APPENDIX

Characteristics of cancer patients from who hepatic microsomal fractions were prepared

Human hepatic microsomal fraction (preparation number)	Age	Sex	Pathology
H (HTL-2)m ; 211287-3	54	M	Pancreatic carcinoma
H (HTL-66)m ; 210592-1	59	M	Colon adenocarcinoma

Characteristics of human hepatic microsomal fractions used

Human hepatic microsomal fractions (preparation number)	Protein concentration (mg/ml)	Cytochrome P450 concentration (nmole/mg)
HTL-2	15.7	0.13
HTL-66	31.6	0.44

Characteristics of patients from who human hepatocytes are prepared

Human hepatocyte preparation	Sex	Age	Pathology
HTL-82	M	70	Colon adenocarcinoma
HTL-83	F	59	Not available
HTL-87	M	66	Rectum adenocarcinoma
HTL-93	F	43	Colon adenocarcinoma

4.2.17 Regulation of the expression of cytochrome P450 gene subfamilies IA, IIA and IIIA by SR 33589B in primary cultures of human hepatocytes (MIV0144)

PROTOCOL #	MIV0144
STUDY DIRECTOR	G. Fabre
STUDY SITE	Sanofi Recherche, France
STUDY PERIOD	August 1992 to January 1993

Study Design

Two standard *in vitro* methods were used to evaluate the induction potential of dronedarone:

1. Enzymatic activity in cultured human hepatocytes (n= 4)
2. Antibody protein formation using Western blot analyses

In the hepatocyte experiment, dronedarone and model CYP inducers were incubated with hepatocytes obtained from subjects who underwent a partial hepatectomy. The characteristics of the subjects are presented in the Appendix. Enzyme activity was determined by evaluating the formation rate of specific metabolites by model CYP substrates. The substrates and inducers used for this evaluation are in Table 112.

Table 112: CYP450 Enzyme substrates and inhibitors (per Applicant's report)

CYP Enzyme	Substrate/Metabolite System	Inducer
1A2	7-ethoxyresorufin O-deethylation phenacetin O-deethylation	ß-naphthoflavone
2A6	coumarin 7-hydroxylation	dexamethasone
3A	nifedipine oxidation	phenobarbital

Reviewer Comment on Selected Enzyme Probes

The probe substrates and inducers are consistent with the recommendations in the Drug Interaction Guidance; the compounds are either preferred or acceptable substrates or inducers.

The Western blot analyses evaluated the CYP1A and CYP3A subfamilies; polyclonal antibodies for the enzymes were obtained from Inserum in France.

Compounds

- Dronedarone hydrochloride salt, batch number GD-D7-11-3 and DJ-07-51-5
- CYP enzyme substrates and inhibitors were obtained from commercial sources

Results

Hepatocytes

The results of the enzymatic studies are summarized in Table 113. The values reported indicate the degree of change in enzyme activity upon incubation with varying dronedarone concentrations and model substrates. Generally, the model inducers produced a significant increase in the metabolism of the probe substrates. Only phenobarbital yielded non-significant increases in enzyme activity (range of activity was 0.6 to 4.2). The reason for phenobarbital's poor induction is unclear.

Table 113: Metabolism of dronedarone in the presence of CYP enzyme inhibitors

Treatment	Substrates			
	7-Ethoxy resorufin (P450IA1)	Phenacetin (P450IA2)	Coumarin (P450IIA)	Nifedipine (P450IIIA)
Untreated (DMSO)	1	1	1	1
Dexamethasone 50 µM	0.3 - 1.4	1.5 - 1.5	4.0 - 8.0	1.2 - 8.2
β-Naphthoflavone 50 µM	2.4 - 18.4	3.7 - 22.1	1.2 - 1.7	0.4 - 1.8
Phenobarbital 2 mM	1.0 - 6.4	1.7 - 4.0	0.9 - 2.7	0.6 - 4.2
SR 33589B; 0.5 µM	0.6 - 2.6	1.2 - 1.4	0.8 - 1.3	0.4 - 1.1
SR 33589B; 2 µM	0.5 - 2.2	1.0 - 2.2	0.8 - 1.0	0.1 - 3.2
SR 33589B; 5 µM	0.4 - 1.6	0.7 - 1.2	0.8 - 1.7	0.3 - 1.5
SR 33589B; 20 µM	0 - 0.8	0.7 - 0.7	0.9 - 1.0	0 - 1.5
SR 33589B; 50 µM	0	NP	NP	NP

NP = not performed
n = 2 to 4 according to the availability of microsomal proteins

Overall, these findings suggest that the hepatocyte system was suitable to assess dronedarone's induction potential. Dronedarone did not induce enzymatic activity for any of the tested CYP enzymes, indicating that dronedarone is unlikely to increase the metabolism of CYP1A or CYP3A substrates at therapeutic concentrations (< 0.5 µM). It is noted that dronedarone concentrations > 5 µM were cytotoxic; these concentrations decreased the amount of protein.

Western Blot Analyses

The Western blot analyses indicated that the preparations were adequate to evaluate enzyme activity. The treatment of hepatocytes with B-naphthoflavone and dexamethasone produced increases in the protein bands corresponding to CYP1A2 and CYP3A, respectively. Dronedarone did not increase the protein bands of CYP1A2 or CYP3A; suggesting dronedarone does not induce the activity of these two enzymes.

Recommendations/Conclusions

The findings from Study MIV0144 provide the following relevant metabolism information that is acceptable for labeling and other purposes:

Enzymatic activity measured in cultured hepatocytes and Western blot analyzed indicate that dronedarone does not induce the enzymatic activity of CYP1A2, CYP2A6 or CYP3A. Based on the finding that CYP3A activity is not induced, dronedarone will not induce the enzymatic activity of CYP2C8, 2C9, or 2C19, as these enzymes are typically co expressed.

Appendix

Characteristics of patients (Caucasian humans) who underwent partial hepatectomy

Preparation	Sex	Age	Pathology
HTL-93	M	43	Colon adenocarcinoma
HTL-94	M	68	Colon adenocarcinoma
HTL-100	F	30	Hepatic adenoma
HTL-102	M	60	Colon adenocarcinoma

4.2.18 In vitro investigation of SR33589B trans-epithelial transport polarisation and inhibitory potency towards the active efflux of vincristine and digoxin using Caco-2/TC-7 cells monolayers (AIV0062)

PROTOCOL #	AIV0062
STUDY SITE	Sanofi Recherche, France
STUDY PERIOD	April – September 2000

Study Design

Standard procedures for *in vitro* drug transport studies were used. Caco-2/TC-7 cell monolayers (INSERM U-178, Villejuif – France) were used. Dronedarone was dissolved in DMSO at concentrations up to 20 mM and incubated for up to four hours. The trans-epithelial transport ("Apical → Basal" and "Basal →Apical" directions) for dronedarone (20 µM), vincristine (20 µM) and digoxin (20 µM) were evaluated in the absence and presence of 1 mM quinidine. Quinidine served as a potent efflux inhibitor. The basal to apical direction represents drug efflux. Samples were collected at 0, 1, 2 and 4 hours. In another set of experiments, the inhibition of [^{3}H]-vincristine (1 µM) and [^{3}H]-digoxin (1µM) active effluxes by cyclosporine A, verapamil, quinidine and dronedarone were assessed. The concentrations of the inhibitor ranged from 0.01 to 3000 µM. The incubation period, sampling times and transport direction were similar to those in the previously described experiment. Drug levels were quantified by HPLC with UV detection (230 nm) and liquid scintillation counting.

Experimental Design Notes (per Applicant)

- The study conditions were optimized to evaluate active efflux, rather than for the determination of an optimum 'Apical to Basal' trans-epithelial permeability.
- The highest concentration of dronedarone evaluated was 100 µM since above this value, the compound was cytotoxic as observed from the mannitol transport rate values.

Test Compounds

- Dronedarone hydrochloride salt; batch number 97-01213
- Quinidine, Sigma Chemicals
- Vincristine [G-3H]-vincristine ; specific activity = 5.5 Ci/mmol; Amersham Pharmacia Biotech
- [G-3H]-digoxin; (specific activity = 19 Ci/mmol) ; NEN Dupont
- D-[1-3H(N)]-mannitol (19.7 Ci/mmol) ; NEN Dupont
- Cyclosporine A, Sigma Chemicals
- Verapamil, Sigma Chemicals

Analyses

For each transport experiment the permeability coefficient, P_{app}, in cm/sec was determined by the following equation.

$$P_{app} = (dQ/dt) \times \left(\frac{1}{A \times Co}\right)$$

where : dQ = Amount of compound transported (expressed in nmoles)
dt = time interval during which transport is measured
A = surface area of the filter (*i.e.* 4.7 cm^2)
Co = initial concentration of test compound.

IC_{50} values were determined for each inhibitor using standard calculations.

Results

Polarisation of the trans-epithelial transport of dronedarone

The trans-epithelial transport of dronedarone in the presence and absence of quinidine is summarized in Table 114.

Table 114: Polarisation of dronedarone in vitro trans epithelial transport

SR33589 (20 µM)	P_{app} (10^{-7} cm.sec^{-1})
Apical to Basal	5.95 ± 2.12
Basal to Apical	14.80 ± 3.62
Apical to Basal + Quinidine	11.10 ± 0.00
Basal to Apical + Quinidine	17.00 ± 2.75

The results show that, under these experimental conditions, SR33589 undergoes a moderate active efflux with a nearly 2.5- fold factor between the 'Apical to Basal' and ' Basal to Apical' P app values (P_{app}BA : AB). This finding suggests dronedarone may be a moderate PGP substrate. The PGP substrate status of dronedarone could not be supported by the results obtained with quinidine, a PGP inhibitor. The presence of 1 mM quinidine did not produce any clear effect. According to the applicant, quinidine's apparent lack of effect was mostly due to the largely incomplete recovery yields observed in these experiments (only 13 to 50 % of the initial amount present in the incubation system).

Polarisation of the trans-epithelial transport of vincristine and digoxin

The trans-epithelial transport of vincristine and digoxin in the presence and absence of quinidine is summarized in Table 115.

Table 115: Polarisation of vincristine and[^{3}H] digoxin in vitro trams epithelial transport

	Vincristine *Papp* (10^{-7} cm.sec^{-1})	Digoxine *Papp* (10^{-7} cm.sec^{-1})
Apical to Basal	1.08 ± 0.65	4.59 ± 0.95
Basal to Apical	29.80 ± 2.86	113 ± 0.83
Apical to Basal + Quinidine	1.02 ± 0.29	44.60 ± 1.91
Basal to Apical + Quinidine	10.60 ± 0.82	42.10 ± 6.40

Both vincristine and digoxin exhibited a marked polarisation of their trans-epithelial transport as shown by their P_{app}BA : AB ratios (> 25). For both compounds, the presence of 1 mM quinidine drastically decreased the value of P_{app} 'Basal to Apical', indicating that drug efflux was decreased. These results demonstrated that both vincristine and digoxin active efflux were inhibited by quinidine, a broad spectrum PGP inhibitor.

Reviewer Comment on PGP Test System

The results from this study indicate that the PGP test system was suitable: digoxin is an acceptable PGP substrate and quinidine is an acceptable PGP inhibitor, per Drug-Drug interaction Guidance. Vincristine is not listed as an acceptable PGP substrate in the Guidance, however, it is structurally and pharmacologically related to vinblastine, an acceptable PGP substrate.

Inhibition of active efflux of vincristine and digoxin to determine IC values

The inhibition of the active efflux of [^{3}H]-vincristine (1 µM) and digoxin in the presence of cyclosporine, verapamil, quinidine and dronedarone were determined (Table 116 and Table 117).

Table 116: Inhibition of vincristine efflux by inhibitors

Inhibitors	IC_{20}* (µM)	IC_{50} (µM)	IC_{90}* (µM)
Cyclosporin A	0.35	1.08 ± 0.20	5
Verapamil	1	9.6 ± 8.5	2000
Quinidine	11	30.5 ± 4.8	75
SR33589B	0.30	0.97 ± 1.17	200

Table 117 Inhibition of digoxin efflux by inhibitors

Inhibitors	IC_{20}* (µM)	IC_{50} (µM)	IC_{90}* (µM)
Cyclosporin A	0.30	1.35 ± 0.33	6
SR33589B	0.22	2.05 ± 0.66	25

* IC_{20} and IC_{90} values were determined graphically

The cyclosporine A IC_{50} value with digoxin as substrate is consistent with literature values (per Guidance), suggesting that the system is suitable. Based on the digoxin information, dronedarone appears to have similar inhibitor potency as cyclosporine A.

Noting the stated limitation of the vincristine data (vincristine is not a preferred substrate), the inhibition data obtained with vincristine also support the finding that dronedarone is a potent PGP inhibitor. Dronedarone was as potent as cyclosporine A with respect to efflux inhibition and these two compounds were more potent inhibitors than verapamil and quinidine.

The dronedarone IC_{50} values exceed therapeutic dronedarone concentrations; however, the IC_{20} values are within the therapeutic concentration range. Therefore, dronedarone may have some potential to inhibit the efflux of PGP substrates. In sum, the inhibition data suggest that dronedarone is a potent PGP inhibitor at therapeutic concentrations.

Recommendations/Conclusions

There are two major deficiencies in this study:

1. The lack of optimization of system: this led to incomplete recovery yields in some experiments (< 50 % of the initial amount present in the incubation system).
2. The effect of dronedarone's active metabolite, SR35021, was not assessed. This evaluation would have been useful because SR35021 could be a potent PGP inhibitor, as is the case with a structurally related compound, amiodarone, and its active metabolite. Thus, dronedarone and SR35021 may have a potential additive to synergistic effect on

PGP inhibition that should be taken into account when attempting to predict the potential in vivo consequences of the in vitro effects demonstrated in this study

Despite the stated two limitations of the study, the findings from Study AIV0062 are acceptable for labeling, as appropriate:

1. Relative to vincristine or digoxin, which are model PGP efflux pump substrates (relative permeability > 25); dronedarone (relative permeability 2.5) has limited efflux potential.
2. SR33589 appears to be as potent an inhibitor as cyclosporine A, with respect to the ability to inhibit the efflux of digoxin and vincristine. The order of increasing numerical IC_{50} values for the two substrates, vincristine and digoxin, were:
    - For vincristine- dronedarone < cyclosporine A < verapamil < quinidine
    - For digoxin- cyclosporine A < dronedarone
3. Based on the in vitro IC20 values, dronedarone may inhibit the efflux of PGP substrates, thereby increasing the plasma exposure of PGP substrates.

4.2.19 Influence of repeated oral doses of Rifampicin [inducer of cytochrome P4503A4 (CYP3A4)] on the pharmacokinetic profile of dronedarone in healthy male subjects (INT3683)

PROTOCOL #	INT3683
INVESTIGATOR	Dr. D. E. De Vries
STUDY SITE	PHARMA BIO RESEARCH, INTERNATIONAL B.V., Science Park, 9471 GP Zuidlaren The Netherlands
STUDY PERIOD	February – March 1999

Rationale for Drug-Drug Interaction Study

	Rifampicin	Dronedarone
Indication/Mechanism of Action	Adjunctive treatment of tuberculosis; short-term management to eliminate meningococci from nasopharynx in *Neisseria meningitidis* carriers	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic
Metabolites	Forms an active metabolite, 25-0-desacetylrifampin	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	Hepatically metabolized by deacetylation with feces as primary elimination route (60% to 65%)	Primarily CYP3A substrate Potential PGP substrate and/or inhibitor
CYP Inhibition/Induction	Specific and potent CYP3A4 inducer	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	600 mg/day	400 mg BID

Objectives (per applicant)

Primary

To assess the effect of repeated oral doses of rifampicin on the pharmacokinetic profile of dronedarone (and its metabolite SR35021), given as a single oral dose of 1400 mg dronedarone in fed conditions.

Secondary

- To assess a potential pharmacodynamic resulting effect
- To assess the clinical and biological tolerability of dronedarone given alone and co-administered with rifampicin
- To document plasma concentrations of rifampicin after repeated doses.

Study Design

This was a non-randomized, open-label, non-placebo-controlled, single-group and two-period study. The two study periods were:

- Period 1: Five days in which a single oral dose of 1400 mg dronedarone given on day 1 (fed)
- Period 2: Seven days oral once daily dose of 600 mg rifampicin (fasted); on day 8 single oral dose of 1400 mg dronedarone co-administered with 600 mg rifampicin (fed)

The two doses of dronedarone were given 13 days apart.

Reviewer Note on Study Design
This study utilized a one-sequence cross-over with a single/multiple dosing regimen. The 1400 mg dronedarone dose is higher than the recommended 400 mg BID stated in the proposed label. Dronedarone has a half-life of 25-30 hours; therefore, the 5 days between the first dose of dronedarone and rifampicin is appropriate to allow for adequate drug elimination.

Subject Demographics
Subject demographics are presented in Table 118. All subjects were Caucasian males.

Table 118: Principal demographic characteristics of all subjects (INT 3683)

Parameter	Statistics	Results
Age (years)	N	12
	Mean	22.3
	SD	4.0
	Min	19
	Max	31
Height (cm)	N	12
	Mean	185.8
	SD	6.6
	Min	176
	Max	195
Weight (kg)	N	12
	Mean	80.74
	SD	9.84
	Min	62.5
	Max	96.4

Pharmacokinetic sampling times
The following pharmacokinetic blood samples were drawn at the given times:

- For dronedarone and SR35021: T – 5 min, T1h, T2h, T3h, T4h, T5h, T6h, T8h, T12h, T16h, T24h, T36h, T48h, T72h, and T96h
- For Rifampicin: Day 1 and Day 8 at T – 5 min, T1h, T1h + 55 min, T3h + 30 min, T5h + 30 min, T6h + 30 min, T8h + 30 min, T10h + 30 min, T14h + 30 min , T18h + 30 min, and T24h

Formulation

- Dronedarone: 200 mg film-coated tablets, batch number 9801501
- Rifampicin: 300 mg capsules, batch number 970002 (provided by applicant, without additional information on source)

Bioanalytical methods
Dronedarone and SR35021 concentrations were determined using a validated liquid chromatography-mass spectrometry (LC-MS/MS) method. The assay performance was acceptable as illustrated in Table 119.

Table 119: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the range of 0.5 ng/ml to 50 ng/ml; $R^2 >$ 0.993	Satisfactory
Between day Precision	CVs were not provided	Cannot assess
Accuracy	Accuracy values were not provided; however all individual QC values were within 15% of nominal concentrations	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided *	Cannot assess
	SR35021 Assay	
Linearity	The assay was linear over the range of 0.5 ng/ml to 50 ng/ml ; $R^2 >$ 0.992	Satisfactory
Between day Precision	CVs were not provided	Cannot assess
Accuracy	Accuracy values were not provided; however all individual QC values were within 15% of nominal concentrations	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided *	Cannot assess

* The validation report includes chromatograms that indicate assay specificity

Rifampicin plasma concentrations were determined using a validated high - performance liquid chromatography (HPLC) with ultraviolet detection method. The assay performance was acceptable as illustrated in Table 120.

Table 120: Performance of Rifampicin Assay

Parameter	Measure	Reviewer Comment
	Rifampicin Assay	
Linearity	The assay was linear over the 0.2 µg/ml to 20 µg/mL range; $R^2 >$ 0.998	Satisfactory
Between day Precision	CV was < 4%	Satisfactory
Accuracy	QC samples were between 2 % and 4 % of nominal concentration	Satisfactory
LLOQ	0.20 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined after each treatment:

- For dronedarone and SR35021: C_{max}, t_{max}, AUC_{last}, AUC and $t_{1/2}$
- For rifampicin: C_{max}, t_{max}, and AUC_{0-24h}

Pharmacodynamics (Activity)

The following pharmacodynamic (PD) parameters were determined: HR, and PR-, QRS-, QT-QTc-intervals, T-wave amplitude and hourly average AUC_{0-12}, peak values and time to peak values. Electrocardiogram (ECG) measurements were obtained at the following times:

- Screening
- Period 1: Day 0 at 8:00 pm, Day 1 at T-30, T2h, T4h, T6h, T8h, T12h, T24h, T48h, T72h and T96h
- Period 2: Day 1 and Day 7
- Period 2: Day 8 at T- 30 min, T2h, T4h, T6h, T8h, T12h, T24h, T48h, T72h and T96h; Day 15 (end- of- study visit).

Statistical methods

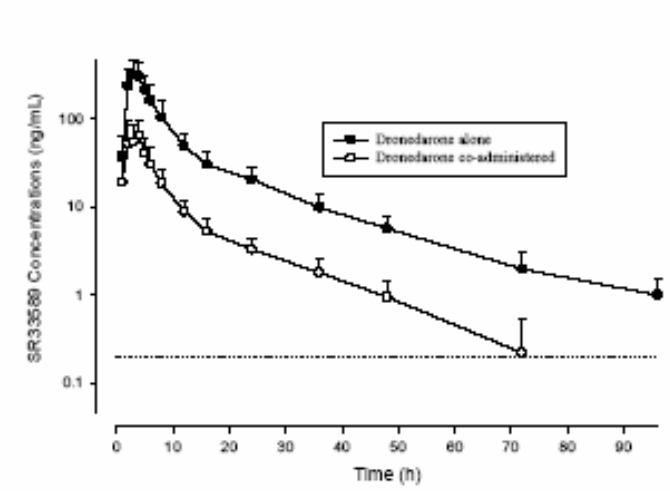
Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Dronedarone alone was the reference treatment and dronedarone + rifampicin was the test treatment. Pharmacodynamic measures were also analyzed using standard statistical approaches.

Results

Dronedarone Pharmacokinetics

The mean dronedarone plasma concentration time profiles following administration of dronedarone alone and dronedarone co-administered with rifampicin are depicted in Figure 61.

Figure 61: Mean (SD) dronedarone plasma concentration – time profile in after dronedarone alone and dronedarone co-administered with rifampicin (n = 11)



Dronedarone PK measures are summarized in Table 121

Table 121: Mean (±SD) values of dronedarone plasma pharmacokinetic parameters after dronedarone alone and dronedarone co-administered with rifampicin (n = 11)

Parameter (units)	Dronedarone alone Period 1	Dronedarone co-administered Period 2
C_{max} (ng/mL)	353 (119)	82.6 (38.1)
t_{max} (h)	3.3 (0.8)	3.2 (0.9)
AUC_{last} (ng.h/mL)	2505 (983)	464 (190)
AUC (ng.h/mL)	2533 (991)	488 (184)
$t_{1/2}$ (h)	18.7 (3.6)	18.0 (11.0)

Dronedarone exposure was greatly decreased (>4-fold in Cmax and >5 -fold in AUC) in presence of rifampicin 600 mg (Table 122 and Table 123).

Table 122: Ratio estimates and 95% CI calculated for Cmax treatment effect (dronedarone co-administered versus dronedarone alone) of dronedarone and SR35021

Parameter	SR33589		SR35021	
(units)	Ratio	95% CI	Ratio	95% CI
C_{max} (ng/mL)	0.226	[0.15, 0.33]	1.073	[0.78, 1.48]

Reviewer Note on Confidence Intervals (Dronedarone PK)

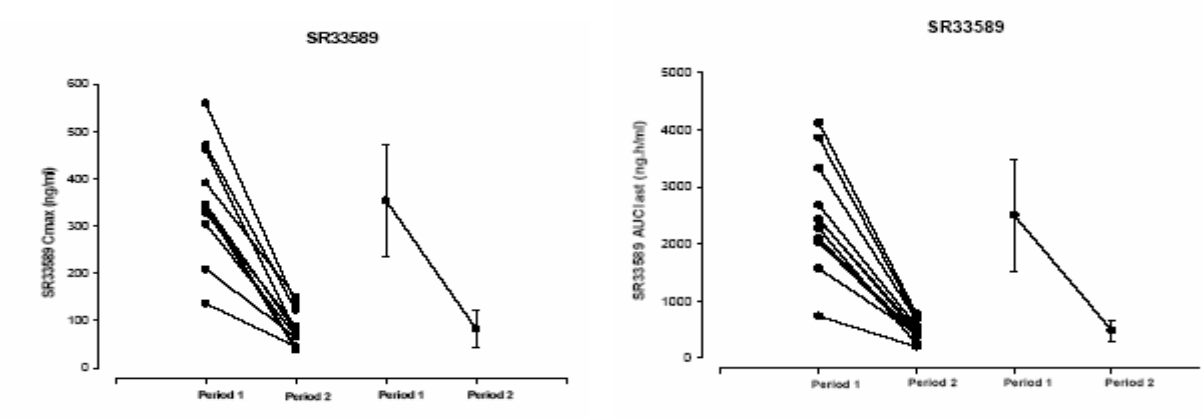
For regulatory purposes, 90 % confidence intervals are preferred over 95 % confidence intervals. In this study, the width of the confidence interval for dronedarone is not of consequence, because the geometric mean ratio is much smaller than one and the associated 90 % confidence intervals are much smaller than the default no effect range (0.8 to 1.25 based on 90 % confidence interval).

Table 123: Ratio estimates and 95% CI calculated for AUClast and AUC treatment effect (dronedarone co-administered versus dronedarone alone) of dronedarone and SR35021

Parameter (units)	SR33589		SR35021	
	Ratio	95% CI	Ratio	95% CI
AUC_{last} (ng.h/mL)	0.185	[0.12, 0.28]	0.813	[0.60, 1.10]
AUC (ng.h/mL)	0.195	[0.13, 0.29]	0.816	[0.60, 1.10]

The match stick plots in Figure 62 further illustrate the observed decrease in dronedarone exposure when co-administered with rifampicin; all subjects had a decrease in Cmax in the presence of rifampicin.

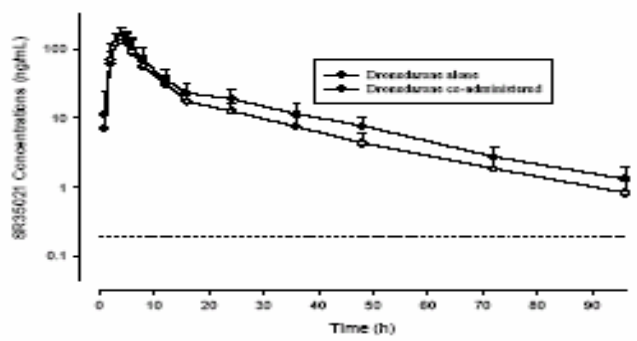
Figure 62: Individual and mean (±SD) Cmax values (ng/mL) and AUClast values (ng.h/mL) of dronedarone after a single dose of dronedarone alone and dronedarone co-administered (n=11)



SR35021 Pharmacokinetics

The mean SR35021 plasma concentration time profiles following administration of dronedarone alone and dronedarone co-administered with rifampicin are depicted in Figure 63.

Figure 63: Mean (SD) SR35021 plasma concentrations in logarithmic scale (left) and in linear scale (right) after dronedarone alone and dronedarone co-administered (n = 11)



SR35021 PK measures are shown in Table 124.

Table 124: Mean (±SD) values of SR35021 plasma pharmacokinetic parameters after dronedarone alone and dronedarone co-administered with rifampicin (n=11)

Parameter (units)	Dronedarone alone Period 1	Dronadarone co-administered Period 2
C_{max} (ng/mL)	153 (57.1)	160 (55)
t_{max} (h)	4.2 (0.4)	3.8 (0.9)
AUC_{last} (ng.h/mL)	1655 (525)	1345 (433)
AUC (ng.h/mL)	1690 (530)	1378 (436)
$t_{1/2}$ (h)	18.2 (1.9)	20.8 (4.8)

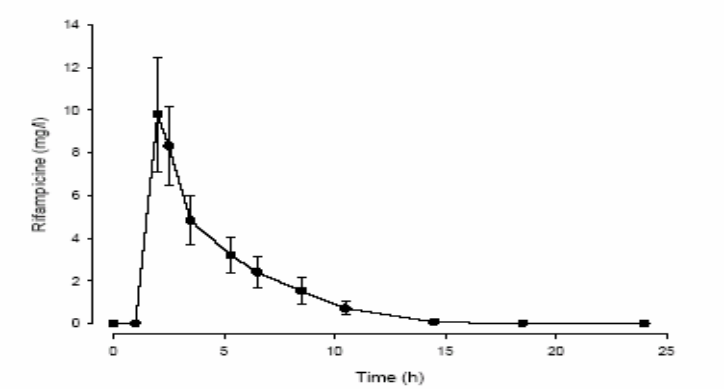
Geometric mean ratios and associated 95% CI of the SR35021 PK measures are presented in Table 122 and Table 123.

After rifampicin treatment, SR35021 Cmax and AUC values did not change significantly. The confidence interval crossed one; therefore, the results are not statistically significant.

Rifampicin Pharmacokinetics

Mean plasma concentrations after repeated administrations of rifampicin are plotted in Figure 64.

Figure 64: Mean (±SD) rifampicin plasma concentration – time profile after repeated dose rifampicin co-administered with a single oral dose dronedarone



Rifampicin PK are summarized in Table 125. The PK values are consistent with the values obtained in previous studies, suggesting that single dose administration of dronedarone does not alter rifampicin exposure.

Table 125: Mean (±SD) values of plasma pharmacokinetic parameters of rifampicin after repeated administrations of rifampicin and single dose of dronedarone

PK Measures	**C_{max} (mg/L)**	**t_{max} (h)**	**AUC $_{0\text{-}24h}$ (µg.h/L)**
Mean	10.5	1.2	41.4
SD	1.6	0.4	9.0

Pharmacodynamics

As shown in Table 126, relative to dronedarone alone, dronedarone plus rifampicin showed no statistically significant difference in hourly AUCs for HR, QRS interval, PR interval, QT interval, or QTc interval.

Table 126: Summary of derived variables for ECG Parameters – Difference estimates with 95% confidence intervals (average hourly AUC for values from 30 minutes pre-dose to 12h post-dose)

Parameter	Parameter	Difference Estimate	Standard Error Estimate	F test Significance level	Difference 95% CI
HEART RATE (bpm)	HEART RATE (bpm)	-1.8636	2.5254	0.4691	[-7.13, 3.40]
PR INTERVAL (ms)	PR INTERVAL (ms)	-11.3182	7.3558	0.1396	[-26.66, 4.03]
QRS INTERVAL (ms)	QRS INTERVAL (ms)	1.4818	1.2968	0.2667	[-1.22, 4.19]
QT INTERVAL (ms)	QT INTERVAL (ms)	4.4818	4.5657	0.3380	[-5.04, 14.01]
QTc INTERVAL (ms)	QTc INTERVAL (ms)	-0.3909	7.0756	0.9565	[-15.15, 14.37]
T WAVE AMPLITUDE (µV)	T WAVE AMPLITUDE (µV)	48.1091	78.6512	0.5476	[-115.95, 212.17]

Reviewer Comment on Pharmacodynamic Results

As a CYP3A4 inducer, rifampicin is expected to decrease dronedarone, a CYP3A4 substrate, exposure; therefore, its affect on PD parameters from a safety perspective is not of concern. However, dronedarone's effectiveness may be compromised because sub-therapeutic exposure will be achieved.

Applicant's Safety Summary

There were no serious adverse events (SAEs) or deaths in this study. A total of 37 treatment emergent AEs (TEAEs) were reported in this study, 11 of which occurred during co-administration of dronedarone with rifampicin. The reported AEs included headache, abdominal pain, diarrhea, nausea, tongue discoloration, euphoria, rhinitis, and chrompatopsia.

Recommendations/Conclusions

1. Rifampicin (600 mg) given once daily for 8 days induced dronedarone metabolism; consequently dronedarone plasma concentrations were decreased (Cmax decreased > 75% and AUC decreased > 80%), relative to administration of dronedarone alone.
2. Rifampicin did not affect SR 35021 exposure.
3. Sub-therapeutic dronedarone exposures did not appear to alter the HR, QRS interval, PR interval, QT interval, or QTc interval in a clinically significant manner from a safety perspective

Labeling (Precautions Section)

Applicant's proposed labeling

Co-administration of rifampicin and other potent CYP3A4 inducers such as pentobarbital, carbamazepine, phenytoin, St John's Wort are not recommended as they decrease dronedarone exposure.

Reviewer Proposed Labeling

Rifampicin and other potent CYP3A4 inducers such as pentobarbital, carbamazepine, phenytoin, St John's Wort should not be used concomitantly with dronedarone.

4.2.20 Interaction study between repeated oral doses of dronedarone and repeated oral doses of losartan in healthy young male subjects - Randomized, open-labeled, non-placebo-controlled, three-treatment, crossover study (INT 4884)

PROTOCOL #	INT4884
INVESTIGATOR	Steven De Bruyn
STUDY SITE	Research Unit Stuivenberg, SGS Biopharma, Lange Beeldekensstraat 267, B-2060 Antwerpen, Belgium
STUDY PERIOD	July – October, 2002

Rationale for Drug-Drug Interaction Study

	Losartan	Dronedarone
Indication/Mechanism of Action	Treatment of hypertension; reduce risk of stroke in patients with hypertension and left ventricular hypertrophy; treatment of diabetic nephropathy/ Angiotensin II receptor antagonist	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic
Metabolites	Active carboxylic acid	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP2C9, CYP3A4	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Usual starting dose – 50 mg QD; Can be administered QD or BID at total daily doses of 25 to 100 mg	400 mg BID

Objectives (per applicant)

Primary

- To assess the effect of repeated oral doses of 400 mg dronedarone BID on the pharmacokinetic (PK) profile of losartan and its metabolite E-3174 after repeated oral doses of 100 mg losartan AD for 14 days
- To assess the effect of repeated oral doses of 100 mg QD losartan on the PK profile of dronedarone and its metabolite SR35021 after repeated oral doses of 400 mg BID dronedarone for 14 days

Secondary

- To assess the potential effect of dronedarone on the pharmacodynamic (PD) effect of losartan in reducing resting BP
- To assess the clinical and biological tolerability of dronedarone and losartan given alone, and also the co-administration

Study Design

This was an open-labeled, non-placebo-controlled, repeated oral dose, randomized, 3-treatment, and 3-period crossover study with a seven to thirteen day washout phase between periods. Subjects were enrolled into one of six treatment sequences as shown in Table 127. In each treatment sequence, each subject received one of the following three treatments for 14 days:

- Dronedarone (D) 400 mg BID
- Losartan (L) 100 mg QD
- Coadministration (D + L)

Subject Demographics

Subject demographics are summarized in Table 127.

Table 127: Subject Demographic Data (INT 4884)

Parameter	Statistics/ Category	Total (N=29)
Age (yrs)	N	29
	Mean	30.7
	SD	6.5
	Min	18
	Max	40
Weight (kg)	N	29
	Mean	75.77
	SD	8.53
	Min	56.8
	Max	93.7
Height (cm)	N	29
	Mean	178.5
	SD	7.6
	Min	166
	Max	191
BMI (kg/m^2)	N	29
	Mean	23.82
	SD	2.64
	Min	17.7
	Max	28.2
Gender	Male	29 (100%)
Race	Caucasian	29 (100%)

Pharmacokinetic sampling times

Pharmacokinetic blood samples were drawn as follows:

- Dronedarone and SR35021: before morning administration on Days 1, 2, 4, 8, 10, 12, and 14, and then at 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours after dosing on Day 14, for each period of treatment
- Losartan and E-3174: before administration on Days 1, 2, 4, 8, 10, 12, and 14, and then at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours after dosing on Day 14, for each period of treatment

Formulation

- Dronedarone 400 mg, batch number CL-03936
- Losartan (Cozaar™, Merck) 50 mg tablets, batch number (batches 0280 0161,0280 0162, 0280 0163, 0280 0164)

Bioanalytical methods

Dronedarone and SR35021 plasma concentrations were determined using a validated liquid chromatography-tandem mass (LC-MS/MS) method (DOH0309). The assay performance was acceptable as illustrated in Table 128.

Table 128: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the range of 0.500 to 300 ng/ml; $R^2 > 0.992$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however, all individual QC values were within 15% of nominal concentrations except for a few outliers	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the range of 0.500 to 300 ng/ml; $R^2 > 0.995$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed

* The validation report includes chromatograms that indicate assay specificity

Losartan and E-3174 plasma concentrations were determined using a validated LC-MS/MS method (CEPHAC-CP025015). The assay performance was acceptable as illustrated in Table 129.

Table 129: Performance of Losartan and E-3174 Assay

Parameter	Measure	Reviewer Comment
	Losartan Assay	
Linearity	The assay was linear over the range of 0.500 to 1000 ng/mL; R^2 not available	Satisfactory
Between day Precision	CV varied from 1.67% to 8.37 %	Satisfactory
Accuracy	QC samples were between 3.7% and 17.73% (at LLOQ) of nominal concentrations	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
	E-3174 Assay	
Linearity	The assay was linear over the from 0.500 ng/mL to 1000 ng/mL; R^2 not provided	Satisfactory
Between day Precision	CV varied from 2.04% to 18.5% (at LLOQ)	Satisfactory
Accuracy	QC samples were between 0.27% and 11.64% of nominal concentrations	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) parameters were determined for dronedarone, SR35021, losartan, and E-3174:

- Days 1 to 13: C_{trough}
- Day 14 of each treatment: C_{max}, t_{max}, C_{min}, AUC_{0-12} (for dronedarone and

SR35021), AUC_{0-24} (for losartan and E-3174), R_{met} (for dronedarone and SR35021) using the following ratio: $AUC_{0-12\ (metabolite)}$/ $AUC_{0-12\ (drug)}$

Pharmacodynamics

The following pharmacodynamic (PD) parameters were determined: changes in baseline in supine and standing position, systolic blood pressure (SBP), diastolic (DBP), and heart rate (HR).

Statistical methods

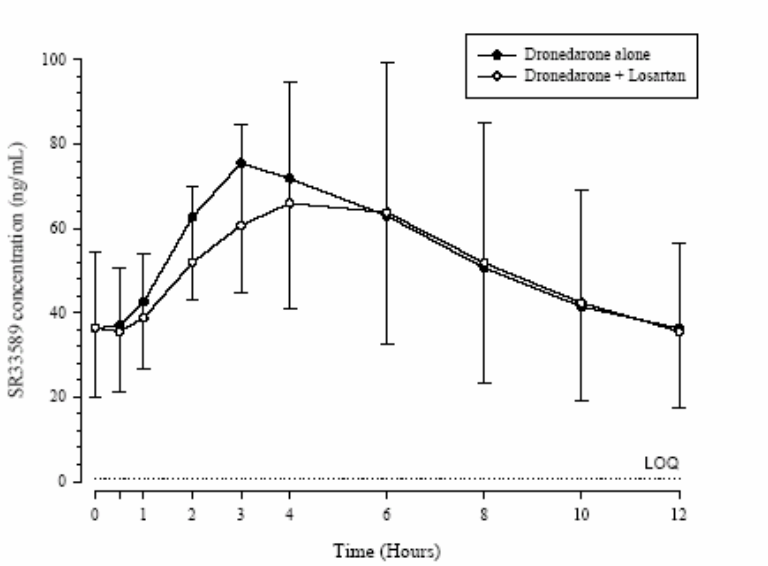
Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Dronedarone alone was the reference treatment and dronedarone + losartan was the test treatment. Pharmacodynamic measures were also analyzed using standard statistical approaches.

Results

Dronedarone Pharmacokinetics

The mean plasma concentration-time profiles for dronedarone after administration of dronedarone 400 mg BID in the absence and presence of losartan are depicted in Figure 65.

Figure 65: Mean (±SD) dronedarone plasma concentrations after repeated oral 400 mg BID administration of dronedarone alone or coadministration (n=25)



Dronedarone PK measures are summarized in Table 130. Dronedarone exposure showed a statistically significant decrease in Cmax (~12%) but no change in AUC in the presence of losartan. The associated confidence interval for Cmax; however, nearly falls within the no effect range (0.8 to 1.25 based on 90% confidence interval). Therefore, this decrease is not clinically significant.

Table 130: Mean (CV%) dronedarone pharmacokinetic parameters, their ratio estimates, and 90% confidence intervals (n=25) after repeated oral 400 mg BID administration of dronedarone alone or co- administrated with losartan

PK Parameters	Dronedarone Alone	Dronedarone+ Losartan	Ratio Estimates[b] and 90% CI
SR33589			
C_{max} (ng/mL)	80.4 (39)	71.9 (47)	0.879 [0.79; 0.97]
t_{max} (h)[b]	3.00 [2.00 – 6.07]	4.00 [2.00 – 6.02]	p=0.0069
AUC_{0-12} (ng.h/mL)	650 (43)	616 (50)	0.930 [0.86; 1.01]

a – Ratio dronedarone + losartan/dronedarone, p-value for difference between treatments
b – Median values (Min-Max)

The match stick plots in Figure 66 and Figure 67 further illustrate the minimal decrease in dronedarone Cmax and lack of change in AUC during the coadministration of dronedarone and losartan. It should be noted that individual plots for both Cmax and AUC show both increases and decreases.

Figure 66: Individual, mean (±SD), and geometric mean Cmax values of dronedarone after repeated oral administration of dronedarone alone or in the presence of losartan (n=25)

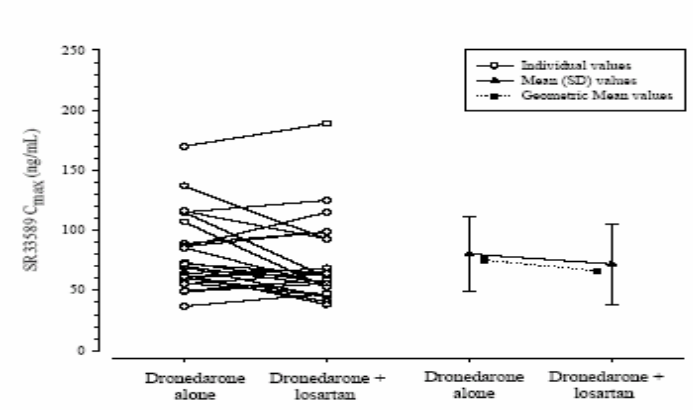
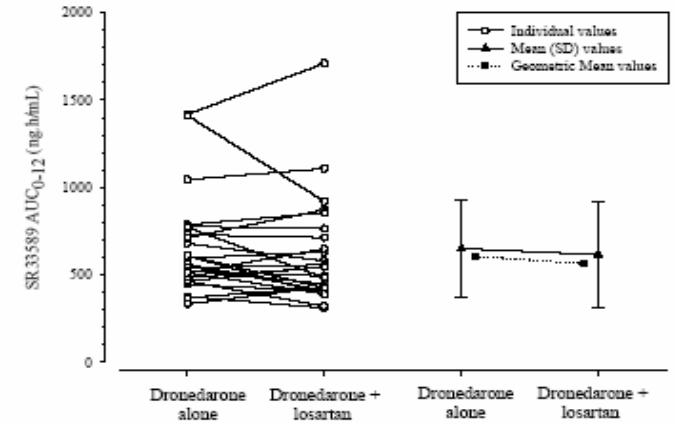


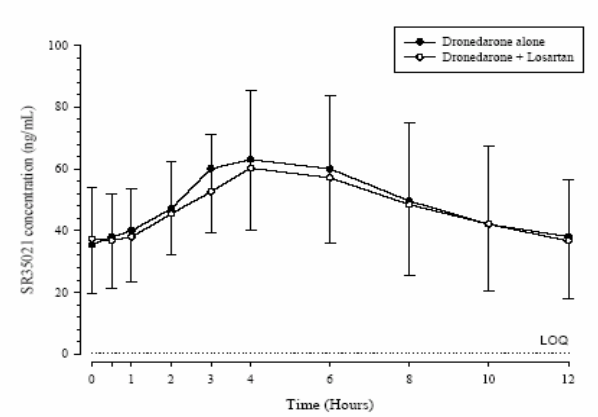
Figure 67: Individual, mean (±SD), and geometric mean AUC_{0-12} values of dronedarone after repeated oral administration of dronedarone alone or in the presence of losartan (n=25)



SR35021 Pharmacokinetics

The mean SR35021 plasma concentration-time profiles following administration of dronedarone 400 mg BID with or without losartan are depicted in Figure 68.

Figure 68: Mean (±SD) SR35021 plasma concentrations after repeated oral 400 mg BID administration of dronedarone alone or coadministered with losartan (n=25)



SR35021 PK measures are summarized in Table 131. No significant change in Cmax and AUC with co-administration of dronedarone and losartan was observed.

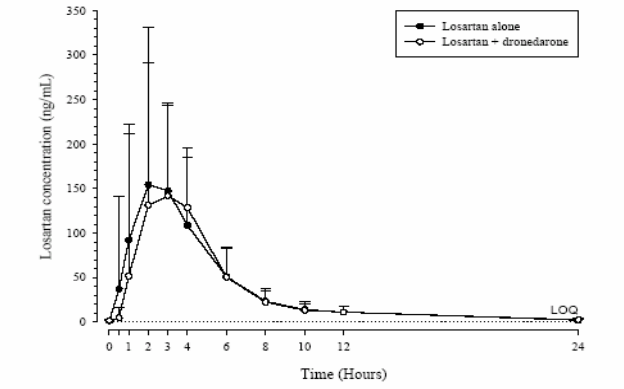
Table 131: Mean (CV %) dronedarone and SR35021 pharmacokinetic parameters, their ratio estimates, and 90% confidence intervals (n=25) following administration of dronedarone alone and in the presence of losartan

PK Parameters	Dronedarone Alone	Dronedarone + Losartan	Ratio Estimates and 90% CI
C_{max} (ng/ml)	66.4 (36)	62.8 (41)	0.942 (0.88; 1.00)
T_{max} (h)	4.00 [3.00 – 6.07]	4.00 =[3.00 – 8.00]	p=0.5590
AUC_{0-12} (ng. h/ml)	601 (41)	573 (46)	0.947 [0.90; 1.00]

Losartan Pharmacokinetics

The mean losartan plasma concentration-time profiles following administration of 100 mg QD losartan alone or coadministered with dronedarone 400 mg BID are depicted in Figure 69.

Figure 69: Mean (±SD) losartan plasma concentrations after repeated oral 100 mg QD administration of losartan alone or coadministration (n=27)



Losartan PK measures shown in Table 132 indicate no significant change in exposure was observed when losartan was coadministered with dronedarone. The mean values for Cmax and AUC shown in the match stick plots (Figure 69 and Figure 70) show a trend towards decreased exposure; however, individual subject values show both increases and decreases in Cmax and AUC.

Table 132: Mean (CV %) losartan and E-3174 pharmacokinetic parameters, their ratio estimates and 90% confidence interval (n=27) following administration of losartan alone or coadministered with dronedarone

PK Parameters	Losartan Alone	Losartan+ Dronedarone	Ratio Estimates[a] and 90% CI
Losartan			
C_{max} (ng/mL)	284 (53)	245 (75)	0.821 [0.66; 1.03]
t_{max} (h)[b]	2.02 [0.470 – 6.00]	3.00 [1.00 – 6.00]	p=0.2549
AUC_{0-24} (ng.h/mL)	842 (37)[c]	782 (47)[d]	0.925 [0.84; 1.01]
E-3174			
C_{max} (ng/mL)	459 (48)	346 (49)	0.750 [0.67; 0.84]
t_{max} (h)[b]	4.00 [2.97 – 6.03]	4.00 [3.00 – 6.02]	p=0.4806
AUC_{0-24} (ng.h/mL)	3210 (39)	2560 (40)[c]	0.788 [0.73; 0.85]

Figure 70: Individual, mean (±SD), and geometric mean Cmax values of losartan after repeated oral administration of losartan alone or coadministration with dronedarone (n=27)

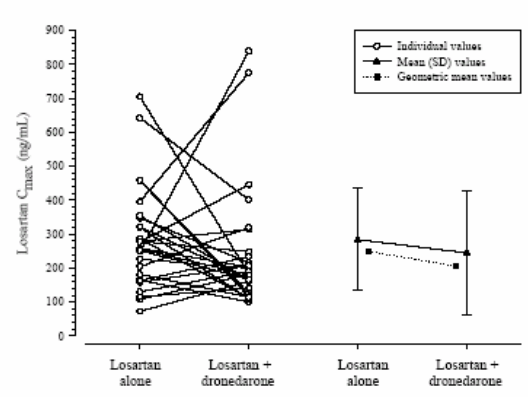
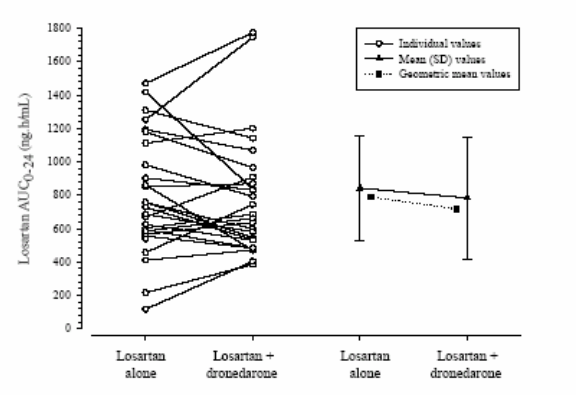


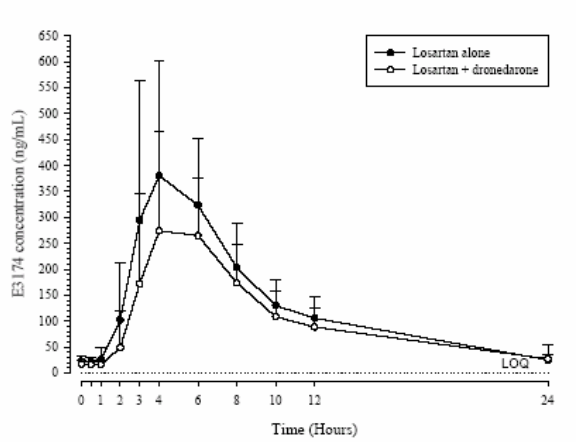
Figure 71: Individual, mean (±SD), and geometric mean AUC0-24 values of losartan after repeated oral administration of losartan alone or coadministration with dronedarone (n=27)



E-3174 Pharmacokinetics

The mean E-3174 plasma concentration-time profiles following administration of 100 mg QD losartan alone or coadministered with dronedarone 400 mg BID are depicted in Figure 72.

Figure 72: Mean (±SD) E-3174 plasma concentrations after repeated oral administration of 100 mg QD losartan alone or coadministered with dronedarone (n=27)



E-3174 PK measures are shown in Table 132. There was a statistically significant decrease in E-3174 exposure (about 25% for both Cmax and AUC) when losartan was coadministered with dronedarone relative to when losartan was administered alone.

Pharmacodynamics

Relative to dronedarone alone, dronedarone plus losartan showed the following):

- HR: Addition of dronedarone to losartan is not associated with a change in HR; however, addition of losartan to dronedarone was associated with an increase in HR of 4.05 bpm for difference in changes from baseline ($p<0.001$) at Day 14. The clinical significance of this increase is not clear.
- DBP: No treatment effect was observed
- SBP: There was a significant treatment x time interaction for SBP changes from baseline ($p=0.045$), but there was no significant treatment effect at Day 14 for SBP changes from baseline and for differences in derived AUCs, whatever the comparison, coadministration versus dronedarone or coadministration versus losartan.

Applicant's Safety Summary

There were no serious adverse events (SAEs), deaths or significant adverse events in this study. Treatment emergent adverse events (TEAEs) occurred in all three treatment groups. The incidence of TEAEs was 71.4% during treatment with dronedarone alone, 62.1% during losartan alone, and 85.2% during coadministration. Nervous system-, GI-, and general disorders were the most frequently reported TEAEs overall. Most TEAEs were of mild intensity, and all subjects recovered without corrective treatment. No subjects permanently discontinued study drug treatment due to TEAEs.

Table 133: Analysis in repeated measures of changes from baseline up to 11.5 hours and of corresponding AUC [0.5 – 11.5] – 95% confidence intervals for pairwise differences between treatments

			Difference in Delta			
Parameter	Derived parameter	Difference tested	Estimate	Standard error of the mean	95% confidence interval	Flag of signif. level
HR (bpm)	Delta value	SR vs L: overall	-1.68	1.31	[-4.3, 0.94]	
		SR+L vs L: overall	2.37	1.29	[-0.22, 4.96]	
		SR+L vs SR: overall	4.05	1.31	[1.43, 6.68]	**
	AUC[0.5-11.5]	SR vs L	-1.78	1.34	[-4.47, 0.91]	
		SR+L vs L	2.39	1.32	[-0.26, 5.05]	
		SR+L vs SR	4.18	1.34	[1.48, 6.87]	**
DBP (mmHg)	Delta value	SR vs L: overall	0.75	1.30	[-1.87, 3.37]	
		SR+L vs L: overall	1.15	1.29	[-1.44, 3.74]	
		SR+L vs SR: overall	0.40	1.31	[-2.22, 3.03]	
	AUC[0.5-11.5]	SR vs L	0.81	1.34	[-1.88, 3.5]	
		SR+L vs L	1.34	1.32	[-1.31, 4]	
		SR+L vs SR	0.53	1.34	[-2.16, 3.23]	
SBP (mmHg)	Delta value	SR vs L: overall	1.75	1.65	[-1.56, 5.06]	
		SR+L vs L: overall	0.36	1.63	[-2.91, 3.63]	
		SR+L vs SR: overall	-1.39	1.65	[-4.7, 1.92]	
	AUC[0.5-11.5]	SR vs L	1.71	1.67	[-1.64, 5.05]	
		SR+L vs L	-0.45	1.65	[-3.76, 2.86]	
		SR+L vs SR	-2.15	1.67	[-5.5, 1.2]	

Recommendations/Conclusions

1. Losartan (100 mg) does not affect the PK of dronedarone
2. The active metabolite of losartan, E-3174, showed a statistically significant decrease in exposure (about 25% for both Cmax and AUC) after administration of losartan with dronedarone, relative to losartan alone. Losartan undergoes minimal conversion to its metabolite. Therefore, this decrease in exposure is not likely to cause a decrease in losartan's therapeutic effect.
3. There were no significant treatment effects on SBP and DBP after administration of losartan and dronedarone.
4. The addition of losartan to dronedarone (but not the reverse) caused an increase in HR of 4.05 bpm; however, the clinical implication of this increase is not clear.

Labeling

Applicant's Proposed Labeling: No interaction was observed between dronedarone and losartan.

Reviewer's Comment: The proposed labeling is acceptable based on the PK information in INT 4884. No dose adjustments for dronedarone or losartan are needed when administered together.

4.2.21 Pharmacokinetic interaction of repeated oral 40 mg o.d. pantoprazole on repeated oral 400 mg b.i.d. dronedarone in healthy young male subjects - Open-labeled, non placebo-controlled, randomized, 2-treatment, 2-period crossover study (INT3560)

PROTOCOL #	INT 3560
INVESTIGATOR	Dr. Nicolas Fauchoux
STUDY SITE	Biotrial, Rue Jean-Louis Bertrand, Technopole Atalante Villejean, 35000 Rennes, France
STUDY PERIOD	October - November 2002

Rationale for Drug-Drug Interaction Study

	Pantoprazole	Dronedarone
Indication/Mechanism of Action	Short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease ; maintenance of healing of erosive esophagitis; treatment of pathological hypersecretory conditions/	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic
Metabolites	Several metabolites with no significant pharmacologic activity	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP2C19, CYP3A4	Primarily CYP3A substrate
CYP Inhibitory Potential	None	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	40 mg	400 mg BID

Objectives (per applicant)

Primary: To assess the effect of repeated oral doses of pantoprazole on the pharmacokinetic (PK) profile of dronedarone and its N-debutyl metabolite, SR35021, after repeated oral doses of dronedarone given in fed conditions.

Secondary: To assess the clinical and biological safety of dronedarone given alone and of dronedarone + pantoprazole co-administration in healthy male subjects.

Study Design

This was an open-labeled, non-placebo-controlled, repeated-dose, randomized, 2-treatment, and 2-period crossover study with a washout period of 10 days. Subjects were randomized to one of two treatment sequences (Sequence 1: Treatment A then Treatment B; Sequence 2: Treatment B then Treatment A) that included the following treatment periods:

- Treatment A (dronedarone alone): 400 mg twice a day (BID) dronedarone for seven days
- Treatment B (dronedarone co-administered with pantoprazole): 400 mg BID dronedarone + 40 mg once a day (QD) pantoprazole for seven days

Subject Demographics

Subject demographics are presented in Table 134.

Table 134: Summary of subject demographic data (INT 3560)

Parameter (Unit)	Statistics / Category	Total (N=18)
Age (years)	N	18
	Mean (SD)	28.0 (5.6)
	Min - Max	21 - 40
Weight (kg)	N	18
	Mean (SD)	74.03 (8.23)
	Min - Max	57.0 - 88.5
Height (cm)	N	18
	Mean (SD)	178.6 (7.7)
	Min - Max	165 - 194
BMI (kg/m^2)	N	18
	Mean (SD)	23.23 (2.37)
	Min - Max	19.5 - 27.5
Gender	Male (N,%)	18 (100)
Race	Caucasian (N,%)	18 (100)

Pharmacokinetic sampling times

Pharmacokinetic blood samples were drawn as follows:

- Dronedarone and SR35021: before dose administration on Days 1, 2, 4, 6, 7, and on Day 7 at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours after dosing.
- Pantoprazole: before dose administration on Day 1 and Day 7, and on Day 7 at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after the co-administration.

Formulation

- Dronedarone 400 mg tablets (formula 2E3) batch number CL-03936
- Pantoprazole (Inipomp™, Sanofi-Synthelabo) 40 mg enteric-coated tablets, batch number (22007)

Bioanalytical methods

Dronedarone and SR35021 plasma assays

Dronedarone and SR35021 plasma concentrations were determined by a validated Liquid Chromatography-Mass Spectrometry (LC-MS/MS) method (DOH0239). The assay performance was acceptable as shown in Table 135.

Table 135: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	Linear over range of 0.5 to 300 ng/ml; $R^2 > 0.996$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed
	SR35021 Assay	
Linearity	Linear over range of 0.5 to 300 ng/ml; $R^2 > 0.995$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed

* The validation report includes chromatograms that indicate assay specificity

Pantoprazole assay

Pantoprazole plasma concentrations were determined by a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 136.

Table 136: Performance of Pantoprazole Assay

Parameter	Measure	Reviewer Comment
	Pantoprazole Assay	
Linearity	Linear over the range of 20.0 to 2000 ng/mL; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 10%	Satisfactory
Accuracy	QC samples were between 1.06% and 3.5% of nominal concentration	Satisfactory
LLOQ	20 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) parameters were determined:

- Dronedarone and SR35021: Ctrough, tmax, Cmax, AUC0-12, Rmet ($AUC_{0\text{-}12\ metabolite}/AUC_{0\text{-}12\ drug}$)
- Pantoprazole: Ctrough, Cmax, tmax, $AUC_{0\text{-}24}$

Statistical methods

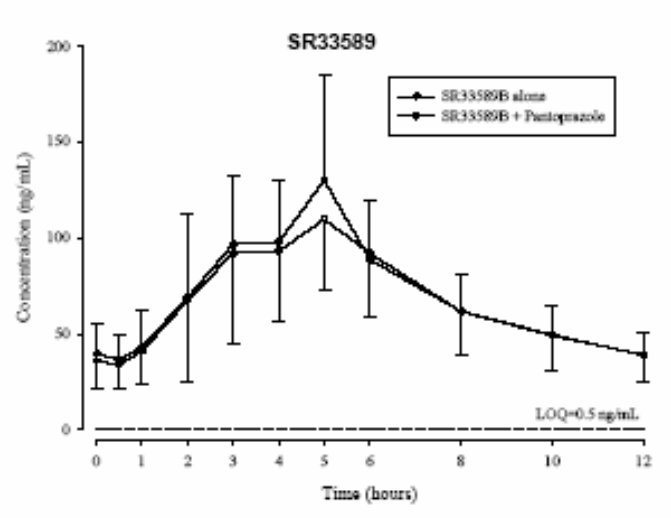
Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Dronedarone alone was the reference treatment and dronedarone + pantoprazole was the test treatment.

Results

Dronedarone Pharmacokinetics

The mean plasma concentration-time profiles for dronedarone following administration of dronedarone 400 mg BID in the absence and presence of pantoprazole are depicted in Figure 73.

Figure 73: Mean (SD) dronedarone plasma concentrations observed after seven days repeated administration of dronedarone alone or co-administered with pantoprazole (n=17)



Dronedarone PK measures and ratio estimates are summarized in Table 137 and Table 138. There was no statistically significant change observed in dronedarone exposure when dronedarone was administered with pantoprazole. The 90% confidence intervals are almost entirely within the no effect range (0.8 to 1.25), suggesting the interaction is not clinically significant.

Table 137: Mean (SD) and CV% values of dronedarone and SR35021 pharmacokinetic parameters obtained after seven days repeated administration of dronedarone alone or co-administered with pantoprazole (n=17)

PK Parameter *Mean (SD) – CV%*	SR33589B Alone	SR33589B + Pantoprazole
	SR33589	
C_{max} (ng/mL)	122 (42.6) 35%	138 (53.3) 39%
t_{max} (h)[a]	5.00 [3.00-6.00]	5.00 [2.00-5.00]
AUC_{0-12} (ng.h/mL)	817 (283) 35%	849 (239) 28%
C_{trough} (ng/mL)	36.0 (14.0) 39%	39.6 (15.9) 40%
	SR35021	
C_{max} (ng/mL)	119 (37.2) 31%	127 (42.0) 33%
t_{max} (h)[a]	5.00 [3.00-6.00]	5.00[3.00-6.00]
AUC_{0-12} (ng.h/mL)	930 (320) 34%	951 (309) 32%
C_{trough} (ng/mL)	48.1 (22.5) 47%	52.2 (18.3) 35%
$R_{met\ (AUC0-12)}$ Geometric mean	1.14	1.10

[a] Median and range for t_{max}

Table 138: Treatment ratio estimates (dronedarone + pantoprazole vs. dronedarone alone) and 90% confidence interval

Parameter	Ratio Estimate	90% CI of Ratio Estimate
SR33589		
C_{max}	1.13	[0.98; 1.31]
AUC_{0-12}	1.07	[1.00; 1.16]
t_{max}[a]	0.00	[-0.50; 0.50]
SR35021		
C_{max}	1.07	[0.94; 1.20]
AUC_{0-12}	1.03	[0.97; 1.09]
t_{max}[a]	0.00	[-0.50; 0.50]
R_{met}	0.96	[0.90; 1.02]

Figure 74: Individual and mean (SD) dronedarone Cmax values (ng/mL) obtained after 7 days repeated administration of dronedarone alone or co-administered with pantoprazole (n=17)

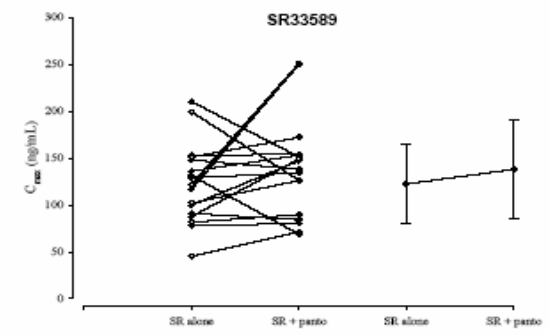
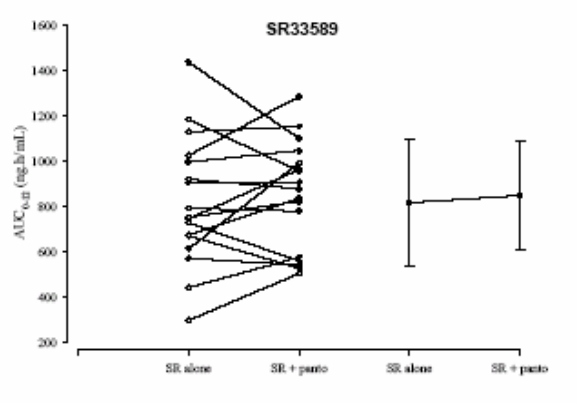


Figure 75: Individual and mean ± (SD) dronedarone AUC0-12 values (ng.h/mL) obtained after 7 days repeated administration of dronedarone alone or co-administered with pantoprazole (n=17)

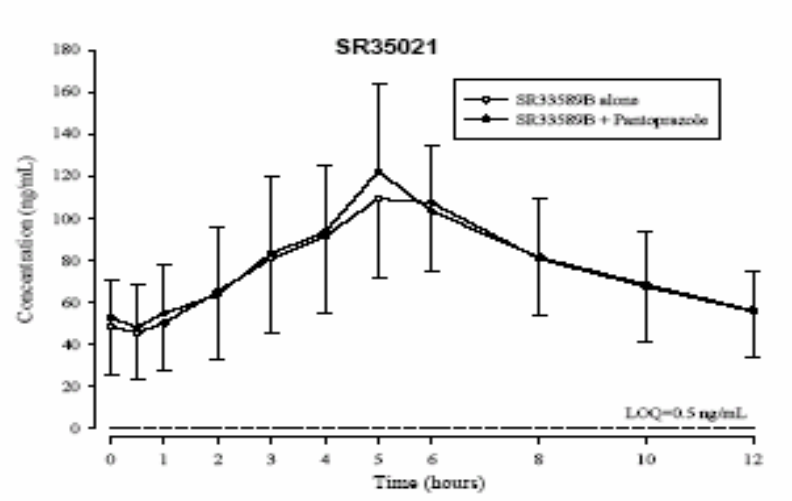


The match stick plots for dronedarone Cmax and AUC values are shown in Figure 74 and Figure 75. Although the plots for the mean values show a minimal upward trend in Cmax and AUC, there are some individual subject plots that show both increases and decreases.

SR35021 Pharmacokinetics

The mean plasma concentration-time profiles for SR35021 following administration of dronedarone 400 mg BID in the absence and presence of pantoprazole are depicted in Figure 76.

Figure 76: Mean (SD) SR35021 plasma concentrations observed after 7 days repeated administration of dronedarone alone or co-administered with pantoprazole (n=17)

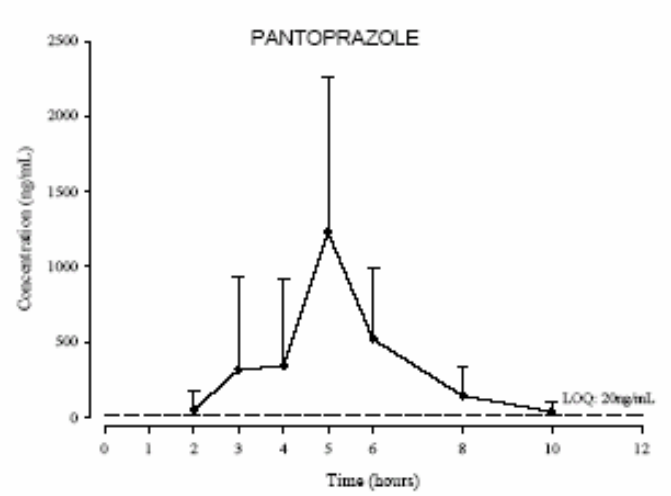


SR35021 PK and ratio estimates are summarized in Table 137 and Table 138. There was no statistically significant change observed in exposure of SR35021 when dronedarone was administered with pantoprazole.

Pantoprazole Pharmacokinetics

The mean pantoprazole plasma concentration-time profiles following administration of pantoprazole 40 mg QD co-administered with dronedarone 400 mg BID are depicted in Figure 77.

Figure 77: Mean (SD) pantoprazole plasma concentrations obtained after a 7-day repeated pantoprazole co-administration with dronedarone



Pantoprazole PK are summarized in Table 139. The PK values are consistent with the values obtained in previous studies, suggesting that single dose administration of dronedarone does not alter pantoprazole exposure.

Table 139: Descriptive statistics of pantoprazole pharmacokinetic parameters obtained after repeated pantoprazole co-administration with dronedarone (Day 7)

Parameter	C_{max} (ng/mL)	t_{max} (hours)	$AUC_{0\text{-}24h}$ (ng.h/mL)
N	17	17	17
Mean (SD)	1671 (825)	4.59 (1.00)	5367 (3240)
CV%	49	22	60
Minimum - Maximum	450 - 3083	3.00 – 6.00	1562 – 12237
Median	1712	5.00	4886
Geometric Mean	1470	4.47	4452

Applicant's Safety Summary

There were no serious adverse events (SAEs), deaths or significant adverse events in this study. Treatment emergent adverse events (TEAEs) occurred in both treatment groups. The incidence of TEAEs was 22.2% during treatment with dronedarone alone, and 58.8% during coadministration. GI, nervous system, and general disorders were the most frequently reported TEAEs overall. One subject permanently discontinued study drug treatment due to TEAEs.

Recommendations/Conclusions

Pantoprazole (40 mg) once daily over 7 days did not cause a statistically significant change in exposure of dronedarone or SR35021, indicating that pantoprazole does not affect the PK of dronedarone.

Labeling

Sponsor's Proposed Labeling

Other Information
Pantoprazole (40 mg once daily), a drug increasing gastric pH without any effect on cytochrome P450, did not interact significantly on dronedarone pharmacokinetics.

The proposed labeling is acceptable based on the PK information in INT3560.
No dose adjustments for dronedarone or pantoprazole are needed when administered together.

Reviewer Proposed Alternative Language

Pantoprazole (40 mg once daily), a drug increasing gastric pH without any effect on cytochrome P450, did not have a significant effect on dronedarone pharmacokinetics.

4.2.22 Interaction study between repeated oral doses of dronedarone and repeated oral doses of simvastatin in healthy male subjects - randomized, open-labeled, 3-treatment, cross-over study (INT 4880)

PROTOCOL #	INT4880
INVESTIGATOR	Dr Regine Rouzier
STUDY SITE	Center CAP, Clinique Rech, 9, Avenue Charles Flahault, 34094 Montpellier Cedex 5
STUDY PERIOD	Nov 2001 – April 2002

Rationale for Drug-Drug Interaction Study

	Simvastatin	Dronedarone
Indication/Mechanism of Action	Lipid-altering agent/Inhibitor of HMG-CoA reductase	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic
Metabolites	β-hydroxyacid of simvastatin, 6'-hydroxy, 6'-hydroxymethyl, 6'-exomethylene derivatives (metabolites are active)	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	Hydrolysis, hepatic first-pass metabolism, CYP3A4 substrate	Primarily CYP3A substrate
CYP Inhibitory Potential	None	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Recommended – 20-40 mg/day; Max – 80 mg/day	400 mg BID

Objectives (per applicant)

Primary objectives

- To assess the effect of repeated oral doses of dronedarone on the PK profile of simvastatin (SV) and its metabolite, simvastatin acid (SVA), after repeated oral doses of 40 mg QD SV
- To assess the effect of repeated oral doses of SV on the PK profile of dronedarone and its metabolite SR35021 after repeated oral doses of 400 mg BID dronedarone

Secondary objectives

To assess the clinical and biological tolerability of dronedarone given alone, of SV give alone and of dronedarone co-administered with SV

Study Design

This was an open-label, repeated oral dose, randomized, and 3-treatment by 3-period crossover study, with washouts of seven to 13 days between periods. Subjects were randomly allocated to one of six sequences that included (in varying order), the three following treatment periods:

- Period 1: Repeated oral administrations of dronedarone 400 mg at 8:00 AM and at 08:00 PM at the end of a standardized meal for 14 days
- Period 2: Repeated oral administrations of 40 mg SV at 8:00 AM at the end of a standardized breakfast for 14 days

- Period 3: Repeated oral administrations of dronedarone 400 mg and SV 40 mg at 8:00 AM at the end of a standardized breakfast and repeated oral administrations of dronedarone 400 mg at 08:00 PM at the end of a standardized dinner for 14 days

Subject Demographics

Subject demographics are presented in Table 140.

Table 140: Summary of subject demographic data (INT 4880)

Parameter (unit)	Statistics/Category	Total (N=24)
Age (years)	N Mean (SD) Min - Max	24 27.5 (4.9) 20-35
Weight (kg)	N Mean (SD) Min - Max	24 73.59 (7.86) 58.2-88.4
Height (cm)	N Mean (SD) Min - Max	24 179.3 (5.3) 164-189
Body mass index (kg/m2)	N Mean (SD) Min - Max	24 22.86 (1.93) 19.9-26.1
Gender	Male (N,%)	24 (100%)
Race	Caucasian (N,%)	24 (100%)

Pharmacokinetic sampling times

Pharmacokinetic blood samples were drawn as follows:

- dronedarone and SR35021: before morning administration on Day 1, 3, 7, 10 and 12 and before morning administration and then 0.5, 1, 2, 3, 4, 6, 8, 10, 12 hours after dosing on Day 14, for each period of treatment.
- Simvastatin and SVA: before administration on Day 1, 3, 7, 10 and 12 and before administration and then 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing on Day 14, for each period of treatment.

Formulation

- Dronedarone 400 mg tablets, batch number CL-03936.
- Simvastatin 20 mg tablets, batch number 214509

Pharmacokinetics

The following pharmacokinetic (PK) parameters were determined for dronedarone, SR35021, SV and SVA at Day 14 of each period of treatment: C_{max}, t_{max}, C_{max}, C_{trough}, AUC_{0-12}, AUC_{0-24}, R_{met} ($AUC_{0-12\ metabolite}/AUC_{0-12\ drug}$).

Pharmacodynamics

The following pharmacodynamic (PD) parameters were determined: HR, PR-interval, QRS-interval, QT-interval, QTc-interval, T-wave amplitude.

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Dronedarone alone was the reference treatment and dronedarone + simvastatin was the test treatment.

Bioanalytical methods

The plasma concentrations of the dronedarone and its circulating metabolite SR35021 (N-debutyl) were determined by a validated liquid chromatography-mass spectrometry (LC-MS/MS) method. The assay performance was acceptable as shown in Table 141.

Table 141: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the range of 0.5 to 300 ng/ml; $R^2 > 0.996$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the range of 0.500 to 300 ng/ml; $R^2 > 0.990$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided *	Cannot be assessed

* The validation report includes chromatograms that indicate assay specificity

The plasma concentrations of SV and SVA were determined by a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 142.

Table 142: Performance of Simvastatin and Simvastatin Acid

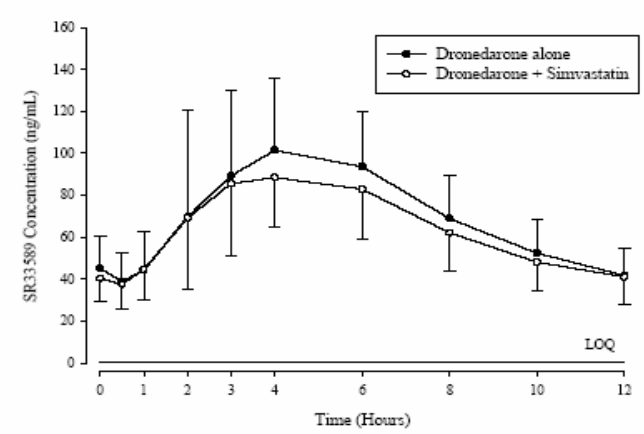
Parameter	Measure	Reviewer Comment
	Simvastatin Assay	
Linearity	The assay was linear over the range of 0.5 to 1000 ng/mL; $R^2 > 0.994$	Satisfactory
Between day Precision	CV < 6.7%	Satisfactory
Accuracy	QC samples were between 0.6 and 7.8 % of nominal concentration	Satisfactory
LLOQ	0.1 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
	Simvastatin Acid Assay	
Linearity	The assay was linear over the range of 0.5 ng/mL to 1000 ng/mL; $R^2 > 0.992$	Satisfactory
Between day Precision	CV < 7.0	Satisfactory
Accuracy	QC samples were between -4.0 and 3.0 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Results

Dronedarone Pharmacokinetics

The mean dronedarone plasma concentration-time profiles for dronedarone 400 mg BID in the absence and presence of simvastatin are depicted in Figure 78.

Figure 78: Mean (SD) dronedarone plasma concentrations observed after repeated dronedarone 400 mg BID oral administrations, alone or co-administered with SV 40 mg (n=23)



Dronedarone PK measures are summarized in Table 143. Dronedarone exposure was similar in the presence and absence of simvastatin as shown in Table 143. The associated confidence intervals were almost entirely within the no effect range (0.8 to 1.25 based on 90% confidence interval); suggesting, this change is not clinically significant.

Table 143: Mean (CV%) dronedarone and SR35021 PK parameters, their ratio estimates and 90% CI, observed on Day 14 (n=23)

PK Parameter Mean (CV%)	Dronedarone alone	Dronedarone + Simvastatin	Ratio estimates[b] and 90% CI
SR33589			
C_{max} (ng/mL)	118.7 (37)	104.2 (25)	0.89 [0.78 ; 1.02]
t_{max} (h)[a]	4	3	p=0.126
AUC_{0-12} (ng.h/mL)	846 (30)	777 (25)	0.92 [0.85 ; 1.00]
SR35021			
C_{max} (ng/mL)	87.2 (23)	79.9 (24)	0.92 [0.84 ; 1.00]
t_{max} (h)[a]	6	6	p=0.245
AUC_{0-12} (ng.h/mL)	755 (24)	678 (27)	0.89 [0.84 ; 0.95]
R_{mat} (AUC_{0-12})	0.93 (26)	0.89 (23)	0.97 [0.90 ; 1.04]

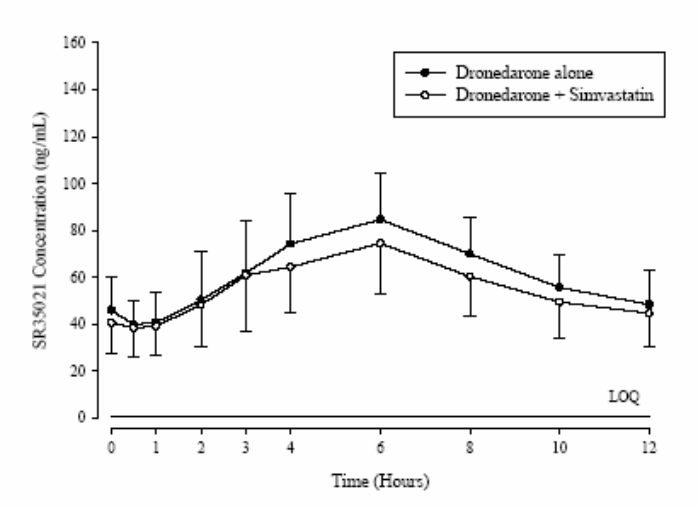
a : Median values, b : ratio dronedarone + simvastatin / dronedarone, p-value for difference between regimens

SR35021 Pharmacokinetics

The mean plasma concentration-time profiles for SR35021 following administration of dronedarone with or without simvastatin are depicted in Figure 79. SR35021 PK are summarized in Table 143.

SR35021 exposure was similar in the presence and absence of simvastatin.

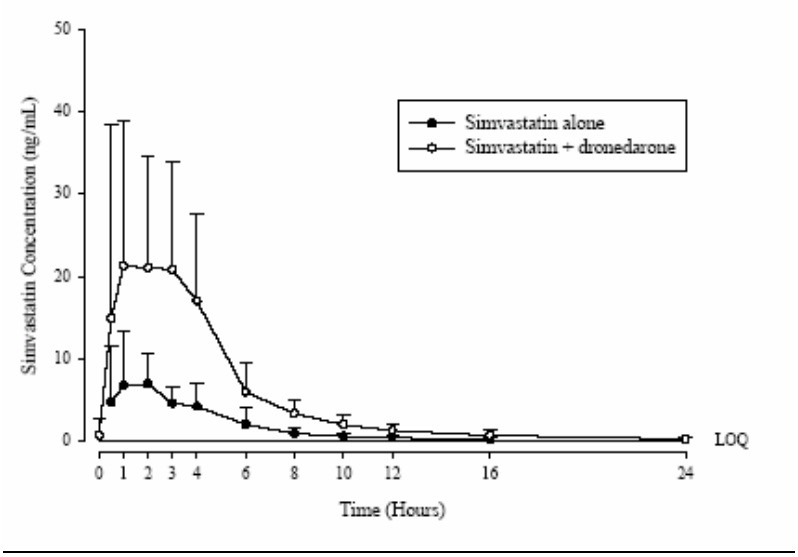
Figure 79: Mean (SD) SR35021 plasma concentrations observed after repeated dronedarone 400 mg BID oral administrations, alone or co-administered with SV 40 mg (n=23)



Simvastatin Pharmacokinetics

The mean simvastatin plasma concentration-time profiles following administration of 40 mg QD simvastatin alone or coadministered with dronedarone 400 mg BID are depicted in Figure 80.

Figure 80: Mean (SD) SV plasma concentrations observed after repeated SV 40 mg QD administrations, alone or co-administered with dronedarone 400 mg BID (n=24)



SV PK measures are summarized in Table 144.

Table 144: Mean (CV%) SV and SVA PK parameters, their ratio estimates and 90% CI, observed on Day 14 (n=24)

PK Parameter Mean (CV%)	Simvastatin alone	Simvastatin + Dronedarone	Ratio estimates[b] and 90% CI
Simvastatin			
C_{max} (ng/mL)	10.7 (55)	38.6 (42)	3.75 [3.16 ; 4.44]
t_{max} (h)[a]	2	2	p=0.767
AUC_{0-24} (ng.h/mL)	34.4[c] (44)	125.8[d] (30)	3.90 [3.18 ; 4.76]
Simvastatin acid			
C_{max} (ng/mL)	3.8 (57)	8.1 (43)	2.14 [1.76 ; 2.60]
t_{max} (h)[a]	5	4	p=0.072
AUC_{0-24} (ng.h/mL)	29.3[c] (44)	60.3[c] (48)	1.96 [1.63 ; 2.35]

a : Median values, b : ratio simvastatin + dronedarone / simvastatin, p-value for difference between regimens, c: n=23, d: n=22

As shown in Table 144, simvastatin exposure was increased in the presence of dronedarone by almost 4-fold for both Cmax and AUC. Clinically, dronedarone may increase the therapeutic and undesirable side effects of simvastatin when administered together. Simvastatin (and other HMG-CoA reductase inhibitors that are CYP3A4 substrates) may require dose adjustments and safety monitoring (discussed further in Labeling section) when given with dronedarone.

The match stick plots for SV Cmax and AUC are shown in Figure 81 and Figure 82. These plots further illustrate the increase in SV exposure when co-administered with dronedarone.

Figure 81: Individual, mean (SD) and geometric mean SV Cmax values observed after repeated oral administration of SV alone or co-administered with dronedarone (n=24)

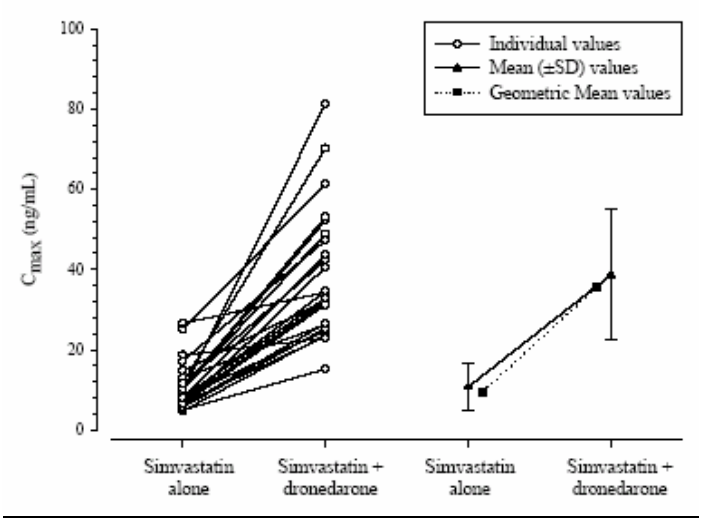
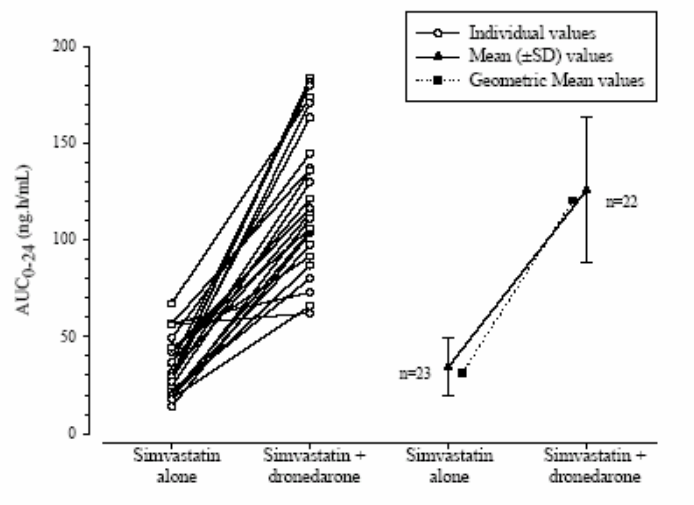


Figure 82: Individual, mean (SD) and geometric mean SV AUC0-24 values observed after repeated oral administration of SV alone or co-administered with dronedarone (n=24)

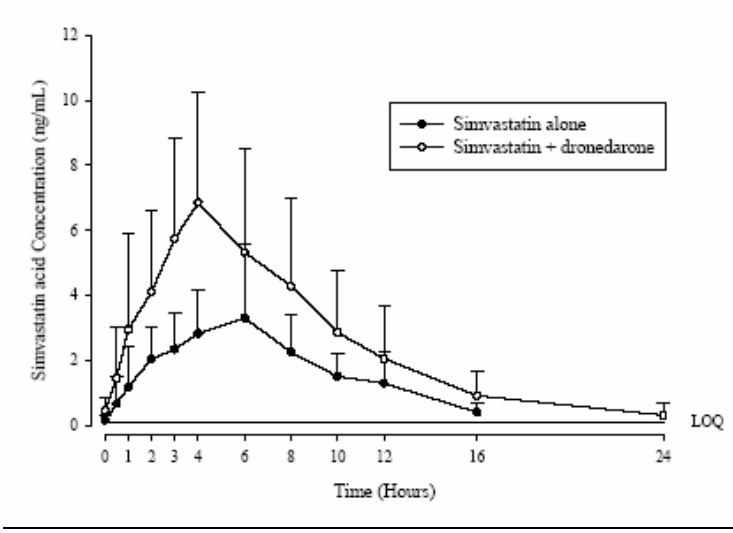


SVA Pharmacokinetics

The mean SVA plasma concentration-time profiles following administration of 40 mg QD simvastatin alone or coadministered with dronedarone 400 mg BID are depicted in Figure 83.

SVA PK are summarized in Table 144. SVA exposure increased by approximately 2-fold for both Cmax and AUC. Clinically, this increase in exposure may affect the activity, therapeutic and undesirable side effects, of simvastatin. Again, dose adjustments are needed and will be discussed in the section on Labeling.

Figure 83: Mean (SD) SVA plasma concentrations observed after repeated SV 40 mg QD oral administrations, alone or co-administered with dronedarone 400 mg BID (n=24).



The match stick plots for SV Cmax and AUC are shown in Figure 84 and Figure 85. These plots further illustrate the increase in SVA exposure when co-administered with dronedarone.

Reviewer Comment on SVA Cmax and AUC Plots After Administration of Simvastatin with and without Dronedarone

- Cmax: Overall, there is an increase in Cmax and most subjects have an increase; however, a few individual plots show a clear decrease.
- AUC: Overall, there is an increase in AUC; however, a few of the individual plots show a slight decrease.

Figure 84: Individual, mean (SD) and geometric mean SVA Cmax values observed after repeated oral administration of SV alone or co-administered with dronedarone (n=24)

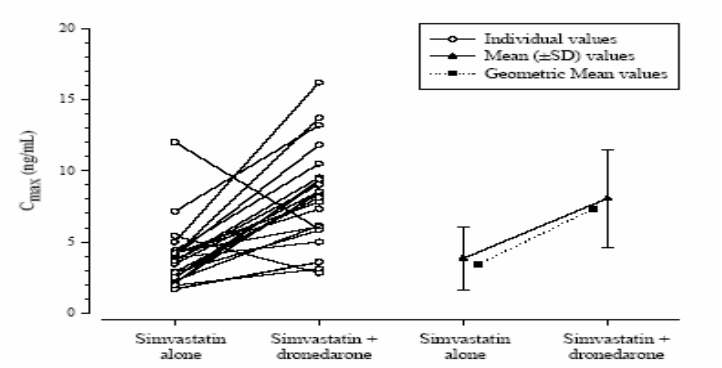
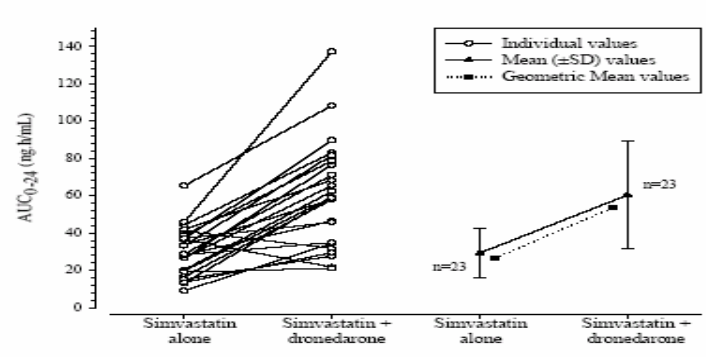


Figure 85: Individual, mean (SD) and geometric mean SVA AUC0-24 values observed after repeated oral administration of SV alone or co-administered with dronedarone (n=24)



Applicant's Safety Summary

There were no deaths or serious adverse events (SAEs) reported during this study.
Four subjects reported treatment emergent adverse events (TEAEs) on both dronedarone alone, and on dronedarone co-administered, *versus* five subjects on SV alone. One subject discontinued treatment due to an AE. The reported AEs that occurred during the co-administration of dronedarone and simvastatin included pain, headache, and rash.

Recommendations/Conclusions

- Simvastatin (40 mg) given once daily over 14 days did not affect dronedarone pharmacokinetics.
- Dronedarone (400 mg) given twice daily over 14 days inhibited simvastatin metabolism; consequently, plasma concentrations for simvastatin and its metabolite were elevated (simvastatin: 4-fold increase in Cmax and AUC, SVA: 2-fold increase in Cmax and AUC).

Labeling

Sponsor's Proposed Labeling
Dronedarone (400 mg twice daily) increased simvastatin and simvastatin acid exposure by 4-fold and 2-fold, respectively.

Reviewer's Comments on Labeling
The proposed labeling is not acceptable. Due to the large increase in simvastatin exposure when co-administered with dronedarone, simvastatin dose adjustments and monitoring should be included in the label. The following statement is recommended.

> *In patients taking simvastatin concomitantly with dronedarone, therapy should be started or adjusted to the lowest dose of simvastatin (10 mg) (See **PRECAUTIONS**). Treatment with an alternative HMG Co-A reductase inhibitor that is not a CYP3A substrate should be considered.*

4.2.23 Pharmacokinetic and Pharmacodynamic Effects of Single and Repeated Oral Doses of SR33589B and of Propranolol Given Alone or Coadministered in Healthy Male Subjects (INT 2636)

PROTOCOL #	INT2636
INVESTIGATOR	Wolfgang Tetzloff, MD
STUDY SITE	Iphar Institut fur Klinische Pharmakologie GmbH, Germany
STUDY PERIOD	January – May 1996

Background Information on Study Drugs (Propranolol and Dronedarone)

	Propranolol	Dronedarone
Indication	Beta blocker; Used in the management of hypertension, angina, cardiac arrhythmias, ventricular tachycardias, and essential tremor; used to reduce cardiovascular mortality post-myocardial infarction; used for prophylaxis of migraines	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic.
Metabolites	4-hydroxypropranolol (HOP), naphthoxylactic acid, and propranolol glucuronide	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites.
Metabolic Pathway	Extensive first pass metabolism, mostly by CYP2D6. (Some metabolism by CYP1A2 and 2C19). Cleared by the urine.	Primarily CYP3A substrate.
CYP Inhibitory Potential	N/A	Low to moderate potential to inhibit CYP3A and CYP2D6, as well as PGP.
Highest Recommended Dose/Studied Dose	Available in oral and injectable formulations. The dose can range from 30 – 640 mg/day depending on the indication. The dose can be titrated.	800 mg once daily (oral)

Objectives (per applicant)

- Primary: to assess the effect of repeated oral doses of dronedarone on propranolol pharmacokinetics at steady state
- Secondary:
    - to assess the effect of repeated oral doses of dronedarone on propranolol pharmacodynamics at steady state
    - to assess the pharmacokinetic (PK) and pharmacodynamic (PD) interaction of a single oral dose of dronedarone and a single oral dose of propranolol
    - to assess the tolerability of dronedarone and propranolol given alone or together

Study Design

This was an open-label and non placebo-controlled study. The study treatments were given according to the following schedule:

- Days 2 – 8: 80 mg propranolol QD
- Days 9 – 22: washout period
- Day 23: 800 mg dronedarone (one dose)
- Days 26 – 32: 80 mg propranolol and 800 mg dronedarone QD

Subjects received dronedarone and propranolol after a standard breakfast.

Reviewer Note on Study Design
Identifying metabolic differences in patient groups based on genetic polymorphisms should be understood and examined in this study. The reason for this is due to the variation in metabolism of CYP2D6 among people of different populations. The dose of dronedarone used in this study was 800 mg QD, which is the proposed therapeutic dose of 400 mg BID.

Subject Demographics
The study was conducted in Caucasian males. Subject demographic characteristics are shown in Table 145.

Table 145: Demographic characteristics (INT2636)

Parameter (Units)	Mean	SD	Minimum	Maximum
Age (years)	27.8	5.1	20.0	36.0
Weight (kg)	70.9	5.5	60.1	80.8
Height (cm)	176.4	5.8	164.0	185.0

Pharmacokinetic sampling times
Blood samples were collected at:

- Pretreatment: Days 2, 3, 5, 7, 23, 26, 27, 29, and 31.
- Post-treatment:
  - Days 2, 3, and 26 at 1, 2, 3, 4, 5, 6, 8, and 12 hours
  - Days 8 and 32 at 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours

Formulation

- Dronedarone: 100 mg capsules, batch number M303S
- Propranolol (Avlocardyl®): 40 mg tablet, batch number 4227

Bioanalytical methods
Dronedarone and SR35021: Plasma concentrations were measured using high performance liquid chromatography (HPLC) with ultraviolet (UV) detection. The assay method was acceptable as illustrated in Table 146.

Table 146: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 5.0 to 1000 ng/mL range	Satisfactory
Between day Precision	CV was < 9% of nominal concentration	Satisfactory
Accuracy	QC samples were between 3% to 7% of nominal concentration	Satisfactory
LLOQ	5.0 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 5.0 to 1001.9 ng/mL range	Satisfactory
Between day Precision	CV was < 11% of nominal concentration	Satisfactory
Accuracy	QC samples were between 3% to 15% of nominal concentration	Satisfactory
LLOQ	5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Propranolol: Plasma concentrations were measured using HPLC with fluorimetric detection, after liquid extraction. The assay performance was acceptable as illustrated in Table 147.

Table 147: Performance of Propranolol Assay

Parameter	Measure	Reviewer Comment
	Propranolol Assay	
Linearity	The linear range of the assay was not provided.	Cannot be assessed
Between day Precision	CV was < 6 % of nominal concentration.	Satisfactory
Accuracy	QC samples were between 3.12% to 4.91% of nominal concentration	Satisfactory
LLOQ	1.0 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Pharmacokinetics

The following pharmacokinetic (PK) parameters were measured for dronedarone and SR35021:

Days 23, 26, and 32: C_{max}, t_{max}, AUC_{0-24}

Day 32: R_{ac} (ratio accumulation factor) = AUC_{0-24} repeated dose / AUC_{0-24} single dose

Days 26, 27, 29, 31, 32, and 33: C_{bt} (trough concentration)

The following PK parameters were measured for propranolol:

- Days 2, 7, 26, and 32: C_{max}, t_{max}, AUC_{0-12}, and AUC_{last}
- Days 8 and 32: R_{ac} = AUC_{last} repeated dose / AUC_{last} single dose
- Days 3, 5, 7, 8, 9, 26, 27, 29, 31, 32, and 33: C_{bt}

Pharmacodynamics

The following pharmacodynamic (PD) parameters were determined:

- Vital signs (heart rate, systolic blood pressure, and diastolic blood pressure)
- Electrocardiogram (ECG) at rest and after submaximal exercise on Days 1 (pretreatment), 2, 8, 23, 26, and 32 at T0, T1, T3, and T8.

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The time to reach steady state was assessed.

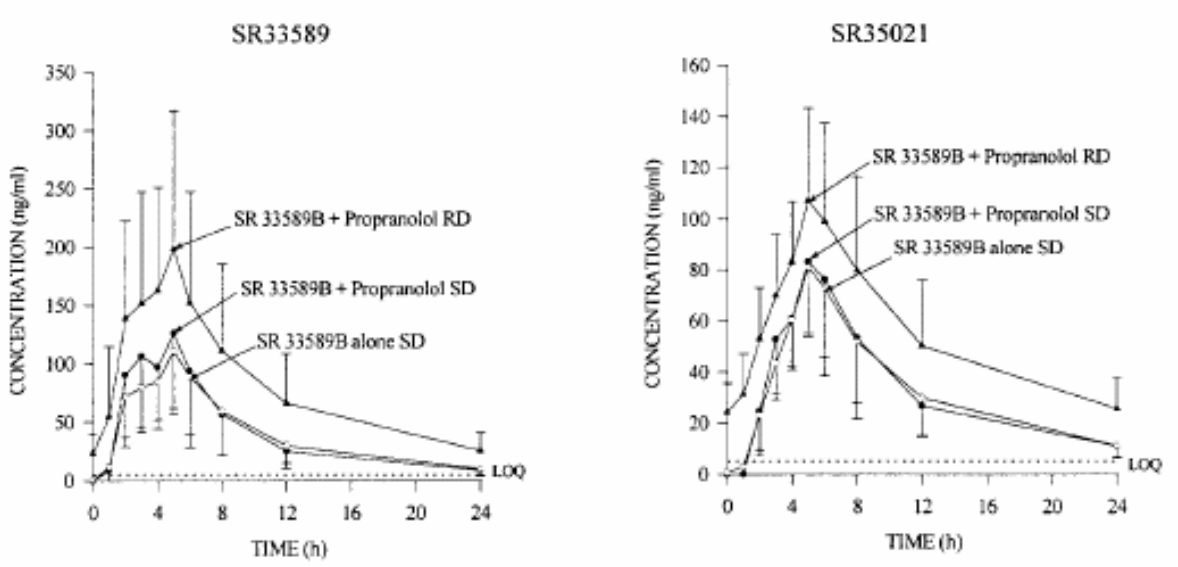
Resting vital signs were summarized by the parameter AUC_{0-8}, and analyzed for 'treatment' effects and chronological ('time') effects using repeated measures analysis of variance. Exercise vital signs were analyzed in a similar manner.

Results

Dronedarone and SR35021

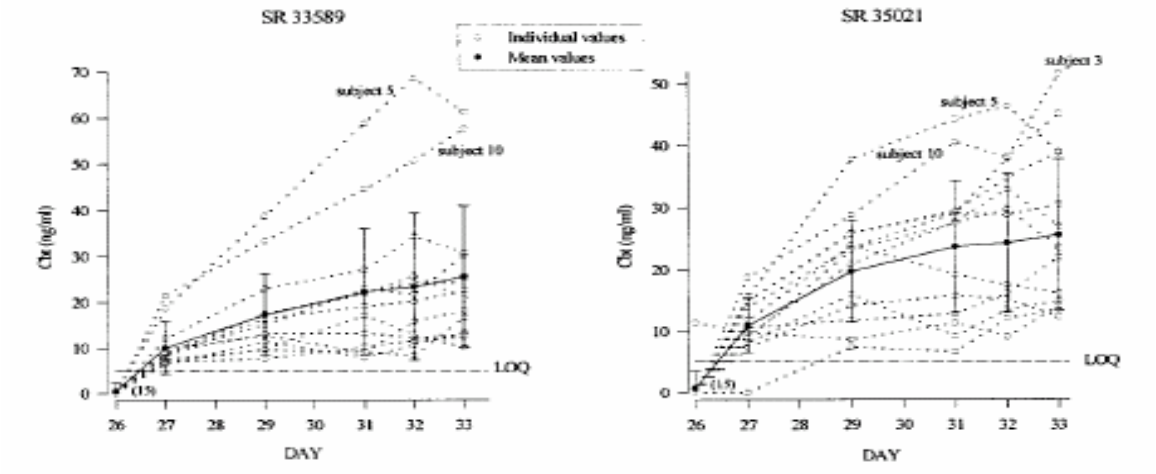
The mean plasma concentration versus time curves of dronedarone and SR35021 obtained after single and repeated administrations of dronedarone alone or with propranolol are shown in Figure 86.

Figure 86: Time course of mean values of plasma concentrations of dronedarone and SR35021 obtained after single (SD) and repeated daily (RD) doses of 800 mg dronedarone alone or combined with daily doses of 80 mg propranolol



Individual and mean C_{bt} values of dronedarone and SR35021 after coadministration of dronedarone plus propranolol for seven days are shown in Figure 87.

Figure 87: Individual and mean C_{bt} values of dronedarone and SR35021 obtained after repeated daily doses of 800 mg dronedarone alone or combined with daily doses of 80 mg of propranolol on Days 26 to 33



Based on statistical analyses, steady state was reached by the sixth daily administration of dronedarone.

Table 148, Table 149, Table 150, and Table 151 show the dronedarone and SR35021 PK measures after the administration of dronedarone alone (Day 23) or with propranolol (Days 26-32).

Table 148: Dronedarone PK Measures Following Administration of Dronedarone +/- Propranolol

SR33589 Parameters (units)		SR33589B Alone	SR33589B + Propranolol	
		Single Dose (Day 23)	Single Dose (Day 26)	Repeated Dose (Day 32)
C_{max} (ng/ml)	Mean	140.5	131.2	219.9
	SD	59.9	58.3	104.5
	CV%	43	44	48
t_{max} (h)	Mean	3.63	4.25	4.06
	SD	1.37	1.39	1.57
	CV%	38	33	39
AUC_{0-24} (ng.h/ml)	Mean	983.1	950.9	1943.0
	SD	447.1	419.3	1098.9
	CV%	45	44	57

Table 149: Confidence intervals (CI) for dronedarone PK parameters obtained after administration of dronedarone alone (Day 23) versus dronedarone plus propranolol (Day 26)

SR33589B alone (Day 23) versus SR33589B + Propranolol (Day 26)			
SR33589 Parameter	'Treatment' Effect P-Value*	90% CI	95% CI
C_{max}	0.3570	0.78, 1.08	0.75, 1.12
AUC_{0-24}	0.5865	0.86, 1.08	0.84, 1.11

* = statistically significant if $p < 0.05$

Table 150: Mean, SD, and CV% for SR35021 pharmacokinetic parameters

SR35021 Parameters (units)		SR33589B Alone	SR33589B + Propranolol	
		Single Dose (Day 23)	Single Dose (Day 26)	Repeated Dose (Day 32)
C_{max} (ng/ml)	Mean	85.9	90.2	111.3
	SD	28.8	32.8	36.1
	CV%	34	36	32
t_{max} (h)	Mean	5.13	5.13	4.94
	SD	0.72	1.20	1.44
	CV%	14	23	29
AUC_{0-24} (ng.h/ml)	Mean	768.6	759.6	1295.7
	SD	278.4	284.7	510.7
	CV%	36	37	39

Table 151: Confidence intervals for SR35021 PK parameters obtained after administration of dronedarone alone (Day 23) versus dronedarone plus propranolol (Day 26)

SR33589B alone (Day 23) versus SR33589B + Propranolol (Day 26)			
SR35021 Parameter	'Treatment' Effect P-Value*	90% CI	95% CI
C_{max}	0.5201	0.93, 1.16	0.91, 1.19
AUC_{0-24}	0.8217	0.86, 1.12	0.83, 1.16

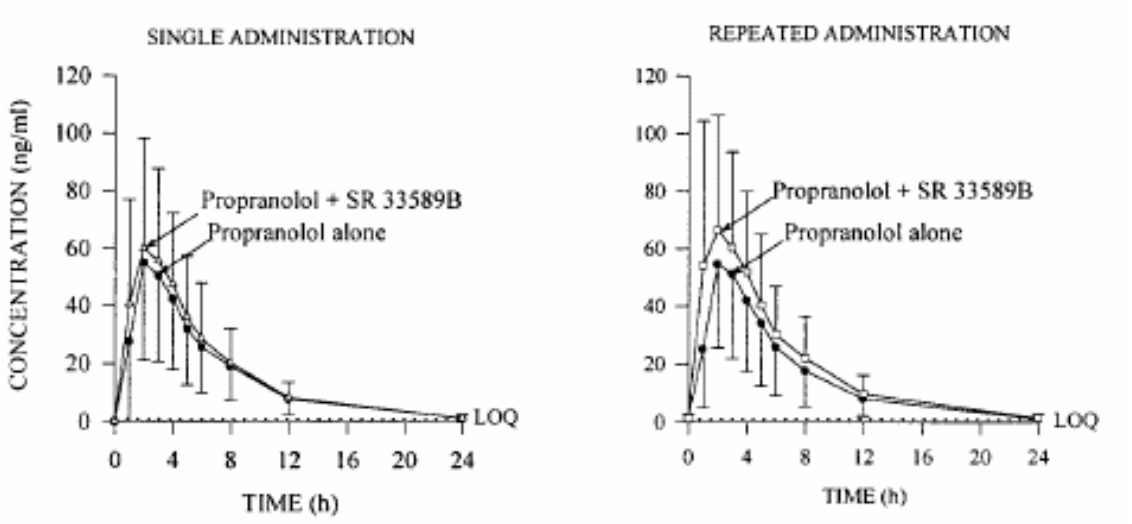
* = statistically significant if $p < 0.05$

The C_{max} and AUC of dronedarone and SR35021 are not altered upon single dose. The increase in dronedarone exposure upon repeated doses of dronedarone and propranolol is likely due to dronedarone accumulation.

Propranolol

Mean propranolol plasma concentrations versus time curves obtained after single and repeated administrations of propranolol alone or with dronedarone are shown in Figure 88.

Figure 88: Time course of mean values for plasma concentrations of propranolol obtained after single and repeated daily doses of 80 mg propranolol alone or combined with daily doses of 800 mg dronedarone



The mean, SD, and CV% values of propranolol PK measures after single and repeated daily dosing of propranolol alone (Days 2 and 8) or coadministered with dronedarone (Days 26 and 32) are shown in Table 152. P values and confidence intervals (CI) are shown in Table 153 and Table 154.

Table 152: Mean, standard deviation (SD) and coefficient of variance (CV%) for propranolol pharmacokinetics parameters

Propranolol Parameters (units)	Statistic	Propranolol Alone		SR33589B + Propranolol	
		Single Dose (Day 2)	Repeated Dose (Day 8)	Single Dose (Day 26)	Repeated Dose (Day 32)
C_{max} (ng/ml)	Mean	59.79	57.68	68.65	75.38
	SD	33.77	31.47	40.53	42.05
	CV%	56	55	59	56
t_{max} (h)	Mean	2.19	2.26	2.06	2.00
	SD	0.66	0.57	1.06	0.89
	CV%	30	25	51	45
AUC_{0-12} (ng.h/ml)	Mean	318.75	313.88	359.14	403.76
	SD	178.62	175.01	188.07	234.77
	CV%	56	56	52	58
AUC_{last} (ng.h/ml)	Mean	360.85	354.73	403.30	455.06
	SD	210.30	214.63	225.67	284.21
	CV%	58	61	56	62
R_{ac}	Mean	-	1.00	-	1.16
	SD	-	0.25	-	0.20
	CV%	-	25	-	17

Table 153: Confidence intervals (CIs) for propranolol PK parameters obtained after single dosing with propranolol alone (Day 2) versus dronedarone plus propranolol (Day 26)

Single Dosing: Propranolol Alone (Day 2) versus SR33589B + Propranolol (Day 26)			
Propranolol Parameter	**'Treatment' Effect P-Value***	**90% CI**	**95% CI**
C_{max}	0.1359	0.98, 1.39	0.95, 1.44
AUC_{0-12}	0.0692	1.02, 1.34	0.99, 1.38
AUC_{last}	0.0944	1.00, 1.33	0.97, 1.37

* = statistically significant if p <0.05

Table 153 shows that dronedarone did not significantly change propranolol PK (CIs included), however the CI's were outside of the no-effect interval.

Table 154: Confidence intervals for propranolol PK parameters obtained after repeated dosing with propranolol alone (Day 8) versus dronedarone plus propranolol (Day 32)

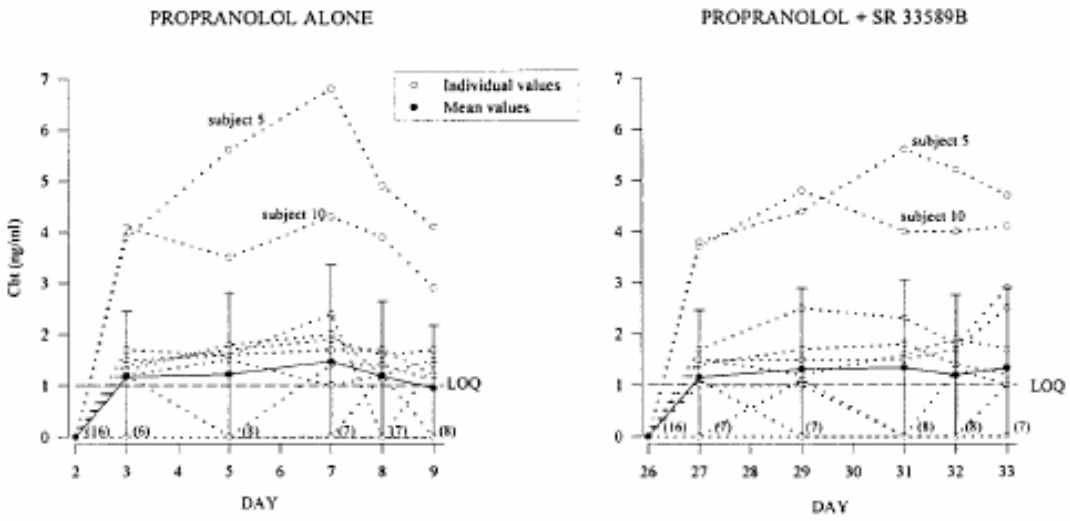
Repeated Dosing: Propranolol Alone (Day 8) versus SR33589B + Propranolol (Day 32)			
Propranolol Parameter	**'Treatment' Effect P-Value***	**90% CI**	**95% CI**
C_{max}	0.0061	1.16, 1.69	1.12, 1.76
AUC_{0-12}	0.0050	1.16, 1.62	1.12, 1.68
AUC_{last}	0.0053	1.16, 1.62	1.11, 1.68
R_{ac}	0.0234	1.05, 1.33	1.03, 1.37

* = statistically significant if p <0.05

Table 154 shows a significant change in propranolol PK levels after repeated dosing of dronedarone and propranolol.

Individual and mean values for the C_{bt} of propranolol on Days 3 to 9 after the administration of propranolol alone on Days 2 to 9, and on Days 27 to 33 after administration of dronedarone plus propranolol on Days 26 to 32 are shown in Figure 89.

Figure 89: Individual and mean C_{bt} values of propranolol obtained after repeated daily doses of 80 mg propranolol alone or combined with daily doses of 800 mg dronedarone



The combined analysis of C_{bt} values for Days 3 to 9 and those observed for days 27 to 33 showed no statistically significant 'day' effect, 'treatment' effect, or 'day-by-treatment' interactions.

Propranolol steady state was reached 24 hours after the first dose, whether propranolol was administered alone or coadministered with dronedarone.

Pharmacodynamics

1. Resting Conditions

AUC values for heart rate (HR) and ECG parameters are shown in Table 155.

Table 155: Summary of AUC_{0-8} values for ECG parameters at rest after repeated dosing of propranolol with or without dronedarone

Parameter (units)	Day 8 vs. Day 1 Mean Value (%)		Day 32 vs. Day 1 Mean Value (%)		Day 32 vs. Day 8	
					Mean Value	P-Value*
HR (bpm.h)	-45.5	(-8.9)	-32.7	(-6.4)	12.8	0.184
PQ (ms.h)	42.4	(3.9)	139.3	(11.9)	96.9	<0.001
QRS (ms.h)	-0.1	(0.0)	6.3	(0.7)	6.4	0.394
QT (ms.h)	111.3	(3.6)	137.1	(4.4)	25.9	0.467
QTc (ms.h)	-59.7	(-1.9)	15.6	(0.5)	75.3	<0.001
T-wave (mm.h)	1275.6	(28.3)	153.5	(7.9)	-1122.1	0.001

Day 1 = Baseline (pretreatment), Day 8 = last day of repeated dosing (steady state) with propranolol, Day 32 = last day of repeated dosing of SR33589B plus propranolol
% = percent change from Day 1
* = statistically significant if $p<0.05$

Resting ECG heart rate decreased compared to baseline after repeated once daily dosing of propranolol alone (-9%), and after coadministration of dronedarone and propranolol (-6%). The changes from baseline in resting ECG parameters after single oral administration of propranolol or single oral coadministration of dronedarone and propranolol were similar to those seen after repeated dosing.

Resting HR, systolic blood pressure (BP), and diastolic BP (Table 156) decreased after repeated oral administration of propranolol alone and after coadministration with dronedarone.

Table 156: Summary of AUC_{0-8} values for vital signs at rest after repeated dosing of propranolol with or without dronedarone

Parameter (Units)	Day 8 vs. Day 1 Mean Value (%)		Day 32 vs. Day 1 Mean Value (%)		Day 32 vs. Day 8	
					Mean Value	P-Value*
HR (bpm.h)	-42.7	(-8.1)	-22.2	(-4.3)	20.4	0.038
SBP (mmHg.h)	-48.3	(-5.0)	-71.8	(-7.6)	-23.6	0.055
DBP (mmHg.h)	-52.3	(-9.9)	-61.9	(-11.9)	-9.7	0.324

Day 1 = Baseline (pretreatment), Day 8 = last day of repeated dosing (steady state) with propranolol, Day 32 = last day of repeated dosing of SR33589B plus propranolol
% = percent change from Day 1
* = statistically significant if $p<0.05$

2. Exercise Conditions

The changes in PD measures under exercise conditions are shown in Table 157.

Table 157: Summary of AUC_{0-8} values for vital signs during submaximal exercise after repeated dosing of propranolol with or without dronedarone

Parameter (Units)	Day 8 vs. Day 1 Mean (%)		Day 32 vs. Day 1 Mean (%)		Day 32 vs. Day 8	
					Mean	P-Value
HR (bpm.h)	-176.0	(-16.1)	-226.8	(-20.7)	-50.8	<0.001
SBP (mmHg.h)	-170.3	(-11.7)	-266.8	(-18.2)	-96.6	<0.001
DBP (mmHg.h	-11.5	(-1.5)	-46.8	(-6.9)	-35.3	0.005

Day 1 = pretreatment, Day 8 = last day of repeated dosing (steady state) with propranolol,
Day 32 = last day of repeated dosing of SR33589B plus propranolol
% = percent change from Day 1
* = statistically significant if p<0.05

During submaximal exercise, there was a decrease in HR, systolic BP, and diastolic BP from baseline after repeated oral administration of propranolol alone and after coadministration with dronedarone.

The decreases in HR, systolic BP, and diastolic BP were all statistically significantly greater after the drugs were coadministered compared to propranolol alone.

According to the applicant, none of the changes in the ECG parameters or vital signs at rest or during submaximal exercise were considered to be clinically relevant. The applicant's conclusion appears reasonable as only small decreases in HR, systolic BP, and diastolic BP were seen. Also, the dose of propranolol can be titrated if needed to counter undesirable effects.

Applicant's Safety Summary

Five subjects reported nine adverse events (AEs) during the study. None of the AEs were considered by the investigator to be serious; three were of moderate intensity, and the other six were of mild intensity. Of the three AEs of moderate intensity, one was in the propranolol alone arm and the other two were in the propranolol and dronedarone arm. None of the AEs required corrective therapy, however, three subjects discontinued. No deaths were reported.

Recommendations/Conclusions

1. Repeated dose administration of dronedarone and propranolol significantly increased plasma concentrations of propranolol at steady state (16% to 33%).
2. Single dose administration of 800 mg dronedarone and 80 mg propranolol did not modify the PK profile of propranolol, dronedarone, or SR35021, relative to administration of dronedarone or propranolol alone.
3. The PD effects (HR, systolic BP, diastolic BP, and ECG parameters) of propranolol or dronedarone given alone were potentiated when the two compounds were coadministered.

Reviewer Comment

At steady state, mean plasma levels of propranolol coadministered with dronedarone were higher than those obtained after repeated administration of propranolol alone. This may be explained by the inhibition of CYP2D6 mediated metabolism of propranolol since it has been demonstrated that dronedarone can potentially inhibit CYP3A4 and 2D6. However, these increases (plasma concentrations of 16% to 33%) do not appear clinically relevant.

Applicant's Proposed Labeling
Due to the pharmacokinetic interaction and possible pharmacodynamic interaction, beta blockers should be used with caution concomitantly with dronedarone.

Reviewer Note on Label
The sponsor adequately states a caution against using propranolol while taking dronedarone. The labeling is acceptable. Propranolol doses can be titrated to achieve the desired effect.

4.2.24 Interaction study between repeated oral doses of dronedarone and repeated ascending oral doses of verapamil in healthy young male subjects - Three-group, randomized, open-labeled, three-treatment, crossover study (INT 4882)

PROTOCOL #	INT4882
INVESTIGATOR	Wolfgang Tetzloff, MD
STUDY SITE	MDS Pharma Services, Arnikastrasse 4; 85635 Hohenkirchen-Siegerstsbrunn; Germany
STUDY PERIOD	May – September 2002

Background Information on Study Drugs (Verapamil and Dronedarone)

	Calan (Verapamil)	Dronedarone (SR33589)
Indication	Calcium Channel Blocker; For the treatment of angina, arrhythmias, and essential hypertension.	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic.
Metabolites	Twelve metabolites have been identified in plasma, mostly in trace amounts. The major metabolite is norverapamil.	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites.
Metabolic Pathway	First-pass effect; Predominantly biotransformed by CYP3A4, however CYP1A2 and members of the CYP2C family are also involved in the metabolism. 70% is excreted in the urine as metabolites.	Primarily CYP3A substrate.
CYP Inhibitory Potential	Predominantly CYP3A4.	Low to moderate potential to inhibit CYP3A and CYP2D6, as well as PGP.
Highest Recommended Dose/Studied Dose	Available in sustained release (SR) and immediate release (IR) formulations. The dose can range from 80 – 480 mg/day depending on the indication and can be titrated.	400 mg BID.

Objectives (per applicant)

- Primary:
  - to assess the effect of repeated oral doses of 400 mg BID dronedarone on the pharmacokinetic (PK) profile of verapamil and its metabolite norverapamil after repeated oral doses of verapamil sustained release (SR) formulation for 14 days
  - to assess the effect of repeated oral doses of verapamil SR formulation on the PK profile of dronedarone and its metabolite SR35021 after repeated oral doses of 400 mg BID dronedarone for 14 days
  - to assess the pharmacodynamics of dronedarone and ascending doses of verapamil given alone and coadministered (magnitude of the prolongation of PR-interval and of QTc) at the end of the repeated doses

  Secondary: to assess the clinical and biological tolerability of dronedarone given alone, of verapamil SR formulation given alone at different dose levels, and of dronedarone coadministered with verapamil SR formulation

Study Design
This was an open-label, non placebo-controlled, 3-group, randomized, 3-treatment (dronedarone alone, verapamil alone, and coadministration), and 3-period crossover design with 7- to 14-day washout between periods. The treatment period was 14 days.

Reviewer Note on Study Design
The study design was consistent with the FDA recommended Drug-Drug Interaction Guidance. The doses used in the study were the proposed therapeutic doses. The formulation of verapamil, Isoptin SR was used because it is more common, and the Covera-HS formulation was not appropriate for an interaction study because of its PK profile.

The study was stopped after Group 1 due to a documented PK interaction. It was decided not to continue onto Groups 2 and 3. This is a conservative approach, and is acceptable.

Subject Demographics
The study was conducted in healthy, young, male subjects. Subject demographic characteristics are shown in Table 158.

Table 158: Summary of subject characteristics (INT4882)

Treatment Sequence/ Parameter (Unit)	123 (N=4)	132 (N=4)	213 (N=3)	231 (N=4)	312 (N=3)	321 (N=3)	Total (N=21)
Age (yrs)							
N	4	4	3	4	3	3	21
Mean (SD)	30.3 (3.1)	30.8 (9.6)	31.0 (4.4)	29.0 (5.6)	33.0 (5.3)	30.3 (5.0)	30.6 (5.3)
Min – max	26 - 33	22 - 40	28 - 36	24 - 36	27 - 37	25 - 35	22 - 40
Weight (kg)							
N	4	4	3	4	3	3	21
Mean (SD)	80.43 (5.22)	71.63 (2.57)	79.57 (6.87)	76.07 (10.61)	75.40 (6.16)	73.90 (2.77)	76.15 (6.45)
Min – max	73.1 - 85.3	69.0 - 74.3	75.4 - 87.5	63.8 - 86.8	70.2 - 82.2	72.2 - 77.1	63.8 - 87.5
Height (cm)							
N	4	4	3	4	3	3	21
Mean (SD)	177.3 (3.6)	179.8 (1.7)	180.7 (4.6)	183.5 (3.3)	176.0 (2.6)	179.3 (4.9)	179.5 (3.9)
Min – max	172 - 180	178 - 182	178 - 186	179 - 187	174 - 179	176 - 185	172 - 187
BMI (kg/m²)							
N	4	4	3	4	3	3	21
Mean (SD)	25.60 (0.78)	22.18 (0.39)	24.33 (0.84)	22.55 (2.78)	24.43 (2.66)	22.97 (0.45)	23.64 (1.93)
Min - max	24.7 - 26.6	21.8 - 22.6	23.8 - 25.3	18.8 - 24.8	21.9 - 27.2	22.5 - 23.4	18.8 - 27.2
Gender (n, %)							
Male	4 (100)	4 (100)	3 (100)	4 (100)	3 (100)	3 (100)	21 (100)
Race (n, %)							
Caucasian	4 (100)	4 (100)	3 (100)	4 (100)	3 (100)	3 (100)	21 (100)

Program: /SR33589B/INT4882/CSR/bs/pgm rpt/i4demog.sas (07JAN05 - 16:44)
The treatment in any sequence is defined as follows: 1=dronedarone; 2=verapamil; and 3=coadministration

Formulation
- Dronedarone: 400 mg tablet, batch number CL-04530
- Verapamil: 120 mg tablet (Isoptin SR™), batch number 39911

Pharmacokinetic sampling times
Plasma concentrations of dronedarone, SR35021, verapamil, and norverapamil were determined at scheduled times.
- Dronedarone and SR35021 samples were collected:
  - On Days 1, 2, 4, 8, 12, and 14: before morning administration
  - On Day 14: at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after dosing

- Verapamil and norverapamil samples were collected:
  - On Days 1, 2, 4, 8, 12, and 14: before morning administration
  - On Day 14: at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after dosing

Pharmacokinetics
The following pharmacokinetic (PK) parameters were measured for dronedarone and SR35021: C_{trough}, C_{max}, t_{max}, AUC_{0-12}, and R_{met}.
The following PK parameters were measured for verapamil and norverapamil: C_{trough}, C_{max}, t_{max}, AUC_{0-24}, and R_{met}.

Pharmacodynamics
The following pharmacodynamic (PD) parameters were determined from 12-lead electrocardiogram (ECG) parameters (manual reading):
- primary criteria: PR- and QTcB/F calculation
- secondary criteria: QRS- and QT-intervals, and HR

Bioanalytical methods
Dronedarone and SR35021: Plasma concentrations were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method (DOH0239). The assay method was acceptable as illustrated in Table 159.

Table 159: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.50 to 300 ng/mL range; $R^2 > 0.996$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers.	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.50 to 300 ng/mL range; $R^2 > 0.991$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers.	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Verapamil and Norverapamil: Plasma concentrations were determined by a validated high-performance liquid chromatography (HPLC) method with ultraviolet (UV) detection. The assay performance was acceptable as illustrated in Table 160.

Table 160: Performance of Verapamil and Norverapamil Assays

Parameter	Measure	Reviewer Comment
	Verapamil Assay	
Linearity	The assay was linear over the 10.0 to 500 ng/mL range; $R^2 > 0.994$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were within 15% of nominal concentrations.	Satisfactory
LLOQ	10.0 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	Norverapamil Assay	
Linearity	The assay was linear over the 10.0 to 500 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers.	Satisfactory
LLOQ	10.0 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The time to reach steady state was assessed.

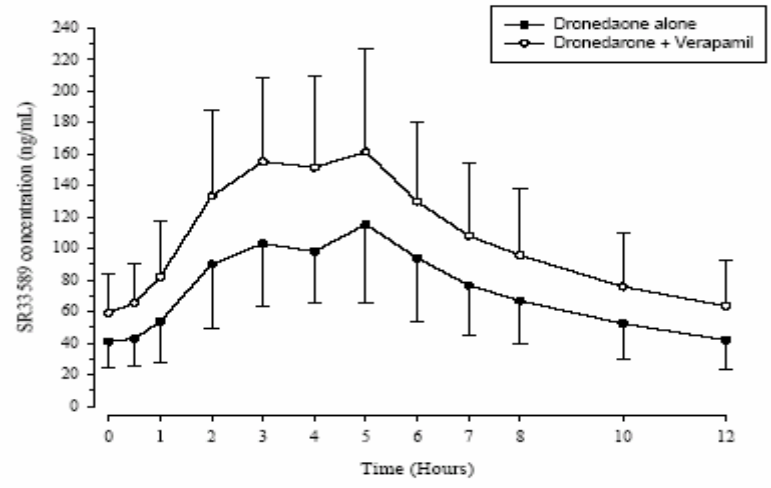
Pharmacodynamic measures were also analyzed using standard statistical approaches. The PD analysis consisted of a comparison of effects on PR-interval prolongation and cardiac repolarization (QTcB, QTcF) after repeated administration of each treatment (verapamil or dronedarone) alone and of the coadministration (verapamil + dronedarone) for PR-interval, QTcB and QTcF.

Results

Dronedarone and SR35021

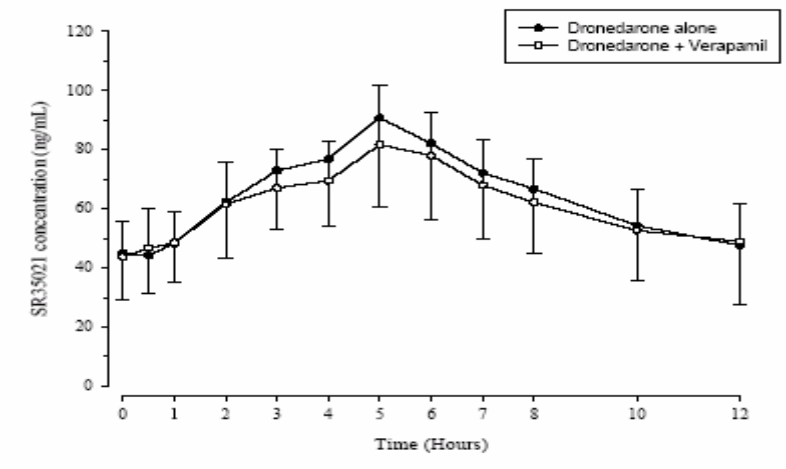
The mean plasma concentration time profiles of dronedarone are shown in Figure 90.

Figure 90: Mean (SD) dronedarone plasma concentrations after repeated oral administration of dronedarone alone (400 mg BID) or coadministration with verapamil (240 mg QD) – Day 14



The mean plasma concentration time profiles of SR35021 are shown in Figure 91.

Figure 91: Mean SR35021 plasma concentrations after repeated oral administration of dronedarone alone (400 mg BID) or coadministration with verapamil (240 mg QD) – Day 14



Mean trough concentrations of dronedarone and SR35021 are graphically summarized in Figure 92 and Figure 93.

Figure 92: Mean dronedarone C_{trough} observed after repeated oral administration of dronedarone alone or coadministration with verapamil

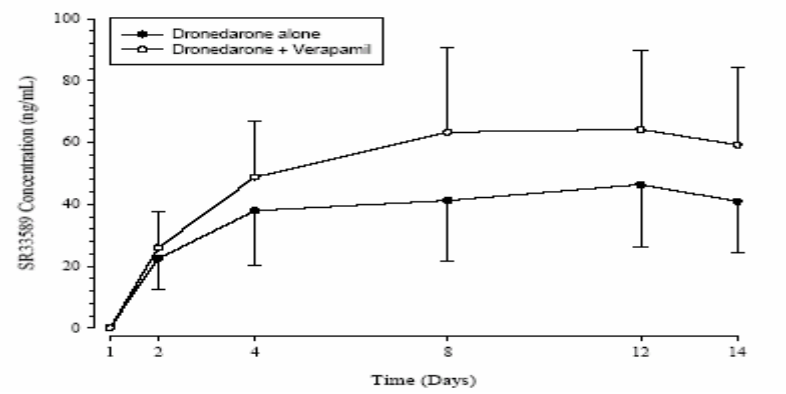
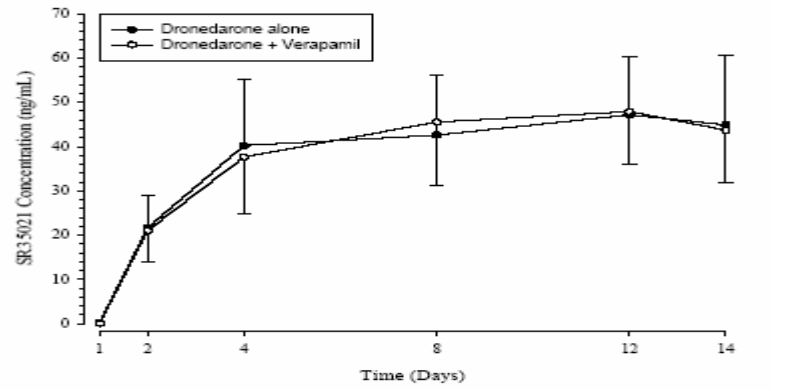


Figure 93: Mean SR35021 C_{trough} observed after repeated oral administration of dronedarone alone or coadministration



Average steady state for dronedarone and SR35021 were reached within four days for dronedarone alone or coadministration with verapamil.

Table 161: Mean (coefficient of variation [CV%]) pharmacokinetic parameters of dronedarone and SR35021 and their ratio estimates and 90 % CI obtained after repeated doses of dronedarone or coadministration with verapamil

PK Parameters	Dronedarone Alone[a]	Dronedarone + Verapamil[b]	Ratio Estimates[c] and 90% CI
Dronedarone			
C_{max} (ng/mL)	135 (32)	188 (30)	1.42 [1.31 - 1.53]
t_{max} (h)[d]	3.00 [2.00 - 5.00]	3.00 [2.00 - 5.00]	p=0.78
AUC_{0-12} (ng.h/mL)	895 (34)	1310 (35)	1.48 [1.38 - 1.58]
SR35021			
C_{max} (ng/mL)	98.0 (33)	88.2 (19)	0.93 [0.83 - 1.04]
t_{max} (h)[d]	5.00 [2.00 - 7.00]	5.00 [2.00 - 7.00]	p=0.22
AUC_{0-12} (ng.h/mL)	781 (27)	742 (19)	0.98 [0.92 - 1.04]

[a] n=19
[b] n=18
[c] Ratio dronedarone + verapamil/dronedarone, p-value for difference between treatments
[d] Median values [Min – Max]

Table 161 shows the dronedarone and SR35021 PK parameters, their ratio estimates, and 90% confidence intervals. The statistical analysis performed on the PK parameters showed that:

- C_{max} and AUC_{0-12} of dronedarone obtained after coadministration were increased by 1.42-fold and 1.48-fold, respectively compared with those observed after dronedarone alone: the 90% CIs were outside the equivalence interval of 0.80 to 1.25
- C_{max} and AUC_{0-12} of SR35021 obtained after coadministration were similar compared with those observed after dronedarone alone: the 90% CIs were within the equivalence interval of 0.80 to 1.25
- Median t_{max} of dronedarone and SR35021 were similar after dronedarone alone or coadministration

These results show that the steady state of dronedarone was increased in the presence of verapamil, potentially leading to increased exposure of the drug as verapamil inhibited dronedarone metabolism.

Verapamil and Norverapamil

Figure 94and Figure 95 show that the mean plasma concentrations of verapamil and norverapamil were increased after concomitant repeated oral administration of dronedarone compared to verapamil alone.

Steady State

The average verapamil steady state was reached at about Day 3 when verapamil was administered alone, and delayed to Day 4 when coadministered with dronedarone. Average norverapamil steady state was reached at about Day 2 when verapamil was administered alone and at about Day 3 when coadministered with dronedarone.

Figure 94: Mean verapamil plasma concentrations after repeated oral administration of verapamil alone or coadministration – Day 14

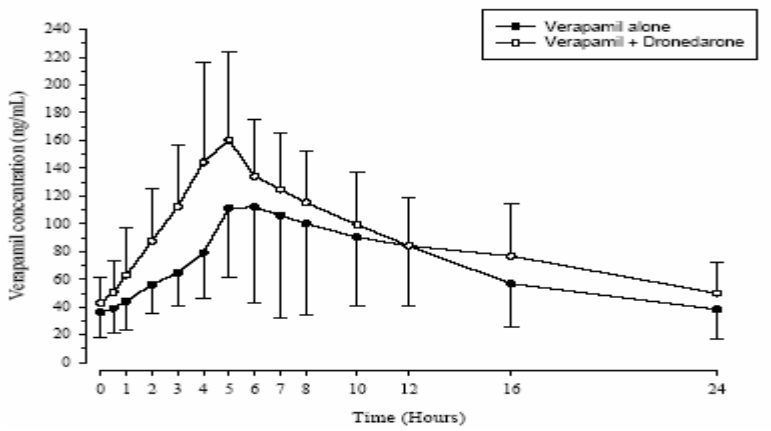


Figure 95: Mean norverapamil plasma concentrations after repeated oral administration of verapamil alone or coadministration – Day 14

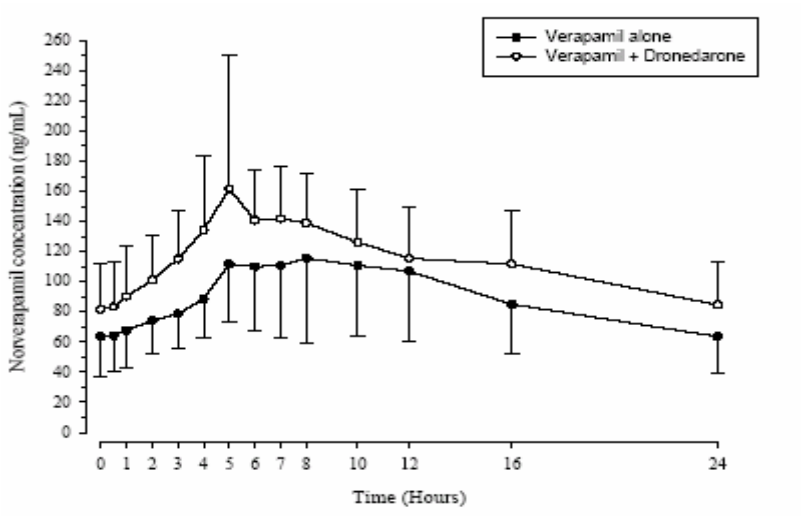


Table 162 shows the PK parameters for verapamil and norverapamil.

Table 162: Mean (CV%) pharmacokinetic parameters of verapamil and norverapamil and their ratio estimates and 90 % CI obtained after repeated administration of verapamil alone or coadministration with dronedarone

PK Parameters	Verapamil Alone[a]	Verapamil + Dronedarone[b]	Ratio Estimates[c] and 90% CI
Verapamil			
C_{max} (ng/mL)	132 (59)	175 (42)	1.40 [1.13 - 1.73]
t_{max} (h)[d]	5.50 [3.02 - 12.0]	5.00 [2.00 - 8.00]	p=0.02
AUC_{0-24} (ng.h/mL)	1670 (46)	2130 (34)	1.30 [1.14 - 1.48]
Norverapamil			
C_{max} (ng/mL)	129 (45)	169 (51)	1.31 [1.08 - 1.59]
t_{max} (h)[d]	6.00 [5.00 - 12.00]	6.00 [5.00 - 10.0]	p=0.83
AUC_{0-24} (ng.h/mL)	2150 (37)	2740 (27)	1.29 [1.15 - 1.44]

[a] n=18
[b] n=17
[c] Ratio verapamil + dronedarone /verapamil, p-value for difference between treatments
[d] Median values [Min – Max]

Statistical analysis reveals that:

- C_{max} and AUC_{0-24} of verapamil after coadministration were increased by 1.4-fold and 1.3-fold respectively, compared with the values observed after verapamil alone; the 90% CI were outside the equivalence interval of 0.80 to 1.25
- C_{max} and AUC_{0-24} of norverapamil after coadministration were increased by 1.31 and 1.29-fold respectively, compared with the values observed after verapamil alone; the 90% CI was outside the equivalence interval of 0.80 to 1.25
- Median value of verapamil time to reach peak plasma concentration (t_{max}) was significantly different after repeated dronedarone alone or after coadministration. For norverapamil, there was no significant difference.

Overall, the increase in verapamil exposure suggests that dronedarone inhibits the metabolism of verapamil.

Pharmacodynamics

The changes in ECG measures from baseline are shown in Table 163.

Table 163: Twelve-lead ECG changes from baseline (Day 1 T-0.5 h) between T0.5-T11.5 on Day 14- pair-wise comparisons for coadministration versus verapamil alone, and versus dronedarone alone, respectively

Change from Baseline in ECG Parameters	Time	Treatment Contrast (Coadministration vs Reference)†	N	Mean[a] Difference [Coadmin. – Reference] (msec)	Coadmin. mean[b] change (msec)	Reference	Reference[c] Mean[b] Change (msec)	95% CI	
								Lower	Upper
Change QTcB (msec)	-	Coadministration vs Drone	18	11.8	36.2	Dronedarone	24.4	4.3	19.3
		Coadministration vs Vera	18	21.5	36.2	Verapamil	14.7	13.9	29.0
Change QTcF (msec)	-	Coadministration vs Drone	18	13.1	33.2	Dronedarone	20.1	6.5	19.8
		Coadministration vs Vera	18	24.4	33.2	Verapamil	8.8	17.7	31.1
Change PR (msec)*	0.5	Coadministration vs Drone	18	4.9	11.5	Dronedarone	6.6	-3.2	13.1
		Coadministration vs Vera	18	10.5	11.5	Verapamil	1.1	2.3	18.6
	1.0	Coadministration vs Drone	18	1.4	12.3	Dronedarone	10.9	-4.1	6.8
		Coadministration vs Vera	18	14.4	12.3	Verapamil	-2.1	8.8	20.0
	2.0	Coadministration vs Drone	18	6.1	13.1	Dronedarone	7.0	-2.0	14.2
		Coadministration vs Vera	18	13.8	13.1	Verapamil	-0.7	5.7	21.8
	3.0	Coadministration vs Drone	18	7.2	16.4	Dronedarone	9.2	-0.7	15.2
		Coadministration vs Vera	18	18.6	16.4	Verapamil	-2.1	10.6	26.5
	4.0	Coadministration vs Drone	18	11.3	23.6	Dronedarone	12.3	2.1	20.4
		Coadministration vs Vera	18	16.6	23.6	Verapamil	7.0	7.5	25.7
	6.0	Coadministration vs Drone	18	18.8	29.5	Dronedarone	10.7	8.5	29.0
		Coadministration vs Vera	18	11.3	29.5	Verapamil	18.2	1.1	21.5
	8.0	Coadministration vs Drone	18	14.3	18.8	Dronedarone	4.5	7.4	21.2
		Coadministration vs Vera	18	5.9	18.8	Verapamil	12.9	-1.2	12.9
	10.0	Coadministration vs Drone	18	8.5	14.9	Dronedarone	6.4	1.8	15.3
		Coadministration vs Vera	18	4.9	14.9	Verapamil	9.9	-1.8	11.7
	11.5	Coadministration vs Drone	18	7.3	9.9	Dronedarone	2.6	-1.6	16.1
		Coadministration vs Vera	18	2.0	9.9	Verapamil	7.9	-6.8	10.9

Program: /SR33589B/INT4882/CSR/bs/pgm rpt/a6ecgt12 covfin.sas out = a6ecgt12 covfin.html (14JAN05 - 07:28)

† Coadministration is dronedarone +verapamil; reference is either verapamil or dronedarone

[a] Mean difference = LSM (coadministration) minus LSM (reference)

[b] Mean is LSM (Least Square Means)

[c] Sample size for reference group: n=17 for verapamil alone and n=16 for dronedarone alone for all endpoints.

"-" Overall time; no significant treatment*time interaction

* Significant treatment*time interaction

The analysis of changes from baseline over [T0.5h-11.5h] on Day 14 showed:

- statistically significant treatment-by-time interaction only for PR and statistically significant treatment and time differences for QT effects.
- PR prolongation with a significant change from 0.5 to 6 hours for verapamil vs. verapamil and dronedarone, and for dronedarone vs. coadministration with a significant change from 4 hours to 10 hours.

- QTcB and QTcF also showed statistically significant treatment and time effects resulting in QTcB and QTcF prolongation.

Applicant's Safety Summary
Only one subject experienced TEAEs (treatment emergent adverse events) during coadministration. The incidence of TEAEs was higher in the dronedarone group than in the verapamil group. There were no deaths or SAEs (serious adverse events) in any groups and only one adverse event (maculopapular rash) led to study drug discontinuation during treatment with verapamil alone.

Gastrointestinal disorders were the most frequent TEAEs reported with dronedarone alone. Only one subject had a TEAE (hematuria) during the coadministration period. No deaths or SAEs were reported.

Recommendations/Conclusions
1. Verapamil increased the steady state dronedarone C_{max} and AUC_{0-12} by 1.4-1.5-fold and did not modify steady state exposure of SR35021. Dronedarone and SR35021 t_{max} were not affected by verapamil coadministration compared with dronedarone alone.
2. Dronedarone increased steady state verapamil C_{max} and AUC_{0-24} by 1.4-1.3-fold and steady state norverapamil C_{max} and AUC_{0-24} by 1.3-fold. Verapamil t_{max} was shortened by coadministration of dronedarone and verapamil compared with verapamil alone whereas norverapamil t_{max} was not affected.
3. Coadministration showed statistically significant increases in PR, QTcB, and QTcF compared with dronedarone alone or verapamil alone.

Applicant's Proposed Labeling
Due to the pharmacokinetic interaction and possible pharmacodynamic interaction, calcium antagonists with depressant effects on sinus and atrio-ventricular node such as verapamil and diltiazem should be used concomitantly with dronedarone with caution.

Reviewer Note on Label
The applicant's proposed labeling is acceptable. The increase in dronedarone exposure caused by verapamil does not appear clinically significant. Verapamil dosage can be titrated, therefore, the verapamil dose may be adjusted, if needed, during coadministration with dronedarone.

4.2.25 An interaction study to investigate a potential effect of repeated oral ingestion of grapefruit juice on the pharmacokinetic profile of single and repeated oral doses of dronedarone in young healthy male subjects (INT4886)

PROTOCOL #	INT4886
INVESTIGATOR	Dr. Thierry Duvauchelle
STUDY SITE	ASTER, 3-5, rue Eugene Millon, 75015 PARIS, France
STUDY PERIOD	March – September 2002

Background Information on Study Drugs (Grapefruit Juice and Dronedarone)

	Grapefruit Juice	Dronedarone (SR33589)
Indication	Used as a beverage.	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic.
Metabolites	N/A	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites.
Metabolic Pathway	N/A	Primarily CYP3A substrate.
CYP Inhibitory Potential	Inhibitor of CYP3A4.	Low to moderate potential to inhibit CYP3A and CYP2D6, as well as PGP.
Highest Recommended Dose/Studied Dose	One regular strength glass daily with breakfast.	400 mg BID.

Objectives (per applicant)

- Primary: to assess the effect of repeated oral ingestion of grapefruit juice (GFJ) on the single dose pharmacokinetics (PK) of dronedarone and, its metabolite, SR35021 in fasted and fed conditions; to assess the effect of repeated oral ingestion of GFJ on repeated dose PK of dronedarone and, its metabolite, SR35021 in fed conditions.
- Secondary: to assess the clinical and biological tolerability of dronedarone given alone versus dronedarone co-administered with GFJ.

Study Design

This was a randomized, open-label, non placebo-controlled, two treatment (dronedarone + GFJ or dronedarone + water), 2-period crossover study, with at least a 10 day washout between periods.

There were three treatment phases in each of the two treatment arms:

- Phase 1: 300 mL GFJ was taken three times daily on Days 1-7, with a single dronedarone dose of 400 mg on Day 4 in fasted conditions.
- Phase 2: 300 mL GFJ was taken three times per day continuing on Days 8-10, with a single dose of dronedarone (400 mg) on Day 8 in fed conditions.
- Phase 3: 300 mL GFJ was taken three times daily on days 11-20, with repeated dronedarone doses of 400 mg twice a day in fed conditions. On day 20, there was only a morning drug administration.

(Non-carbonated water was substituted for GFJ in the second treatment arm.)

Reviewer Note on Study Design
The study design was consistent with the FDA-recommended drug-drug interaction Guidance; doses of both compounds were relevant to clinical use.

Subject Demographics
All subjects were Caucasian males between the ages of 18 and 39, as shown in Table 164:.

Table 164: Subject Demographics (INT4886)

Parameter	Statistics/ Category	Total (N=24)
Age (yrs)	N Mean (SD) Minimum - Maximum	24 27.9 (4.9) 18 - 39
Weight (kg)	N Mean (SD) Minimum - Maximum	24 68.22 (9.19) 53.6 – 86.2
Height (cm)	N Mean (SD) Minimum - Maximum	24 176.0 (6.0) 165 - 189
BMI (kg/m2)	N Mean (SD) Minimum - Maximum	24 21.96 (2.36) 18.2 – 25.0
Gender	Male	24 (100%)
Race	Caucasian	24 (100%)

Pharmacokinetic sampling times
The following pharmacokinetic blood samples were drawn at the given times for dronedarone and SR35021:

- Day 4: before dosing and then 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, and 48 hours after dosing
- Day 8: before dosing and then 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, and 48 hours after dosing
- Days 17, 18, and 19: before morning administration
- Day 20: before dosing and then 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after dosing

Formulation
Dronedarone: 400 mg tablets, batch number CL-04794

- GFJ: double strength reconstituted, batch numbers U1121 and U1323. The main components were bergamotin, 6',7' dihydroxybergamotin, and naringin

Bioanalytical methods
Plasma concentrations of dronedarone and SR35021 were determined using a validated liquid chromatography-mass spectrometry method, DOH0239. The assay method was acceptable as illustrated in Table 165.

Table 165: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.500 to 300 ng/mL range; R^2 > 0.980	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	All individual QC values were within 15% of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.500 to 300 ng/mL range; R^2 > 0.991	Satisfactory
Between day Precision	CVs were not provided	Cannot be assessed
Accuracy	All individual QC values were within 15% of nominal concentration	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Pharmacokinetics

The following pharmacokinetic (PK) parameters were measured for dronedarone and SR35021:

- Day 4 and Day 8: C_{max}, t_{max}, AUC_{last}, AUC, R_{met}, and $t_{1/2}$
- Day 20: C_{trough}, C_{min}, C_{max}, t_{max}, AUC_{0-12}, and R_{met}

Statistical methods

PK parameters for dronedarone and SR35021 were summarized by descriptive statistics. Standard statistical methods were used to evaluate PK drug-drug interactions. Occurrence of steady state was assessed using C_{trough} values.

Results

Dronedarone Pharmacokinetics

As shown in Figure 96, Figure 97, and Figure 98, the mean plasma concentrations of dronedarone were increased after concomitant, repeated, oral ingestion of GFJ 300 mL TID with both dronedarone single dose in fasted or fed conditions, and with dronedarone repeated doses in fed conditions.

Dronedarone steady state was reached after seven days of repeated oral administration alone, or co-administered with repeated ingestion of double strength GFJ.

Figure 96: Mean dronedarone plasma concentrations observed after a single 400 mg oral administration under fasted conditions, alone or co-administered with GFJ

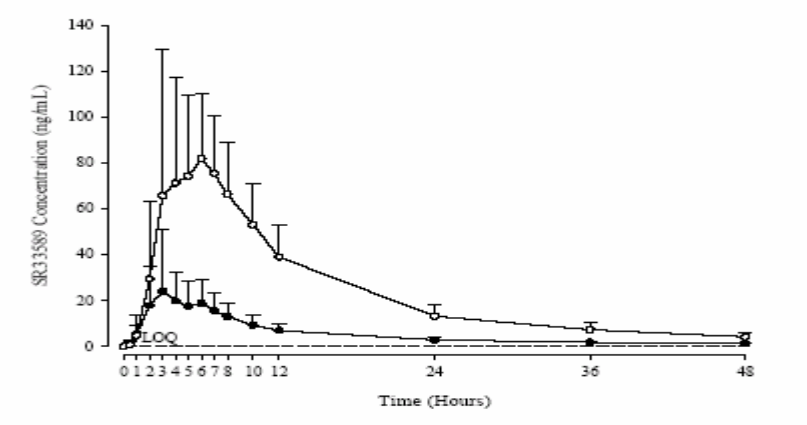


Figure 97: Mean dronedarone plasma concentrations observed after a single 400 mg oral administration under fed conditions, alone or co-administered with GFJ

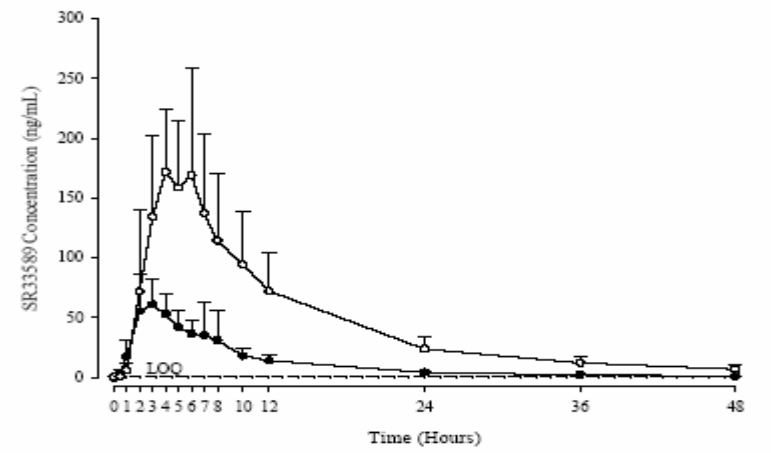
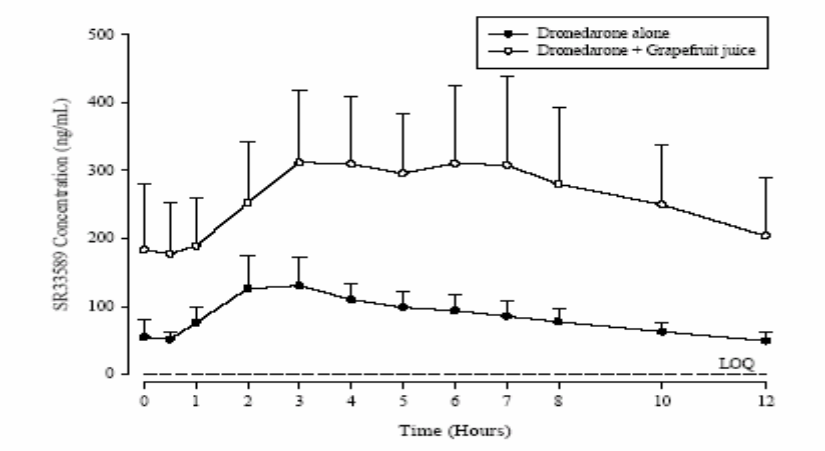


Figure 98: Mean dronedarone plasma concentrations observed after a 10 day repeated 400 mg BID oral administration under fed conditions, alone or co-administered with GFJ



Dronedarone PK measures are summarized in Table 166.

Table 166: Mean (coefficient of variation [CV%]) PK parameters of dronedarone and their ratio estimates and 90% confidence interval (CI) obtained after dronedarone oral administrations, alone or co-administered with GFJ (n=20)

PK Parameter Mean (CV%)	Dronedarone alone	Dronedarone+ grapefruit juice	Ratio estimates[b] and 90% CI
SR33589			
Single administration under fasted conditions			
C_{max} (ng/mL)	29.3 (91)	102 (49)	3.89 [3.03, 4.99]
t_{max} (h)[a]	3	6	1.50 [0.50, 2.50][c]
AUC_{last} (ng.h/mL)	268 (46)	1153 (37)	4.36 [3.62, 5.26]
$t_{1/2z}$ (h)	18.1 (26)[d]	14.3 (16)	-
AUC (ng.h/mL)	304 (42)[d]	1244 (38)	4.11 [3.42, 4.93]
Single administration under fed conditions			
C_{max} (ng/mL)	74.2 (41)	204 (43)	2.77 [2.35, 3.27]
t_{max} (h)[a]	3	4	1.50 [0.99, 2.50][c]
AUC_{last} (ng.h/mL)	564 (29)	2189 (36)	3.83 [3.39, 4.32]
$t_{1/2z}$ (h)	12.9 (21)	12.9 (14)	-
AUC (ng.h/mL)	588 (29)	2320 (36)	3.87 [3.44, 4.36]
Repeated b.i.d. administration under fed conditions			
C_{max} (ng/mL)	147 (31)	364 (33)	2.48 [2.16, 2.84]
t_{max} (h)[a]	3	4	2.00 [1.00, 2.50][c]
AUC_{0-12} (ng.h/mL)	1028 (21)	3186 (34)	3.00 [2.68, 3.36]

As shown in Table 166, relative to dronedarone alone, concomitant, repeated, oral ingestion of double strength GFJ:

- increased dronedarone C_{max} and AUC obtained after a single oral administration of dronedarone in fasted conditions, by approximately 4 fold.
- increased dronedarone C_{max} and AUC obtained after a single oral administration of dronedarone in fed conditions, by approximately 3 fold and 4 fold, respectively.
- increased dronedarone C_{max} and AUC_{0-12} obtained after repeated oral administration of dronedarone BID in fed conditions, by approximately 3 fold.

Time to reach peak plasma concentration (t_{max}) was delayed by 1.5 to 2 hours after concomitant, repeated, oral ingestion of GFJ, compared to that observed after dronedarone alone.

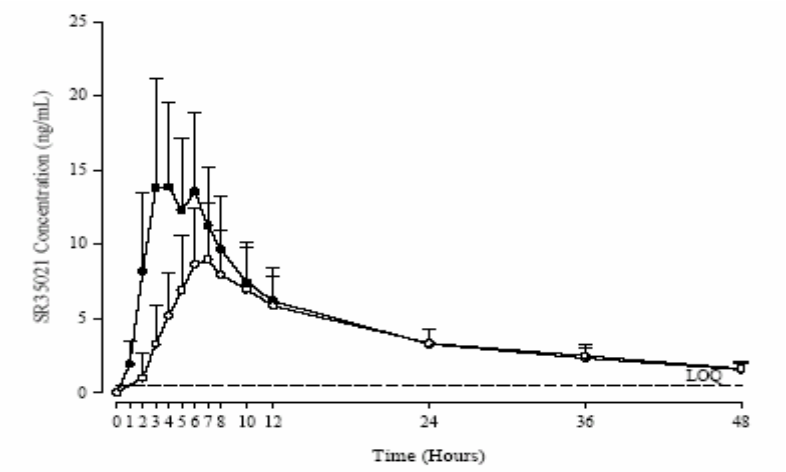
Reviewer Comment on Dronedarone PK Results

The most clinically relevant results are those of repeated administration of dronedarone BID under fed conditions, because this is the way the drug is intended to be taken.

SR35021 Pharmacokinetics

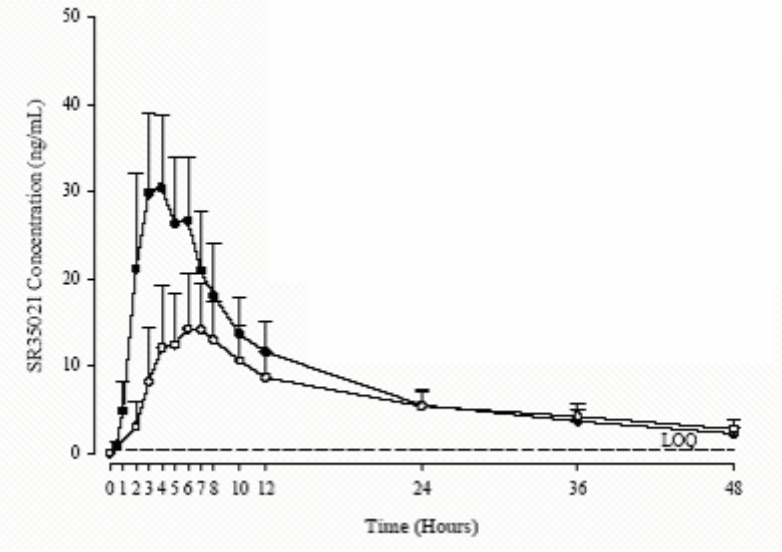
The mean SR35021 plasma concentration time profiles observed after a single dronedarone 400 mg oral administration under fasted conditions, alone or co-administered with GFJ are depicted in Figure 99. In the figure the curve with the filled in symbols refers to dronedarone alone and the open symbol is dronedarone + grapefruit.

Figure 99: Mean SR35021 plasma concentrations observed after a single dronedarone dose under fasted conditions, alone or coadministered with GFJ



The mean SR35021 plasma concentrations observed after a single dronedarone 400 mg oral administration under fed conditions, alone or co-administered with GFJ are depicted in Figure 100. In the figure the curve with the filled in symbols refers to dronedarone alone and the open symbol is dronedarone + grapefruit.

Figure 100: Mean SR35021 plasma concentrations observed after a single dronedarone dose under fed conditions, alone or coadministered with GFJ



The mean SR35021 plasma concentrations observed after a 10-day repeated dronedarone 400 mg BID oral administration under fed conditions, alone or co-administered with GFJ are depicted in Figure 101.

Figure 101: Mean SR35021 plasma concentrations observed after a 10 day repeat dronedarone BID dose under fed conditions, alone or coadministered with GFJ

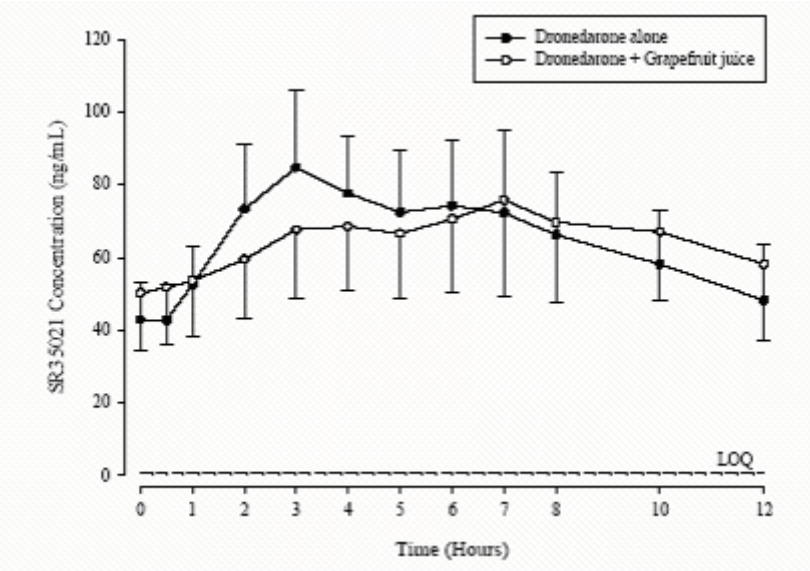


Table 167: Mean (CV%) PK parameters of SR35021 and their ratio estimates and 90% CI obtained after dronedarone oral administrations, alone or co-administered with GFJ (n=20)

PK Parameter Mean (CV%)	Dronedarone alone	Dronedarone + grapefruit juice	Ratio estimates[b] and 90% CI
SR35021			
Single administration under fasted conditions			
C_{max} (ng/mL)	16.7 (39)	9.41 (41)	0.56 [0.47, 0.67]
t_{max} (h)[a]	3	6.5	2.50[e] [1.50, 3.50]
AUC_{last} (ng.h/mL)	224 (30)	181 (29)	0.82 [0.72, 0.92]
$t_{1/2z}$ (h)	21.3 (23)	23.0[d] (19)	-
AUC (ng.h/mL)	273 (27)	241[e] (26)	0.90 [0.80, 1.00]
$R_{incl}(C_{max})$	0.68 (28)	0.11 (67)	0.14 [0.11, 0.19]
R_{incl}(AUC)	0.95[d] (23)	0.23[e] (53)	0.22 [0.19, 0.26]
Single administration under fed conditions			
C_{max} (ng/mL)	34.2 (25)	16.0 (41)	0.45 [0.37, 0.54]
t_{max} (h)[a]	3.5	6	2.50[e] [1.50, 3.00]
AUC_{last} (ng.h/mL)	416 (26)	299 (32)	0.71 [0.62, 0.81]
$t_{1/2z}$ (h)	19.2 (31)	25.9 (44)	-
AUC (ng.h/mL)	497[d] (24)	393[f] (32)	0.82 [0.74, 0.91]
$R_{incl}(C_{max})$	0.51 (37)	0.09 (62)	0.16 [0.12, 0.21]
R_{incl}(AUC)	0.86[d] (27)	0.21[f] (37)	0.23 [0.20, 0.28]
Repeated b.i.d. administration under fed conditions			
C_{max} (ng/mL)	87.8 (24)	79.5 (32)	0.89 [0.79, 0.99]
t_{max} (h)[a]	3	6	2.00[e] [1.50, 3.00]
AUC_{0-12} (ng.h/mL)	790 (23)	784 (28)	0.98 [0.89, 1.08]
$R_{incl}(C_{max})$	0.64 (26)	0.23 (33)	0.36 [0.32, 0.40]
$R_{incl}(AUC_{0-12})$	0.78 (20)	0.26 (32)	0.33 [0.29, 0.36]

The SR35021 PK measures obtained following administration of dronedarone with or without grapefruit are summarized in Table 167.

SR35021 C_{max} and AUC_{0-12} obtained after repeated oral administration of dronedarone 400 mg BID in fed conditions, co-administered with repeated oral ingestion of double strength GFJ, were similar to those observed after dronedarone alone. In all cases, median values of SR35021 time to reach peak plasma concentration (t_{max}) was delayed by 2 to 2.5 hours after concomitant, repeated, oral ingestion of GFJ compared to that observed after dronedarone alone.

SR35021 exposures, observed after a single, oral administration of dronedarone in fasted and in fed conditions, and after repeated oral administration of dronedarone in fed conditions, tended to be lower than dronedarone exposures; the metabolic ratio (R_{met} = ratio of the AUC or C_{max} of the metabolite to the parent drug) ranged from 0.51 to 0.95. R_{met} decreased when dronedarone was co-administered with the repeated ingestion of GFJ. These findings support the observation that GFJ inhibits dronedarone metabolism because less SR35021 is formed in the presence of GFJ than in the absence of GFJ.

Applicant's Safety Summary
Safety assessments included recording of adverse events (AEs), ECG, vital signs (BP and HR), hematology, biochemistry, and urinalysis. There was only one serious adverse event (SAE) reported (first degree AV block). No deaths were reported. Three subjects reported adverse events while on dronedarone, including dizziness, somnolence, and headache. Five other subjects reported adverse events while on dronedarone and GFJ, including first degree AV block, palpitations, abnormal liver function, hypotension, and other minor events. The first degree AV block and abnormal liver function led to discontinuation.

Recommendations/Conclusions
The following PK information generated in this study is acceptable for labeling purposes, as appropriate.

1. Grapefruit juice (GFJ) inhibited dronedarone metabolism; consequently dronedarone plasma concentrations were increased by repeated ingestion of 300 mL of GFJ (double strength) three times per day, relative to dronedarone alone. Dronedarone C_{max} and AUC increased ~2.5 to 3 fold following repeated administration twice a day under fed conditions.
2. SR35021 C_{max} and AUC obtained after repeated administration of dronedarone with GFJ were not significantly changed under fed conditions.

Applicant's Proposed Labeling
Drug Interactions: Repeat doses of double strength 300 mL grapefruit juice three times daily resulted in a 3 fold increase in dronedarone exposure. As grapefruit juice increases dronedarone exposure, patients should be warned to avoid grapefruit juice beverages while taking dronedarone.

Reviewer Note on Label
The sponsor adequately states a warning regarding consuming GFJ while taking dronedarone. The labeling is acceptable, considering the fact that GFJ inhibits dronedarone metabolism.

4.2.26 Pharmacokinetic interaction of repeated oral 400 mg BID dronedarone for 10 days on repeated oral 0.25 mg QD digoxin in healthy young male subjects - Randomized, double-blind, placebo-controlled, two-sequence, two-treatment, crossover study (INT5189)

PROTOCOL #	INT5189
INVESTIGATOR	Dr. Evelyne Guenole
STUDY SITE	Therapharm Recherches, 5, Boulevard Henri Becquerel, F – 14052 Caen Cedex 4 France
STUDY PERIOD	May – September 2004

Background Information on Study Drugs (Digoxin and Dronedarone)

	Digoxin	Dronedarone (SR33589)
Indication	Cardiac Glycoside; Inhibits sodium/potassium ATPase; For the treatment of mild to moderate heart failure, and control of ventricular response rate in patients with chronic atrial fibrillation.	Proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter. Anti-arrhythmic.
Metabolites	3 β-digoxigenin, 3-keto- digoxigenin, and their glucuronide and four sulfate conjugates.	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites.
Metabolic Pathway	Not dependent on CYP450; Substrate of P-glycoprotein (PGP)	Primarily CYP3A substrate.
CYP Inhibitory Potential	Does not inhibit or induce CYP450.	Low to moderate potential to inhibit CYP3A and CYP2D6, as well as PGP.
Highest Recommended Dose/Studied Dose	Available in tablets, capsules, elixir, and injection. The dose can range from 125 to 500 mcg depending on the indication and can be titrated.	400 mg BID.

Background Information

A previous dronedarone/digoxin interaction study (INT2634) performed in healthy young male subjects at the dosage of 400 mg once daily (QD) for dronedarone and 0.25 mg digoxin QD (with a loading dose of 0.75 mg) showed that dronedarone increased the digoxin AUC0-24 by 27%. In addition, a pharmacodynamic interaction was observed with a slight increase in heart rate (HR) (64.2 vs. 61.6 bpm) and a slight prolongation of QTc (395 vs. 381 msec) after seven days digoxin + dronedarone coadministration vs. digoxin alone (Emax analysis). These changes were not considered to be of clinical significance.

The proposed dronedarone dose is 400 mg BID, as opposed to the 400 mg QD used in the previous study. The current study used the proposed dronedarone dosage.

Objectives (per applicant)

- Primary: to assess the effect of repeated oral doses of 400 mg twice daily dronedarone on the pharmacokinetic (PK) profile of digoxin after repeated oral doses of 0.25 mg QD digoxin
- Secondary: to assess the clinical and laboratory safety of dronedarone coadministered with digoxin as compared to that of digoxin coadministered with placebo in healthy young male subjects

Study Design
This was a randomized, double-blind, placebo-controlled, repeat dose, two-sequence, two-treatment, and two-period crossover study with a minimum 10-day washout between periods. The treatments were:

- Treatment A - digoxin + placebo of dronedarone:
  - loading dose of 0.75 mg digoxin on Day 1 (0.50 mg in the morning and 0.25 mg in the evening, with 12 hours between the two administrations)
  - Day 2 – 10: a daily maintenance dose of 0.25 mg digoxin in the morning
  - Day 1 – 10: digoxin coadministered with placebo BID
- Treatment B - digoxin + dronedarone:
  - same as Treatment A, except placebo replaced by 400 mg BID dronedarone

Reviewer Note on Study Design
The study design was consistent with the FDA recommended Drug-Drug Interaction Guidance. The doses of digoxin and dronedarone used in the study were within the range of those used in normal clinical practice. However it is unclear why only males were included in the study.

Subject Demographics
Subject demographic characteristics are shown in Table 168.

Table 168: Summary of subject demographic data (INT5189)

		Dronedarone+Digoxin/ Placebo+Digoxin (N=10)	Placebo+Digoxin/ Dronedarone+Digoxin (N=10)	Overall (N=20)
Age (years)	N	10	10	20
	Mean (SD)	22.4 (2.5)	25.3 (6.8)	23.9 (5.2)
	Min - Max	19 - 27	18 - 39	18 - 39
Weight (kg)	N	10	10	20
	Mean (SD)	67.4 (5.9)	68.6 (4.2)	68.0 (5.0)
	Min - Max	60 - 77	62 - 74	60 - 77
Height (cm)	N	10	10	20
	Mean (SD)	173.9 (3.3)	177.5 (5.9)	175.7 (5.0)
	Min - Max	171 - 180	169 - 186	169 - 186
BMI (kg/m^2)	N	10	10	20
	Mean (SD)	22.30 (2.17)	21.78 (1.37)	22.04 (1.78)
	Min - Max	18.9 - 26.3	19.6 - 23.6	18.9 - 26.3
Gender [n (%)]	Male	10 (100)	10 (100)	20 (100)
Race [n (%)]	Caucasian	9 (90.0)	9 (90.0)	18 (90.0)
	Black	1 (10.0)	1 (10.0)	2 (10.0)

Pharmacokinetic sampling times
Plasma and urine samples were collected at scheduled times.

- Dronedarone and SR35021 samples were collected:
  - On Days 1, 2, 3, 5, 7, 9, and 10 – before morning administration
  - On Day 10 – at 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after morning administration in both periods
- Digoxin plasma samples were collected:
  - On Days 1, 2, 3, 5, 7, 9, and 10 – before administration
  - On Day 10 – at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after last administration in both periods

- Digoxin urine samples were collected:
  - On Day 1 – before first digoxin administration
  - On Day 10 – in the 0-24 hour interval in both periods

Formulation

- Dronedarone: 400 mg tablet (2E3), batch number CL-04530
- Digoxin: 0.25 mg tablet, batch number 386127
- Placebo: 0 mg, batch number CL-04404

Bioanalytical methods

Dronedarone and SR35021: Plasma concentrations were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method (DOH0292). The assay method was acceptable as illustrated in Table 169.

Table 169: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.50 to 300 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CVs were not provided.	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers.	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the to 0.50 to 300 ng/mL range; $R^2 >$ 0.995	Satisfactory
Between day Precision	CVs were not provided.	Cannot be assessed
Accuracy	Relative bias values were not provided; however all individual QC values were within 15% of nominal concentrations except for a few outliers.	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Digoxin: Plasma concentrations were determined by a validated radio-immuno assay method. The assay performance was acceptable as illustrated in Table 170.

Table 170: Performance of Digoxin Assays

Parameter	Measure	Reviewer Comment
	Digoxin Assay	
Linearity	The assay was linear over the 0.05 to 8.0 ng/mL range for plasma. The assay was linear over the 0.1 to 8.0 ng/mL range for urine.	Satisfactory
Between day Precision	CV was < 11% for plasma. CV was < 10% for urine.	Satisfactory
Accuracy	QC samples were between 1.25% to 11.25% of nominal concentrations for plasma. QC samples were between 1.43% and 19% of nominal concentrations for urine.	Satisfactory Not acceptable
LLOQ	0.2 ng/mL in plasma and 0.5 ng/mL in urine	Satisfactory
Specificity	Radio-immuno assay does not yield chromatograms.	Cannot be assessed

* Chromatograms were provided in the validation report indicating assay specificity.

Pharmacokinetics

- The following pharmacokinetic (PK) parameters were measured for dronedarone and SR35021: C_{trough}, C_{max}, t_{max}, and AUC_{0-12}.
- The following PK parameters were measured for digoxin: C_{trough}, C_{max}, t_{max}, AUC_{0-24}, Ae_{0-24} (cumulative amount excreted in the urine), fe_{0-24} (fraction of the dose excreted in the urine), and CL_{R0-24} (renal clearance).

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The time to reach steady state was assessed graphically from plots of C_{trough}.

Results

Dronedarone and SR35021

Mean (SD) dronedarone and SR35021 plasma concentration versus time profiles after repeated administration of dronedarone 400 mg BID for 10 days are shown in Figure 102.

Figure 102: Mean (SD) dronedarone and SR35021 plasma concentration versus time profiles on Day 10 after a 10-day repeated administration of dronedarone with digoxin

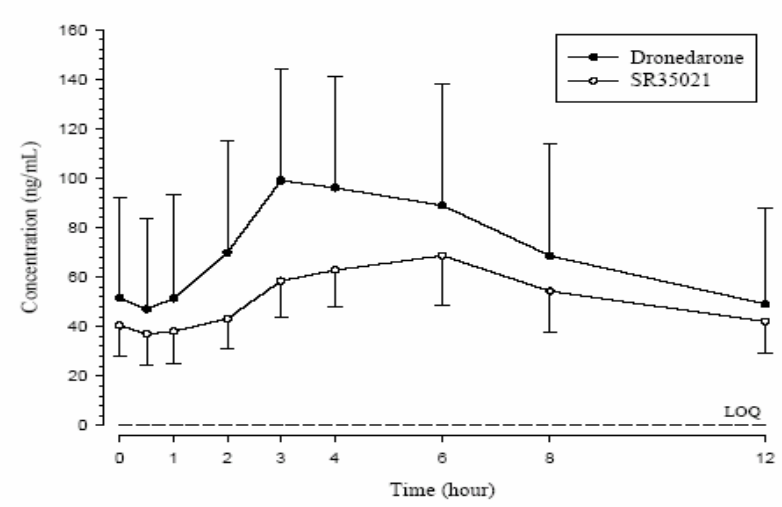


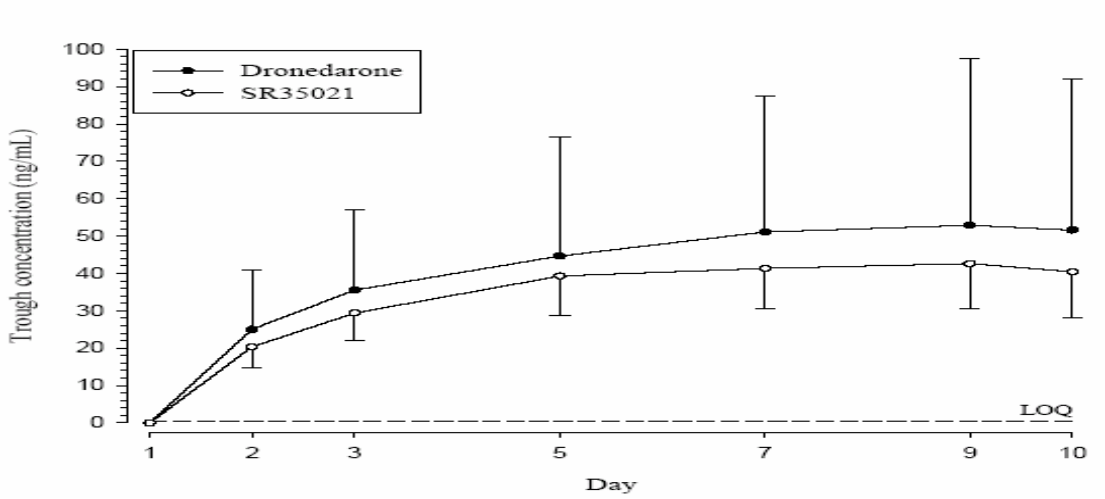
Table 171 shows the dronedarone and SR35021 PK parameters.

Table 171: Summary of dronedarone and SR35021 plasma PK parameters obtained on Day 10 after a 10-day repeated 400 mg BID administration of dronedarone

Parameter	Dronedarone	SR35021
C_{max} (ng/mL)		
Mean (CV%)	109 (44)	70.8 (28)
Min - Max	48.3 - 256	47.9 - 130
t_{max} (hour)		
Median	3.0	6.0
Min - Max	2.0 - 6.0	3.0 – 6.0
AUC_{0-12} (ng.h/mL)		
Mean (CV%)	868 (59)	636 (27)
Min - Max	380 - 2760	392 – 1120

Mean trough plasma concentrations of dronedarone and SR35021 from Day 1 to Day 10 during a 10-day repeated BID 400 mg oral dose of dronedarone and digoxin are graphically summarized in Figure 103.

Figure 103: Mean dronedarone and SR35021 C_{trough} (ng/mL) from Day 1 to Day 10 after a 10 day repeated BID 400 mg oral dose of dronedarone and digoxin

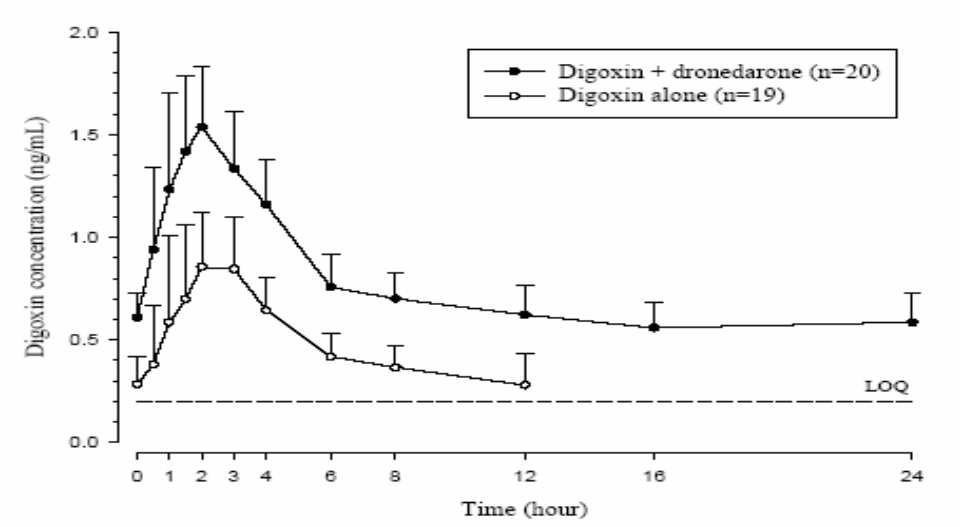


When coadministered with digoxin, average steady state of dronedarone and SR35021 was reached after four treatment days of repeated BID administration of dronedarone. Individual steady state was reached after five treatment days for dronedarone and four treatment days for SR35021.

Digoxin

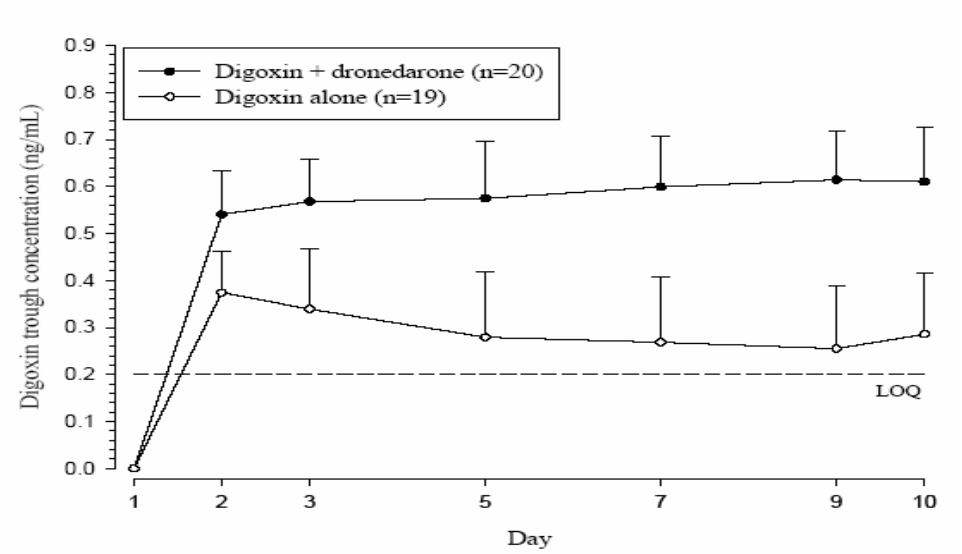
Figure 104 shows the mean (SD) digoxin plasma concentration versus time profiles observed on Day 10 after digoxin was administered for 10 days alone or with dronedarone.

Figure 104: Mean (SD) digoxin plasma concentrations on Day 10 after digoxin 0.25 mg QD administered alone or with dronedarone 400 mg BID



Mean (SD) digoxin C_{trough} observed from Day 1 to Day 10 after a 0.75 mg loading dose on Day 1 followed by a 0.25 mg dose of digoxin administered alone or with dronedarone are shown in Figure 105.

Figure 105: Mean (SD) digoxin trough plasma concentrations from Day 1 to Day 10 after digoxin 0.25 mg QD administered alone of with dronedarone 400 mg BID



According to the applicant, graphical inspection showed that coadministration of dronedarone did not modify steady state conditions for digoxin which was reached within two-treatment days using a 0.75 mg loading dose. However, based on the graphs, it appears that steady state for digoxin alone was achieved by Day 5, rather than Day 2.

Table 172 shows the plasma and urine PK parameters for digoxin observed on Day 10.

Table 172: Mean (CV%) digoxin plasma and urine PK parameters obtained on Day 10 after digoxin administered for 10 days alone or with dronedarone

Parameter	Digoxin + Dronedarone (n=20)	Digoxin Alone (n=19)	Ratio Estimate[a] [90% CI]
Plasma			
C_{max} (ng/mL)	1.71 (17)	1.02 (33)	1.75 [1.58, 1.93]
t_{max}[c] (hour)	2.0 (1.0 – 3.0)	3.0 (1.0 – 4.0)	-0.5 [-1.00, 0.00][b]
AUC_{0-24} (ng.h/mL)	18.0 (18)	7.73 (45)	2.57 [2.21, 2.98]
Urine			
Ae_{0-24} (mg)	0.139 (28)	0.097 (32)	1.45 [1.19, 1.78]
fe_{0-24} (%)	55.8 (28)	38.8 (32)	NA
CL_{R0-24} (L/h)	7.80 (27)	14.2 (41)	0.57 [0.46, 0.69]

[a] geometric mean ratio: digoxin + dronedarone/digoxin alone
[b] estimate of median difference [90% CI of median difference]
[c] median (minimum-maximum)
NA=not applicable

The analysis performed on digoxin parameters showed that, relative to digoxin alone, a 10-day concomitant administration of dronedarone 400 mg BID and digoxin 0.25 mg QD led to:

- a significant increase in digoxin C_{max} by 1.75-fold
- a significant increase in digoxin AUC_{0-24} by 2.57-fold

- no relevant changes in digoxin t_{max}
- a significant decrease in digoxin renal clearance by 43%
- a significant increase in amount of the digoxin dose excreted in urine by 1.45-fold

Reviewer Note
Based upon the results of this study, it is shown that dronedarone has the potential to inhibit PGP; this increases the levels of digoxin in the body. Digoxin renal clearance is inhibited due to the inhibition of PGP pumps in the kidney, thus there is an increase in the amount of digoxin excreted in the urine.

Applicant's Safety Summary
Overall, the tolerability of dronedarone in coadministration with digoxin was satisfactory. The incidence of any treatment emergent adverse events (TEAEs) was lower in dronedarone + digoxin group compared to placebo + digoxin group. These TEAEs included periorbital hematoma, headache, dysuria, and epistaxis. All TEAEs were of mild to moderate intensity. There were no serious adverse events (SAEs) reported, including deaths. One subject discontinued study drug due to an AE.

Recommendations/Conclusions
This review addresses only the PK interactions between digoxin and dronedarone.

1. Relative to digoxin alone, steady state digoxin C_{max} was significantly increased by 1.75-fold after a 10-day concomitant administration of dronedarone 400 mg BID while t_{max} was not modified. A significant increase in steady state AUCs ranging between 2.03-fold and 2.57-fold was observed.

2. Relative to digoxin alone, concomitant administration of dronedarone led to a significant decrease in digoxin renal clearance by 43%. Steady state Ae_{0-24} was significantly increased by 1.45-fold.

Applicant's Proposed Labeling
Due to the pharmacokinetic interaction and possible pharmacodynamic interaction, digoxin should be used with caution concomitantly with dronedarone and patients should be closely monitored for serum digoxin levels.

Reviewer Note on Label
The sponsor adequately states a caution when using digoxin while taking dronedarone. The labeling is acceptable. A dose adjustment is not required when administering dronedarone along with digoxin, because digoxin dosage can be titrated to optimize digoxin safety and efficacy.

4.2.27 Influence of repeated oral doses of ketoconazole [inhibitor of cytochrome P4503A4 (CYP3A4)] on the pharmacokinetic profile of dronedarone in healthy male subjects (INT3561)

PROTOCOL #	INT3561
INVESTIGATOR	Dr Wolfgang Tetzloff
STUDY SITE	IPHAR GmbH Arnikastrasse 4 85365 Höhenkirchen-Siegertsbrunn, Germany
STUDY PERIOD	March – June, 1999

Rationale for Drug-Drug Interaction Study

Background Information on Study Drugs (Ketoconazole and Dronedarone)

	Ketoconazole	Dronedarone
Indication/Mechanism of Action	Broad spectrum antifungal agent. Indicated for the treatment of some systemic fungal infections	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Forms several inactive metabolites	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	Hepatically metabolized, with bile as the primary elimination route	Primarily CYP3A substrate
CYP Inhibitory Potential	Potent CYP3A inhibitor	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	The recommended initial oral dose is 200 mg QD; however dosage may be increased to 400 mg QD	400 mg BID

Objectives (per applicant)

- Primary: to assess the effect of repeated oral doses of ketoconazole on the pharmacokinetic profile of SR33589 (dronedarone) and its N-debutyl metabolite SR35021 after a single oral ascending dose of dronedarone given under fed conditions.
- Secondary: to assess a potential pharmacodynamic resulting effect, to assess the clinical and biological tolerability of dronedarone, alone and co-administered with ketoconazole and to document plasma concentrations of ketoconazole after repeated doses.

Study Design

This was a non-randomized, open-label, non placebo-controlled and two-period study. The two treatment periods were:

- Period 1: one day dronedarone (100 or 200 mg) alone followed by 5-day washout
- Period 2: seven days ketoconazole (200 mg QD) alone and one day co-administration of dronedarone+ ketoconazole.

There was a 13-day washout period between the 100 and 200 mg dose levels, for a given subject.

Reviewer Note on Study Design

Typically, drug interaction studies with ketoconazole are conducted at 400 mg QD to show the full magnitude of drug interaction. However, the use of a lower ketoconazole dose, 200 mg QD,

is consistent with the FDA-recommended drug-drug interaction Guidance because the safety concerns obviate the need for conducting the study at the highest recommended dose of either ketoconazole or dronedarone.

Subject Demographics
Subject demographics are presented in Table 173. All subjects were Caucasian males.

Pharmacokinetic sampling times
The following pharmacokinetic blood samples were drawn at the given times:

- For dronedarone and SR35021: 35 min before dosing and 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours postdose.
- For Ketoconazole: Day 1 and Day 8 at 35 min before dosing and on Day 8 at 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours postdose.

Formulation

- Dronedarone: 100 mg capsules, lot number 98-01946
- Ketoconazole: 200 mg tablets, lot number 98-J28/751 (no additional product information was provided)

Table 173: Subject Demographic Data (INT3561)

Parameter	Statistics	Dronedarone		Total
		100 mg	200 mg	
Age (years)	N	6	6	12
	Mean	27.3	32.5	29.9
	SD	5.0	3.4	4.9
	Min	22	28	22
	Max	35	38	38
Height (cm)	N	6	6	12
	Mean	184.5	181.0	182.8
	SD	3.3	7.3	5.7
	Min	179	173	173
	Max	189	193	193
Weight (kg)	N	6	6	12
	Mean	78.80	81.00	79.90
	SD	7.32	6.07	6.52
	Min	70.1	75.4	70.1
	Max	88.3	91.6	91.6

Bioanalytical methods

Dronedarone and SR35021 Assays
Dronedarone and SR35021 concentrations were determined using a validated electrospray LC-MS/MS method. The assay performance was acceptable:

- Linear range for dronedarone and SR35021 was 0.5 – 50 ng/mL; R^2 for dronedarone > 0.993 for all runs, except one run where R^2 was 0.976; R^2 for SR35021 > 0.992
- QC charts were provided, but no summarized values for CV or relative bias were provided; however, individual QC samples were within 15 % of nominal concentrations, suggesting assay was accurate
- Chromatograms were not provided so specificity could not be assessed, however, the validation report, which includes chromatograms, demonstrates assay specificity

Ketoconazole Assay

Ketoconazole plasma concentrations were determined by a validated HPLC (with ultraviolet detection) method. The assay performance was acceptable as illustrated in Table 174.

Table 174: Performance of Ketoconazole Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 10 to 5000 ng/mL range; $R^2 > 0.990$	Satisfactory
Between day Precision	CV was < 12 %	Satisfactory
Accuracy	QC samples were between -5 and 13 % of nominal concentration	Satisfactory
LLOQ	10 ng/ml	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined after each treatment:

- For dronedarone and SR35021: Cmax, tmax, AUClast, AUC and $t_{1/2}$
- For ketoconazole: Cmax, tmax, Cmin, and AUC_{0-24h}.

Pharmacodynamics

The following pharmacodynamic (PD) measures were determined: heart rate (HR), and PR-, QRS-, QT- and QTc- intervals, T-wave amplitude, hourly average AUC_{0-12}, peak values and time to peak values. Electrocardiogram (ECG) measurements were obtained at the following times:

- Screening
- Period 1: Day 0 at 8:00 am, and Day 1 at 30 minutes before dosing and 2, 4, 6, 8, 12, 24, 48, 72 and 96 hours post dose
- Period 2: Day 1 and Day 7 at 8:00 am
- Period 2: Day 8 at 30 minutes before dosing and 2, 4, 6, 8, 12, 24, 48, 72 and 96 hours post dose

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Dronedarone alone was the reference treatment and dronedarone + ketoconazole was the test treatment. Pharmacodynamic measures were also analyzed using standard statistical approaches.

Results

Dronedarone Pharmacokinetics

The mean plasma concentration-time profiles for dronedarone (100 and 200 mg doses) following administration of dronedarone with or without ketoconazole are depicted in Figure 106.

Dronedarone PK measures are summarized in Table 175. Dronedarone exposure was greatly increased (> 8-fold in Cmax and > 15-fold in AUC) in the presence of ketoconazole (200 mg) at both the 100 and 200 mg dronedarone dose levels (Table 176).

Figure 106: Mean dronedarone plasma concentration-time profiles following administration of dronedarone +/- ketoconazole

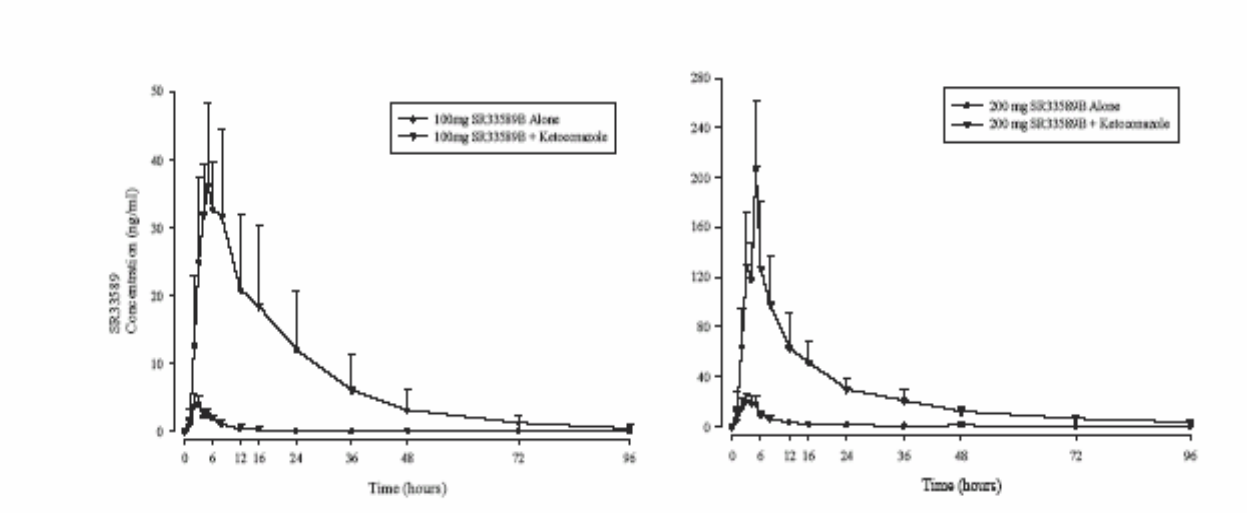


Table 175: Mean (SD) dronedarone PK measures in healthy males following single dose administration with or without ketoconazole (n=6)

Parameter	100 mg dronedarone		200 mg dronedarone	
	Alone (Period 1)	+keto (Period 2)	Alone (Period 1)	+keto (Period 2)
C max (ng/mL)	4.6 (1.1)	43.3 (10.5)	23.8 (4.6)	206.6 (54.1)
t max (h)	2.8 (1.2)	4.7 (1.9)	3.5 (1.1)	5.0 (0.0)
AUClast (ng.h/mL)	20 (8)	726 (376)	163 (44)	2559 (677)
AUC (ng.h/mL)	30 (7)a	745 (383)	160 (45)a	2692 (714)
t1/2 (h)	4.7 (2.3)a	17.8 (5.6)	16.2 (4.0)a	25.1 (4.6)

a- n = 4; keto = ketoconazole

Table 176: Dronedarone geometric mean ratios and associated 95 % confidence intervals for Cmax and AUC in the presence and absence of 200 mg ketoconazole

Parameter	100 mg dronedarone		200 mg dronedarone	
	Ratio	95% CI	Ratio	95% CI
C_{max} (ng/mL)	9.4	7.5-11.7	8.6	6.9-10.7
AUC_{last} (ng.h/mL)	35.9	26.6-48.4	15.8	11.7-21.3
AUC (ng.h/mL)	25.2	18.7-34.0	16.6	12.3-22.3

There appeared to be a dose dependent increase in AUC. This dose dependency is likely related to the non-linear nature of dronedarone PK. Nevertheless at both dronedarone dose levels there is a significant increase in dronedarone AUC and Cmax (> 8-fold) indicating that ketoconazole strongly inhibits dronedarone metabolism, as expected.

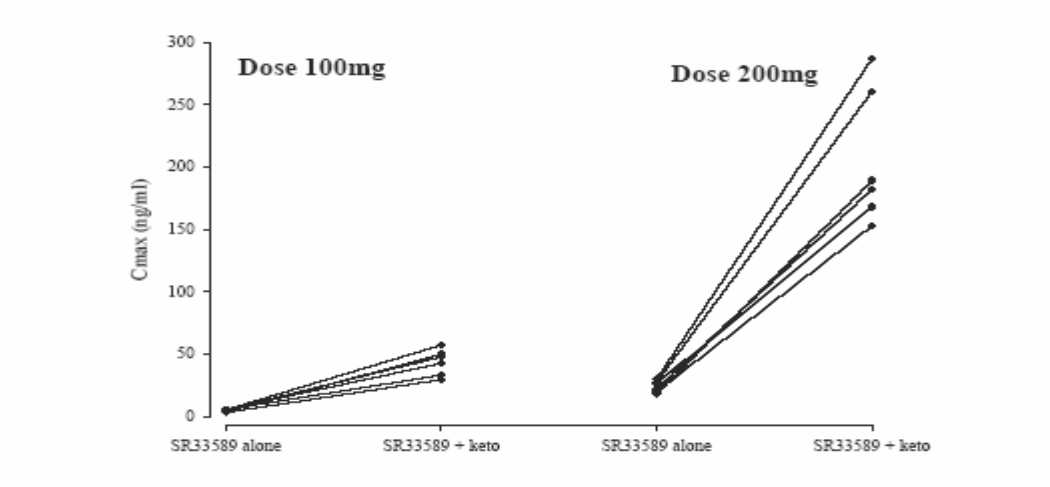
Reviewer Note on Confidence Intervals

For regulatory purposes, 90 % confidence intervals (CIs) are preferred over 95 % CIs. In this study, the type of CI, 90 % or 95 %, and its width is not of consequence, because the geometric

mean ratio is much greater than one and the associated 90 % confidence intervals will be much greater than the default no effect range (0.8 to 1.25 based on 90 % confidence interval).

The match stick plots in Figure 107 further illustrate the observed increase in dronedarone exposure when co-administered with ketoconazole; all subjects had Cmax increases in the presence of ketoconazole.

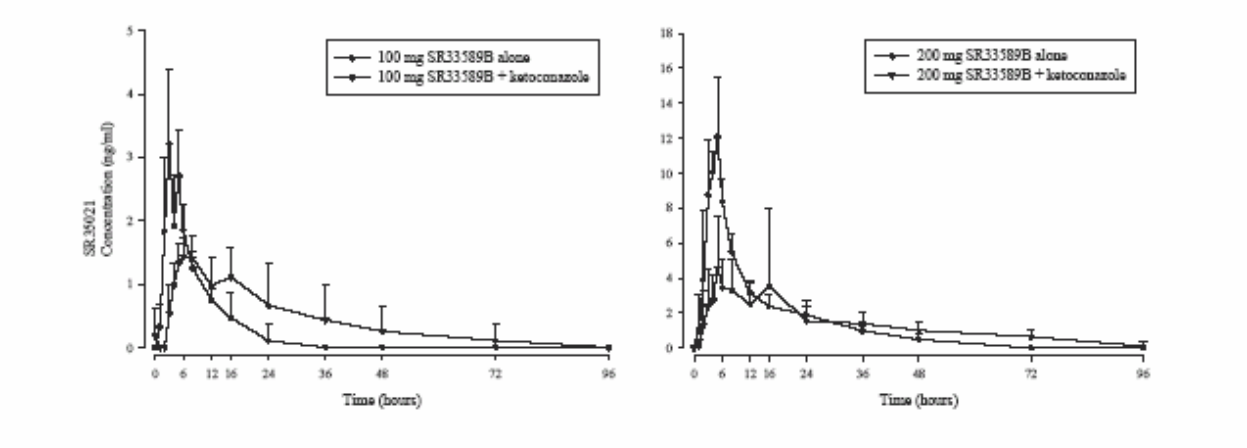
Figure 107: Individual and mean dronedarone Cmax values following administration of dronedarone with our without ketoconazole



SR35021 Pharmacokinetics

The mean SR35021 plasma concentration time profiles following administration of 100 mg or 200 mg with or without ketoconazole are depicted in Figure 108.

Figure 108: Mean SR35021 plasma concentration-time profile following administration of dronedarone with or without ketoconazole



SR35021 PK measures are shown in Table 177.

Table 177: SR30521 PK measures in healthy males following administration of dronedarone in the presence or absence of ketoconazole

Parameter	100 mg dronedarone		200 mg dronedarone	
	Alone(Period 1)	+keto(Period 2)	Alone(Period 1)	+keto(Period 2)
C_{max} (ng/mL)	3.6 (0.8)	1.7 (0.2)	13.6 (1.2)	5.0 (3.8)
t_{max} (h)	3.3 (0.8)	7.3 (4.3)	4.3 (1.0)	7.0 (4.4)
AUC_{last} (ng.h/mL)	21 (6)	34 (29)	123 (21)	118 (77)
AUC (ng.h/mL)	26 (7)[b]	NC	142 (22)[c]	NC
$T_{1/2}$ (h)	8.2 (5.3)[a]	NC	16.7 (3.8)[c]	43.6 (10.1)[c]

a : n=4 ; b : n=3 ; c : n=5 NC: not calculable keto: ketoconazole

Geometric mean ratios and associated 95% CI of the SR35021 PK measures are presented in Table 178.

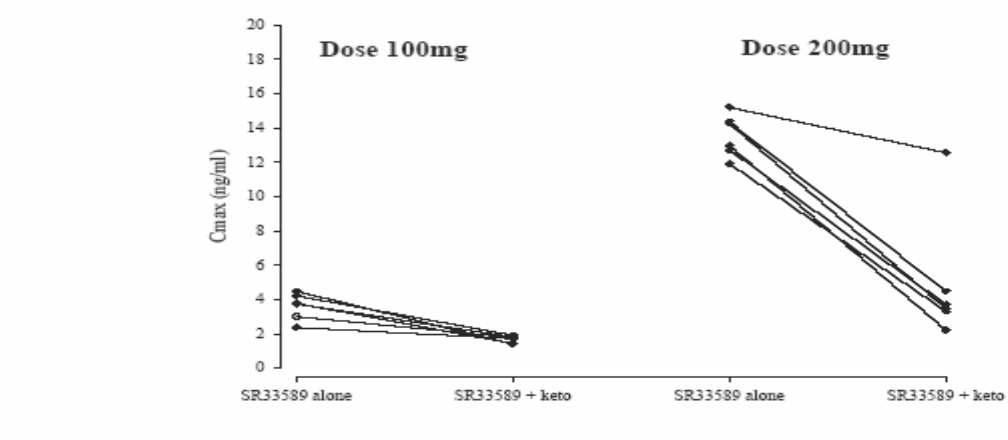
Table 178: SR35021 Geometric mean ratios for Cmax and AUC and associated confidence intervals obtained in dronedarone-ketoconazole drug interaction study

Parameter	100 mg dronedarone		200 mg dronedarone	
	Ratio	95% CI	Ratio	95% CI
Cmax (ng/mL)	0.48	[0.3-0.7]	0.31	[0.2-0.5]
AUClast (ng.h/mL)	1.3	[0.7-2.3]	0.8	[0.5-1.5]

SR35021 Cmax values were significantly decreased, but no statistically significant difference was observed in AUC last values.

The match stick plots in Figure 109 further illustrate the observed decrease in dronedarone Cmax when co-administered with ketoconazole. This finding supports the observation that ketoconazole inhibits dronedarone metabolism because less SR35021 is formed in the presence of ketoconazole than in the absence of ketoconazole.

Figure 109: Matchstick plots showing change in SR35021 for individual subjects following administration of dronedarone +/- ketoconazole



Ketoconazole Pharmacokinetics

The mean(SD) ketoconazole PK values after repeated 8-day of 200 mg ketoconazole dose with 100 mg or 200 mg dronedarone (period 2) are summarized in Table 179.

Table 179: Mean (SD) ketoconazole PK measures following administration of ketoconazole and dronedarone

Dronedarone dose	C_{max} (ng/mL)	t_{max} (h)	C_{min} (ng/mL)	AUC_{0-24h} (ng.h/mL)
100 mg	2778 (948)	2.3 (0.8)	21.2 (13.7)	17642 (7464)
200 mg	3233 (1147)	3.2 (1.2)	64.0 (43.1)	23420 (10871)

The ketoconazole PK values are consistent with the values obtained in previous studies, suggesting that single dose administration of dronedarone does not alter ketoconazole exposure.

Pharmacodynamics

The applicant's pharmacodynamic analysis on ECG parameters (Table 180) indicated:

1. PR interval

There was statistically significant PR-prolongation (hourly and peak) when dronedarone (100 mg and 200 mg dronedarone pooled) was co-administered with ketoconazole, compared to dronedarone alone.

2. QTc interval

The average hourly QTc AUC value for dronedarone + ketoconazole was approximately 4 ms greater than dronedarone alone. On the other hand, the increase in peak QTc was not statistically significant.

Figure 110 and Figure 111 depict the mean changes (relative to baseline, T-30 minutes) in PR and QTc values over time (12 hour dosing period). PR-time and QTc-time values exhibited high inter-patient variability. This variability may have been decreased if baseline values were available over the entire sampling period, not just at the initial time point, because ECG measures tend to exhibit a circadian pattern.

Figure 110: Mean Changes in PR* over time following administration of 200 mg dronedarone and 200 mg dronedarone + ketoconazole

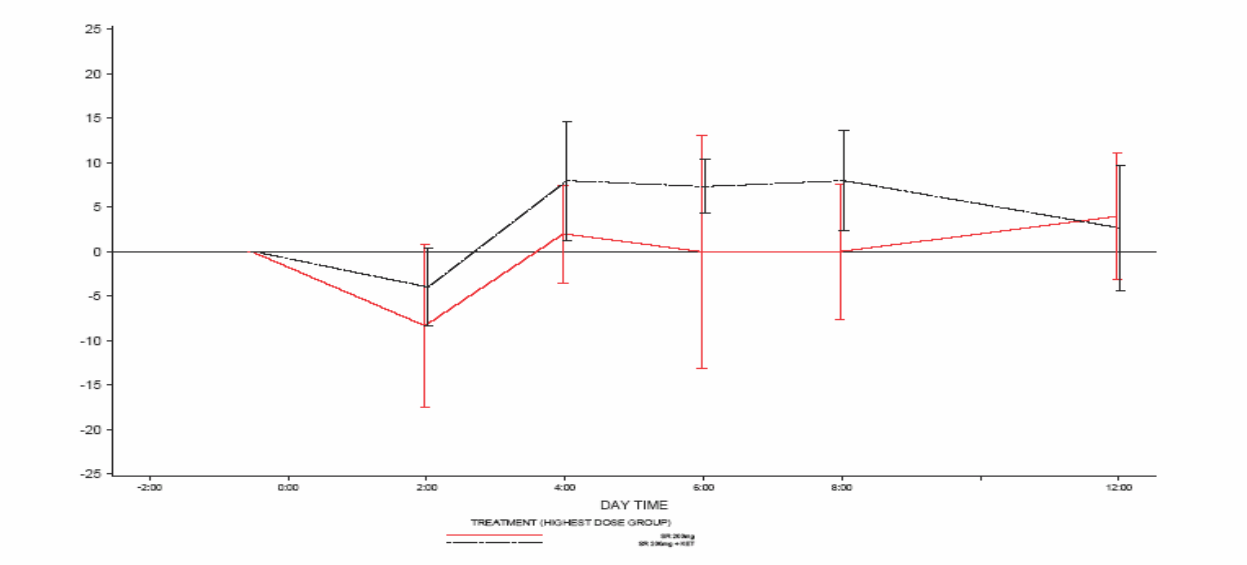
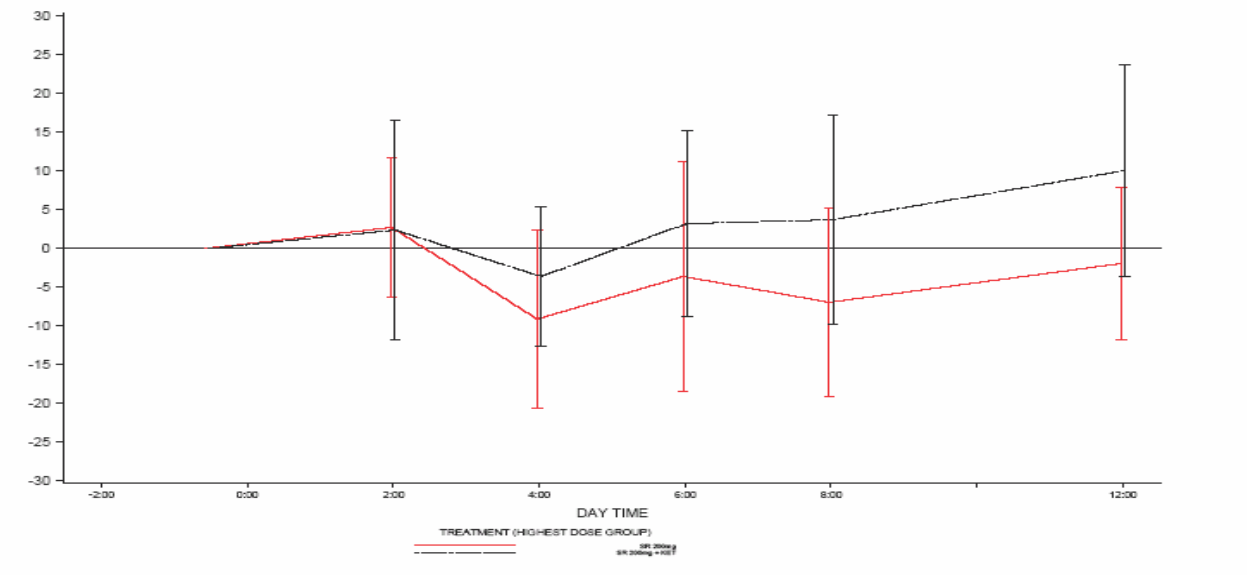


Figure 111: Mean (SD) QTc* changes (baseline corrected) with time after administration of 200 mg alone and 200 mg dronedarone + ketoconazole



* top curves (black lines) represent ketoconazole + dronedarone and lower curves (red lines) represent dronedarone alone

Reviewer Comment on Pharmacodynamic Results

The clinical relevance of the increased PR interval and hourly QTc AUC is not clear. The dronedarone exposures obtained in this study via metabolic inhibition are several folds higher than anticipated clinical exposures.

Table 180: Analysis of PR-interval and QTc values following dronedarone alone and dronedarone + ketoconazole

Parameter	Dronedarone dose	Mean (SD) by treatment		Mean difference (SD)	Difference estimate [95% CI]	p value
		alone	with keto			
PR-interval						
hourly	100 mg (N=6)	158.3 (19.2)	165.9 (19.0)	7.6 (3.2)		
AUC (ms)	200 mg (N=6)	169.5 (17.9)	186.8 (27.6)	17.3 (12.0)		
	pooled (N=12)	163.9 (18.7)	176.3 (25.1)		12.4 [6.8 ; 18.1]	0.0006
peak (ms)	100 mg (N=6)	165.3 (20.0)	174.0 (19.1)	8.7 (5.9)		
	200 mg (N=6)	177.3 (16.7)	194.7 (29.8)	17.3 (16.1)		
	pooled (N=12)	171.3 (18.7)	184.3 (26.2)		13.0 [5.2 ; 20.8]	0.0041
QTc						
hourly	100 mg (N=6)	399.3 (9.5)	403.0 (10.6)	3.7 (4.4)		
AUC (ms)	200 mg (N=6)	395.4 (14.4)	399.5 (18.7)	4.1 (7.3)		
	pooled (N=12)	397.3 (11.8)	401.2 (14.6)		3.9 [0.02 ; 7.7]	0.0488
peak (ms)	100 mg (N=6)	409.0 (8.4)	411.7 (11.2)	2.7 (5.9)		
	200 mg (N=6)	405.7 (13.5)	409.3 (19.6)	3.7 (11.0)		
	pooled (N=12)	407.3 (10.8)	410.5 (15.3)		3.2 [-2.5 ; 8.9]	0.2433

Applicant's Safety Summary

There were no serious adverse events (SAEs), deaths or significant adverse events in this study. A total of four adverse effects were reported in this study, but none occurred during co-administration of dronedarone with ketoconazole. The reported adverse events were mild first

degree AV block on dronedarone alone immediately prior to co-administration and a mild headache on ketoconazole.

Recommendations/Conclusions
The following PK information generated in Study INT3561 is acceptable for labeling purposes, as appropriate.

Pharmacokinetics

- Ketoconazole (200 mg) given once daily over eight days inhibited dronedarone metabolism; consequently dronedarone plasma concentrations were elevated (Cmax increased ~ 9-fold and AUC increased > 16-fold), relative to when dronedarone was given alone.
- The increase in dronedarone exposure showed some dose dependency, particularly with AUC values, which may be reflective of dronedarone's non-linear PK.
- Relative to when dronedarone was given alone, dronedarone + ketoconazole, led to decreased SR35021 formation.

Pharmacodynamics

- Statistically significant PR- prolongation was observed with dronedarone co-administered with ketoconazole compared to dronedarone alone
- Super-therapeutic dronedarone exposures did not appear to alter the QTc interval in a clinically significant manner; the maximum increase in QTc was 4 ms and no QTc value exceeded 450 ms.

Overall the pharmacodynamic changes do not appear clinically relevant.

Labeling
The applicant has proposed to contraindicate potent CYP3A metabolic inhibitors, such as ketoconazole, during dronedarone therapy.

Reviewer's Note on Applicant's Labeling Proposal
The proposal to contraindicate potent inhibitors appears reasonable and will minimize the risk of observing undesirable ECG changes. Additionally, the large increase in dronedarone exposure may have additional undesirable side effects that have been documented in other studies; in general exposures associated with administration of dronedarone doses ≥ 800 mg do not have an acceptable safety profile.

4.2.28 Pharmacokinetic interaction of repeated oral 400 mg BID dronedarone on repeated oral 400 mg BID theophylline in healthy young male subjects: randomized, placebo-controlled, double-blind, 2-sequence, 2-treatment crossover study (INT5084)

PROTOCOL #	INT5084
INVESTIGATOR	Dr Regine Rouzier
STUDY SITE	Center CAP, Clinique Rech, 9, Avenue Charles Flahault, F - 34094 Montpellier Cedex 5
STUDY PERIOD	June – November 2004

Background Information on Study Drugs (Theophylline and Dronedarone)

	Theophylline	Dronedarone
Indication/Mechanism of Action	Bronchodilator used in treatment of chronic Asthma and chronic obstructive pulmonary disease	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Several oxidative metabolites are formed	Several metabolites including, debutylated SR35021* (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP1A2 substrate	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Titrated and has a relatively narrow therapeutic index; highest dose is 400 mg	400 mg BID

*SR35021 has minimal potential to inhibit CYP1A2 (Ki = 31 μM)

Objectives (per applicant)

- Primary: To assess the effect of repeated oral 400 mg twice a day (BID) dronedarone on the pharmacokinetic (PK) profile of theophylline after repeated oral 400 mg BID theophylline, both dronedarone and theophylline being given in fed conditions.
- Secondary: To assess the clinical and laboratory safety of dronedarone co-administered with theophylline as compared to that of theophylline co-administered with placebo of dronedarone in healthy young male subjects.

Study Design

This was a single center, randomized, double-blind, placebo-controlled, two-period and two-period crossover study. The two treatment periods were:

- Period 1: 400 mg dronedarone twice daily + 400 mg theophylline twice daily
- Period 2: 400 mg theophylline twice daily + placebo dronedarone

There was a 10-day washout period between treatments.

Subject Demographics

Subject demographics are presented in Table 181. Five subjects did not complete the study: four in theophylline + dronedarone and one in theophylline + placebo.

Table 181: Subject Demographics (Study 5084)

Parameter (unit)	Statistics/Category	Overall Subjects (N=39)
Age (years)	N Mean (SD) Min-Max	39 24.6 (4.5) 18-39
Weight (kg)	N Mean (SD) Min-Max	39 69.08 (5.07) 60.0-80.5
Height (cm)	N Mean (SD) Min-Max	39 176.3 (6.5) 164-192
BMI (kg/m²)	N Mean (SD) Min-Max	39 22.27 (1.72) 18.8-25.7
Gender	Male (N,%)	39 (100)
Race	Caucasian (N,%) Black (N,%) Asian / oriental (N,%) Other (N,%)	34 (87.2) 3 (7.7) 1 (2.6) 1 (2.6)

Pharmacokinetic sampling times

The following pharmacokinetic blood samples were drawn at the given times:

- For dronedarone and SR35021: before morning dose (Ctrough) on Days 1, 3, 5, 7, 9, and 10 and 0.5, 1, 2, 3, 6, 8, 10 and 12 hours after administration on Day 10.
- For theophylline: before morning dose (Ctrough) on Days 1, 3, 5, 7, 9, and 10 and 0.5, 1, 2, 3, 6, 8, 10 and 12 hours after administration on Day 10.

Formulation

- Dronedarone: 400 mg tablets, batch number CL-04530
- Theophylline: 400 mg tablets (Teva LP), batch number 02475
- Dronedarone Placebo: 0 mg tablets, batch number CL-04404

Bioanalytical methods

Dronedarone and SR35021 Assays

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 182.

Table 182: Performance of SR35021 and Dronedarone Assays

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.990$	Satisfactory
Between day Precision	CV was not provided	Cannot be assessed
Accuracy	Mean relative bias values were not provided, however, individual QC samples were all within 15 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.993$	Satisfactory
Between day Precision	CV was not provided	Cannot be assessed
Accuracy	Mean relative bias values were not provided, however, individual QC samples were all within 15 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* chromatograms provided in the validation report demonstrate assay specificity

Theophylline Assays

Theophylline plasma concentrations were determined by a validated HPLC method with UV detection. The assay performance was acceptable as illustrated in Table 183.

Table 183: Performance of Theophylline Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 50 to 20000 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 8 %	Satisfactory
Accuracy	QC samples were between 0 and 2.5 % of nominal concentration	Satisfactory
LLOQ	50 ng/ml	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined after each treatment:

- For dronedarone and SR35021: Ctrough before morning administration on Days 1 to 10 and Cmax, tmax, AUC_{0-12} on Day 10
- For theophylline: Ctrough from Day 1 to Day 10 and Cmax, tmax and AUC_{0-12} on Day 10.

Statistical methods

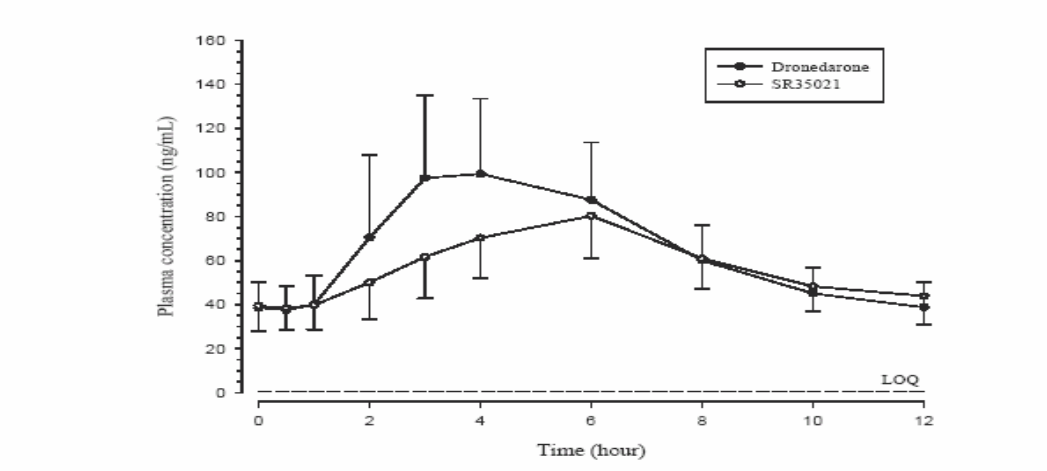
Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. Theophylline + placebo was the reference treatment and dronedarone + theophylline was the test treatment.

Results

Dronedarone Pharmacokinetics

The mean plasma concentration-time profiles for dronedarone and SR35021 are depicted in Figure 112.

Figure 112: Mean dronedarone and SR35021 plasma concentration-time profile under fasted and fed conditions



Dronedarone and SR35021 PK measures are summarized in Table 184.

Table 184: Mean (SD) dronedarone and SR35021 PK measures in healthy males following administration of dronedarone with theophylline(n=33)

Parameter	Dronedarone	SR35021
C_{max} (ng/mL)	117 (31)	82.6 (22)
t_{max} (hour)[a]	3.0 (2.0 – 6.0)	6.0 (2.0 - 8.0)
AUC_{0-12} (ng.h/mL)	799 (25)	699 (22)

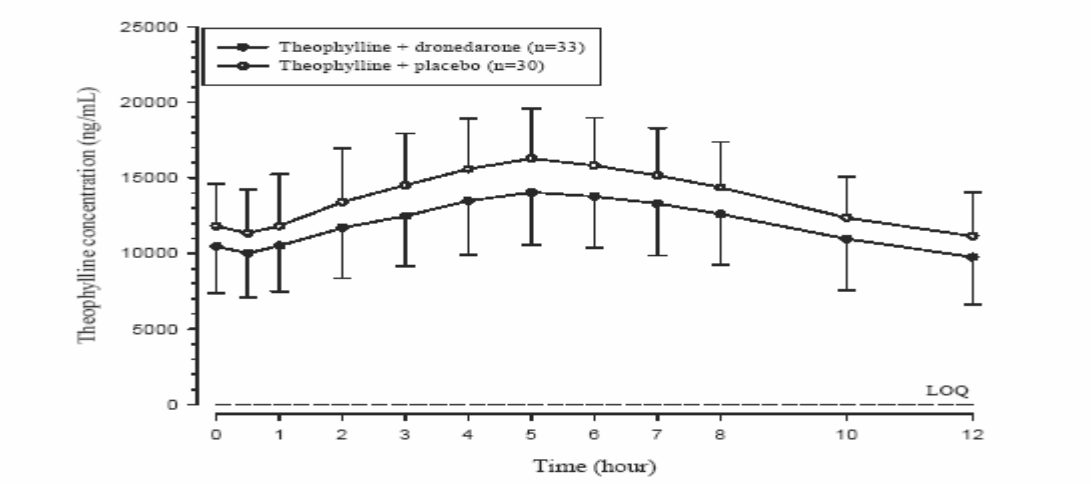
[a]: median (min-max)

The dronedarone and SR35021 PK data are consistent with those obtained in other studies where dronedarone was administered alone; this finding suggests that theophylline does not affect dronedarone PK.

Theophylline PK

The theophylline plasma concentration-time profile is depicted in Figure 113.

Figure 113: Theophylline plasma concentration-time profiles in the presence and absence of dronedarone



Theophylline PK measures and exposure comparisons are summarized in Table 185.

Table 185: Theophylline mean (CV%) and geometric mean ratios and associated 90 % confidence intervals in the presence and absence of 400 mg theophylline

Parameter	Theophylline + dronedarone (n=33)	Theophylline+ placebo (n=30)	Ratio estimate[a] [90% CI]
C_{max} (ng/mL)	14400 (25)	16600 (20)	0.830 [0.800, 0.860]
t_{max}[b] (hour)	5.0 (2.0 – 8.0)	5.0 (3.0 – 8.0)	0 [-0.50, 0.02][c]
AUC_{0-12} (ng.h/mL)	145000 (27)	166000 (22)	0.822 [0.796, 0.850]

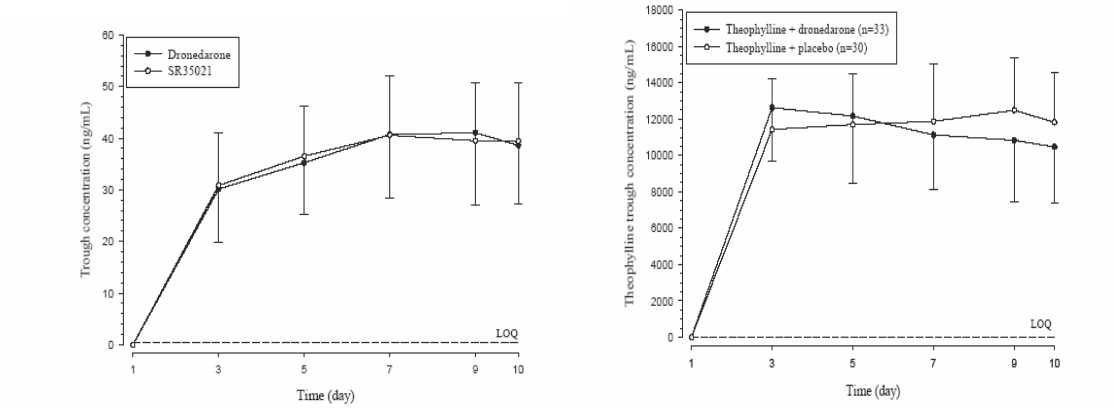
[a]: geometric mean ratio: theophylline + dronedarone/theophylline + placebo
[b]: median (minimum-maximum)
[c]: estimate of median difference [90% CI of median difference]

The confidence intervals indicate that dronedarone decreases theophylline exposure by ~ 20 %; however, this decrease in exposure may not be clinically significant as the decrease is almost entirely within the default no effect confidence interval region (0.80 -1.25).

Attainment of Steady State

Dronedarone steady state was achieved on Day 7 (Figure 114). The time to reach steady state (Tss) for theophylline was delayed in the presence of dronedarone: theophylline + placebo: Tss = three days vs. theophylline + dronedarone Tss steady state = nine days

Figure 114: Time to achieve dronedarone, SR35021, and theophylline steady state



Applicant's Safety Summary

No deaths or serious AEs (SAEs) occurred during the study. Initial insomnia, nausea, and headache were the most frequently reported treatment emergent (TE) AEs in both treatments. Three subjects discontinued study drug due to TEAEs: TEAEs were mainly GI-related (n = 3). The report indicates that six subjects discontinued study drug due to hypertheophyllinemia (theophylline concentrations > 20 µg/mL), but the five of these subjects were on placebo treatment. It is noted that hypertheophyllinemia was not considered an AE.

Dronedarone presence caused an increase in QTc values, relative to the QTc values obtained with theophylline alone: QTc > 450 ms were observed in 5/36 subjects during theophylline + placebo and 10/36 during theophylline + dronedarone treatment.

Recommendations/Conclusions

The following PK information generated in Study INT3561 is acceptable for labeling purposes, as appropriate:

After a 10-day concomitant administration of dronedarone 400 mg BID with 400 mg BID theophylline, relative to theophylline alone, there was approximately a 20 % decrease in steady state of theophylline AUC_{0-12}. These changes may not be clinically significant as the AUC change was just outside the no-effect default lower boundary, whereas the Cmax was within the default no-effect range.

Labeling

The applicant's proposed labeling is acceptable as it adequately reflects the study findings. A dosage adjustment does not appear warranted based on the study findings. Theophylline dosage may be titrated upwards, if needed.

4.2.29 Study on the interaction between a single oral dose of warfarin and repeated oral doses of SR33589B in healthy male subjects (INT3353)

PROTOCOL #	INT3353
INVESTIGATOR	Dr. W. Tetzloff
STUDY SITE	IPHAR - Institut für Klinische Pharmakologie GmbH - Arnikastrasse 4 - D- 85635 Höhenkirchen- Siegerstsbrunn
STUDY PERIOD	March – May 1998

Background Information on Study Drugs (Warfarin and Dronedarone)

	Warfarin	Dronedarone
Indication/Mechanism of Action	Anticoagulant used for several indications including treatment of thromboembolic complications associated with atrial fibrillation	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Several metabolites formed including hydroxylated and reduced (alcohol) species. These metabolites have minimal activity.	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	Undergoes stereo-selective metabolism (S-isomer is five times as active as R-isomer and primarily responsible for clinical effectiveness). Multiple CYP enzymes but CYP2C9 appears predominant	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Dose titrated to achieve adequate anticoagulation based on international normalized ratio	400 mg BID

Objectives (per applicant)

Primary: To assess the effect of repeated oral doses of SR33589B (dronedarone) on the pharmacokinetic profile of warfarin given as a single oral dose.

Secondary

- To assess the pharmacodynamic effects of both warfarin alone and warfarin co-administered with dronedarone
- To estimate the effect of a single oral dose of warfarin on the pharmacokinetics of SR33589 at steady- state
- To assess the tolerability of dronedarone administered both alone and with warfarin.

Study Design

This was an open-labeled, randomized, two-period cross-over study with a 21-day wash out between two warfarin administrations. The following two sequences were followed, where warfarin was given as a single dose on each occasion:

1. warfarin/dronedarone+ warfarin sequence- Day 1, warfarin alone and 14 consecutive days of dronedarone with warfarin concomitantly administered on Day 8

2. dronedarone + warfarin /warfarin sequence- fourteen consecutive days of dronedarone with warfarin concomitantly administered on the Day 8, and one day of warfarin administration alone.

The warfarin dose was 30 mg and the dronedarone dose was 600 mg BID.

Reviewer's Note on Previously Conducted Warfarin-Dronedarone Drug Interaction Study
In a previous study a sequence effect was observed with warfarin administration; however, results obtained in that study are qualitatively and quantitatively similar to the current study. The source of the sequence effect is unclear.

Subject Demographics
Key subject demographic characteristics are as follows:

- Sex: all male subjects
- Race: all Caucasian
- Weight (Range): 69.9 – 86.0 kg
- Age (range): 26 – 45 years

All subjects, except one (Subject 002), completed the study.

Formulation

- Dronedarone: 200 mg capsules, batch number 96-00198
- Warfarin: 10 mg tablets, batch number 7002 (commercially available source)

Pharmacokinetic sampling times
The following pharmacokinetic blood samples were drawn at the given times:

- R- and S- warfarin: before warfarin administration then 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours after administration
- Dronedarone and SR35021: before the morning administration of dronedarone on Days 1, 3, 5, 7, 8, 9, 10, 11, 12 and 14 of dronedarone treatment.
- Dronedarone and SR35021: On Days 7 and 8 of dronedarone administration, samples were taken 1, 2, 3, 4, 5, 6, 8 and 12 hours after the morning administration of dronedarone.

Pharmacokinetics
The following pharmacokinetic (PK) measures were determined after each treatment:

- R-warfarin and S-warfarin: Cmax, tmax, AUClast, AUC and $t_{1/2}$ after single administration of warfarin alone or with repeated administration of dronedarone.
- Dronedarone and SR35021:
    - Cmax, tmax and AUC_{0-12} after repeated administration of dronedarone alone or with a single administration of warfarin
    - Ctrough on Day 3, 5, 7, 8, 9, 10, 11, 12 and 14 days after repeated administration.

Activity/Pharmacodynamics
The pharmacodynamic effects, prothrombin time (%) and international normalized ratio (INR), of warfarin alone and co-administered with dronedarone were determined.

Bioanalytical methods

Dronedarone and SR35021 Assays

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 186.

Table 186: Dronedarone and SR35021 assay performance

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV was < 6 %	Satisfactory
Accuracy	QC samples were between -1 and 3 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory
	SR35021	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV was < 6 %	Satisfactory
Accuracy	QC samples were between -3 and 4 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory

* chromatograms provided in validation report that indicate assay specificity

R- and S-Warfarin concentrations were determined by HPLC with UV detection. The assay performance was acceptable as shown in Table 187.

Table 187: Performance of Warfarin Assay

Parameter	Measure	Reviewer Comment
	R-warfarin Assay	
Linearity	The assay was linear over the 10 to 2000 ng/mL range	Satisfactory
Between day Precision	CV was < 7 %	Satisfactory
Accuracy	QC samples were within 7 % of nominal concentration	Satisfactory
LLOQ	10 ng/ml	Satisfactory
Specificity	Chromatograms were not provided	Cannot be assessed
	S-warfarin Assay	
Linearity	The assay was linear over the 10 to 2000 ng/mL range	Satisfactory
Between day Precision	CV was < 7 %	Satisfactory
Accuracy	QC samples were within 6 % of nominal concentration	Satisfactory
LLOQ	10 ng/ml	Satisfactory
Specificity	Chromatograms were not provided	Cannot be assessed

Statistical methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The reference treatments were dronedarone alone and warfarin alone and the test treatment was warfarin + dronedarone.

PD measures were analyzed using ANOVA and 95 % confidence intervals for the differences in the treatment means were determined. Variables included in the analyses were INR and percentage prothrombin time (PT), overall hourly average PT, maximum INR, the time of maximum INR (rank transformed), minimum PT (percentage) and the time of the minimum PT (rank transformed). These variables are further defined in the following table.

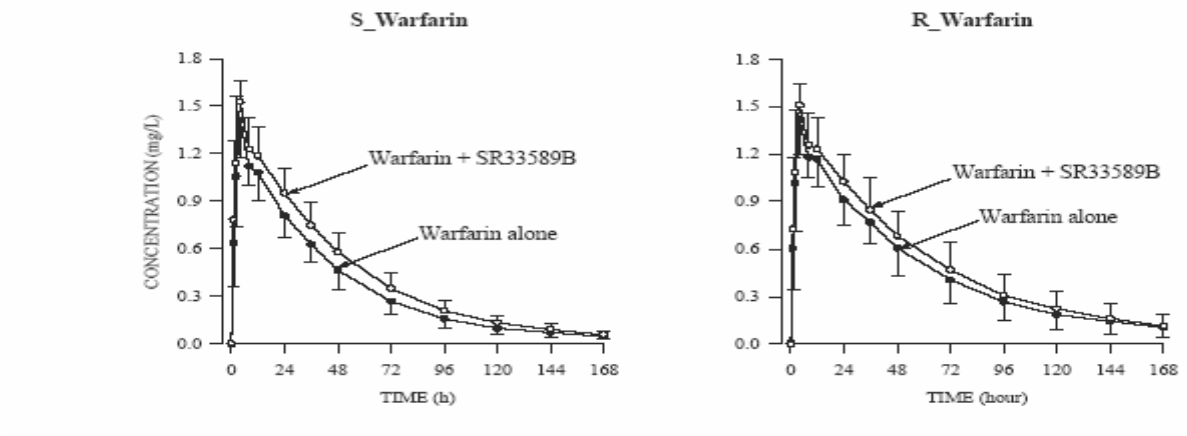
Parameter	Calculated Measure	Calculation
Prothrombin INR	Overall hourly average	AUC^f/168$^+$
	Maximum	Largest increase from T_0
	Time of maximum	Time of largest increase from T_0
Prothrombin Time (%)	Overall hourly average	AUC^f/168$^+$
	Minimum	Largest decrease from T_0
	Time of minimum	Time of largest decrease from T_0

f AUC = Area Under the Curve calculated using the trapezoidal rule.
\+ 168 hours is the overall time interval

Reviewer Note on PD Statistical Analyses
INR is the most commonly used warfarin PD measure, therefore, this review focuses on INR results.

Results
Warfarin Pharmacokinetics
The plasma concentration-time profiles for S- and R-warfarin are depicted in Figure 115.

Figure 115: S- and R-warfarin plasma concentration-time profiles following single dose administration of warfarin and dronedarone (multiple dose for eight days before warfarin)



The mean (± SD) and CV% of R- and S- warfarin plasma pharmacokinetic parameters obtained after a single 30 mg administration of warfarin (n = 16) alone or with dronedarone are shown in Table 188.

Table 188: Mean (CV %) S- and R-warfarin PK measures following administration of warfarin +/- dronedarone

Parameter	S-warfarin		R-warfarin	
	warfarin alone	warfarin + SR33589B	warfarin alone	warfarin + SR33589B
C_{max} (mg/L)	1.44 (0.20) 14%	1.54 (0.13) 9%	1.45 (0.17) 12%	1.51 (0.13) 9%
t_{max} (h)	4.37 (2.43) 56%	4.00 (1.26) 32%	5.24 (2.79) 53%	4.49 (2.35) 52%
AUC_{last} (mg.h/L)	60.1 (11.2) 19%	71.7 (13.0) 18%	76.8 (18.6) 24%	85.5 (21.1) 25%
AUC (mg.h/L)	63.0 (12.2) 19%	75.0 (14.3) 19%	84.9 (24.1) 28%	94.3 (28.5) 30%
$t_{½}$ (h)	40.4 (4.8) 12%	38.1 (4.3) 11%	49.1 (9.5) 19%	46.8 (12.2) 26%

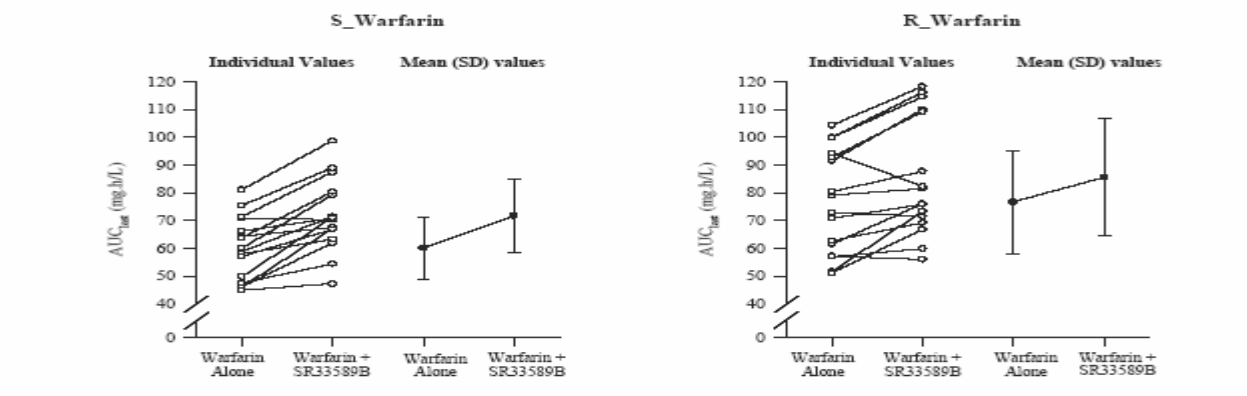
The ratio estimates and 90% confidence intervals (CIs) calculated for Cmax and AUC treatment effect (warfarin + dronedarone versus warfarin alone) of S- and R-warfarin and R- warfarin are shown in Table 189.

Table 189: S- and R- warfarin geometric mean ratios and associated 90 % CIs in the presence and absence of 400 mg dronedarone

Parameter	S-warfarin		R-warfarin	
	Ratio	90% CI	Ratio	90% CI
C_{max}	1.07	[1.00 , 1.14]	1.04	[0.98 , 1.11]
AUC_{last}	1.19	[1.13 , 1.26]	1.11	[1.06 , 1.18]
AUC	1.19	[1.13 , 1.26]	1.11	[1.05 , 1.18]

Most subjects had increased warfarin exposure in the presence of dronedarone as indicated from Table 189 and Figure 116. However, the increase in exposure is generally within the default no effect CI range, suggesting that co-administration of dronedarone with warfarin does not result in a clinically significant PK interaction.

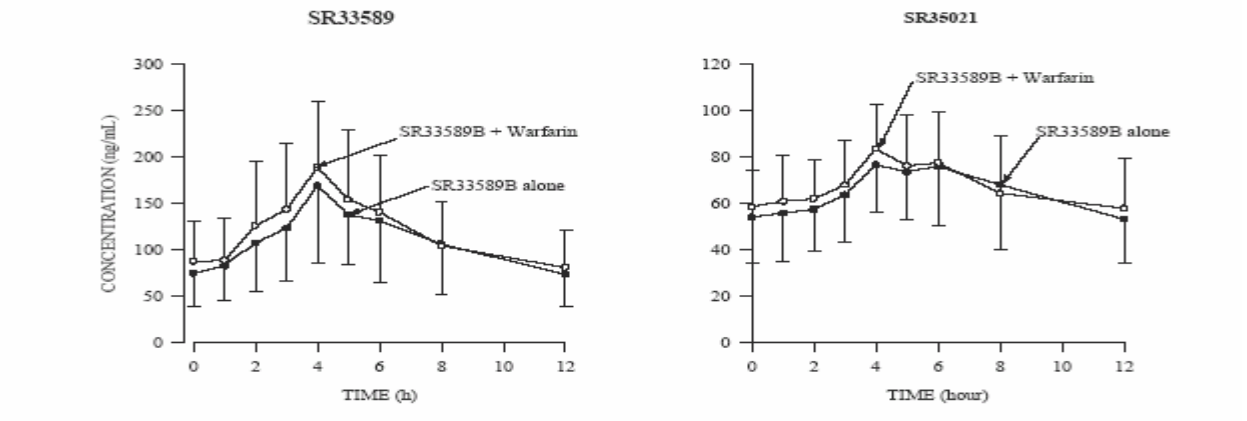
Figure 116: Individual and mean S- and R- warfarin AUCs following administration of warfarin +/- dronedarone



Dronedarone PK

The mean plasma concentration-time profiles for dronedarone are depicted in Figure 117.

Figure 117: Dronedarone plasma concentration-time profiles following administration of dronedarone +/- single dose administration of warfarin



Dronedarone and SR35021 PK measures are summarized in Table 190 and Table 191.

Table 190: Mean (CV %) dronedarone and SR35021 PK measures following administration of warfarin +/- dronedarone

Parameter	SR33589		SR35021	
	SR33589B alone	SR33589B + warfarin	SR33589B alone	SR33589B + warfarin
C_{max} (ng/mL)	175 (79) 45%	191 (72) 38%	86.0 (23.4) 27%	86.5 (19.4) 22%
t_{max} (h)	4.13 (1.36) 33%	3.81 (0.75) 20%	5.31 (1.58) 30%	4.97 (1.40) 28%
AUC_{0-12h} (ng.h/mL)	1312 (581) 44%	1424 (630) 44%	775 (247) 32%	802 (227) 28%

Table 191: S- and R- warfarin geometric mean ratios and associated 90 % confidence intervals in the presence and absence of 400 mg dronedarone

Parameter	SR33589		SR35021	
	Ratio	90% CI	Ratio	90% CI
C_{max}	1.13	[1.05 , 1.22]	1.02	[0.96 , 1.09]
AUC_{0-12h}	1.08	[1.02 , 1.15]	1.04	[0.99 , 1.10]

The dronedarone and SR35021 PK data indicate that warfarin does not alter dronedarone or SR35021 PK significantly.

Activity (Pharmacodynamics)

The PD (INR) results are summarized in the following figures and tables. The PD data related to INR, the most clinically relevant parameter, indicate the following:

- overall hourly average INR for subjects co-administered dronedarone and warfarin was 7 % greater than that for subjects receiving warfarin alone (p= 0.007)
- maximum INR for warfarin alone and warfarin + dronedarone was similar (p = 0.096)
- time of maximum INR overlapped in the two treatment groups
- no statistically significant effects were observed for INR at T0, suggesting that prothrombin times had returned to T0 levels at the end of the wash out period.
- there were no sequence or period effects

Figure 118: Effects of warfarin +/- dronedarone administration on INR

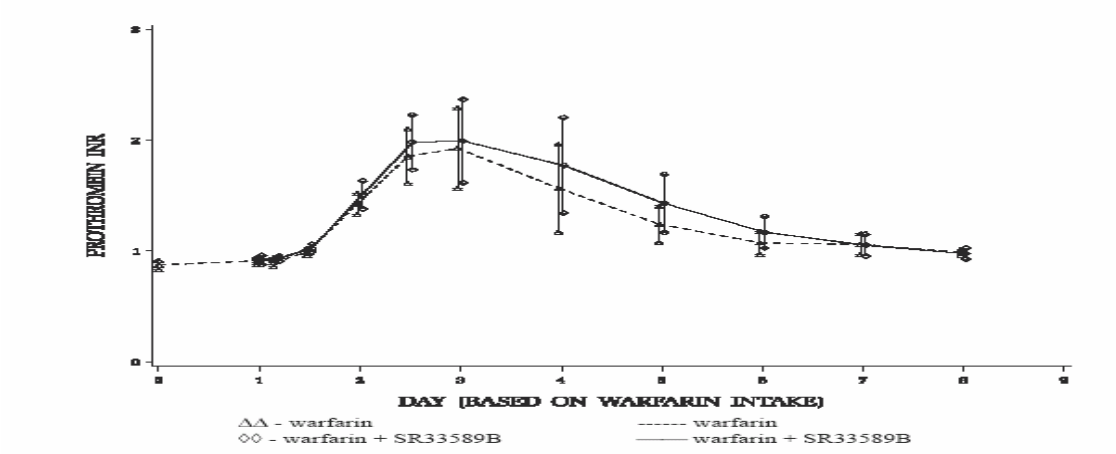


Table 192: INR values following administration of warfarin +/- dronedarone

Prothrombin Time	Parameter	Statistic	Warfarin	SR33589B + warfarin	(S+W)/W estimate (approx. 95% CI)[a]
INR	Overall Hourly Average	Mean (SD)	1.32 (0.31)	1.41 (0.37) *	107.0% (102.3%, 111.7%)
	Maximum	Mean (SD)	1.99 (0.68)	2.10 (0.73)	105.8% (98.8%, 112.8%)
	Time of Maximum	Median (Min-Max)	1.75 (1.00-3.00)	1.50 (1.50-3.00)	NA

* Significantly different from warfarin, $p < 0.01$.
[a] 95 % confidence intervals (CI) were calculated for the differences in treatment means
NA – Not applicable.

Table 193: Analysis of prothrombin time

Prothrombin Time	Parameter	P-Values		
		Sequence	Period	Treatment
INR	PT at T0	0.7494	0.1229	0.6749
	Overall Hourly Average	0.5904	0.0206	0.0065
	Maximum	0.4983	0.0569	0.0959
	Time of Maximum (Ranks)	0.3770	0.6109	0.6109

Applicant's Safety Summary

Overall, concomitant administration of dronedarone with warfarin was well tolerated. Four subjects each experienced a single adverse event (AE) in this study, only one of which led to the withdrawal of a subject. The AEs were as follows: asymptomatic non-sustained ventricular tachycardia (n = 2), second degree atrioventricular block type 1 (n =1) and headache (n = 1).

Recommendations/Conclusions

The following findings from study INT3353 are acceptable for labeling as appropriate:

- Co-administration of a single dose of warfarin with dronedarone does not alter the PK of dronedarone or SR35021
- Relative to administration of warfarin alone (single dose), administration of dronedarone at 600 mg BID for seven days followed by concomitant administration of a single dose of warfarin, increases warfarin AUC by 11 % but has no effect on Cmax. The AUC increase does not appear clinically relevant based on PK measures, as the confidence intervals are generally within the default no effect range.
- Relative to administration of warfarin alone, co-administration of warfarin +/- dronedarone did not alter the INR maximum value or time of maximum value; however, the overall hourly average prothrombin time for subjects co-administered dronedarone and warfarin was significantly greater for INR (7 % increase) when subjects received the warfarin dose alone. However, this INR increase does not appear clinically significant.

Labeling

The labeling should reflect the study findings. A dosage adjustment does not appear warranted based on the study findings. However, precautionary language may be included indicating that INR time may increase (resulting in increased bleeding) when warfarin is co-administered with dronedarone, relative to when warfarin is administered alone. This effect may result from the increased warfarin exposure. It is noted that the warfarin dosage can be titrated to modulate this undesirable effect, if needed.

4.2.30 Interaction study between repeated oral doses of dronedarone and repeated oral doses of nisoldipine in healthy male subjects - randomized, open-labeled, 3 treatments, crossover study (INT4881)

PROTOCOL #	INT4881
INVESTIGATOR	Mark Allison, M. D.
STUDY SITE	MDS Pharma Services, 4639 South 36th Street, Phoenix, AZ 85040,
STUDY PERIOD	January – April 2002

Background Information on Study Drugs (Nisoldipine and Dronedarone)

	Nisoldipine	Dronedarone
Indication/Mechanism of Action	Calcium channel blocker commonly prescribed in cardiac patients	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Hydroxylated active metabolite (activity $1/10^{th}$ that of parent)	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP3A substrate with low oral bioavailability	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Therapy initiated at 20 mg QD and drug titrated	400 mg BID

Objectives (per applicant)

Primary

- To assess the effect of repeated oral doses of dronedarone on the pharmacokinetic (PK) profile of nisoldipine after repeated oral doses of 20 mg once daily (QD)
- To assess the effect of repeated oral doses of nisoldipine on the PK profile of dronedarone after repeated oral doses of 400 mg twice daily (BID)

Secondary

- To assess the clinical and biological tolerability of dronedarone given alone, of nisoldipine given alone, and of dronedarone co-administered with nisoldipine
- To assess the potential pharmacodynamic (PD) effect of dronedarone when co-administered with nisoldipine

Study Design

This was an open-label, non-placebo-controlled, repeated oral doses, randomized, 3-treatment, 3-period and crossover study. The washout period was seven to 13 days. The three treatments were

- dronedarone 400 mg BID alone for 14 days
- nisoldipine 20 mg QD alone for 14 days
- dronedarone and nisoldipine co-administration for 14 days

Reviewer Note on Nisoldipine Dose
The nisoldipine dose is not the highest recommended dose (60 mg). Use of a dose lower than the highest recommended dose is acceptable, if driven by safety concerns.

Subject Demographics
Subject demographics are summarized in Table 194.

Table 194: Subject demographics (Study 4881)

Parameter	Statistics/ Category	Total (N=28)
Age (yrs)	N Mean (SD) Min - Max	28 26.0 (4.2) 19 - 34
Weight (kg)	N Mean (SD) Min - Max	28 74.21 (9.19) 57.7 – 89.7
Height (cm)	N Mean (SD) Min - Max	28 175.1 (7.1) 164 - 193
BMI (kg/m^2)	N Mean (SD) Min - Max	28 24.21 (2.86) 18.8 – 27.9
Gender	Male (N,%)	28 (100%)
Race	Caucasian (N,%) Black (N,%) Hispanic (N,%)	25 (89.3%) 2 (7.14%) 1 (3.57%)

Formulation
- Dronedarone: 400 mg tablet, batch number CL-04141
- Nisoldipine (Sular) 20 mg tablets, batch number 4548F

Pharmacokinetic sampling times
The following pharmacokinetic blood samples were drawn at the given times:
- Dronedarone and SR35021: pre-morning dose on Days 1, 2, 4, 8, 10, 12 and 14
- Dronedarone and SR35021: 0.5, 1, 2, 3, 4, 6, 8, 10, 12 hours after dosing on Day 14
- Nisoldipine: before administration on Days 1, 2, 4, 8, 10, 12 and 14
- Nisoldipine: 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours after dosing on Day 14, for each period of treatment.

Pharmacokinetics
The following PK measures were determined:
- Dronedarone and SR35021- Ctrough, Cmax , tmax, AUC_{0-12}, and Rmet (SR35021 AUC_{0-12}/SR33589 and AUC_{0-12} ratio)
- Nisoldipine- Ctrough, Cmax, tmax, AUC_{0-24}.

Activity/Pharmacodynamics
The following primary pharmacodynamic (PD) variables were determined: heart rate, electrocardiogram (ECG) intervals (PR- interval and corrected QT value calculated with the Bazett formula [QTc]). The secondary PD variables were QRS- and QT-interval.

Statistical Methods
Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The reference treatments were dronedarone alone and nisoldipine alone and the test treatment was nisoldipine + dronedarone. Standard statistical methods were used to evaluate pharmacodynamics.

Bioanalytical methods
Dronedarone and SR35021 Assays
Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method (DOH0239). The assay performance was acceptable as shown in Table 195.

Table 195: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV values were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided, however, the majority of individual QC samples were within 15 % of nominal concentration.	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided	Satisfactory
	SR35021	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.993$	Satisfactory
Between day Precision	CV value was not provided	Cannot be assessed
Accuracy	Relative bias values were not provided, however, the majority of individual QC samples were within 15 % of nominal concentration.	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity*	Chromatograms were not provided	Cannot be assessed

* assay validation report includes chromatograms that indicate assay specificity

Nisoldipine concentrations were determined by a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 196.

Table 196: Performance of Nisoldipine Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 0.10 to 25 ng/mL range; $R^2 > 0.993$	Satisfactory
Between day Precision	CV was < 9 %	Satisfactory
Accuracy	QC samples were between -1.9 and – 3.4 % of nominal concentration	Satisfactory
LLOQ	0.10 ng/ml	Satisfactory
Specificity	Chromatograms were not provided	Cannot be assessed

Results
PK data were available from 26 subjects; two subjects were withdrawn from the study.

Dronedarone and SR35021 Pharmacokinetics
The dronedarone and SR35021 plasma concentration-time curves are depicted in Figure 119 and Figure 120, respectively.

The pharmacokinetic measures of dronedarone and SR35021 after dronedarone administration with or without nisoldipine are summarized in Table 197.

Figure 119: Dronedarone plasma concentration-time profiles following administration of dronedarone +/- nisoldipine

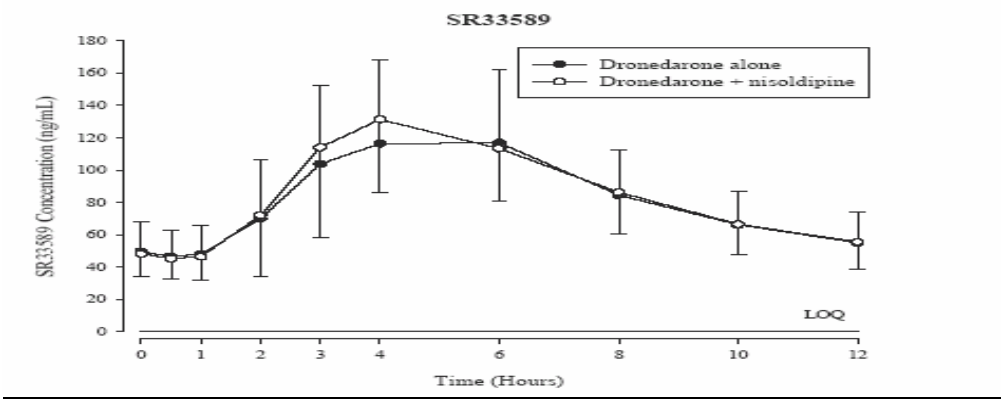


Figure 120: SR35021 plasma concentration-time profiles following administration of dronedarone +/- nisoldipine

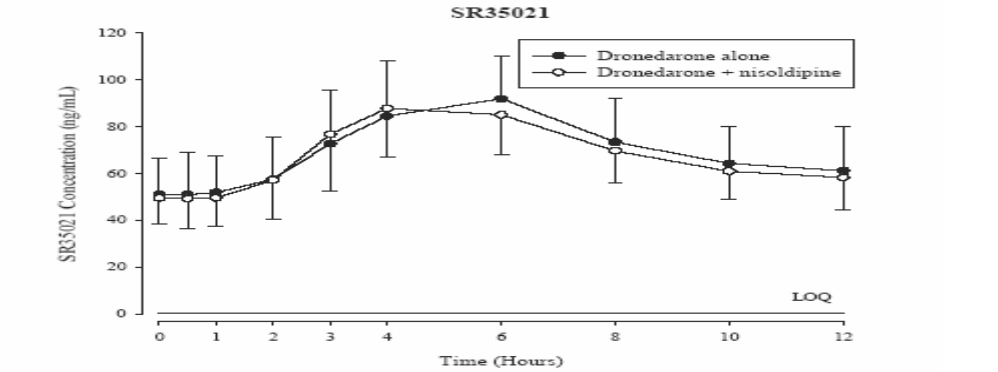


Table 197: Dronedarone and SR35021 PK Measures following administration of dronedarone +/- nisoldipine

PK Parameters	Dronedarone Alone	Dronedarone + Nisoldipine	Ratio Estimates[b] and 90% CI
	SR33589		
C_{max} (ng/mL)	134 (38)	144 (32)	1.12 [1.02; 1.22]
t_{max} (h)*	5	4	p=0.188
AUC_{0-12} (ng.h/mL)	1008 (34)	1039 (28)	1.07 [1.01; 1.12]
	SR35021		
C_{max} (ng/mL)	95.7 (21)	93.8 (20)	1.00 [0.94; 1.06]
t_{max} (h)*	6	4	p=0.02
AUC_{0-12} (ng.h/mL)	852 (23)	828 (18)	0.99 [0.94; 1.04]
R_{met} (AUC_{0-12})	0.90 (26)	0.84 (24)	-

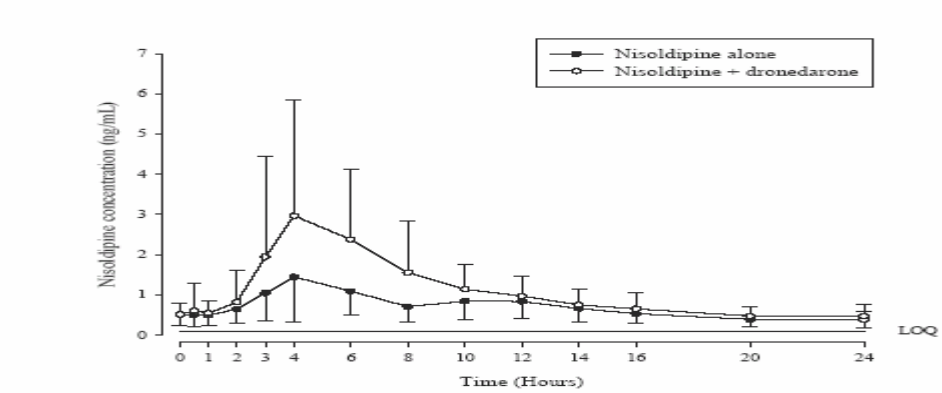
* Median values
[b] ratio dronedarone + nisoldipine / dronedarone, p-value for difference between treatments

The data indicate that nisoldipine does not alter dronedarone PK in a clinically significant manner (confidence interval within no effect range).

Nisoldipine Pharmacokinetics

The nisoldipine plasma concentration-time profiles following administration of nisoldipine with or without dronedarone are depicted in Figure 121.

Figure 121: Nisoldipine plasma concentration time profile in the presence and absence of dronedarone



The nisoldipine PK measures obtained following administration of nisoldipine with or without dronedarone are presented in Table 198.

Table 198: Nisoldipine PK Measures following administration of nisoldipine +/- dronedarone (n = 26)

PK Parameter Mean (CV%)	Nisoldipine Alone	Nisoldipine + Dronedarone	Ratio Estimates[b] and 90% CI
C_{max} (ng/mL)	1.76 (60)	4.10 (74)	2.13 [1.55; 2.93]
t_{max} (h)[a]	4	4	p=0.377
AUC_{0-24} (ng.h/mL)	16.8 (41)	26.4 (51)	1.50 [1.08; 2.10]

[a] Median values
[b] ratio nisoldipine + dronedarone / nisoldpine, p-value for difference between treatment

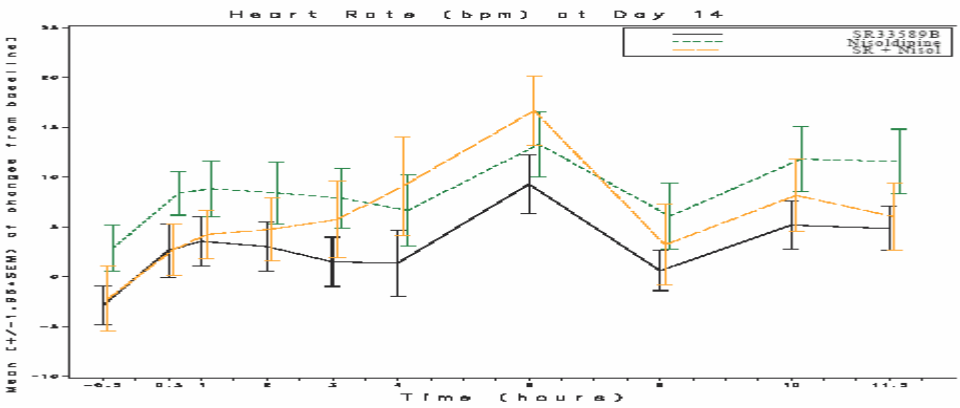
Co-administration of dronedarone increased mean nisoldipine Cmax and AUC_{0-24} by 2.1- fold and 1.5- fold, respectively. This finding suggests dronedarone inhibited nisoldipine metabolism.

Pharmacodynamics

The pharmacodynamic (PD) data for the nisoldipine-dronedarone interaction are graphically illustrated in the following figures and Table 199. Each PD measure is discussed in turn.

- Heart rate

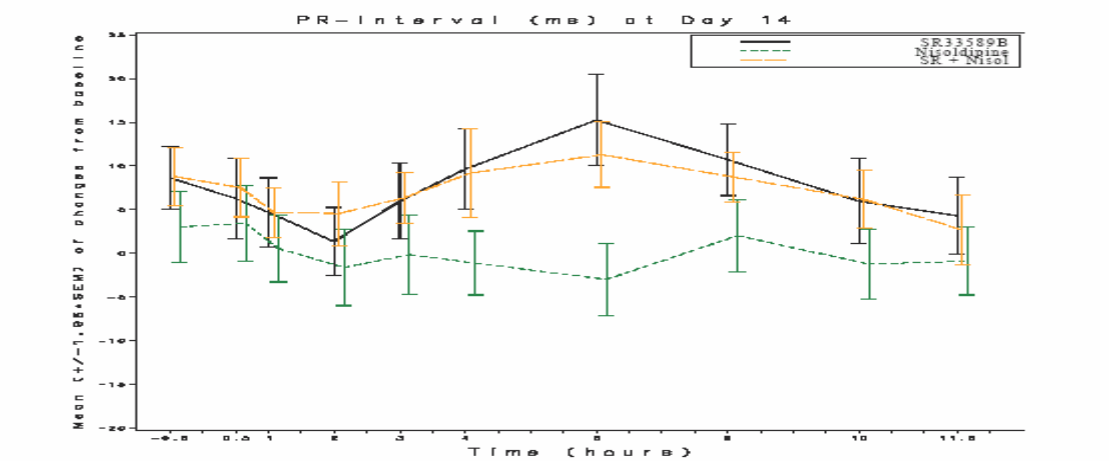
Figure 122: Changes in Heart Rate (Day 14 vs. Baseline) following administration of dronedarone alone, nisoldipine alone and nisoldipine + dronedarone



After 14 days of treatment, the change from baseline HR for nisoldipine alone was greater than that of dronedarone alone. However, there was no difference between the co-administration treatment and either treatment given alone, suggesting that there was no PD interaction on HR.

- PR Interval

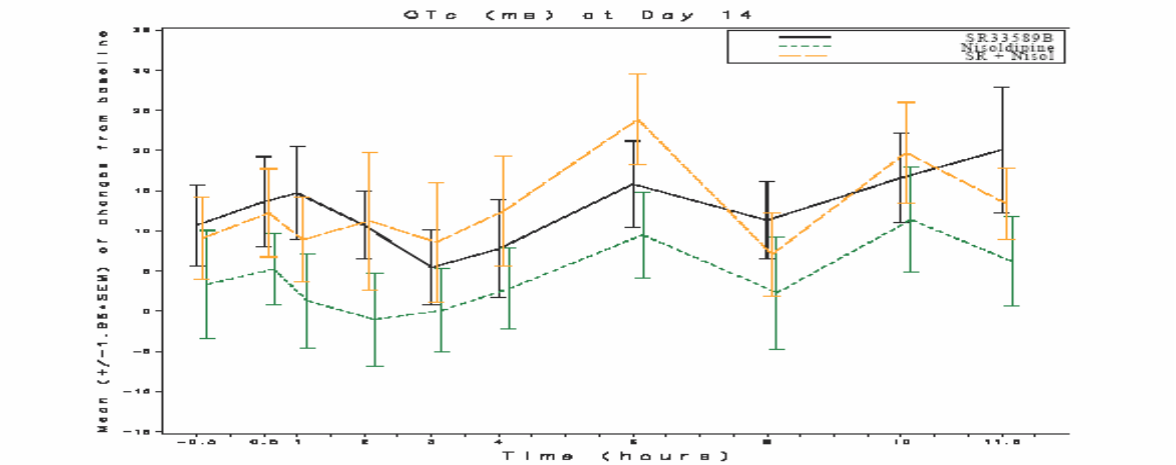
Figure 123: Changes in PR interval (Day 14 vs. Baseline) following administration of dronedarone or nisoldipine alone and nisoldipine + dronedarone



A statistically significant difference in mean change from baseline (Day 1 pre-dose) PR-interval over 12 hours on Day 14 was seen between the co-administration and the nisoldipine alone treatments. However, the mean increases in PR-interval were similar after repeated doses of dronedarone given alone or in combination with nisoldipine. The data suggest that there was no PD interaction on PR-interval, and the observed significant difference in PR- interval after repeated co-administration versus nisoldipine alone was probably due to the dronedarone effect.

- QTc

Figure 124: Changes in QTc interval (Day 14 vs. Baseline) following administration of dronedarone or nisoldipine alone and nisoldipine + dronedarone



A statistically significant difference in mean change from baseline (Day 1 pre-dose) QTc over 12 hours on Day 14 was seen between the co-administration and the nisoldipine alone treatments. However, the mean increases in QTc were similar after repeated doses of dronedarone given alone or in co-administration with nisoldipine. The data suggest that there was no PD interaction on QTc and the observed significant difference in QTc after repeated co-administration versus nisoldipine alone was probably due to the dronedarone effect.

Table 199: Pharmacodynamic data of the Day 14 mean difference estimates in averaged changes from baseline over 12 hours

Parameter (Unit)	Estimates of Mean Differences [95% CI]		
	Nisol. – Drone. (N = 26)	Co-admin. – Nisol. (N = 26)	Co-admin. – Drone. (N = 26)
Heart rate (bpm)	5.61 [2.17, 9.05]	-2.68 [-6.11, 0.76]	2.93 [-0.52, 6.39]
PR-interval (ms)	-7.38 [-11.21, -3.55]	6.60 [2.77, 10.43]	-0.78 [-4.62, 3.07]
QTc (ms)	-8.73 [-14.05, -3.42]	8.46 [3.15, 13.78]	-0.27 [-5.61, 5.07]

Applicant's Safety Summary

No deaths or serious adverse events were reported during the study. All reported treatment-emergent adverse events (TEAEs) were mild in severity. TEAEs were almost twice as common in the dronedarone + nisoldipine treatment group compared to the dronedarone or nisoldipine alone treatment groups. The most common TEAEs were dizziness, headache, palpitations, nausea, and vomiting. Vital signs and ECG measures were comparable between treatment groups.

Recommendations/Conclusions

The following findings from study INT4881 are acceptable for labeling as appropriate:

- co-administration of nisoldipine (20 mg QD) and dronedarone (400 mg BID) increased nisoldipine Cmax and AUC_{0-24} by 2.1-fold and 1.5-fold, respectively, relative to nisoldipine alone
- dronedarone exposure was not altered by nisoldipine
- there did not appear to be a pharmacodynamic interaction between dronedarone and nisoldipine with respect to their effect on PR, QTc or HR.

Labeling Comments

The applicant's labeling proposal is acceptable as it reflects the study findings. A dosage adjustment does not appear warranted during nisoldipine and dronedarone co-administration although nisoldipine exposure is increased. The therapeutic dosage range is approximately 10 to 60 mg; therefore, initiating therapy at 20 mg (typical initial dosage) with dronedarone, will lead to nisoldipine exposures that fall within therapeutic range. Subsequently, the nisoldipine dosage can be titrated, as needed depending on the safety and effectiveness of the nisoldipine-dronedarone regimen. In sum, precautionary language should be included in the label to indicate that patients receiving dronedarone and nisoldipine as part of therapy may have an increase in nisoldipine concentrations that may exacerbate adverse events associated with high nisoldipine exposure.

Reviewer's Note on Applicant's Labeling

The applicant's labeling is satisfactory although it does not provide specific precautionary language with regard to the consequences of increased nisoldipine concentrations. This omission is acceptable because the increase in nisoldipine concentration is only 50 % and nisoldipine dosage is routinely titrated during therapy.

4.2.31 Dose escalation study of the tolerability and pharmacodynamic effects of dronedarone on top of metoprolol in healthy male volunteers (PDY3828)

PROTOCOL #	PDY3828
INVESTIGATOR	Henri Caplain, MD
STUDY SITE	Aster Clinical Research Center, 3 and 5 rue Eugène Millon, 75015 Paris, France,
STUDY PERIOD	May – October, 1999

Background Information on Study Drugs (Metoprolol and Dronedarone)

	Metoprolol	Dronedarone
Indication/Mechanism of Action	Beta blocker used in the treatment of hypertension, angina pectoris and heart failure	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Several metabolites are formed; exhibits stereo-selective metabolism (S and R). Metabolites are inactive	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP2D6 substrate	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Initial dosage varies depending on indication; subsequently dosage is titrated. Dose range: 12.5 to 200 mg daily	400 mg BID

Objectives (per applicant)

- to assess the tolerability and the pharmacodynamic effects in particular on myocardial contractility of escalating doses of dronedarone on top of metoprolol in healthy male volunteers
- to assess other pharmacodynamic effects of study drug and to assess effects of dronedarone on the pharmacokinetics (PK) of metoprolol at steady state.

Study Design

This was a randomized, double-blind, placebo-controlled, repeated dose and dose-escalating study. The following treatments were given over a 13 day period: five days metoprolol followed by eight days metoprolol + dronedarone. The metoprolol dosage was 200 mg once daily (QD) and dronedarone 400, 600, or 800 mg twice daily (BID) or placebo under fed conditions.

Subject Demographics

Subject demographics are summarized in Table 200. Forty-nine subjects were treated; however 39 subjects were evaluable for pharmacokinetics and 44 for pharmacodynamics.

Formulation

- Dronedarone: 200 mg tablets, batch number 98-01499
- Dronedarone placebo: batch number 99-02198
- Metoprolol: 200 mg tablets, batch number 99-02197

Table 200: Subject demographics (PDY3828)

Parameter	Statistics/ Category	Placebo	800 mg	1200 mg	1600 mg	All
Age (years)	N	13	6	9	21	49
	Mean	28.3	31.2	30.2	29.1	29.4
	SD	3.22	4.17	5.07	3.98	4.02
	Min	25	27	24	24	24
	Max	36	38	39	40	40
Height (cm)	N	13	6	9	21	49
	Mean	176.8	179.3	178.1	177.9	177.8
	SD	6.35	7.61	7.10	7.11	6.79
	Min	168	165	167	163	163
	Max	188	187	187	189	189
Weight (kg)	N	13	6	9	21	49
	Mean	71.49	75.13	72.72	70.19	71.60
	SD	8.701	5.474	10.18	7.858	8.230
	Min	56.5	69.2	59.1	57.8	56.5
	Max	82.4	83.2	89.0	85.7	89.0
Gender [n (%)]	Male	13 (100%)	6 (100%)	9 (100%)	21 (100%)	49(100%)
Race [n (%)]	Caucasian	13 (100%)	6 (100%)	9 (100%)	21 (100%)	49 (100%)

Pharmacokinetic sampling times

The following pharmacokinetic blood samples were drawn at the given times:

- Dronedarone and SR35021
  - Day 6 before administration, and Days 7, 9, 11 at Time 0 (T0)
  - Day 13 at T0 and 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after dosing.
- Metoprolol and alpha-hydroxy-metoprolol
  - Day 0, 5, 7, 9, 11 and 13 before treatment
  - Days 5 and 13 at T0, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h post dose

Bioanalytical methods

Dronedarone and SR35021 Assays

Dronedarone and SR35021 concentrations were determined by LC-MS/MS (DOH0151). The assay performance was acceptable as shown in Table 201.

Table 201: Performance of Dronedarone and SR35021 Assay

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CV < 12 %	Acceptable
Accuracy	QC samples were between -1.8 and 3.3 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory
	SR35021	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.982$	Satisfactory
Between day Precision	CV was < 18 % for low QC sample (close to LLOQ) and CV < 10 % for mid and high QC samples	Satisfactory
Accuracy	QC samples were between -2.8 and 1.7 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory

* chromatograms were included in the assay validation report that demonstrate specificity

Metoprolol and alpha-hydroxy-metoprolol

Metoprolol and alpha-hydroxy-metoprolol concentrations were determined by HPLC. The assay performance was acceptable as shown in Table 202.

Table 202: Performance of Warfarin Assay

Parameter	Measure	Reviewer Comment
	Metoprolol Assay	
Linearity	The assay was linear over the 5 to 1000 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 8 %	Satisfactory
Accuracy	QC samples were between 2.5 and 4.2 % of nominal concentration	Satisfactory
LLOQ	5 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
Parameter	Measure	Reviewer Comment
	alpha-hydroxy-metoprolol Assay	
Linearity	The assay was linear over the 5 to 1000 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 10 %	Satisfactory
Accuracy	QC samples were between 2.3 and 7.0 % of nominal concentration	Satisfactory
LLOQ	5 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Pharmacokinetics

The following PK measures were determined:

- For Dronedarone and SR35021- Cmax, tmax, Cmin, and $AUC_{0\text{-}12h}$
- For metoprolol and alpha-hydroxy-metoprolol- Cmax, tmax, Cmin, and $AUC_{0\text{-}24h}$

Activity/Pharmacodynamic Endpoint

The primarily and secondary endpoints were measured by a variety of techniques including, Doppler echocardiography, phonocardiogram, carotidogram and transthoracic electrical impedance cardiogram. The primary endpoints were mean velocity of endocardial circumferential fiber shortening (Vcfmean), left ventricular ejection fraction (LVEF), and cardiac output (CO); secondary endpoints were HR, stroke volume, systolic time interval corrected to HR (electromechanical systole [QS 2i]), and cardiac index.

Statistical Methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The reference treatment was metoprolol alone and metoprolol + dronedarone was the test treatment.

The pharmacodynamic analyses were based on the change in Day 5 and Day 13 measurements (CHG Day13- 5), using a one-way ANOVA model with term for dose.

Results

CYP2D6 metabolic status

Initial genotyping indicated that 2 out of the 44 available subjects were poor metabolizers (PMs: Subjects No. 2 and No. 5 in dronedarone 800 mg/day (BID) group). A more sophisticated analysis that allowed characterization of rare or unknown mutations indicated that three subjects initially identified as extensive metabolizers (EM) were PM (Subjects 28 and 32 in dronedarone 1600 mg/day BID group and subject 13 in placebo group). The report indicates that eight subjects did not undergo genotyping. According to the applicant the PK profile of these eight subjects were consistent with the results obtained for the 39 EM subjects, thus, they were considered EM in the analysis.

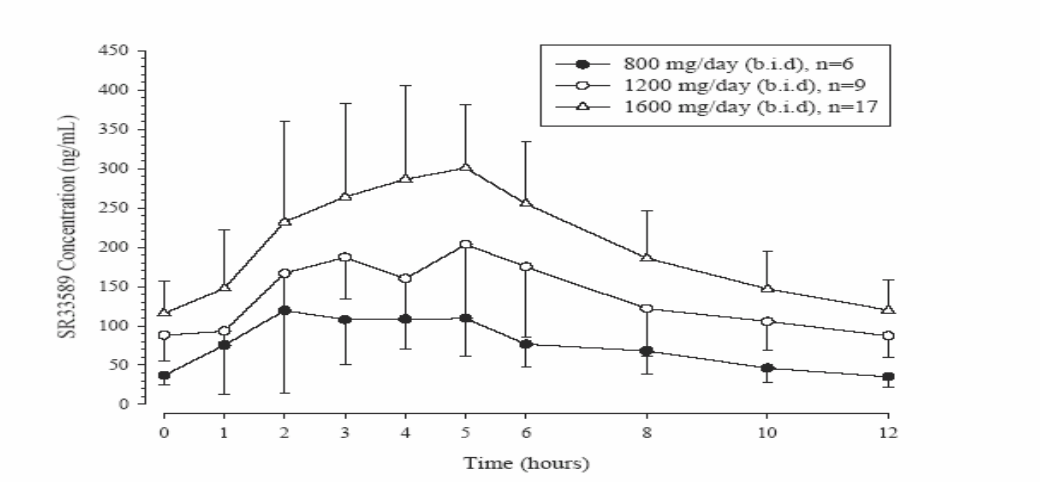
Reviewer Note on CYP2D6 status

The applicant correctly indicates that the evaluation of dronedarone's CYP2D6 inhibition potency is not possible, if the enzyme is not expressed (such as with PMs), therefore the statistical analyses would be performed using the results of the 39 remaining EM subjects. This approach is reasonable however all data could have been analyzed to make the study findings globally applicable because the general population includes PM, EM and other CYP2D6 metabolizers.

Dronedarone Pharmacokinetics

The dronedarone plasma concentration-time curves obtained following administration of dronedarone with metoprolol are depicted in Figure 125.

Figure 125: Dronedarone plasma concentration-time profiles following administration of dronedarone with metoprolol



The dronedarone PK measures are summarized in Table 203; based on a comparison to historical data, metoprolol does not appear to alter dronedarone PK.

Table 203: Dronedarone PK Measures following administration of dronedarone with metoprolol

Mean (SD) Parameters	SR33589B Treatment		
	800 mg/day (b.i.d.) n=6	1200 mg/day (b.i.d.) n=9	1600 mg/day (b.i.d.) n=17
C_{min} (ng/mL)	33.3 (12.0)	74.5 (27.4)	106.0 (36.9)
C_{max} (ng/mL)	167.1 (77.8)	240.7 (65.9)	348.5 (100.3)
t_{max} (h) *	4.0	4.0	4.0
AUC_{0-12h} (ng.h/mL)	912 (347)	1657 (449)	2455 (734)

a: median values

SR35021 Pharmacokinetics

The SR35021 plasma concentration-time curves following dronedarone administration with metoprolol are depicted in Figure 126.

The SR35021 PK measures are summarized in Table 204; based on a comparison to historical data, metoprolol does not appear to alter SR35021 PK.

Figure 126: SR35021 plasma concentration-time profiles following administration of dronedarone +/- metoprolol

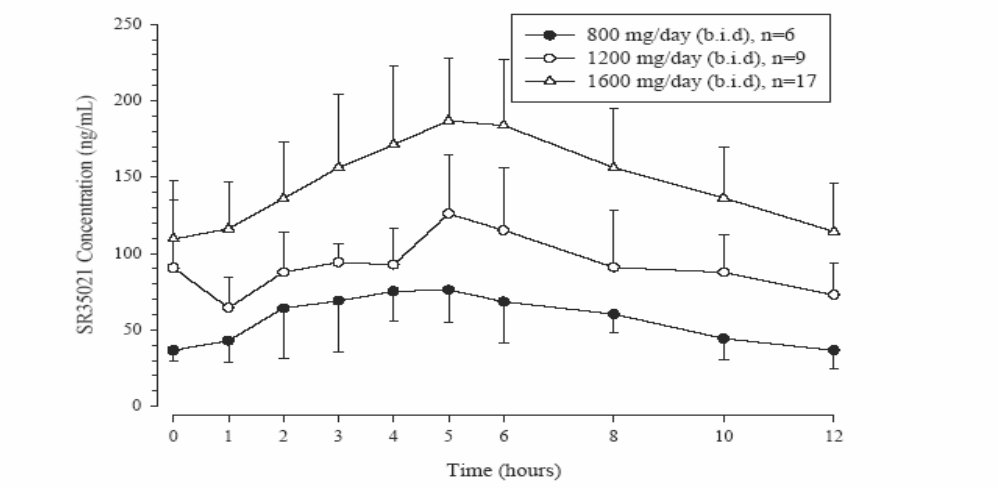


Table 204: SR35021 PK Measures following administration of dronedarone + metoprolol

Mean (SD) Parameters	SR33589B Treatment		
	800 mg/day (b.i.d.) n=6	1200 mg/day (b.i.d.) n=9	1600 mg/day (b.i.d.) n=17
C_{min} (ng/mL)	33.5 (8.8)	58.6 (17.8)	102.6 (28.7)
C_{max} (ng/mL)	88.2 (29.0)	155.9 (38.5)	198.3 (45.1)
t_{max} (h) *	5.5	5.0	5.0
AUC_{0-12h} (ng.h/mL)	689 (187)	1111 (249)	1794 (398)

a: median values

Metoprolol Pharmacokinetics

The metoprolol plasma concentration-time curves following co-administration of metoprolol with varying dronedarone doses and placebo are depicted in Figure 127.

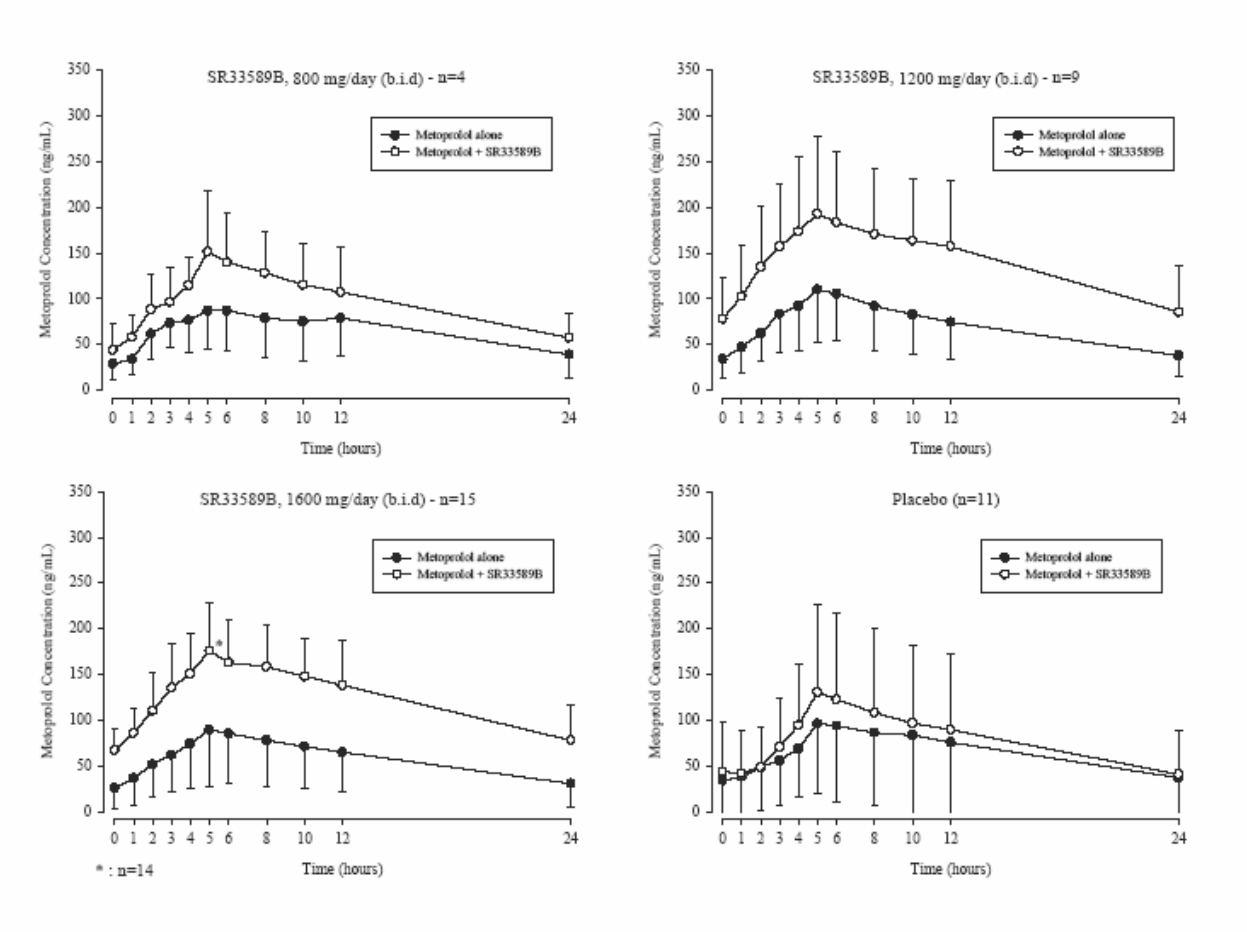
The metoprolol PK measures obtained following administration of metoprolol with or without dronedarone are presented in Table 205.

Table 205: Metoprolol PK Measures following administration of metoprolol +/- dronedarone (n = 26)

Parameters	SR33589B/Placebo Treatment			
	Placebo (n=11)	*800 mg/day (b.i.d.) n=4*	*1200 mg/day (b.i.d.) n=9*	*1600 mg/day (b.i.d.) n=15*
Metoprolol alone (day 5)				
C_{min} (ng/mL)	30.3 (43.4)	27.9 (17.5)	31.8 (18.4)	23.1 (20.4)
C_{max} (ng/mL)	100.6 (86.4)	92.7 (39.8)	111.4 (56.5)	96.2 (61.8)
t_{max} (h)*	5.0	4.0	5.0	5.0
AUC_{0-24h} (ng.h/mL)	1541 (1563)	1555 (803)	1662 (863)	1386 (909)
Metoprolol + SR33589B (day 13)				
C_{min} (ng/mL)	36.3 (44.5)	41.8 (26.6)	76.0 (44.6)	62.3 (27.2)
C_{max} (ng/mL)	134.1 (96.8)	162.6 (55.5)	195.8 (86.8)	180.9 (51.3)
t_{max} (h)*	5.0	5.0	5.0	5.0
AUC_{0-24h} (ng.h/mL)	1862 (1689)	2318 (846)	3361 (1534)	2980 (948)

*: median values

Figure 127: Metoprolol plasma concentration time profile in the presence and absence of dronedarone



The Cmax data (Table 206) indicate that administration of dronedarone resulted in increased metoprolol exposure (Day 13 vs. Day 5) relative to administration of metoprolol alone; this increase was dependent to some extent on the dronedarone dose (numerically, the 1600 mg dose produced a greater increase in metoprolol exposure than the 800 and 1200 mg doses. The applicant's analysis indicates that on Day 13 there was a significant difference between metoprolol Cmax obtained after placebo and after dronedarone treatment for the 1600 mg/day treatment (p= 0.0044). This difference was not significant for the other dronedarone treatments (800 mg/day and 1200 mg/day).

Table 206: Metoprolol Cmax comparisons for dronedarone-metoprolol drug interaction evaluation

	Contrast Day 13 / Day 5			
	Placebo (n=11)	SR33589B 800 mg/day (b.i.d.) (n=4)	SR33589B 1200 mg/day (b.i.d.) (n=9)	SR33589B 1600 mg/day (b.i.d.) (n=15)
Ratio	1.34	1.84	1.78	2.23
90% CI	[1.08-1.66]	[1.29-2.64]	[1.40-2.26]	[1.86-2.69]
95% CI	[1.03-1.73]	[1.20-2.84]	[1.34-2.37]	[1.79-2.79]

The findings for $AUC_{0\text{-}24h}$ data (Table 207) were qualitatively similar to the Cmax findings: Day 13 metoprolol exposure was 1.6- to 2.5-fold greater than Day 5 exposure. At Day 13 a

significant difference was observed between metoprolol AUC_{0-24h} obtained after placebo treatment and after dronedarone treatment, for the 1200 mg/day treatment (p= 0.0118), and for the 1600 mg/day treatment (p= 0.0078). For the 800 mg/day treatment this difference was not significant.

Table 207: Metoprolol AUC comparisons for dronedarone-metoprolol drug interaction evaluation

	Contrast Day 13/Day 5			
	Placebo (n=11)	**SR33589B 800 mg/day (b.i.d.) (n=4)**	**SR33589B 1200 mg/day (b.i.d.) (n=9)**	**SR33589B 1600 mg/day (b.i.d.) (n=15)**
Ratio	1.29	1.63	2.08	2.53
90% CI	[1.08-1.55]	[1.21-2.20]	[1.70-2.54]	[2.17-2.95]
95% CI	[1.04-1.61]	[1.14-2.34]	[1.63-2.64]	[2.10-3.05]

Overall the data indicate, metoprolol's metabolism is inhibited by dronedarone.

α-hydroxy-metoprolol pharmacokinetics

The plasma concentration time profile of α-hydroxy-metoprolol following administration of metoprolol alone or metoprolol co-administered with dronedarone is shown in Figure 128; PK measures for α-hydroxy-metoprolol are presented in Table 208.

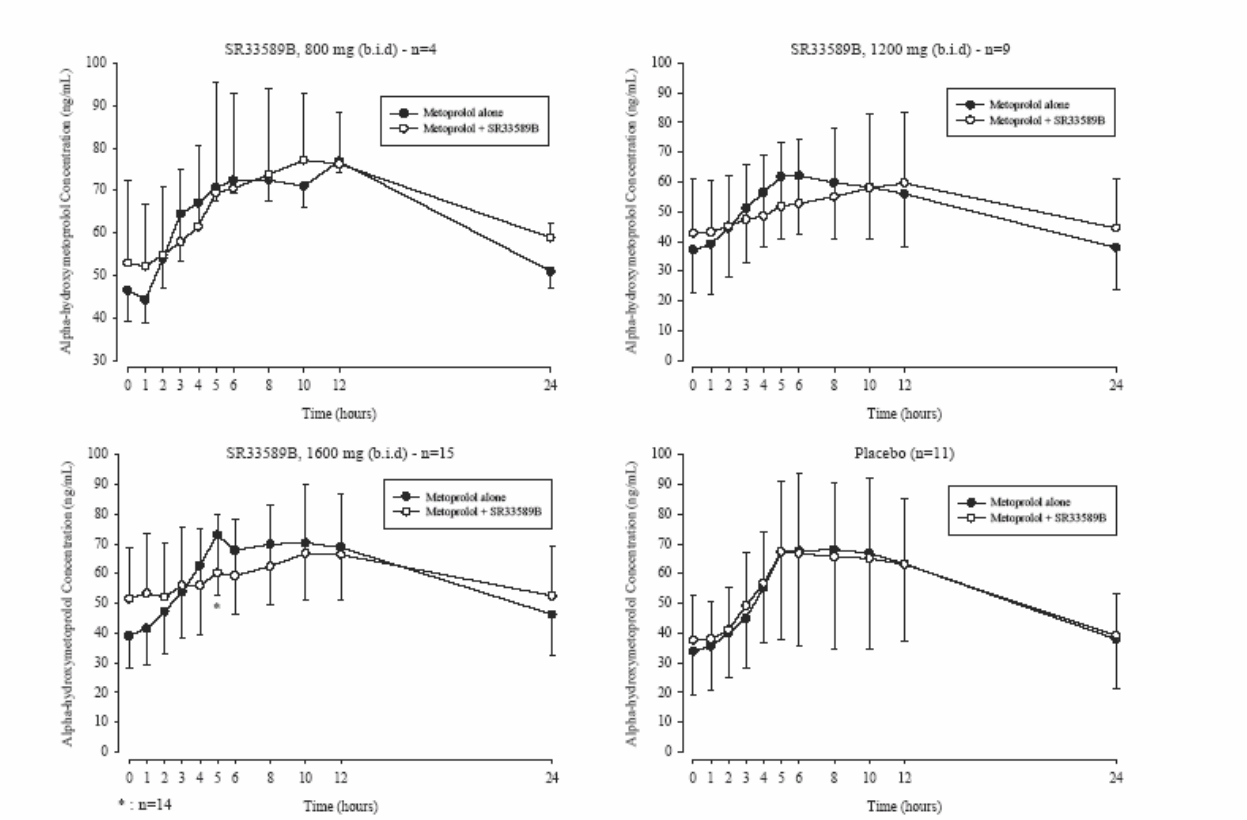
Table 208: Alpha-hydroxy-metoprolol PK measures obtained following administration of metoprolol +/- dronedarone

Mean (SD) Parameters	**SR33589B/Placebo Treatment**			
	Placebo (n=11)	***800 mg/day (b.i.d.) n=4***	***1200 mg/day (b.i.d.) n=9***	***1600 mg/day (b.i.d.) n=15***
Metoprolol alone (day 5)				
C_{min} (ng/mL)	31.9 (13.9)	43.6 (5.0)	34.4 (13.0)	37.6 (11.4)
C_{max} (ng/mL)	72.2 (33.2)	77.4 (1.5)	64.1 (21.5)	75.1 (22.4)
t_{max} (h)*	10.0	12.0	6.0	8.0
AUC_{0-24h} (ng.h/mL)	1294 (526)	1541 (38)	1216 (395)	1421 (376)
Metoprolol + SR33589B (day 13)				
C_{min} (ng/mL)	34.7 (14.3)	49.5 (17.3)	42.0 (17.6)	46.6 (17.0)
C_{max} (ng/mL)	70.7 (26.7)	81.7 (16.6)	60.4 (24.8)	70.6 (22.4)
t_{max} (h)*	5.1	10.9	12.0	12.0
AUC_{0-24h} (ng.h/mL)	1309 (453)	1615 (298)	1247 (492)	1428 (443)

*: median values , a: n=15

Administration of dronedarone with metoprolol did not appear to alter α-hydroxymetoprolol's PK, relative to when metoprolol was administered alone; geometric mean ratios and 90 % confidence intervals were not provided.

Figure 128: alpha-hydroxy metoprolol plasma concentration time profiles following administration of metoprolol +/- varying dronedarone doses or placebo



Pharmacodynamics

Three sets of PD parameters were assessed: Doppler echocardiography (DEC), contractility and cardiac impedance.

Reviewer Note on Study Design (Sample size)

The applicant notes that they intentionally increased sample size for the 1600 mg group relative to the other dronedarone dose groups to test the protocol hypotheses. Consequently, findings in the 1600 mg group must be considered as the most robust; the opposite is true for the 800 mg group because of the sample size differences. According to the applicant subjects were included in the lower dose groups mainly to verify good tolerability, thus allowing dose-escalation to the 1600 mg daily target. It is noted that the proposed clinical dosage of dronedarone is 400 mg BID.

DEC parameters (Primary PD Endpoints)

The statistical analyses for DEC parameters are summarized in Table 209.

Table 209: DEC comparisons

Parameter (unit)	Comparison SR33589B Versus Placebo	Mean Difference Estimate	95% CI Lower Bound	95% CI Upper Bound	P-value
VCFMean (sec-1)	800 mg	-0.03	-0.20	0.14	0.7563
	1200 mg	-0.11	-0.26	0.04	0.1509
	1600 mg	-0.28	-0.41	-0.14	0.0002
FS	800 mg	-0.01	-0.06	0.04	0.7911
	1200 mg	-0.03	-0.07	0.02	0.1892
	1600 mg	-0.07	-0.10	-0.03	0.0011
LVEF (%)	800 mg	-10.89	-21.02	-0.76	0.0358
	1200 mg	-2.13	-11.06	6.81	0.6334
	1600 mg	-9.37	-17.01	-1.73	0.0175
HR (bpm)	800 mg	-2.92	-7.72	1.88	0.2265
	1200 mg	-3.25	-7.48	0.98	0.1285
	1600 mg	-3.68	-7.30	-0.06	0.0463
CO (L/min)	800 mg	-1.12	-1.92	-0.32	0.0075
	1200 mg	-0.00	-0.71	0.70	0.9937
	1600 mg	-0.44	-1.07	0.18	0.1555

Overall, there was a trend toward statistically significant difference between the 1600 mg dose group versus placebo (Day 5 vs. Day 13). Dronedarone dosages that produced statistically significant differences from placebo are summarized below:

- For Vcfmean, only 1600 mg group
- For FS, only 1600 mg group
- For LVEF, both 800 and 1600 mg group, where 800 mg produced larger change
- For HR, only 1600 mg group
- For CO, only 800 mg group

Contractility parameters(Secondary PD Endpoints)

The difference estimates for phonocardiogram parameters are summarized in Table 210.

Results on secondary contractility parameters, assessed by phonocardiogram/carotidogram and impedance cardiogram showed similar trends in all dose groups with QS 2i showing the most significant changes.

Table 210: Contractility parameters

Parameter (unit)	Comparison SR33589B Versus Placebo	Mean Difference Estimate	95% CI Lower Bound	95% CI Upper Bound	P-value
QS2i (ms)	800 mg	10.39	1.49	19.29	0.0233
	1200 mg	12.97	5.12	20.82	0.0018
	1600 mg	20.36	13.65	27.07	0.0000
LVETi (ms)	800 mg	-4.57	-15.27	6.14	0.3929
	1200 mg	2.96	-6.52	12.44	0.5314
	1600 mg	12.90	4.53	21.28	0.0035
PEPi (ms)	800 mg	13.92	1.91	25.93	0.0243
	1200 mg	9.11	-1.53	19.75	0.0910
	1600 mg	7.10	-2.30	16.49	0.1343
RR (ms)	800 mg	79.83	-42.31	201.97	0.1940
	1200 mg	14.06	-93.66	121.77	0.7933
	1600 mg	35.46	-56.64	127.56	0.4411

For all cardiac impedance parameters, HR, stroke volume, and cardiac index, the changes of largest magnitude were observed in the 800 mg and 1600 mg groups (Table 211).

Table 211: Cardiac Impedance Parameters expressed as change from Day 5 to Day 13 (Mean differences between Dronedarone and Placebo)

Parameter (unit)	Comparison SR33589B Versus Placebo	Mean Difference Estimate	95% CI Lower Bound	95% CI Upper Bound	P-value
HR (bpm)	800 mg	-5.33	-9.65	-1.02	0.0168
	1200 mg	-3.22	-7.03	0.58	0.0946
	1600 mg	-5.19	-8.59	-1.80	0.0037
Stroke Volume (mL)	800 mg	-13.42	-30.67	3.83	0.1239
	1200 mg	-12.92	-28.13	2.30	0.0939
	1600 mg	-13.29	-26.30	-0.28	0.0455
Cardiac Index (L/min/m2)	800 mg	-0.68	-1.22	-0.15	0.0138
	1200 mg	-0.55	-1.02	-0.08	0.0240
	1600 mg	-0.71	-1.12	-0.31	0.0009

- For HR, the differences versus placebo were statistically significant in the 800 mg and 1600 mg groups
- For stroke volume, the difference versus placebo was statistically significant in only the 1600 mg group
- For cardiac index, the differences versus placebo for all dronedarone dose groups were statistically significant

PD Summary

The PD findings suggest that combining dronedarone with metoprolol may alter cardiac parameters; however, the effect appears more dependent on the dronedarone dose than on an interaction between metoprolol and dronedarone per se. Consistent changes were observed only with the 1600 mg dose; this may be a function of larger sample size for this dose group compared the other dose groups, allowing the effect to be statistically realized. It is noted that the 1600 mg daily dose is double the proposed clinical dose, therefore the effects observed may not be applicable to the proposed dronedarone clinical usage.

Applicant's Safety Summary

No serious adverse events (SAEs) or deaths were reported. There was a trend towards increased AE reporting as dronedarone dose increased. Other salient safety highlights include:

- more heart rate and rhythm disorders were reported in placebo subjects (~ 90 %) relative to dronedarone (16.7% of 800 mg subjects, 77.8% of 1200 mg subjects, and 75% of 1600 mg subjects).
- GI system disorders were reported in all treatment groups; the incidences of GI disorders increased with dronedarone dose (16.7% in the 800 mg group, 22.2% in the 1200 mg group, and 50% in the 1600 mg group). These GI incidences were higher than in both the metoprolol alone (4.1%) and placebo (7.7%) groups.

Four subjects discontinued from study due to AEs, 3 of which were heart rate and rhythm disorders and the remaining due to severe rash. All subjects recovered without corrective treatment except in the case of rash, which was treated with cetirizine. High increases in alanine

aminotransferase (ALT) and/or aspartate aminostranferase (AST) values at Day 13 or Day 20 were observed in some subjects; the investigator considered the increases at the 1600 mg dose clinically relevant. Exercise tolerance was good and the same workload could be reached with a lower heart rate during submaximal exercise. Holter monitoring showed a dose related heart rate-lowering effect and no evidence of proarrhythmia.

Recommendations/Conclusions
The findings from this study should be viewed within the context that the proposed clinical dosage is 400 mg BID vs. 1600 mg/day, the dose at which most clinical effects were observed. The following information from study PDY3828 is acceptable for labeling as appropriate:

Pharmacokinetics

- Relative to administration of metoprolol alone, metoprolol exposure was increased by 1.6 to 2.5- fold (AUC and Cmax) after concomitant administration of dronedarone for eight days; this finding suggests that dronedarone inhibits metoprolol metabolism. The PK interaction appeared dose-dependent, particularly with respect to the AUC measure.
- Dronedarone does not alter alpha-hydroxy-metoprolol exposure when dronedarone is co-administered with metoprolol

Pharmacodynamics
Relative to administration of placebo (metoprolol alone)

- Vcfmean was significantly reduced when co-administered with dronedarone 1600 mg daily; this finding indicates a reduction in myocardial contractility. Results on other contractility parameters using a different technique show a similar trend.
- QS2i increased with all dronedarone doses supporting the hypothesis of a decrease in contractility induced with dronedarone, particularly as dose increased.
- Cardiac index decreased after the addition of dronedarone (all dronedarone doses), with the 1600 mg dose yielding the greatest decrease

Labeling
The applicant's labeling proposal is acceptable: states results of study and mentions potential pharmacodynamic effects with beta blockers, such as metoprolol.

4.2.32 Influence of repeated oral doses of nifedipine and of repeated oral doses of diltiazem (inhibitors of cytochrome P450 3A4) on the pharmacokinetic profile of dronedarone in healthy male subjects, preliminary study (INT4074)

PROTOCOL #	INT4074
INVESTIGATOR	Dr Wolfgang Tetzloff
STUDY SITE	Phoenix International Iphar, Arnikastrasse 4, D- 85635 Höhenkirchen- Siegertsbrunn, Germany
STUDY PERIOD	January – May 2000

Rationale for Drug-Drug Interaction Study

Table 212: Background Information on Study Drugs (Diltiazem and Nifedipine and Dronedarone)

	Diltiazem and Nifedipine	Dronedarone
Indication/Mechanism of Action	Calcium channel blockers used as antihypertensive and for angina	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Diltiazem: two major metabolites (desacetyl and demethyl) and other metabolites Nifedipine: numerous metabolites	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	Diltiazem: Extensively metabolized by liver Nifedipine: extensively metabolized; appears to be metabolized by CYP3A	Primarily CYP3A substrate
CYP Inhibitory Potential	Nifedipine: CYP3A (Ki = 10 -22 µM) and PGP inhibitor Diltiazem: CYP3A and PGP inhibitor, and metabolites have inhibitory activity	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Diltiazem: dosage varies depending on indication; range of doses is 120 to 540 mg QD (initial for hypertension 120 to 240 mg) and dosage is titrated Nifedipine: Usual maintenance dose is 30 to 60 mg QD (initial 30 mg) and is titrated to a maximum of 90 mg QD	400 mg BID

Objectives (per applicant)

Primary

To assess the effect of repeated oral doses of nifedipine and of repeated oral doses of diltiazem, separately, on the pharmacokinetic profile of SR33589 and its N-debutyl metabolite SR35021 after a single oral ascending dose of dronedarone given in fed conditions.

Secondary

- to assess a potential pharmacodynamic resulting effect of each co-administration on electrocardiogram (ECG) parameters, heart rate (HR) and blood pressure
- to assess the clinical and biological tolerability of dronedarone given alone, and co-administered with nifedipine or with diltiazem
- to document plasma concentrations of nifedipine during and after repeated doses
- to document plasma concentrations of diltiazem during and after repeated doses

Study Design

This was a non-randomized, open-label, non-placebo-controlled, sequential design, and 2-period study. The treatments over the two periods follow.

- Period 1: a single dose of dronedarone alone (400, 800, 1200 and 1600 mg)
- Period 2: From Day 1 to day 4, 20 mg BID repeated oral doses of nifedipine. On Day 5 a single oral dose of dronedarone co-administered with a single oral dose of 20 mg nifedipine in the morning and a single oral dose of nifedipine alone.

Alternatively in Period 2, diltiazem 240 mg BID was administered according to the same schedule as nifedipine, except on Day 5 only a morning dose was given (no evening dose).

There was a 4-day washout period between Period 1 and Period 2.

Reviewer Note on Study Design (Evaluated Dronedarone Doses)

For dronedarone administered with nifedipine, only the 400 and 1600 mg dronedarone dose groups were studied because, no effect was seen at the 400 mg dose level. For dronedarone administered with diltiazem, the 1600 mg dose was substituted with the 1200 mg dose to avoid potential safety issues associated with high dronedarone exposure. The selected dronedarone doses appear reasonable.

It should be noted that neither diltiazem nor nifedipine were studied at their highest approved doses, 540 mg QD and 90 mg QD, respectively; the Drug Interaction Guidance recommends using the highest approved dose, unless there are safety concerns. This study should have been conducted at higher diltiazem and nifedipine doses to determine maximal interaction, particularly with respect to pharmacodynamic interaction potential.

Subject Demographics

Subject demographics are summarized in Table 213.

Table 213: Subject demographics (Study 4074)

Parameter	Statistics	Dronedarone				Total
		400 mg	800 mg	1200 mg	1600 mg	
Age (years)	N	12	6	6	6	30
	Mean	26.8	36.7	31.3	33.3	31.0
	SD	3.3	3.7	8.1	5.0	6.1
	Min	20	31	23	25	20
	Max	33	40	39	39	40
Height (cm)	N	12	6	6	6	30
	Mean	179.3	181.2	181.5	177.2	179.7
	SD	4.2	6.3	5.5	4.4	5.0
	Min	174	171	174	171	171
	Max	187	189	187	182	189
Weight (kg)	N	12	6	6	6	30
	Mean	78.7	73.2	82.0	77.5	78.0
	SD	7.2	5.5	7.6	7.9	7.3
	Min	67.7	65.5	73.9	65.0	65.0
	Max	91.8	81.0	94.2	88.6	94.2
BMI (kg/m^2)	N	12	6	6	6	30
	Mean	24.5	22.3	24.9	24.8	24.2
	SD	2.01	1.15	2.43	3.32	2.37
	Min	20.2	21.1	21.4	19.8	19.8
	Max	28.7	24.3	27.5	29.3	29.3

Formulation

- Dronedarone: 200 mg tablet, batch number 98-01645
- Nifedipine: 20 mg slow release tablet (Adalat®, Bayer, Germany); batch number Ch-B:CAUUN1
- Diltiazem: 240 mg slow release capsules (Dilzem®, Goedexke, Germany; batch number Ch-B:0323079

Pharmacokinetic sampling times

The following pharmacokinetic blood samples were drawn at the given times:

- Day 1 (period 1)- samples were collected at predose (5 minutes before dosing) and 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72 and 96 hours post dose
- For nifedipine (period 2)- samples were collected predose on Day 1, predose on Day 1 before second dose, on Day 2 before first dose, on Day 3 before second dose, on Day 3 before second dose, on Day 4 before dosing and Day 4 before second dose
- For diltiazem (period 2)- samples were collected predose on Day 1, on Day 2 before first dose, on Day 3 before second dose, and on Day 4 before dosing

Pharmacokinetics

The following PK measures were determined:

- SR33589 and SR35021: Cmax, tmax, AUClast, AUC, $t_{1/2z}$ on Day 1 (Period 1) and on Day 5 (Period 2);
- Nifedipine: trough levels from Day 1 to Day 4, and Cmax, Cmin, tmax, $AUC_{0\text{-}12h}$ on Day 5 (Period 2);
- Diltiazem: trough levels from Day 1 to Day 4, and Cmax, Cmin, tmax, $AUC_{0\text{-}24h}$ on Day 5 (Period 2).

Activity/Pharmacodynamics

The following PD measures were determined:

- Vital signs (Heart rate or HR and blood pressure or BP)
- ECG parameters (PR-, QRS-, QT- and QTc intervals) were determined

Reviewer Note on PD Assessment

Ideally a placebo group should have been included to offer a more objective assessment of PD effects and safety.

Statistical Methods

Standard pharmaco-statistical methods were used to evaluate PK drug-drug interaction. The reference treatment was dronedarone alone and the test treatments were dronedarone + diltiazem or nifedipine. Pharmacodynamics were assessed by standard methods.

Bioanalytical methods

<u>Dronedarone and SR35021 Assays</u>

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as shown in Table 214.

Table 214: Performance of Dronedarone and SR35021 Assay

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.989$	Satisfactory
Between day Precision	CV was < 13 %	Satisfactory
Accuracy	QC samples were between -2.7 and 4.0 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory
Parameter	Measure	Cannot be assessed
	SR35021	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.994$	Satisfactory
Between day Precision	CV was < 10 %	Satisfactory
Accuracy	QC samples were between -4.6 and 1.6 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms were provided in assay validation report that indicate assay specificity

Nifedipine Assay

Nifedipine concentrations in plasma were determined by gas chromatography with electronic capture detection. The assay performance was acceptable as shown in Table 215.

Table 215: Performance of Nifedipine Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 1.0 to 500 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 11 %	Satisfactory
Accuracy	QC samples were between 10 and 15 % of nominal concentration	Satisfactory
LLOQ	1 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Diltiazem and diltiazem metabolites

The concentration of diltiazem and its metabolites in plasma samples were determined by HPLC. The assay performance was acceptable as shown in Table 216.

Table 216: Performance of Diltiazem Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 5 to 500 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV was < 4 %	Satisfactory
Accuracy	QC samples were between -6 and 2 % of nominal concentration	Satisfactory
LLOQ	5 ng/ml	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Results

Dronedarone and SR35021 Pharmacokinetics (+/- diltiazem)

The dronedarone and SR35021 plasma concentration-time profiles are depicted in Figure 129.

The mean (CV%) pharmacokinetic parameters of dronedarone and SR35021 after dronedarone administration with or without diltiazem are summarized in Table 217 and Table 218.

Figure 129: Dronedarone and SR35021 plasma concentration-time profiles following administration of dronedarone +/- diltiazem

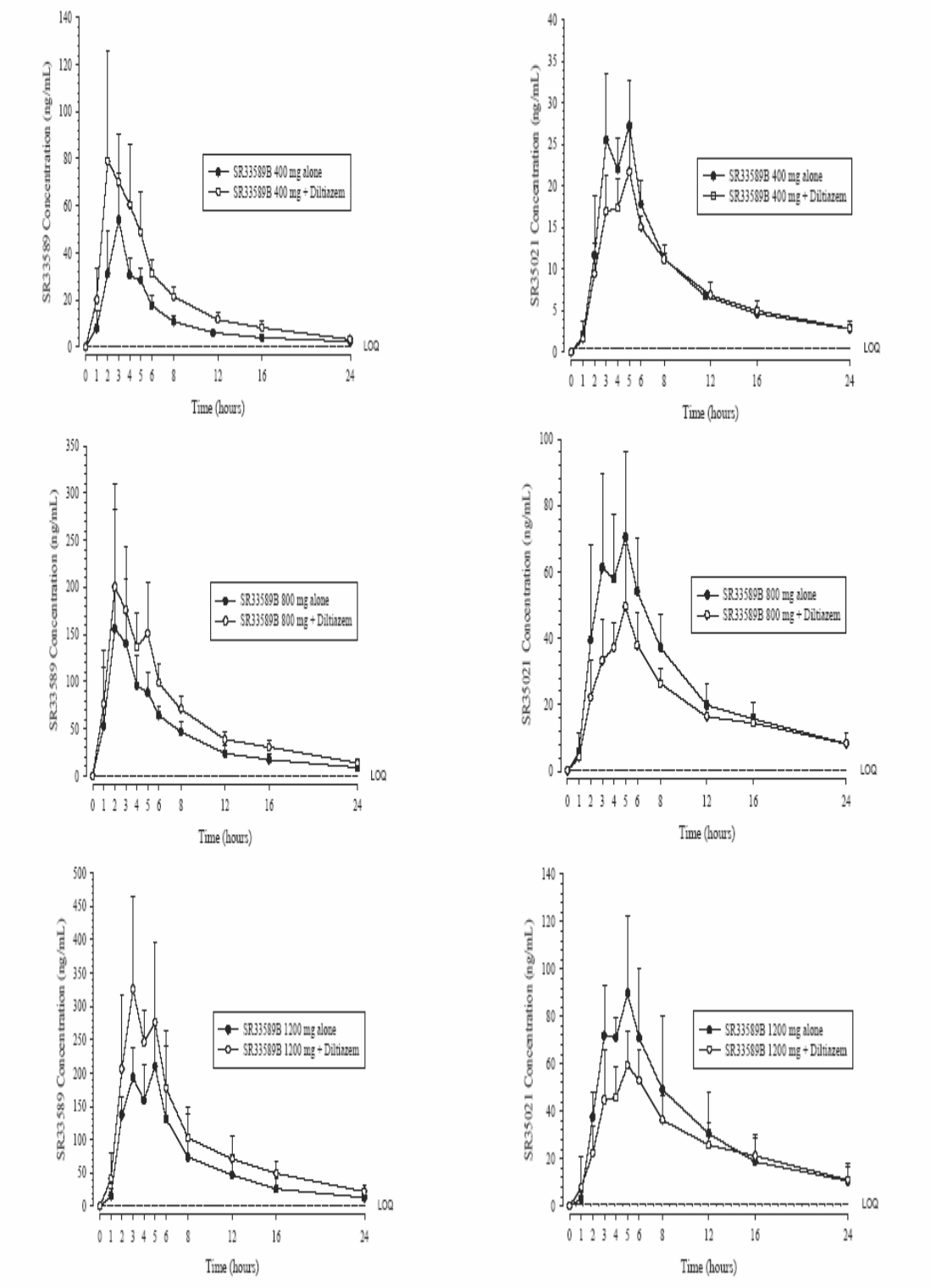


Table 217: Dronedarone PK Measures following administration of dronedarone +/- diltiazem

Mean (SD)	Dronedarone 400 mg (n=6)		Dronedarone 800 mg (n=6)		Dronedarone 1200 mg (n=6)	
Parameters	*alone*	*+diltiazem*	*alone*	*+diltiazem*	*alone*	*+diltiazem*
C_{max} (ng/mL)	56.6 (18.6)	93.9 (35.7)	187.1 (111.4)	225.6 (90.0)	258.0 (161.8)	387.5 (122.1)
t_{max} (h)[a]	3.0	2.0	3.0	2.5	3.0	3.0
t_{last} (h)	50.0 (11.8)	64.0 (19.6)	80.1 (19.7)	92.0 (9.8)	92.0 (9.8)	96.0 (0.0)
AUC_{last} (ng.h/mL)	304 (80)	559 (132)	1183 (464)	1790 (489)	1814 (1042)	2808 (786)
$t_{1/2z}$ (h)	15.2 (4.8)	14.4 (2.6)[b]	19.6 (4.1)	21.3 (5.1)	22.5 (2.5)	27.5 (3.7)
AUC (ng.h/mL)	320 (86)	581 (145)[b]	1213 (462)	1823 (497)	1852 (1072)	2885 (825)

Table 218: Dronedarone and SR35021 PK Measures following administration of dronedarone +/- diltiazem

Mean (SD)	Dronedarone 400 mg (n=6)		Dronedarone 800 mg (n=6)		Dronedarone 1200 mg (n=6)	
Parameters	*alone*	*+diltiazem*	*alone*	*+diltiazem*	*alone*	*+diltiazem*
C_{max} (ng/mL)	31.2 (4.8)	22.1 (4.4)	74.3 (26.0)	49.7 (18.6)	94.4 (32.0)	59.9 (13.4)
t_{max} (h)[a]	3.0	5.0	5.0	5.0	4.0	5.0
t_{last} (h)	72.0 (0.0)	64.0 (12.4)	96.1 (0.2)	92.0 (9.8)	88.0 (12.4)	96.0 (0.0)
AUC_{last} (ng.h/mL)	292 (14)	263 (32)	877 (224)	701 (157)	1070 (560)	950 (314)
$t_{1/2z}$ (h)	21.9 (4.9)	23.4 (6.8)	21.1 (2.4)	23.8 (2.9)	19.2 (4.4)	21.3 (4.6)
AUC (ng.h/mL)	314 (19)	298 (55)	904 (226)	739 (165)	1100 (584)	988 (340)

Consistent with previous studies, dronedarone exposure increased in a greater than dose proportional manner from the 400 to 1200 mg dose levels.

The applicant's statistical analyses revealed that there was no significant dose-by-treatment effect for any of the PK measures, therefore, drug-drug interaction analyses were pooled across dronedarone dose groups. Table 219 summarizes the drug-drug interaction results.

Table 219: Dronedarone Drug interaction results following administration of dronedarone +/- diltiazem

PK Measure	Dronedarone + diltiazem /dronedarone alone
Cmax	1.51 (1.31 -1.75)
AUClast	1.69 (1.55 – 1.85)

The interaction results indicate that diltiazem increased dronedarone AUC and Cmax by ~ 60 %, suggesting that diltiazem inhibited dronedarone metabolism. This finding is expected because dronedarone is a CYP3A substrate and diltiazem is a moderate CYP3A inhibitor.

SR35021 exposure was decreased in the presence of diltiazem, relative to when dronedarone was administered alone, which is consistent with CYP3A metabolic inhibition.

Dronedarone and SR35021 Pharmacokinetics (+/- nifedipine)

The dronedarone and SR35021 plasma concentration-time curves are depicted in Figure 130.

The mean (CV%) pharmacokinetic parameters of dronedarone and SR35021 after dronedarone administration with or without nifedipine are summarized in Table 220 and Table 221.

Figure 130: Dronedarone and SR35021 plasma concentration-time profiles following administration of dronedarone +/- nifedipine

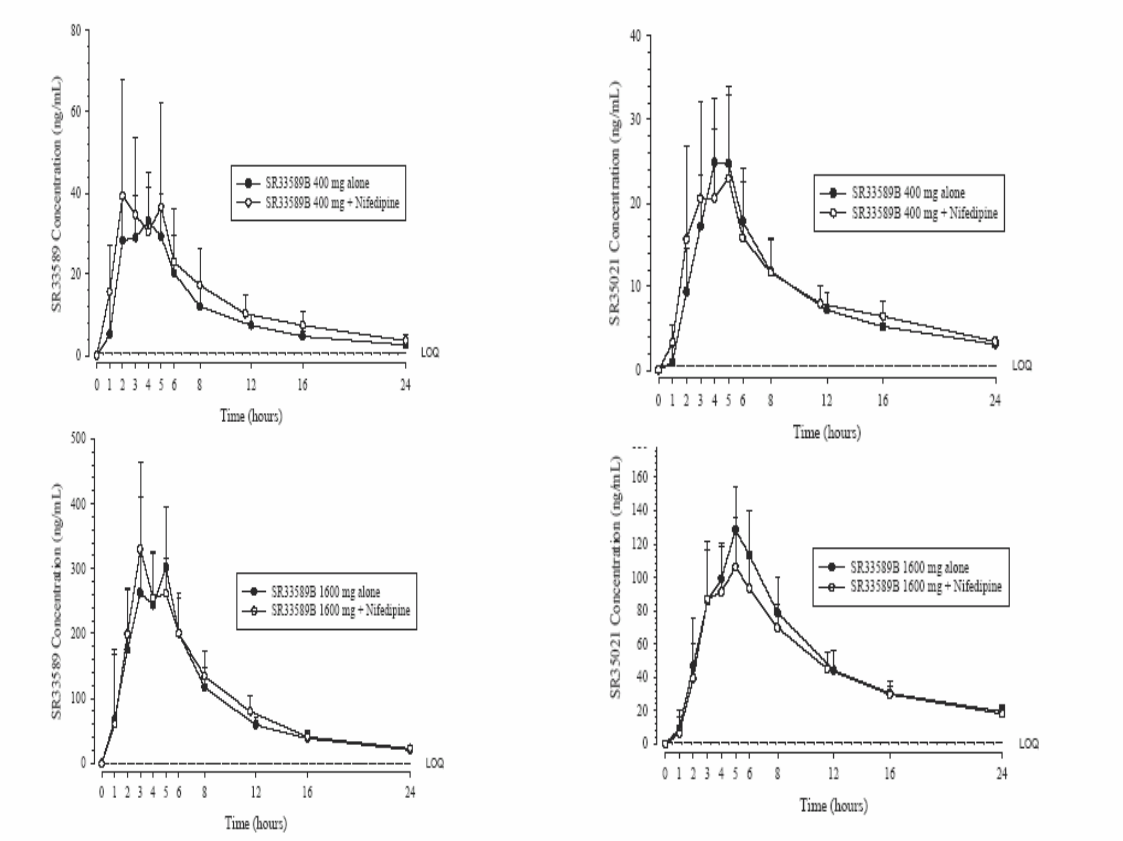


Table 220: Dronedarone PK Measures following administration of dronedarone +/- nifedipine

Mean (SD)	Dronedarone 400 mg (n=6)		Dronedarone 1600 mg (n=6)	
Parameters	*alone*	*+ nifedipine*	*alone*	*+ nifedipine*
C_{max} (ng/mL)	38.4 (9.7)	55.1 (20.9)	348.9 (125.2)	338.0 (124.2)
t_{max} (h)[a]	2.5	2.0	5.0	3.0
t_{last} (h)	50.0 (11.8)	64.0 (12.4)	96.0 (0.0)	96.0 (0.0)
AUC_{last} (ng.h/mL)	297 (85)	412 (186)	2664 (722)	2943 (856)
$t_{1/2z}$ (h)	14.5 (3.6)	19.4 (6.8)	20.1 (4.6)	22.9 (3.4)
AUC (ng.h/mL)	312 (88)	432 (189)	2700 (741)	2995 (883)

Table 221: SR35021 PK Measures following administration of dronedarone +/- nifedipine

Mean (SD)	Dronedarone 400 mg (n=6)		Dronedarone 1600 mg (n=6)	
Parameters	*alone*	*+ nifedipine*	*alone*	*+ nifedipine*
C_{max} (ng/mL)	26.6 (6.5)	26.9 (10.7)	128.6 (25.6)	106.5 (28.7)
t_{max} (h)[a]	4.5	3.0	5.0	5.0
t_{last} (h)	76.0 (9.8)	76.0 (9.8)	96.0 (0.0)	96.0 (0.0)
AUC_{last} (ng.h/mL)	288 (76)	317 (87)	1713 (379)	1606 (343)
$t_{1/2z}$ (h)	24.3 (5.7)	26.1 (10.5)	17.6 (1.8)	20.2 (3.1)
AUC (ng.h/mL)	310 (72)	345 (83)	1746 (382)	1655 (353)

The applicant's statistical analyses revealed that there was no significant dose-by-treatment effect for any of the dronedarone PK measures (nifedipine interaction), therefore, drug-drug interaction analyses were pooled across dronedarone dose groups. Table 222 summarizes the drug-drug interaction results.

Table 222: Dronedarone Drug interaction results following administration of dronedarone +/- nifedipine

PK Measure	Dronedarone + nifedipine/ dronedarone alone
Cmax	1.15 (0.96 – 1.37)
AUClast	1.20 (1.07 – 1.34)

Relative to dronedarone alone, nifedipine did not change dronedarone Cmax, but AUClast was increased ~ 20 %; this finding suggests nifedipine marginally inhibits dronedarone metabolism.

There was a statistically significant dose-by-treatment effect for SR35021 AUClast and AUC during nifedipine co-administration with dronedarone; therefore, the dose groups were analyzed separately. No statistically significant treatment effect was observed for SR35021 Cmax.

Table 223: Dronedarone Drug interaction results following administration of dronedarone +/- nifedipine

Measure	Geometric Mean ratio and 90 % CI for Dronedarone + nifedipine/dronedarone alone	
	Dronedarone 400 mg	Dronedarone 1600 mg
Cmax	0.67 [0.63 – 0.72]	0.89 [0.77 – 1.02]
AUClast	1.10 [0.99-1.22]	0.94 [0.86-1.02]

Diltiazem Pharmacokinetics

The diltiazem, desacetyl diltiazem and N-demethyl desacetyl diltiazem plasma concentration-time profiles following administration of diltiazem with varying dronedarone doses are depicted in the following three figures.

Reviewer Note: Exclusion of Subject 30

The applicant notes that Subject Number 30 in the dronedarone 1200 mg dose group, was considered an outlier: 5-fold higher in N-demethyl desacetyl diltiazem plasma concentrations and 2.6-fold higher in desacetyl diltiazem plasma concentrations, as compared to other subjects. The diltiazem plots do not include Subject 30; including Subject 30 had a major impact on the mean results. Overall, exclusion of this subject's results appears reasonable, however the applicant should have determined why Subject 30 had different results from the other subjects.

Figure 131: Diltiazem plasma concentration time profile following administration of diltiazem and dronedarone

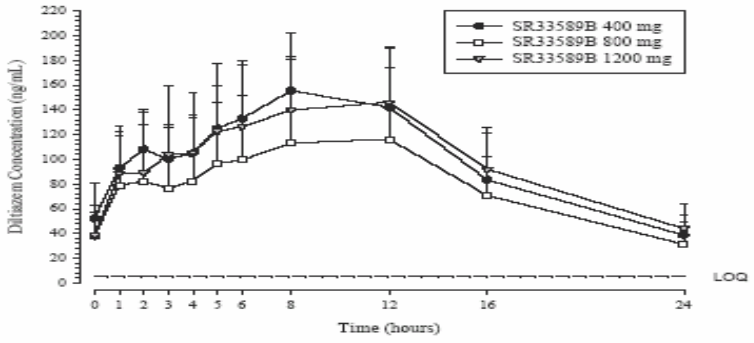


Figure 132: Desacetyl Diltiazem plasma concentration time profile following administration of diltiazem and dronedarone

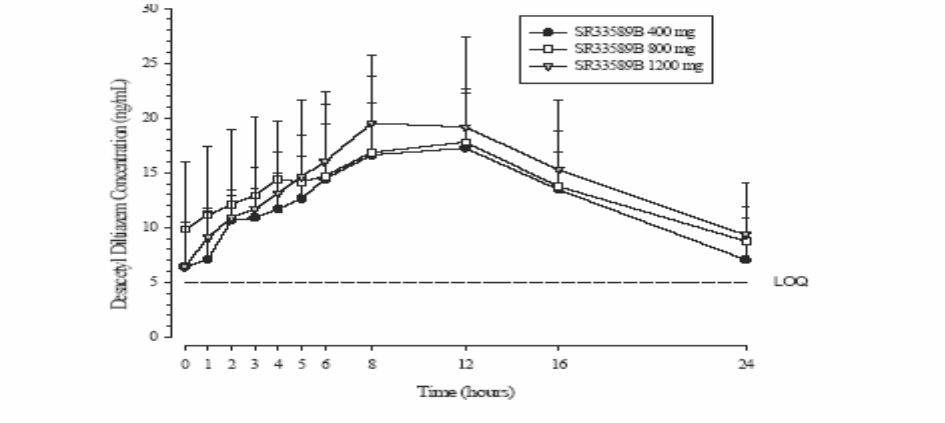
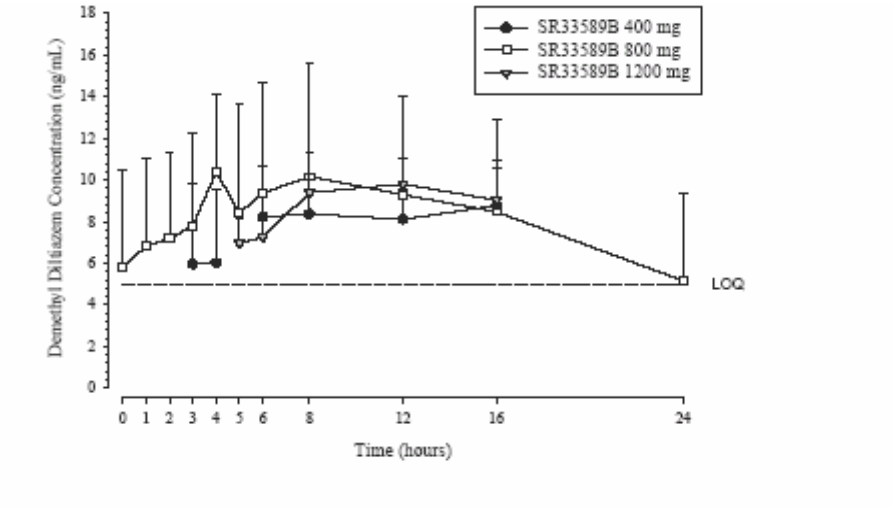


Figure 133: Demethyl desacetyl plasma concentration time profile following administration of diltiazem and dronedarone



The mean (CV%) pharmacokinetic parameters of diltiazem and its two major metabolites following administration of dronedarone and diltiazem are summarized in Table 224 and Table 225.

Table 224: Diltiazem PK Measures following administration of dronedarone +/- diltiazem

Mean (SD)	Dronedarone treatment		
Parameters	*400 mg (n=6)*	*800 mg (n=6)*	*1200 mg (n=6)*
C_{min} (ng/mL)	36.6 (10.2)	30.8 (23.9)	37.7 (19.8)
C_{max} (ng/mL)	163.8 (38.7)	121.2 (70.1)	150.6 (43.1)
t_{max} (h) [a]	8.0	10.0	10.0
$AUC_{0\text{-}24h}$ (ng.h/mL)	2445 (533)	1936 (1222)	2449 (874)

a: median values

PK of diltiazem and its metabolites did not appear dependent on dronedarone dose, especially, when Subject 30 was omitted from the PK analysis.

Table 225: PK Measures of diltiazem metabolites following administration of dronedarone +/- diltiazem

Mean (SD) Parameters	Dronedarone treatment			
	400 mg (n=6)	*800 mg (n=6)*	*1200 mg (n=6)*	*1200 mg (n=5) Without No.30*
Desacetyl diltiazem				
C_{min} (ng/mL)	6.0 (3.3)	7.5 (6.2)	11.6 (13.2)	6.4 (4.0)
C_{max} (ng/mL)	18.4 (5.6)	18.8 (7.5)	26.4 (15.9)	20.1 (3.8)
t_{max} (h)[a]	10.0	12.0	10.0	8.0
AUC_{0-24h} (ng.h/mL)	298 (98)	330 (180)	493 (356)	351 (79)
N-Demethyl desacetyl diltiazem				
C_{min} (ng/mL)	BLQ (NC)	BLQ (NC)	17.7 (40.4)	BLQ (NC)
C_{max} (ng/mL)	9.9 (2.0)	11.8 (3.8)	35.3 (61.4)	10.2 (1.5)
t_{max} (h)[a]	12.0	8.0	14.0	12.0
AUC_{0-24h} (ng.h/mL)	141 (48)	192 (110)	692 (1307)	159 (66)

a: median values
BLQ: Below the LOQ, NC: Not calculable

Nifedipine Pharmacokinetics

The nifedipine plasma concentration-time profiles following administration of nifedipine with dronedarone are depicted in Figure 134.

Figure 134: Nifedipine plasma concentration time profiles following administration of nifedipine and dronedarone

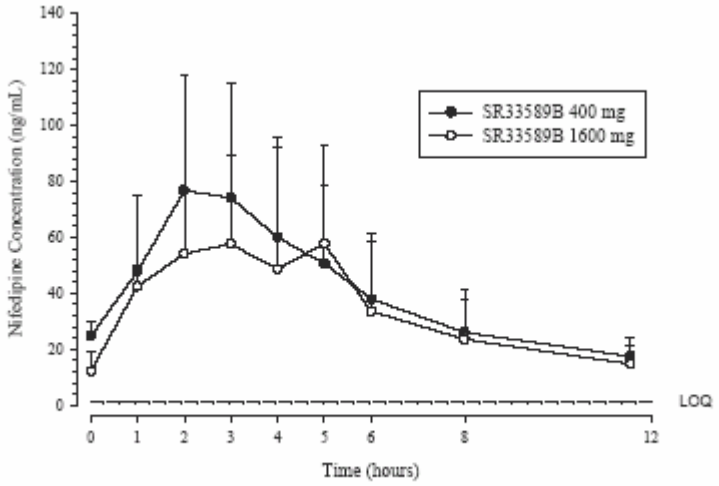


Table 226: Performance of Nifedipine Assay

Mean (SD) Parameters	Dronedarone treatment	
	400 mg (n=6)	*1600 mg (n=6)*
C_{min} (ng/mL)	6.7 (5.6)	6.7 (2.4)
C_{max} (ng/mL)	47.6 (18.3)	47.8 (13.1)
t_{max} (h)[a]	2.5	3.5
AUC_{0-12h} (ng.h/mL)	274 (128)	256 (71)

a: median values

PK of nifedipine did not appear dependent on dronedarone dose.

Pharmacodynamics

ECG Data

The ECG data obtained during dronedarone alone and dronedarone with diltiazem or nifedipine are presented in Table 227.

Table 227: ECG data of the Day 5 (co-administration) vs. Day 1 (dronedarone alone) mean difference in averaged changes from baseline over 12 hours (only statistically significant contrasts reported)

Parameter	Significant contrasts ($p < 0.05$)	Estimate [95% CI]
PR (ms)	SR+diltiazem vs SR alone	
	- overall doses (N = 18)	14.37 [12.15 ; 16.59]
	- 400 mg (N = 6)	19.22 [15.37 ; 23.07]
	- 800 mg (N = 6)	12.44 [8.60 ; 16.29]
	- 1200 mg (N = 6)	11.44 [7.60 ; 15.29]
	- at T2	17.56 [12.11 ; 23.00]
	- at T4	12.44 [7.00 ; 17.89]
	- at T6	14.00 [8.56 ; 19.44]
	- at T8	16.22 [10.78 ; 21.66]
	- at T12	21.33 [15.89 ; 26.78]
QRS (ms)	SR+nifedipine vs SR alone	
	- 1600 mg (N = 6)	1.78 [0.29 ; 3.27]
QT (ms)	SR+nifedipine vs SR alone	
	- overall doses (N = 12)	-4.39 [-8.30 ; -0.47]
	SR+diltiazem vs SR alone	
	- overall doses (N = 18)	5.79 [2.71 ; 8.87]
	In the diltiazem group only :	
	- 800 mg vs 400 mg	19.89 [0.84 ; 38.94]
	- 1200 mg vs 400 mg	26.38 [7.32 ; 45.43]
QT_c (ms)	SR+diltiazem vs SR alone	
	- overall doses (N = 18)	3.80 [1.85 ; 5.74]

Diltiazem

For Diltiazem co-administration, PR- interval, QT- interval and QTc values were significantly changed by the addition of diltiazem to dronedarone.

- PR- interval: the co-administration effect was detected to be statistically significant
  - overall doses (p= 0.0001)
  - between doses (p- value for dose by administration interaction= 0.0101)
  - between time points (p-value for administration by time interaction= 0.0012).

It is noted that there was significantly lower PR prolongation in the 1200 mg dronedarone dose group than in the 400 mg dronedarone dose group.

- QT- intervals were also significantly prolonged after addition of diltiazem to dronedarone
  - overall doses
  - significantly prolonged in the 800 mg and 1200 mg dronedarone dose groups compared to the 400 mg dose group, suggesting a dose-response may exist; however data were highly variable (wide confidence interval)
- QTc interval was significantly prolonged after addition of diltiazem to dronedarone; however : the prolongation was ~ 4 ms over all doses. The QTc prolongation due to diltiazem was not significantly different between dronedarone dose groups or between time points.

Nifedipine

For nifedipine, only QRS- and QT- intervals values were significantly changed by the addition of nifedipine to dronedarone.

- QRS- interval was prolonged only in the highest dronedarone dose group (1600 mg)
- QT- interval, showed a statistically significant overall effect of the co-administration (p-value = 0.0283); there was a decrease in QT interval

Vital Signs

The changes in vital signs (Dronedarone + co-administered drug vs. Dronedarone alone) are summarized in Table 228.

Table 228: Vital Sign data of the Day 5 (co-administration) vs. Day 1 (dronedarone alone) mean difference in averaged changes from baseline over 12 hours (only statistically significant contrasts reported)

Parameter	Significant contrasts (p < 0.05)	Estimate [95% CI]
HR (bpm)	In the diltiazem group only	
	- 800 mg vs 400 mg	-7.57 [-13.18 ; -1.96]
	- 1200 mg vs 400 mg	-8.04 [-13.65 ; -2.43]
SBP (mmHg)	SR+nifedipine vs SR alone	
	- overall doses (N = 12)	-3.25 [-5.42 ; -1.07]
	SR+diltiazem vs SR alone	
	- overall doses (N = 18)	-1.92 [-3.67 ; -0.16]
	- at T12 (N = 18)	-8.22 [-12.51 ; -3.94]
	In the diltiazem group only	
	- 800 mg vs 400 mg	-9.71 [-18.06 ; -1.35]
	- 1200 mg vs 400 mg	-12.39 [-20.74 ; -4.04]

Diltiazem

For diltiazem group, addition of diltiazem to dronedarone, caused ~ 2 mmHg decrease in SBP, relative to administration of dronedarone alone. There appeared to be a dronedarone dose-effect for both heart rate and SBP; this effect was independent of diltiazem presence.

- HR: Relative to the 400 mg dose, the 800 mg (p-value = 0.0130) and 1200 mg (p-value = 0.0159) dronedarone doses decreased heart rate (bradycardic effect)
- SBP: relative to the 400 mg, the 800 mg and 1200 mg dronedarone doses caused systolic hypertension
- DBP: No change was observed in DBP values.

Nifedipine

- SBP: For nifedipine, co-administration of nifedipine and dronedarone only affected SBP values relative to dronedarone alone; when nifedipine was added to dronedarone, mean SBP decreased by ~ 3 mmHg (p- value= 0.0037).
- DBP and HR: No change was observed in DBP or HR values.

PD Summary

In sum, the PD measures were generally changed (statistically significant) when either diltiazem or nifedipine was added to dronedarone compared to when dronedarone was administered alone. However, these changes tended to be small and do not appear clinically relevant. Overall dose effects with respect to the dronedarone group are summarized as follows:

1. PR for diltiazem + dronedarone vs. dronedarone increased by ~14 ms
2. QT interval for diltiazem + dronedarone vs. dronedarone increased by ~2 ms

3. QT interval for nifedipine + dronedarone vs. dronedarone decreased by ~4 ms
4. QTc for diltiazem + dronedarone vs. dronedarone increased by ~ 4 ms
5. QRS for nifedipine + dronedarone vs. dronedarone increased by 2 ms
6. SBP for diltiazem + dronedarone vs. dronedarone decreased by 2 mmHg and nifedipine + dronedarone vs. dronedarone decreased by 3 mmHg

Applicant's Safety Summary
There were no serious AEs (SAEs) or deaths reported, and no discontinuations occurred due to treatment emergent AEs. First- degree atrio-ventricular blocks were reported in three subjects, during co-administration of 400 and 1200 mg dronedarone with diltiazem, and 1600 mg with nifedipine; these three AEs were judged to be likely related to dronedarone treatment. Subjects recovered without corrective treatment. Diarrhea was reported by three subjects in the 1600 mg group co- administered with nifedipine and by one subject in each of the 800, 1200, and 1600 mg groups on dronedarone alone; relationships to treatment were judged to be unknown. Potentially clinically significant abnormalities (PCSAs) were observed in hematology, biochemistry, vital signs and ECGs; PCSAs were sporadic and no particular trends in treatment groups emerged.

Recommendations/Conclusions
The following findings from study INT4084 are acceptable for labeling as appropriate.

Pharmacokinetics
Relative to administration of dronedarone alone, concomitant administration of
1) diltiazem increased dronedarone AUC and Cmax by 1.51- and 1.69-fold respectively
2) nifedipine increased dronedarone AUC and Cmax by 1.15- and 1.20- fold, respectively.

Overall, plasma concentrations of SR35021 were decreased during co-administration with diltiazem whereas, SR35021 remained the same when co-administered with nifedipine. The differential metabolite formation in the presence of diltiazem compared to nifedipine may be due to the difference in inhibitory potential of the two compounds; although diltiazem is a less potent and inhibitor than nifedipine, diltiazem metabolites contribute significantly to metabolic inhibition that may make diltiazem effectively a more potent inhibitor than nifedipine

Pharmacodynamics
Relative to administration of dronedarone alone, co-administration of dronedarone with diltiazem increases mean PR-prolongation by 14.37 ms, increases mean QT- prolongation by 5.79 ms, and increased mean QTc-prolongation by 3.80 ms, based on all dronedarone doses. Statistically relevant decreased in SBP were observed: for diltiazem, SBP was decreased by approximately 2 mmHg and for nifedipine SBP was decreased by ~ 3 mmHg. However the listed changes in PD measures do not appear clinically relevant, as they are of relatively small magnitude.

Labeling
The labeling should reflect the study findings. A dronedarone dosage adjustment does not appear warranted based on the study findings; however, precautionary language may be included indicating that there is a potential decrease in SBP when dronedarone and nifedipine or diltiazem and other calcium channel blockers are co-administered.

4.2.33 Effect of repeated oral doses of 800 mg b.i.d. dronedarone on the pharmacokinetic profile of oral contraceptive in healthy female subjects - randomized, double- blind, placebo controlled study (INT4695)

PROTOCOL #	INT4695
INVESTIGATOR	Wolfgang Tetzloff, MD
STUDY SITE	Phoenix International Iphar, Arnikastrasse 4, 3- 85635, Höhenkirchen- Siegersbrunn, Germany
STUDY PERIOD	May 2001 – January 2002

Background Information on Study Drugs [Stediril (Ethinylestradiol/ levonorgestrel) and Dronedarone]

	Ethinylestradiol/ levonorgestrel	Dronedarone
Indication/Mechanism of Action	Oral contraceptive	Anti-arrhythmic: proposed for the maintenance of normal sinus rhythm and to decrease ventricular rate in patients with atrial fibrillation or atrial flutter.
Metabolites	Multiple metabolites are formed from each of the Stediril components	Several metabolites including, debutylated SR35021 (major), and hydroxy and oxidative metabolites
Metabolic Pathway	CYP3A primarily	Primarily CYP3A substrate
CYP Inhibitory Potential	None reported for either component	Low to moderate potential to inhibit CYP3A and CYP2D6 as well as PGP
Highest Recommended Dose/Studied Dose	Dependent on product there are different combinations of the components	400 mg BID

Objectives (per applicant)

Primary

To assess the plasma concentrations of ethinylestradiol and levonorgestrel on the fifteenth day of the oral contraceptive treatment co-administered with placebo, and of the oral contraceptive treatment co-administered with dronedarone.

Secondary

- To assess the clinical and biological safety of dronedarone in healthy female subjects under oral contraceptive.
- To assess the pharmacokinetic (PK) parameters of SR33589 (dronedarone) and SR35021 on the last day of dronedarone administration.
- To measure the ratio 6ß-hydroxycortisol/cortisol as a marker of CYP3A4 enzyme induction.

Study Design

This was a randomized, double-blind, placebo-controlled, repeated-dose and 2x2 cross-over study in healthy female volunteers. The following treatments were administered:

1. Dronedarone 1600 mg/day (800 mg BID) for 10 days (Day 6 to 15)
2. Placebo administration for 10 days (Day 6 to 15)
3. Stediril once daily in the morning after meal for 21 days (Day 1 to 21)

There were two periods separated by a 5- to 7-day washout.

Subject Demographics
Subject demographics are summarized in Table 229.

Table 229: Subject demographics (Study 4695)

Parameter	Statistics/ Category	Total
Age (yrs)	N	21
	Mean	26.1
	SD	6.0
	Minimum	18
	Maximum	37
Weight (kg)	N	21
	Mean	61.80
	SD	7.12
	Minimum	50.8
	Maximum	79.9
Height (cm)	N	21
	Mean	166.8
	SD	5.8
	Minimum	158
	Maximum	180
Body mass index (kg/m^2)	N	21
	Mean	22.24
	SD	2.47
	Minimum	18.0
	Maximum	27.0
Oral temperature (celsius)	N	21
	Mean	36.54
	SD	0.38
	Minimum	35.9
	Maximum	37.3
Gender	Female	21 (100%)
Race	Caucasian	21 (100%)

Formulation
- Dronedarone: 200 mg tablets; batch number 98-01649
- Dronedarone placebo: tablets; batch number 98-01541
- Stediril 30: tablet containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel; batch number G1671B

Pharmacokinetic and urine sampling times
The following pharmacokinetic blood samples were drawn at the given times:
- Ethinylestradiol and levonorgestrel- before dosing on Day 1, and before dosing and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after Stediril 30® administration on Day 15.
- Dronedarone and SR35021: before dosing on Day 6, before dosing and 0.5, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours after the morning dronedarone administrations on Day 15, and 12 hours after the evening administration on Day 15.

Urine samples were collected over 24 hours, from Day 5 to Day 6 and from Day 15 to Day 16 to determine cortisol and 6ß-hydroxycortisol concentrations.

Pharmacokinetics
The following PK measures were determined:
- For ethinylestradiol and levonorgestrel - Cmax, tmax, Cmin and AUC_{0-24h}
- For dronedarone and SR35021- Cmax, tmax, Cmin and AUC_{0-12h}

Pharmacodynamics
The ratio of 6ß-hydroxycortisol to cortisol urine concentrations is the only pharmacodynamic measure (endogenous compounds).

Statistical Methods
Standard pharmaco-statistical methods were used to evaluate drug-drug interactions. The reference treatment was Stediril (Ethinylestradiol/ levonorgestrel) alone and the test treatment was Stediril + dronedarone.

Standard statistical methods were used for the pharmacodynamic assessment; these methods were similar to those for the drug-drug interaction evaluation: urinary 6ß-hydroxycortisol/ cortisol ratios at Day 15 (test) were compared to those at baseline (Day 5- reference). This evaluation was conducted to estimate the effect of dronedarone on CYP3A activity.

Bioanalytical methods
Ethinylestradiol
Plasma concentrations of ethinylestradiol were determined by a validated gas chromatography-mass spectrometry method. The assay performance was acceptable as shown in Table 230.

Table 230: Performance of ethinylestradiol Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 10 to 500 pg/mL range; $R^2 > 0.945$	Satisfactory
Between day Precision	CV was < 9 %	Satisfactory
Accuracy	QC samples were between 0 and 6 % of nominal concentration	Satisfactory
LLOQ	10 pg/mL	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory

Levonorgestrel
Plasma concentrations of levonorgestrel were determined by a validated gas chromatography-mass spectrometry method. The assay performance was acceptable as shown in Table 231.

Table 231: Performance of levonorgestrel Assay

Parameter	Measure	Reviewer Comment
Linearity	The assay was linear over the 0.1 to20.0 ng/mL range; $R^2 > 0.990$	Satisfactory
Between day Precision	CV was < 12 %	Satisfactory
Accuracy	QC samples were between -0.7 and 6.7 % of nominal concentration	Satisfactory
LLOQ	0.1 ng/ml	Satisfactory
Specificity	Chromatograms were provided that demonstrate specificity	Satisfactory

Dronedarone and SR35021 Assays
Plasma concentrations of dronedarone and SR35021 were determined using a validated liquid chromatography-mass spectrometry method (DOH0239). The assay performance was acceptable as shown in Table 232.

Table 232: Performance of dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range	Satisfactory
Between day Precision	CV values were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided, however individual QC samples were within 15 % of nominal concentration	Acceptable
LLOQ	0.5 ng/ mL	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory
Parameter	Measure	Reviewer Comment
	SR35021	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range	Satisfactory
Between day Precision	CV values were not provided	Cannot be assessed
Accuracy	Relative bias values were not provided, however individual QC samples were within 15 % of nominal concentration	Acceptable
LLOQ	0.5 ng/ mL	Satisfactory
Specificity	Chromatograms were not provided*	Satisfactory

Cortisol and 6ß- hydroxycortisol (Bioanalytical methods in urine)
Urine concentrations of cortisol and 6ß- hydroxycortisol were determined by LC/MS/MS. The assay performance was acceptable as shown in Table 233.

Table 233: Performance of Cortisol 6ß- hydroxycortisol Assays

Parameter	Measure	Reviewer Comment
	cortisol	
Linearity	The assay was linear over the 1.0 to 150 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CV was < 12 %	Satisfactory
Accuracy	QC samples were between -9.5 and 17.8 % of nominal concentration	Satisfactory
LLOQ	1 ng/mL	Satisfactory
Specificity	Chromatograms were provided	Satisfactory
	6-beta hydrocortisol	
Linearity	The assay was linear over the 5 to 750 ng/mL range; $R^2 > 0.994$	Satisfactory
Between day Precision	CV was < 12 %	Satisfactory
Accuracy	QC samples were between -26 and 14 % of nominal concentration; bias values > 15 % were typically associated with the low QC samples (number of samples 3 out of 30 QC samples)	Acceptable
LLOQ	5 ng/mL	Satisfactory
Specificity	Chromatograms were provided	Satisfactory

Results

Dronedarone and SR35021 Pharmacokinetics
The dronedarone and SR35021 plasma concentration-time curves following administration of dronedarone and Stediril are depicted in Figure 135 and Figure 136.

The dronedarone and SR35021 PK measures are presented in Table 234.

Figure 135: Dronedarone plasma concentration-time profile following administration of dronedarone and Stediril

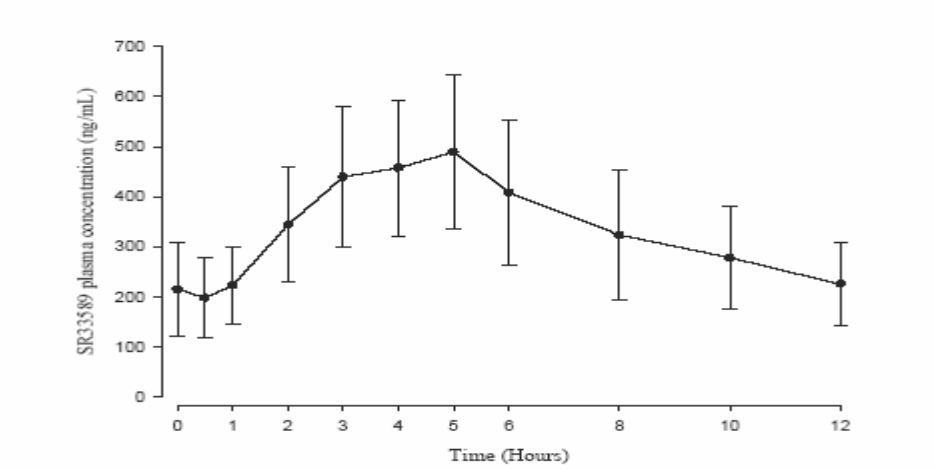


Figure 136: SR35021 plasma concentration time profile following administration of dronedarone and Stediril

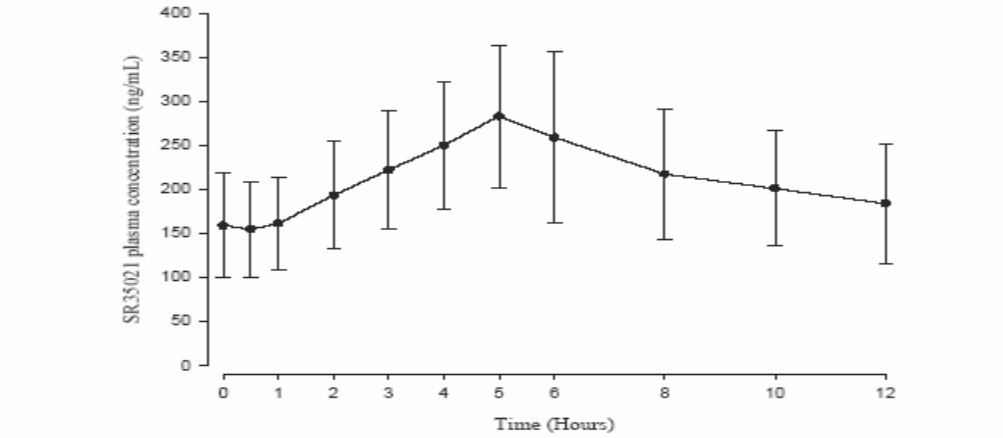


Table 234: Dronedarone PK measures following co-administration of dronedarone (800 mg BID) and Stediril

Day 15	C_{max} (ng/mL)	t_{max} (h)[a]	C_{min} (ng/mL)	$AUC_{0\text{-}12h}$ (ng.h/mL)
Mean	515	4.5	186	4086
CV%	28	22	39	31

[a] median value

Table 235: SR35021 PK measures following co-administration of dronedarone (800 mg BID) and Stediril

Day 15	C_{max} (ng/mL)	t_{max} (h)*	C_{min} (ng/mL)	$AUC_{0\text{-}12h}$ (ng.h/mL)
Mean	297	5.0	144	2588
CV%	31	26	37	30

*: median value

Based on a cross study comparison, Stediril does not appear to alter dronedarone PK.

Levonorgestrel and ethinylestradiol Pharmacokinetics

The ethinylestradiol and levonorgestrel plasma concentration time profiles obtained following administration of Stediril with or without dronedarone are depicted in Figure 137 and Figure 138.

Figure 137: Mean ethinylestradiol plasma concentration time profiles following administration of Stediril +/- dronedarone

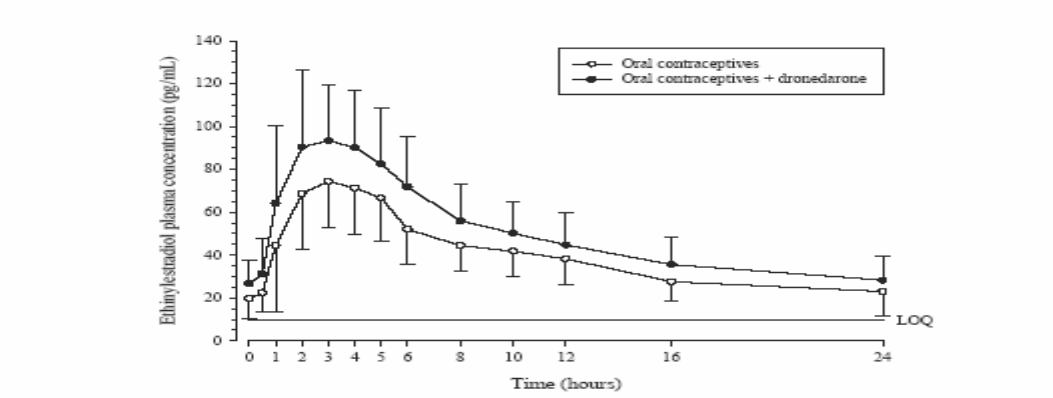
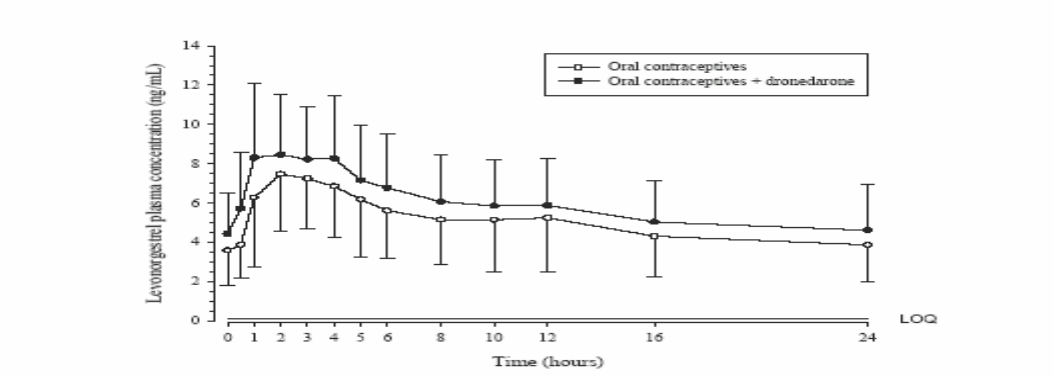


Figure 138: Mean levonorgestrel plasma concentration time profiles following administration of Stediril +/- dronedarone



The ethinylestradiol and levonorgestrel PK measures obtained following administration of Stediril with or without dronedarone are presented in Table 236.

The PK data indicate that dronedarone generally increased the exposure of the components of Stediril; the maximum mean increase was 28 %. Generally, confidence intervals were outside the no effect upper region (ranged from 1.05 to 1.38).

Reviewer comment on PK results

Typically, the concern with drug-drug interactions with respect to oral contraceptives involves a reduction in exposure of the hormones (Stediril components) that may lead to lack of effectiveness. In this case, there appears to be an increase in exposure of the Stediril components; however the mean increase is less than 30 % and unlikely to be clinically significant.

Table 236: Ethinylestradiol and levonorgestrel PK Measures following administration of Stediril +/- dronedarone (n = 18)

PK Parameter Mean (CV%)	Stediril 30® Alone	Stediril 30®+ Dronedarone	Ratio Estimates[b] and 90% CI
	ethinylestradiol		
C_{max} (pg/mL)	86.6 (28)	104.4 (26)	1.22 [1.14 – 1.30]
C_{min} (pg/mL)	18.3 (50)	24.5 (43)	1.22 [1.10 – 1.35]
t_{max} (h)[a]	3.0	2.1	-
AUC_{0-24h} (pg.h/mL)	947.9 (28)	1206.8 (30)	1.28 [1.18 – 1.38]
	levonorgestrel		
C_{max} (ng/mL)	8.8 (36)	9.8 (31)	1.13 [1.05 – 1.21]
C_{min} (ng/mL)	3.4 (50)	4.1 (49)	1.22 [1.12 – 1.32]
t_{max} (h)[a]	2.0	1.0	-
AUC_{0-24h} (ng.h/mL)	121.5 (45)	142.6 (39)	1.19 [1.11 – 1.27]

[a] : Median values, [b] : ratio Stediril 30®+dronedarone / Stediril 30®

Pharmacodynamics using 6-ß cortisol to cortisol ratio (Assessing Dronedarone CYP3A Induction Potential)

The urinary concentrations of 6-ß cortisol, cortisol and the 6-ß cortisol to cortisol ratio are summarized in Table 237.

Table 237: Pharmacodynamic Measurements (Comparisons of Cortisol ratios on Day 15 to Day 5)

Parameters	Day 15 / Day 5 Ratio Estimates and 90% CI	
	Dronedarone Treatment	Placebo Treatment
6β-hydroxycortisol	0.70 [0.53 ; 0.93]	0.74 [0.56 ; 0.98]
cortisol	0.47 [0.37 ; 0.60]	1.13 [0.89 ; 1.43]
6β-hydroxycortisol / cortisol ratio	1.48 [1.21 ; 1.80]	0.65 [0.54 ; 0.80]

Theoretically, the urinary 6ß-hydroxycortisol excretion is a measure of induction of CYP3A4 activity, as the metabolic pathway of cortisol to 6ß- hydroxycortisol is mediated by CYP3A4. Cortisol and 6ß-hydroxycortisol are endogenous compounds that can be readily measured. Generally, strong inducers such as rifampicin significantly increase (> 3-fold) the 6ß-hydroxycortisol daily excretion whereas urinary cortisol is not significantly modified. The referenced ratio was increased by ~ 1.5-fold in this study.

In the present study, the following observations were made:

1. production of 6ß-hydroxycortisol was similar during dronedarone treatment as compared to during placebo (Day 15/ Day 5 ratio of 0.70 and 0.74, respectively).
2. urinary cortisol concentration was decreased (Day 15/ Day 5 ratio of 0.47) during the dronedarone treatment, whereas it was not statistically significantly changed during the placebo treatment (Day 15/ Day 5 ratio of 1.13).
3. the 6ß- hydroxycortisol/cortisol ratio was increased by 1.48-fold during the dronedarone treatment

Although there was an increase in the ratio used to assess induction, the increase was not consistent with an induction mechanism: production of 6ß- hydroxycortisol was not increased during dronedarone treatment (remained constant), and cortisol concentration decreased, rather than remained constant. It should be noted that dronedarone did not exhibit induction properties in *in vitro* metabolism studies. The apparent induction findings were also not supported by the observations with the Stediril components. If dronedarone causes CYP3A induction, this

induction does not appear to have clinical relevance because, overall, dronedarone appeared to exhibit CYP3A inhibitory characteristics: increased the exposure of CYP3A substrates, ethinylestradiol and levonorgestrel.

Reviewer Note on Assessing Dronedarone CYP3A induction potential
A more definitive assessment of dronedarone's induction potential could be made by:
1) including a positive control (known enzyme inducer), such as rifampin
2) studying PK of a pure CYP3A substrate, such as midazolam.

Applicant's Safety Summary
No deaths or serious AEs (SAEs) were reported during this study. Adverse events were reported more frequently in the dronedarone+ Stediril 30 ® group (12/ 19 subjects) than the placebo+ Stediril 30 ® and Stediril 30 ® alone groups. Gastro-intestinal disorders were the most common treatment emergent AEs (TEAEs); these disorders included, diarrhea, abdominal pain and nausea. Other reported AEs were headache and atrioventricular (AV) block. The Investigator considered the AV block as related to study drug treatment. Frequency of Potentially clinically significant abnormalities (PCSAs) was somewhat higher in the dronedarone+ Stediril 30 ® group versus placebo, for decreases in systolic blood pressure (SBP) (9/20 versus 4/20 subjects) and diastolic blood pressure (DBP) (5/20 versus 2/20). In regards to QTc- interval PCSAs, in the dronedarone+ Stediril 30 ® group changes of between 30 and 60 ms were observed in 13/20 subjects, versus 3/20 in the placebo+ Stediril 30 ® group. No QTc over 500 ms was observed in any group. Few PCSAs in other ECG parameters were observed.

Recommendations/Conclusions
The following findings from Study INT4695 are acceptable for labeling as appropriate:

- Relative to administration of Stediril alone, dronedarone administration resulted in an approximately 25 % increase in ethinylestradiol exposure (Cmax, Cmin and AUC).
- Relative to administration of Stediril alone, dronedarone administration resulted in an approximately 18 % increase in levonorgestrel exposure (Cmax, Cmin and AUC).
- A slight apparent CYP3A induction effect was observed for dronedarone based on the 6ß-hydroxycortisol/cortisol ratio: (HC/Cr): HC/Cr increased with dronedarone administration by 1.48-fold relative to when dronedarone was absent. However the validity of this induction effect is not clear. Additionally, this effect does not appear clinically relevant: inhibition effect appears to override potential induction.

Labeling
The applicant's proposed labeling is acceptable. Based on the PK and pharmacodynamic results of this study, co-administration of dronedarone is unlikely to modify the efficacy of the oral contraceptives.

4.2.34 Study on the tolerability of SR33589B given twice daily as repeated ascending oral doses in healthy male subjects (Study TDR3549).

PROTOCOL #	TDR3549
INVESTIGATOR	Dr. W. Tetzloff
STUDY SITE	iphar, Institut für Klinische Pharmakologie GmbH, Arnikastrasse 4, D - 85635 Höhenkirchen- Siegertsbrunn, Germany
STUDY PERIOD	July 1998 to May 1999

Objectives (per applicant)

- Primary Objective

To assess the safety of repeated ascending oral doses of SR33589 (dronedarone) given twice daily for 10 days under fed conditions in healthy male subjects to determine the maximum tolerated dose (MTD).

- Secondary Objectives

To assess the effect of repeated ascending oral doses of dronedarone given twice daily on

1. electrocardiogram (ECG)
2. vital signs and exercise test parameters in order to determine the dose with the maximum pharmacodynamic effects in healthy subjects
3. to assess the PK profile of dronedarone and its N-debutyl metabolite SR35021
4. to identify the potential relationship between plasma levels and pharmacodynamics.

Reviewer Note

This review focuses on the PD information (secondary objectives) and PK information obtained at steady state that address dronedarone diurnal variation. Other PK studies provide comprehensive PK information.

Study Design

This was an ascending-dose, randomized, double- blind, placebo-controlled repeated-dose study in five successive groups. The following treatments were administered under fed conditions: dronedarone 800, 1000, 1400, 1200 and 1600 mg BID and placebo for 14 days

Subject Demographics

Subject demographics are presented in Table 238.

Formulation (2E3 Formulation)

- Dronedarone 200 mg capsules; batch number 96-00365
- Dronedarone placebo capsules; batch number 96-00344

Pharmacokinetic sampling times

Blood samples were collected at the following times:

- pretreatment and at 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 hours post-treatment for the single dose administration
- pretreatment and at 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 16 and 24 hours after the 7-day repeated administration
- pretreatment and at 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours after the 14-day repeated administration.

Table 238: Subject Demographics (TDR3549)

Parameter	Statistics	Placebo	800 mg b.i.d.	1000 mg b.i.d.	1200 mg b.i.d.	1400 mg b.i.d.	1600 mg b.i.d.
Age (years)	N Mean (SD) Min - Max	10 34.2(5.3) 26 - 40	6 29.5(6.4) 21 - 38	6 30.8(7.1) 22 - 39	7 37.0(3.4) 32 - 40	6 28.7(7.2) 21 - 38	6 29.5(3.1) 26 - 35
Height (cm)	N Mean (SD) Min - Max	10 178.0 (6.2) 168- 187	6 180.9 (4.0) 175- 186	6 181.3 (3.5) 178- 187	7 180.2 (4.2) 175- 186	6 183.5 (4.9) 176- 189	6 178.8 (4.0) 174- 183
Weight (kg)	N Mean (SD) Min - Max	10 73.1(5.9) 61.7 - 84.0	6 77.0(5.6) 69.1 - 83.9	6 76.0(6.6) 65.8 - 86.0	7 82.1(5.1) 74.5 - 87.9	6 81.3(7.5) 69.9 - 91.3	6 74.2(3.5) 68.6 - 77.5
BMI (kg/m^2)	N Mean (SD) Min - Max	10 23.1(1.8) 20.9 - 26.4	6 23.6(2.1) 21.2 - 26.0	6 23.1(2.1) 20.7 - 26.5	7 25.3(1.6) 22.4 - 26.6	6 24.1(1.7) 21.3 - 26.0	6 23.2(1.7) 21.3 - 25.5

Bioanalytical Methods

Plasma was assayed for dronedarone and its N-debutyl metabolite, SR35021, using HPLC with UV detection. The assay performance was acceptable and had the following characteristics:

- Linear for both compounds over the 0.5 to 50 ng/mL range; $R^2 > 0.992$ for SR35021 and $R^2 > 0.992$ for dronedarone
- CV < 8 % for SR35021 and CV < 7 % for dronedarone QC samples
- Relative bias for SR35021 QC samples between -4.5 and 5.7 % of nominal concentration Relative bias for dronedarone QC samples between 0.1 and 11.8 % of nominal concentration
- Chromatograms were not provided; however, chromatograms included in the validation report demonstrate assay specificity

Pharmacokinetics

The following dronedarone and SR35021 PK measures were determined

- Day 1: $AUC_{0\text{-}12h}$, Cmax, Tmax and Rmet
- Days 2, 4, 6, 8, and 10: Ctrough
- Day 10: $AUC_{0\text{-}12h}$, Cmax, Tmax, $AUC_{0\text{-}24}$, Rmet and Rac

Pharmacodynamics (Activity)

Pharmacodynamic effects were assessed under resting conditions and during exercise test. ECG parameters (PR- QRS, QT- intervals, QTc, T-wave amplitude, and RR interval), and vital signs (diastolic blood pressure, systolic blood pressure, and heart rate) were determined. ECG parameters were measured before and during treatment at regular time points during the resting phase and at regular time points during the exercise tests. A 24-hr Holter ECG was also performed on Day 8 of the treatment to evaluate the diurnal patterns of QT, QTc and RR intervals as a function of dronedarone dose.

Statistical Methods

Pharmacokinetics

Standard pharmaco-statistical analyses were used to evaluate the following:

- Diurnal variation via ratios of means for half-day differences (night-time vs. daytime administration) for Cmax, $AUC_{0\text{-}12}$ and Ctrough, tmax, half-day

- Dose effects on the Day 10 $t_{1/2z}$ values
- Accumulation ratios of means
- Dose proportionality for AUC_{0-12} and Cmax via log transformed power model
- Steady-state assessment using log transformed Ctrough

Pharmacodynamics

ANOVA was used for most statistical evaluations. The following evaluations were made for resting and exercise test conditions.

Comparison of baseline raw data across dose groups

Comparison of changes from baseline (Day 1 and Day 10)

The ANOVA model took repeated measures into account and included terms for dose and time effects, and the dose by time interaction. Two approaches were adopted depending on if the dose by time interaction was statistically significant:

- If dose by time interaction was statistically significant (p-value ≤ 0.10), then a one-way ANOVA with a fixed term for dose was performed at each time point, separately. Pairwise dose comparisons were then performed and mean differences with 95% confidence intervals (CIs) estimated within the ANOVA framework.
- If the dose by time interaction was not statistically significant (p-value > 0.10), then the following synthetic variables were defined for each subject: hourly Area Under the Curve (AUC), maximum value of the parameter (Emax) over 12 hours post dose and the corresponding time of E max(tmax). AUC and Emax were compared between dose levels using a one-way ANOVA with a fixed term for dose, and mean differences with corresponding 95% CIs for pairwise comparisons were estimated within the ANOVA framework. Tmax was compared between dose levels using the non-parametric Kruskal-Wallis test.

ANOVA with repeated measures was applied to the hourly mean values and the 24-hour mean of HR (bpm), RR-, QT-, and QTc (Bazett) intervals (ms) measured from the 24-hour ECG recordings.

Reviewer Note on Statistical analyses

This review focuses on the following:

- Pharmacodynamics- Day 10 results compared to baseline
- Pharmacokinetics- diurnal variation

Results

Dronedarone PK

The plasma concentration time profiles for dronedarone and SR35021 following single and multiple dose oral administration are depicted in Figure 139 and Figure 140.

Figure 139: Mean dronedarone plasma concentration-time profiles following BID and QD dosing

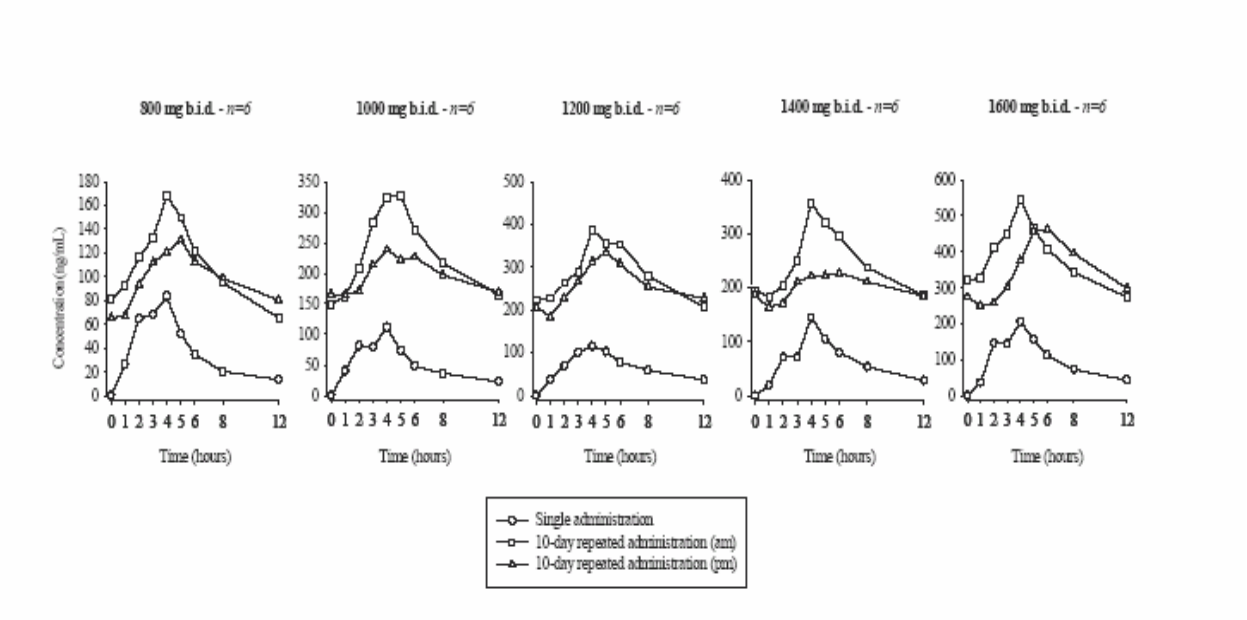
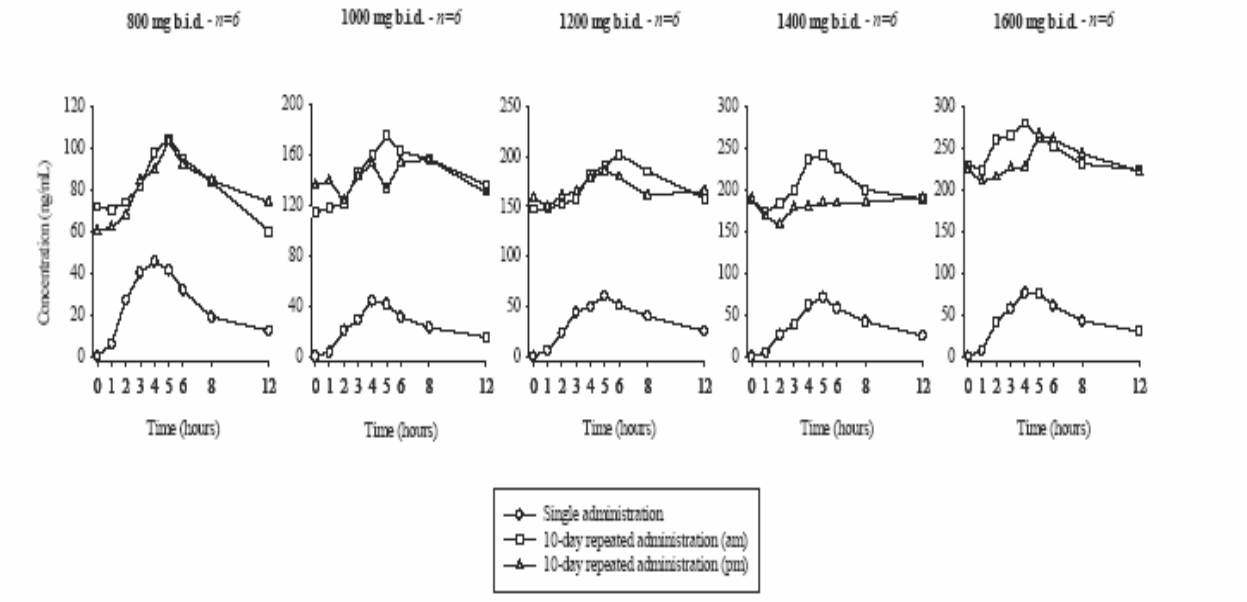


Figure 140: Mean SR35021 plasma concentration-time profiles following BID and QD dosing



The mean (SD) PK parameters of dronedarone after repeated administration of dronedarone 400, 600 or 800 mg BID and 800, 1200 or 1600 mg QD are shown in Table 239 and Table 240.

Table 239: Dronedarone PK measures following administration of dronedarone at different dose levels

C_{max} (ng/mL)	Dose administered				
	800 mg b.i.d.	1000 mg b.i.d.	1200 mg b.i.d.	1400 mg b.i.d.	1600 mg b.i.d.
C_{max}- Single administration					
Mean	86.7	132	135	147	223
SD	16.8	55.7	56.6	90.0	51.5
CV%	19	42	42	61	23
C_{max} - 10-days repeated administration (daytime)					
Mean	177	337	400	363	552
SD	57.7	92.8	131	118	139
CV%	33	28	33	33	25
C_{max} - 10-days repeated administration (night-time)					
Mean	136	264	343	242	476
SD	29.1	122	130	90.1	141
CV%	21	46	38	37	30

Table 240: Dronedarone PK measures following administration of dronedarone at different dose levels

AUC (ng.h/mL)	Dose administered				
	800 mg b.i.d.	1000 mg b.i.d.	1200 mg b.i.d.	1400 mg b.i.d.	1600 mg b.i.d.
AUC_{0-12} - Single administration					
Mean	432	609	790	742	1155
SD	81.2	203	368	499	271
CV%	19	33	47	67	24
AUC_{0-12} - 10-days repeated administration (daytime)					
Mean	1291	2758	3397	2919	4525
SD	303	819	1442	1138	953
CV%	23	30	42	39	21
AUC_{0-12} - 10-days repeated administration (night-time)					
Mean	1182	2783	3105	2416	4253
SD	200	1102	1281	907	1146
CV%	17	40	41	38	27
AUC_{0-24} - 10-days repeated administration (daytime and night-time)					
Mean	2473	5540	6501	5335	8778
SD	449	1619	2719	1996	2040
CV%	18	29	42	37	23

Highlights

- Accumulation: approximately 2- to 3- fold accumulation occurs (Day 10 vs. Day 1)
- Diurnal variation occurs: Daytime Cmax > Nighttime Cmax
- Steady state achieved within 10 days

Overall the PK findings in this study are consistent with those in previous PK studies.

SR35021 PK

PK characteristics of SR35021 are similar to dronedarone, as demonstrated in previous studies; however SR35021 results will not be presented in this review.

Table 241: Dronedarone PK measures following administration of dronedarone at different dose levels

C_{trough} (ng/mL)	Dose administered				
	800 mg b.i.d.	1000 mg b.i.d.	1200 mg b.i.d.	1400 mg b.i.d.	1600 mg b.i.d.
Day 2 (daytime)					
Mean	38.8	64.7	82.4	89.3	121
SD	11.0	29.8	57.2	40.4	45.9
CV%	28	46	69	45	38
Day 4 (daytime)					
Mean	65.2	111	147	115	215
SD	16.0	51.9	58.8	31.8	50.1
CV%	24	47	40	28	23
Day 6 (daytime)					
Mean	83	113	197	149	203
SD	19.2	46.7	116.8	64.6	49.4
CV%	23	41	59	43	24
Day 8 (daytime)					
Mean	74.9	134	233	164	280
SD	14.9	43.4	143	60.5	86.6
CV%	20	32	61	37	31
Day 10 (daytime)					
Mean	80.7	150	223	195	322
SD	14.7	31.7	117.4	80.4	70.2
CV%	18	21	53	41	22

Pharmacodynamics (Activity)

Several PD measures were determined in this study; the changes in these measures with respect to dronedarone dose are summarized in the following tables and figures. It should be noted that the results in italics (tables) are not statistically significant.

Resting Conditions (Day 10 Results)

1. PR Interval

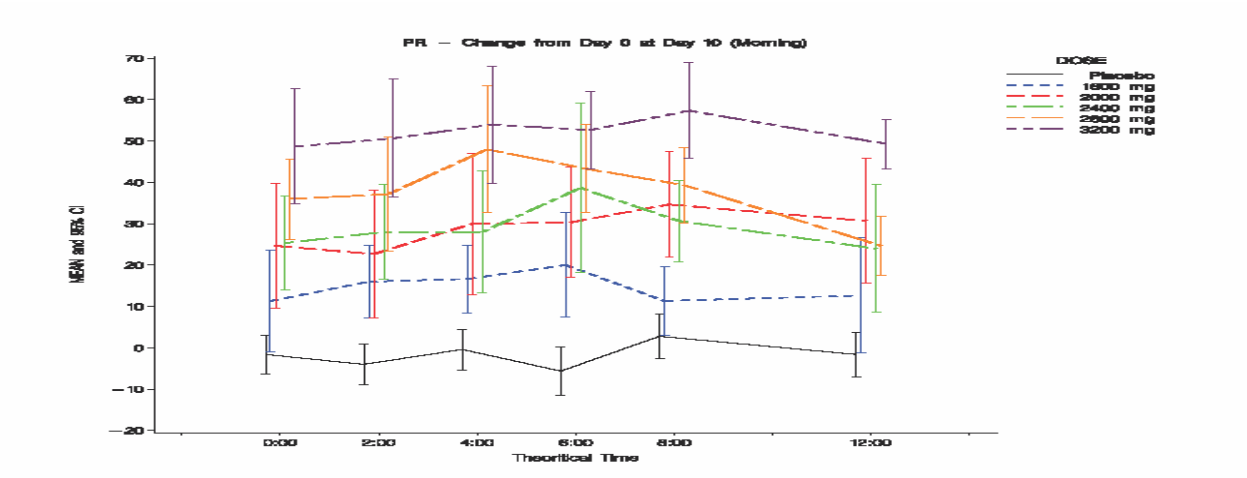
On Day 10 there was a statistically significant overall treatment effect ($p < 0.0001$) thus pairwise comparison was done between dose groups using AUC and Emax measures. As shown in Table 242, PR prolongation was statistically significantly higher in all active dose groups compared to placebo.

Table 242: Differences in the PR* AUC and Emax for various dose groups on Day 10 (resting conditions)

Analysis	Difference	Estimate [95% CI] (Day)	Estimate [95% CI] (Night)
AUC	Placebo vs 800 mg b.i.d	16.0 [4.0 ; 28.0]	19.0 [6.2 ; 31.8]
	Placebo vs 1000 mg b.i.d.	31.0 [19.0 ; 43.1]	25.4 [12.6 ; 38.2]
	Placebo vs 1200 mg b.i.d.	30.9 [18.9 ; 42.9]	22.8 [9.9 ; 35.6]
	Placebo vs 1400 mg b.i.d.	39.8 [27.8 ; 51.8]	32.9 [20.1 ; 45.7]
	Placebo vs 1600 mg b.i.d.	54.2 [42.2 ; 66.2]	46.3 [33.5 ; 59.1]
	800 mg b.i.d vs 1000 mg b.i.d.	15.0 [1.6 ; 28.4]	*6.4 [-8.0 ; 20.7]*
	800 mg b.i.d vs 1200 mg b.i.d.	14.9 [1.5 ; 28.3]	*3.7 [-10.6 ; 18.1]*
	800 mg b.i.d vs 1400 mg b.i.d.	23.7 [10.3 ; 37.2]	*13.9 [-0.5 ; 28.2]*
	800 mg b.i.d vs 1600 mg b.i.d.	38.2 [24.8 ; 51.6]	27.3 [12.9 ; 41.6]
E_{max}	Placebo vs 800 mg b.i.d	15.9 [0.1 ; 31.6]	23.3 [8.9 ; 37.8]
	Placebo vs 1000 mg b.i.d.	29.2 [13.5 ; 44.9]	26.7 [12.2 ; 41.1]
	Placebo vs 1200 mg b.i.d.	35.2 [19.5 ; 50.9]	24.3 [9.9 ; 38.8]
	Placebo vs 1400 mg b.i.d.	43.9 [28.1 ; 59.6]	38.7 [24.2 ; 53.1]
	Placebo vs 1600 mg b.i.d.	52.5 [36.8 ; 68.3]	44.7 [30.2 ; 59.1]
	800 mg b.i.d vs 1000 mg b.i.d.	19.3 [1.7 ; 36.9]	*1.0 [-15.1 ; 17.1]*
	800 mg b.i.d vs 1400 mg b.i.d.	28.0 [10.4 ; 45.6]	*15.3 [-0.8 ; 31.5]*
	800 mg b.i.d vs 1600 mg b.i.d.	36.7 [19.1 ; 54.3]	21.3 [5.2 ; 37.5]

At night-time, the range of differences in PR prolongation was smaller than in daytime. It is unclear if this diurnal variation is due to the different plasma concentrations. There was a trend towards a linear dose-response relationship as illustrated in Figure 141.

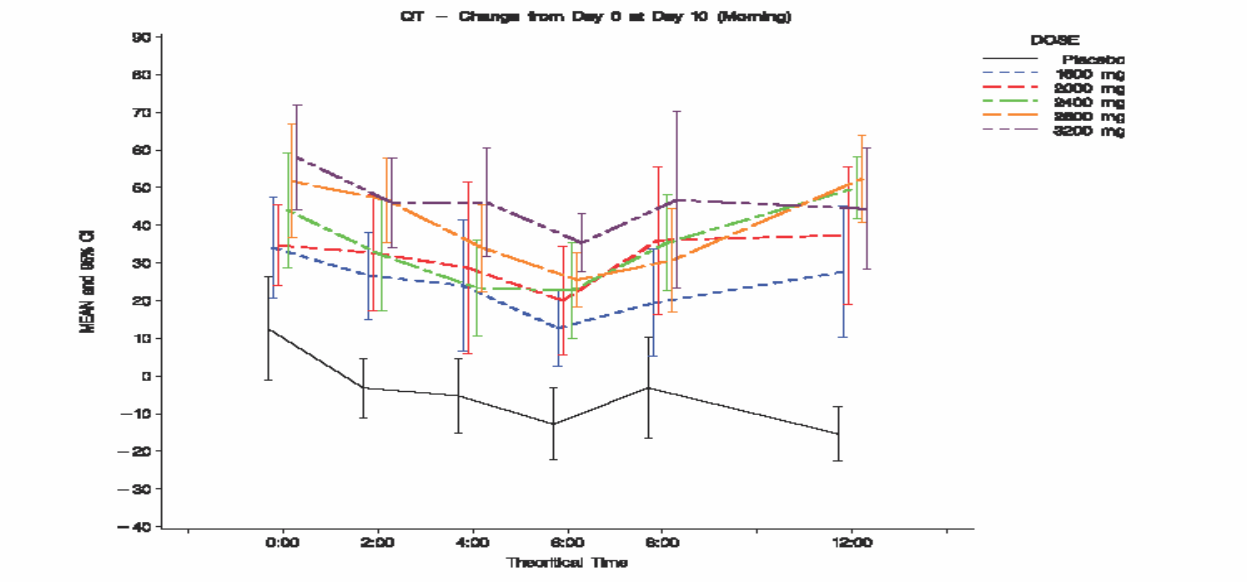
Figure 141: Relationship between change in PR and time at different dronedarone dose levels (morning)



2. QT Interval

Relative to placebo, dronedarone treatment generally increased the QT interval (Figure 142 and Table 243.

Figure 142: Relationship between change in QT and time at different dronedarone dose levels (morning)



There appeared to be diurnal variation with respect to QT prolongation: the QT prolongation before the morning dose at all dose levels seemed lower than prior to the evening dose. The reason for the diurnal variation is not clear. There was also a fairly wide range fluctuation in QT interval prolongation that appeared to be both time- and dose-dependent.

There was a trend towards increasing QT interval with increasing dose.

Table 243: Change in QT interval over time at different dronedarone dose levels

Parameter	Theoretical time	Difference	Estimate [95% CI] (Day)	(Night)
QT-interval (ms)	T0	Placebo vs 800 mg b.i.d.	21.5 [1.9 ; 41.1]	43.1 [25.2 ; 60.9]
		Placebo vs 1000 mg b.i.d.	22.2 [2.6 ; 41.8]	52.7 [34.9 ; 70.6]
		Placebo vs 1200 mg b.i.d.	31.5 [11.9 ; 51.1]	65.4 [47.5 ; 83.3]
		Placebo vs 1400 mg b.i.d.	39.2 [19.6 ; 58.8]	67.7 [49.9 ; 85.6]
		Placebo vs 1600 mg b.i.d.	45.5 [25.9 ; 65.1]	59.7 [41.9 ; 77.6]
		800 mg b.i.d. vs 1200 mg b.i.d.	*10.0 [-11.9 ; 31.9]*	22.3 [2.4 ; 42.3]
		800 mg b.i.d. vs 1400 mg b.i.d.	*17.7 [-4.3 ; 39.6]*	24.7 [4.7 ; 44.6]
		800 mg b.i.d. vs 1600 mg b.i.d.	24.0 [2.1 ; 45.9]	*16.7 [-3.3 ; 36.6]*
		1000 mg b.i.d. vs 1600 mg b.i.d.	23.3 [1.4 ; 45.3]	*7.0 [-13.0 ; 27.0]*
	T2	Placebo vs 800 mg b.i.d.	29.9 [13.6 ; 46.1]	34.3 [10.8 ; 57.7]
		Placebo vs 1000 mg b.i.d.	35.9 [19.6 ; 52.1]	34.9 [11.5 ; 58.4]
		Placebo vs 1200 mg b.i.d.	35.2 [19.0 ; 51.4]	36.3 [12.8 ; 59.7]
		Placebo vs 1400 mg b.i.d.	49.9 [33.6 ; 66.1]	40.9 [17.5 ; 64.4]
		Placebo vs 1600 mg b.i.d.	49.2 [33.0 ; 65.4]	68.3 [44.8 ; 91.7]
		800 mg b.i.d. vs 1400 mg b.i.d.	20.0 [1.8 ; 38.2]	*6.7 [-19.6 ; 32.9]*
		800 mg b.i.d. vs 1600 mg b.i.d.	19.3 [1.2 ; 37.5]	34.0 [7.8 ; 60.2]
		1000 mg b.i.d. vs 1600 mg b.i.d.	*13.3 [-4.8 ; 31.5]*	33.3 [7.1 ; 59.6]
		1200 mg b.i.d. vs 1600 mg b.i.d.	*14.0 [-4.2 ; 32.2]*	32.0 [5.8 ; 58.2]
		1400 mg b.i.d. vs 1600 mg b.i.d.	*-0.7 [-18.8 ; 17.5]*	27.3 [1.1 ; 53.6]
	T4	Placebo vs 800 mg b.i.d.	29.3 [9.0 ; 49.6]	34.4 [13.6 ; 55.2]
		Placebo vs 1000 mg b.i.d.	34.0 [13.7 ; 54.3]	23.7 [3.0 ; 44.5]
		Placebo vs 1200 mg b.i.d.	28.6 [8.3 ; 48.9]	*20.4 [-0.4 ; 41.2]*
		Placebo vs 1400 mg b.i.d.	39.3 [19.0 ; 59.6]	31.7 [11.0 ; 52.5]
		Placebo vs 1600 mg b.i.d.	51.3 [31.0 ; 71.6]	61.9 [41.1 ; 82.7]
		800 mg b.i.d. vs 1600 mg b.i.d.	*22.0 [-0.7 ; 44.7]*	27.5 [4.3 ; 50.7]
		1000 mg b.i.d. vs 1600 mg b.i.d.	*17.3 [-5.4 ; 40.0]*	38.2 [14.9 ; 61.4]
		1200 mg b.i.d. vs 1600 mg b.i.d.	*22.7 [0.0 ; 45.4]*	41.5 [18.3 ; 64.7]
		1400 mg b.i.d. vs 1600 mg b.i.d.	*12.0 [-10.7 ; 34.7]*	30.2 [6.9 ; 53.4]
	T6	Placebo vs 800 mg b.i.d.	25.5 [10.8 ; 40.2]	39.9 [20.0 ; 59.8]
		Placebo vs 1000 mg b.i.d.	32.8 [18.1 ; 47.5]	36.5 [16.6 ; 56.4]
		Placebo vs 1200 mg b.i.d.	35.5 [20.8 ; 50.2]	27.2 [7.3 ; 47.1]
		Placebo vs 1400 mg b.i.d.	38.3 [23.6 ; 53.0]	47.9 [28.0 ; 67.8]
		Placebo vs 1600 mg b.i.d.	48.1 [33.4 ; 62.8]	51.5 [31.6 ; 71.4]
		800 mg b.i.d. vs 1600 mg b.i.d.	22.7 [6.2 ; 39.1]	*11.7 [-10.6 ; 33.9]*
		1200 mg b.i.d. vs 1600 mg b.i.d.	*12.7 [-3.8 ; 29.1]*	24.3 [2.1 ; 46.6]

Parameter	Theoretical time	Difference	Estimate [95% CI] (Day)	(Night)
QT-interval (ms)	T8	Placebo vs 800 mg b.i.d.	*22.5[-0.1 ; 45.1]*	45.5[24.6 ; 66.4]
		Placebo vs 1000 mg b.i.d.	39.2[16.6 ; 61.8]	45.5[24.6 ; 66.4]
		Placebo vs 1200 mg b.i.d.	38.5[15.9 ; 61.1]	42.2[21.3 ; 63.1]
		Placebo vs 1400 mg b.i.d.	33.9[11.3 ; 56.5]	48.5[27.6 ; 69.4]
		Placebo vs 1600 mg b.i.d.	49.9[27.3 ; 72.5]	72.2[51.3 ; 93.1]
		800 mg b.i.d. vs 1600 mg b.i.d.	27.3 [2.1 ; 52.6]	26.7 [3.3 ; 50.0]
		1000 mg b.i.d. vs 1600 mg b.i.d.	*10.7 [-14.6 ; 35.9]*	26.7 [3.3 ; 50.0]
		1200 mg b.i.d. vs 1600 mg b.i.d.	*11.3 [-13.9 ; 36.6]*	30.0 [6.6 ; 53.4]
		1400 mg b.i.d. vs 1600 mg b.i.d.	*16.0 [-9.3 ; 41.3]*	23.7 [0.3 ; 47.0]
	T12	Placebo vs 800 mg b.i.d.	43.1 [25.2 ; 60.9]	45.6 [25.7 ; 65.5]
		Placebo vs 1000 mg b.i.d.	52.7 [34.9 ; 70.6]	41.3 [21.4 ; 61.1]
		Placebo vs 1200 mg b.i.d.	65.4 [47.5 ; 83.3]	56.9 [37.1 ; 76.8]
		Placebo vs 1400 mg b.i.d.	67.7 [49.9 ; 85.6]	48.3 [28.4 ; 68.1]
		Placebo vs 1600 mg b.i.d.	59.7 [41.9 ; 77.6]	70.9 [51.1 ; 90.8]
		800 mg b.i.d. vs 1200 mg b.i.d.	22.3 [2.4 ; 42.3]	*11.3 [-10.9 ; 33.5]*
		800 mg b.i.d. vs 1400 mg b.i.d.	24.7 [4.7 ; 44.6]	*2.7 [-19.5 ; 24.9]*
		800 mg b.i.d. vs 1600 mg b.i.d.	*16.7 [-3.3 ; 36.6]*	25.3 [3.1 ; 47.5]
		1000 mg b.i.d. vs 1600 mg b.i.d.	*7.0 [-13.0 ; 27.0]*	29.7 [7.5 ; 51.9]
		1400 mg b.i.d. vs 1600 mg b.i.d.	*-8.0 [-28.0 ; 12.0]*	22.7 [0.5 ; 44.9]

Reviewer Note

The applicant notes that a statistically significant (p = 0.0109) treatment by time interaction was detected for QT-interval at baseline, in daytime, possibly due to a difference in mean values between

placebo and 1000 mg BID groups at T0. However, the applicant does not consider this interaction likely to compromise treatment group comparison with respect to changes from baseline. The applicant's interpretation appears reasonable and is acceptable; however, the applicant should have determined the reason for this unexpected observation. Potentially the subject could have committed a protocol violation.

3. QTc Interval

On Day 10 there was no treatment by time interaction for QTc. As shown in Table 244, the subsequent analyses indicated:

- Relative to placebo there was a statistically significant overall treatment effect (p = <0.0001) for QTc with respect to Emax and AUC
- QTc prolongation was correlated to dose

Table 244: Change in QTc as a function of dronedarone dose

Analysis	Difference	Estimate [95% CI] (Day)	Estimate [95% CI] (Night)
AUC	Placebo vs 800 mg b.i.d	10.5 [1.9 ; 19.1]	16.7 [6.3 ; 27.0]
	Placebo vs 1000 mg b.i.d.	27.0 [18.3 ; 35.6]	23.4 [13.1 ; 33.8]
	Placebo vs 1200 mg b.i.d.	24.5 [15.8 ; 33.1]	23.4 [13.1 ; 33.8]
	Placebo vs 1400 mg b.i.d.	29.8 [21.1 ; 38.4]	30.0 [19.6 ; 40.3]
	Placebo vs 1600 mg b.i.d.	31.1 [22.4 ; 39.7]	35.4 [25.1 ; 45.8]
	800 mg b.i.d vs 1000 mg b.i.d.	16.5 [6.8 ; 26.1]	*6.8 [-4.8 ; 18.3]*
	800 mg b.i.d vs 1200 mg b.i.d.	14.0 [4.3 ; 23.6]	*6.8 [-4.8 ; 18.3]*
	800 mg b.i.d vs 1400 mg b.i.d.	19.3 [9.6 ; 28.9]	13.3 [1.7 ; 24.9]
	800 mg b.i.d vs 1600 mg b.i.d.	20.6 [10.9 ; 30.2]	18.7 [7.2 ; 30.3]
E_{max}	Placebo vs 800 mg b.i.d	12.9 [1.2 ; 24.7]	16.4 [3.3 ; 29.5]
	Placebo vs 1000 mg b.i.d.	30.3 [18.5 ; 42.0]	22.1 [9.0 ; 35.2]
	Placebo vs 1200 mg b.i.d.	23.8 [12.0 ; 35.5]	19.1 [6.0 ; 32.2]
	Placebo vs 1400 mg b.i.d.	30.6 [18.9 ; 42.3]	36.9 [23.8 ; 50.0]
	Placebo vs 1600 mg b.i.d.	34.4 [22.7 ; 46.2]	37.2 [24.1 ; 50.3]
	800 mg b.i.d vs 1000 mg b.i.d.	17.3 [4.2 ; 30.4]	*5.7 [-9.0 ; 20.3]*
	800 mg b.i.d vs 1400 mg b.i.d.	17.7 [4.6 ; 30.8]	20.5 [5.9 ; 35.1]
	800 mg b.i.d vs 1600 mg b.i.d.	21.5 [8.4 ; 34.6]	20.8 [6.2 ; 35.5]

4. T-wave amplitude

A statistically significant treatment effect was detected for AUC and Emax on both daytime and nighttime measures (Table 245).

Table 245: Change in T-wave amplitude as a function of dronedarone dose

Analysis	Difference	Estimate [95% CI] Daytime	Estimate [95% CI] Night-time
AUC	Placebo vs 800 mg b.i.d	-157 [-302 ; -12.2]	*-112 [-253 ; 29.6]*
	Placebo vs 1000 mg b.i.d.	-204 [-349 ; -58.6]	-195 [-336 ; -53.4]
	Placebo vs 1200 mg b.i.d.	-183 [-328 ; -38.0]	-170 [-311 ; -28.5]
	Placebo vs 1400 mg b.i.d.	-228 [-373 ; -83.3]	-208 [-349 ; -67.0]
	Placebo vs 1600 mg b.i.d.	-296 [-441 ; -151]	-284 [-425 ; -143]
	800 mg b.i.d vs 1600 mg b.i.d.	*-139 [-301 ; 22.9]*	-173 [-330 ; -14.7]
E_{max}	Placebo vs 800 mg b.i.d	-213 [-363 ; -63.0]	*-146 [-301 ; 8.1]*
	Placebo vs 1000 mg b.i.d.	-251 [-401 ; -101]	-237 [-391 ; -82.2]
	Placebo vs 1200 mg b.i.d.	-237 [-386 ; -86.6]	*-154 [-309 ; 0.3]*
	Placebo vs 1400 mg b.i.d.	-276 [-425 ; -126]	-254 [-409 ; -99.9]
	Placebo vs 1600 mg b.i.d.	-363 [-513 ; -213]	-301 [-455 ; -146]

Table 246 summarizes the mean differences in Emax for changes from baseline in ECG parameters on Day 10 in the 800 mg (lowest dose) and 1600 mg (highest dose) BID groups, compared to placebo. The findings for the 800 and 1600 mg groups support the existence of a dose-response relationship for the ECG measures, as the effect of 1600 mg was always numerically greater than that of 800 mg in the same direction.

Table 246: Mean differences in Emax for changes from baseline in ECG parameters on Day 10

ECG parameters on Day 10	Placebo vs 800 mg bid	Placebo vs 1600 mg bid
PR-interval (ms) (daytime)	15.9	52.5
QT-interval (ms) (daytime)	29.3 (T4h)	51.3 (T4h)
QT-interval (ms) (night-time)	34.4 (T4h)	72.2 (T8h)
QTc-interval (ms) (daytime)	12.9	34.4
QTc-interval (ms) (night-time)	16.4	37.2
T-wave (µV) (daytime)	- 213	- 363

5. Heart rate

On Day 10, a treatment difference was detected on hourly AUC and E_{max} for both daytime and night-time measures.

Table 247: Mean differences in Emax for changes from baseline in HR parameters on Day 10

Analysis	Difference	Estimate [95% CI] on Day 10	
		Daytime	Night-time
AUC	Placebo vs 800 mg b.i.d	-4.5 [-8.2 ; -0.8]	-7.7 [-11.0 ; -4.5]
	Placebo vs 1000 mg b.i.d.	*-3.4 [-7.2 ; 0.3]*	-3.9 [-7.2 ; -0.7]
	Placebo vs 1200 mg b.i.d.	*-1.7 [-5.4 ; 2.0]*	-4.1 [-7.3 ; -0.8]
	Placebo vs 1400 mg b.i.d.	-4.0 [-7.7 ; -0.3]	-4.2 [-7.5 ; -1.0]
	Placebo vs 1600 mg b.i.d.	-6.1 [-9.9 ; -2.4]	-6.5 [-9.7 ; -3.2]
	800 mg b.i.d vs 1000 mg b.i.d.	*1.1 [-3.1 ; 5.2]*	3.8 [0.1 ; 7.5]
	800 mg b.i.d vs 1200 mg b.i.d.	*2.8 [-1.4 ; 7.0]*	3.7 [0.0 ; 7.3]
E_{max}	Placebo vs 800 mg b.i.d	*-3.0 [-6.8 ; 0.7]*	-8.1 [-12.5 ; -3.6]
	Placebo vs 1000 mg b.i.d.	*-3.4 [-7.1 ; 0.4]*	-7.9 [-12.3 ; -3.5]
	Placebo vs 1200 mg b.i.d.	*-2.2 [-5.9 ; 1.5]*	-6.7 [-11.2 ; -2.3]
	Placebo vs 1400 mg b.i.d.	-5.5 [-9.3 ; -1.8]	-6.4 [-10.8 ; -2.0]
	Placebo vs 1600 mg b.i.d.	-6.5 [-10.3 ; -2.8]	-8.7 [-13.2 ; -4.3]

Only the two highest dose groups (1400 mg and 1600 mg) were able to affect the maximum change in HR relative to placebo during the daytime; conversely, during the nighttime, all dronedarone doses had higher maximum changes in HR than placebo. There was no clear dose-response (HR) relationship

6. SBP

There was no clear dose-response in SBP; however, the 800 mg and 1200 mg BID exhibited a higher decrease in SBP than placebo (Table 248).

Table 248: Mean differences in Emax for changes from baseline in ECG parameters on Day 10

Difference	Estimate [95% CI]
Placebo vs 800 mg b.i.d	-6.4 [-12.3 ; -0.5]
Placebo vs 1200 mg b.i.d.	-9.1 [-15.0 ; -3.2]

7. DBP

There was no clear dose-response in DBP; however, there were differences between placebo and some dronedarone dose groups in DBP at T8 and T12 (Table 249).

Table 249: Mean differences in Emax for changes from baseline in DBP parameters on Day 10 (nighttime)

Theoretical time	Difference	Estimate [95% CI]
T8	Placebo vs 800 mg b.i.d	-11.2 [-17.7 ; -4.7]
	Placebo vs 1200 mg b.i.d.	-10.2 [-16.7 ; -3.7]
	Placebo vs 1600 mg b.i.d.	-8.2 [-14.7 ; -1.7]
T12	Placebo vs 1200 mg b.i.d.	-12.7 [-20.4 ; -4.9]
	Placebo vs 1400 mg b.i.d.	-11.5 [-19.2 ; -3.8]
	Placebo vs 1600 mg b.i.d.	-12.5 [-20.2 ; -4.8]

The maximal differences in vital signs are summarized in Table 250.

Table 250: Mean differences in Emax for changes from baseline in DBP parameters on Day 10 (nighttime)

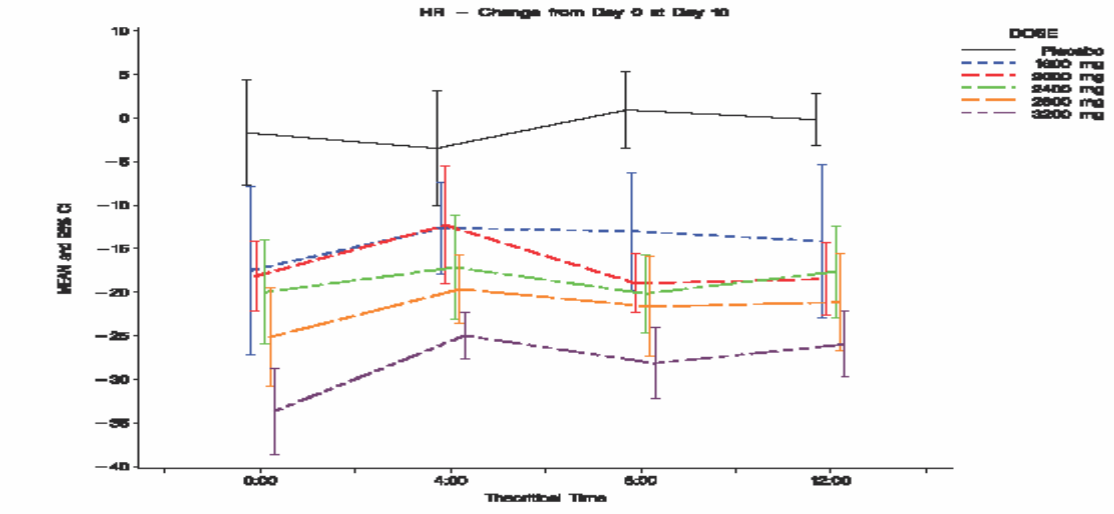
Vital signs	Placebo vs 800 mg bid	Placebo vs 1600 mg bid
HR (bpm)	- 3.0	- 6.5
SBP (mmHg)	- 13.5 (T8h)	-12.2 (T8h)
DBP (mmHg)	- 11.2 (T8h)	- 12.7 (T12h)

Exercise Tests (Day 10 Results)

1. HR

The heart rate changes from baseline as a function of dronedarone dose are shown in Figure 143.

Figure 143: Heart Rate Changes form Day 0 and Day 10 during exercise testing



The decrease in all active groups was statistically significantly greater than in the placebo group, at all time points. A statistically significant decrease in maximum HR was observed at all time points during the exercise test. For example at T0 (after exercise test), before morning administration on Day 10, the range of relative HR decrease was 15 bpm (placebo vs. 800 mg BID) to 32 bpm (placebo vs. 1600 mg BID). There was a linear trend between dose and response, but it was not clear if a plateau effect had been achieved.

Table 251: Pairwise Comparisons of Heart Rate obtained during Exercise Test for Various dronedarone doses

Theoretical time	Difference	Estimate	95% CI
T0	Placebo vs 800 mg b.i.d	-15.8	[-24.7 ; -6.9]
	Placebo vs 1000 mg b.i.d.	-16.5	[-25.4 ; -7.6]
	Placebo vs 1200 mg b.i.d.	-18.3	[-27.2 ; -9.4]
	Placebo vs 1400 mg b.i.d.	-23.5	[-32.4 ; -14.6]
	Placebo vs 1600 mg b.i.d.	-32.0	[-40.9 ; -23.1]
	800 mg b.i.d vs 1600 mg b.i.d.	-16.2	[-26.1 ; -6.2]
T4	Placebo vs 800 mg b.i.d	-9.2	[-17.3 ; -1.0]
	Placebo vs 1000 mg b.i.d.	-8.8	[-17.0 ; -0.7]
	Placebo vs 1200 mg b.i.d.	-13.7	[-21.8 ; -5.5]
	Placebo vs 1400 mg b.i.d.	-16.2	[-24.3 ; -8.0]
	Placebo vs 1600 mg b.i.d.	-21.5	[-29.6 ; -13.4]
	800 mg b.i.d. vs 1600 mg b.i.d.	-12.3	[-21.4 ; -3.2]
T8	Placebo vs 800 mg b.i.d	-13.9	[-20.8 ; -7.0]
	Placebo vs 1000 mg b.i.d.	-19.9	[-26.8 ; -13.0]
	Placebo vs 1200 mg b.i.d.	-21.1	[-27.9 ; -14.2]
	Placebo vs 1400 mg b.i.d.	-22.6	[-29.4 ; -15.7]
	Placebo vs 1600 mg b.i.d.	-29.1	[-35.9 ; -22.2]
	800 mg b.i.d vs 1400 mg b.i.d.	-8.7	[-16.3 ; -1.0]
	800 mg b.i.d vs 1600 mg b.i.d.	-15.2	[-22.8 ; -7.5]
T12	Placebo vs 800 mg b.i.d	-14.0	[-21.0 ; -6.9]
	Placebo vs 1000 mg b.i.d.	-18.3	[-25.3 ; -11.3]
	Placebo vs 1200 mg b.i.d.	-17.5	[-24.5 ; -10.4]
	Placebo vs 1400 mg b.i.d.	-21.0	[-28.0 ; -13.9]
	Placebo vs 1600 mg b.i.d.	-25.8	[-32.8 ; -18.8]
	800 mg b.i.d vs 1600 mg b.i.d.	-11.8	[-19.7 ; -4.0]

2. SBP

Relative to placebo, a statistically significant decrease in SBP occurred at T4 and T8 for some active dose groups; however the 1000 mg BID dose group did not produce an effect (Table 252).

Table 252: Pairwise Comparisons of SBP during Exercise Test for Various dronedarone doses

Theoretical time	Difference	Estimate	95% CI
T4	Placebo vs 800 mg b.i.d	-23.9	[-38.5 ; -9.3]
	Placebo vs 1400 mg b.i.d.	-21.2	[-35.8 ; -6.6]
T8	Placebo vs 800 mg b.i.d	-15.9	[-31.6 ; -0.1]
	Placebo vs 1200 mg b.i.d.	-29.4	[-45.1 ; -13.6]
	Placebo vs 1400 mg b.i.d.	-18.0	[-33.8 ; -2.3]
	Placebo vs 1600 mg b.i.d.	-17.4	[-33.1 ; -1.6]

There was no clear dose-response relationship.

3. DBP

No treatment differences could be detected on Day 10 for maximum DBP in exercise tests.

Twenty-four (24) hour Holter ECG (summary)

Highlights of the 24-hr Holter ECG data are summarized in the following section. All plots were generated by the applicant and are consistent with the provided data. Table 253 provides a summary of the p-values for the various tested hypotheses. ECG parameters are addressed in turn. It should be noted that there were no statistically significant differences in the tested variables

among different treatment groups prior to drug administration and no statistically significant differences in the placebo group between screening and Day 8.

Table 253: Summary of p-values for various tested hypotheses

Dependent Variable	H1: p-Value Dose Effect	H2: p-Value* Hour Effect	H3: p-Value* Hour-Dose Interaction	H4: p-Value Placebo vs. Drug Contrast
RR Scrn	0.5785	<0.0001	0.5019	0.9288
RR Day8	0.1508	<0.0001	0.5974	0.0407
Del RR	0.0759	<0.0001	0.2752	0.0063
QT Scrn	0.9493	<0.0001	0.9164	0.6759
QT Day8	<0.0001	<0.0001	0.2062	<0.0001
Del QT	<0.0001	<0.0001	0.3711	<0.0001
QTc Scrn	0.9304	<0.0001	0.0654	0.6435
QTc Day8	<0.0001	0.0166	0.7624	<0.0001
Del QTc	0.0014	<0.0001	0.0975	<0.0001

- QT-interval and QTc

Relative to placebo, there was a statistically significant increase induced by steady-state dronedarone treatment; conversely placebo did not induce QT changes (placebo Day 8 vs. Placebo Day 0).

- RR interval

There were no statistically significant differences among all treated groups on Day 8. However, when all drug treated groups were contrasted against placebo, both RR Day 8 ($p = 0.0407$) and the difference between RR on Day 8 and screening ($p= 0.0063$) were statistically significant.

- Dose-Response

The dose-response curves were statistically significantly linear with respect to relative prolongation of 24-hour mean QT, QTc, and RR intervals induced by 8-day treatment with dronedarone or placebo (Figure 144, Figure 145, and Figure 146).

Figure 144: QT % increase as a function of dronedarone dose

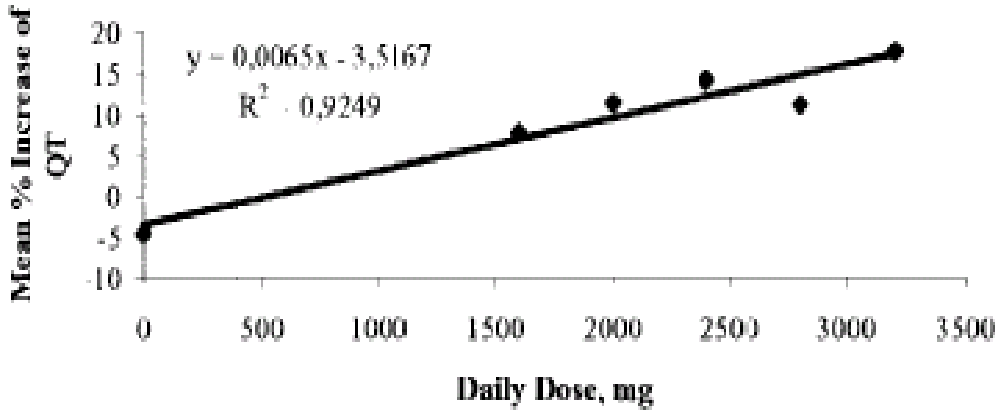


Figure 145: Mean QT % increase as a function of dronedarone dose

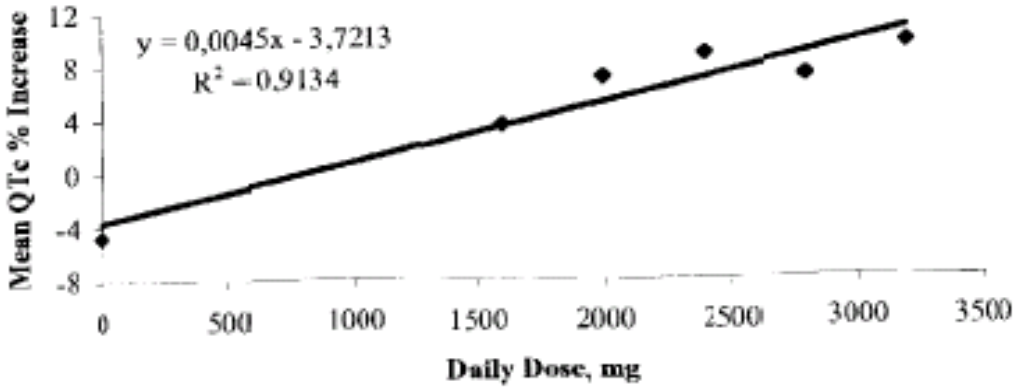
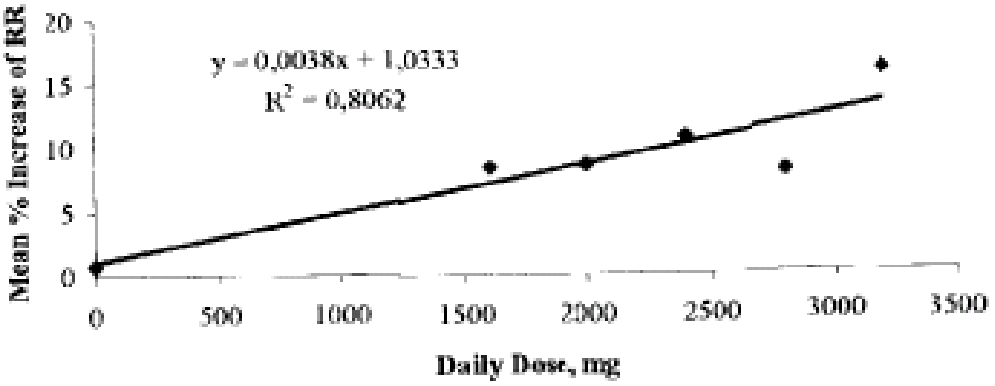


Figure 146: RR dose response



1. Circadian patterns

Statistically significant hourly fluctuations occurred in all groups at screening as well as on Day 8, but only QT and RR exhibited a clearly recognizable circadian pattern common to all treatment groups.

In the following plots on circadian variation, Placebo refers to placebo group and Dose 16, 20, 24, 28 and 32 refer to 800, 1000, 1200, 1400 and 1600 mg BID dronedarone, respectively.

Figure 147: RR circadian variation at screen (left panel) and on Day 8 (right panel)

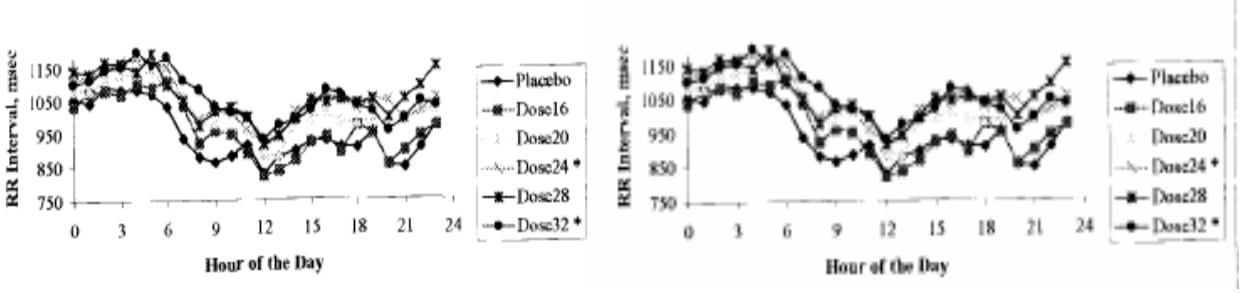


Figure 148: QT circadian variation at screen (left panel) and on Day 8 (right panel)

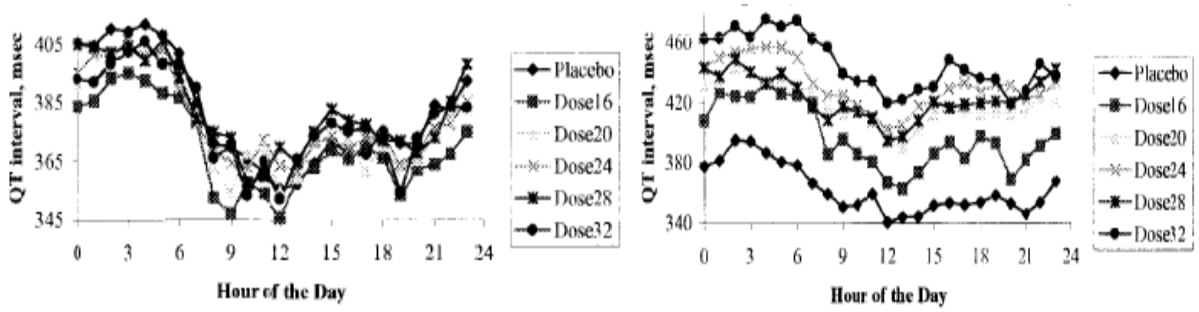
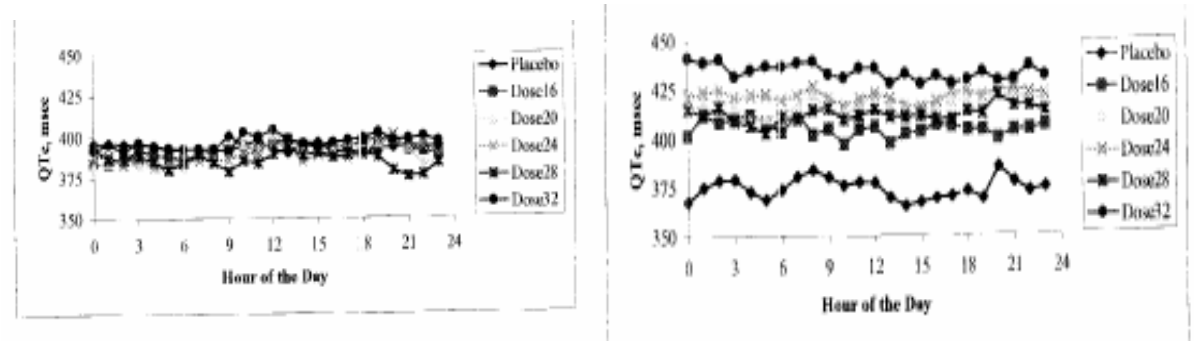


Figure 149: QTc circadian variation at screen (let panel) and on Day 8 (right panel)



Applicant's Safety Analyses

The most frequent adverse event (AE) was atrioventricular (AV) block, occurring in 16 subjects on dronedarone. All these episodes were mild and the subjects recovered. The second most frequent AE was non-sustained ventricular tachycardia (n = 9, five subjects on dronedarone and four subjects on placebo). Three subjects (one on 1400 mg BID and two on 1600 mg) had QTc prolongation (> 450 ms), declared as an AE. Gastro-intestinal disorders appeared at doses of 1000 mg BID and above.

Conclusions/Recommendations

The following findings from Study TDR3549 are acceptable, although the dosages evaluated in this study are more than two times higher than the proposed clinical dosages. These additional, high doses help potentially define the dronedarone exposure (dose)-response relationship.

Pharmacokinetics

- Overall, the dronedarone pharmacokinetic results obtained in Study TDR3549 are similar to those obtained in other dronedarone pharmacokinetic studies.
- Diurnal variation in dronedarone pharmacokinetics occurs

Pharmacodynamics

All conclusions are

- Resting Conditions: PR-, QT- and QTc intervals increased with dronedarone dose and there were trends towards a linear dose-response relationship. T-wave amplitude decreased with dose. Heart rate (HR) tended to decrease with active dronedarone doses; however there was no clear dose-response relationship. Diastolic and systolic blood

pressures (DBP and SBP) were decreased with some active dronedarone doses at some time points; however, the effect was not consistent and there was no clear dose-response relationship.

- Exercise Test: HR was decreased by all active dose groups, and a linear trend in dose-response was evident. Some active dose groups lowered SBP, but dronedarone did not appear to have a consistent DBP lowering effect.
- ECG Holter: Dronedarone significantly prolonged QT- and QTc- intervals and had a moderate effect on prolonging RR-intervals. A linear dose-response relationship was observed for dronedarone and the prolongation of the mentioned ECG parameters. Circadian patterns were evident at screening and after eight days of treatment with respect to the QT and RR intervals.

Overall, the PD results indicate that dronedarone exhibits anti-arrhythmic properties (prolongs repolarization) as well as decreases heart rate.

4.2.35 Dissolution Methodology and Specification

Background on Dronedarone Tablet Formulations*

Several dronedarone formulations were developed: the final formulation (to-be-marketed), 2E5 is identical to the 2E3 formulation used in the pivotal clinical trials. Bioequivalence was demonstrated between 2E2 formulation, used in the Phase 2 trials, and 2E3 formulation. Most of the dissolution method development was carried out with the 2E2 formulation. The use of 2E2 for dissolution development is acceptable because the 2E2 has similar physicochemical characteristics as the 2E5 formulation.

Formulations*

200 mg film- coated tablets, reference 2E2 used for Phase 2B, 400 mg film-coated tablets, reference 2E3 used for Phase 3, reference 2E4 used for primary stability batches, and reference 2E5 to be marketed

Development of the dissolution method

Aim (per applicant)

To select a method applicable to the final 400 mg formulation with ability to discriminate tablet composition and process changes, yet to ensure that 85 % of drug substance will be dissolved in 60 minutes, as recommended for BCS 2 compound.

Reviewer Note on BCS

Specific BCS information was not provided by the applicant or reviewed in detail; however the provided solubility information indicate that dronedarone is a low solubility compound. The *in vivo* data do not demonstrate high permeability: absolute bioavailability < 20 %. The applicant will be asked to provide additional permeability information to support the high permeability designation.

Selection of Dissolution Medium

According to the applicant, the dissolution method development was based on dronedarone physicochemical characteristics; the main characteristic considered was solubility. The solubility of dronedarone hydrochloride in aqueous solutions was obtained in different media and pH as summarized in Table 254 and Figure 150.

Table 254: Dronedarone dissolution in various media

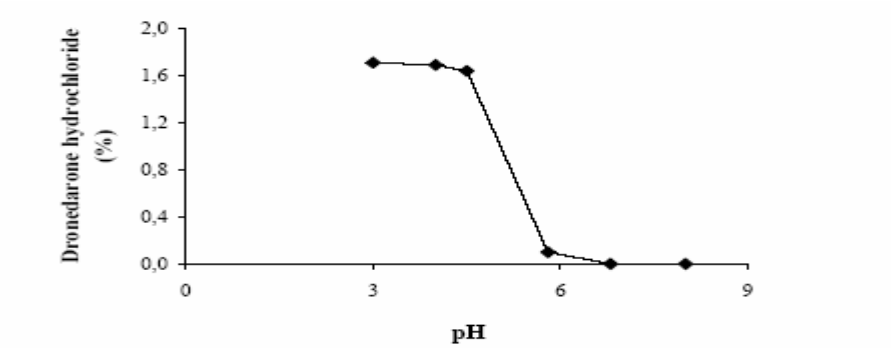
Solvents	Solubility
Water	0.64 mg/ml
Hydrochloride medium (KCl 0.05 M/HCl) pH 1.2	< 0.01 mg/ml
Phosphate medium (KH_2PO_4 0.05 M/NaOH) pH 6.8	< 0.01 mg/ml
Phosphate medium (KH_2PO_4 0.05 M/NaOH) pH 8.0	< 0.01 mg/ml
Ethanol (96 per cent)	113.6 mg/ml
Macrogol 400	13.2 mg/g
Lauroyl macrogolglycerides, type 1500	3.0 [a] mg/g

[a] Solubility determined at 60°C given the semi-solid characteristic of the ingredient at room temperature

The solubility information suggests:

- Dronedarone has low aqueous solubility in strongly acid or basic media; the highest aqueous solubility (~1.7 mg/ml) is obtained over the 3.0- 4.5 pH range in phosphate buffer
- Dronedarone is highly soluble in ethanol

Figure 150: Dronedarone solubility in aqueous solution at 25^{O} C in phosphate buffer systems



Dissolution testing conditions for the 400 mg tablet formulation included the following:

- dissolution media from pH 1 to 6.8
- addition of surfactant
- different apparatus- paddle (varying agitation speed) and basket

Results

1. **Influence of medium pH** on Dissolution of 400 mg tablet (2E3 formulation without coating suspension)

- **Method**: paddle apparatus with rotation speeds of 75 rpm and 100 rpm in 1000 ml of media at 37 ± 0.5° C for 60 minutes.
- **Findings**: as shown in Table 255, the most feasible dissolution results occur over the pH range of 3.5- 4.6; the best buffer systems were the phosphate (pH 4.5) and acetate (pH 4.6) buffers. As expected, dissolution was faster at 100 rpm compared to 75 rpm.

Table 255: Dissolution of 400 mg dronedarone tablets in various media (pH 1 to 7)

Media	pH	Speed (r/min)	Dissolution (%) after 60 min Mean (3 individual values)
HCl 0.1N	1.0	75	7 (7 ; 7; 7)
Acetate buffer	3.5	75	82 (83 ; 94 ; 69)
	4.0		88 (82 ; 84 ; 97)
	4.6		85 (77 ; 93 ; 84)
Phosphate buffer	4.5	75	83 (89 ; 78 ; 81)
	5.7		30 (30 ; 31 ; 28)
	7.0		1 (0 ; 1 ; 1)
Tris acetate buffer	4.5	75	9 (9 ; 9 ; 9)
Acetate buffer	4.6	100	94 (96 ; 93 ; 92)
Phosphate buffer	4.5	100	96 (100 ; 97 ; 90)

Conclusion: dissolution should be carried out in pH 3 to 4.5 media

2. **Effect of Addition of surfactants** on dissolution of 400 mg tablet formulation (2E3, without coating suspension) and 200 mg (base) film-coated tablets, reference 2E2

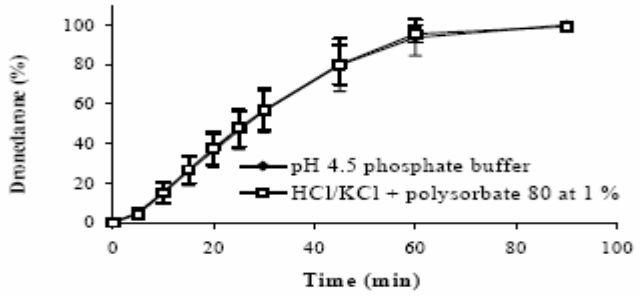
- **Method**: same as for influence of medium with the following exceptions- rotation speed of only 75 rpm used, and media (pH ~ 4.5 only) contained surfactants [(sodium dodecyl sulfate (SDS) or polysorbate 80]. The applicant noted that SDS (0.2 or 0.5 %) could not be used with pH 4.5 phosphate buffer, since a precipitate is formed; similarly a precipitate was formed by the addition of 0.2 or 0.1 % SDS.

- **Findings**: as shown in Table 24, dissolution is not significantly more rapid in media containing a surfactant than those obtained in the media without surfactant.

Table 256: Dissolution of 400 mg dronedarone tablets in pH ~ 4.5 media containing surfactant

Media	pH	Dissolution (%) after 60 min Mean (3 individual values)
Acetate buffer	4.6	85 (77 ; 93 ; 84)
Acetate buffer + SDS 0.2 %	4.6	85 (71 ; 91 ; 91)
Acetate buffer + SDS 0.5 %	4.6	81 (81 ; 73 ; 87)
Phosphate buffer	4.5	83 (89 ; 78 ; 81)
Phosphate buffer + polysorbate 80 at 0.2 %	4.4	83 (86 ; 82 ; 82)
Phosphate buffer + polysorbate 80 at 0.5 %	4.4	76 (79 ; 77 ; 74)

Figure 151: Dissolution profiles of 2E2 formulation in different media

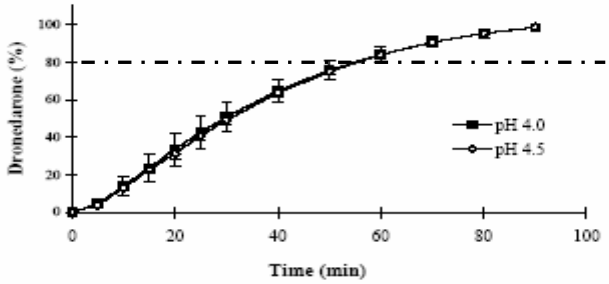


Conclusion: Addition of surfactant does not lead to further optimization of dissolution method (medium); however, addition of surfactant may decease variability in dissolution based on limited data (Dissolution was more variable in Phosphate buffer at pH 4.5 than in Phosphate buffer at pH 4.4 that included 0.2 % polysorbate 80).

3. **Selection of pH**

- **Method:** Same approach as described previously, however only pH 4.0 and 4.5
- **Findings:** As shown in Figure 152, dissolution profiles overlapped at the two studied pHs; however, sink conditions were achieved at pH 4.5.

Figure 152: Comparative dissolution profiles of 400 mg (base) film-coated tablets, reference 2E3 (batch BBU6- 180) at pH 4.0 and pH 4.5 (paddle at 75 rpm)



Conclusion: further dissolution development should be carried out at pH 4.5

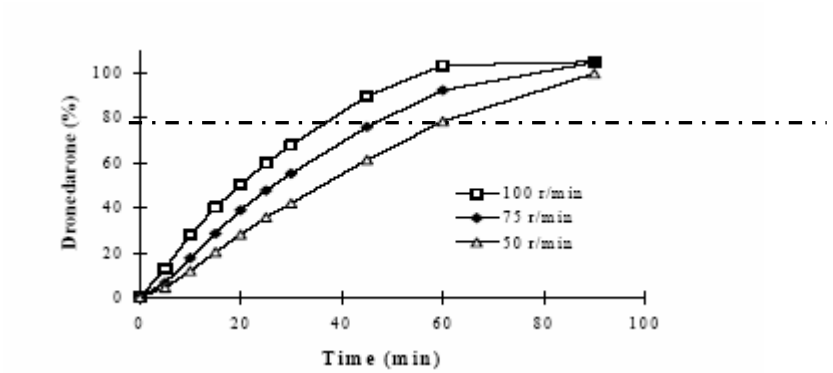
OVERALL SUMMARY ON DISSOLUTION MEDIUM

The medium should be at pH 4.5; this can be achieved using a phosphate buffer system with a surfactant to potentially minimize variability.

Selection of Paddle Speed

- **Method**: Three paddle speeds were tested- 50, 75 and 100 rpm in pH 4.5 phosphate buffer.
- **Findings:** As shown in Figure 153, dissolution increased as paddle speed increased. Dissolution with a paddle stirrer speed of 100 rpm led to about 100 % of dronedarone dissolved after 60 minutes.

Figure 153: Dissolution profile of 2E2 formulation (technical batch 3) at different rotation speeds

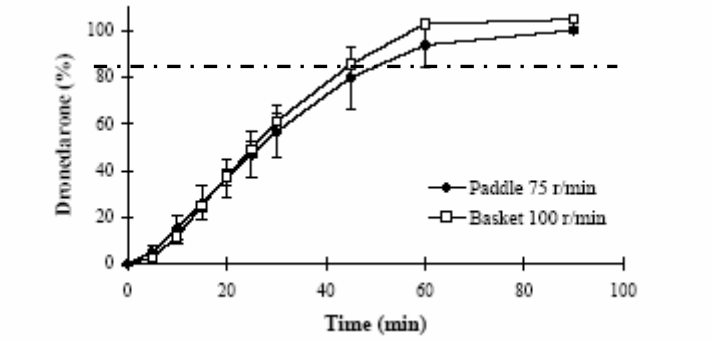


Conclusion: Rotation speed of 75 rpm should be used rather than 100 rpm, to avoid the potential loss of the discriminatory power.

Selection of Apparatus: Paddle vs. Basket

- **Method:** The basket method was compared with the paddle method using 200 mg film-coated tablets, reference 2E2 and pH 4.5 phosphate buffer. The methods were tested under the following conditions (designated as maximal speeds):100 and 75 rpm for the basket and paddle, respectively.
- **Findings:** As shown in Figure 154, dissolution profiles appear comparable

Figure 154: Dissolution profile of 2E2 formulation (batch 99- 02753) with paddle and basket methods



Conclusion: Since paddle and basket methods produced comparable dissolution, the paddle was selected.

Discriminating properties of the dissolution method

According to the applicant, the proposed dissolution method has discriminating ability specifically with respect to quantity of poloxamer and quantity of granulation water. The applicant notes that there was no in vitro/in vivo correlation (IVIVC) for dronedarone formulations (results form, GAR3585 study).

The discriminatory ability of the proposed dissolution method is supported by the following dissolution profiles.

Figure 155: Dissolution profiles of 400 mg (base) tablets (n = 6) containing different quantities of poloxamer 407 (expressed as percent)

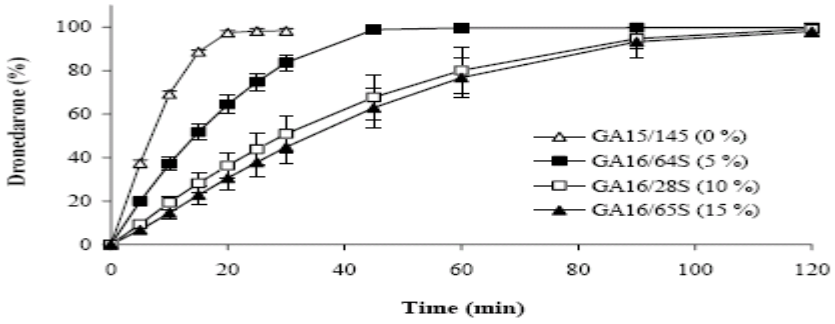
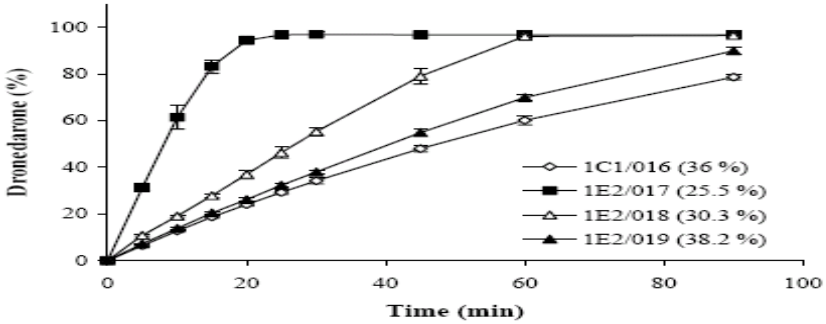


Figure 156: Dissolution profiles* of dronedarone hydrochloride 400 mg (base) tablets (n = 6) manufactured with increasing amounts of granulation water (expressed as %)



* profiles were obtained in media at pH = 4

The figures show that:

- as poloxamer content increased, the initial dissolution rate decreased
- as water content increased, generally, the initial dissolution rate decreased

Reviewer Note on Discriminatory Ability

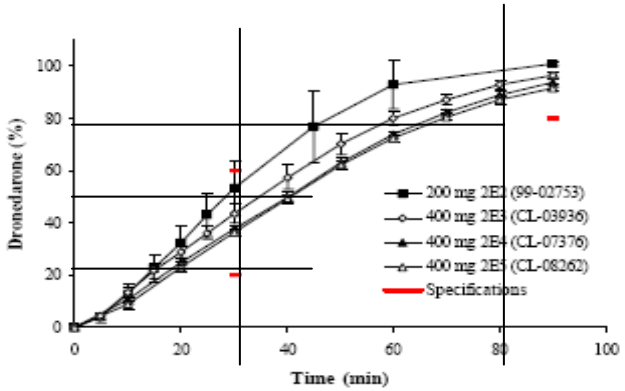
The findings on discriminatory ability are relevant as they cover the range of poloxamer concentrations and amount of granulation water for various dronedarone formulations that were evaluated during drug development. The final formulation has 10 % poloxamer and water is removed during the manufacturing process. For the water study, the pH of the media was 4 rather than the proposed pH = 4.5; however, this is acceptable as dissolution at pH 4 and 4.5 are comparable.

Conclusion: The dissolution method has discriminatory ability with respect to determining the content of poloxamer and granulation water. The main limitation of the study is the lack of assessment of different manufacturing processes, such as varying pressure and temperature. The applicant will be asked to test for these other characteristics.

Comparative dissolution profiles of film-coated tablets*

Comparative dissolution profiles of film-coated tablets are depicted in Figure 157. As shown in the dissolution profiles of all formulations appear generally comparable (formal f2 comparisons were not done). These comparisons appear to support the discriminatory ability of the dissolution method, as separation in profiles is observed between formulations with different particle size (2E2 vs. 2E3, 2E4, and 2E5).

Figure 157: Dissolution profiles of 200 mg (base) film- coated tablets, reference 2E2 and 400 mg (base) film- coated tablets, references 2E3, 2E4 and 2E5 with the pH 4.5 method



* Formulations

200 mg film-coated tablets, reference 2E2 manufactured with fine/medium particle size of drug substance for Phase 2B and

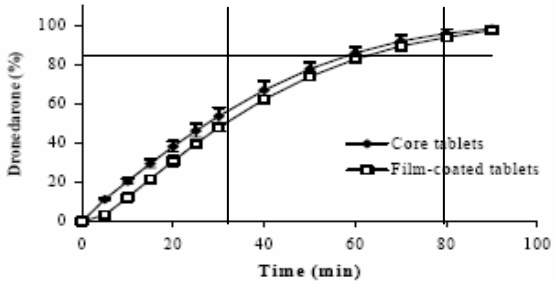
400 mg film-coated tablets, reference 2E3 manufactured with milled drug substance for Phase 3, exhibit similar bioavailability as 2E2.

400 mg film-coated formulation, reference 2E5 intended for marketing has same qualitative and quantitative compositions as the reference 2E3 used in the pivotal Phase 3 efficacy/ safety studies with only a minor punch marking modification.

2E4 formulation was used for primary stability batches,

Compared to core tablets, a slight delay in dissolution is obtained for 400 mg film-coated tablets (reference 2E3); this delay appears due to the dissolution of the coating observed at the beginning of the curve until 5 minutes.

Figure 158: Dissolution profiles of 400 mg (base) core tablets (batch RD35- 08) and film- coated tablets (batch BBU6- 180), reference 2E3 with the pH 4.5 method



Conclusion: Overall, dissolution of to-be-marketed formulation, 2E5 is comparable to that of Phase 2 and Phase 3 formulations. It should be noted that there is no IVIVC for dronedarone tablets; therefore minor dissolution differences do not necessarily result in *in vivo* differences.

PROPOSED DISSOLUTION METHODOLOGY
Apparatus: paddle at 75 rpm; Medium: 1000 ml of pH 4.5 phosphate buffer

Reviewer Comment on Methodology
Based on the information provided, the proposed methodology is acceptable; however, the method may be limited by the overall poor dissolution profile of dronedarone that is related to dronedarone solubility.

PROPOSED DISSOLUTION SPECIFICATION
- Not less than 20 % and not more than 60 % dissolved after 30 min
- Q = 75 after 90 min

Applicant's Rationale for setting Q specifications
The applicant indicates that during the development of the dissolution method they could not routinely obtain 85 % dissolution of the drug substance after 60 minutes; this was mainly due to the poor solubility of the drug substance.

Reviewer Comment on Specification
Based on the poor solubility profile of dronedarone and its putative BCS designation, the setting of a two-point dissolution specification is reasonable. However, the data do not support the applicant's specification proposal. The proposed specifications, particularly Q = 75 after 90 minutes, are not rigid enough to ensure product quality. Per the Dissolution Guidance for Industry, the following criteria should be considered for slowly dissolving or poorly water soluble drugs such as dronedarone to characterize product quality:
- Two point specification: specification at 15 minutes including a dissolution range or window and specification at later time point such as 30, 45, or 60 minutes
- Dissolution profile

Using the two point approach the data suggest (visual inspection of dissolution profiles, particularly in Figure 157 and Figure 158):
- Not less than 20 % and not more than 50 % is dissolved within 20 minutes
- Not less than 70 to 75 % is dissolved within 60 minutes

It is challenging to define the dissolution specification due to incomplete dissolution of dronedarone using the chosen method. Consequently, it is also feasible to use a complete dissolution profile in the interim while the dissolution method is optimized further.

Reviewer's Dissolution Recommendations
- Dissolution Method: applicant's proposal is acceptable
- Dissolution specification: 1) Not less than 25 % and not more than 50 % is dissolved within 30 minutes 2) Q = 80 % in 80 minutes

Additionally, the applicant should evaluate the discriminatory ability of the dissolution method when different manufacturing conditions, such as varying temperature and pressure conditions, are used.

APPENDIX

Composition of dronedarone hydrochloride 400 mg (base) film-coated tablets (reference 2E5)

Ingredients	Compendial grade	Function	Unit quantity (mg/tablet)	% (w/w)
CORE				
Drug substance				
Dronedarone hydrochloride (a)	In-house monograph	Active substance	426.00 (b)	65.54
Excipients				
Hypromellose (6 mPa)	Ph. Eur.-USP	Binder	26.00	4.00
Maize starch	Ph. Eur.-NF	Diluent-Disintegrant	45.50	7.00
Crospovidone (type A)	Ph. Eur.-NF	Disintegrant	65.00	10.00
Poloxamer 407	Ph. Eur.-NF	Solubilizing agent	40.00 (c)	6.15
Lactose monohydrate (d)	Ph. Eur.-NF	Diluent	41.65	6.41
Colloidal anhydrous silica	Ph. Eur.-NF	Flow aid	2.60	0.40
Magnesium stearate (e)	Ph. Eur.-NF	Lubricant/Anti-adherent	3.25	0.50
Purified water (f)	Ph. Eur.-USP	Granulation solvent	-	-
Core mass			***650***	***100***
COATING/POLISHING				
Hypromellose (6 mPa.s)	Ph. Eur.-USP	Film agent	7.25	72.50
Titanium dioxide	Ph. Eur.-USP	Opacifier	1.00	10.00
Macrogol 6000	Ph. Eur.-NF	Plasticizer	1.75	17.50
Purified water (f)	Ph. Eur.-USP	Coating solvent	-	-
Film-coating mass			***10***	***100***
Carnauba wax	Ph. Eur.-NF	Polishing agent	Traces	-
Film-coated tablet mass			***660***	

(a) The strength of the tablet is expressed as base (dronedarone)
(b) Corresponds to 400 mg of the base
(c) Corresponds to 10 % of the dronedarone quantity (400 mg)
(d) BSE free
(e) From vegetable origin
(f) Removed during manufacture

4.3 Consult Review (Pharmacometric)

Pharmacometrics Review

NDA:	21-913
Compound:	Dronedarone HCl (Multac)
Submission Dates:	10 June 2005
Sponsor:	Sanofi Aventis
PM Reviewer:	Christine Garnett, PharmD
PM Team Leader and Secondary Reviewer	Joga Gobburu, PhD

Table of Contents

1 EXECUTIVE SUMMARY

Dronedarone (SR33589B) is a new anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds that also includes amiodarone. The proposed indications are rhythm and rate control in patients with atrial fibrillation or atrial flutter and to decrease ventricular rate. The sponsor has proposed one dosage strength, 400 mg BID, for both indications and in all subpopulations of patients.

Recommendation

After reviewing the data collected in the DAFNE clinical trial, a concentration (dose)-response relationship for the primary endpoint (time to AF recurrence) could not be established. Possible reasons for the lack of a concentration (dose)-response includes concomitant use of beta blockers and higher dropout rate in the 1600 mg dose group due to adverse events.

Comments to Sponsor

Please forward the following comments to the sponsor which pertains to the population pharmacokinetic analysis of dronedarone:

- In future submissions, any concentrations and/or subjects that have been excluded from the analysis should be maintained in the datasets. For this analysis, the sponsor identified 123 concentrations (from 10 subjects) as outliers and excluded these observations from the dataset.

Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The sponsor submitted one dose-ranging trial, DAFNE (DRI13550). This was a multinational, multicenter, double-blind, placebo-controlled study. Three doses of dronedarone, 800, 1200, and 1600 mg daily (b.i.d.), were tested in the maintenance of sinus rhythm in patients undergoing cardioversion for AF. The primary endpoint was time to AF recurrence.

There was no trend for an increasing or decreasing concentration (dose)-response relationship for the primary endpoint. The longest median time was 60 days, observed in the 800 mg group, compared to 5 days in the placebo group. Covariates structural heart disease and duration of current AF episode at baseline did not have significant effects. Exploratory analyses of patient covariates showed that beta blockers increased the time to AF recurrence. This concomitant medication was unevenly distributed in the primary analysis population (PPM, see Figure (10.1)1) with approximately 40% of subjects in the placebo and 800 mg groups and approximately 20% in the 1200 and 1600 mg groups taking a beta blocker. Furthermore, there were more subjects in the 1600 mg dose group who dropped out of the study due to adverse events (gastrointestinal-related). This may have also contributed to the lack of a concentration (dose)-response.

There was a trend for lower ventricular rate at AF recurrence with higher concentrations of dronedarone. This relationship is illustrated in Figure 4. In addition, the sponsor showed a statistically significant lower heart rate at recurrence compared to placebo in each of the three treatment groups.

In the DAFNE trial the incidence and severity of treatment-emergent diarrhea was dose related, with the highest dose group (1600 mg) having the highest incidence and intensity of diarrhea. Diarrhea does not, however, appear to be related to plasma concentrations of dronedarone. There

was no difference in trough concentrations of dronedarone for subjects with and without diarrhea (see Figure 5).

Treatment with dronedarone caused an elevation of serum creatinine. In DAFNE creatinine clearance is reduced throughout the study (Days 1-150) in the treatment groups. After treatment is discontinued for 10 days, creatinine clearance returns to baseline.

A population analysis of pooled concentration-time data from three phase 3 clinical trials showed that the data followed a two-compartment model with first order elimination and absorption. Data for this analysis represented steady state concentrations from a 800 mg daily dose (400 mg bid) in 73% of the study population. It has been shown in other studies that the pharmacokinetics were nonlinear between 800 mg to 1600 mg daily doses of dronedarone.

Mean population parameter parameters for CL/F and V/F were 290 L/h for a 83 kg male and 3140 L, respectively. Between-subject variability, expressed as %CV, in CL/F and V/F were 30% and 110%. The residual variability, expressed as a standard deviation, was 14 ng/mL.

The significant covariates explaining between-subject variability in CL/F were sex, weight and age. There were no significant covariates for V/F. In this dataset, the influence of renal function, congestive heart failure degree, CYP3A4 inhibitors co-administration (mainly moderate CYP3A4 inhibitors, since strong inhibitors were contraindicated), race or study on the model parameters was not statistically significant.

The model was not used by the sponsor to justify the dose or to make labeling statements.

Christine Garnett, Pharm.D. _____
RD/FT Initialed by Joga Gobburu, Ph.D. _____

cc: NDA 21-913, HFD-120, HFD-860 (Garnett, Marroum, Kumi, Gobburu), Central Documents Room (CDR-Biopharm)

2 INTRODUCTION

The sponsor submitted a NDA for a new chemical entity, dronedarone HCl. Dronedarone (SR33589B) is a new anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds that also includes amiodarone. There are two main physical-chemical differences that distinguish dronedarone from amiodarone: 1) the absence of iodine substituents on the benzofurane ring that was expected to eliminate thyroid side effects, and 2) the adjunction of a methane-sulfonamyl group that was expected to make the drug less lipophilic and therefore less subject to tissue accumulation (a probable mechanism of amiodarone organ toxicity).

The sponsor is seeking two indications for dronedarone: rhythm and rate control in patients with atrial fibrillation or atrial flutter and to decrease ventricular rate. The sponsor has proposed one dosage strength, 400 mg BID, for both indications and in all subpopulations of patients.

Data to support these indications came from four controlled clinical trials which are summarized in the following table. The DAFNE study was the only dose-ranging trial. The sponsor also conducted an additional controlled clinical trial in patients with severe congestive heart failure, EFC4966/ANDROMEDA, which is not included in the table.

Table (2.7.3.1) 1 - Adequate and well-controlled studies providing evidence of the efficacy of dronedarone in the proposed indications

Study Identifier	Study design	Indication	
		Maintenance of Sinus Rhythm	Control of Ventricular Rate
DRI3550/DAFNE	Maintenance of normal sinus rhythm after cardioversion for atrial fibrillation – dose-ranging	supportive	supportive
EFC3153/EURIDIS	Maintenance of normal sinus rhythm after conversion of AF/AFL	confirmatory	supportive
EFC4788/ADONIS	Maintenance of normal sinus rhythm after conversion of AF/AFL	confirmatory	supportive
EFC4508/ERATO	Control of ventricular rate during AF	--	confirmatory

The focus of this review is to address the following key questions based on the submitted exposure-response data from the DAFNE clinical trial:

1. Is there a concentration-response relationship for the effectiveness endpoints 1) time to AF recurrence and 2) ventricular rate?
2. Is there a concentration-response relationship for treatment-emergent diarrhea?
3. Does elevated serum creatinine return to baseline after dronedarone treatment is discontinued?

The sponsor also submitted a population pharmacokinetic analysis of data collected in ADONIS, EURIDIS, and ANDROMEDA clinical trials. Results from this analysis are considered by the reviewer to only be supportive since the analysis was not used to support the dose nor used to in the label. A brief description of the population pharmacokinetic model is also included in this review.

3 QUESTION-BASED REVIEW

3.1 Is there a concentration-response relationship for the effectiveness endpoints 1) time to AF recurrence and 2) ventricular rate?

To assess whether there is a concentration–response relationship for the primary endpoint, mean individual trough concentration values from each dose group (Figure 1) were pooled and stratified into concentration quartiles (Figure 2). There were 15 subjects with missing trough concentrations; 4 in the 800 mg, 6 in the 1200 mg, and 5 in the 1600 mg groups.

Figure 1. Distribution of mean individual trough concentrations by dose group. The lines represent the mean ± 1 SD of trough concentrations from the combined phase 3 clinical trials (ADONIS and EURIDIS) where subject received 400 mg bid dronedarone.

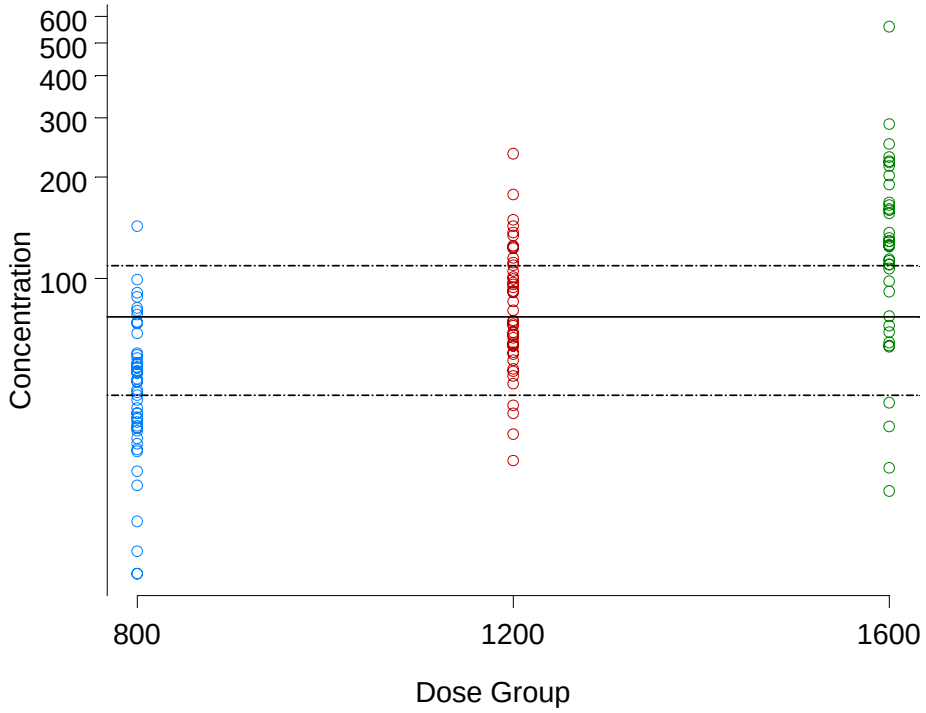
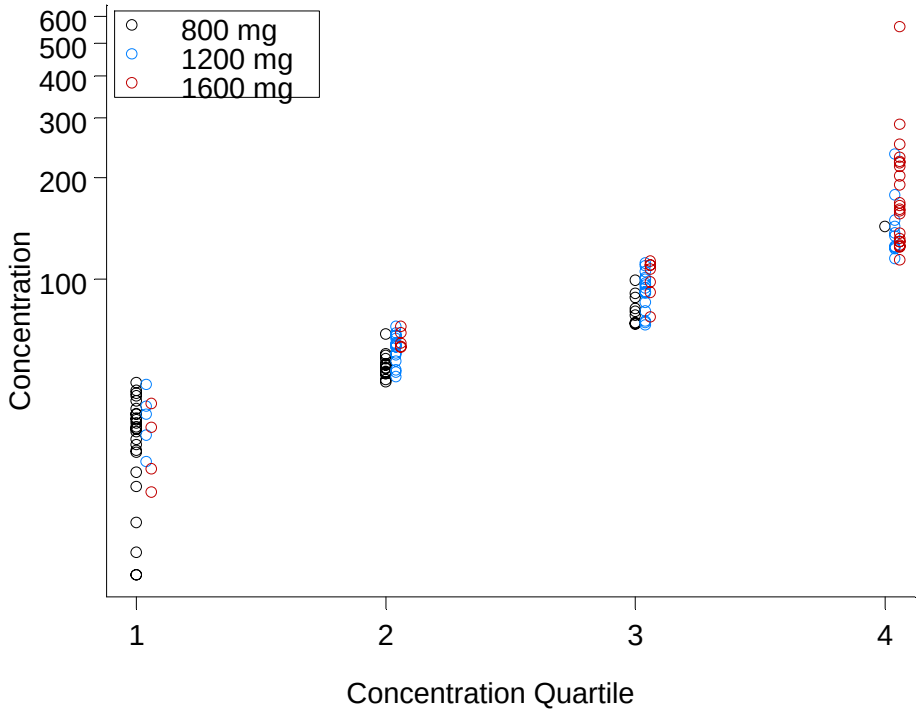


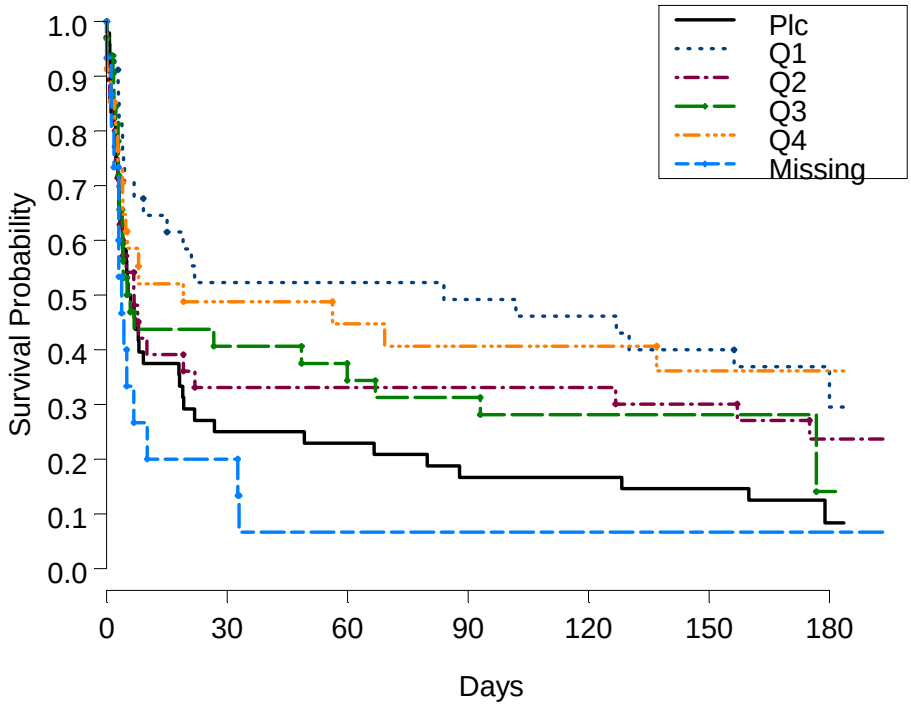
Figure 2. Distribution of mean individual trough concentrations by quartile.



Kaplan Meier survival curves for time to AF recurrence (days) by concentration quartile is shown in Figure 3. There was no trend for increasing or decreasing concentration-response relationships. The median time to recurrence was longest for the group of subjects with the lowest concentrations (Q1); median = 84 days.

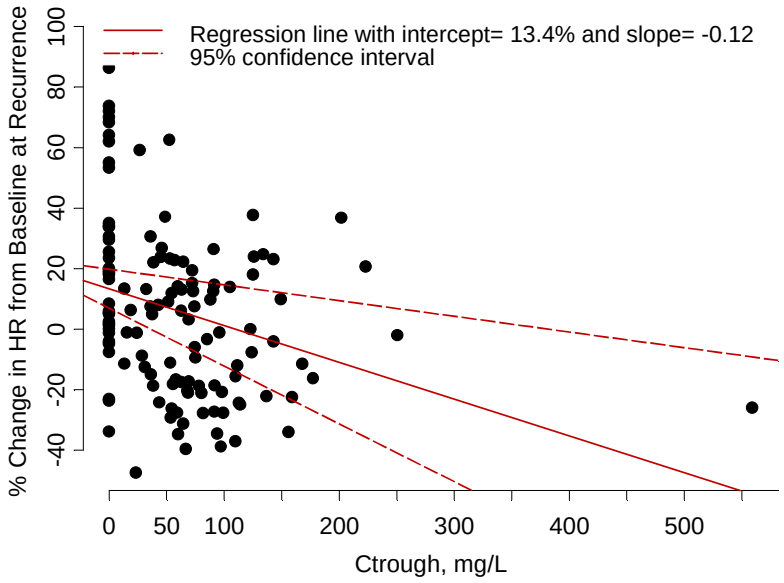
Fourteen of the 15 subjects (93.3%) with missing concentration experienced AF recurrence. The median (range) of event times for this group were 3.4 (.003 to 33) days. Therefore, the majority of subjects (12/14, 86%) in this group had an event prior to the scheduled pharmacokinetic sample on Day14.

Figure 3. Kaplan-Meier Survival Curves by Concentration Quartile (Q1 = 13.3-49.5, Q2 = >9.5-72.4, Q3 = >2.4-113.5, and Q4 = >113.5-559)



To assess the concentration-response relationship for ventricular rate control at recurrence, a scatter plot of percent change in heart rate from baseline vs. trough concentration is shown in Figure 4. For this plot, baseline was defined as the ventricular rate (measured by ECG) during the initial AF episode prior to dronedarone treatment. There was a trend for lower heart rate at AF recurrence with higher trough concentrations. Subjects with missing trough concentrations were excluded from the analysis.

Figure 4. Ventricular Rate Control vs. Trough Concentration



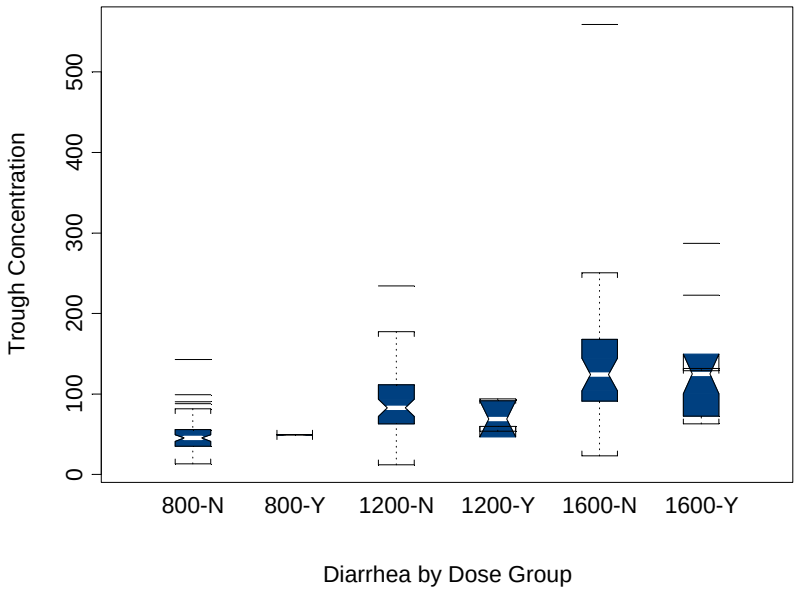
3.2 Is there a concentration-response relationship for treatment-emergent diarrhea?

In the DAFNE trial the incidence and severity of treatment-emergent diarrhea was dose related, with the highest dose group (800 mg bid) having the highest incidence and intensity of diarrhea (Table 1). Diarrhea does not, however, appear to be related to plasma concentrations of dronedarone. There was no difference in trough concentrations of dronedarone for subjects with and without diarrhea (Figure 5).

Table 1. Overview of Diarrhea TEAE

Intensity	Placebo N=66	800 mg N=76	1200 mg N=66	1600 mg N=62	Total Drug N=204
Total	2 (3.0)	2 (2.6)	5 (7.6)	17 (27.4)	24 (11.8)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.8)	3 (1.5)
Moderate	0 (0.0)	1 (1.3)	1 (1.5)	5 (8.1)	7 (3.4)
Mild	2 (3.0)	1 (1.3)	4 (6.1)	9 (14.5)	14 (6.9)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)

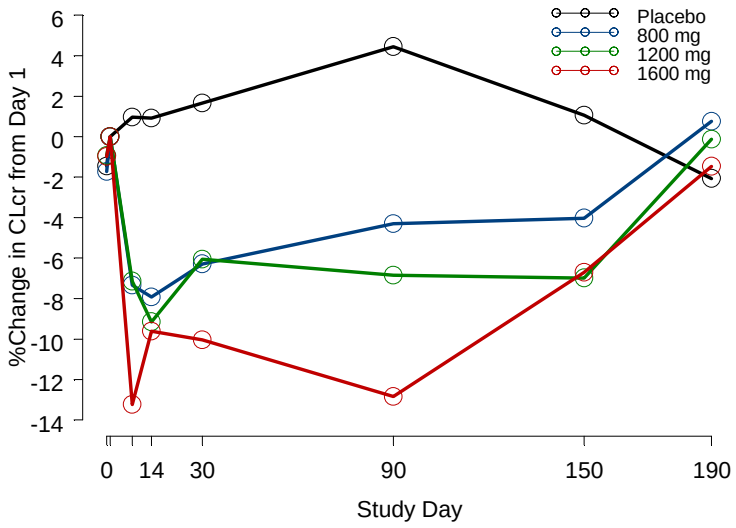
Figure 5. Boxplots of Trough Concentrations for Subjects With (Y) and Without (N) Diarrhea by Dose Group



3.3 Does elevated serum creatinine return to baseline after dronedarone treatment is discontinued?

Treatment with dronedarone caused an elevation of serum creatinine. Figure 6 shows that creatinine clearance is reduced throughout the study (Days 1-150). After treatment is discontinued for 10 days, serum creatinine returns to baseline. This is illustrated in Figure 6 by Day 190 which represents the last patient visit at 10 days after stopping study drug.

Figure 6. Mean Percent Change in CLcr by Study Visit



4 DAFNE CLINICAL TRIAL (DRI13550)

4.1 Study Design

This was a multinational, multicenter, double-blind, placebo-controlled, dose-ranging study, referred to as DAFNE (Dronedarone Atrial FibrillatioN study after Electrical cardioversion). Three doses of dronedarone, 800, 1200, and 1600 mg daily (b.i.d.), were tested in the maintenance of sinus rhythm in patients undergoing cardioversion for AF. A Safety Committee blinded to treatment allocation (the Chairman only had access to an unblinded treatment list) was formed to monitor patient safety. The overall study design and its duration are summarized in the following figure.

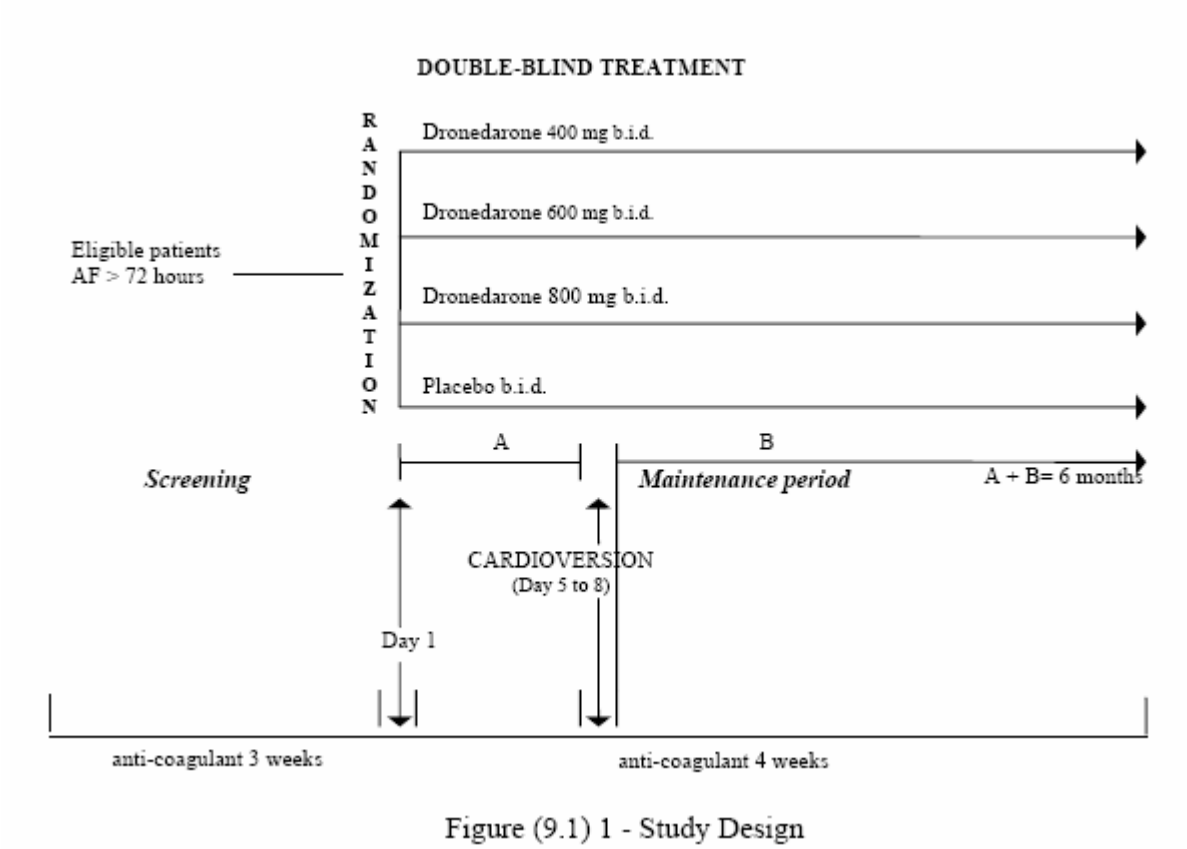


Figure (9.1) 1 - Study Design

Included in the study were adult male and female patients who currently have persistent atrial fibrillation as defined as duration of more than 72 hours but less than 12 months. The AF could be unassociated with structural heart disease (lone AF) or associated with ischemic, hypertensive, hemodynamically insignificant primary valvular heart disease or dilated cardiomyopathy (left ventricular ejection fraction had to be ≥35%). Patients were excluded if they had NYHA class III and IV congestive heart failure, left ventricular ejection fraction <35%, QT > 500 ms, and were taking concomitant treatments with strong CYP3A4 inhibitor drugs. The primary endpoint was time to first recurrence of AF (duration > 10 minutes) in patients converted to sinus rhythm, based on transtelephonic ECG monitoring and 12-lead ECG monitoring. Secondary endpoints included the ventricular rate at time of recurrence and the number of subjects converted to sinus rhythm.

4.2 Results

4.2.1 Subject Disposition

The following table shows the number of subjects who were enrolled and completed the trial. More subjects in the 1600 mg dose group withdrew from the study than from the other dose groups. Treatment emergent adverse events were the most common reason for study withdrawal. Gastro-intestinal system disorders, leading to 9 (4.4%) patient discontinuations, were the most frequently reported; this was linked to frequency in the 1600 mg group in particular, in which 7 patients discontinued.

Table (10.1.1) 1 - Number (%) of Patients by Reasons for End of Treatment during the Whole Study and Maintenance Period

Study period	Reason	Placebo n (%)	800 mg n (%)	1200 mg n (%)	1600 mg n (%)	P- value[a]
Whole study	Patients entered	66	76	66	62	
	Adverse event	0 (0.0)	3 (3.9)	5 (7.6)	15[b] (24.2)	
	Patient request	1 (1.5)	0 (0.0)	1 (1.5)	0 (0.0)	
	Protocol deviation	0 (0.0)	2 (2.6)	0 (0.0)	2 (3.2)	
	Other[c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	
	Total	1 (1.5)	5 (6.6)	6 (9.1)	18 (29.0)	<0.0001
	Completed[d]	65	71	60	44	
	Cardioversion failure	17	16	7	11	
	Lack of efficacy	40	32	35	23	
	Prescribed dosing	8	23	18	10	
Maintenance	Patients entered	49	56	56	44	
	Adverse event	0 (0.0)	1 (1.8)	3 (5.4)	10 (22.7)	
	Patient request	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Other[c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	
	Total	1 (2.0)	1 (1.8)	3 (5.4)	11 (25.0)	
	Completed[d]	48	55	53	33	
	Lack of efficacy	40	32	35	23	
	Prescribed dosing	8	23	18	10	

a: Fisher's exact test on the total number of patients who ended treatment prematurely.
b: Including 1 non-treatment emergent AE (Patient No. 2202007)
c: Other = in spite of recurrence, patient felt better under treatment and continued for a period of time; he was eventually withdrawn in respect of protocol.
d: Patients withdrawn for conversion failure/lack of efficacy and those completing prescribed dosing were considered completed.

4.2.2 Analysis Populations

The sponsor identified four efficacy analysis populations: ITT, PP, ITTM, and PPM. The following diagram describes each of the analysis populations. This review will focus on the 199 subjects in the PPM population.

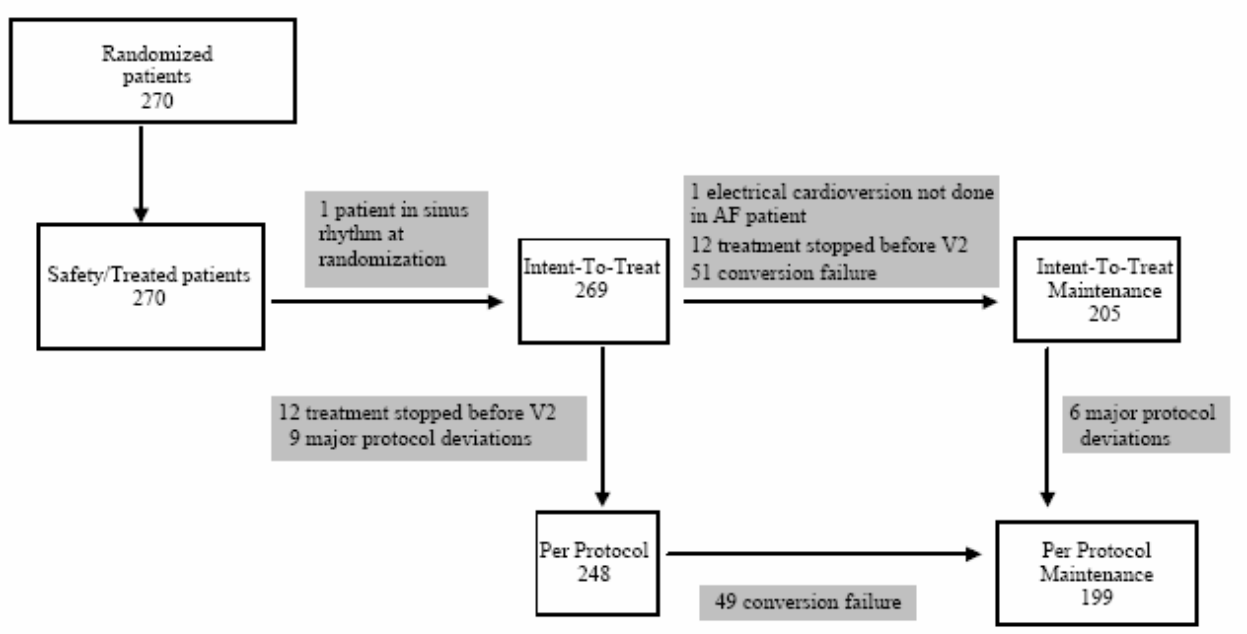


Figure (10.1) 1 - Analysis Population Flow Chart

4.2.3 Subject Demographics and Other Baseline Characteristics

A summary of patient demographics, cardiovascular history, duration of baseline AF episodes, and left ventricular ejection fraction for the PPM population are shown in Tables (10.4.1)3, (10.4.2)2, (10.4.3)2, and (10.4.4)2, respectively. A statistically significant difference in the duration of AF episodes (p=0.0133) was detected among group. All other baseline characteristics were similar across treatment groups.

With respect to concomitant medications, more subjects in the placebo and 800 mg dose group were taking beta blockers (Table (2.7.3.3.1.2)6). There were similar percentages of patients taking anticoagulant therapy, digoxin, and calcium channel blockers.

Table (10.4.1) 3 - Demographic Characteristics in Primary Efficacy Analysis Population: Per Protocol Maintenance

Demographic Characteristics	Placebo	800 mg	1200 mg	1600 mg	Total	p-value[a]
Age (yr)						
N	48	54	54	43	199	0.7047
Mean (SD)	65.6 (8.4)	64.0 (13.0)	63.7 (8.7)	62.3 (11.7)	63.9 (10.6)	
Range	46 to 80	24 to 81	39 to 78	29 to 79	24 to 81	
Age by class-n (%)						
18-40yr		4 (7.4)	1 (1.9)	3 (7.0)	8 (4.0)	
40-65yr	19 (39.6)	20 (37.0)	29 (53.7)	19 (44.2)	87 (43.7)	
65-75yr	20 (41.7)	18 (33.3)	14 (25.9)	17 (39.5)	69 (34.7)	
≥75yr	9 (18.8)	12 (22.2)	10 (18.5)	4 (9.3)	35 (17.6)	
Weight (kg)						
N	48	54	54	43	199	0.5905
Mean (SD)	80.82 (12.99)	81.80 (13.78)	83.38 (16.65)	84.35 (14.41)	82.54 (14.52)	
Range	54.5 to 120.0	54.0 to 119.9	54.0 to 136.0	62.0 to 135.0	54.0 to 136.0	
Height (cm)						
N	47	52	54	43	196	0.9629
Mean (SD)	172.87 (8.77)	170.37 (9.51)	171.11 (8.83)	171.51 (9.70)	171.42 (9.17)	
Range	146.0 to 190.0	150.0 to 200.0	141.0 to 187.0	156.0 to 209.0	141.0 to 209.0	
Missing	1	2	0	0	3	
Race – n (%)						
Caucasian	48 (100.0)	54 (100.0)	54 (100.0)	43 (100.0)	199 (100.0)	
Gender – n (%)						
Male	38 (79.2)	31 (57.4)	38 (70.4)	29 (67.4)	136 (68.3)	0.1297
Female	10 (20.8)	23 (42.6)	16 (29.6)	14 (32.6)	63 (31.7)	

a: ANOVA on age, height and weight, Fisher's exact test on gender

Table (10.4.2) 2 - Number (%) of Patients by Presence of Structural Heart Disease and Cardiovascular History in Primary Efficacy Analysis Population: Per Protocol Maintenance

Variable	Placebo N=48 n (%)	800 mg N=54 n (%)	1200 mg N=54 n (%)	1600 mg N=43 n (%)	Total N=199 n (%)	p-value[b]
Structural heart disease[a]	32 (66.7)	28 (51.9)	30 (55.6)	25 (58.1)	115 (57.8)	0.4864
Ischemic heart disease	13 (27.1)	11 (20.4)	10 (18.5)	9 (20.9)	43 (21.6)	
Congestive heart failure	11 (22.9)	8 (14.8)	13 (24.1)	5 (11.6)	37 (18.6)	
Valvular dysfunction	24 (50)	19 (35.2)	17 (31.5)	16 (37.2)	76 (38.2)	
Cardiac arrhythmias	3 (6.3)	8 (14.8)	6 (11.1)	5 (11.6)	22 (11.1)	
Arterial hypertension	27 (56.3)	28 (51.9)	27 (50)	19 (44.2)	101 (50.8)	

a: Includes congestive heart failure and/or ischemic heart disease and/or valvular dysfunction
b: Fisher's exact test

Table (10.4.3) 2 - Duration of Current Atrial Fibrillation Episode in Days in Primary Efficacy Analysis Population: Per Protocol Maintenance

Statistics	Placebo	800 mg	1200 mg	1600 mg	Total	p-value[a]
N	48	54	54	43	199	0.0177
Mean	76.1	116.8	90.4	111.3	98.7	
SD	60.3	70.3	71.2	93.8	75.3	
Median	57.5	105.0	72.5	72.0	76.0	
Minimum	9	18	4	7	4	
Maximum	311	283	343	328	343	

a: Kruskal Wallis test

Table (10.4.4) 2 - Left Atrium Measure and Left Ventricular Ejection Fraction in Primary Efficacy Analysis Population: Per Protocol Maintenance

	Placebo	Dronedarone 800 mg	Dronedarone 1200 mg	Dronedarone 1600 mg
	(N=48)	(N=54)	(N=54)	(N=43)
Left atrium diameter				
n	47	50	50	40
Mean	46.0	44.3	45.1	45.1
SD	9.5	6.3	6.0	6.3
Median	45.0	44.5	45.5	45.5
Minimum	25	26	30	33
Maximum	75	60	63	62
Missing	1	4	4	3
Left ventricular ejection fraction				
n	48	53	53	42
Mean	56.8	55.0	53.8	54.7
SD	10.1	8.8	12.2	10.7
Median	59.5	55.0	55.0	55.5
Minimum	36	35	35	35
Maximum	73	73	88	77
Missing	0	1	1	1

PGM= SR33589/DRI3550/NDAMHR/fr52583/PGM RPT/i8DaphLeftAtrium.sas OUT= OUTPUT/I4DAPHPPM Left.html (03JAN2005 - 15:50)

Table (2.7.3.3.1.2) 6 - Number (%) of patients according to baseline intake of specific medications - Per Protocol Maintenance population (DRI3550/DAFNE)

	Placebo (N=48)	Dronedarone 400 mg BID (N=54)	Dronedarone 600 mg BID (N=54)	Dronedarone 800 mg BID (N=43)
Oral anticoagulant	46 (95.8%)	50 (92.6%)	50 (92.6%)	40 (93.0%)
ACE inhibitors or A II receptor antagonists	21 (43.8%)	21 (38.9%)	22 (40.7%)	12 (27.9%)
ACE inhibitors	19 (39.6%)	16 (29.6%)	17 (31.5%)	10 (23.3%)
A II receptors antagonist	2 (4.2%)	5 (9.3%)	5 (9.3%)	2 (4.7%)
Digitalis	15 (31.3%)	20 (37.0%)	19 (35.2%)	18 (41.9%)
Digoxin	15 (31.3%)	19 (35.2%)	19 (35.2%)	18 (41.9%)
Digitalin	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Beta blocking agents	21 (43.8%)	24 (44.4%)	13 (24.1%)	9 (20.9%)
Beta blocking agents (except Sotalol)	21 (43.8%)	22 (40.7%)	13 (24.1%)	8 (18.6%)
Diuretics	9 (18.8%)	14 (25.9%)	17 (31.5%)	12 (27.9%)
Diuretics (other than spironolactone)	9 (18.8%)	13 (24.1%)	17 (31.5%)	12 (27.9%)
Spironolactone	1 (2.1%)	2 (3.7%)	1 (1.9%)	0 (0.0%)
Statins	6 (12.5%)	13 (24.1%)	7 (13.0%)	6 (14.0%)
Metabolized by CYP3A4	5 (10.4%)	11 (20.4%)	7 (13.0%)	5 (11.6%)
Not metabolized by CYP3A4	1 (2.1%)	2 (3.7%)	0 (0.0%)	1 (2.3%)
Chronic antiplatelet therapy	3 (6.3%)	1 (1.9%)	2 (3.7%)	2 (4.7%)
NSAID	2 (4.2%)	0 (0.0%)	3 (5.6%)	1 (2.3%)
Moderate inhibitors of CYP3A4	1 (2.1%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
Calcium antagonists with heart rate lowering effects (a)	1 (2.1%)	0 (0.0%)	1 (1.9%)	0 (0.0%)

PGM= SR33589/OVERALL/ISEMHR/BS/PGM RPT/i4DAFbasemed.sas OUT= OUTPUT/I4DAF basemedPPM.html (23MAR2005 - 16:19)

(a) Restricted to diltiazem, verapamil and bepridil.

NSAID=nonsteroidal anti-inflammatory drug.

4.2.4 Efficacy

4.2.4.1 Primary Endpoint

The primary endpoint was time to first recurrence of AF from conversion. Kaplan-Meier curve is shown in Figure (11.1.1)1 and Table (11.1.1)1. No dose effect was observed in the primary analysis. Median values for the time to AF were 5.32, 59.92, 4.31, and 5.18 days for the placebo, 800, 1200 and 1600 mg dose groups. Covariate analysis on the presence of structural heart disease and duration of current AF episodes at baseline did not reveal significant effects. Time to AF recurrence in the 800 mg group represented a risk reduction of 55%.

Figure (11.1.1)1. Kaplan-Meier Plot for Time to First Recurrence of AF from Conversion [reviewer's figure from independent analysis of data]

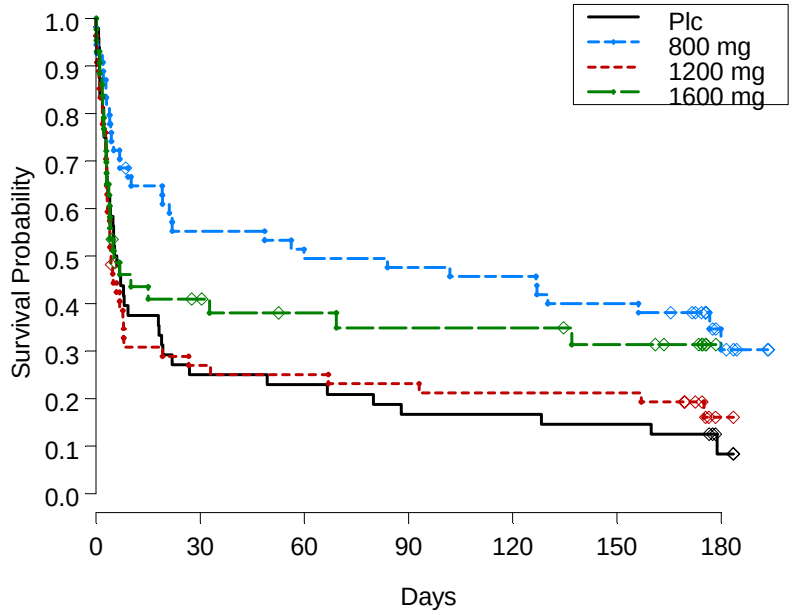


Table (11.1.1) 1 - Time to Atrial Fibrillation Recurrence (Days) - Primary Analysis on the Per Protocol Maintenance Population

Parameters	Statistics	Placebo N=48	800 mg N=54	1200 mg N=54	1600 mg N=43	Cox's model results
Time to AF recurrence						
Duration in sinus rhythm (days)	Median	5.32	59.92	4.31	5.18	Dose effect p=0.7188
	Minimum	0.028	0.059	0.002	0.089	Covariate SHD p=0.0737
	Maximum	183.5	193.6	183.5	178.5	Covariate AFD p=0.2943
Risk versus placebo	Risk ratio		0.45	0.95	0.68	
	95% CI		0.28 / 0.72	0.62 / 1.45	0.42 / 1.11	

SHD = presence of structural heart disease, AFD = duration of the current AF episode
pgm=DRI3550//biom/clinic/SR33589/DRI3550/CSR/biere/program/r_ped04.sas/10OCT2001 8:04

The sponsor performed an exploratory analysis using a stepwise Cox model to further evaluate the lack of a dose response relationship. The covariates used in this analysis were AF duration at randomization, previous ECV, previously treated, first AF episode, age, sex, CHR antecedent, ischemic heart disease antecedent, valvular dysfunction antecedent, left atrium size, shortening fraction, ejection fraction, digoxin, beta blocker, left CHF baseline, weight, and NYHA class. The only significant covariates were beta blockers and ejection fraction. Beta blockers increased the time to recurrence and, unexpectedly, ejection fraction decreased the time to recurrence.

When adjusted to these covariates, the dose effect was still not significant, and the comparison between placebo and 800 mg remained highly significant.

Table (11.1.1) 3 - Risk Ratio and Associated p-value - Exploratory Analysis of Covariates on Time to Atrial Fibrillation Recurrence in the Per Protocol Maintenance Population

Factors	800 mg vs placebo	1200 mg vs placebo	1600 mg vs placebo	Comparison between 4 doses
Treatment	0.407, p = 0.0003	0.895, p = 0.635	0.636, p = 0.089	0.954, p = 0.578
Beta blockers	0.518, p = 0.011	0.824, p = 0.436	0.421, p = 0.004	0.690, p = 0.050
Age	0.944, p = 0.625	0.798, p = 0.091	0.878, p = 0.300	0.922, p = 0.292
Ejection fraction	1.273, p = 0.055	1.114, p = 0.290	1.239, p = 0.082	1.179, p = 0.058
Structural heart disease	1.008, p = 0.976	0.860, p = 0.512	0.932, p = 0.796	0.747, p = 0.096

4.2.4.2 Secondary Endpoints

Ventricular Rate at Time of Recurrence

Table (11.1.3) 2 summarizes the ventricular rate in case of AF recurrence for the PPM population. There was a statistically significant difference between groups for ventricular rate in case of recurrence (p=0.0001). The 800, 1200, and 1600 mg dronedarone groups had statistically lower ventricular rates compared to placebo.

Table (11.1.3) 2 - Ventricular Rate (bpm) in Case of Recurrence: Analysis on Per Protocol Maintenance Population

Ventricular rate (bpm)	Statistics	Placebo	800 mg	1200 mg	1600 mg	p-value [a]
Observed value	N	43	35	44	28	0.0001
	Mean	102.9	89.7	83.6	85.1	
	SD	21.9	20.5	17.3	21.1	
	Median	99.0	90.0	82.5	79.0	
	Minimum	71	52	52	52	
	Maximum	151	141	122	143	
Adjusted difference versus placebo	Mean		-13.2	-19.2	-17.8	
	95% CI		-22.2 / -4.1	-27.8 / -10.7	-27.5 / -8.1	

a: ANOVA
<ref>pgm=DRI3550//biom/clinic/SR33589/DRI3550/CSR/armagnac/program/r_hrrec4.sas (13DEC2000 10:25)

Number of Subjects Converted to Sinus Rhythm

As shown in Table (11.1.3)1, there was a significant dose effect (p=0.0261) in the incidence of conversion without electrical cardioversion; in the 1600 mg group the incidence of conversion was different from placebo (14.81% versus 3.13%, respectively).

Table (11.1.3) 1 - Number (%) of Patients Converted to Sinus Rhythm without Electrical Cardioversion: Per Protocol Population

Variable	Statistics	Placebo N=64	800 mg N=69	1200 mg N=61	1600 mg N=54	p-value[a]
Incidence of conversion	n	2	4	5	8	0.0261
	%	3.13	5.80	8.20	14.81	
	95% CI	0.38 to 10.84	1.60 to 14.18	2.72 to 18.10	6.62 to 27.12	
Incidence versus placebo	Change		2.67	5.07	11.69	
	95% CI		-4.30 to 9.64	-3.03 to 13.17	1.30 to 22.08	

a: Cochran-Armitage trend test

pgm=DRI3550//biom/clinic/SR33589/DRI3550/CSR/armagnac/program/t_cvsp3.sas (10OCT2001 13:53)

In the dronedarone dose groups in the PP population the incidences of successful electrical cardioversion were: 77.3% (800 mg), 87.9% (1200 mg), and 76.6% (1600 mg) of patients compared to 73.0% of placebo patients. There was no statistically significant dose effect among treatment groups.

ECG Parameters

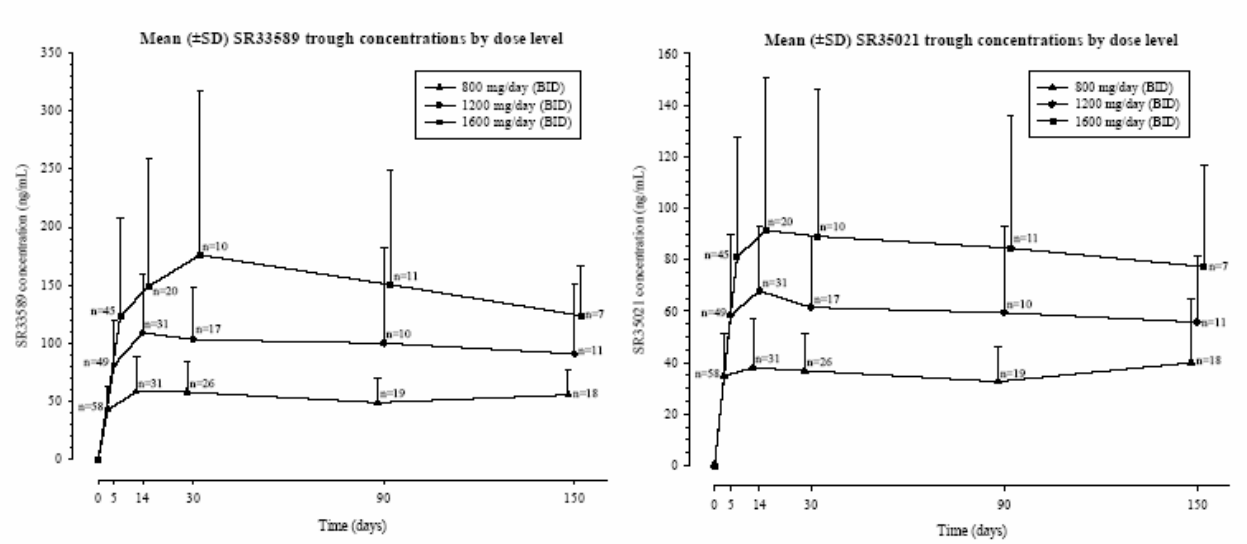
The ECG changes were consistent with the known electrophysiological properties of the drug and were well tolerated.

- The PR-interval was longer by 13.4, 16.6, and 28.4 ms in the 800, 1200 and 1600 mg groups respectively (p=0.0031, ANOVA).
- There was no clear effect on QRS-interval compared to placebo.
- The mean QTc-interval values were quite variable and a difference was found at later visits, mainly due to longer QTc-intervals in the 1600 mg group (p=0.0024 ANOVA).

4.2.5 Pharmacokinetic-Pharmacodynamic Relationship

Plasma samples for the analysis of dronedarone (SR33589) and its active metabolite (SR35021) were collected in 222 subjects. The sponsor define samples collect between 2-8 h after dosing as "CMAX" and between 0 to <2 h and 8-18 h as "CTROUGH." Samples collected outside these intervals were undefined and not used for analysis. The following figure shows the mean CTROUGH at each study visit.

Figure: Mean (SD) SR33589 (left) and SR35021 (right) Ctrough vs. Visit Day

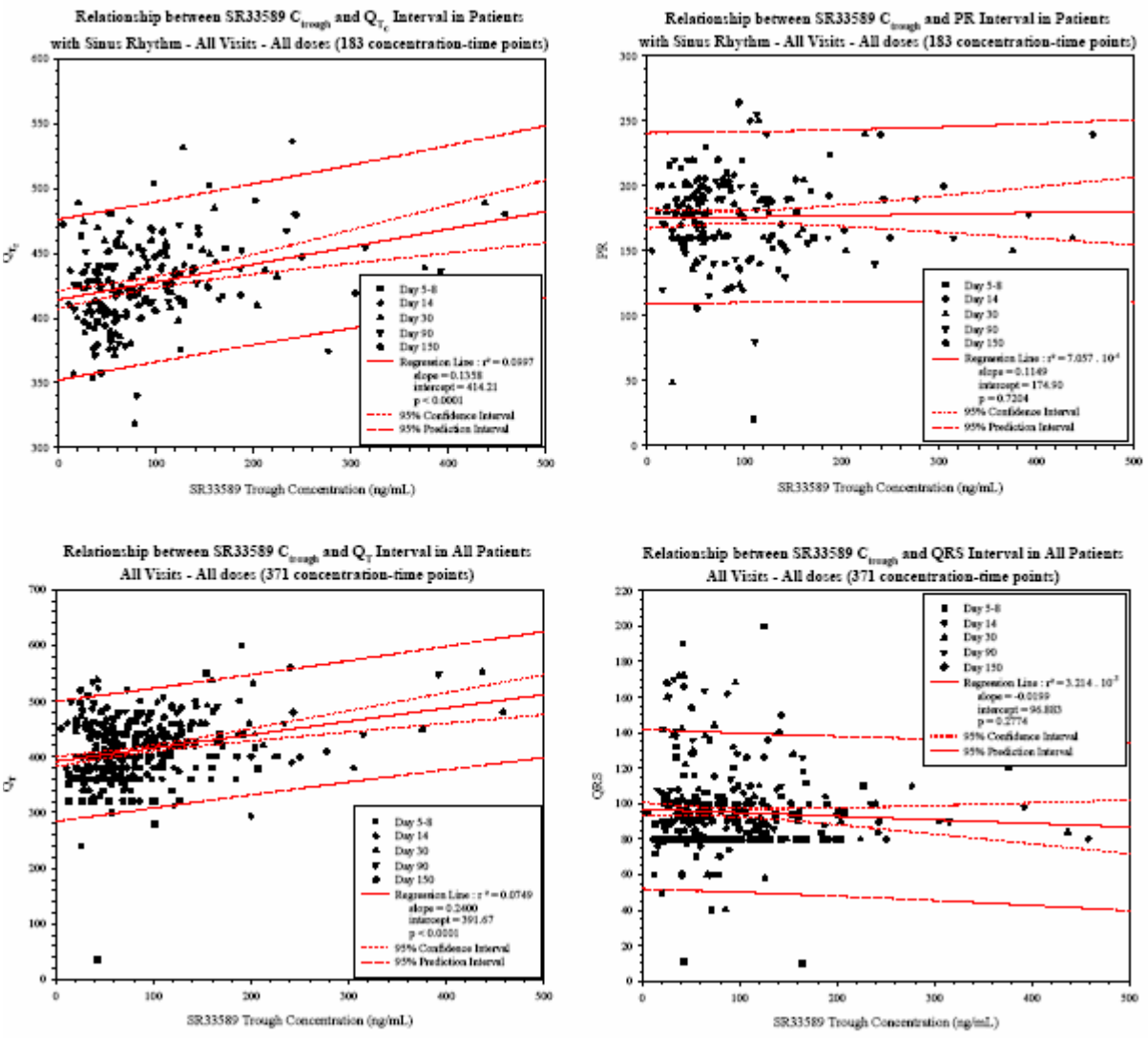


The sponsor performed ANOVA analyses on CTROUGH values to assess the impact of age, sex, day, weight, and CYP3A inhibitors.

The sponsor assessed the relationship between SR33589 CTROUGH and the time to first AF recurrence. No dose concentration effect was observed and the longest median time to recurrence occurred in the lower CTROUGH group Similar results were obtained using SR33589 +SR35021 CTROUGH.

The relationship between SR33589 and SR35021 CTROUGH and main ECG parameters (QTc, PR, QT, and QRS intervals, and Heart Rate) was studied by regression analysis. Figure (15.3.2)5 shows no clear relationship was observed between CTROUGH and ECG values. However, significant results were observed between SR33589 CTROUGH and the QTc and QT intervals ($p<0.0001$ for both).

Figure (15.3.2)5: Individual SR33589 CTROUGH Levels (ng/mL) as a Function of Electrocardiogram Parameters



4.2.6 Safety

4.2.6.1 Adverse Events

An overview of TEAEs, by type and treatment group, is provided in Table (12.2.1)1. A statistically significant dose effect was observed when AF recurrences were excluded from the evaluation of TEAEs: 47%, 53.9%, 65.2%, and 72.6% of patients receiving placebo, 800 mg, 1200 mg, and 1600 mg, respectively, reported TEAEs (p=0.00006,Cochran-Armitage test).

Table (12.2.1) 1 - Overview of Patients with at Least One Treatment Emergent Adverse Event Including or Excluding the Atrial Fibrillation Recurrences: All Treated Patients

	Placebo N=66 n (%)	800 mg N=76 n (%)	1200 mg N=66 n (%)	1600 mg N=62 n (%)	Dronedarone N=204 n (%)
Including AF recurrences					
Patients with any AEs[a]	56 (84.8)	61 (80.3)	57 (86.4)	53 (85.5)	171 (83.8)
Patient with any drug related AEs[b]	38 (57.6)	36 (47.4)	45 (68.2)	40 (64.5)	121 (59.3)
Patient with any AEs of severe intensity	5 (7.6)	2 (2.6)	3 (4.5)	7 (11.3)	12 (5.9)
Patients with SAEs[c]	3 (4.5)	2 (2.6)	5 (7.6)	7 (11.3)	14 (6.9)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Patient permanently discontinued study drug for any AE[d]	40 (60.6)	36 (47.4)	40 (60.6)	38 (61.3)	114 (55.9)
Patient permanently discontinued study drug for AEs not considered in analysis[e]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Excluding AF recurrences					
Patients with any AEs[a]	31 (47.0)	41 (53.9)	43 (65.2)	45 (72.6)	129 (63.2)
Patient with any drug related AEs[b]	18 (27.3)	26 (34.2)	31 (47.0)	37 (59.7)	94 (46.1)
Patient with any AEs of severe intensity	2 (3.0)	2 (2.6)	3 (4.5)	7 (11.3)	12 (5.9)
Patients with SAEs[c]	3 (4.5)	1 (1.3)	5 (7.6)	7 (11.3)	13 (6.4)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Patients permanently discontinued study drug for any AE[d]	0 (0.0)	3 (3.9)	5 (7.6)	15 (24.2)	23 (11.3)
Patient permanently discontinued study drug for AEs not considered in analysis[e]	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)

N = number of patients exposed, n = number of patients with at least one AE,% = percentage of patients
Treatment-emergent = Onset date or worsening from first intake to last intake + 10 days
a: include non serious and serious adverse events
b: exclude relationship to study drug assessed by the investigator ='no'
c: include SAEs leading to death
d: Including 1 non emergent AE
e: Non emergent AE: One patient was discontinued for an AE that was reported prior to treatment initiation.
pgm=/biom/clinic/SR33589/DRI3550/CSR/clin/program/r_aesum.sas out=output/r_aesum (16AUG2001 15:56)

Gastrointestinal AEs

Diarrhea was the most frequent TEAE and was reported in a total of 24 dronedarone patients (11.8%); the dose effect was statistically significant (p<0.00001, Cochran-Armitage trend test). The following table summarizes the diarrhea TEAE. The incidence of diarrhea was the same in male and female populations (11.8% each) and was slightly higher in patients ≥65 years (12.9%) than in patients <65 years (10.7%).

No difference was observed between the mean CTROUGH of patients with and without diarrhea. Analysis of the time to diarrhea showed that most of the episodes occurred within the first 48 hours after dosing.

Table: Overview of Diarrhea TEAEs

Intensity	Placebo N=66	800 mg N=76	1200 mg N=66	1600 mg N=62	Total Drug N=204
Total	2 (3.0)	2 (2.6)	5 (7.6)	17 (27.4)	24 (11.8)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.8)	3 (1.5)
Moderate	0 (0.0)	1 (1.3)	1 (1.5)	5 (8.1)	7 (3.4)
Mild	2 (3.0)	1 (1.3)	4 (6.1)	9 (14.5)	14 (6.9)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)

Figure. Mean CTROUGH for Subjects with and without Diarrhea

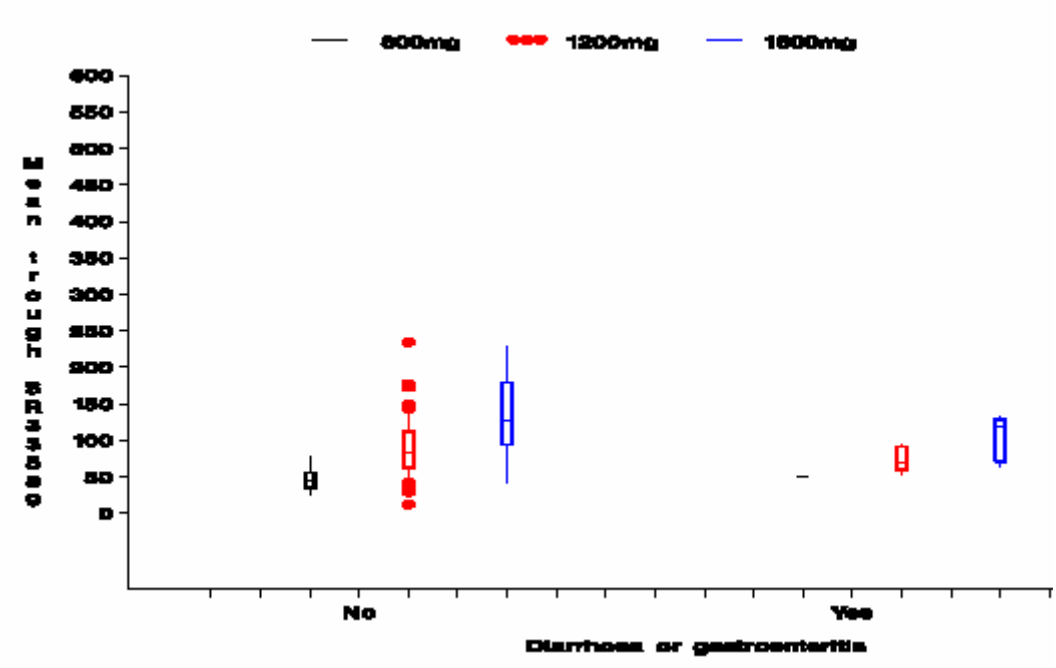
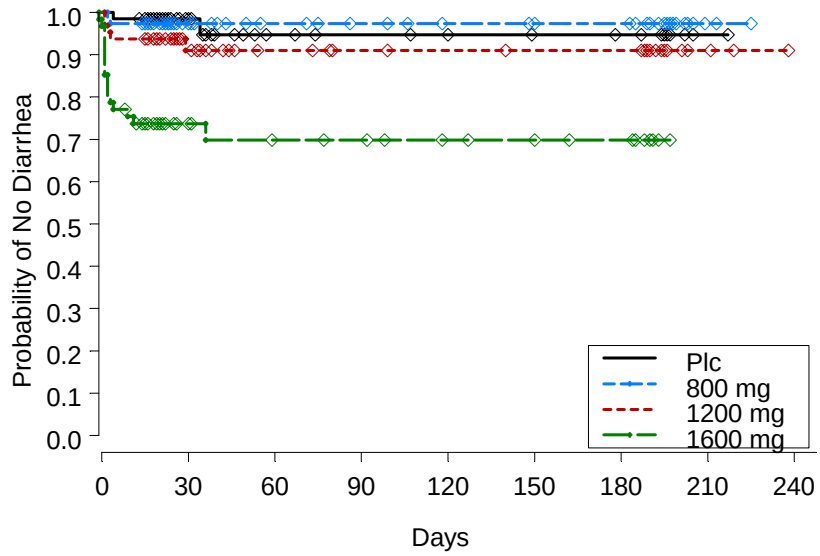


Figure. Kaplan-Meier Plot of Time to Diarrhea by Treatment Group



Heart rate and rhythm disorders and other cardiovascular disorders

The overall incidence of the heart rate and rhythm disorders did not increase with dose, nor did the incidence by preferred term categories. In the placebo group, 5 patients (7.6%) experienced supraventricular tachycardia, versus 20 patients (9.8%) on dronedarone. There were no torsades de pointes reported during the study.

4.2.6.2 Deaths and other SAEs

There was one death during this study. Patient 22050008 (1600 mg) suffered trauma due to an accidental injury on Day 162, at which time study drug was permanently discontinued. The patient's condition worsened and he died 4 weeks later. The accidental injury was judged by the investigator to have no relationship to study drug.

A total of 13 patients (6.4%) taking dronedarone and 3 patients (4.5%) on placebo reported SAEs. The overall frequency of SAEs reported increased with the dose of dronedarone: 1 patient (1.3%), 5 patients (7.6%), and 7 patients (11.3%) in the 800 mg, 1200 mg, and 1600 mg groups., respectively, reported SAEs, a total of 13 patients (6.4%).

4.2.6.3 Other Safety Measures

There was no evidence of variations in values for laboratory parameters, or unexpected variations in vital signs, in dronedarone groups. There was no evidence of thyroid, ocular nor pulmonary side effects.

5 POPULATION PK ANALYSIS

The following diagram summarizes the overview of the sponsor's modeling process.

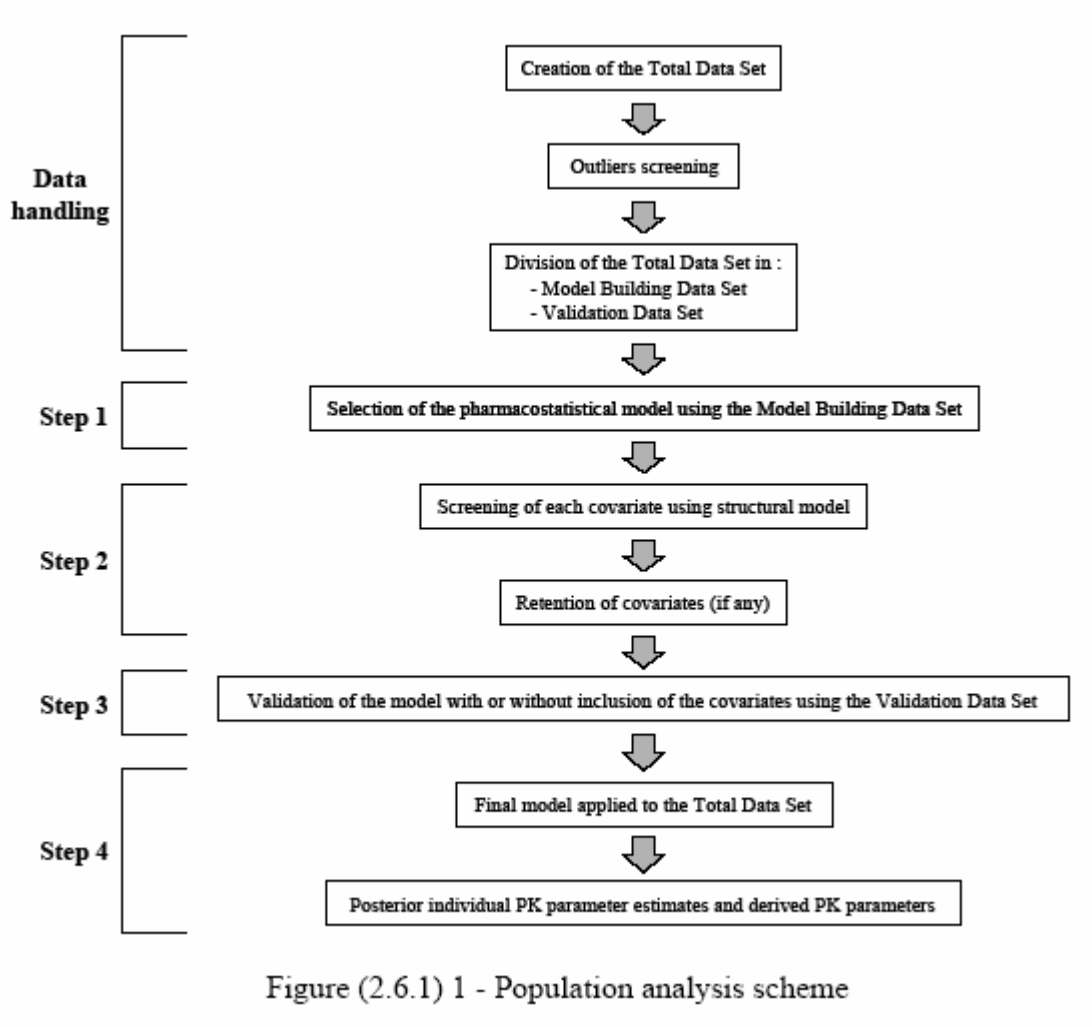


Figure (2.6.1) 1 - Population analysis scheme

5.1 Data

The population pharmacokinetic model was based on combined data from three phase III multiple dose studies, EURIDIS, EDONIS, and ANDROMENDA. The sponsor identified 126 concentrations for 10 subjects as outliers. These concentrations were deleted from the analysis datasets. The total number of subjects available for analysis was 839 which contributed 2786 plasma concentrations.

Table of Studies Included in Population Pharmacokinetic Analysis

Study	Design	Sampling	No Samples	No. Subjects Median (range) samples per subject
EURIDIS	Multicenter, multinational, double-blind, parallel-group, placebo-controlled, phase III studies of dronedarone 800 mg daily (400 mg bid) in patients with history of AF	Trough concentrations: Day 7 ± 2, Day 21 ± 3, Month 4 ± 5 days, Month 9 ± 5 days, and Month 12 ± 5 days.	1301	328 4 (1–8)
EDONIS			1032	290 4 (1–7)
ANDROMENDA	Multicenter, multinational, double-blind, parallel-group, placebo controlled study of dronedarone 800 mg daily (400 mg bid) in patients with symptomatic CHF.	Month 1 at pre-dose, 2h, 4h, 6h, 8h, 10h and 12h post-dose.	453	221 2 (1–8)
Total			2786 + 126 deleted as outliers = 2912	839 + 10 deleted as outliers =849

The sponsor divided the total dataset into two subsets that were used for model building and model validation. The model building dataset was composed of 589 patients (1984 samples) and the validation dataset was composed of 250 patients (802 samples). A summary of patient characteristics in each of the datasets are shown in Table (3.4)1.

Table (3.4) 1 - Mean and standard deviation of the patients demographic characteristics in the Model Building, the Validation and the Total Data Sets

Covariate or characteristic	Model Building Data Set	Validation Data Set	Total Data Set
Mean values (SD)			
Age (years) [a]	65.1 (10.5)	64.6 (11.6)	65.0 (10.8)
Body Weight (Kg)	84.0 (16.9)	83.9 (17.2)	84.0 (17.0)
Height (cm)	173 (10.0)	173 (9.38)	173 (9.83)
Number of patients (%)			
ADONIS + EURIDIS (%) [a]	434 (73.7 %)	184 (73.6 %)	618 (73.7 %)
ANDROMEDA (%) [a]	155 (26.3 %)	66 (26.4 %)	221 (26.3%)
CL_{CR} < 80 mL/min	370 (62.8 %)	148 (59.2 %)	518 (61.7 %)
CL_{CR} ≥ 80 mL/min	219 (37.2 %)	102 (40.8 %)	321 (38.3 %)
Sex (Males) [a]	424 (72.0 %)	180 (72.0 %)	604 (72.0 %)
Sex (Females) [a]	165 (28.0 %)	70 (28.0 %)	235 (28.0 %)
Caucasians (%)	577 (98.0 %)	241 (96.4 %)	818 (97.5 %)
Blacks (%)	3 (0.5 %)	2 (0.8 %)	5 (0.6 %)
Asians (%)	3 (0.5 %)	2 (0.8 %)	5 (0.6 %)
Others (%)	6 (1.0%)	5 (2.0%)	11 (1.3 %)
No Congestive Heart Failure (CHF)	346 (58.7 %)	159 (63.6 %)	505 (60.2 %)
CHF – NYHA Score 1	24 (4.1 %)	13 (5.2 %)	37 (4.4 %)
CHF – NYHA Score 2	132 (22.4 %)	39 (15.6 %)	171 (20.4 %)
CHF – NYHA Score 3	84 (14.3 %)	38 (15.2 %)	122 (14.5 %)
CHF – NYHA Score 4	3 (0.5 %)	1 (0.4 %)	24 (0.5 %)
No CYP3A4 inhibitor co-admin. [b]	541 (91.8 %)	224 (89.6 %)	765 (91.2 %)
Moderate CYP3A4 inhibitor co-admin. [b]	46 (7.8 %)	25 (10.0 %)	71 (8.5 %)
Strong CYP3A4 inhibitor co-admin. [b]	1 (0.2 %)	0	1 (0.1 %)
Both moderate & strong CYP3A4 inhibitor co-admin. [b]	1 (0.2 %)	1 (0.4 %)	2 (0.2 %)
Total	589	250	839

[a]: covariates used in the drawing lot procedure

[b]: CYP3A4 inhibitor co-administration was considered if its duration represented at least 80% of the dronedarone treatment duration.

5.2 Pharmacokinetic Models

5.2.1 Structural and Random Variance Models

The sponsor explored one- and two- compartmental models with first order absorption and elimination for analyzing the concentration-time data. Models were parameterized in terms of CL/F and V/F. A lag time was also tested. Inter-individual variability in PK parameters was modeled using proportional and additive models. Residual error was modeled using proportional, additive, power, and combined proportional plus additive models. In total, 994 NONMEM runs were performed and the selection of the best structural model was based the objective function value, the sponsor's pre-specified acceptance criteria, and diagnostic plots.

The sponsor selected a two-compartment model with first order absorption (measured by ka) and elimination (evaluated by CL/F) from the central compartment (V2/F) as the best model to describe the data. CL/F and V2/F were log-normally distributed. Residual error was described by a additive model. Interindividual variability for Q/F could not be estimated (no minimization or 95%CIs on ηQ/F or θQ/F included zero) and ka was fixed to the value obtained in the preliminary PopPK analysis performed on the pool of TDR2395 and DRI3550 data.

The sponsor assessed the impact of the fixed value of ka on the model by performing 17 runs with different ka values. The different fixed ka values tested ranged from 0.15 h-1 to 1 h-1 with a step-size of 0.05 h–1. Figure (3.5.1.1.1) 1 shows that ka = 0.291 was the best parameter value.

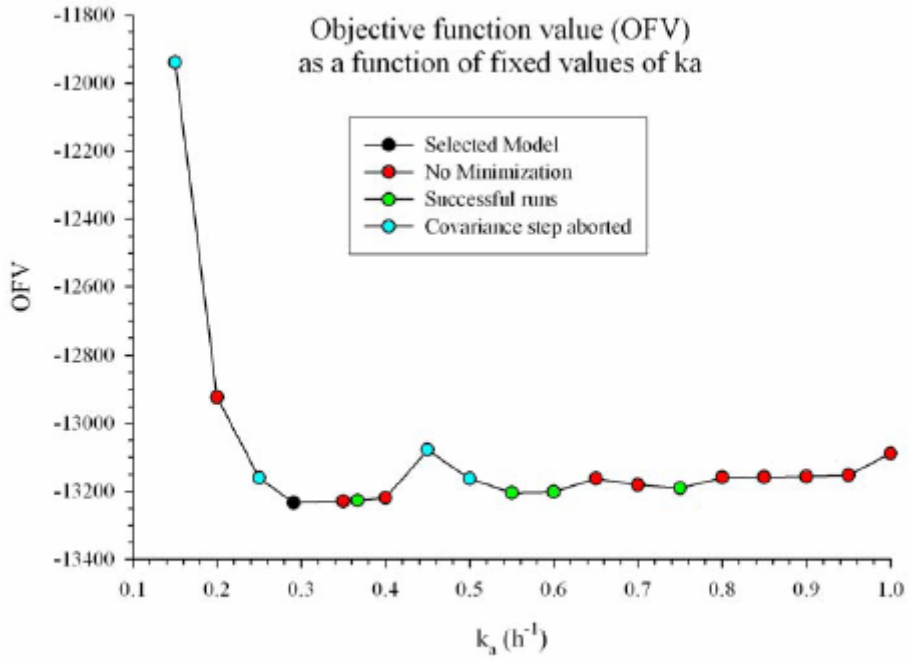


Figure (3.5.1.1.1) 1 - Impact of the fixed value of k_a on OFV

The following table shows the parameter estimates for the structural model.

	FINAL ESTIMATE	%RSE	95% CONFIDENCE INTERVAL LBOUND	UBOUND	DESCRIPTOR/ VARIABILITY
THETA					
1	353	2.27%	337	369	CL
2	3.32e+003	8.43%	2.77e+003	3.87e+003	V2
3	333	13.7%	244	422	Q
4	6.12e+003	14.9%	4.33e+003	7.91e+003	V3
5	0.291	...	...	...	KA
OMEGA					INTERINDIVIDUAL VARIABILITY
1,1	0.122	8.69%	0.101	0.143	CV = 34.9%
2,2	1.31	13.4%	0.965	1.65	CV = 114%
3,3	0.651	39.0%	0.153	1.15	CV = 80.7%
SIGMA					RESIDUAL VARIABILITY
1,1	0.000192	7.08%	0.000165	0.000219	SD = 0.0139

*Indicates 95% confidence interval that includes zero
%RSE is percent relative standard error (100% x SE/EST)

5.2.2 Covariate Models

The sponsor evaluated the influence of body weight, age, height, sex, race, study, renal function (normal vs. impaired), CHF status (no CHF vs. CHF), and CYP3A4 inhibitor indicator (yes vs. no). The sponsor evaluated linear, exponential, and power functional forms of the parameter-continuous covariate relationship. Dichotomous and categorical variables were evaluated as proportional or additive shifts.

After screening all covariates using EXPOSE software, the sponsor identified WGT, HGT, AGE, SEX and CAUC together with NYHO, ICCL, INHI and study as potential covariates for CL/F, V2/F and V3/F. A univariate stepwise forward addition method in NONMEM was used to test the significance of each covariate in explaining the interindividual variability in population PK parameters. A change in objective function of 10.83 (corresponding to a $p<0.001$ for a chi-squared distribution with 1 degree of freedom) was used as the inclusion criteria. Once all significant covariates were included in the model, the sponsor performed a univariate stepwise backward elimination of covariates. For a covariate to be retained in the model the objective function had to increase by 10.83 ($p<0.001$ for chi-square distribution with 1 degree of freedom) when it was removed from the model.

A total of 103 NONMEM runs were performed and Table (3.5.2.2)2 summarizes the results of the stepwise addition of covariates. None of the covariates tested should explain the interindividual variability in V2/F and V3/F, based on the statistical criteria of change in objective function of 10.83.

Table (3.5.2.2) 2 - Covariates retained in the PopPK model

Analysis step	Selected model	ΔOFV [a]	ΔIIV [b]
PSM [c]	No covariate	NA	NA
Step 1	$TVCL1 = \theta_{(1)} * (WGT / 83) ** \theta_{(6)}$	-77.8	- 18 %
Step 2	$TVCL2 = TVCL1 * SEX + TVCL1 * \theta_{(7)} * (1-SEX)$	-24.3	- 3.8 %
Step 3	$TVCL3 = TVCL2 * AGE / (\theta_{(8)} + AGE)$	-11.9	- 3.0 %

[a]: Difference in OFV before and after covariate inclusion. A difference of at least 10.83 is needed for statistical significance ($p<0.001$).
[b]: Difference in interindividual variability, as expressed by the percentage of decrease of variance, before and after covariate inclusion.
[c]: PSM = Pharmacostatistical model. NA: Not Applicable.
In the equations of Step 1, 83 Kg is the median values of WGT.

Table (3.5.5) 1 - Effects of sequential covariate deletion on NONMEM OFV

Purpose / Covariate	ΔOFV	Observations
Final model, all subsequent runs compared to this run	NA	Terms for WGT, SEX and Age on CL/F
Delete WGT on CL/F	49.0	Kept
Delete SEX on CL/F	24.6	Kept
Delete AGE on CL/F	11.9	Kept

NA: Not applicable.

The following table shows the parameter estimates and precision of estimates for the covariate model. Diagnostic plots of the covariate model are also shown.

	FINAL ESTIMATE	%RSE	95% CONFIDENCE INTERVAL LBOUND	UBOUND	DESCRIPTOR/ VARIABILITY
THETA					
1	301	5.12%	271	331	CL
2	3.47e+003	7.98%	2.93e+003	4.01e+003	V2
3	349	6.07%	307	391	Q
4	6.15e+003	9.67%	4.98e+003	7.32e+003	V3
5	0.291	...	...	...	KA
6	0.500	17.0%	0.333	0.667	WGT_on_CL
7	0.827	4.01%	0.762	0.892	Sex on CL
8	-12.1	18.9%	-16.6	-7.61	AGE_on_CL
OMEGA					INTERINDIVIDUAL VARIABILITY
1,1	0.0933	8.46%	0.0778	0.109	CV = 30.5%
2,2	1.29	12.5%	0.974	1.61	CV = 114%
3,3	0.662	13.7%	0.485	0.839	CV = 81.4%
SIGMA					RESIDUAL VARIABILITY
1,1	0.000193	2.45%	0.000184	0.000202	SD = 0.0139

*Indicates 95% confidence interval that includes zero
%RSE is percent relative standard error (100% x SE/EST)

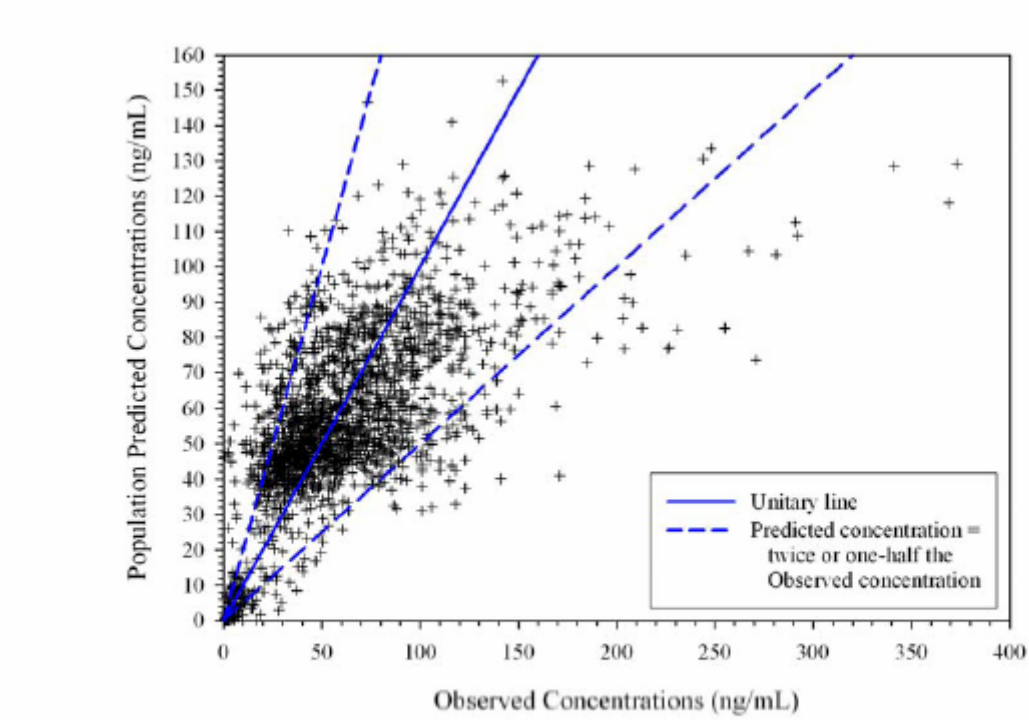


Figure (3.5.4) 1 - Relationship between population predicted and observed dronedarone plasma concentrations in the Model Building Data Set (n=589 patients)

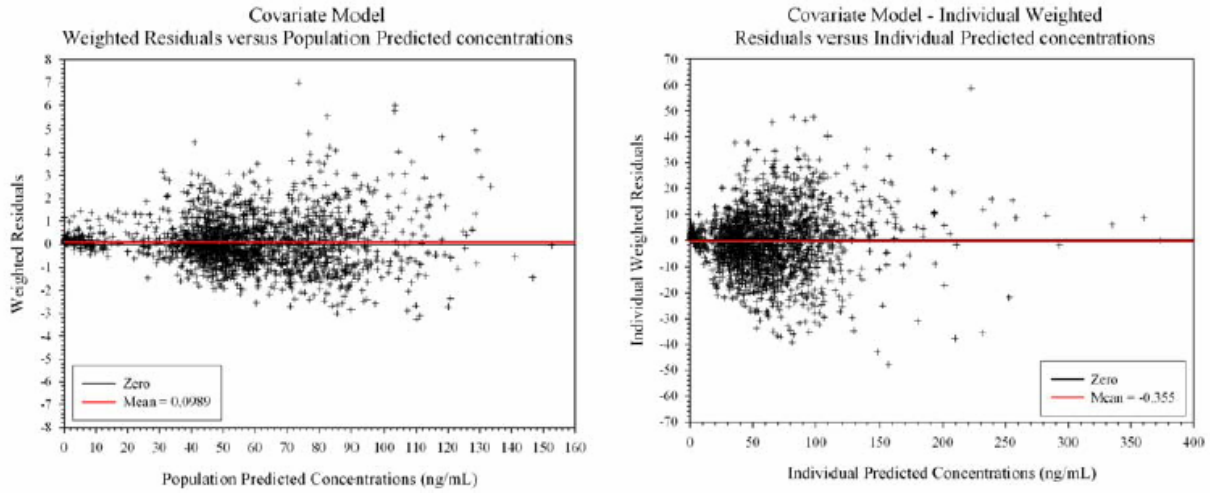


Figure (3.5.4) 3 - Relationship between population weighted residuals and population predicted concentrations (*left*) and individual weighted residuals and individual predicted concentrations (*right*)

5.2.3 Model Qualification

The final model obtained in the Model Building Data Set was validated using its parameters as prior estimates for the assessment of the individual parameters and concentrations of the patients from the Validation Data Set. The estimation step was omitted using MAXEVAL=0 option to obtain the individual estimates based on the final population estimates of θ, ω and σ. Table

(3.5.6.1)1 and Table (3.5.6.2)1 shows the performance of the population-predicted and individual-predicted concentrations, as expressed by bias, precision and AFE.

Table (3.5.6.1) 1 - Performance of the population concentrations prediction, assessed on the Model Validation Data Set (values in parenthesis were expressed in % of mean C_{Obs} values)

Concentrations (ng/mL)	n= 250 ; 802 concentration-time points	
	Mean	**SD**
Observed (reference)	60.5	45.9
Population Predicted	54.3	26.3
Student paired t test	p-value < 0.0001	
WRES (Mean, 95%CI)	0.136 [0.0594 – 0.212]	
Regression characteristics		
Slope	0.403	
Intercept	29.9	
Correlation coefficient r	0.706	
Criteria in ng/mL (%)	**Value**	**95% CI**
Bias (%)	6.21 (10 %)	[3.92 – 8.50]
Precision (%)	33.7 (56%)	[30.1 – 36.9]
AFE	1.68	

Table (3.5.6.2) 1 - Performance of the individual concentrations prediction, assessed on the Validation Data Set (values in parenthesis were expressed in % of mean C_{Obs} values)

Concentrations (ng/mL)	n=250 ; 802 time points	
	Mean	**SD**
Observed (reference)	60.5	45.9
Individual Predicted	60.8	43.1
Student paired t test	P value = 0.535	
IWRE (Mean, 95%CI)	-0.260 [-1.08 – 0.562]	
Regression characteristics		
Slope	0.907	
Intercept	5.87	
Correlation coefficient r	0.967	
Criteria in ng/mL (%)	**Value**	**95%CI**
Bias (%)	-0.260 (-0.43 %)	[-1.08 – 0.560]
Precision (%)	11.8 (20 %)	[10.8 – 12.8]
AFE	1.34	

5.2.4 Final Model

To obtain parameter estimates for the final population model, the model building and validation datasets were combined and analyzed, using the final parameter estimates of the covariate model as the initial estimates of the final model. The following table shows the final parameter estimates. PK parameters were nearly identical between the final model from the model building and total dataset analyses.

	FINAL ESTIMATE	%RSE	95% CONFIDENCE INTERVAL LBOUND	UBOUND	DESCRIPTOR/ VARIABILITY	
THETA						
1	290	3.93%	268	312		CL
2	3.14e+003	6.43%	2.74e+003	3.54e+003		V2
3	316	4.75%	287	345		Q
4	6.34e+003	7.82%	5.37e+003	7.31e+003		V3
5	0.291	...	...	...		KA
6	0.528	14.0%	0.383	0.673		WGT_on_CL
7	0.843	3.32%	0.788	0.898		Sex on CL
8	-12.9	12.9%	-16.2	-9.65		AGE_on_CL
OMEGA					INTERINDIVIDUAL VARIABILITY	
1,1	0.0913	7.15%	0.0785	0.104	CV =	30.2%
2,2	1.20	11.8%	0.924	1.48	CV =	110%
3,3	0.495	11.2%	0.386	0.604	CV =	70.4%
SIGMA					RESIDUAL VARIABILITY	
1,1	0.000201	2.00%	0.000193	0.000209	SD =	0.0142

*Indicates 95% confidence interval that includes zero
%RSE is percent relative standard error (100% x SE/EST)

The robustness of the final model and the accuracy of parameter estimate (SE computation) was assessed using a nonparameteric bootstrap methodology. Table (3.5.7.2)1 shows a comparison between the uncertainty in parameter estimates obtained from NONMEM and from 500 bootstrap datasets.

Table (3.5.7.2) 1 - Comparison of final model parameters and bootstrap results (results from the 500 successful runs)

Parameter	NONMEM Estimate	Bootstrap Estimate (SD)	Difference %	NONMEM % RSE	Bootstrap % RSE	NONMEM 95%CI	Bootstrap 5th - 95th percentiles
$\theta_{(1)}$ in [CL/F = $\theta_{(1)}$ * WGT/ 83], L/h	290	296 (14.2)	-2.03 %	3.93 %	4.37 %	[268 – 312]	[269 – 316]
$\theta_{(6)}$ in [CL/F = $\theta_{(1)}$ * (WGT / 83) ** $\theta_{(6)}$]	0.528	0.554 (0.0762)	-4.69 %	14.0 %	12.7 %	[0.383 – 0.673]	[0.430 – 0.688]
$\theta_{(7)}$ Gender effect on CL/F for female	0.843	0.856 (0.0250)	-1.52 %	3.32 %	3.15 %	[0.788 – 0.898]	[0.820- 0.901]
$\theta_{(8)}$ in [CL/F = TVCL*AGE / ($\theta_{(8)}$ + AGE)]]	-12.9	-11.2 (1.92)	15.2 %	12.9 %	18.8 %	[-16.2 – -9.65]	[-14.5 - -8.54]
Central volume V2/F [$\theta_{(2)}$], L	3140	2959 (418)	6.12 %	6.43 %	5.81 %	[2740 – 3540]	[2179 – 3530]
Inter-compartmental clearance Q/F [$\theta_{(3)}$], L/h	316	350 (75.4)	-9.71 %	4.75 %	5.24 %	[287 – 345]	[266 – 513]
Peripheral volume V3/F [$\theta_{(4)}$], L	6340	6919 (1055)	-8.37 %	7.82 %	7.73 %	[5370 – 7310]	[5430 – 8886]
Absorption rate constant k_a [$\theta_{(5)}$], h^{-1}	0.291 FIXED						
Interindividual variability (CV%)							
CL/F	30.2 %	30.1 % (1.11)	< 1 %	7.15 %	7.76 %	[28.0 % – 32.2 %]	[28.3 – 31.9]
V2/F	110 %	114 % (9.91)	-3.51 %	11.8 %	12.1 %	[96.1 % – 122 %]	[100 – 133]
V3/F	70.4 %	49.4 % (30.8)	42.5 %	11.2 %	>10[12]	[62.1 % – 77.7 %]	[0 – 84.4]
Residual variability - $Y = C_{ipred} + \varepsilon$							
σ (SE[ε] in ng/mL)	0.0142	0.0143 (0.000462)	< 1 %	2.00 %	2.14 %	[0.0139 – 0.0145]	[0.0136 – 0.0150]

Clinical Application of PK Model

Neither dosing regimen decisions nor labeling statements were based on the results of the model. As a result, the reviewer considers the model to be only supportive.

5.4 Reviewer's Comments

- In future submissions, any concentrations and/or subjects that have been excluded from the analysis should be maintained in the datasets. For this analysis, the sponsor identified 123 concentrations (from 10 subjects) as outliers and excluded these observations from the dataset.

6 APPENDICES

6.1 NM-TRAN CODE FOR BASE STRUCTURAL MODEL

```
Jan 5 2005 13:50
Compiler Version: DIGITAL Visual Fortran Optimizing Compiler Version 6.0 (Update A)
Fortran Options: /optimize:1 /fpe:0
;Model Desc: base model
;Project Name: model refinement
;Project ID: DRONEDARONE - ANDROMEDA, EURIDIS & ADONIS STUDIES
; Premier run BICOMP - $PK proportionnel, 3 ETAs (Ka FIXED & Q sans ETA), $ERROR Additif
$PROB RUN# 209 (Dronedarone - ANDROMEDA, EURIDIS & ADONIS Studies)
$INPUT C ID TIME AMT DV ADDL II MDV EVID SEX AGE CAUC WGT HGT ICCL NYH0
INHI STUD IDEN
$DATA CONSTRUC.CSV IGNORE=C
;Data file name must use the .csv extension (e.g. 12a.csv)
$SUBROUTINES ADVAN4 TRANS4
$PK
TVCL = THETA(1)
CL = TVCL * EXP(ETA(1))
ETCL = ETA(1)
TVV2 = THETA(2)
V2 = TVV2 * EXP(ETA(2))
ETV2 = ETA(2)
TVQ = THETA(3)
Q = TVQ
TVV3 = THETA(4)
V3 = TVV3 * EXP(ETA(3))
ETV3 = ETA(3)
TVKA = THETA(5)
KA = TVKA
S2 = V2
$ERROR
W = 1
IPRED = F
IRES = DV - IPRED
IWRES = IRES
Y = F + ERR(1)
$THETA
(0, 460) ;[CL]
(0, 1860) ;[V2]
(0, 212) ;[Q]
(0, 4240) ;[V3]
(0.291 FIXED) ;[KA]
;*****************************************************************
;A "descriptor" for the THETA parameter may be added in [] after a semicolon
; eg. ;[KA] or [CL, L/hr]
;Start initial estimates for OMEGA and SIGMA on the line below the $OMEGA or $SIGMA
;After the initial estimate, there must be a ';' followed by
; 'A', 'F', 'P' or 'N' enclosed in brackets '[]'.
;The enclosed letter is not case sensitive.
;No spaces are allowed in the brackets.
; A=additive error, F=off-diagonal covariance, P=proportional error, N=not defined
;*****************************************************************
$OMEGA
0.2 ;[P] INTERIND VAR IN CL
0.2 ;[P] INTERIND VAR IN V2
```

```
0.2 ;[P] INTERIND VAR IN V3
$SIGMA
0.005 ;[A] ADDITIVE COMPONENT
$EST PRINT = 5 MAXEVAL = 9000 NOABORT POSTHOC METHOD = 1 INTERACTION
$COVARIANCE
$TABLE FILE=209.TAB ID TIME DV IPRED IRES IWRES TVCL CL ETCL TVV2 V2 ETV2
TVQ Q TVV3 V3 ETV3 TVKA KA SEX AGE CAUC WGT HGT ICCL NYH0 INHI STUD
IDEN NOPRINT ONEHEADER
$TABLE FILE=patab209 ID TVCL CL ETCL TVV2 V2 ETV2 TVQ Q TVV3 V3 ETV3 TVKA
KA NOPRINT ONEHEADER
$TABLE FILE=cotab209 ID WGT HGT AGE NOPRINT ONEHEADER
$TABLE FILE=catab209 ID SEX CAUC ICCL NYH0 INHI STUD NOPRINT ONEHEADER
$TABLE FILE=sdtab209 ID TIME IPRED IRES IWRES NOPRINT ONEHEADER
```

6.2 NM-TRAN CODE FOR COVARIATE MODEL

```
Jan 17 2005 11:24
Compiler Version: Compaq Visual Fortran Optimizing Compiler Version 6.1
Fortran Options: /optimize:1 /fpe:0
;Model Desc: base model
;Project Name: step3c
;Project ID: DRONEDARONE - ANDROMEDA, EURIS & ADONIS STUDIES
; Premier run BICOMP - $PK proportionnel, 3 ETAs (Ka FIXED & Q sans ETA), $ERROR Additif
$PROB RUN# Step3_004 (Dronedarone - ANDROMEDA, EURIDIS & ADONIS Studies)
$INPUT C ID TIME AMT DV ADDL II MDV EVID SEX AGE CAUC WGT HGT ICCL NYH0
INHI STUD IDEN
$DATA CONSTRUC.CSV IGNORE=C
;Data file name must use the .csv extension (e.g. 12a.csv)
$SUBROUTINES ADVAN4 TRANS4
$PK
Cov1 = THETA(1) * ( WGT / 83 ) ** THETA(6)
TVCL = (Cov1 * SEX + Cov1 * THETA(7) * (1-SEX)) * AGE / (THETA(8) + AGE)
CL = TVCL * EXP(ETA(1))
ETCL = ETA(1)
TVV2 = THETA(2)
V2 = TVV2 * EXP(ETA(2))
ETV2 = ETA(2)
TVQ = THETA(3)
Q = TVQ
TVV3 = THETA(4)
V3 = TVV3 * EXP(ETA(3))
ETV3 = ETA(3)
TVKA = THETA(5)
KA = TVKA
S2 = V2
$ERROR
W = 1
IPRED = F
IRES = DV - IPRED
IWRES = IRES
Y = F + ERR(1)
$THETA
(0, 353) ;[CL]
(0, 3320) ;[V2]
(0, 333) ;[Q]
(0, 6120) ;[V3]
(0.291 FIXED) ;[KA]
(1) ;[WGT_on_CL]
(1) ;[Sex on CL]
(0.001) ;[AGE_on_CL]
;*****************************************************************
;A "descriptor" for the THETA parameter may be added in [] after a semicolon
; eg. ;[KA] or [CL, L/hr]
;Start initial estimates for OMEGA and SIGMA on the line below the $OMEGA or $SIGMA
;After the initial estimate, there must be a ';' followed by
; 'A', 'F', 'P' or 'N' enclosed in brackets '[]'.
;The enclosed letter is not case sensitive.
;No spaces are allowed in the brackets.
; A=additive error, F=off-diagonal covariance, P=proportional error, N=not defined
;*****************************************************************
```

```
$OMEGA
0.2 ;[P] INTERIND VAR IN CL
0.2 ;[P] INTERIND VAR IN V2
0.2 ;[P] INTERIND VAR IN V3
$SIGMA
0.005 ;[A] ADDITIVE COMPONENT
$EST PRINT = 5 MAXEVAL = 9000 NOABORT POSTHOC METHOD = 1 INTERACTION
$COVARIANCE MATRIX=S
$TABLE FILE=Step3_004.TAB ID TIME DV IPRED IRES IWRES TVCL CL ETCL TVV2 V2 ETV2
TVQ Q TVV3 V3 ETV3 TVKA KA SEX AGE CAUC WGT HGT ICCL NYH0 INHI STUD
IDEN NOPRINT ONEHEADER
$TABLE FILE=patabStep3_004 ID TVCL CL ETCL TVV2 V2 ETV2 TVQ Q TVV3 V3 ETV3 TVKA
KA NOPRINT ONEHEADER
$TABLE FILE=cotabStep3_004 ID WGT HGT AGE NOPRINT ONEHEADER
$TABLE FILE=catabStep3_004 ID SEX CAUC ICCL NYH0 INHI STUD NOPRINT ONEHEADER
$TABLE FILE=sdtabStep3_004 ID TIME IPRED IRES IWRES NOPRINT ONEHEADER
```

6.3 NM-TRAN CODE FOR FINAL MODEL

```
Jan 18 2005 09:00
Compiler Version: Compaq Visual Fortran Optimizing Compiler Version 6.1
Fortran Options: /optimize:1 /fpe:0
;Model Desc: base model
;Project Name: total data set
;Project ID: DRONEDARONE - ANDROMEDA, EURIDIS & ADONIS STUDIES
; Premier run BICOMP - $PK proportionnel, 3 ETAs (Ka FIXED & Q sans ETA), $ERROR Additif
$PROB RUN# final4 (Dronedarone - ANDROMEDA, EURIDIS & ADONIS Studies)
$INPUT C ID TIME AMT DV ADDL II MDV EVID SEX AGE CAUC WGT HGT ICCL NYH0
INHI STUD IDEN
$DATA Total.CSV IGNORE=C
;Data file name must use the .csv extension (e.g. 12a.csv)
$SUBROUTINES ADVAN4 TRANS4
$PK
Cov1 = THETA(1) * ( WGT / 83 ) ** THETA(6)
TVCL = (Cov1 * SEX + Cov1 * THETA(7) * (1-SEX)) * AGE / (THETA(8) + AGE)
CL = TVCL * EXP(ETA(1))
ETCL = ETA(1)
TVV2 = THETA(2)
V2 = TVV2 * EXP(ETA(2))
ETV2 = ETA(2)
TVQ = THETA(3)
Q = TVQ
TVV3 = THETA(4)
V3 = TVV3 * EXP(ETA(3))
ETV3 = ETA(3)
TVKA = THETA(5)
KA = TVKA
S2 = V2
$ERROR
W = 1
IPRED = F
IRES = DV - IPRED
IWRES = IRES
Y = F + ERR(1)
$THETA
(0, 301) ;[CL]
(0, 3470) ;[V2]
(0, 349) ;[Q]
(0, 6150) ;[V3]
(0.291 FIXED) ;[KA]
(0.5) ;[WGT_on_CL]
(0.827) ;[Sex on CL]
(-12.1) ;[AGE_on_CL]
;*****************************************************************
;A "descriptor" for the THETA parameter may be added in [] after a semicolon
; eg. ;[KA] or [CL, L/hr]
;Start initial estimates for OMEGA and SIGMA on the line below the $OMEGA or $SIGMA
;After the initial estimate, there must be a ';' followed by
; 'A', 'F', 'P' or 'N' enclosed in brackets '[]'.
;The enclosed letter is not case sensitive.
;No spaces are allowed in the brackets.
; A=additive error, F=off-diagonal covariance, P=proportional error, N=not defined
;*****************************************************************
```

```
$OMEGA
0.0933 ;[P] INTERIND VAR IN CL
1.29 ;[P] INTERIND VAR IN V2
0.662 ;[P] INTERIND VAR IN V3
$SIGMA
0.000193 ;[A] ADDITIVE COMPONENT
$EST PRINT = 5 MAXEVAL = 9000 NOABORT POSTHOC METHOD = 1 INTERACTION
$COVARIANCE MATRIX=S
$TABLE FILE=final4.TAB ID TIME DV IPRED IRES IWRES TVCL CL ETCL TVV2 V2 ETV2
TVQ Q TVV3 V3 ETV3 TVKA KA SEX AGE CAUC WGT HGT ICCL NYH0 INHI STUD
IDEN NOPRINT ONEHEADER
$TABLE FILE=patabfinal4 ID TVCL CL ETCL TVV2 V2 ETV2 TVQ Q TVV3 V3 ETV3 TVKA
KA NOPRINT ONEHEADER
$TABLE FILE=cotabfinal4 ID WGT HGT AGE NOPRINT ONEHEADER
$TABLE FILE=catabfinal4 ID SEX CAUC ICCL NYH0 INHI STUD NOPRINT ONEHEADER
$TABLE FILE=sdtabfinal4 ID TIME IPRED IRES IWRES NOPRINT ONEHEADER
```

4.4 Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-913	Brand Name (proposed)	Multac
OCPB Division (I, II, III)	I	Generic Name	Dronedarone HCl
Medical Division	CARDIORENAL	Drug Class	Antiarrhythmic
OCPB Reviewer	Robert O. Kumi	Indication(Proposed)	Rhythm and rate control in patients with atrial fibrillation or atrial flutter, to maintain normal sinus rhythm or to decrease ventricular rate
OCPB Team Leader	Patrick Marroum	Dosage Form	Tablets, 400 mg
		Dosing Regimen	400 mg twice daily
Date of Submission	June 10, 2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	, 2006	Applicant	Pharmaceuticals
PDUFA Due Date	April 10, 2006	Priority Classification	To be determined
Division Due Date	TBD		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	16		
I. Clinical Pharmacology				
Mass balance:	x	1		
Isozyme characterization:	x	7		Studies included assessment of inhibition, induction and interactions with potential coadministered drugs
In vitro characterization of Transporters	x	1		PGP transporter
Blood/plasma ratio:				
Plasma protein binding:	X	2		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	4, 1b		b- Study TDR2395 (same study)
multiple dose:	x	1, 1b		
Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:	X	1a		a- Study LIN2890 (same study)
fasting / non-fasting multiple dose:	x	1a		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	18		Most studies evaluate PK effect of study drug/ coadministered drug; some studies evaluate PD
In-vivo effects of primary drug:	X			
In-vitro:				
Subpopulation studies -				
age	X	1		
ethnicity:	X	1		Japanese (cross study)
gender:				
pediatrics:				
geriatrics:				
renal impairment:				Not conducted

hepatic impairment:	X	1		Additional ongoing study. Both submitted and ongoing study compare moderate/healthy
PD:				
Phase 2:	X	5		Four studies evaluated safety, hemodynamic and/or electro-physiological characteristics in patients. One study evaluated effect of study drug on renal function in healthy volunteers
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	1		Dose-ranging study
Phase 3 clinical trial:	X	2d		Pooled data from 3 trials
Population Analyses -				
Data rich:				
Data sparse:	x	1c,d		Pooled data from 3 trials
II. Biopharmaceutics				
Absolute bioavailability:	x	2		
Relative bioavailability -	X	4		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	3		
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x			
Electrophysiololgy Study	X			Conducted as part of Phase I studies
Pharmacodynamic studies				
Total Number of Studies Reviewed			35	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	No	
QBR questions (key issues to be considered)	Has exposure-response been adequately characterized? Are proposed dissolution methodology and specification acceptable?	
Other comments or information not included above		
Primary reviewer Signature and Date	Robert Kumi	
Secondary reviewer Signature and Date	Patrick Marroum	

CC: NDA 21-913, HFD-850(Lee), HFD-860 (Marroum, Mehta, KumiR), Biopharm (CDER)

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/s/

Robert Kumi
3/28/2006 04:18:41 PM
BIOPHARMACEUTICS
Dear All, Please review and pass on ASAP. Thanks. Robert

Christine Garnett
3/30/2006 02:36:50 PM
PHARMACOLOGIST

Jogarao Gobburu
3/30/2006 02:40:32 PM
BIOPHARMACEUTICS

Patrick Marroum
3/30/2006 02:48:27 PM
BIOPHARMACEUTICS

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