3.3:0.3 | -2.9:0.9 |
| | 5.0 h | 6 | 2.3(4.0) | 1.3 | -1.3:9.3 | -1.0:4.0 | -1.0:5.5 |
| | 6.0 h | 6 | -0.8(1.9) | -0.3 | -4.0:1.3 | -1.7:0.3 | -2.3:0.8 |
| | 7.0 h | 6 | -0.7(5.6) | -0.1 | -10.9:5.1 | -1.6:3.4 | -5.3:3.9 |
| | 9.0 h | 6 | -5.8(8.1) | -4.2 | -21.0:1.0 | -7.0:0.3 | -12.5:0.8 |
| | 12.0 h | 6 | 1.2(6.7) | 2.6 | -11.3:7.8 | -0.3:5.8 | -4.3:6.7 |
| 4 | 0.0 h | 6 | 1.5(4.0) | 1.2 | -3.5:7.5 | -1.8:4.5 | -1.8:4.8 |
| | 0.5 h | 6 | 1.0(3.7) | -0.4 | -1.4:8.4 | -0.6:0.4 | -2.0:4.0 |
| | 1.0 h | 6 | -0.2(3.8) | -0.7 | -4.5:6.2 | -3.2:1.5 | -3.3:2.9 |
| | 2.0 h | 6 | 5.3(6.1) | 5.7 | -4.8:14.6 | 4.6:6.2 | 0.3:10.4 |
| | 3.0 h | 6 | 2.6(4.8) | 2.8 | -5.4:9.6 | 1.6:4.3 | -1.4:6.6 |
| | 4.0 h | 6 | 0.4(4.5) | -0.5 | -4.5:8.2 | -2.8:2.5 | -3.3:4.1 |
| | 5.0 h | 6 | 2.2(5.7) | 2.2 | -5.5:11.8 | -0.5:2.8 | -2.5:6.8 |
| | 6.0 h | 6 | 1.0(3.5) | 1.4 | -3.1:6.3 | -2.8:2.9 | -1.9:3.9 |
| | 7.0 h | 6 | 1.7(3.6) | 1.3 | -2.5:7.5 | -1.2:3.8 | -1.2:4.7 |
| | 9.0 h | 6 | -0.1(4.0) | -0.3 | -4.6:5.4 | -3.9:3.1 | -3.3:3.2 |
| | 12.0 h | 6 | 1.2(3.7) | 1.0 | -3.2:5.5 | -2.5:5.2 | -1.9:4.2 |
| 11 | 0.0 h | 6 | 2.6(3.5) | 1.0 | -0.4:8.0 | 0.0:6.0 | -0.3:5.5 |
| | 0.5 h | 6 | 1.5(4.1) | 1.7 | -5.0:6.7 | -0.3:4.2 | -1.9:4.9 |
| | 1.0 h | 6 | -1.3(5.1) | -1.7 | -8.6:5.4 | -4.2:2.8 | -5.5:2.8 |
| | 2.0 h | 6 | 4.5(4.7) | 3.0 | -0.7:10.7 | 1.0:10.0 | 0.6:8.4 |
| | 3.0 h | 6 | 3.3(4.9) | 3.3 | -2.6:8.8 | -1.6:8.4 | -0.8:7.3 |
| | 4.0 h | 6 | 2.2(3.6) | 1.1 | -0.6:8.8 | -0.6:3.4 | -0.7:5.1 |
| | 5.0 h | 6 | 1.2(5.0) | 0.0 | -4.3:9.3 | -2.3:4.3 | -2.9:5.3 |
| | 6.0 h | 6 | 1.1(3.6) | 0.9 | -4.1:5.2 | -1.4:4.9 | -1.9:4.0 |
| | 7.0 h | 6 | 0.7(1.7) | 0.8 | -1.7:2.7 | -1.0:2.3 | -0.8:2.1 |
| | 9.0 h | 6 | -1.9(3.6) | -1.7 | -5.9:1.8 | -4.9:1.1 | -4.8:1.0 |
| | 12.0 h | 6 | -0.2(3.0) | -0.1 | -3.2:4.8 | -3.2:0.8 | -2.6:2.3 |

The sponsor reported analysis results of ΔΔHR for dose level 1R (600 mg) are provided below:

| Heart Rate | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
| 1 | 0.0 h | 6 | -3.1(2.5) | -2.2 | -6.5:-0.8 | -5.8:-0.8 | -5.1:-1.0 |
| | 0.5 h | 6 | -0.6(5.3) | -0.8 | -8.3:5.8 | -3.9:4.8 | -4.9:3.8 |
| | 1.0 h | 6 | -3.6(5.1) | -3.0 | -12.5:2.5 | -4.8:-0.8 | -7.8:0.5 |
| | 2.0 h | 6 | -4.2(7.4) | -3.6 | -15.4:3.6 | -7.8:1.9 | -10.2:1.9 |
| | 3.0 h | 6 | -2.1(5.2) | -2.8 | -8.6:6.1 | -5.6:1.1 | -6.4:2.2 |
| | 4.0 h | 6 | -3.4(4.8) | -3.7 | -10.5:2.5 | -6.2:0.8 | -7.4:0.5 |
| | 5.0 h | 6 | -3.0(2.6) | -3.1 | -6.0:1.4 | -5.3:-2.0 | -5.2:-0.9 |
| | 6.0 h | 6 | -0.6(6.0) | -2.0 | -6.7:9.7 | -5.3:2.7 | -5.5:4.3 |
| | 7.0 h | 6 | 1.9(5.5) | 1.8 | -7.1:8.3 | -0.1:6.9 | -2.6:6.4 |
| | 9.0 h | 6 | -0.3(6.1) | -1.0 | -7.8:6.5 | -4.5:6.2 | -5.3:4.7 |
| | 12.0 h | 6 | -6.8(3.6) | -5.0 | -13.3:-4.3 | -8.7:-4.7 | -9.8:-3.9 |
| 4 | 0.0 h | 6 | -2.3(7.5) | -0.4 | -16.8:3.3 | -2.4:3.3 | -8.4:3.9 |
| | 0.5 h | 6 | -5.4(4.7) | -4.9 | -10.7:2.3 | -10.0:-4.3 | -9.3:-1.5 |
| | 1.0 h | 6 | -0.1(4.7) | -0.4 | -5.9:7.1 | -3.6:2.4 | -4.0:3.7 |
| | 2.0 h | 6 | -7.1(9.1) | -4.9 | -22.6:3.4 | -11.9:-1.9 | -14.6:0.4 |
| | 3.0 h | 6 | -1.8(4.7) | -2.1 | -6.8:3.9 | -6.4:2.9 | -5.8:2.1 |
| | 4.0 h | 6 | 0.3(5.4) | 0.3 | -8.0:8.7 | -1.7:2.0 | -4.2:4.7 |
| | 5.0 h | 6 | -6.3(8.5) | -6.6 | -19.0:5.0 | -11.0:0.4 | -13.3:0.7 |
| | 6.0 h | 6 | -5.4(3.5) | -4.8 | -9.8:-1.5 | -9.2:-2.2 | -8.3:-2.5 |
| | 7.0 h | 6 | -0.4(7.5) | 1.4 | -11.8:7.6 | -6.8:5.6 | -6.6:5.8 |
| | 9.0 h | 6 | -9.2(8.1) | -7.7 | -22.3:2.0 | -13.3:-6 | -15.9:-2.5 |
| | 12.0 h | 6 | -8.1(7.3) | -5.8 | -22.3:-2.3 | -8.6:-3.9 | -14.1:-2.1 |
| 11 | 0.0 h | 6 | -0.4(13.1) | 1.8 | -23.5:15.5 | -4.2:5.8 | -11.2:10.3 |
| | 0.5 h | 6 | -2.7(8.4) | -0.8 | -17.2:7.0 | -6.5:2.2 | -9.6:4.2 |
| | 1.0 h | 6 | 1.1(3.6) | 1.8 | -4.2:4.8 | -2.2:4.4 | -1.9:4.0 |
| | 2.0 h | 6 | -2.3(8.8) | -0.4 | -17.6:8.8 | -5.6:1.1 | -9.6:4.9 |
| | 3.0 h | 6 | -3.6(5.7) | -2.7 | -11.9:4.1 | -7.9:-0.6 | -8.3:1.0 |
| | 4.0 h | 6 | -3.6(4.8) | -1.7 | -9.9:1.4 | -9.2:-0.2 | -7.5:0.4 |
| | 5.0 h | 6 | -3.4(6.8) | -3.5 | -11.0:7.0 | -10.0:0.7 | -9.0:2.2 |
| | 6.0 h | 6 | -4.8(5.9) | -5.6 | -10.6:2.8 | -10.2:0.1 | -9.7:0.0 |
| | 7.0 h | 6 | -6.1(7.2) | -5.2 | -16.6:2.8 | -11.2:-0.9 | -12.0:-0.2 |
| | 9.0 h | 6 | -6.4(8.8) | -6.0 | -20.7:3.7 | -10.0:0.3 | -13.7:0.8 |
| | 12.0 h | 6 | -4.7(8.0) | -2.1 | -20.1:2.6 | -5.1:-1.1 | -11.2:1.9 |

The sponsor reported analysis results of ΔΔPR for dose level 2 (900 mg) are provided below:

| PR Interval | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
| 1 | 0.0 h | 6 | 2.6(5.0) | 3.9 | -7.2:6.4 | 2.8:5.4 | -1.5:6.7 |
| | 0.5 h | 6 | 1.6(3.5) | 0.4 | -1.8:6.6 | -1.4:5.2 | -1.3:4.4 |
| | 1.0 h | 6 | 5.3(4.9) | 5.3 | -1.7:11.3 | 2.6:9.3 | 1.3:9.3 |
| | 2.0 h | 6 | 9.5(3.7) | 8.6 | 4.8:14.5 | 7.1:13.1 | 6.5:12.5 |
| | 3.0 h | 6 | 6.4(4.2) | 6.4 | 1.3:12.6 | 2.6:9.3 | 3.0:9.9 |
| | 4.0 h | 6 | 1.4(6.9) | 0.7 | -8.4:12.2 | -1.1:4.6 | -4.2:7.1 |
| | 5.0 h | 6 | 6.9(5.1) | 6.9 | 0.9:13.9 | 2.5:10.5 | 2.7:11.1 |
| | 6.0 h | 6 | 7.7(10.1) | 5.4 | -4.9:22.7 | 1.4:16.1 | -0.6:16.0 |
| | 7.0 h | 6 | 6.2(3.0) | 5.3 | 3.8:11.8 | 4.1:7.1 | 3.8:8.7 |
| | 9.0 h | 6 | 1.7(5.0) | 0.1 | -4.2:8.4 | -1.2:6.8 | -2.4:5.8 |
| | 12.0 h | 6 | 4.9(5.8) | 5.3 | -5.3:12.3 | 4.3:7.7 | 0.2:9.7 |
| 4 | 0.0 h | 6 | 15.8(7.7) | 13.4 | 6.9:26.6 | 10.9:23.9 | 9.5:22.2 |
| | 0.5 h | 6 | 20.7(4.5) | 20.4 | 14.8:26.4 | 17.1:24.8 | 16.9:24.4 |
| | 1.0 h | 6 | 21.1(5.8) | 19.6 | 15.6:31.2 | 16.6:23.9 | 16.3:25.8 |
| | 2.0 h | 6 | 17.6(11.6) | 20.2 | -3.8:30.2 | 15.2:23.5 | 8.0:27.2 |
| | 3.0 h | 6 | 16.0(7.5) | 15.6 | 4.4:24.4 | 12.1:23.8 | 9.8:22.2 |
| | 4.0 h | 6 | 8.3(10.5) | 10.8 | -8.9:19.1 | 1.1:16.8 | -0.4:16.9 |
| | 5.0 h | 6 | 14.3(9.5) | 13.0 | 2.8:26.1 | 6.5:24.5 | 6.5:22.1 |
| | 6.0 h | 6 | 25.3(9.2) | 27.1 | 8.8:33.8 | 21.8:33.1 | 17.7:32.9 |
| | 7.0 h | 6 | 20.9(8.3) | 21.3 | 9.9:30.6 | 13.3:29.3 | 14.1:27.8 |
| | 9.0 h | 6 | 19.0(5.7) | 19.6 | 11.8:25.8 | 14.1:23.1 | 14.3:23.7 |
| | 12.0 h | 6 | 25.2(10.0) | 25.2 | 9.2:40.5 | 23.5:27.5 | 16.9:33.4 |
| 11 | 0.0 h | 5 | 14.1(5.1) | 15.1 | 6.8:20.8 | 12.1:15.8 | 9.2:19.0 |
| | 0.5 h | 5 | 21.3(8.7) | 24.7 | 9.4:31.4 | 15.7:25.4 | 13.0:29.6 |
| | 1.0 h | 5 | 22.3(4.3) | 22.5 | 15.2:25.8 | 22.5:25.5 | 18.2:26.4 |
| | 2.0 h | 5 | 27.3(10.8) | 29.3 | 10.9:40.9 | 25.9:29.3 | 17.0:37.5 |
| | 3.0 h | 5 | 29.2(7.9) | 30.8 | 18.4:40.1 | 25.8:31.1 | 21.6:36.8 |
| | 4.0 h | 5 | 22.8(5.6) | 22.4 | 15.4:30.8 | 21.1:24.4 | 17.5:28.1 |
| | 5.0 h | 4 | 16.1(11.8) | 16.3 | 4.4:27.4 | 5.9:26.3 | 2.1:30.0 |
| | 6.0 h | 4 | 12.3(7.6) | 15.8 | 0.9:16.6 | 8.1:16.4 | 3.0:21.2 |
| | 7.0 h | 4 | 11.4(8.2) | 11.7 | 3.3:19.0 | 4.3:18.5 | 1.7:21.1 |
| | 9.0 h | 4 | 22.7(3.9) | 23.1 | 17.9:26.6 | 19.6:25.8 | 18.1:27.2 |
| | 12.0 h | 5 | 11.4(6.6) | 11.7 | 1.7:18.0 | 9.0:16.7 | 5.2:17.6 |

The sponsor reported analysis results of ΔΔQRS for dose level 2 (900 mg) are provided below:

| QRS Duration | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
| 1 | 0.0 h | 6 | 0.3(2.4) | 1.2 | -3.3:3.0 | -2.0:1.7 | -1.7:2.3 |
| | 0.5 h | 6 | 2.2(3.6) | 1.0 | -0.7:9.0 | 0.0:3.0 | -0.7:5.2 |
| | 1.0 h | 6 | 1.3(1.6) | 1.1 | -0.4:4.2 | 0.6:1.6 | 0.0:2.6 |
| | 2.0 h | 6 | 5.0(4.4) | 5.1 | -1.4:10.3 | 1.9:9.3 | 1.4:8.7 |
| | 3.0 h | 6 | 1.6(2.9) | 1.8 | -3.2:5.8 | 0.8:2.4 | -0.9:4.0 |
| | 4.0 h | 6 | 4.1(3.4) | 2.3 | 1.5:9.2 | 1.5:7.5 | 1.3:6.8 |
| | 5.0 h | 6 | 4.8(4.3) | 3.2 | 1.3:13.0 | 2.3:5.7 | 1.3:8.3 |
| | 6.0 h | 6 | 2.1(3.4) | 0.7 | -1.3:7.0 | -0.3:5.7 | -0.8:4.9 |
| | 7.0 h | 6 | 1.7(3.8) | 0.8 | -2.7:8.3 | -0.7:3.3 | -1.5:4.8 |
| | 9.0 h | 6 | 0.7(4.3) | 0.0 | -5.3:8.0 | -0.3:2.0 | -2.8:4.3 |
| | 12.0 h | 6 | 3.1(3.2) | 4.1 | -2.4:6.9 | 1.6:4.6 | 0.5:5.8 |
| 4 | 0.0 h | 6 | 5.3(4.8) | 4.4 | 0.6:14.3 | 2.3:5.9 | 1.4:9.3 |
| | 0.5 h | 6 | 7.5(5.2) | 6.2 | 3.0:17.0 | 3.3:9.3 | 3.2:11.8 |
| | 1.0 h | 6 | 8.1(4.6) | 7.1 | 3.1:16.7 | 6.1:8.4 | 4.3:11.9 |
| | 2.0 h | 6 | 11.5(6.6) | 10.0 | 4.8:23.5 | 7.1:13.8 | 6.1:16.9 |
| | 3.0 h | 6 | 8.3(6.8) | 8.2 | 1.2:20.6 | 2.6:9.2 | 2.7:14.0 |
| | 4.0 h | 6 | 8.8(6.7) | 6.4 | 3.1:20.7 | 3.7:12.4 | 3.2:14.3 |
| | 5.0 h | 6 | 7.9(6.8) | 6.0 | 1.7:20.7 | 3.7:9.3 | 2.3:13.5 |
| | 6.0 h | 6 | 8.4(6.9) | 7.8 | 0.4:20.8 | 4.1:9.4 | 2.7:14.1 |
| | 7.0 h | 6 | 9.3(7.6) | 6.5 | 3.5:23.8 | 4.8:10.8 | 3.1:15.6 |
| | 9.0 h | 6 | 6.6(5.2) | 5.3 | 0.8:15.8 | 4.2:8.2 | 2.4:10.9 |
| | 12.0 h | 6 | 7.0(5.8) | 7.2 | 0.8:17.2 | 1.8:7.8 | 2.2:11.8 |
| 11 | 0.0 h | 5 | 8.8(6.8) | 8.2 | 1.2:17.2 | 3.5:14.2 | 2.3:15.3 |
| | 0.5 h | 5 | 9.5(6.9) | 6.9 | 3.2:17.9 | 3.9:15.9 | 3.0:16.1 |
| | 1.0 h | 5 | 10.3(6.9) | 6.6 | 4.6:19.9 | 4.9:15.3 | 3.6:16.9 |
| | 2.0 h | 5 | 16.5(7.0) | 13.3 | 10.3:26.0 | 11.0:21.7 | 9.8:23.1 |
| | 3.0 h | 5 | 11.4(7.7) | 8.6 | 2.9:20.6 | 6.6:18.3 | 4.1:18.7 |
| | 4.0 h | 5 | 11.6(6.3) | 10.7 | 3.7:19.7 | 8.0:16.0 | 5.5:17.7 |
| | 5.0 h | 4 | 10.3(8.8) | 12.0 | -0.7:17.7 | 3.2:17.3 | -0.1:20.6 |
| | 6.0 h | 4 | 11.1(7.0) | 13.3 | 1.2:16.5 | 6.2:16.0 | 2.8:19.3 |
| | 7.0 h | 4 | 11.3(8.2) | 13.6 | 0.1:17.8 | 5.1:17.4 | 1.6:20.9 |
| | 9.0 h | 4 | 9.2(7.1) | 9.8 | 0.3:16.9 | 3.8:14.6 | 0.8:17.6 |
| | 12.0 h | 5 | 7.0(7.0) | 6.3 | -0.4:15.3 | 0.9:12.9 | 0.3:13.7 |

The sponsor reported analysis results of ΔΔHR for dose level 2 (900 mg) are provided below:

| Heart Rate | | | | | | | |
|---|---|---|---|---|---|---|---|
| Day | Time Point | N | MEAN(SD) | MEDIAN | MIN:MAX | Q1:Q3 | 95% CI |
| 1 | 0.0 h | 6 | -5.5(5.1) | -3.3 | -13.5:-0.8 | -10.2:-1.8 | -9.7:-1.3 |
| | 0.5 h | 6 | -0.8(1.4) | -1.1 | -2.2:1.4 | -1.9:0.1 | -1.9:0.3 |
| | 1.0 h | 6 | 0.1(3.9) | 0.6 | -5.4:4.6 | -3.1:3.2 | -3.2:3.3 |
| | 2.0 h | 6 | -7.3(15.5) | -3.5 | -38.0:5.7 | -4.3:-0.3 | -20.1:5.4 |
| | 3.0 h | 6 | 2.8(12.7) | 6.2 | -22.1:11.6 | 3.6:11.2 | -7.6:13.2 |
| | 4.0 h | 6 | -4.8(16.7) | -4.0 | -32.8:16.8 | -9.8:4.8 | -18.6:8.9 |
| | 5.0 h | 6 | -9.0(7.8) | -9.4 | -18.3:2.1 | -16.6:-2.6 | -15.5:-2.6 |
| | 6.0 h | 6 | -6.2(4.9) | -6.2 | -14.7:-0.3 | -7.0:-3.0 | -10.2:-2.2 |
| | 7.0 h | 6 | -1.5(4.3) | -3.0 | -5.2:5.8 | -4.8:1.2 | -5.1:2.1 |
| | 9.0 h | 6 | -3.1(2.2) | -3.1 | -6.2:-0.2 | -4.9:-1.2 | -5.0:-1.3 |
| | 12.0 h | 6 | 0.4(4.7) | -1.3 | -4.5:7.5 | -2.8:4.8 | -3.5:4.3 |
| 4 | 0.0 h | 6 | -0.8(6.3) | 2.2 | -10.2:5.2 | -7.2:3.2 | -6.0:4.4 |
| | 0.5 h | 6 | -1.3(4.6) | -1.5 | -7.7:6.3 | -3.3:-0.3 | -5.1:2.4 |
| | 1.0 h | 6 | 0.6(5.8) | 0.0 | -7.8:9.5 | -2.2:3.8 | -4.2:5.3 |
| | 2.0 h | 6 | -6.7(9.7) | -5.1 | -23.7:5.9 | -8.7:-3.4 | -14.7:1.3 |
| | 3.0 h | 6 | 1.3(8.9) | 4.2 | -13.8:9.9 | -4.1:7.2 | -6.0:8.6 |
| | 4.0 h | 6 | -4.1(16.6) | -1.2 | -30.4:12.3 | -15.4:11.6 | -17.7:9.6 |
| | 5.0 h | 6 | -6.4(6.2) | -7.1 | -14.9:2.4 | -10.3:-1.3 | -11.5:-1.2 |
| | 6.0 h | 6 | -4.2(3.5) | -4.4 | -9.6:-0.2 | -5.9:-0.6 | -7.0:-1.3 |
| | 7.0 h | 6 | -2.7(3.9) | -2.1 | -8.1:1.3 | -6.4:1.3 | -5.9:0.6 |
| | 9.0 h | 6 | -3.6(4.8) | -1.2 | -10.4:0.3 | -9.1:0.3 | -7.5:0.4 |
| | 12.0 h | 6 | -3.1(5.4) | -1.4 | -11.6:2.1 | -7.3:1.4 | -7.5:1.4 |
| 11 | 0.0 h | 5 | 2.5(6.0) | 0.1 | -4.5:10.1 | -0.5:7.1 | -3.3:8.2 |
| | 0.5 h | 5 | 5.5(9.9) | 7.1 | -7.9:18.5 | 0.1:9.5 | -4.0:14.9 |
| | 1.0 h | 5 | 6.2(4.4) | 7.2 | 0.2:11.8 | 3.8:7.8 | 2.0:10.4 |
| | 2.0 h | 5 | -2.2(14.1) | 3.5 | -26.2:8.5 | -3.2:6.2 | -15.7:11.2 |
| | 3.0 h | 5 | 10.3(13.5) | 9.7 | -7.3:28.3 | 3.7:17.0 | -2.6:23.1 |
| | 4.0 h | 5 | -7.1(12.0) | -8.4 | -25.1:6.6 | -9.1:0.6 | -18.5:4.4 |
| | 5.0 h | 4 | -5.2(6.0) | -3.3 | -13.8:-0.2 | -8.8:-1.5 | -12.2:1.9 |
| | 6.0 h | 4 | -0.4(3.5) | -1.0 | -3.5:3.8 | -3.3:2.5 | -4.6:3.8 |
| | 7.0 h | 4 | 3.7(3.3) | 4.1 | -0.8:7.3 | 1.4:5.9 | -0.2:7.6 |
| | 9.0 h | 4 | -1.9(4.6) | -2.2 | -7.2:3.8 | -5.2:1.3 | -7.3:3.5 |
| | 12.0 h | 5 | -2.5(7.4) | -1.3 | -10.7:6.3 | -9.3:2.7 | -9.5:4.6 |

### 5.1.2 Exposure-Response Analysis

*Dose Level 1: 600 mg/day*

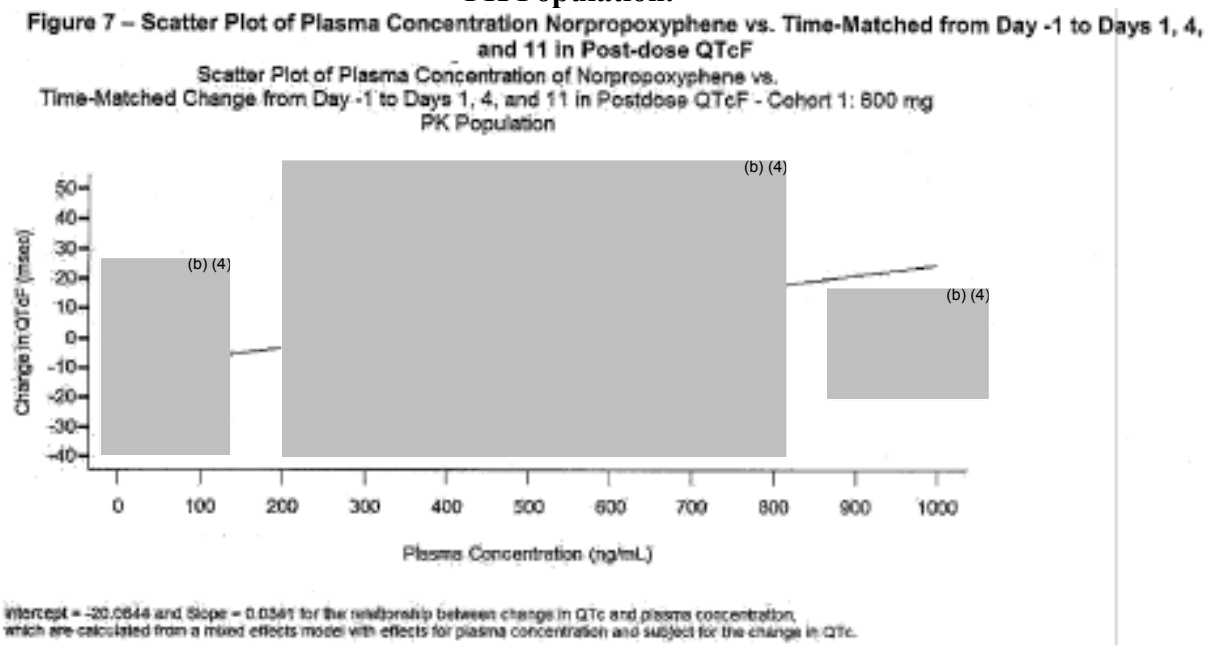
One active treatment subject showed seven instances of a QTcF of greater than 450 ms during Day 11, with the highest reading being 467 ms at Hour 0. There were 15 instances where the change from baseline was greater than 30 ms, and all instances occurred on Day 11, with four subjects crossing the threshold at varying time point, but every time point of Day 11 had at least one subject with a QTcF increase of greater than 30 ms. The largest change was 55.7 ms at Hour 12.

Mean QTcF changes greater than 10 ms from placebo and baseline occurred on Day 4 (Hours 6, 7, and 9) and at every time point for Day 11. The largest mean QTcF change from placebo and baseline was 30.5 ms on Day 11, Hour 7.

The 95% upper bound CI of greater than 10 ms for the corrected QT interval is of regulatory concern. The 95% upper bound CI QTcF duration (placebo and baseline

adjusted) exceeded 10 ms on Day 1 (Hours 5 and 6), Day 4 (Hours 0, 2, 3, 4, 5, 6, 7, 9, and 12) and at every time point for Day 11. The highest value for the upper bound 95% CI for QTcF duration was 43.5 ms on Day 1, Hour 96. The QTcF duration showed a concentration-dependent prolongation. A plot of the change in QTcF vs. plasma concentrations of norpropoxyphene (Figure 5) demonstrates an increase in QTcF as concentrations increase (slope equals 0.034), suggesting an increase of 1000 ng/mL of norpropoxyphene may incrementally increase QTcF by 34 ms.

**Figure 5: Scatter Plot of Plasma Concentration Norpropoxyphene Versus Time-Matched from Day -1 to Days 1, 4, and 11 in Post-dose QTcF for Cohort 1: 600 mg PK Population.**




*Source: Sponsor's IND70462_SDN039.pdf pg 90.*

*Dose Level 1R: 600 mg/day*

The lowest active treatment baseline mean QTcF duration was 394.1 ms at Hour 12, while the highest baseline mean QTcF duration was 404.7 ms at Hour 0.5. The lowest placebo baseline mean QTcF duration was 405.9 ms at Hour 4, while the highest baseline mean QTcF duration was 413.5 ms at Hour 0.5.

- The largest mean active treatment change from placebo and baseline readings occurred on Day 4 at Hour 6 (18.4±12.9).
- There were 3 instances where the change from baseline was greater than 30 ms in the active treatment group. All three occurred on Day 11. These occurred at Hours 0 (34.7 ms), 4 (30.7 ms), and 7 (32 ms).
    - The largest change was 34.7 ms (Day 11, Hour 0).

No instances of a post-treatment absolute QTcF interval reading of greater than 450 ms were seen. There was no instance of a post-treatment QTcF increase of greater than 60 ms from baseline. One subject on active treatment showed a change in QTcF greater than 30 ms on three occasions (Day 11, Hours 0 [34.7 ms], 4 [30.7 ms], and 7[32.3 ms]).

Mean active treatment QTcF changes greater than 10 ms from placebo and baseline occurred on Day 4 (Hours 3 [12.4 ms], 4 [10.4 ms], 6 [18.4 ms], 7 [17.1 ms], and 9 [11.4 ms]) and Day 11 (Hours 1 [10.7 ms], 2 [14.7 ms], 6 [11.3 ms], and 7 [14.5 ms]).

- The largest mean QTcF change from placebo and baseline was 18.4 ms on Day 4, Hour 6.

The active treatment 95% upper bound CI of greater than 10 ms for the corrected QT interval was observed at multiple time points. The 95% upper bound for the corrected QT interval was observed at multiple time points. The 95% upper bound CI QTcF duration (placebo and baseline adjusted) exceeded 10 ms on Day 1 (Hour 6 [14.8 ms]), Day 4 (all time points; range 12.3-29.0 ms), and on Day 11 (all time points; range 10.6-24.7 ms).

- The highest value for the upper bound 95% CI for QTcF duration was 29.0 ms on Day 4, Hour 6.

The QTcF duration did not show a concentration-dependent prolongation.

*Dose Level 2: 900 mg/day*

A review of the cardiodynamic data from Dose Level 2 appears to confirm an apparent ECG signal present with an increase from baseline in QTc, PR, and QRS intervals with accumulation of drug over the 11 days of therapy. Key QTcF interval data from Dose Level 2 for subjects receiving active treatment is presented below:

**QTcF Interval:**

No subject had an absolute QTcF interval greater than 500 ms post-treatment. Two instances of post-treatment absolute QTcF interval readings of greater than 450 ms were seen. One was on Day 4 at Hour 2 (454.7 ms) and the other occurred on Day 11 at Hour 2 (459.3 ms). Both occurred in the same patient.

There was no instance of a post-treatment QTcF increase of greater than 60 ms from baseline. Twenty instances of QTcF increases of greater than 30 ms were seen:

- On Day 4, 6 instances occurred with 3 being in one subject. Two instances were seen in another subject with one instance in a third subject. The largest change from baseline was 37.0 ms at Hour 6.
- On Day 11, 14 instances occurred with 7 being in one subject. Six instances were seen in another subject with one instance in a third subject. The largest change from baseline was 45.3 ms at Hour 1.

Mean active treatment QTcF changes greater than 10 ms from placebo and baseline occurred on Day 4 and 11:

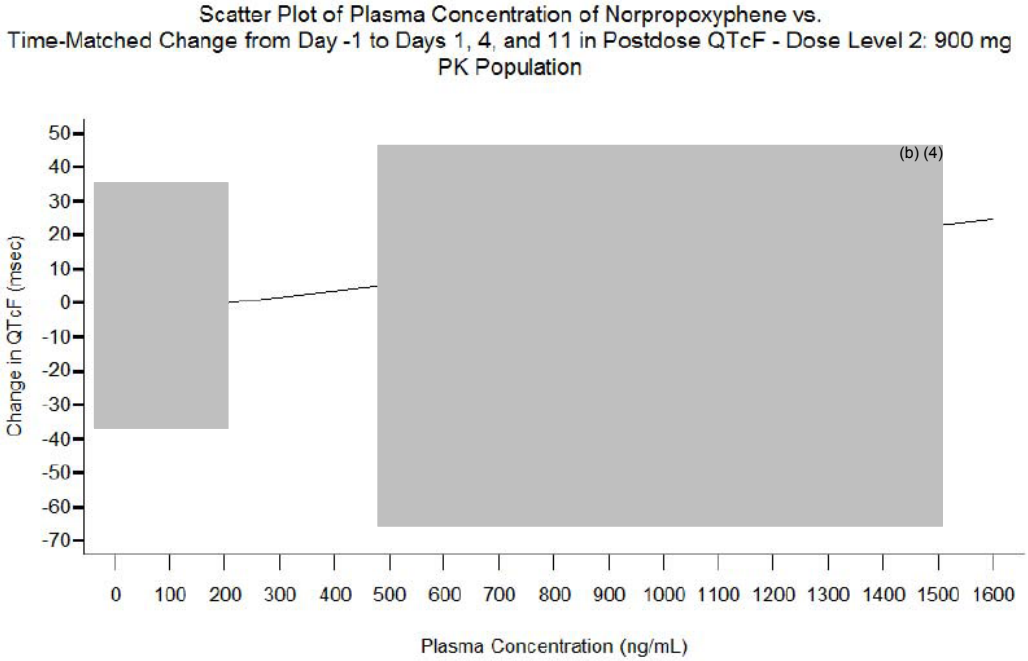
- On Day 4, mean changes from placebo and baseline exceeded 10 ms at 8 time points (i.e. Hours 0, 1, 2, 5, 6, 7, 9, and 12). The largest mean change was 24.1±12.4 ms at Hour 7.
- On Day 11, 10 time points (i.e. all time points except Hour 12) showed a mean change from placebo and baseline of greater than 10 ms. The largest mean change was 35.0±14.6 ms at Hour 2.

Active treatment 95% upper bound CI of greater than 10 ms for the Fridericia's corrected QT Interval was observed at multiple time points:

- On Day 1, 3 time points met this threshold (i.e. Hour 0.5 [11.4 ms], Hour 5 [10.7 ms], and Hour 7 [15.4 ms]), and on Day 4 all time points met this threshold (i.e. range of 15.9 -35.6 ms).
- On Day 11, all time points met this threshold (i.e. range of 24.7 - 50.3 ms).

A plot of the change in QTcF vs. plasma concentrations of norpropoxyphene (Figure 6) demonstrates an increase in QTcF as concentrations increase (slope equals 0.018), suggesting an increase of 1000 ng/mL of norpropoxyphene may incrementally increase QTcF by 18 ms.

**Figure 6 Scatter Plot of Plasma Concentration of Norpropoxyphene Versus Time-Matched Change from Day -1 to Days 1, 4, and 11 in Post dose QTcF – Dose Level 2: 900 mg PK Population**




*Source: Sponsor's XP20C-101 Cardiodynamic Report (Dose Level 2 - 2010Oct03).pdf pg 80.*

*Reviewer's Comments: The sponsor only performed individual dose concentration-ΔΔQTcF analyses for norpropoxyphene instead of pooling all available data. The selection of only norpropoxyphene is acceptable even though both propoxyphene and norpropoxyphene have similar hERG channel interactions as concentrations of norpropoxyphene are 4- to 6-fold greater than propoxyphene. A major deficiency in the analysis concerns not including concentration-ΔΔQTcF observations across all three studies and is addressed in the reviewer's analysis. The individual analyses are one*

*reason why a concentration-ΔΔQTcF relationship may not have been identified by the sponsor for the Dose 1R cohort. The slopes identified by the sponsor in the individual analyses agrees with the estimated slope by the reviewer (0.0255 ms per ng/mL norpropoxyphene).*

## 5.2 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

### 5.1 Highlights of Clinical Pharmacology

| | | | | |
|---|---|---|---|---|
| | **Multiple Dose Interval and Duration** | Darvon-N is given orally. The usual dosage is one 100 mg propoxyphene napsylate every 4 hours as needed for pain. The maximum dose of Darvon-N is 6 tablets per day (ie, 600 mg maximum total daily dose). Do not exceed the maximum daily dose. | | |
| | | **Propoxyphene** | | |
| **Exposures Achieved at Maximum Tested Dose [Mean (%CV)]** | **Single Dose** | | Cmax | AUC |
| | | | ng/mL | ng*h/mL |
| | | Study XP20B-101[1] | | |
| | | 100 mg, single dose est.[a] | 55 | N/A |
| | | Darvon-N Label[2] | 50-100 | N/A |
| | | | | |
| | | Study XP20B-101 | | |
| | | 100 mg, after 2 doses (administered 4 hours apart)[b] | 96.29 (43.0) | 966.34 (43.6)[c] |
| | | | | 1033.6[b] (43.0)[d] |
| | | **Norpropoxyphene (metabolite)** | | |
| | | | Cmax | AUC |
| | | | ng/mL | ng*h/mL |
| | | Study XP20B-101[1] | | |
| | | 100 mg, single dose est.[a] | 115 | N/A |
| | | Darvon-N Label | 100-200 | N/A |
| | | | | |
| | | Study XP20B-101 | | |
| | | 100 mg, after 2 doses (administered 4 hours apart)[b] | 197.07 (33.4) | 5838.8 (27.9)[c] |
| | | | | 6153.3[b] (28.1)[d] |
| | **Multiple Dose** | **Propoxyphene** | | |
| | | | Cmaxss | $AUCss_{(0\text{-}8h)}$ |
| | | | ng/mL | ng*h/mL |
| | | Study XP20B-102[3] | | |
| | | 100 mg q4h (56 total doses)[f] | 179.7 (37.9) | 1132.1 (37.0) |
| | | | | |
| | | **Norpropoxyphene (metabolite)** | | |
| | | | Cmaxss | $AUCss_{(0\text{-}8h)}$ |
| | | Study XP20B-102 | ng/mL | ng*h/mL |
| | | 100 mg q4h (56 total doses)[f] | 896.1 (24.3) | 6119.1 (23.7) |
| | | | | |

| | | | | |
|---|---|---|---|---|
| **Range of linear PK** | Linear PK is anticipated following administration of 100mg, 200mg, and 300mg doses of propoxyphene napsylate (Darvon-N Label).[4] | | | |
| **Accumulation at steady state [Mean (%CV)]** | Repeated doses of propoxyphene lead to increasing plasma concentrations of both propoxyphene and norpropoxyphene.<br><br>At steady-state in study XP20B-102, there were increases of 3.3X and 7.8X in propoxyphene and norpropoxyphene Cmax, respectively, when compared to the single-dose estimates from study XP20B-101. Steady-state data provided below: | | | |
| | **Propoxyphene** | | | |
| | Study XP20B-102 | Cmaxss | Cminss | $AUC_{(0\text{-}8h)}$ |
| | 100 mg q4h (56 total doses)[f] | 179.7 (37.9) | 106.3 (39.7) | 1132.1 (37.0) |
| | | | | |
| | **Norpropoxyphene (metabolite)** | | | |
| | Study XP20B-102 | Cmaxss | Cminss | $AUC_{(0\text{-}8h)}$ |
| | 100 mg q4h (56 total doses)[f] | 896.1 (24.3) | 619.5 (26.9) | 6119.1 (23.7) |
| | | | | |
| **Metabolites** | Major metabolite: Norpropoxyphene | | | |
| **Absorption** | **Absolute/Relative Bioavailability** | | | |
| | | | Data not available. | |
| | | | | |
| | **Tmax** | | Propoxyphene | |
| | | **Darvon-N Label** | 2 – 2.5h | |
| | | | | |
| | | | Norpropoxyphene | |
| | | **XP20B-101 and XP20B-102** | 4h[g] | |
| | | | | |
| **Distribution** | **Vd/F or Vd** | | Mean | |
| | | **Darvon-N Label** | 16 L/kg | |
| | | | | |
| | **% Bound** | | Mean | |
| | | **Darvon-N Label** | Propoxyphene is about 80% bound to plasma proteins. | |

| | | | |
|---|---|---|---|
| **Elimination** | **Route** | **Primary route (Darvon-N Label)** | The major route of metabolism is cytochrome CYP3A4 mediated N-demethylation to norpropoxyphene which is excreted by the kidneys. |
| | | **Percent dose eliminated (Darvon-N Label)** | In 48 h, approximately 20-25% of the administered dose is excreted via the urine, most of which is free or conjugated norpropoxyphene. |
| | | **Other routes (Darvon-N Label)** | Ring hydroxylation and glucuronide formation are minor metabolic pathways. |
| | | | |
| | **Terminal t½** | | **Propoxyphene** |
| | | **Darvon-N Label** | **6 -12h** |
| | | | |
| | | | Norpropoxyphene |
| | | **Darvon-N Label** | 30 -36h |
| | | | |
| | | | |
| | | | |
| | | | |
| | **CL/F or CL** | **Darvon-N Label** | Mean (%CV) |
| | | **CL/F** | 2.6L/min |
| | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Intrinsic Factors** | **Age (Darvon-N Label)** | After oral administration of propoxyphene in elderly patients (age: 70-78 years), much longer half-lives of propoxyphene and norpropoxyphene have been reported (propoxyphene 13 to 35 h, & norpropoxyphene 22 to 41 h). In addition, the AUC was an average of 3-fold higher with Cmax an average of 2.5-fold higher in the elderly when compared to a younger (ages: 20-28 years) population. After multiple oral doses of propoxyphene in elderly patients (age: 70-78 years), the Cmax of the metabolite (norpropoxyphene) was increased 5-fold. | | | | |
| | **Age (Flanagan1989)[5]**<br><br>Dosing (1-week): 65 mg propoxyphene HCl (equivalent to 100mg propoxyphene napsylate) TID<br><br>Reported Values: Median (Range) | | **Propoxyphene** | | **Norpropoxyphene** | |
| | | | **Single-dose** | **Multi-dose** | **Single-dose** | **Multi-dose** |
| | | Half-life(h)<br>Young<br><br>Elderly | **13.0** (6.4-26.4)<br>**35.4** (1.9-86.8) | **22.0** (9.8-49.3)<br>**36.8** (17.4-110) | **22.2** (16.3-28.0)<br>**40.9** (28.4-106) | **22.1** (15.6-34.0)<br>**41.8** (32.9-62.8) |
| | | Cmax (ng/mL)<br>Young<br><br>Elderly | **59** (26-90)<br>**156** (39-366) | **116** (51-214)<br>**239** (151-509) | **195** (151-229)<br>**193** (112-283) | **673** (477-839)<br>**1100** (775-1500) |
| | | AUC[h] (ng*h/mL)<br>Young<br><br>Elderly | **509** (217-1309)<br>**1402** (177-3976) | **731** (163-1420)<br>**1155** (467-2664) | **N/A**<br><br>**N/A** | **N/A**<br><br>**N/A** |
| | **Sex** | No data identified to support any gender differences. | | | | |
| | **Race** | No data identified to support any ethnicity differences. | | | | |
| | **Renal Impairment (Darvon-N Label)** | After oral administration of propoxyphene in anephric patients, the AUC and Cmax were an average of 76% and 88% greater, respectively. Dialysis removes only insignificant amounts (8%) of the administered dose of propoxyphene. | | | | |
| | **Renal Impairment (Gibson1980)[6]**<br><br>Dosing: 130mg propoxyphene HCl<br><br>Reported Values: Mean (± SD) | | **Propoxyphene** | | **Norpropoxyphene** | |
| | | | **Single-dose** | | **Single-dose** | |
| | | **Half-life (h)**<br>**Anephric[i]** | **8** | | **15** | |
| | | Cmax (ng/mL)<br>Normal<br>Anephric | **92.4** (± 32.8)<br>**174** (± 71) | | **229** (± 92)<br>**288** (± 87) | |
| | | AUC[i] (ng*h/mL)<br>Normal<br>Anephric | **434** (± 184)<br>**762** (± 314) | | **2620** (± 1230)<br>**4100** (± 1640) | |
| | **Hepatic Impairment (Darvon-N Label)** | After oral administration of propoxyphene in patients with cirrhosis, plasma concentrations of propoxyphene were considerably higher and norpropoxyphene concentrations were much lower than in control patients. This is presumably because of a decreased first-pass metabolism of orally administered propoxyphene in these | | | | |

<table>
<tr><td></td><td></td><td colspan="3">patients. The AUC ratio of norpropoxyphene: propoxyphene wais significantly lower in patients with cirrhosis (0.5 to 0.9) than in controls (2.5 to 4).</td></tr>
<tr><td></td><td rowspan="4">Hepatic Impairment (Giacomini1980)[7]<br><br><u>Dosing</u>:<br>130mg propoxyphene HCl<br><br><u>Reported Values</u>:<br>Mean (± SD)</td><td></td><td>Propoxyphene</td><td>Norpropoxyphene</td></tr>
<tr><td></td><td>Single-dose</td><td>Single-dose</td></tr>
<tr><td>Half-life (h)<br>Cirrhotic[i]</td><td>22</td><td>55</td></tr>
<tr><td>Cmax (ng/mL)<br>Normal<br>Cirrhotic</td><td>92 (± 33)<br>275 (± 197)</td><td>229 (± 92)<br>65 (± 30)</td></tr>
<tr><td></td><td>AUC[j] (ng*h/mL)<br>Normal<br>Cirrhotic</td><td><br>434 (± 184)<br>837 (± 504)</td><td><br>1740 (± 920)<br>478 (± 251)</td></tr>
<tr><td>Extrinsic Factors</td><td>Drug interactions (Darvon-N Label)</td><td colspan="3">The metabolism of propoxyphene may be altered by strong CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazadone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) leading to enhanced propoxyphene plasma levels. On the other hand, strong CYP3A4 inducers such as rifampin may lead to enhanced metabolite (norpropoxyphene) levels.<br><br>Propoxyphene is also thought to possess CYP3A4 and CYP2D6 enzyme inhibiting properties. Coadministration with a drug that is a substrate of CYP3A4 or CYP2D6, may result in higher plasma concentrations and increased pharmacologic or adverse effects of that drug.<br><br><u>Information from Somogyi2004</u>[8]: t1/2 extrapolated to be ~15 hours for propoxyphene and ~24 hours for norpropoxyphene with the expectation that peak and total exposure in this sub-group is less than the exposure observed in subjects with hepatic impairment (ie, cirrhotics).</td></tr>
<tr><td></td><td>Food effects<br><br><u>Dosing</u>:<br>100 mg propoxyphene napsylate at Time 0 and 4h.</td><td colspan="3">Data from study XP20B-101[1] indicated that food had no effect on the extent of absorption (AUC) of propoxyphene or norpropoxyphene under fed compared to fasted conditions. However, Cmax for propoxyphene and norpropoxyphene were 70% amd 30% higher, respectively, in the presence of food.<br><br>Modified Release (Fed) vs. Modified Release (Fasting)<br>Ratios of LSM (90% Confidence Intervals)<br><table><tr><td></td><td>Propoxyphene</td><td>Norpropoxyphene</td></tr><tr><td>AUC inf</td><td>93.1% (88.7-97.8%)</td><td>105.3% (100.1-110.8%)</td></tr><tr><td>AUC 0-t</td><td>93.2% (88.5-98.1%)</td><td>107.3% (101.9-113.0%)</td></tr><tr><td>Cmax</td><td>169.1% (152.3-187.6%)</td><td>129.4% (119.4-140.3%)</td></tr></table></td></tr>
</table>

| | | | |
|---|---|---|---|
| **Elimination** | **Route** | **Primary route (Darvon-N Label)** | The major route of metabolism is cytochrome CYP3A4 mediated N-demethylation to norpropoxyphene which is excreted by the kidneys. |
| | | **Percent dose eliminated (Darvon-N Label)** | In 48 h, approximately 20-25% of the administered dose is excreted via the urine, most of which is free or conjugated norpropoxyphene. |
| | | **Other routes (Darvon-N Label)** | Ring hydroxylation and glucuronide formation are minor metabolic pathways. |
| | | | |
| | **Terminal t½** | | **Propoxyphene** |
| | | **Darvon-N Label** | **6 -12h** |
| | | | |
| | | | Norpropoxyphene |
| | | **Darvon-N Label** | 30 -36h |
| | | | |
| | | | |
| | | | |
| | | | |
| | **CL/F or CL** | **Darvon-N Label** | Mean (%CV) |
| | | **CL/F** | 2.6L/min |
| | | | |

| | |
|---|---|
| **Expected High Clinical Exposure Scenario** | The proposed supratherapeutic dosing regimen for propoxyphene napsylate in the Thorough QT study is a titration procedure (over 2 days) up to 200mg q4h (ie, 1200mg/day) to be continued for 9 days to achieve steady-state conditions. The anticipated concentrations at steady-state (which are 2X the Cmax and AUC values from XP20B-102[3]) are:<br><br>Propoxyphene:<br>Cmax (358 ng/mL, which is 6.5-fold single-dose Cmax in healthy adults)<br>$AUC_{0\text{-}inf}$ (2264.2 ng*h/mL, which is 2.3-fold 2-dose AUC in healthy adults)<br><br>Norpropoxyphene:<br>Cmax (1792 ng/mL, which is 15.6-fold single-dose Cmax in healthy adults);<br>$AUC_{0\text{-}inf}$ (12,238.2 ng*h/mL, which is 2.1-fold 2-dose AUC in healthy adults)<br><br>These maximum concentrations are expected to be in excess of, or comparable to, the following Clinical Exposure Scenarios:<br><br>**1)** A hepatically impaired patient achieving steady-state concentrations of propoxyphene and norpropoxyphene upon administration of BID propoxyphene napsylate 100 mg. At this dosing regimen, patients would be expected to achieve the following concentrations[i]:<br><br>**Hepatic Impairment:**<br>Propoxyphene<br>Cmax (437 ng/mL, which is 7.9-fold single-dose Cmax in healthy adults)<br><br>Norpropoxyphene<br>Cmax (232 ng/mL, which is 2.0-fold single-dose Cmax in healthy adults)<br><br>**2)** An elderly patient who is administered 100 mg propoxyphene napsylate TID for 7 days (as in Flanagan1989[5]).<br><br>**Elderly:**<br>Propoxyphene<br>Cmax (239 ng/mL, which is 4.3-fold single-dose Cmax in healthy adults)<br>AUC[h] (1155 ng/mL, which is 1.2-fold 2-dose AUC in healthy adults)<br><br>Norpropoxyphene<br>Cmax (1100 ng/mL, which is 9.6-fold single-dose Cmax in healthy adults)<br>AUC (not available in reference) |

| | |
|---|---|
| | 3) A renally impaired patient achieving steady-state concentrations of propoxyphene and norpropoxyphene upon administration of q4h propoxyphene napsylate 100 mg. At this dosing regimen, patients would be expected to achieve the following concentrations[m]:<br><br>**Renal Impairment**:<br>Propoxyphene<br>Cmax (302 ng/mL, which is 5.5-fold the single-dose Cmax in healthy adults)<br><br>Norpropoxyphene<br>Cmax (904 ng/mL, which is 7.9-fold the single-dose Cmax in healthy adults)<br><br>4) An anephric patient who is administered a single-dose of 200 mg propoxyphene napsylate (as in Gibson1980[6]).<br><br>**Renal Impairment**:<br>Propoxyphene<br>Cmax (174 ng/mL, which is 3.2-fold the single-dose Cmax in healthy adults)<br>AUC[j] (763 h*ng/mL, which is .8-fold the 2-dose AUC in healthy adults)<br><br>Norpropoxyphene<br>Cmax (288 ng/mL, which is 2.5-fold the single-dose Cmax in healthy adults)<br>AUC[j] (4100 h*ng/mL, which is .7-fold the 2-dose AUC in healthy adults)<br><br>5) A hepatically impaired patient who is administered a single-dose of 200 mg propoxyphene napsylate (as in Giacomini1980[7]).<br><br>**Hepatic Impairment**:<br>Propoxyphene<br>Cmax (275 ng/mL, which is 5-fold the single-dose Cmax in healthy adults)<br>AUC[k] (837 h*ng/mL, which is .9-fold the 2-dose AUC in healthy adults)<br><br>Norpropoxyphene<br>Cmax (65 ng/mL, which is .6-fold the single-dose Cmax in healthy adults)<br>AUC[k] (478 h*ng/mL, which is .08-fold the 2-dose AUC in healthy adults) |

a. Single-dose PK parameters estimated from study XP20B-101 Figure 4 (Treatment C: Darvocet-N 100 IR tablet dosed at Time 0 and 4h).

b. These PK parameters from study XP20B-101 reflect Cmax and AUC after administration of Darvocet-N 100 IR tablet dosed at Time 0 and 4h. PK sampling occurred over 5 days post-dose.

c. AUC(0-t) where t equals the time of the Last Quantifiable Sample over the 5 day sampling period.

d. AUC(0-inf)

e. Single-dose PK parameters estimated from XP20B-101 Figure 10 (Treatment C: Darvocet-N 100 IR tablet dosed at Time 0 and 4h).

f. PK parameters reflect Cmax and AUC at steady-state after administration of Darvocet-N 100 IR tablet dosed at Time 0 and 4h on Day 9. PK sampling occurred over 8 hours post-dose on Day 9.

g. Tmax estimated from XP20B-101 Figure 10 (Treatment C) and XP20B-102 Figure 10 (Treatment B).

h. AUC(0-inf) for single-dose; AUC(0-8) for multiple-dose.

i. Half-life (h) was determined using the data available in the respective reference.

j. AUC(0-12) for propoxyphene; AUC(0-24) for norpropoxyphene.

## 5.3 TABLE OF STUDY ASSESSMENTS

| Study Phase → | Screen | Study Day | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Event ↓ | ++ | -2 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| Informed Consent | X | | | | | | | | | | | | | | | |
| Demographic Data | X | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | |
| Record Concomitant Meds | X | | | | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | | | | |
| Weight[1] | X | | | | | | | | | | | | | | | X |
| HIV/Hepatitis B and C | X | | | | | | | | | | | | | | | |
| Body temperature[2] | X | | | | | | | | | | | | | | | X |
| BP/Pulse/Resp (supine)[3] | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Ortho BP/Pulse (stand)[4] | X | X | | | | | | | | | | | | | | |
| Safety ECG (12-lead)[5] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Oxygen Saturation[6] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Chem/Hem/UA[7] | X | | | | | | | | | | | | | | | X |
| Urine Drug Screen[8] | X | X | | | | | | | | | | | | | | |
| Serum Pregnancy Test[9] | X | X | | | | | | | | | | | | | | X |
| ALT, AST, Alkaline phosphatase[10] | | X | | | | | X | | | X | | | | X | | |
| Amylase, lipase[11] | | X | | | | | X | | | X | | | | X | | |
| Physical Examination[12] | X | X | | | | | | | | | | | | | | X |
| Neurological Assessment[13] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Check-in Questionnaire | | X | | | | | | | | | | | | | | |
| Telemetry[14] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Events Monitor/Query[15] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PK Sampling[16] | | | | X | | | | | | | | | | X | X | |
| Cardiodynamic Sampling[17] | | | X | X | | | | | | | | | | X | X | |
| Dosing[18] | | | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Confinement[19] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Footnotes appear on the following page.

++ Screening procedures will be completed within the 28 days prior to dosing

1. Body weight will be measured at screening and at end-of-study (approximately Hour 12 on Day 13) or upon early withdrawal.
2. Body temperature will be measured at screening and check-in.
3. Blood pressure, pulse, and respiratory rate will be evaluated at screening, check-in, and every 12 hours beginning at Hour 0 of Day -1 through release from the clinic on Day 13 or upon early withdrawal.
4. Blood pressure and pulse will be taken after 2 minutes standing at screening and check-in. This is an orthostatic measurement and should be taken immediately after the vital signs taken in the supine position.
5. 12-lead ECG will be taken at screening, check-in, and at Hour 0 and 12 on Days -1 through 13 (or upon early withdrawal).
6. Oxygen saturation will be evaluated via a pulse oximeter at screening, check-in, and every 12 hours beginning at Hour 0 of Day -1 through release from the clinic on Day 13 or upon early withdrawal.
7. Serum chemistry, hematology, and urinalysis will be performed at screening and at end-of-study (approximately Hour 12 on Day 13) or upon early withdrawal.
8. A urine drug screen will be performed at screening and check-in.
9. For females, a serum pregnancy test will be performed at screening, check-in, and at end-of-study (approximately Hour 12 on Day 13) or upon early withdrawal.
10. ALT, AST, and alkaline phosphatase will be evaluated at check-in and at Hour 0 (predose) on Days 4, 7, and 11.
11. Amylase and lipase will be evaluated at check-in and at Hour 0 (predose) on Days 4, 7, and 11.
12. A licensed physician will examine each subject at screening, check-in, and at end-of-study (approximately Hour 12 on Day 13) or upon early withdrawal.
13. A neurological assessment will be completed at screening and every 12 hours beginning at check-in on Day -2 through release from the clinic on Day 13 or upon early withdrawal.
14. Continuous 24-hour telemetry will be performed from Hour 0 of Day -1 though release from confinement on Day 13 or upon early withdrawal.
15. Subjects will be observed for signs and symptoms of adverse events during the entire period of confinement. A specific inquiry regarding AEs will be made prior to each dose, at Hour 0 on Day 12 and 13, and prior to release from confinement on Day 13.
16. PK blood samples will be collected on Days 1, 11 and 12 at Hour 0 (predose) and Hours 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12 hour.
17. Cardiodynamic sampling will be obtained on Days -1, 1, 11, and 12 via ECG extractions from the Holter monitor data at Hour 0 (predose on dosing days) and Hours 0.5, 1, 2, 3, 4, 5, 6, 7, 9, and 12.
18. Dosing will take place at Hour 0 and 12 on Day 1, at Hours 0, 8, and 16 on Day 2, at Hours 0, 4, 8, 12, 16, and 20 on Days 3 through 10, and at Hour 0 on Days 11 and 12.
19. Subjects will be confined to the clinic from Day -2 (at a time designated by study staff) through completion of the end-of-study procedures on Day 13 or upon early withdrawal.

*From QT-IRT protocol review dated February 2, 2010*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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