CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-425

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 22-425	Submission Date(s): 06/27/2008, 07/31/2008, 10/27/08, 11/03/08, 12/03/2008, and 12/10/2008
Relevant IND(s)	49,484
Submission Type; Code	N_000
PDUFA Goal Date	April 30, 2009 (extended from January 30, 2009 by major amendment received on December 3, 2008)
Brand Name (proposed)	MULTAQ
Generic Name	Dronedarone hydrochloride
Formulation; Strength(s)	Tablet (film-coated); 400 mg
Class/Indication	Anti-arrhythmic/ in patients with a history of, or current atrial fibrillation or atrial flutter, for the reduction of the risk of cardiovascular hospitalization or death.
Applicant	Sanofi-Aventis
Reviewer	Robert O. Kumi, Ph.D.
Secondary Reviewer	Elena Mishina, Ph.D.
OCP Division	1
OND Division	Cardiovascular and Renal Products
Briefing Date	Not Applicable: A briefing was not held

Table of Content

1 Executive Summary

Background

NDA 22-425, MULTAQ (dronedarone hydrochloride), is proposed for patients with a history of, or current atrial fibrillation or atrial flutter, for the reduction of the risk of cardiovascular hospitalization or death. Dronedarone hydrochloride was previously submitted as NDA 21-913 for a similar patient population but with a different indication. The Action Letter for NDA 21-913 was issued on August 29, 2006 and listed deficiencies that included clinical pharmacology and biopharmaceutics comments. NDA 22-245 was initially submitted as an amendment to NDA 21-913 and referred to as a "Complete Response" to the Action Letter. The Agency determined that a new indication was being sought, thus, a new NDA was required. An advisory committee will be held for Multaq in late February 2009, as dronedarone is a new molecular entity.

Dronedarone is a benzofuran derivative in the same class as amiodarone, an approved anti-arrhythmic agent. Dronedarone is an anti-arrhythmic agent that has electrophysiological properties associated with all four Vaughan-Williams classes. If approved, Multaq will be marketed as a 400 mg strength tablet. The proposed dronedarone dosage is 400 mg twice daily; each dose should be given with the morning and evening meal. The applicant conducted a fairly comprehensive clinical development program for dronedarone in NDA 21-913 and the findings are applicable to NDA 22-425. Two new clinical pharmacology studies were included in NDA 22-425; these studies were conducted in patients (impaired hepatic function and impaired renal function) and included healthy subjects as controls. Dronedarone was administered orally in these studies. In addition, three in vitro metabolism studies were conducted. This review addresses the clinical pharmacology/biopharmaceutics information related to the complete response and relevant new clinical pharmacology information.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the information submitted to NDA 22-425. The clinical pharmacology and biopharmaceutics information provided in NDA 22-425 is acceptable. Please refer to previous NDA 21-913 for detailed labeling recommendations; an additional labeling comment is listed below. NDA 22-425 includes updated labeling in the required Prescription Drug Labeling format.

New Labeling Comment Regarding Impaired Hepatic Function

Based on the findings of the Hepatic Impairment study, patients with moderately impaired hepatic function should be monitored closely for adverse events when receiving dronedarone. This recommendation is based on the fact that these patients had numerically higher plasma concentrations than subjects with normal hepatic function after receiving the proposed dosing regimen (400 mg dronedarone BID). The exposure values in these patients were highly variable and tended to be relatively higher suggesting that some patients may achieve supra-therapeutic dronedarone concentrations. There is no exposure-response information to support the safe use of dronedarone that could result in supra-therapeutic dronedarone concentrations. Based on the available pharmacokinetic information, dronedarone should be contraindicated in patients with severe hepatic impairment, unless there is clinical experience with these patients, supporting its safe use.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Previously, the applicant conducted a fairly comprehensive clinical pharmacology and biopharmaceutics for dronedarone hydrochloride (NDA 21-913). The current NDA 22-425 includes five new studies involving the assessment of the effect of hepatic function, creatininemia, and in vitro metabolism.
Additional studies were submitted in NDA 22-425, including reanalysis of population pharmacokinetic data using "modern approaches" and reanalysis of other pharmacokinetic studies. These additional studies were not reviewed as they did not provide any new information.

Key Clinical Pharmacology and Biopharmaceutics Findings and Information

Intrinsic Factors (Special Populations): Impact of Impaired Hepatic Function
Following repeated administration (7 days) of dronedarone 400 mg twice daily (proposed regimen), dronedarone exposure in patients with moderate hepatic impairment was not statistically significantly different (at the 95 % confidence interval) from that in subjects with normal hepatic function (Table 1).

Table 1: Statistical comparisons of dronedarone PK measures in hepatic impairment study

PK Measure	Ratio Estimate or p-value	95 % Confidence Interval
Cmax	1.20	0.63 – 2.28
AUC	1.32	0.75 – 2.33
Half-life	P = 0.37	NA

Plasma concentrations were generally more variable and numerically higher in patients with impaired hepatic function, relative to subjects with normal hepatic function (Table 2).

Table 2: Dronedarone Mean (CV %) pharmacokinetic measures in hepatic impairment study

PK Measure	Hepatic impaired patients (n =8)	Healthy Subjects (n = 8)
Cmax (ng/mL)	134 (93)	90.4 (44)
Tmax* (h)	2.5 [1 – 5]	3.5 [2 – 6]
AUC (ng.h/mL)	618 (71)	395 (37)

* Median [range] reported for Tmax

Patients with moderate hepatic impairment had a relatively high degree of variability (CV above 70 %) and numerically higher exposure than subjects with normal hepatic function.

Pharmacodynamics (Creatininemia)/Pharmacokinetics: Impact of Impaired Renal Function
Following repeated administration (14 days) of dronedarone 400 mg twice daily to elderly subjects with normal renal function and different degrees of renal impairment (mild and moderate)

- Creatinine plasma concentrations increased over the first three days, peaking on Day 5
- Creatinine plasma concentrations decreased to baseline level three days after treatment discontinuation (Day 17)

- The magnitude of creatinine changes was independent of renal function
- Dronedarone plasma concentrations were similar across renal function strata (Table 3)

Table 3: Dronedarone PK measures in healthy males in renal impairment study

PK Parameter	Normal n=6	Mild n=7	Moderate n=6
C_{max} (ng/mL)	169 ± 64.9 (38) [156]	152 ± 43.8 (29) [146]	151 ± 60.5 (40) [141]
t_{max} (h)	4.00 (4.00 , 6.00)	4.00 (2.00 , 6.00)	4.00 (4.00 , 6.00)
$AUC_{0-\tau}$ (h.ng/mL)	1440 ± 545 (38) [1330]	1160 ± 213 (18) [1140]	1270 ± 583 (46) [1160]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} where values are Median (Min, Max)

In Vitro Metabolism

- SR35021, the major metabolite of dronedarone, is metabolized primarily by CYP3A and by CYP2D6 to a minor extent; other non-CYP enzymes may also be involved in SR35021 metabolism
- Dronedarone and SR35021 have a low potential to inhibit CYP2B6 enzymatic activity, based on I/Ki calculations ($I^*/Ki < 0.1$). The apparent Ki for SR35021 was 56.9 µM and that for dronedarone was 12.0 µM
- Dronedarone and SR35021 have a low potential to inhibit CYP2C8 enzymatic activity, based on I/Ki calculation ($I^*/Ki < 0.1$). The apparent Ki for SR35021 was 36.6 µM and that for dronedarone was above 100 µM;

* I represents in vivo Cmax: 0.467 µM for SR33589 (260 ng/mL) and 0.360 µM for SR35021 (180 ng/mL); Ki represents inhibition constant.

Signatures

Primary Clinical Pharmacology Reviewer — Robert O. Kumi

Acting Team Leader — Elena Mishina

CC: NDA 22-425 Mishina Uppoor Mehta Kumi (HFD 860)

2 QUESTION BASED REVIEW

This clinical pharmacology and biopharmaceutical review for NDA 22-425 employs an abridged version of the 'Question Based Review' (QBR) since most QBR elements were addressed in the original dronedarone application (ND 21-913). Please refer to NDA 21-913 for information on human pharmacokinetics and bioavailability of dronedarone. The QBR elements addressed in detail in this Clinical Pharmacology Review are Intrinsic Factors (effect of impaired hepatic function) Pharmacodynamics (related to creatininemia and renal function), and Extrinsic factors (in vitro metabolism). In all, five studies were reviewed.

2.1 What are the general attributes of dronedarone hydrochloride?

Regulatory History

The clinical pharmacology information provided in NDA 21-913 was deemed acceptable by the office of clinical pharmacology; however, the following comments were to be conveyed to the sponsor, as appropriate.

Comments to Sponsor

- Please indicate when results from the hepatic impairment study, POP5820, will be submitted to the Agency. Without this information, the product labeling will be restrictive in this patient population
- You have not adequately addressed the issue of dose-response in the target population; therefore dosage adjustment is not feasible during dronedarone therapy.
- You have not provided sufficient permeability information to support dronedarone designation as BCS 2. Please provide all available information that demonstrate dronedarone is a high permeability compound.
- The dissolution methodology is acceptable, however, we do not agree with your dissolution specification. Based on the data provided the following specification is more appropriate: 1) Not less than (b) (4) and not more than (b) (4) is dissolved within 30 minutes 2) Q = (b) (4) at 90 minutes
- 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.

Ultimately, the 29 August 2006 Action Letter for NDA 21-913 included the comments related to permeability and dissolution only. The unaddressed comments were directly or indirectly addressed fully or in part in NDA 22-245. Currently, the Office on New Drug Quality Assessment (ONDQA) is responsible for dissolution evaluations; whereas, OCP determines BCS classification. New dissolution information was included in NDA 22-425; no new permeability information was provided, thus there was no need for additional OCP evaluation. For the remaining comments: 1) The POP5820 study was included in the new NDA, 2) dose-response, though desirable, was not conducted for the new indication, and 3) The comment related to population PK analysis can be forwarded to the Applicant in the Action Letter for NDA 22-425.

2.2 What are the general clinical pharmacology characteristics of dronedarone?

The clinical pharmacology program for dronedarone was comprehensive and evaluated previously for NDA 21-913.

Design Features of Clinical Study

One clinical efficacy study, EFC5555 (ATHENA), was conducted to support the proposed indication. ATHENA was a double-blind, well-controlled study of 2327 placebo and 2301 patients receiving dronedarone for a mean duration of 21 months. According to the applicant, the study population mirrors the AF/AFL population for which the drug is targeted. The primary endpoint was time to first hospitalization for cardiovascular reasons or death.

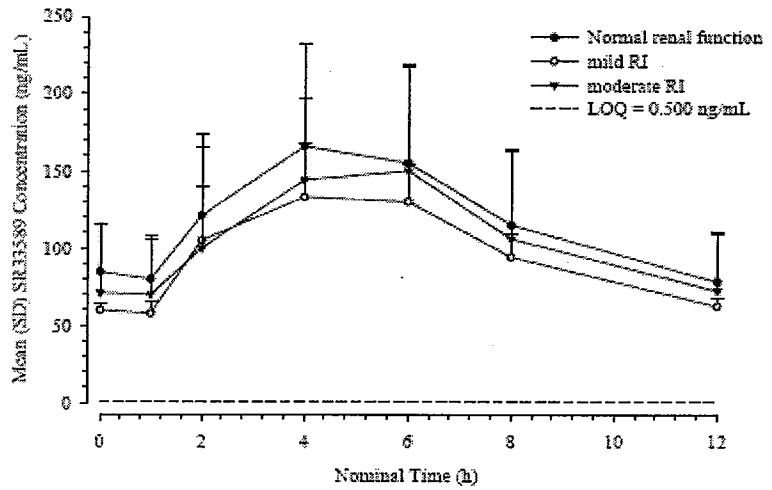
Pharmacodynamics (Creatininemia)/Pharmacokinetics

This study confirmed the previous observation of plasma creatinine increase under dronedarone treatment. The effect of dronedarone treatment on plasma creatinine did not appear to be related to kidney function, and the effect stabilized after about 3 to 5 days of treatment. Plasma creatinine returned to baseline about 3 days after discontinuation of dronedarone treatment. Dronedarone exhibits similar pharmacokinetic parameter values in steady-state conditions irrespective of the population (subjects with normal renal function and subjects with mild and moderate renal impairment) studied. These results are consistent with the very minor urinary excretion of dronedarone and SR35021.

Dronedarone Pharmacokinetics

The mean dronedarone plasma concentration-time profiles for subjects with normal renal function and impaired renal function are depicted in the figure below.

Figure 1: Mean dronedarone plasma concentration-time profile in renal impairment study



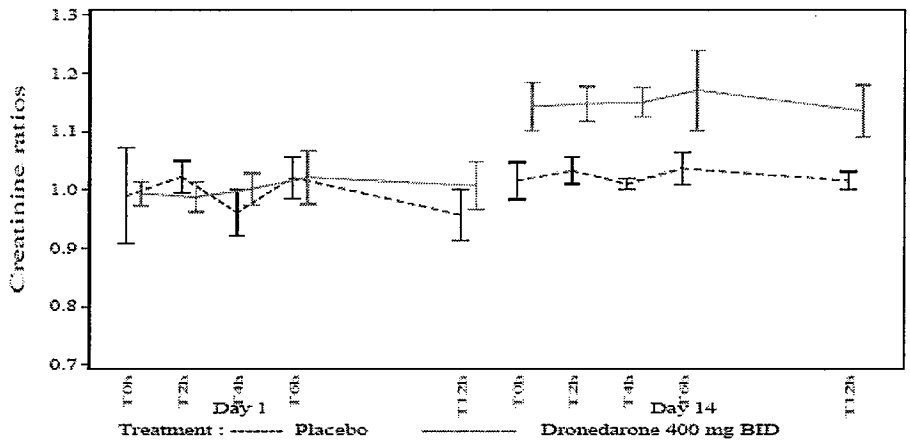
The report did not include a formal statistical comparison of PK measures across the treatment groups as such a comparison was not one of the stated study objectives. However, based on the current study results, renal impairment will not alter dronedarone PK. This finding is expected as dronedarone is excreted to a minimal extent renally, and a previous study had demonstrated that the degree of renal impairment did not alter dronedarone PK.

Dronedarone Pharmacodynamics (PD)

There was no difference in creatinine ratios among renal function strata; thus, the findings for moderate renal impairment can be extrapolated to subjects with normal renal function and mild renal impairment. By inspection, the following figure suggests that for subjects with moderate renal impairment:

- there is no difference in creatinine ratios (baseline vs. given Day) between placebo and dronedarone on Day 1
- there is a difference in the creatinine ratios between placebo and dronedarone on Day 14

Figure 2: Time-matched ratios vs. baseline in creatinine concentration on Day 1 and Day 14 (moderate renal impairment)



The clinical relevance of the 10 to 20 % increase in plasma creatinine concentrations is unclear according to the Medical Reviewer. However, the clinical studies and labeling provide specific instructions related to dronedarone and creatinine. In essence, these instructions indicate that: a) creatininemia is reversible upon discontinuation of dronedarone and b) creatininemia should not lead to discontinuation of ACE inhibitors or other compounds that are known to increase plasma creatinine concentration.

Three key findings related to the time course of effect (creatininemia) were:

1) The maximum PD effect (plasma creatinine concentration) was reached on Day 5.
2) Plasma creatinine concentrations returned to baseline levels three days after the last study drug intake.
3) Plasma concentrations exhibited a similar time course as creatinine concentrations.

2.3 What intrinsic factors affect dronedarone exposure (Effect of moderate hepatic impairment)

Patients with moderately impaired hepatic function had numerically higher (~ 25 %) plasma concentrations than subjects with normal hepatic function after receiving the proposed dosing regimen (400 mg dronedarone BID). However, exposure values were highly variable and tended to be higher in patients, suggesting that some patients may achieve supra-therapeutic dronedarone concentrations. Consequently, patients with moderately impaired hepatic function who receive dronedarone should be monitored closely for adverse events. There are no PK data on patients with severe hepatic impairment. According to the Medical Reviewer, the degree of hepatic impairment was not documented in the clinical studies. Patients with severe hepatic impairment should not receive dronedarone in the absence of clinical experience with these patients or

exposure-response data, supporting its safe use. As expected, SR35021 exposure decreased (approximately 50 %) in patients compared with healthy subjects, as dronedarone is primarily hepatically cleared. These decreases were statistically significant for Cmax, but not AUC.

The table below summarizes the PK data obtained in the hepatic impairment study.

Table 4: Dronedarone Pharmacokinetic measures in hepatic impairment study (400 mg BID)

PK Parameter Mean (CV %)	Healthy Subjects, N=8	Hepatically Impaired Patients, N=8
	First Administration – Day 1	
Cmax (ng/mL)	134 (93)	219 (72)
Tmax (h)	2.5 [1 – 5]	3.5 [2 – 6]
AUC_{0-12}	618 (71)	395 (37)
	Repeated Administration – Day 7	
Cmax (ng/mL)	219 (72)	143 (25)
Tmax (h)	3.5 [2 – 6]	4.5 [2 – 5]
AUC_{0-12}	1820 (71)	1040 (22)

The following two tables summarize the exposure comparisons for dronedarone (Table 5) and SR35021 (Table 6) in the hepatic impairment study. As noted, there is no statistical difference in dronedarone exposure between subjects with normal hepatic function and those with moderate hepatic function. For SR35021, there is a trend towards decreased exposure for patients with moderate hepatic function, relative to subjects with normal function, because SR35021 is formed by hepatic processes. It should be noted that the statistical comparisons were done at the 95 % confidence interval rather than the recommended 90 % confidence interval.

Table 5: Statistical comparisons of dronedarone PK measures in hepatic impairment study (400 mg BID regimen)

Parameter	Ratio Estimate or p-value	95 % Confidence Interval
Cmax	1.20	0.63 – 2.28
AUC_{0-12}	1.32	0.75 – 2.33
T1/2	P = 0.37	NA
Unbound AUC	1.88	1.10 – 3.22

Table 6: SR30621 Geometric mean ratios and associated confidence intervals under fasted and fed conditions

Parameter	Ratio Estimate or p-value	95 % Confidence Interval
Cmax	0.44	0.25 – 0.79
AUC_{0-12}	0.53	0.28 – 1.01
T1/2	P = 0.04	NA
Unbound AUC	0.62	0.38 – 1.03

2.4 What extrinsic factors affect dronedarone or SR35021 pharmacokinetics (In vitro metabolism)

SR35021 was metabolized by CYP3A primarily and CYP2D6 to a lesser extent; there was also evidence that other non-CYP enzymes may be involved in SR35021 metabolism. Neither dronedarone nor SR35021 demonstrated the potential to inhibit CYP2C8 or CYP2B6 metabolism

SR35021 Metabolism

Study MIH0138 investigated SR35021 metabolism via microsomes, Supersomes and hepatocytes using standard in vitro techniques. In the microsome study, where SR35021

was incubated with active and inactive microsomes with or without NADPH, the following was observed (Table 7):

- No NADPH-dependent metabolism of SR35021 at either 0.2 μM (100 ng/mL) or at 2 μM (1000 ng/mL)
- Inactive microsomes did not deplete SR 35021 to as great a degree as active microsomes

Together these findings suggest that SR35021 metabolism involves microsomes, however, the metabolism is not solely dependent on CYP enzymes that require NADPH for activity

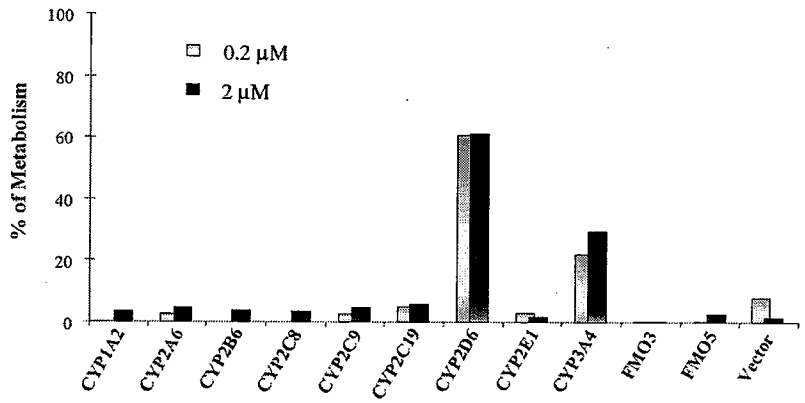
Table 7: Metabolism of SR35021 in human liver microsomes (Standard Conditions*)

Microsome Preparation	SR35021 Nominal (μM)	SR35021 Observed (μM)		Percent of Control (%)
		Control [a] (-NADPH)	Reaction [a] (+NADPH)	
Active	0.2	0.155	0.148	95.5
	2	1.27	1.27	100
Inactive[b]	0.2	0.201	0.200	99.5
	2	2.31	2.35	102

[a] Mean of duplicate preparations
[b] Microsomes were inactivated by heat
* 0.25 mg/mL protein, 37°C for 30 min

With Supersomes™ (Human cDNA Expressed CYP Isoforms), CYP2D6 and CYP3A metabolized SR35021 at both reaction mixture concentrations of 0.2 and 2 μM (figure below). Other CYP and non-CYP enzymes had minimal impact on SR35021 metabolism.

Figure 3: SR35021 metabolism by Supersomes



Additional studies were conducted with hepatocytes +/- specific enzyme inhibitors: quinidine for CYP2D6 and ketoconazole for CYP3A. Based on the inhibition results, the contribution of CYP2D6 and CYP3A to SR35021 metabolism was approximately 6 and 22 %, respectively.

CYP2B6 and CYP2C8 Inhibition Potential of dronedarone and SR35021

Standard procedures for determining inhibition potential were used. For CYP2C8 the probe substrate was paclitaxel and for CYB2B6 the probe substrate was bupropion. Ki values and proposed inhibition mechanisms for the two enzymes are summarized in the following table.

Table 8: Effect of SR33589* / SR35021* on Bupropion Hydroxylation in Human Liver Microsomes

Compound	Inhibition Model	Apparent Ki μM	I/Ki	Likelihood of inhibition
	Paclitaxel for CYP2C8			
Dronedarone	Not reported	> 100	< 0.01	Low
SR35021	Noncompetitive	36.6	0.0	Low
	Bupropion for CYP2B6			
Dronedarone	Mixed	12.0	0.039	Low
SR35021	Mixed	56.9	0.006	Low

* Concentrations: 0.467 μM for SR33589 or dronedarone (260 ng/mL) and 0.360 μM for SR35021 (180 ng/mL).

Reviewer note on Dronedarone and SR35021 concentrations

The dronedarone concentrations exceed therapeutic concentrations by more than 10-fold.

Based on current FDA guidelines (I/Ki), the inhibition data indicate that SR33589 and SR35021 have a low potential to significantly inhibit the clearance of drugs metabolized by CYP2B6 or CYP2C8. All I/Ki values are less than 0.1

2.5 What assay was used to measure dronedarone and SR35021 plasma concentrations in clinical pharmacology studies?

The standard, previously validated LC/MS/MS dronedarone assay used in NDA 21-913 was utilized in the clinical pharmacology studies for NDA 22-425. Within study assay validation was also conducted and the assay performances were acceptable. Please refer to individual study reviews in Appendix for additional details.

3 Labeling Comments

Please refer to the clinical pharmacology review for NDA 21-913 for detailed labeling recommendations. The only additional labeling comment for NDA 22-425 is related to cautionary use in patients with moderate hepatic impairment and contraindication in patients with severe hepatic impairment (see Recommendations Page 3)

4 APPENDIX

4.1 Proposed Labeling

23 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Clin Pharm/Bio-*__1___

4.2 Individual Study Reviews

4.2.1 Effect of Pharmacokinetics and safety of dronedarone after repeated oral doses for 7 days in patients with moderate hepatic impairment in comparison with healthy matched subjects - Non-randomized, non placebo-controlled, open-labeled, 2 parallel-group study (POP5820)

INVESTIGATORS	Kenneth C. Lasseter, MD and Thomas C. Marbury, MD
STUDY SITE	Clinical Pharmacology Associates, Miami, FL and Orlando Clinical Research Center, Orlando, FL
STUDY PERIOD	July, 2004 – April, 2005

Objectives (per applicant):

Primary

To assess the pharmacokinetics of dronedarone and its metabolite, SR35021, in patients with moderate hepatic impairment after repeated oral doses of dronedarone for 7 days given in fed conditions compared with healthy sex-, age- and weight-matched subjects.

Secondary

- To assess the pharmacodynamics of dronedarone based on ECG parameters and on vital signs (HR and BP)
- To assess the clinical and laboratory tolerability of dronedarone in patients with moderate hepatic impairment and in healthy subjects

Study Design

This was a multicenter, comparative, non-randomized, non-placebo-controlled, open-labeled, 2 parallel-group and repeated oral dose study. Dronedarone was administered initially as repeated 400 mg once daily (OD) doses. Based on an interim safety and PK evaluation, additional subjects and patients with moderate hepatic impairment (Child Pugh Class B) were included and treated with 400 mg once daily (OD), or 400 mg twice daily (BID). All subjects received a standardized meal (fed conditions)

Reviewer Note

This review is focused on the pharmacokinetic information; specifically, the 400 mg BID regimen, as this is the proposed dronedarone dosage. However, once daily information is included in this review for completeness.

Subject Demographics

The subject demographics are summarized in Table 9. Twenty six subjects were enrolled; however, twenty-four subjects completed the study: the eight at the 400 mg OD dose and 18 at the 400 mg BID dose. Two subjects in the 400 mg BID dose group discontinued the study: one healthy subject due to a treatment emergent adverse events or TEAEs (No. 840002103) and one patient with hepatic impairment due to investigator/subject request (No. 840001003).

Table 9: Subject Demographic Data

Parameter (unit)	Statistics/ Category	Dronedarone 400 mg OD		Dronedarone 400 mg BID		Overall
		Healthy subjects (N=4)	Hepatic impairment (N=4)	Healthy subjects (N=9)	Hepatic impairment (N=9)	(N=26)
Age (yrs)	N	4	4	9	9	26
	Mean (SD)	51.3 (4.8)	52.5 (3.4)	53.4 (8.7)	54.0 (6.9)	53.2 (6.7)
	Min - Max	45 - 55	48 - 56	46 - 69	45 - 65	45 - 69
Weight (kg)	N	4	4	9	9	26
	Mean (SD)	80.45 (14.66)	82.25 (16.90)	74.81 (11.41)	76.33 (14.49)	77.35 (13.31)
	Min - Max	67.0 - 96.3	67.3 - 99.5	57.3 - 90.0	53.2 - 100.0	53.2 - 100.0
Height (cm)	N	4	4	9	9	26
	Mean (SD)	178.0 (12.4)	168.0 (6.8)	166.8 (9.0)	169.8 (8.0)	169.7 (9.2)
	Min - Max	160 - 188	160 - 175	152 - 180	156 - 183	152 - 188
BMI (kg/m^2)	N	4	4	9	9	26
	Mean (SD)	25.40 (4.04)	28.90 (4.01)	26.82 (2.99)	26.44 (3.86)	26.79 (3.55)
	Min - Max	19.5 - 28.4	24.7 - 33.6	20.6 - 30.1	18.4 - 31.9	18.4 - 33.6
Gender	Male (N,%)	3 (75.0)	3 (75.0)	5 (55.6)	5 (55.6)	16 (61.5)
	Female (N,%)	1 (25.0)	1 (25.0)	4 (44.4)	4 (44.4)	10 (38.5)
Race	Black (N,%)	0 (0)	0 (0)	1 (11.1)	0 (0)	1 (3.8)
	Caucasian (N,%)	1 (25.0)	2 (50.0)	2 (22.2)	8 (88.9)	13 (50.0)
	Other (N,%)	3 (75.0)	2 (50.0)	6 (66.7)	1 (11.1)	12 (46.2)

PGM= SR33589B/POP5820/CSR/BS/PGM RPT/i4demo.sas OUT= OUTPUT/I4 demo1.html (09AUG2005 - 12:53)

Blood (Pharmacokinetic) sampling times

Blood samples were collected at the following times on the specified days:

- Day 1 and Day 7: predose and 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours
- Day 2, 4, 5 and 6: predose
- Day 7: predose and then 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 and 72 hours on Day 7 after repeated administration of dronedarone 400 mg OD or BID.

Plasma unbound concentrations of dronedarone and SR35021 were assessed in blood (plasma) collected at the following times on the specified days:

- Day 1 and Day 7: predose and 2, 4, 6, 12 and 24 hours after repeated administration of dronedarone 400 mg OD
- Day 1 and Day 7: predose and 2, 4, 6, 12 hours on after repeated administration of dronedarone 400 mg BID

Formulation

Dronedarone, 400 mg tablets; Batch number: CL-04530

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in Table 10.

Table 10: Performance of Dronedarone and SR35021 Assays (DOH0036)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.50 to 300 ng/mL range^	Satisfactory
Between day Precision	CV data were not provided	Cannot be assessed
Accuracy	The majority of QC samples 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 to 0.50 to 300 ng/mL range^	Satisfactory
Between day Precision	CV data were not provided	Satisfactory
Accuracy	The majority of QC samples were within 15 % of nominal concentration	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

^ Neither r nor R^2 values were provided; however, based on the validation report the assay is linear over the evaluated range
*The validation report for the assay included chromatograms that suggest the assay was specific

Unbound concentrations of dronedarone and SR35021 in human plasma dialysate were determined by equilibrium dialysis (turboflow extraction) and LC/MS-MS method. The assay performance was acceptable for both compounds and had the following characteristics:

- LOQ = 10 pg/mL
- Linear range: 10 to 500 pg/mL; r > 0.98
- The majority of QC samples were within 15 % of nominal concentration

Pharmacokinetics

The following dronedarone and SR35021 pharmacokinetic measures were estimated:

- Day 1: Cmax, tmax, AUC_{0-24} for OD regimen or AUC_{0-12} for BID regimen
- Day 7: Ctrough, Cmax, tmax, AUC_{0-24} for OD regimen, or AUC_{0-12} for BID regimen, t1/2z, and CL_{0-24}/F, Vdz/F for dronedarone only
- accumulation ratio (Rac) (Day 7/Day 1) for dronedarone and SR35021, calculated based on AUC_{0-24} for OD regimen and AUC_{0-12} for BID regimen, as well as Cmax
- metabolic ratio (Rmet: ratio of SR35021/dronedarone AUCs) after single and repeated administrations
- Day 1 and on Day 7: unbound fractions of dronedarone and SR35021 concentration were assessed; unbound AUC_{0-12} for BID regimen and unbound AUC_{0-24} for OD regimen

Statistical methods

Standard pharmaco-statistical methods were used to evaluate the effect of impaired hepatic function on dronedarone and SR35021 pharmacokinetics. The subjects with normal hepatic function served as the reference treatment group and subjects with impaired hepatic function

were the treatment group. The population and day effects were assessed separately for each dronedarone dose level with a linear mixed effect model:

PK parameter = Population +Day + Population*Day + Subject (Population) +
Error with random term for Subject and fixed term otherwise.

Cmax and AUCs were log-transformed before analysis. For these parameters, population ratio estimates and 95% CIs were computed within the above model framework, and then these estimates were converted to a ratio of geometric means by antilog transformation. It is noted that 95 % confidence intervals (CIs) rather than 90 % CIs (typical) were used to compare drug exposure (geometric mean estimates and associated CIs).

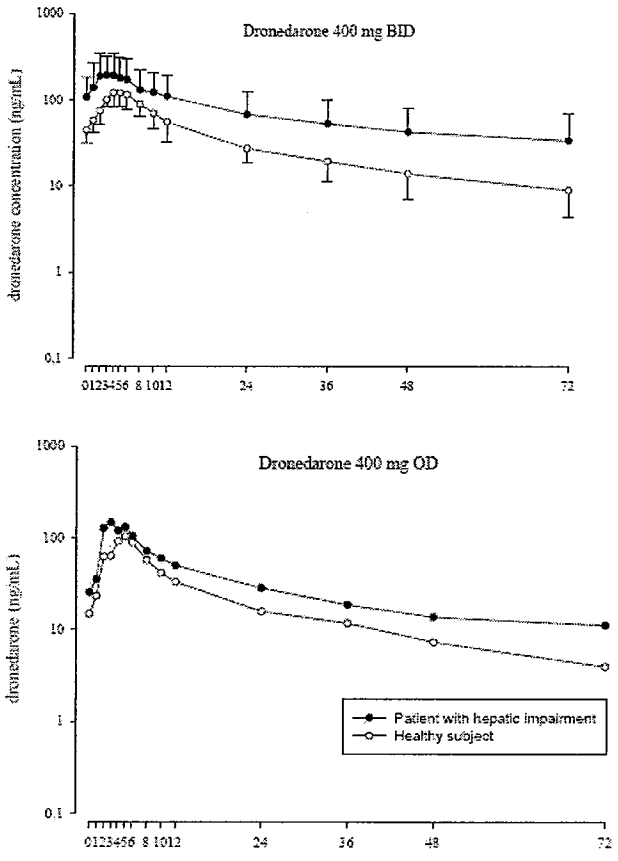
Additional statistical analyses were conducted to describe dronedarone and SR35021 PK.

Results

Dronedarone Pharmacokinetics

The mean dronedarone plasma concentration-time profiles in the two study groups are shown in Figure 4.

Figure 4: Mean dronedarone plasma concentration-time profiles following 400 mg BID dosing (upper panel) and 400 mg OD (lower panel) under fed conditions- filled circles (hepatic impairment) and open circles (healthy)



Dronedarone PK measures are summarized in Table 11 and the PK measures are statistically compared in Table 12. As noted previously, this review focuses on the 400 mg BID results.

Table 11: Dronedarone pharmacokinetic measures in hepatic impairment study

PK parameter Mean (CV%)	Dronedarone 400 mg OD		Dronedarone 400 mg BID	
	Hepatic impaired patient n=4	Healthy subject n=4	Hepatic impaired patient n=8	Healthy subject n=8
	First administration – Day 1			
C_{max} (ng/mL)	99.6 (31)	90.0 (52)	134 (93)	90.4 (44)
t_{max} (h)[a]	3 [2 ; 5]	5 [3 ; 5]	2.5 [1 ; 5]	3.5 [2 ; 6]
AUC[d] (ng.h/mL)	778 (26)	531 (50)	618 (71)[b]	395 (37)
Unbound fraction %[c]	0.279 (26)	0.255 (5)	0.498 (26)	0.337 (15)
Unbound AUC[d] (ng.h/mL)	2.15 (36)	1.35 (48)	2.77 (59)	1.30 (32)
	Repeated administration – Day 7			
C_{max} (ng/mL)	167 (23)	126 (63)	219 (72)	143 (25)
t_{max} (h)[a]	4 [2 ; 5]	3 [1 ; 5]	3.5 [2 ; 6]	4.5 [2 ; 5]
AUC[d] (ng.h/mL)	1510 (38)	1010 (60)	1820 (71)	1040 (22)
$t_{1/2z}$ (h)	28.3 (44)	24.9 (21)	43.2 (35)	38.0 (62)
Unbound fraction %[c]	0.291 (29)	0.251 (32)	0.515 (27)	0.356 (15)
Unbound AUC[d] (ng.h/mL)	4.25 (38)	2.20 (58)	8.70 (59)	3.66 (22)

[a]: median [Min : Max] values, [b]: n=7, [c]: mean values of unbound fractions observed at each sampling time in each day, [d]: AUC = AUC_{0-24} for the OD regimen and AUC_{0-12} for the BID regimen

Table 12: Statistical comparisons of dronedarone PK measures in hepatic impairment study

Parameter	Dronedarone 400 mg OD		Dronedarone 400 mg BID	
	Ratio Estimate or p-value	95% C.I.	Ratio Estimate or p-value	95% C.I.
C_{max}	1.63	[0.40 ; 6.73]	1.20	[0.63 ; 2.28]
AUC[a]	1.81	[0.53 ; 6.14]	1.32	[0.75 ; 2.33]
$t_{1/2z}$	p=0.79	-	p=0.37	-
Unbound AUC[a]	2.01	[0.69 ; 5.87]	1.88	[1.10 ; 3.22]

[a]: AUC = AUC_{0-24} for the OD regimen and AUC_{0-12} for the BID regimen

The comparisons (impaired hepatic function vs. normal hepatic function) indicate the following:

- there was a non statistically significant increase by 20 percent and 30 percent in dronedarone Cmax and AUC_{0-12}, respectively
- Dronedarone t1/2z was not different
- Dronedarone plasma unbound fractions were statistically significantly increased ~ 2-fold

Reviewer Comment on Interpretation of PK comparisons

- The data indicate that there was a high variability in exposure, particularly in subjects with impaired hepatic function (CV 71 % vs. 25 % after repeated administration). This finding coupled with the relatively wide confidence intervals suggests that some patients with impaired hepatic function may be at an additional risk for experiencing adverse events associated with dronedarone administration. There is limited information on dronedarone exposure-response, thus the ramifications of hepatic impairment cannot be clearly delineated currently.

- The change in unbound fractions is unlikely to be clinically significant due to relatively small magnitude of the change 0.32 to 0.52 %.

Metabolic ratio

The metabolic ratio, Rmet, observed on Day 7 after repeated BID oral administration of dronedarone was lower in patients with hepatic impairment (0.33 to 0.36) compared with healthy subjects (0.71 to 0.99). The finding is expected as less hepatically-generated metabolite will be formed in patients with impaired hepatic function relative to those with normal hepatic function.

Accumulation ratio

The accumulation ratios were pooled for the two subject groups (populations) because the population term did not have a statistically significant effect. As summarized in the following table, both patients with moderate hepatic impairment and healthy subjects had statistically significant increases in exposure upon 7-day repeat dosing: 75 % increase for Cmax and 193 % increase for AUC.

Table 13: Accumulation Ratio in Hepatic Impairment Study (Pooled across populations)

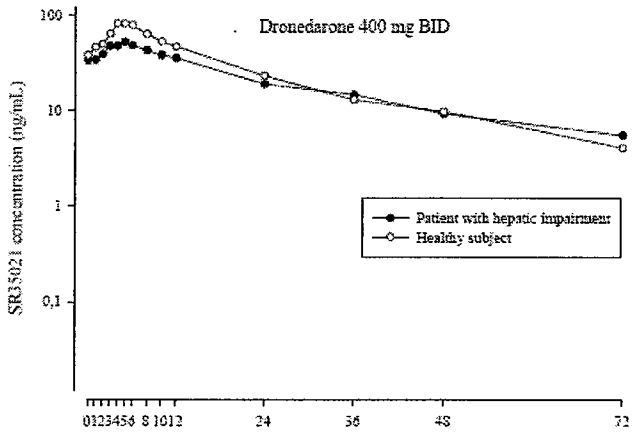
Parameter	Dronedarone 400 mg OD		Dronedarone 400 mg BID	
	R_{ac} *estimate*	95% C.I.	R_{ac} *estimate*	95% C.I.
C_{max}	1.32	[0.80 ; 2.16]	1.75	[1.36 ; 2.26]
AUC[a]	1.74	[1.30 ; 2.32]	2.93	[2.36 ; 3.63]

[a]: AUC = AUC_{0-24} for the OD regimen and AUC_{0-12} for the BID regimen

SR35021 Pharmacokinetics

The mean SR35021 plasma concentration-time profiles are depicted in the following figure.

Figure 5: Mean SR35021 plasma concentration-time profile following administration of dronedarone 400 mg BID in hepatic impairment study



The PK measures for SR35021 are summarized in the following two tables. Based on the statistical comparisons (Table 15) for the BID regimen, relative to subjects with normal hepatic function, subjects with impaired hepatic function had:

- a statistically significantly lower Cmax

- a statistically significantly longer half-life
- tended to have lower AUC

Table 14: SR30521 PK measures in hepatic impairment study

PK parameter Mean (CV%)	Dronedarone 400 mg OD		Dronedarone 400 mg BID	
	Hepatic impaired patient n=4	Healthy subject n=4	Hepatic impaired patient n=8	Healthy subject n=8
	First administration – Day 1			
C_{max} (ng/mL)	24.3 (46)	51.7 (40)	22.1 (46)	46.6 (27)
t_{max} (h)[a]	4.5 [4 ; 6]	5 [4 ; 6]	4 [2 ; 5]	5 [3 ; 6]
AUC[d] (ng.h/mL)	218 (41)	398 (35)	162 (38)	240 (30)
Unbound fraction %[c]	1.48 (12)	1.20 (18)	2.02 (24)	1.70 (11)
Unbound AUC[d] (ng.h/mL)	3.12 (33)	4.56 (22)	3.08 (33)	4.01 (27)
	Repeated administration – Day 7			
C_{max} (ng/mL)	38.4 (30)	59.6 (52)	54.5 (63)	94.1 (25)
t_{max} (h)[a]	5.5 [3 ; 6]	4 [2 ; 6]	5 [3 ; 12]	5 [4 ; 6]
AUC[d] (ng.h/mL)	468 (22)	712 (45)	502 (68)	732 (26)
$t_{1/2z}$ (h)	25.1 (27)	25.4 (28)	35.5 (57)	21.4 (26)
Unbound fraction %[c]	1.48 (9)	1.20 (25)	2.08 (25)	1.77 (13)
Unbound AUC[d] (ng.h/mL)	6.89 (20)	7.79 (32)	9.22 (56)	12.7 (14)
Rmet	0.36 (57)	0.99 (66)	0.33 (67)	0.71 (14)

a: median [Min ; Max] values, b: n=7, c: mean values of unbound fractions observed at each sampling time in each day, [d]: AUC = AUC_{0-24} for the OD regimen and AUC_{0-12} for the BID regimen

Table 15: SR30621 Geometric mean ratios and associated confidence intervals under fasted and fed conditions

Parameter	Dronedarone 400 mg OD		Dronedarone 400 mg BID	
	Ratio Estimate or p-value	95% C.I.	Ratio Estimate or p-value	95% C.I.
C_{max}	0.59	[0.24 ; 1.43]	0.44	[0.25 ; 0.79]
AUC[a]	0.62	[0.31 ; 1.25]	0.53	[0.28 ; 1.01]
$t_{1/2z}$	p=0.98	-	p=0.04	-
Unbound AUC[a]	0.78	[0.48 ; 1.27]	0.62	[0.38 ; 1.03]

[a]: AUC = AUC_{0-24} for the OD regimen and AUC_{0-12} for the BID regimen

There was no difference in the accumulation ratio (AUC or Cmax) between the two populations (data not shown).

Applicant's Safety Summary

There were no deaths or serious adverse events (AEs) reported during the study. One healthy subject discontinued study drug on Day 1, due to non-serious treatment emergent AEs (blurred vision, hyperhydrosis, tremor, asthenia, dry mouth, headache), reported 3.5 hours after the first 400 mg dose of the BID regimen. Few potentially clinically significant abnormalities (PCSAs) were observed in hematology and in vital signs, at both doses and in both populations. No PCSAs of delta QTcB/QTcF >60 ms were recorded. PCSAs in QTcB/QTcF >450 ms (males) or >470 ms (females) were recorded mainly in patients with hepatic impairment taking 400 mg

BID. The mean values of QTc intervals at baseline were higher in patients compared with healthy subjects. Diarrhea

Recommendations/Conclusions

- Average steady state of dronedarone and SR35021 was reached after 3 to 6 treatment days for both populations (patients with moderate hepatic impairment and healthy subjects) receiving the proposed 400 mg BID regimen
- Based on the 95 % confidence interval, non-statistically significant increases of 1.2- to 1.3-fold in dronedarone Cmax and AUCs were observed after single and repeated dronedarone 400 mg BID administration in patients with moderate hepatic impairment, compared with healthy subjects. However, exposure values were highly variable in patients, suggesting that some patients may achieve supra-therapeutic dronedarone concentrations. Consequently, patients with moderately impaired hepatic function and severe hepatic dysfunction should be monitored closely for adverse events; potentially, subjects with impaired hepatic function should not receive dronedarone, unless there's clinical experience with these patients, supporting its safe use.
- SR35021 exposure decreased approximately 50 % (Cmax and AUCs) in patients compared with healthy subjects; however, these decreases were statistically significant, for Cmax, but not AUC.
- Dronedarone plasma unbound fractions were slightly higher in patients compared with healthy subjects, with a 2-fold increase in unbound AUCs. However, the change in the unbound fraction did not appear clinically significant
- Dronedarone t1/2z was not different in patients compared with healthy subjects, with a mean dronedarone t1/2z of 38 to 43 hours in the BID regimen for both populations.
- SR35021 plasma unbound fraction remained approximately similar for the 2 populations, for each dose regimen.
- After repeated oral administration of dronedarone 400 mg BID, the accumulation ratio was about 1.8 and 2.9, respectively, for dronedarone Cmax and AUC0-12 across both populations, and 2.1 and 3.1, respectively, for SR35021.

4.2.2 A randomized, double-blinded, placebo-controlled, two parallel group study to assess the effect before, during, and after treatment with 400 mg BID of oral dronedarone for 14 days on creatininemia in elderly male subjects (PDY5850)

INVESTIGATORS	Kenneth C. Lasseter, MD and Thomas C. Marbury, MD
STUDY SITE	Clinical Pharmacology Associates, 2060 N.W. 22nd Avenue, Miami, FL 33142, USA
STUDY PERIOD	November 2004 – January, 2008

Objectives (per applicant):

Primary objective

To evaluate the effect of oral dronedarone compared with placebo on the pharmacodynamics of creatininemia during and after drug administration in elderly subjects.

Secondary objectives

- To assess the effect of oral dronedarone compared with placebo on plasma/urine markers of the RAAS and associated factors including PRA, aldosterone, angiotensin II, cortisol, urea, uric acid, NMN, sodium, and potassium in elderly subjects.
- To document the plasma concentrations of dronedarone and SR35021 during and after treatment
- To assess the relationship between plasma concentrations of dronedarone and/or SR35021 in conjunction with creatininemia.

Study Design

This was a multi-center, randomized, placebo-controlled, double-blinded study, with a 3-day placebo run-in period followed by a 14-day repeated dosing of dronedarone or placebo. Thirty-three elderly male subjects were enrolled and divided into three strata according to their creatinine clearance (CLcr) calculated at screening with the Cockroft and Gault formula:

- CLcr >30 to 50 mL/min- subjects with moderate renal impairment
- CLcr >50 to 80 mL/min- subjects with mild renal impairment
- CLcr >80 mL/min- subjects with normal renal function

Additionally some subjects received placebo. All subjects received standardized meals.

Subject Demographics

Subject demographics are presented in the following table. Of the 33 randomized subjects, 29 completed the study. Two subjects recruited at the New Orleans center discontinued after Hurricane Katrina (Subjects No. 840002001 and No. 840002002), and 2 other subjects withdrew consent (Subjects No. 840001027 and No. 840001006).

Table 16: Subject Demographic Data

Parameter (unit)	Statistics/ Category	Strata(*)					
		Normal		Mild		Moderate	
		Placebo (N=4)	Dronedarone 400 mg BID (N=6)	Placebo (N=4)	Dronedarone 400 mg BID (N=7)	Placebo (N=4)	Dronedarone 400 mg BID (N=8)
Age (Yrs)	N	4	6	4	7	4	8
	Mean (SD)	66.8 (1.5)	66.3 (1.0)	74.5 (4.4)	69.6 (4.4)	71.5 (5.6)	72.5 (5.3)
	(Min , Max)	(65 , 68)	(65 , 68)	(69 , 78)	(65 , 78)	(66 , 79)	(65 , 79)
Weight (kg)	N	4	6	4	7	4	8
	Mean (SD)	88.43 (8.11)	88.40 (6.23)	75.70 (7.44)	70.00 (6.50)	72.33 (7.11)	63.29 (10.79)
	(Min , Max)	(80.5 , 97.3)	(79.5 , 98.2)	(66.4 , 84.1)	(63.6 , 81.8)	(64.1 , 81.2)	(50.0 , 81.2)
Height (cm)	N	4	6	4	7	4	8
	Mean (SD)	171.0 (8.0)	175.7 (4.1)	167.3 (4.6)	168.4 (5.4)	168.0 (6.3)	163.4 (8.6)
	(Min , Max)	(165 , 182)	(170 , 180)	(162 , 172)	(165 , 180)	(160 , 175)	(147 , 172)
BMI (kg/m2)	N	4	6	4	7	4	8
	Mean (SD)	30.24 (1.99)	28.64 (1.62)	27.06 (2.48)	24.73 (2.73)	25.76 (3.68)	23.77 (3.92)
	(Min , Max)	(28.1 , 32.9)	(26.9 , 31.3)	(24.4 , 29.8)	(21.0 , 29.3)	(22.2 , 29.1)	(17.8 , 28.3)
Gender	Male	4 (100.0%)	6 (100.0%)	4 (100.0%)	7 (100.0%)	4 (100.0%)	8 (100.0%)
Race	Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	2 (25.0%)
	Caucasian/White	1 (25.0%)	3 (50.0%)	0 (0.0%)	2 (28.6%)	1 (25.0%)	3 (37.5%)
	Other(Hispanic)	3 (75.0%)	3 (50.0%)	4 (100.0%)	5 (71.4%)	2 (50.0%)	3 (37.5%)

(*) Strata were defined at screening with creatinine clearance calculated from Cockroft and Gault formula as:
Moderate:]30 – 50 mL/min], Mild:]50 - 80 mL/min], Normal: >80 mL/min
Program: /SR33589B/PDY5850/CSR/bs/pgm rpt/i4dem1.sas out=/output/Table i4dem1.html (25APR2008 - 14:54)

Blood (Pharmacokinetic) sampling times

Blood samples were drawn at the following times on the specified days:

- Day 1: predose, and 2, 4, 6, 12 hours postdose
- Days 2, 3, 4, 5, 7, 10, 12 predose
- Day 14: predose and 1, 2, 4, 6, 8, 12 hours postdose
- On Days 15 (24 hours), 16 (48 hours), 17 (72 hours), 18 (96 hours), 21 (168 hours), 24 (240 hours), 27 (312 hours), and 28 (336 hours).

Formulation

- Dronedarone 400 mg tablets; Batch numbers: CL-05232 and CL-09176
- Placebo tablets; Batch numbers: CL-04404, CL-08265 and CL-08546

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay was the same as that used in POP5820 and the assay performance was acceptable (data not included in this review).

Pharmacokinetics

The following plasma pharmacokinetic (PK) parameters were determined for dronedarone and SR35021 by non-compartmental analysis: Cmax, tmax, and AUC_{0-12}.

Statistical methods

Pharmacodynamics

- Analysis of primary endpoint:
    - time-matched ratios of plasma creatinine concentrations at Day 1 (single dose) and Day 14 (repeated doses) versus baseline (Day –1) were calculated
    - ratios versus baseline in trough concentrations during treatment and follow-up periods.

These parameters were then analyzed as log-transformed data, using a linear mixed effects model that included terms for subject as random effect, for treatment, stratum, time (or day) and treatment-by-time (or treatment by- day) interactions as fixed effects. Point estimates and 95% confidence intervals (CIs) of differences between treatment means of dronedarone versus placebo were computed and converted to ratios of geometric means.

- Analysis of secondary endpoints:
    - plasma urea, uric acid, ^{1}N-methylnicotinamide, plasma renin activity, aldosterone, cortisol, and angiotensin II, time-matched ratios were calculated, and analyzed for differences
    - ratios of listed endpoints versus baseline in trough concentrations during treatment and follow up.

These parameters were analyzed in the same manner as the primary endpoint.

Pharmacokinetics

Dronedarone and SR35021 plasma concentrations were summarized using descriptive statistics.

Pharmacokinetic/Pharmacodynamic relationship

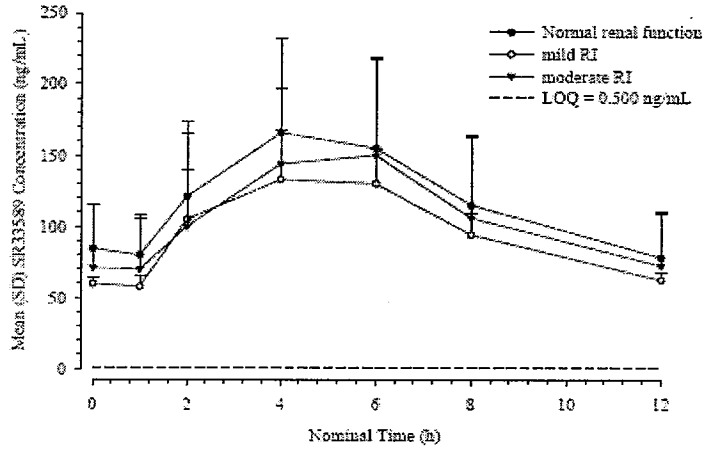
The relationship between dronedarone or SR35021 plasma concentrations and creatinine plasma concentrations was investigated, by day, stratum, and overall.

Results

Dronedarone Pharmacokinetics

The mean dronedarone plasma concentration-time profiles for subjects with normal renal function and impaired renal function are depicted in the figure below.

Figure 6: Mean dronedarone plasma concentration-time profile under fasted and fed conditions



The report did not include a formal statistical comparison of PK measures across the treatment groups; as such a comparison was not one of the stated study objectives. However, by inspection the data (table below) suggest renal impairment will not alter dronedarone PK. This finding is expected as dronedarone is not excreted renally; furthermore, a previous study in NDA 21-913 had demonstrated that the degree of renal impairment did not alter dronedarone PK. It is noted that dronedarone affects tubular secretion, thereby increasing plasma creatinine concentrations.

Table 17: Dronedarone PK measures on Day 14 in subjects with normal, mild, and moderately impaired renal function

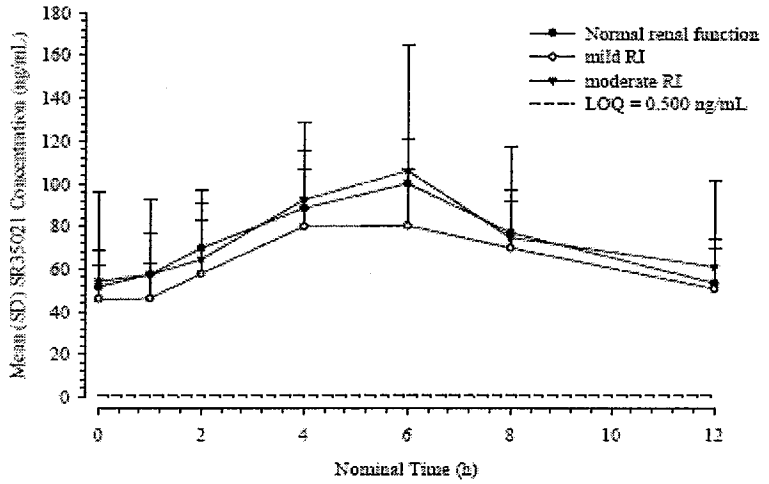
PK Parameter	Normal n=6	Mild n=7	Moderate n=6
C_{max} (ng/mL)	169 ± 64.9 (38) [156]	152 ± 43.8 (29) [146]	151 ± 60.5 (40) [141]
t_{max} (h)	4.00 (4.00 , 6.00)	4.00 (2.00 , 6.00)	4.00 (4.00 , 6.00)
$AUC_{0-\tau}$ (h.ng/mL)	1440 ± 545 (38) [1330]	1160 ± 213 (18) [1140]	1270 ± 583 (46) [1160]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} where values are Median (Min, Max)

SR35021 Pharmacokinetics

The mean SR35021 plasma concentration time profile under fasted and fed conditions is depicted in the following figure.

Figure 7: Mean SR35021 plasma concentration-time profile under fed and fasted conditions



SR35021 PK measures in the study are shown in the table below. As observed with dronedarone, SR35021 PK were not altered by renal function.

Table 18: SR30521 PK measures in renal impairment study

PK Parameter	Normal n=6	Mild n=7	Moderate n=6
C_{max} (ng/mL)	100 ± 20.8 (21) [98.5]	88.5 ± 23.9 (27) [85.6]	103 ± 52.4 (51) [92.8]
t_{max} (h)	6.00 (4.00 , 6.00)	6.00 (4.00 , 8.00)	4.00 (4.00 , 6.00)
AUC_{0-12} (h.ng/mL)	898 ± 243 (27) [873]	786 ± 245 (31) [751]	907 ± 489 (54) [806]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} where values are Median (Min, Max)

Dronedarone Pharmacodynamics (PD)

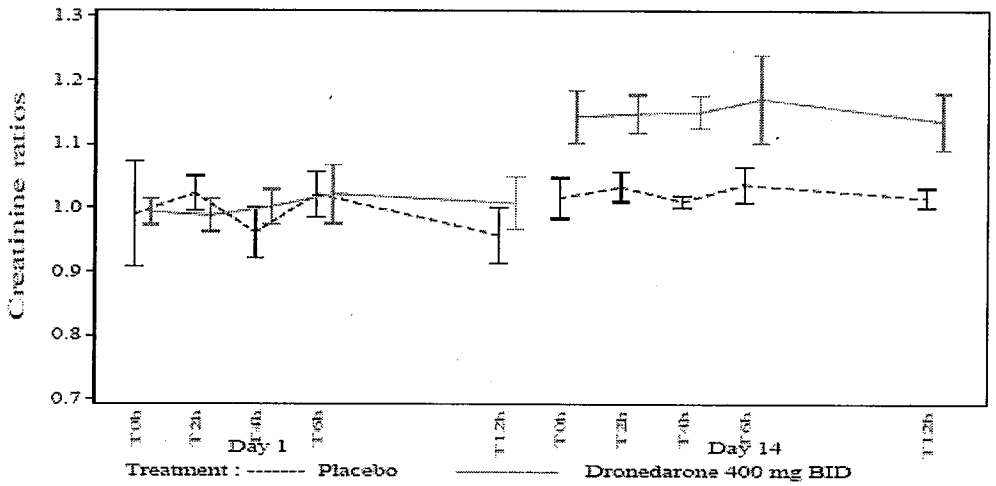
Primary PD Criteria: Plasma creatinine concentrations

The following observations were made based on a comparison of 400 mg BID vs. placebo

- On Day 14: Over the 12 hour period there was an increase in plasma creatinine concentration time-matched ratios versus baseline for dronedarone 400 mg BID ($p < .001$); the ratio of dronedarone versus placebo was 1.117 across strata (stratum effect not significant).
- On Day 1: No statistically significant difference existed
- Day 1 to Day 14: trough plasma creatinine concentration ratios versus baseline for dronedarone 400 mg BID ($p < .001$); the ratio of dronedarone versus placebo was 1.084 across strata (stratum effect not significant).

The listed findings are depicted and highlighted in the following figure.

Figure 8: Time-matched ratios vs. baseline in creatinine concentration on Day 1 and Day 14 (moderate renal impairment)



Secondary criteria:

The report notes that differences were evident between the dronedarone and placebo groups during pretreatment, suggesting that the results related to secondary pharmacodynamic measures should be viewed with caution.

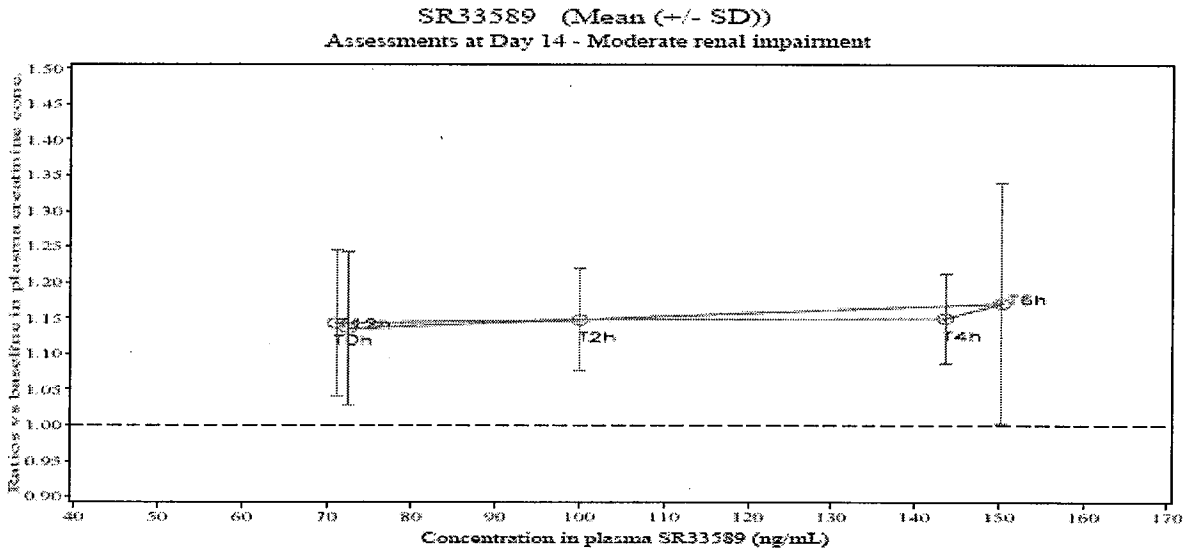
Reviewer Note on Secondary Criteria

Due to the reports stated limitations regarding secondary parameters, this reviewer decided to exclude findings related to the secondary parameters from this review.

Pharmacokinetic/pharmacodynamic (PK/PD) results: Onset/Offset of Primary PD effect
Some key PK/PD findings were as follows:

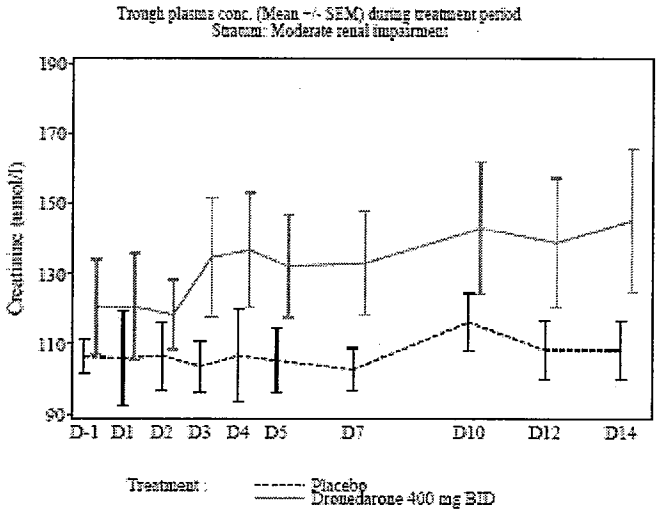
- On Day 14 when PK and PD steady-state had been achieved, the maximal pharmacodynamic effect occurred at 12 hours postdose, later than the tmax of plasma dronedarone and SR35021 concentrations (4 and 6 hours postdose, respectively). In essence this finding suggests that hysteresis occurs: within a dosing interval, the pharmacodynamic effect on plasma creatinine concentrations lagged behind plasma drug concentrations; however, graphically, the hysteresis was negligible as shown in the figure below.

Figure 9: Time-matched ratios in plasma creatinine concentration vs. dronedarone concentration on Day 14 (



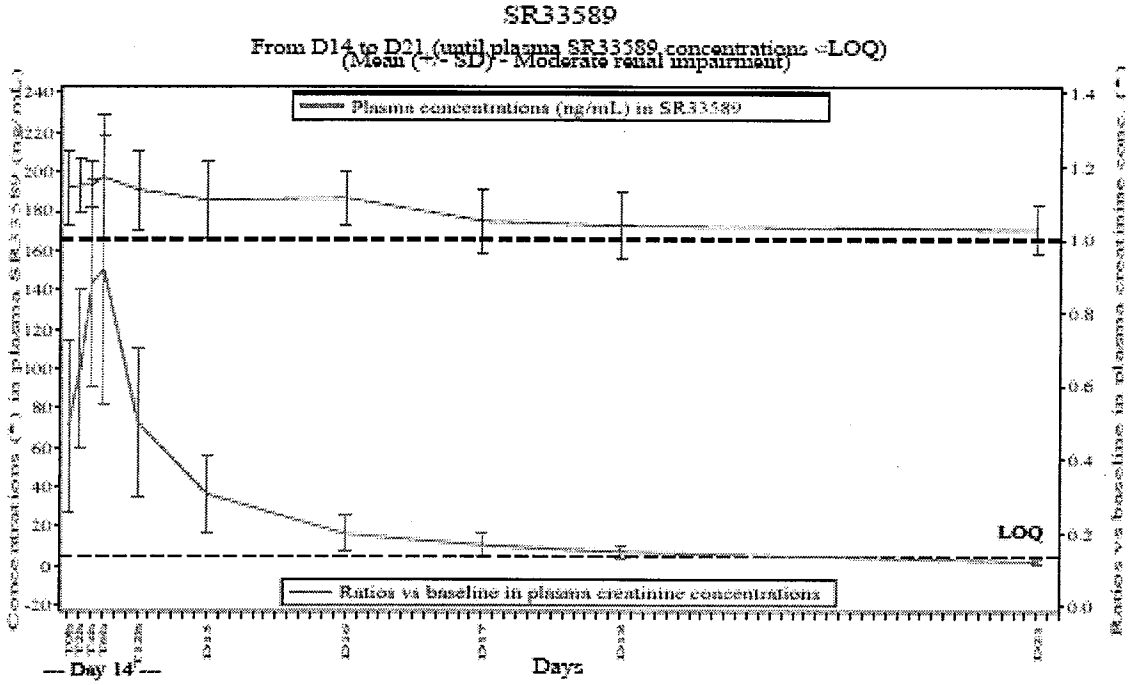
- The maximum pharmacodynamic effect (plasma creatinine concentration) was reached on Day 5.

Figure 10: Trough plasma creatinine concentration during treatment period (moderate renal impairment)



- Plasma creatinine concentrations returned to baseline levels three days after the last study drug intake. (Figure 11). The upper panel (green line) shows change in plasma creatinine concentration as a function of time; lower panel (red line) is plasma concentration-time profile for dronedarone

Figure 11: Trough plasma creatinine concentration and plasma concentrations following last dronedarone dose (moderate renal impairment)



Note: (*) Plasma concentrations at Day 14
Trough plasma concentrations from Day 15 to Day 21
LOQ = 5 ng/mL
Last study drug administration = Day 14 - 8:00 am (TOH)

- On Day 17, remaining concentrations of dronedarone and SR35021 were similar irrespective of the studied population and were lower than trough concentrations (data not shown).

Applicant's Safety Summary

No deaths, SAEs, or TEAEs leading to treatment discontinuation were reported during the study. Overall, TEAEs were reported in 8/21 (38.1%) subjects in the dronedarone 400 mg BID group and in 5/12 (41.7%) subjects in the placebo group. Only a few potentially clinically significant abnormalities (PCSAs) in clinical laboratory parameters and vital signs were recorded in both treatment groups and in all strata.

No subjects had QTc ≥500 ms. Overall, PCSAs of QTc >450 ms were recorded in 6/21 subjects in the dronedarone group,distributed across all strata and associated in 2 cases with a QTc change from baseline >60 ms, versus 2/12 subjects in the placebo group.

Recommendations/Conclusions

- This study confirmed the previous observation of plasma creatinine increase under dronedarone treatment. The effect of dronedarone treatment on plasma creatinine did not appear to be related to kidney function, and stabilized after about 3 to 5 days of treatment. Plasma creatinine returned to baseline about three days after discontinuation of dronedarone.
- Dronedarone and SR35021 exhibit similar pharmacokinetic parameter values in steady-state conditions irrespective of the population studied (normal renal function and subjects with mild and moderate renal impairment). These results are consistent with the very minor urinary excretion of dronedarone and SR35021.

4.2.3 Determination of the Cytochrome P450 (CYP) Isoforms Involved in the Oxidative Metabolism of SR35021 in vitro (MIH0138)

PROTOCOL #	MIV0159
Investigator	Carolyne Lieu
STUDY SITE	Sanofi Aventis, Malvern, Pennsylvania
STUDY PERIOD	October 2004 - February 2005

Objective (per applicant)

To determine the cytochrome P450 (CYP) isoforms involved in the oxidative metabolism of SR35021 and to assess the contribution from relevant CYP isoforms to overall hepatic metabolism using *in vitro* techniques.

Study Design

Standard procedures for in vitro metabolism studies were used. Microsome preparations were prepared from human liver or insect cells transfected with human CYP cDNA, or cryopreserved human hepatocytes. SR35021 was mixed with pooled microsomes. The SR35021 (primary metabolite of dronedarone) concentrations were between 0.2 and 2 µM (100 ng/mL and 1000 ng/mL). Two sets of studies were conducted.

1. Metabolism of SR35021 by individual cDNA expressed isoforms (Supersomes™): Reaction mixtures containing microsomes with a single expressed CYP isoform and SR35021.
2. Inhibition of SR35021 metabolism in human hepatocytes: Suspension cultures containing human hepatocytes, SR35021 and CYP selective inhibitors.

The isoforms investigated were CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. The experiments included appropriate controls to ensure that the enzyme system was viable (e.g. selective CYP substrates, inactive microsomes and system +/- NADPH). SR35021 concentrations were determined by a validated LC/MS-MS method.

Compounds

- SR35021, batch number APS-15-15-1
- CYP enzyme substrates and inhibitors were obtained from commercial sources

Results

All control systems demonstrated that the system was functional (data are not included in this review).

Microsomes

Key findings from the initial study are summarized as follows (see table below):

- NADPH-dependent metabolism of SR35021 was not observed at either 0.2 μM (100 ng/mL) or 2 μM (1000 ng/mL) concentration.
- Inactive microsomes did not deplete SR 35021 to as great a degree as active microsomes

Together these findings suggest that SR35021 metabolism involves microsomes; however, the metabolism is not solely dependent on CYP enzymes that require NADPH for activity.

Table 19: Metabolism of SR35021 in human liver microsomes (Standard Conditions*)

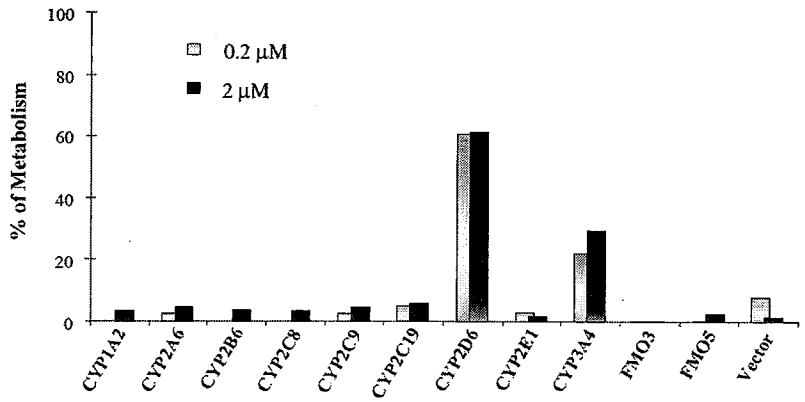
Microsome Preparation	SR35021 Nominal (μM)	SR35021 Observed (μM)		Percent of Control (%)
		Control [a] (-NADPH)	Reaction [a] (+NADPH)	
Active	0.2	0.155	0.148	95.5
	2	1.27	1.27	100
Inactive[b]	0.2	0.201	0.200	99.5
	2	2.31	2.35	102

[a] Mean of duplicate preparations
[b] Microsomes were inactivated by heat
* 0.25 mg/mL protein, 37°C for 30 min

Supersomes

Supersomes™ (Human cDNA Expressed CYP Isoforms) expressing CYP2D6 and CYP3A metabolized SR35021 at both reaction mixture concentrations of 0.2 and 2 μM (figure below). Other CYP enzymes had minimal impact on SR35021 metabolism.

Figure 12: SR35021 metabolism by Supersomes

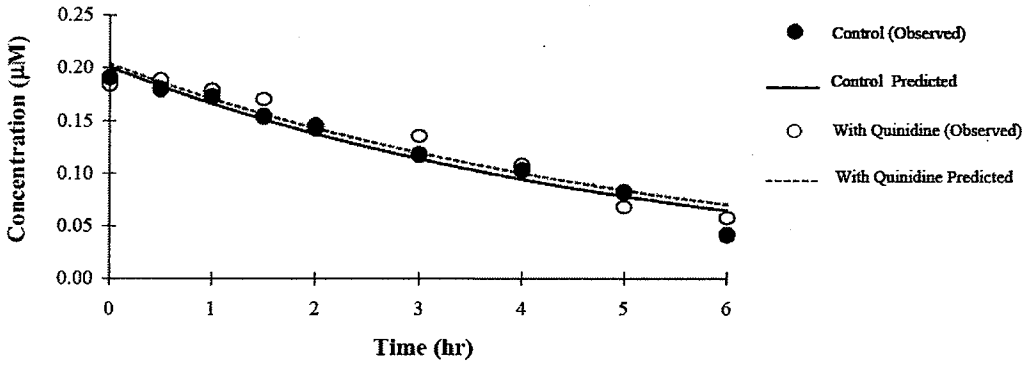


Hepatocytes +/- specific CYP2D6 inhibitor, quinidine

Significant metabolism (data are not included in this review) of 0.2 and 2 μM SR35021 (approximately 80 and 70 %, respectively) was observed in hepatocyte suspensions when

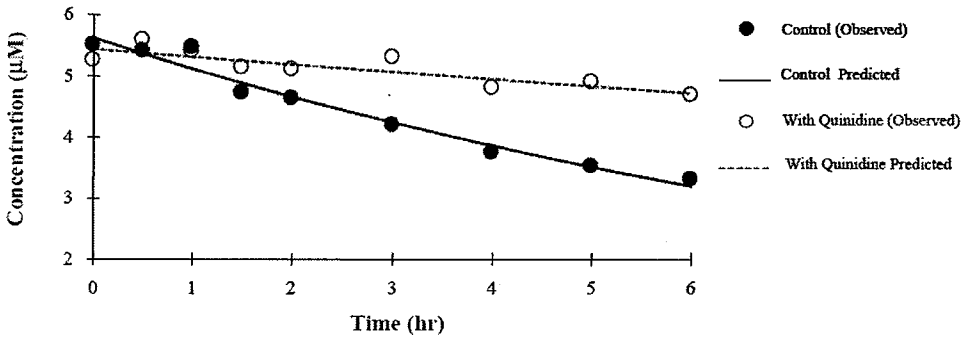
incubated for 6 hr at 37° C. However, quinidine (10 μM), a selective inhibitor of CYP2D6, did not inhibit this metabolism as shown in the following figure. Approximately 6 % of the metabolism could be attributed to CYP2D6

Figure 13: Metabolism of 0.2 μM SR35021 incubated with or without 10 μM quinidine in human hepatocytes



In contrast, bufuralol metabolism, selective for CYP2D6 activity and used as a positive control, showed the hepatocyte cultures were metabolically active and were inhibited by 10 μM quinidine as shown in the figure below.

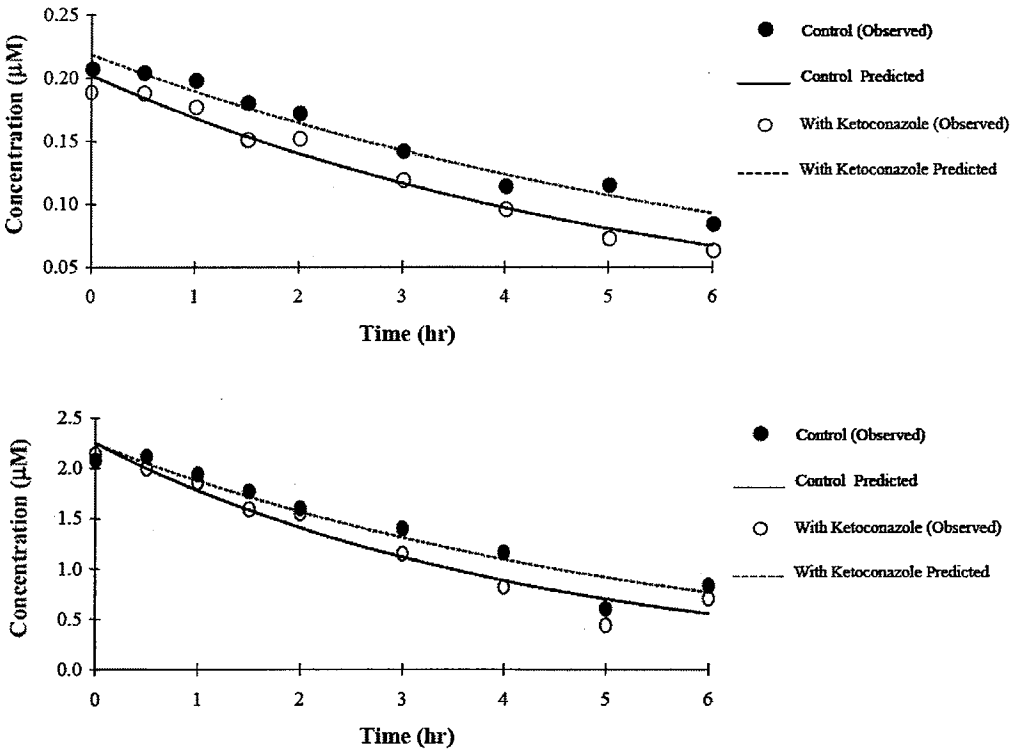
Figure 14: Metabolism of bufuralol incubated with or without 10 μM quinidine in human hepatocytes



Hepatocytes +/- specific CYP3A inhibitor, ketoconazole

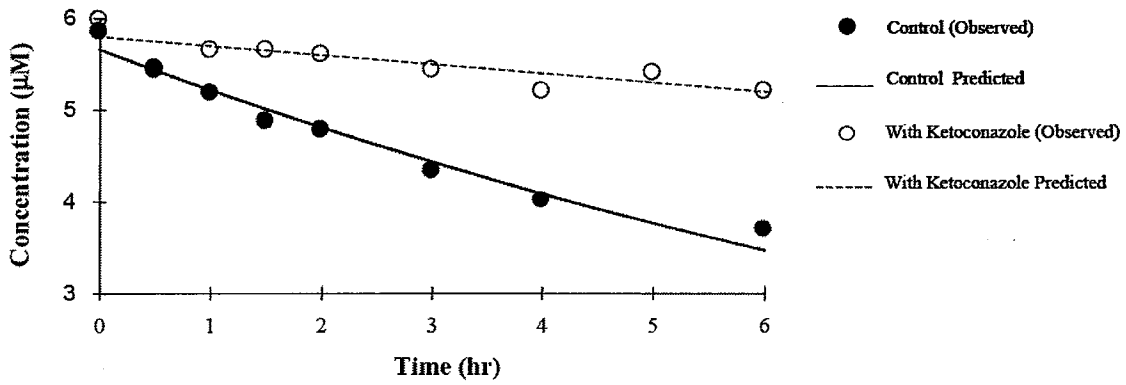
Significant metabolism (data are not shown in this review) of 0.2 and 2 μM SR35021 (~70%) was observed in hepatocyte suspensions when incubated for 6 hr at 37°C. Metabolism of SR35021 in human hepatocyte suspensions containing 1 μM ketoconazole is depicted in the following figure. Based on the inhibition results, the contribution of CYP3A to SR35021 metabolism was approximately 22 %.

Figure 15: Metabolism of SR35021 incubated with or without 1 µM ketoconazole (0.2 µM in upper panel and 2.0 µM in lower panel) in human hepatocytes



Midazolam metabolism, selective for CYP3A activity and used as a positive control, showed the hepatocyte cultures were metabolically active and were inhibited by 1 µM ketoconazole (see following figure)

Figure 16: Metabolism of midazolam incubated with or without 1 µM ketoconazole in human hepatocytes



Recommendations/Conclusions

- NADPH-dependent metabolism of SR35021 was not observed in human liver microsomes, however some NADPH-independent (non-CYP) metabolism was observed.
- CYP2D6 and CYP3A metabolized SR35021 at approximate rates of 6 and 20 % respectively. These results suggest that CYP3A is the major CYP enzyme involved in SR35021 metabolism, but other (non-CYP) enzymes may be involved.

4.2.4 Investigating the Potential for SR33589 and SR35021 (N-debutyl metabolite) to Inhibit Cytochrome P450 2B6 (CYP2B6) Using Human Liver Microsomes in vitro (MIH0441)

Investigator	Steven Ross
STUDY SITE	Sanofi Aventis, Malvern, Pennsylvania
STUDY PERIOD	June – July 2006

Objective (per applicant)

To determine if SR33589 (dronedarone) or SR35021 inhibited the human liver cytochrome P450 (CYP) enzyme CYP2B6 using in vitro methods.

Study Design

Standard procedures for in vitro metabolism studies were used. SR35021 or SR33589 (dronedarone) were mixed with pooled hepatic microsomal fractions (Source: BD Biosciences, Inc.). Microsomes were incubated with the CYP2B6 isoform selective substrate, bupropion, with or without SR33589 or SR35021 or selective inhibitor, for 10 min at 37°C, followed by the addition of an NADPH-generating system in timed sequence and incubated for 15 min. The amount of hydroxybupropion formed was quantified using an LC-MS/MS method for CYP2B6 activity. Appropriate control systems were used to ensure system viability and suitability.

The supplies used in the study are tabulated below.

Table 20: Concentrations of Stock Solutions, Solvents Used In CYB2B6^ Study and Vendors for Chemicals

Isoform	Chemicals	Concentration [a] (mM)	Solvent used [b]	Vendor (location)
CYP2B6	Bupropion	10	MeOH:H_2O (1:1)	Sigma (St. Louis, MO)
	Hydroxybupropion	10	MeOH:H_2O (1:1)	BD Biosciences (Woburn, MA)
	[$^{13}C_6$]-Bupropion	10	MeOH:H_2O (1:1)	IsoSciences (King of Prussia, PA)
	mAb-2B6	10 mg/mL	25 mM Tris	BD Biosciences (Woburn, MA)

[a] Concentrations shown are primary concentrated stock solutions and may not be representative of the working stock concentration: [b] The solvent used to prepare the working stock solution may differ from the solvent used for the preparation of the primary concentrated stock solution.

^ mAb-2B6* is an inhibitor monoclonal antibody

Compounds

- SR33589B, batch number CL-05754
- SR35021A, batch number A-BGD- 040020-P2

Results

As shown in Table 21, SR33589 and SR35021 (200 µM; 111 µg/mL for SR33589, 100 µg/mL for SR35021) inhibited CYP2B6 (defined as ≥30% inhibition relative to control values). Consequently apparent Ki values were determined for inhibition of CYP2B6 in microsome reaction mixtures.

Table 21: Effect of SR33589 and SR35021 on Bupropion Hydroxylation in Human Liver Microsomes

CYP Selective Substrate Assay	Percent of Control Activity		
	SSR33589 (200 µM)	SR35021 (200 µM)	mAb-2B6 (0.025 mg/mL)
CYP2B6 Bupropion hydroxylation	5.65	<1.94[a]	4.64

[a] Below the LLOQ (0.01 µM) of this assay.

Reviewer note on Dronedarone and SR35021 concentrations

The above mentioned concentrations exceed therapeutic concentrations by more than 10-fold thus the findings from the study are not likely to be clinically relevant.

The apparent Ki values for SR33589 and SR35021 inhibition of CYP2B6 in human liver microsome reaction mixtures are tabulated in the following table.

SR Compound	Inhibition Model	Apparent Ki (µM)	I/Ki
SR33589	Mixed	12.0	0.0389
SR35021	Mixed	56.9	0.00633

In the equation, (I) refers to plasma concentrations for SR33589 or SR35021. The highest plasma C_{max} observed in humans at steady state after 400 mg BID dosing across several studies are 0.467 µM for SR33589 (260 ng/mL) and 0.360 µM for SR35021 (180 ng/mL). Based on current FDA guidelines (I/Ki), the inhibition data indicate that SR33589 and SR35021 have a low potential to significantly inhibit the clearance of drugs metabolized by CYP2B6. Inhibition is likely to occur when I/Ki approaches values equal to or greater than 0.1.

CONCLUSION

Neither dronedarone nor SR35021 are likely to inhibit the metabolism of CYP2B6 substrates.

4.2.5 Investigating the potential of SR33589 and SR35021 to inhibit the cytochrome p450 isoform CYP2C8 using pooled human liver microsomes (HLM's) in vitro (MIH0460)

PROTOCOL #	MIV0159
Investigator	Carolyne Lieu
STUDY SITE	Sanofi Aventis, Malvern, Pennsylvania
STUDY PERIOD	October 2004 - February 2005

Objective (per applicant)

To investigate the potential of both SR33589 and its N-debutyl metabolite, SR35021 to inhibit the in vitro enzyme activity of the human hepatic cytochrome P450 isoform, CYP2C8.

Study Design

Standard procedures for in vitro metabolism studies were used. Pooled human liver microsomes (n = 50), obtained from Xenotech, LLC, were co-incubated with the CYP2C8 substrate, paclitaxel, with or without SR33589 or SR35021 or quercetin. Quercetin is a specific CYP2C8 inhibitor. NADPH was added to start the metabolic reaction and incubation allowed to proceed for an additional 15 min. IC50's for SR33589 and SR35021were determined using paclitaxel at a single concentration of 5 μM which approximates its apparent Km value. The concentrations of both SR35021 and SR33589 used in the determination of the IC50 value were 0, 0.01, 0.1, 0.5, 1, 5, 10, 50 and 100 μM. The Ki value for SR35021 was determined using paclitaxel at 1, 2.5, 5, 10 and 25 μM. Each concentration of paclitaxel was incubated with 0.5, 1, 5, 25, 50 and 100 μM SR35021. The amount of the metabolite 6α-hydroxypaclitaxel, which is formed in the CYP2C8 enzyme reaction from paclitaxel, was quantified using a validated LC-MS/MS method. The apparent Ki value for SR35021 inhibition of CYP2C8 was determined by non-linear regression. Appropriate controls were performed concomitantly and included.

Table 22: Concentrations of Stock Solutions, Solvents Used In This Study and Vendors for Chemicals

Chemicals	Stock solution concn (mM) *	Solvent used in assay	Vendor
Paclitaxel	5	MeOH	Sigma-Aldrich
6α-Hydroxypaclitaxel	0.25	MeOH	Cypex
Quercetin	5	DMSO	Sigma-Aldrich

* : Concentrations shown refer to concentrated stock solutions that may not be representative of the working stock solutions.

Compounds

SR33589B and SR35021A, mono-hydrochloride salts, batch numbers: CL-05754 and A-BGD-040020-P2, respectively.

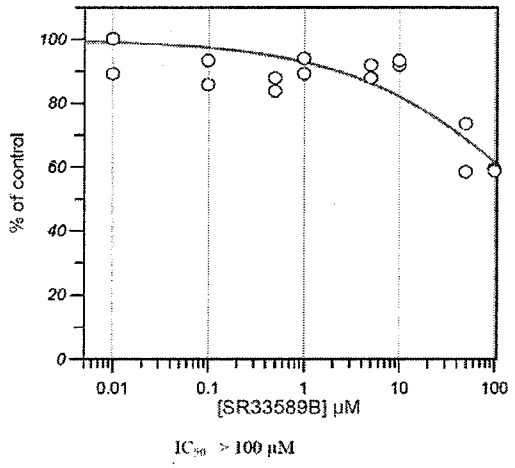
Results

The IC50 values of the specific inhibitor, quercetin were in the range of 2.97 to 5.3 μM in the SR33589 and SR35021 experiments. Thus, the specific inhibitor of CYP2C8, quercetin was effective in reducing the formation of 6α- hydroxypaclitaxel, under the experimental conditions used in this study.

IC50 determination

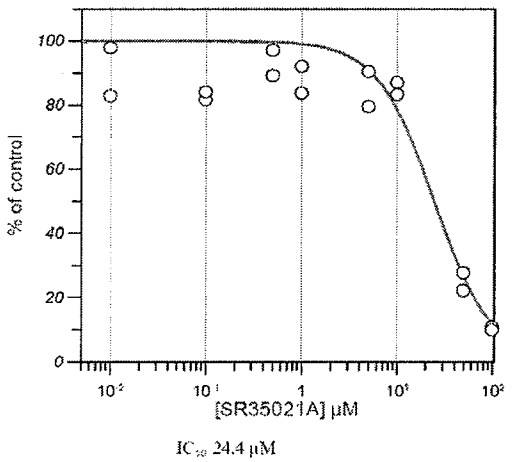
As shown in the figure below, no Ki value was determined for SR33589 as the estimated IC50 value was greater than 100μM (55.5 μg/mL). This exclusion appears reasonable as in vivo dronedarone concentrations are 100 fold lower (< 1 μM) at the proposed dosage.

Figure 17: Plot of % inhibition of control substrate vs. dronedarone concentration



As shown in the following figure, the estimated IC50 value for SR35021 was less than 100 μM. Therefore, the inhibition of CYP2C8 activity was characterized by determining the apparent Ki value.

Figure 18: Plot of % inhibition of control substrate vs. SR35021 concentration



The estimated apparent Ki value for SR35021 was found to be 36.6 μM. Subsequently,

SR35021 was determined to inhibit CYP2C8 activity with an estimated IC50 value of 24.4 μM. According to the report, the inhibition was best described by the non-competitive model. Using the I/Ki model [plasma concentrations of 0.360 μM (180 ng/mL for SR35021)], SR35021 has a low potential to inhibit the metabolism of CYP2C8 substrates. The I/Ki value for SR35021 was ~ 0.0001, demonstrating a low potential to inhibit CYP2C8 metabolism.

CONCLUSION

- Neither SR33589 nor SR35021 have a potential to inhibit the metabolism of CYP2C8 substrates.
- The estimated apparent CYP2C8 Ki value for SR35021 was 36.6 μM and > 100 μM for dronedarone.

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

/s/

Robert Kumi
1/30/2009 03:27:54 PM
BIOPHARMACEUTICS

Elena Mishina
1/30/2009 03:32:59 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-913	Submission Date(s): 06/10/2005
Brand Name (proposed)	Multac
Generic Name	Dronedarone hydrochloride
Reviewer	Robert O. Kumi, Ph.D.
Team Leader	Patrick Marroum, Ph.D.
OCPB Division	1
ORM division	Cardiovascular and Renal Drug Products
Sponsor	Sanofi-Aventis
Relevant IND(s)	49,484
Submission Type; Code	N_000
Formulation; Strength(s)	Tablet, 400 mg
Class/Indication	Anti-arrhythmic/ Rhythm control in patients with atrial fibrillation or atrial flutter, to maintain normal sinus rhythm or to decrease ventricular rate

Briefing Date: 03/27/2005
Briefing Attendees: Raj Madabushi, Joga Gobburu, Phil Colangelo, Mehul Mehta, Christine Garnett, Gail Moreschi, Avi Karkowsky, John Lazor, Hank Malinowski, Nhi Beasley, Peter Hinderling, John Hunt, Norman Stockbridge, Kavita Johal, Albert Chen and Nallani Srikanth

Table of Contents

1 Executive Summary

In NDA 21-913, Multac (dronedarone hydrochloride) is proposed for rhythm control in patients with atrial fibrillation or atrial flutter, to maintain normal sinus rhythm or to decrease ventricular rate. Dronedarone HCl is a benzofuran derivative in the same class as amiodarone, an approved antiarrhythmic agent. Dronedarone is an anti-arrhythmic agent that has electrophysiological properties associated with all four Vaughan-Williams classes. Multac will be marketed as a 400 mg strength tablet. The proposed dronedarone dosage is 400 mg twice daily; each dose should be given with or shortly after the morning and evening meal. According to the applicant, Multac treatment can be initiated in an outpatient setting; additionally, with the proper precautions, Multac can be initiated as soon as amiodarone therapy is stopped or following therapy with Class I and Class III anti-arrhythmic. Numerous clinical and nonclinical studies were conducted to support the Multac NDA including three pivotal trials in the target patient population, over 40 clinical pharmacology (pharmacokinetic studies), and over 10 in vitro studies. The clinical studies were conducted in healthy subjects and various patient groups; dronedarone was administered orally as well as intravenously in these studies.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the information submitted to NDA 21-913. The clinical pharmacology and biopharmaceutics information provided in NDA 21-913 is acceptable. However, the applicant should adequately address the following comments:

Comments to Sponsor

- Please indicate when results from the hepatic impairment study, POP5820, will be submitted to the Agency. Without this information, the product labeling will be restrictive in this patient population
- You have not adequately addressed the issue of dose-response in the target population; therefore dosage adjustment is not feasible during dronedarone therapy.
- You have not provided sufficient permeability information to support dronedarone designation as BCS 2. Please provide all available information that demonstrate dronedarone is a high permeability compound.
- The dissolution methodology is acceptable, however, we do not agree with your dissolution specification. Based on the data provided the following specification is more appropriate: 1) Not less than 25 % and not more than 50 % is dissolved within 30 minutes 2) Q = 80 at 90 minutes
- 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.
- Please refer to the attached, revised label for detailed labeling recomendations

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Over 40 studies were included in the clinical pharmacology and biopharmaceutics development program for the use of dronedarone in patients with atrial fibrillation or atrial flutter; in these studies dronedarone was administered by the oral and intravenous route. Additionally, dronedarone was evaluated in over 10 in vitro studies. Studies included in NDA 21-913 are presented in Appendix 4.1; not all of the submitted studies were reviewed because they were not required for evaluation of the proposed indication.

Key Clinical Pharmacology and Biopharmaceutics Findings and Information

1. Dronedarone Pharmacokinetics (ADME)

Absorption/absolute bioavailability and general pharmacokinetics (PK)

- Dronedarone ***absolute oral bioavailability*** (BA) following administration of a capsule formulation (800 mg) is approximately 15 %, but this value may not be reflective of the absolute oral BA of the to be marketed tablet formulation (proposed 400 mg dose) due to differing food effect (formulation dependent) and dose-dependent pharmacokinetics oral administration
- Administration of ***food*** increases mean dronedarone absorption from approximately 2- (low fat meal) to 5-fold (high fat meal)
- Dronedarone exposure increased in a ***greater than dose proportional manner*** following single and multiple dose administration. For a two-fold increase in dose, the exposure increased by 2.5 to 3.5-fold over the 200 to 1600 dose range
- ***Steady state*** is achieved approximately seven days after repeated administration of 400 mg dronedarone twice daily
- The mean accumulation ratio is ~ 2.6 at the proposed dosage
- Dronedarone exhibits dose- and time-dependent PK
- Dronedarone has limited properties associated with PGP substrate status

Distribution

- Dronedarone is approximately 99 % bound to plasma proteins at therapeutic drug concentrations; the main binding component is albumin
- Following single dose administration of IV dronedarone (40 – 80 mg), the volume of distribution associated with the terminal elimination phase was 2500 – 3400 L

Metabolism and P-glycoprotein

In vitro information

- Dronedarone metabolism was mainly mediated by CYP3A, yielding the major metabolite, SR35021
- Dronedarone has a low inhibitory potential towards major CYPs, including on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The most inhibitory potential was towards CYP3A4 (I/Ki ~ 0.01) and CYP2D6 (I/Ki ~ 0.06)
- Dronedarone exhibited similar PGP inhibitory potential as cyclosporine A by preventing the efflux of two PGP substrates, digoxin and vincristine

In vivo information
Dronedarone is extensively metabolized following dronedarone administration and negligible amounts of intact dronedarone are present in the feces. N-debutylation appears to be the main metabolic pathway of dronedarone, leading to the formation of SR35021; however additional processes occur including oxidation of SR35021, oxidative deamination, and direct oxidation. Ultimately, several metabolites (> 30) are formed and excreted in the urine and feces. SR35021 is not detected following IV administration, suggesting that it is formed mainly presystemically during first pass.

Properties of metabolites
The activities of all the identified metabolites (n > 30) were not tested; however, the major metabolite, SR35021 is 3 to 10 times less potent than dronedarone. SR35021 plasma levels are approximately half that of dronedarone; other individual metabolites account for < 3 % of the administered dronedarone dose. Based on the low exposure of the metabolites, they are unlikely to impact overall activity associated with dronedarone administration, unless they are individually or collectively more potent than dronedarone.

Overall, SR35021 exhibited PK properties (accumulation, half-life, volume of distribution) that were similar to that of dronedarone.

<u>Excretion (Elimination)</u>

- Mass balance indicates that orally administered dronedarone is ultimately excreted in the urine (6 %) and feces (84 %) primarily as metabolites. No unchanged dronedarone was excreted in the urine. Similar findings were obtained following IV administration. Radioactivity was undetectable after two weeks.
- The systemic plasma clearance (IV administration) ranged from 130 to 150 L/h and the apparent oral clearance (CL/F) was ~ 500 L/h for the 400 mg dose.
- Dronedarone half-life following IV administration was between 13 and 19 hours; following oral administration half-life appeared to be dose- and time- dependent ranging from 27 to 32 hours.

2. Pharmacodynamic effects of dronedarone

- Alters electrophysiological measures: generally increases QT-, PR- and RR- and QRS- intervals and decreases T-wave amplitude
- Decreases heart rate (bradycardic effect)
- Tends to decrease blood pressure (systolic and diastolic)
- Causes an increase in serum creatinine levels by inhibiting renal tubular secretion of creatinine; which leads to apparent decrease in renal function (CLcr decreased). However, this effect is reversible upon discontinuation of dronedarone therapy.

3. QT/QTc Information

A clear dose-response relationship was shown for QT prolongation in healthy subjects.

4. Special Populations

- ***Renal Insufficiency:*** The effect of impaired renal function was not evaluated in the dronedarone program

- ***Hepatic insufficiency:*** The effect of impaired hepatic function has not been evaluated, but there is an ongoing study to evaluate this patient population.
- ***Gender:*** Relative to elderly males, elderly females have exposures that are approximately 30 % higher.
- ***Age:*** Relative to healthy young males, healthy elderly males have exposures that are about 40 % higher
- ***Race:*** Relative to healthy male Caucasians, healthy Asian (Japanese) males have exposures that are about 100 % higher

5. Formulation

Dronedarone hydrochloride has been formulated into 400 mg tablets; the to-be-marketed tablets are similar to those used in the pivotal safety/effectiveness trials. It is to be noted that the placebo formulation is identical to the drug formulation, except for the active ingredient.

6. PK/PD drug-drug interaction information

Drug	Classification	Effect of co-administration		
		PD (either or both drugs)	Dronedarone	Other Drug
	Miscellaneous			
digoxin	PGP substrate	NA	NA	↑ 2.5 fold
pantoprazole	decrease gastric pH	NA	↔	NA
theophylline	CYP1A2 substrate	NA	↔	↓ 20 %
	CYP3A function			
rifampicin	inducer	None	↓ 80 %	NA
dilitiazem	weak inhibitor	↑ repolarization time	↑ 60 %	NA
nifedipine	weak inhibitor	Lowered blood pressure	↑ 20 %	NA
grapefruit juice	moderate inhibitor	NA	↑ 3-fold	NA
ketoconazole	strong inhibitor	↑ PR, no effect on QT	↑ ≥ 9-fold	NA
verapamil	Substrate, inhibitor	↑ repolarization time	↑ 40 %	↑ 40 %
nisoldipine	substrate	↔	↔	↑ 100 %
simvastatin	substrate	↔	↔	↑ 4-fold
ethinylestradiol	substrate	NA	NA	↑ 25 %
levonorgestrel	substrate	NA	NA	↑ 18 %
	CYP2C9 function			
losartan	substrate	↑ heart rate	↔	↔
S-warfarin/R-warfarin	substrate	↑ INR by 7 %	↔	↑ AUC 11 %
	CYP2D6 function			
metoprolol	Substrate	↓ cardiac contractility	NA	↑ 60 -150 %
propranolol	substrate	↓ HR, DBP, SBP	↔	↑ 16 to 33 %

7. Dissolution

The Agency's recommended dissolution specification differs from that of the applicant.

Applicant's Proposal

1. Dissolution Method: apparatus- paddle at 75 rpm; medium: 1000 ml of phosphate buffer, at pH 4.5 and 37^{O} C
2. Dissolution Specification: 1) Not less than 20 % and not more than 60 % dissolved after 30 min 2) Q = 75 after 90 min

Reviewer's Recommendation

1. Dissolution Method: applicant's proposal is acceptable
2. Dissolution specification: 1) Not less than 25 % and not more than 50 % is dissolved within 30 minutes 2) Q = 80 at 90 minutes

Signatures

Reviewer: _____

Pharmacometrics Reviewer _____

Team Leader Concurrence _____

2 Question Based Review

2.1 What are the general attributes of dronedarone?

2.1.1 Regulatory Background

Several meetings were held between the Agency and the applicant to discuss the dronedarone development program (IND 49,484). Two major highlights of clinical pharmacology impact were:

- Meetings held on July 13, 2004 and January 3, 2005: Sponsor was asked to study effect of dronedarone in patients with congestive heart failure (CHF)
- End of Phase 2 meeting held on April 9, 2001: Sponsor was asked to study different doses of dronedarone in mortality trial and AF/AFL population to evaluate exposure-response relationships for dosage adjustments

2.1.2 Highlights of chemistry and physical-chemical properties of the drug substance and product

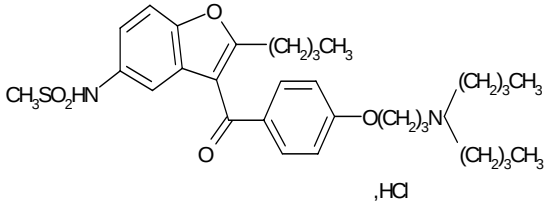
Dronedarone HCl is a benzofuran derivative that is formulated into 400 mg tablets for oral administration. Additional characteristics of dronedarone are as follows:

Chemical name N-{2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl]benzofuran-5-yl}methanesulfonamide, hydrochloride

Molecular weight 593.2

Molecular formula $C_{31}H_{44}N_2O_5$ S. HCl

Structural formula



Appearance white fine powder

Solubility practically insoluble in water and freely soluble in methylene chloride and methanol.

Formulation 400 mg tablet (expressed as base)

Proposed Name Multac contains 400 mg of dronedarone (free base)

Miscellaneous analogue of amiodarone, an approved anti-arrhythmic agent; dronedarone is anticipated to have fewer safety concerns (e.g. thyroid, ophthalmologic and pulmonary) than amiodarone

Miscellaneous Formulation Information

Several formulations (tablets and capsules) were developed; the final formulation was one that minimized food effects, yet provided adequate exposure. Dronedarone was administered mainly as a tablet formulation, but dronedarone was also give as an intravenous oral solution in several studies. The final tablet formulation is referenced as 2E5. The composition of the to-be-marketed formulation is presented in Table 1. It

should be noted that he placebo formulation is identical to the drug formulation, except for the active ingredient.

Table 1: Composition of dronedarone HCl 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

2.1.3 Proposed Mechanism of Action and Indication

The reported primary mechanisms of action of dronedarone are related to anti-arrhythmic activity with effects from all four classes of the Vaughan Williams' classification (VWC). Per VWC dronedarone is a multi-channel blocker inhibiting the potassium currents (including $I_{K(Ach)}$, I_{Kur}, I_{Kr}, I_{Ks}) and thus prolonging cardiac action potential and refractory periods (Class III), the sodium currents (Class Ib), the calcium currents (Class IV) and it non-competitively antagonizes adrenergic activities (Class II).

2.1.4 Proposed Administration Route and Dosage

Dronedarone hydrochloride (Multac®) is intended for oral administration via 400 mg tablets. The recommended dosage is 400 mg twice daily (800 mg daily). Per the applicant, treatment with Multac can be initiated in an outpatient setting. Multac should be taken as one tablet with or shortly after the morning meal and one tablet with or shortly after the evening meal. If the patient is switched to Multac from Class I or Class III anti-arrhythmic therapy the following paradigm should be adopted:

Treatment with Multac can be initiated as soon as amiodarone therapy is stopped. An ECG should be performed in these patients about four hours after drug administration. It is recommended that all other Class I and III anti-arrhythmic be withdrawn for at least five plasma half-lives before starting treatment with Multac.

2.2 What are the general clinical pharmacology characteristics of dronedarone?

2.2.1 Design features of clinical studies used to support dosing in AF/AFL patients

The key design features of the clinical pharmacology and clinical studies used to support dosing in the target population (AF/AFL) are summarized in Table 2.

Table 2: Key design features of the primarily clinical and clinical pharmacology studies supporting proposed indication

	Non-placebo controlled Trials in Healthy Male Subjects (Phase I)		Placebo Controlled Trials in Patients with AF/AFL			
			Phase II	Phase III		
Study	TDR2395	TDR3549	DRI3550/ DAFNE	ERATO EFC4508	EURIDIS EFC3153	ADONIS EFC4788
Descriptor/ Objective	Tolerability following single and multiple oral doses	Tolerability following BID repeated ascending oral doses	maintenance of sinus rhythm after cardioversion of AF- dose-ranging study	control of ventricular rate during AF	maintenance of normal sinus rhythm after conversion of AF/AFL in two "regions" (Europe for EURIDIS and (American Australian- African for ADONIS)	
Doses (mg)	400 to 1000 BID and 800 to 1600 QD	800 to 1600 BID	400, 600 and 800 BID	400 BID	400 BID	
Measures/ Endpoints	ECG parameters Vital Signs PK intensive sampling	MTD, ECG parameters Vital Signs PK intensive sampling	ECG measures Vital Signs PK trough and maximum levels only (defined by time window)	ECG measures Vital Signs PK (sparse sampling for Population PK)		
Indication	NA	NA	Supportive for sinus rhythm maintenance Supportive for ventricular rate control	Confirmatory for ventricular rate control	Confirmatory for sinus rhythm maintenance Supportive for ventricular rate control	

2.2.2 Clinical response (efficacy) endpoints

There were two primary clinical response endpoints in this application depending on the indication:

1. Time in days between randomization and the first AF/AFL recurrence, defined as an episode lasting 10 minutes or more, as indicated by two consecutive 12-lead ECGs or TTEM tracings recorded 10 minutes apart, and both showing AF/AFL confirmed by the ECG Corelab.
2. Change in mean ventricular rate (hr) measured by 24-hour Holter recording at rest on day 14 (steady state) compared to baseline.

2.2.3 Identification and measurement of dronedarone concentrations in plasma

Dronedarone appeared to be adequately identified and measured in most studies; similarly, dronedarone's main metabolite, SR35021 (active compound) was adequately measured and identified. Dronedarone and SR35021 were measured by an array of

validated assays. These assays employed LC/MS/MS and HPLC methodologies. Please refer to Analytical Section (2.6) for additional assay information.

2.2.4 Dronedarone Exposure-Response

The exposure-response evaluation revealed that:

- There was no clear dose-response relationship for effectiveness in the target patient population
- A trend towards a linear dose-response (ECG measures and heart rate) was observed in healthy subjects
- A dose-response relationship existed for safety (incidence and severity of diarrhea and decrease in CLcr).

Three studies provide the main exposure-response information: TDR2395 and TDR3549 (healthy subjects) and DRI3550 or DAFNE (AF/AFL patients). The study designs of these three trials were presented previously.

The Pharmacometrics Reviewer, Dr. Garnett conducted and in-depth review of the DAFNE trial to assess exposure-response with respect to efficacy and safety. Three main questions were addressed by the PM reviewer; each question is addressed in turn:

- Is there a concentration-response relationship for the effectiveness endpoints 1) time to AF recurrence and 2) ventricular rate?
- Is there a concentration-response (safety) relationship for treatment-emergent diarrhea?
- Does elevated serum creatinine return to baseline after dronedarone treatment is discontinued (safety-related)?

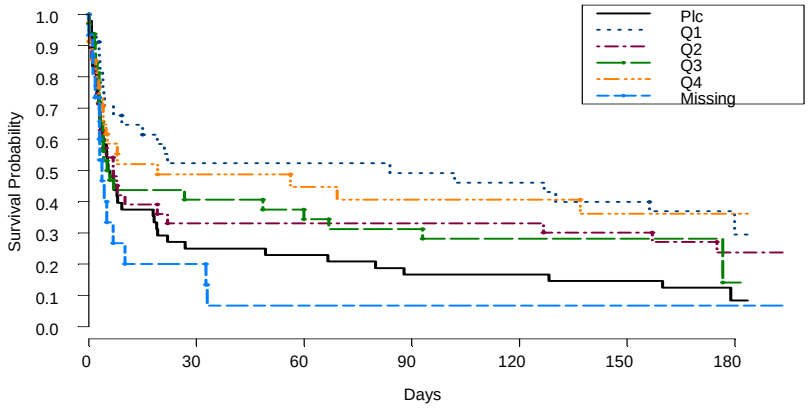
Reviewer Note

The PM Review did not conduct an exposure-response analysis for the data from the pivotal trials because only one dose was studied (400 mg).

2.2.4.1 *Exposure- Effectiveness Assessment*

Figure 1 depicts the Kaplan Meier survival curves for time to AF recurrence (days) by concentration quartile.

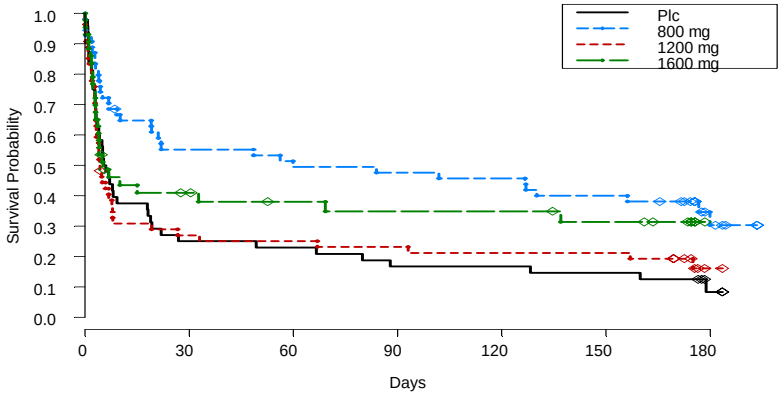
Figure 1: Kaplan-Meier Survival Curves by Concentration (ng/mL) Quartile (Q1 = 13.3-49.5, Q2 = >9.5-72.4, Q3 = >2.4-113.5, and Q4 = >113.5-559)



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. It should be noted that 14 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.

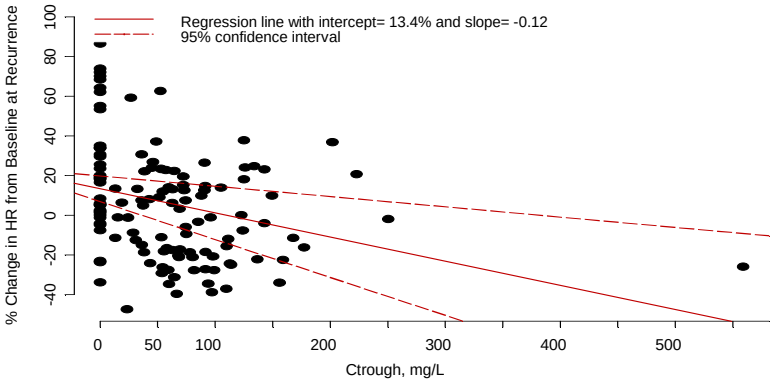
There was no clear dose response as depicted in Figure 2.

Figure 2: Kaplan-Meier Plot for Time to First Recurrence of AF from Conversion [reviewer's figure from independent analysis of data]



The change in heart rate from baseline vs. trough concentration is shown in Figure 3. For this plot, baseline was defined as the ventricular rate (measured by ECG) during the initial AF episode prior to dronedarone treatment.

Figure 3: Ventricular Rate Control vs. Trough Concentration



There was a trend for lower heart rate at AF recurrence with higher trough concentrations. It should be noted that subjects with missing trough concentrations were excluded from the analysis.

2.2.4.2 ***Exposure-Safety Assessment***

- **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 3). However, diarrhea does not appear to be related to plasma concentrations of dronedarone.

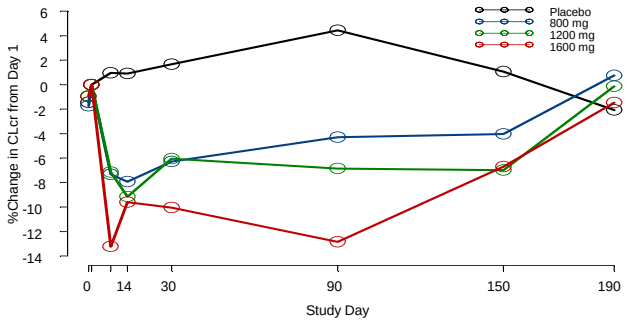
Table 3: Overview of Diarrhea Treatment emergent adverse events

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)

- **Dose-Response and other information related to changes in serum creatinine due to dronedarone administration (PM and Primary Reviewers)**

Treatment with dronedarone caused an elevation of serum creatinine that was reflected in an apparent decrease in creatinine clearance (CLcr). Figure 4 shows that CLcr is reduced throughout the study (Days 1-150) but returns to baseline after treatment is discontinued: CLcr returns to baseline at Day 190 which corresponds to the last patient visit at 10 days after stopping drug.

Figure 4: Mean percent change in CLcr by Study Visit (PM Review)



The impact of short term dronedarone administration on measures of renal function is summarized in Table 4 (PDY5487). In Study PDY5487 dronedarone 400 mg BID was given for seven days. The effect of dronedarone on CLcr was similar in the short term (PDY5487) and long term study (DAFNE): initial decline upon dronedarone administration followed by return to baseline after drug discontinuation (within 14 days).

Table 4: Impact of dronedarone administration on PD measures of renal function

Component	Estimates	Dronedarone vs. placebo	Comment
Renal Sinistrin	GFR	↔	No effect
CLcr	Renal function	↓	
CLcr/CL sinistrin	Renal tubular secretion of creatinine	↓	interferes
PAH	Renal Blood flow (RBF) and tubular organic anion transporter (OAT)	↔	No effect on RBF
NMN renal clearance	Tubular organic cation transporter (OCT)	↓	May impact organic cations eliminated renally
24-hr creatinine clearance	Overall renal function	↔	Findings are inconclusive due to study design
Electrolytes (UFR, Na, K ions)	Excretion and osmolality	↔	No effect on physiological processes

Evaluation of the PD findings (Table 4) suggests that dronedarone decreases apparent renal function (measured by CLcr) by interfering with tubular secretion of creatinine. However, this interference does not appear to significantly alter overall renal function as evidenced by the minimal impact on GFR, renal blood flow and other measures of renal function. Some investigators indicate that an apparent decrease in CLcr alone, does not necessarily signify a worsening of renal function. In light of the findings from study PDY5487, DAFNE and the observations reported by other investigators, it is reasonable to conclude that dronedarone's impact on renal function may not be clinically significant. However, the decrease in the function of OCT suggests that dronedarone may affect the elimination of organic cation that are renally excreted; thus, there is a potential for drug-drug interactions to occur between dronedarone and such compounds.

Primary Reviewer's Note on Potential Study Limitations Related to Trough Estimations and impact on exposure-response analyses

Trough concentrations were defined in a time window (0 to 2 hours post dose and 8 to 18 hours) and may not accurately reflect true trough concentrations. The lack of definitive trough times, typically taken at predose, may contribute to the variability and failure to observe a concentration-response relationship. Additionally, the poor power of the study, due to a limited number of subjects may have impacted the exposure-response analyses; for instance, subjects in the 800 mg BID had a much higher rate of discontinuation due to adverse events than other groups.

Per the PM review, analyses of the patient demographics indicated that all baseline characteristics were similar across treatment groups, apart from the duration of AF episodes (p=0.0133) Additionally, with respect to concomitant medications, more subjects in the placebo and 800 mg dose group were taking beta-blockers. There were similar percentages of patients taking anticoagulant therapy, digoxin, and calcium channel blockers. It is unclear if these differences in baseline characteristics, particularly concomitant medications, may have affected the dose-response relationship. With respect to concomitant medications, it should be noted that in the drug-drug interaction studies, unexpected or idiosyncratic PD effects were observed on occasion. For example in the diltiazem-dronedarone interaction study (INT4084), there was no clear dose response: the

400 mg dronedarone dose produced the greatest PR prolongation, followed by the 800 mg and finally 1200 mg dose. For QT prolongation, there was a dose-response relationship, but data were highly variable. The same study showed a decrease in QT for all dronedarone doses co-administered with nifedipine. These idiosyncratic effects may be due to a combination of synergistic, additive and or antagonistic interactions; ultimately leading to an apparent lack of dose-response.

2.2.4.3 *QT and QTc interval and other electrophysiological measures*

Consistent with it's an anti-arrhythmic property, dronedarone, altered electrophysiological measures, such as QT-, QTc-, PR- and QRS-intervals and T-wave amplitude. A formal QT study was not conducted, however, results from several studies showed consistent trends or statistically significant findings, suggesting that dronedarone prolonged cardiac repolarization. On occasion, dronedarone's effect on EP parameters appeared dependent on concomitant medications.

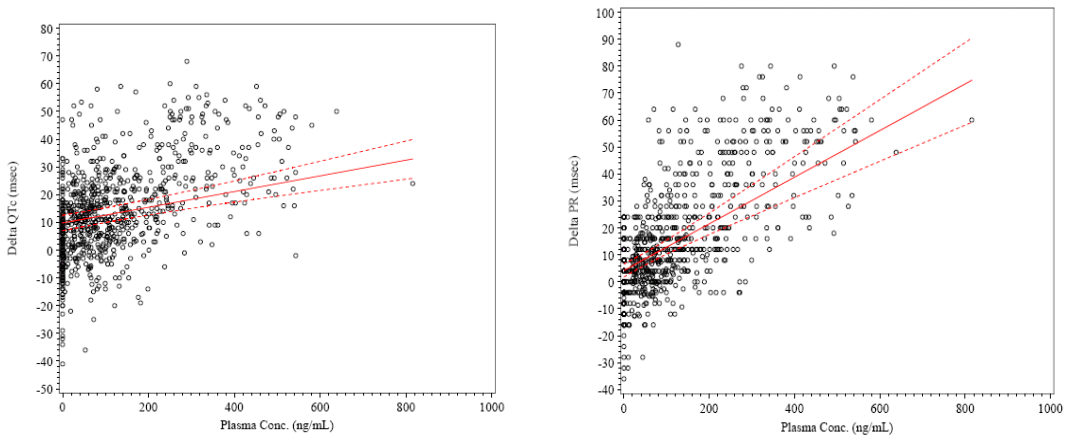
Exposure-Response Evaluation in Healthy Volunteers

In the healthy volunteer dose-response studies, TDR3549 and TDR2395, two salient trends were observed:

- Dronedarone significantly prolonged QT-, QTc- and PR- intervals in a dose-dependent manner (linear or showed trend) over the 800 – 1600 mg QD and 400 to 1600 mg BID dose range
- There was a trend showing that BID dosing had a greater effect than QD dosing on the EP parameters

The applicant summarized the findings on exposure-response (ECG parameters) graphically in Figure 5 using data from TDR2395, TDR3549 and INT4882 (verapamil drug interaction study).

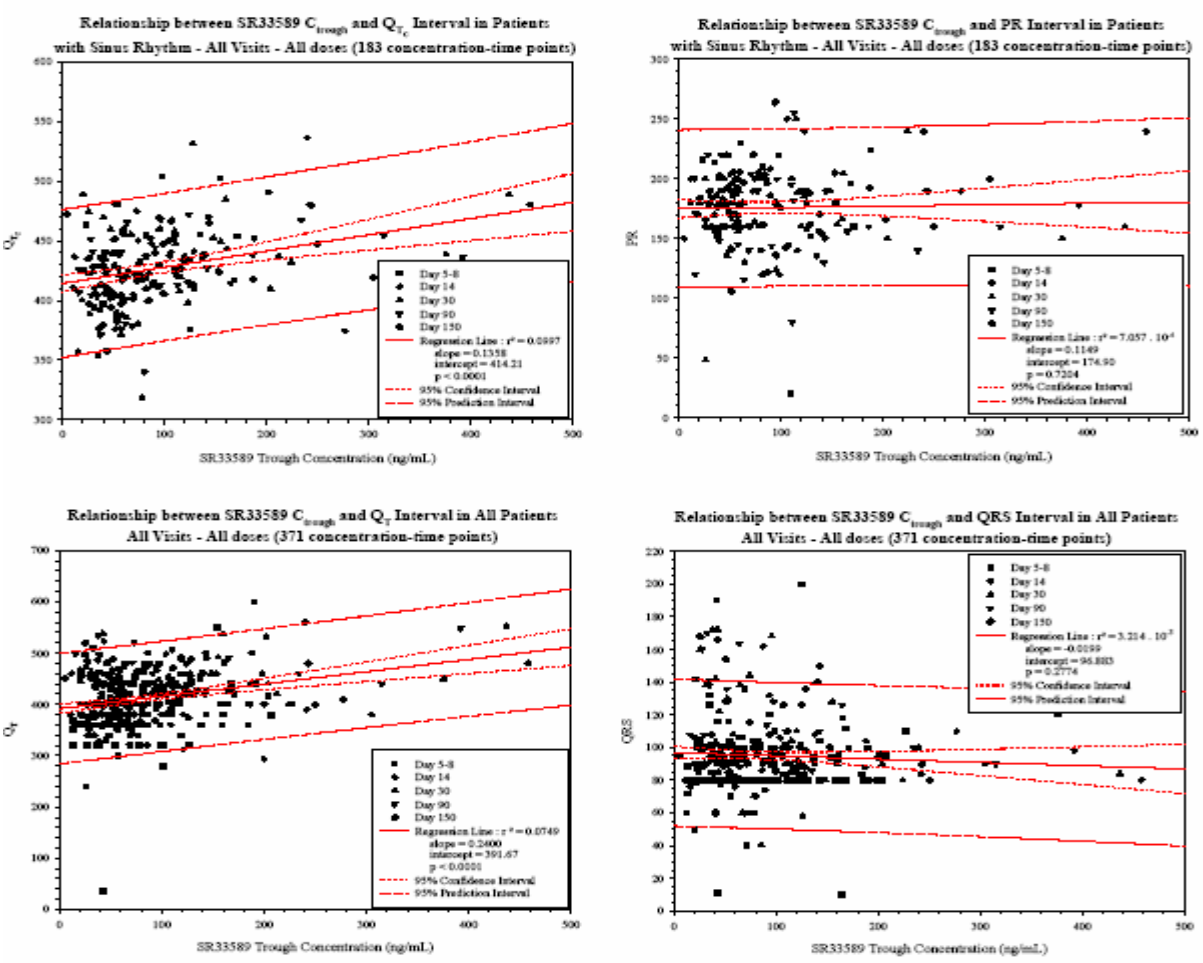
Figure 5: QTc (left panel) and PR (right panel) changes from baseline (ms) versus dronedarone plasma concentrations (ng/mL) with estimated mean linear model and two-sided 95% confidence limits - Pooled data from TDR2395, TDR3549 and INT4882



Exposure-Response Evaluation in Patients

The applicant summarized the exposure-response relationship in the DAFNE trial in Figure 6. There was a trend towards increasing QT and QTc with increasing concentration.

Figure 6: Individual dronedarone Ctrough Levels (ng/mL) as a Function of ECG Parameters



2.2.4.4 Heart Rate and other Vital signs

In the healthy volunteer dose-response studies, TDR3549 and TDR2395, the following two observations were made:

- Dronedarone decreased heart rate during exercise testing in a dose-dependent manner (Figure 7). At rest, the bradycardic effect was not as clear.
- There was no clearly dose-related effect in the BP changes; some active dose groups caused decreases in DBP or SBP but others had no effect Figure 8).

Figure 7: Change in Daily Heart Rate as a function of dronedarone dosage during exercise test

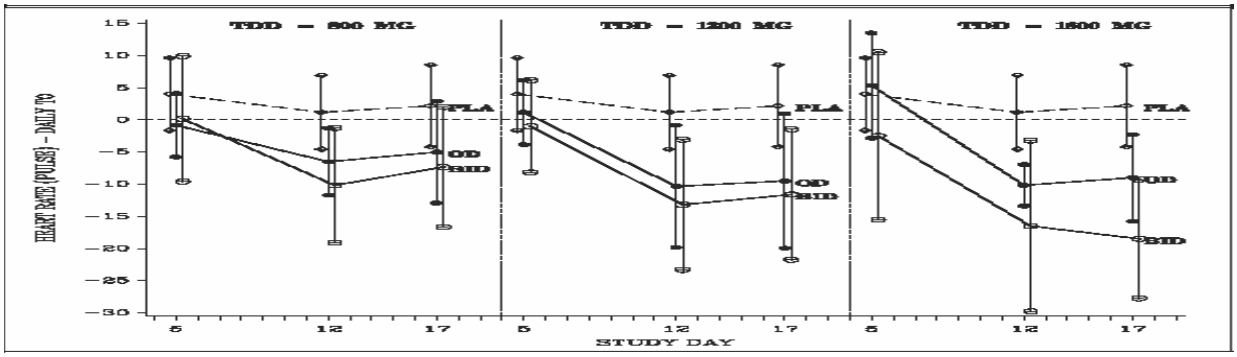
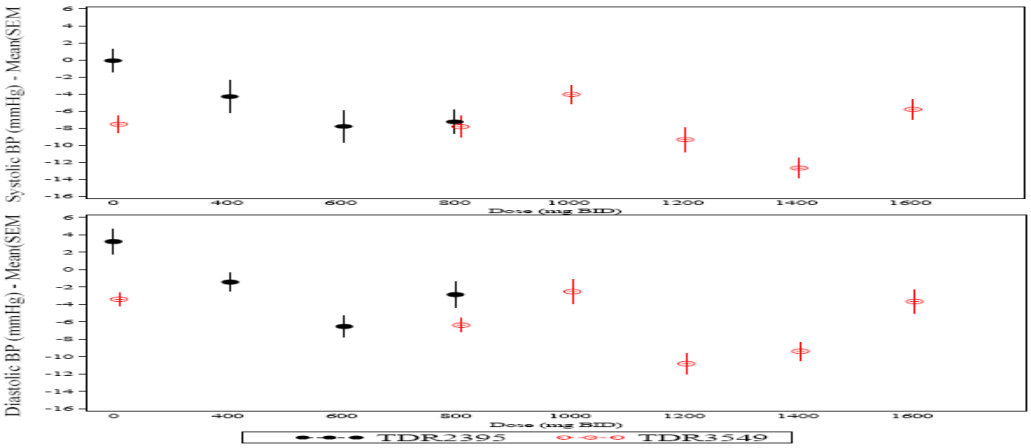


Figure 8: Mean (SEM) changes from baseline in SBP and DBP (mmHg) at 4 hours postdose over the last 5 days of treatment in studies TDR2395 and TDR3549 (per applicant)



Reviewer Note on Sections 2.2.4.3 and 2.2.4.4

Overall, dronedarone induced ECG changes consistent with the electrophysiological properties of the compound, in particular a dose-related anti-adrenergic effect (class II), a prolongation of the PR-interval (class II and/or class IV) but a moderate QT-prolongation (class III). Relative to higher dronedarone doses (>= 800 mg BID) slight changes in PD measures were observed at 400 mg BID.

2.2.4.5 ***Acceptability of applicant's proposed dosage regimen***

The proposed dosage, 400 mg BID, appears adequate based on the known relationship between dose-concentration-response; however, the dose-response relationship has not been adequately defined in patients. It is unclear if the selected dose is optimized with respect to safety and effectiveness because only one dose was studied in the pivotal trials (see Medical Review), and the DAFNE trial did not show a dose-response relationship.

The major unresolved issue is the inadequate characterization of the dronedarone dose-response relationship, specifically there is a:

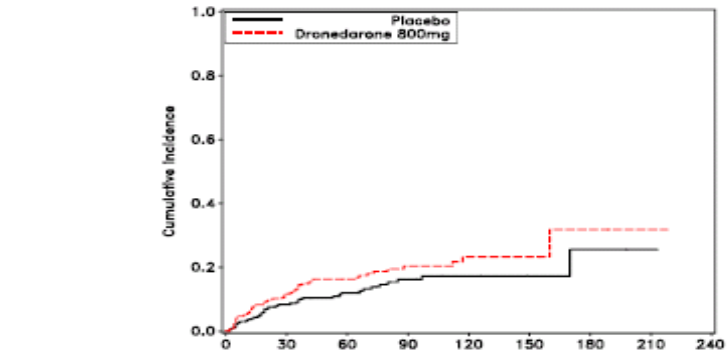
- Lack of response (particularly effectiveness) information at doses < 400 mg
- Minimal response (effectiveness and safety) information at doses > 400 mg
- Lack of dose-ranging information in patients with more advanced heart disease, such as patients with congestive heart failure (CHF), who are likely to use dronedarone
- Lack of dose titration (if needed) information for dronedarone, which is further limited by the availability of only one dosage strength.

Overall the lack of comprehensive dose-response information should limit dronedarone usage to situations were dronedarone exposure is comparable to that obtained at the 400 mg dose, only. In particular, the clinical risk-benefit profile is unknown in the following two situations:

- Concomitant medications that alter dronedarone exposure significantly
- Patient groups that may not respond favorably to a 400 mg dose

In ANDROMEDA, subjects on dronedarone treatment had a greater number of deaths or worsening heart failure than patients on placebo (Figure 9 and Table 5).

Figure 9: Kaplan-Meier cumulative incidence curves for the primary endpoint (death or hospitalization for worsening heart failure)



Nb Exposed at risk								
Placebo	317	234	159	87	41	16	6	1
Dronedarone 800mg	310	232	151	87	49	19	4	1

Table 5: Primary analysis (death or hospitalization for worsening heart failure up to 16 January 2003) of ANDROMEDA trial

	Placebo (N=317)	Dronedarone 800 mg (N=310)
Number of patients who died or were hospitalized for worsening heart failure	40	53
Relative risk[a]	1.38	
95% CI[a]	[0.918 ; 2.088]	
Log-rank's test result (p-value)	0.118	

a: Determined from Cox regression model

The issue of altered dronedarone exposure due to concomitant medications was addressed to some degree in the drug interaction studies and in the pivotal clinical trial that indicated co administration did not lead to significant adverse effects.

2.2.5 Pharmacokinetic characteristics of dronedarone and its major metabolites

Dronedarone pharmacokinetics were determined following oral and IV administration in healthy subjects and in patients with various forms of cardiac disease. The most relevant PK information was obtained from studies LIN2890, POP2769, BEX2770 and PPK2397.

2.2.5.1 *Dronedarone pharmacokinetic measures*

Dronedarone and SR35021 PK measures following single (Day 1) and multiple dose (Day 14) administration are presented in Table 6.

Table 6: Dronedarone and SR35021 PK Measures in Healthy Males Following Single and Multiple Dose Administration (200, 400 and 800 mg BID)

PK Parameters		Dronedarone			SR35021		
		200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]	200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]
C_{max} (ng/mL)	Day 1	23.1 (38)	67.2 (36)	162 (40)	20.8 (21)	49.5 (25)	109 (29)
	Day 14	40.3 (30)	111 (17)	298 (13)	41.2 (27)	107 (22)	282 (21)
t_{max} [a] (h)	Day 1	3 [2; 5]	3 [2; 5]	3 [2; 6]	5 [2; 5]	5 [3; 6]	5 [3; 6]
	Day 14	5 [2; 5]	5 [3; 6]	5 [2; 6]	5 [2; 6]	5 [3; 8]	5 [3; 4 8]
AUC_{0-12} (ng.h/mL)	Day 1	111 (24)	310 (28)	846 (27)	123 (19)	275 (23)	668 (24)
	Day 14	276 (23)	798 (19)	2510 (12)	325 (21)	882 (17)	2680 (20)
$t_{1/2z}$ (h)	Day 1	9.81 (33)	17.6 (56)	19.6 (33)	16.2 (28)	19.2 (24)	21.9 (22)
	Day 14	26.9 (32)	30.0 (29)	31.2 (32)	23.5 (14)	21.1 (16)	20.4 (8)
AUC (ng.h/mL)	Day 1	160 (27)	474 (33)	1310 (26)	237 (23)	545 (22)	1360 (20)
CL/F [d] (L/h)	Day 1	1350 (29)	937 (35)	669 (38)	-	-	-
	Day 14	765 (25)	517 (18)	324 (13)	-	-	-
Vz/F [d] (L)	Day 1	18000 (24)	21000 (31)	17900 (33)	-	-	-
	Day 14	29400 (34)	22800 (41)	14500 (31)	-	-	-

Numbers rounded at 3 significant figures.
[a] median value [Min–Max]
[b] n = 14 at Day 14
[c] n = 16 at Day 14
[d] CL_{0-12}/F and Vz_{0-12}/F at Day 14

2.2.5.2 ***Pharmacokinetic Comparisons: Normal Volunteers vs. Patients***

Overall the PK in patients with AF/AFL appeared comparable to that in healthy subjects; this was shown in the Cmax and Ctrough estimations from ANDROMEDA (Table 7), where intensive sampling was carried out, as well as in the population PK analyses (Table 8).

Table 7: Steady State Dronedarone following 400 mg BID dosing

PK Measure	ANDROMEDA		LIN2890
	400 mg Dose [intensive sampling (n = 11)]	400 mg [all samples (n = 125]	400 mg Dose (n = 16)
AUC (ng·h/mL)	886 (55%)	NR	798 (19)
Cmax (ng/mL)	113 (59)	101 (54)	111 (17)
Ctrough (ng/mL)	NR	64.7 (66)	40 - 50

Table 8: Table (2.7.2.3.4) 1 - Mean (CV%) dronedarone and SR35021 plasma concentrations in patients (DRI3550/DAFNE*, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4966/ANDROMEDA, and EFC4508/ERATO)

	DRI3550			EFC3153	EFC4788	EFC4966	EFC4508
	400 mg BID	600 mg BID	800 mg BID	400 mg BID	400 mg BID	400 mg BID	400 mg BID
Dronedarone							
$C_{trough,av}$ (ng/mL)	42.7-58.0 [a]	81.2-109 [a]	124-176 [a]	65.7 (56)	60.0 (58)	64.7 (66)	56.4 (56)
$C_{max,av}$ (ng/mL)	-	-	-	106 (50)	97.9 (64)	101 (54)	92.0 (107)
SR35021							
$C_{trough,av}$ (ng/mL)	32.6-40.0 [a]	55.7-67.8 [a]	77.2-91.3 [a]	40.0 (44)	38.3 (46)	35.8 (62)	38.2 (33)
$C_{max,av}$ (ng/mL)	-	-	-	59.2 (45)	52.8 (51)	60.6 (50)	50.0 (56)

[a]: range of mean C_{trough} or C_{max} at steady state across visits

2.2.5.3 ***Characteristics of drug absorption***

Based on the Tmax and absolute bioavailability information, overall dronedarone was moderately to poorly absorbed. Peak concentrations were reached between three and six

hours post dose. Food also increased dronedarone exposure by approximately 2- to 5-fold but had a minimal impact on Tmax.

Absolute Bioavailability (Study PPK2397)

The absolute BA study was conducted in healthy subjects who received a dronedarone capsule formulation and IV dronedarone in both fasted and fed states. Results from the fasted state are not reliable due to the small number of subjects and difficulties with assay; the absolute BA in the fasted state was ~ 4 %. The absolute BA in the fed state is ~ 15 % (Table 9); the use of data from the fed state is acceptable because PK data are less variable and dronedarone is recommended to be taken with food.

Table 9: Dronedarone PK Measures following 60 mg dronedarone IV infusion and 800 mg dronedarone oral (fed and fasted) to determine absolute bioavailability

Parameter (units)	Intravenous Fasted	Oral Fasted	Oral Fed	90% CI (Oral Fed / Oral Fasted)	p-value
C_{max} (mg/l)	0.189 (0.034)	0.020 (0.012)	0.120 (0.043)	442 - 900	0.0001
t_{max} (h)	0.67 (0.12)	2.7 (1.3)	4.3 (1.1)	NPT	0.001
AUC_{0-t} (mg/l*h)	0.288 (0.051)	0.108 (0.097)	0.644 (0.282)	481-1169	0.0001
AUC (mg/l*h)	0.350 (0.054)	0.219 (0.209)†	0.721 (0.327)‡	----------	----------
$t_{½}$ (h)	7.5 (3.4)	9.3 (9.5)†	8.9 (6.1)	NPT	0.31
$Vd\lambda_z$ (l)	1837 (713)	----------	----------	----------	----------
Cl_t (l/h)	176 (34)	----------	----------	----------	----------
F (%)	----------	4 (4)†	15 (6)‡	----------	----------

†n=6, ‡n=11

NPT - non-parametric test

However there are two main limitations with the absolute bioavailability information with respect to its applicability to the to-be-marketed (TBM) formulation:

- Study conducted at 800 mg dose level and dronedarone exhibits non-linear PK
- Study conduced with capsule formulation that has different food effect than TBM tablet

Consequently, the utility of the absolute BA findings is unclear and the quantitative absolute BA information obtained with the capsule at the 800 mg dose should not be extrapolated to the TBM tablets that will be administered at 400 mg.

Food Effect

The plasma concentration-time profiles in (Figure 10) and data in Table 11 demonstrate that food increases dronedarone exposure (bioavailability or BA) relative to the fasted state:

1. Food (low fat meal and high fat meal) increases dronedarone BA on average by approximately 2- to 5-fold at the 800 mg dronedarone dose level.
2. The high fat meal had only a slightly greater effect on (~ 40 % increase) than the low fat meal, suggesting that dronedarone may be administered with low or high fat meals.
3. Food did not significantly prolong drug absorption; the median Tmax was 5 hr under fasted and fed conditions.

It is noted that two subjects had far greater food effects than the other subjects. The reason for this finding is unclear; without these two subjects the difference in food effect

between the high fat meal and low fat meal may not have reached statistical significance and the food effect data would be less variable.

Figure 10: Mean dronedarone plasma concentration-time profile under fasted and fed conditions

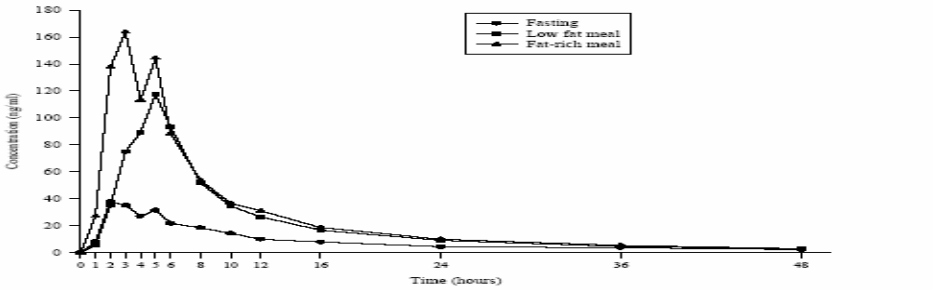


Table 10: Dronedarone PK measures in healthy males following single dose administration under fasted and fed conditions

Parameters (units)	Statistics	Administration		
		Fasted	Low fat meal	Fat-rich meal
C_{max} (ng/ml)	Mean	42.92	128.29	192.40
	Median	40.00	120.80	173.40
	SD	21.50	50.26	90.88
	CV%	50	39	47
t_{max} (h)	Mean	3.67	4.67	3.89
	Median	5.00	5.00	5.00
	SD	1.58	1.00	1.36
	CV%	43	21	35
AUC_{last} (ng.h/ml)	Mean	416.35	975.61	1274.37
	Median	416.00	964.59	1179.63
	SD	106.59	252.08	329.89
	CV%	26	26	26

n = 9

Table 11: Dronedarone geometric mean ratios and associated 90 % confidence intervals* under fed and fasted conditions

Parameters (units)	Low fat meal / fasted	Fat-rich meal / fasted	Fat-rich meal / low fat meal
C_{max} (ng/ml)	3.15 [2.28 - 4.36]	4.59 [3.32 - 6.35]	1.46 [1.05 - 2.01]
AUC_{last} (ng.h/ml)	2.34 [1.99 - 2.75]	3.06 [2.60 - 3.61]	1.31 [1.11 - 1.54]

n = 9

Role of PGP

Relative to vincristine or digoxin, which are model PGP efflux pump substrates (relative permeability > 25); dronedarone (relative permeability 2.5) has limited efflux potential. This finding suggests that dronedarone exposure is unlikely to be affected by coadministration with a PGP inhibitor or inducer via a PGP-based mechanism.

2.2.5.4 Distribution of dronedarone

Following IV administration of dronedarone (40 to 80 mg single dose) the volume of distribution (Vz) associated with the terminal phase was approximately 2500 to 3500 L).

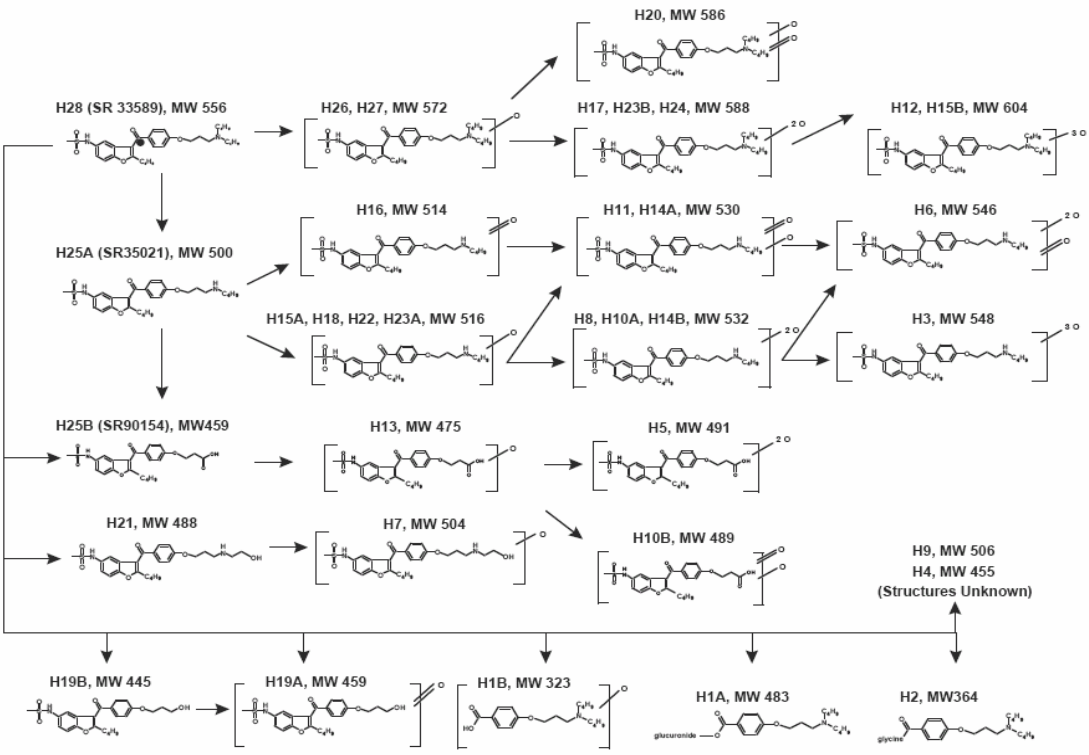
Dronedarone was greater than 99 % bound to plasma proteins and binding was not concentration-dependent over a dronedarone concentration range of 25 to 50000 ng/mL. HSA is the major binding protein, with approximately three times more drug bound to HSA than AAG. These two proteins appear to account for the majority of the plasma protein binding of dronedarone (LPH0006).

SR35021 was also highly bound to plasma proteins: binding was greater than 98 % and not concentration-dependent over the SR35021 concentration range of 25 to 50000 ng/mL. HSA is the major binding protein, with approximately six times more drug bound to HSA than AAG. These two proteins appear to account for the majority of the plasma protein binding of SR35021 (LPH0021).

2.2.5.5 ***Mass Balance Information***

Overall, the mass balance results suggest that the primary route of drug elimination is hepatic via metabolism; the metabolized drug is subsequently removed from the body primarily via feces.

Figure 11: Metabolic pathways of dronedarone via mass balance



(• Denotes the site of the radiolabel)

Healthy adult volunteers received two oral dronedarone doses (0.1 and 0.48 μg/kg) of radiolabeled dronedarone. Total recovery of radioactivity was 90 %: approximately 6% was excreted in the urine and 84% was excreted in the feces. Dronedarone was extensively metabolized; only low amounts of dronedarone were detected in feces and dronedarone was non-existent in urine. Over 30 metabolites were observed. The metabolites formed in feces, urine and plasma were similar. In general, individual metabolites accounted for < 5 % of the radioactive dose, only the metabolite H13 had an amount > 18 % in both urine and feces. In plasma the most abundant metabolites were SR35021 and SR90154 (appeared together as unresolved peak).

Three major pathways of dronedarone metabolism were identified (Figure 11):
1) N-debutylation, followed by oxidation (CYP3A pathway)
2) N- dealkylation to form the propanoic acid metabolite, followed by oxidation
3) Direct oxidation of dronedarone
Additionally, mono- and multiple-hydroxylated metabolites were observed, along with metabolites containing a ketone moiety.

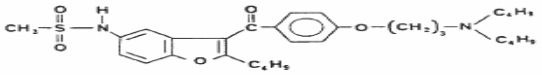
2.2.5.6 ***Metabolism***

In vitro system
In vitro studies with microsomes and human hepatocyte system (MIV0158 and MIV0159) indicated that dronedarone is primarily metabolized by CYP3A to an N-dealkylated moiety, SR35021; this metabolite and dronedarone can undergo further metabolism. These studies also demonstrated that dronedarone is neither a CYP2D6 nor CYP1A2 substrate. However, these studies did not determine if dronedarone is metabolized by other potential CYP pathways such as, CYP2C8, CYP2C9, CYP2C19, CYP2A6 or CYP2E1. The applicant will be asked to reevaluate dronedarone metabolism using current techniques to provide comprehensive labeling information. The metabolism studies included in the NDA were conducted before 1993.

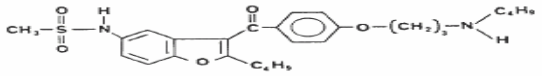
Dronedarone forms several metabolites when incubated with a human hepatocyte or microsome system (Figure 12) The metabolites formed *in vitro* are also formed *in vivo* as demonstrated in the previously described mass balance study.

Figure 12: Dronedarone metabolites identified by HPLC during in vitro studies

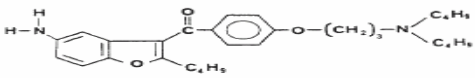
SR 33589



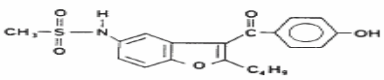
SR 35021



SR 33580



SR 34871



In Vivo Systems
In vivo, SR35021 is the major metabolite, with plasma exposure approximately half that of dronedarone following administration of dronedarone. Generally, SR25021 is formed to a minimal extent following IV administration, suggesting that it is formed primarily during first pass metabolism, rather than in the systemic circulation. Additionally, SR35021 metabolism appears to be formation rate limited. According to the applicant, SR35021 has approximately 1/3rd to 1/10th the anti-arrhythmic activity of dronedarone. Based on the relative activity and exposure, SR35021 is unlikely to contribute significantly to dronedarone activity. The other dronedarone metabolites (minor) have

exposure that is less than 5 % that of dronedarone, therefore their impact on dronedarone overall activity is likely to be negligible unless each individual metabolite or the metabolites collectively possess activity that is comparable to or surpasses that of dronedarone.

Metabolic Ratio

The metabolic ratio, SR35021/Dronedarone for AUC and Cmax on Days 1 and 14 are presented in Table 12.

Table 12: Mean (CV %) metabolic ratio of Cmax and AUC (Study LIN2890)

Dose		200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]
R_{met} C_{max}	Day 1	0.996 (34)	0.795 (32)	0.724 (31)
	Day 14	1.08 (28)	0.973 (20)	0.944 (15)
R_{met} AUC[a]	Day 1	1.55 (25)	1.22 (26)	1.08 (19)
	Day 14	1.22 (24)	1.12 (17)	1.07 (17)

[a] AUC on Day 1 and AUC_{0-12} on Day 14
[b] n = 14 at Day 14
[c] n = 16 at Day 14

Based on Day 1 AUC and Cmax data, more metabolite was formed at lower doses than at higher doses, suggesting saturation in metabolism may occur (non-linear PK). On Day 14, numerically the same trend was observed, but differences in metabolite formation were not as great as on Day 1.

2.2.5.7 ***Excretion and Elimination***

As reported previously in the mass balance findings, following oral administration of dronedarone ~ 84 % of the total radioactivity was found in feces and ~ 6 % in urine. Limited amounts of dronedarone were found in the feces, with no dronedarone in the urine. The recovery was maximal within approximately 180 hours for oral administration.

Following single IV administration, the terminal elimination half-life was between 13 and 18 hours; for oral administration, the elimination half-life appeared both time- and dose-dependent. At the proposed oral dose of 400 mg BID, the half-life after single dose administration was ~ 18 hours and the half-life for multiple dose administration was ~ 30 hours. Overall, dronedarone concentrations appeared to decline in a biphasic manner after achieving Cmax (oral and IV routes).

2.2.5.8 ***Degree of Linearity/Nonlinearity in dose-concentration relationship***

Based on a dose-proportionality assessment and evaluation of dronedarone's PK profile across doses), dronedarone exhibits a slightly non-linear dose-concentration relationship (Table 13) and dose-dependent PK.

Table 13: Dose-proportionality Estimations Following Single and Multiple Dose Administration of Dronedarone 200, 400 and 800 mg Doses

Ratio estimates for dose proportionality at Days 1 and 14

PK Parameters		Ratio Estimate	90% CI
Dronedarone			
C_{max} (ng/mL)	Day 1	2.62	[2.39 – 2.88]
	Day 14	2.77	[2.62 – 2.93]
AUC[a] (ng.h/mL)	Day 1	2.86	[2.67 – 3.06]
	Day 14	3.06	[2.92 – 3.20]
SR35021			
C_{max} (ng/mL)	Day 1	2.24	[2.10 – 2.38]
	Day 14	2.59	[2.46 – 2.73]
AUC[a] (ng.h/mL)	Day 1	2.37	[2.27 – 2.48]
	Day 14	2.82	[2.71 – 2.93]

a: AUC_{0-12} at Day 14.

There was a slightly greater than proportional increase in plasma exposure on Day 1 and Day 14 with increasing dose (pooled data from three dronedarone doses):

- Day 1: 2-fold increase in dose resulted in > 2.6 increase in dronedarone exposure
- Day 14: 2-fold increase in dose resulted in > 2.6 increase in dronedarone exposure

SR350121 exhibited a similar dose-concentration relationship as dronedarone.

CL/F on Day 1 for 400 mg dose was approximately 30 % higher than that of the 800 mg dose; a similar trend was observed on Day 14 for these two doses. The source(s) of the dose dependency is unclear, but is likely due to competing metabolic processes. However saturable elimination does not appear to be a predominant source of non-linearity because apparent terminal half-life was comparable for all dronedarone regimens (~ 30 hours on Day 14). It is noted that for IV administration dose-dependent (PK) were not observed following single doses.

2.2.5.9 *Time Dependency of dronedarone PK*

Dronedarone PK appeared to be time-dependent as shown in Table 6. Considering the proposed therapeutic dose, 400 mg BID, dronedarone CL/F on Day 1 was ~ 40 % higher than that on Day 14. This finding suggests that dronedarone exhibits non-linear PK following oral administration. The source of the non-linearity is not known.

Steady-state dronedarone and SR35021 concentrations were generally reached within seven days; this finding was observed consistently across several studies. Single dose PK were not predictive of multiple dose PK; this was probably due to the observed non-linear PK.

The accumulation ratio (based on linear scale AUCs) for the 400 mg BID dronedarone regimen is ~ 2.6 .

Dronedarone exhibited diurnal variation in plasma concentrations (based on Cmax values): daytime concentrations were about 15 to 30 % greater than night-time concentrations over the 800 to 1600 mg BID dose range (Table 14). No diurnal variation information was available for the proposed dosage regimen.

Table 14: Dronedarone PK measures following administration of dronedarone at different doses (Study TDR3549)

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

2.2.5.10 ***Inter and intra-subject variability in dronedarone PK***

There was moderate to high inter-subject variability in dronedarone PK (Table 14) following oral administration as evidenced by the CV (%). The potential sources of variability can be ascribed to the different metabolizing capacity of individuals, varying rates of absorption and limited drug solubility.

2.3 What Intrinsic Factors Affect Dronedarone Exposure-Response?

Dronedarone exposure appeared to be affected by the following intrinsic factors: age, gender, race and body weight. The findings related to age and gender were primarily from Study POP2769 and the finding on race was obtained from Study TDU4899. The weight finding is primarily based on population pharmacokinetic analyses using data from the pivotal clinical trials. It is noted that the population PK analyses also offer supportive evidence on age and gender effects. The applicant has proposed labeling on gender and age only. The potential effects of some intrinsic factors on dronedarone exposure-response follow.

Renal Insufficiency

The effect of impaired renal function was not assessed in this application. Renal impairment is unlikely to modify dronedarone PK; this conclusion is based on the mass balance study results that indicate dronedarone is not excreted in the urine and only 6 % of the total dose is excreted in urine (metabolites only). No dosage adjustment should be required for patients with impaired renal function.

Hepatic Insufficiency

The effect of impaired hepatic function has not been assessed in this NDA; however, the applicant indicates that there is an ongoing study, POP5820, to address this issue. According to the Medical Reviewer, subjects with impaired hepatic function were excluded from the pivotal trials, therefore there are no data for these subjects.

Reviewer Comment on Hepatic Insufficiency

The findings from the hepatic insufficiency study are critical as dronedarone is primarily metabolized hepatically. Most likely a dosage adjustment will be required for subjects

with impaired hepatic function, as dronedarone is extensively eliminated by the liver. The applicant has indicated (proposed labeling) that dronedarone should be used with caution in patients with moderate and severe hepatic impairment. Per the Hepatic Impairment guidance, drugs should be contraindicated in subjects with severe hepatic impairment, if PK information is not available in this group and the drug is hepatically cleared. Thus, the labeling should be modified to reflect the recommendation in the Guidance. Also, extreme caution should be applied in subjects with any form of hepatic insufficiency, since the exposure-response curve is unknown for exposures exceeding that achieved by 400 mg dronedarone.

Age (Geriatric Patients vs. Young Adults)

Relative to healthy young males, elderly males and females tended to have AUCs and Cmaxs that were approximately 30 to 50 % higher (Table 15, Table 16, and Table 17); however, data were highly variable (POP2769). These differences persisted even after correcting for body weight. The reason for the age differences is unclear as dronedarone is not extensively renally cleared. Typically drugs that are renally cleared show age effects due to the natural decline in renal function as one ages. It is unclear if the clearance differences are due to differential enzyme activity in young vs. old subjects. The population PK analyses indicated that elderly subjects had lower clearance than younger subjects.

Overall the magnitude of change in exposure does not appear large enough to require a dose adjustment based on age.

Table 15: Dronedarone PK measures in healthy males and elderly adults and females following single and multiple dose administration (800 mg QD)

Parameter	Statistic	Young Male		Elderly Male		Elderly Female	
		Day 1	Day 17	Day 1	Day 17	Day 1	Day 17
C_{max} (ng/ml)	Mean	76	130	89	168	142	241
	SD	29	37	27	55	38	62
	CV%	38%	28%	30%	33%	27%	26%
t_{max} (h)	Mean	3.00	4.67	4.67	3.83	4.75	4.83
	SD	1.28	1.15	2.06	1.19	1.42	0.83
	CV%	43%	25%	44%	31%	30%	17%
AUC_{0-24h} (ng.h/ml)	Mean	511	1139	679	1520	1035	2393
	SD	171	318	228	508	303	702
	CV%	33%	28%	34%	33%	29%	29%
R_{ac}	Mean	N/A	2.35	N/A	2.31	N/A	2.35
	SD		0.66		0.72		0.46
	CV%		28%		31%		19%
C_{min} (ng/ml)	Mean	N/A	14.6	N/A	23.2	N/A	39
	SD		6.4		10.4		12.3
	CV%		44%		45%		32%
AUC_{last} (ng.h/ml)	Mean	609	N/A	874	N/A	1335	N/A
	SD	200		308		350	
	CV%	33%		35%		26%	
AUC (ng.h/ml)	Mean	628	N/A	936	N/A	1473	N/A
	SD	205		323		383	
	CV%	33%		35%		26%	
$t_{½}$ (h)	Mean	17.9	24.1	24.3	38.1	28.8	44.6
	SD	4.2	7.2	5.4	10.1	9.8	13.9
	CV%	23%	30%	22%	26%	34%	31%

N/A: Not applicable

Gender

Elderly females tended to have ~ 23 % higher exposure than elderly male subjects after correcting for body weight differences (Table 15, Table 16, Table 17). However, data

were highly variable as evidenced by the wide confidence intervals associated with the point estimates. From this study it is unclear if the gender effect will exist for young subjects because young female subjects were not included in this study. Data from patients (Population PK analyses) suggest that female subjects have a lower clearance than male subjects.

Overall the magnitude of change in exposure does not appear large enough to require a dose adjustment based on gender.

Table 16: Comparison of Cmax and Cmin between elderly subjects and young male subjects

Parameter	Elderly Male vs. Young Male			Elderly Female vs. Elderly Male		
	Ratio	95 % CI	90 % CI	Ratio	95 % CI	90 % CI
C_{max}	1.23	[0.99 , 1.52]	[1.02 , 1.47]	1.54	[1.24 , 1.92]	[1.29 , 1.85]
C_{max} N	1.26	[0.98 , 1.63]	[1.02 , 1.56]	1.23	[0.95 , 1.58]	[0.99 , 1.51]
C_{min} (RD)	1.61	[1.13 , 2.28]	[1.20 , 2.15]	1.75	[1.23 , 2.47]	[1.31 , 2.33]

N: Normalized to 70 kg body weight
RD: Repeated Dose

Table 17: Comparison of AUC between elderly subjects and young male subjects

Parameter	Elderly Male vs. Young Male			Elderly Female vs. Elderly Male		
	Ratio	95% CI	90% CI	Ratio	95% CI	90% CI
$AUC_{0\text{-}24h}$	1.33	[1.04 , 1.69]	[1.08 , 1.62]	1.56	[1.22 , 1.99]	[1.28 , 1.91]
$AUC_{0\text{-}24h}N$	1.37	[1.05 , 1.79]	[1.09 , 1.71]	1.24	[0.95 , 1.62]	[0.99 , 1.55]
AUC_{last} (Day 1)	1.44	[1.10 , 1.88]	[1.16 , 1.80]	1.55	[1.18 , 2.02]	[1.24 , 1.93]
AUC (Day 1)	1.50	[1.15 , 1.95]	[1.20 , 1.87]	1.59	[1.22 , 2.08]	[1.28 , 1.99]

N: Normalized to 70 kg body weight
Day 1: Single Dose

Reviewer Note on Population PK Analyses in relation to Gender and Age

The PM reviewer indicated that the applicant's population model was acceptable, but viewed the model as providing supportive evidence only, because neither dosing regimens nor labeling statements were solely based on the results of the model. Overall the population PK analyses are consistent with the results obtained in POP2769 with regard to age and gender effects. Highlights of the population analyses findings follow.

Population PK Analyses: Findings with respect to Intrinsic Factors

Based on the applicant's analyses, the covariates explaining dronedarone PK variability in patients were gender, weight and age . A two compartmental Population PK model was developed and validated. In brief, the Population PK analyses indicated:

- Mean dronedarone exposure was 30% higher in female patients.
- Mean dronedarone exposure was 23% higher in patients ≥ 65 years compared with patients <65 years.
- For patients with a body weight <50 kg, mean dronedarone exposure was 40% higher compared with patients with a body weight between 50 and 100 kg.

Table 18: Mean (CV%) steady-state dronedarone exposures in patients and according to gender, age, and body weight (population pharmacokinetic analysis from EFC3153/EURIDIS, EFC4788/ADONIS, and EFC4966/ANDROMEDA)

Parameter	All patients (n=839)	Males (n=604)	Females (n=235)	Age (years)		Body Weight (Kg)		
				< 65 (n=390)	≥ 65 (n=449)	< 50 (n=6)	50 – 100 (n=700)	≥ 100 (n=133)
C_{maxSS} [a] (ng/mL)	121 (33)	112 (29)	144 (32)	109 (27)	131 (34)	159 (20)	125 (33)	99.9 (23)
C_{minSS} (ng/mL)	77.1 (42)	69.7 (38)	95.8 (38)	67.1 (37)	85.7 (41)	122 (22)	80.1 (40)	58.8 (37)
AUCss (ng.h/mL)	1230 (34)	1131 (30)	1483 (32)	1096 (28)	1345 (34)	1749 (20)	1271 (33)	988 (25)

[a]: min-max individual Cmax: 51–442 ng/mL

Race

- Japanese

Japanese males appeared to have lower clearance than their Caucasian counterparts receiving a single 400 mg dronedarone dose; this resulted in ~ 100 % exposure increase in Japanese males relative to Caucasian males (Table 19).

Table 19: Mean (CV %) Dronedarone PK Measures in Caucasian and Japanese males

	Caucasian	Asian
PK Measure	Single 400 mg Dose (LIN2890)	Single 400 mg Dose (TDU4899)
AUC (ng·h/mL)	310 (24)	701 (55)
Cmax (ng/mL)	67.2 (36)	123 (58)
Half-life (h)	17.6 (56)	11.9 (17)
Tmax (h)^	3 (2 to 5)	3

^ Tmax reported as median and (range)

The reason for the apparent differences in clearances between the two studied races is unclear, because dronedarone is primarily metabolized by the CYP3A enzyme, which does not exhibit genetic polymorphism.

- Blacks

No PK information is available in Blacks, who are likely to use dronedarone treatment.

2.4 What Extrinsic Factors Affect Dronedarone Exposure Response?

2.4.1 Drug-drug Interactions

The main extrinsic factor that may influence the dronedarone exposure-response is concomitantly administered drugs. Drugs used in AF/AFL are summarized in Table 20 (per applicant).

Drug-drug interaction studies were carried with some of the compounds listed in Table 20; it is noted that certain classes of compounds are not likely to be coadministered due to safety concerns. For example, dronedarone would not be coadministered with amiodarone.

Table 20: Drugs used in AF/AFL treatment

	Rhythm control	Rate control
Anti-arrhythmic		
Class Ia	Disopyramide Procainamide Quinidine	-- -- --
Class Ic	Flecainide Propafenone	-- --
Class II	--	betablockers (eg metoprolol, carvedilol)
Pure Class III	Dofetilide Ibutilide	-- --
Class IV	-- --	diltiazem verapamil
Multifactorial	Sotalol Amiodarone	sotalol amiodarone
Digitalis	-- --	digoxin digitoxin

2.4.1.1 ***CYP Substrate Status***

As indicated in the metabolism section, dronedarone is primarily metabolized by CYP3A; the contribution to dronedarone metabolism, if any, of CYP2C8, CYP2C9, CYP2C19, CYP2A6 or CYP2E1 is unknown. However, dronedarone is not a substrate of CYP2D6 or CYP1A2. Based on the provided *in vitro* information, dronedarone PK is expected to be primarily altered by CYP3A inducers and inhibitors.

2.4.1.2 ***PGP substrate status***

Dronedarone has limited PGP substrate characteristics, thus it is unlikely that dronedarone exposure will be altered by PGP inhibitors or inducers.

2.4.1.3 ***CYP Induction and Inhibition Potential***

Dronedarone does not induce common CYP enzymes (MIV0144). This conclusion was based on *in vitro* assessment of enzymatic activity measured in cultured hepatocytes and Western blot analyses. Specifically, 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 coexpressed with CYP3A.

Dronedarone does not significantly inhibit the activity of CYP1A2, CYP2C9, CYP2C19 and CYP2E1 in human liver microsomes (MIH0007). Therefore clinically, dronedarone is not expected to inhibit the metabolism of compounds metabolized by these enzymes Dronedarone showed the most inhibition potential towards the CYP3A and CYP2D6 enzymes. Assuming *in vivo* dronedarone concentration of 0.2 µM, I/Ki values for CYP3A4 and CYP2D6 inhibition were ~ 0.01 and 0.06 suggesting a low inhibition potential, per Draft Drug Interaction Guidance.

2.4.1.4 ***PGP Inhibition Potential (Role of PGP Transporters)***

Dronedarone appears to be as potent an inhibitor as cyclosporine A, with respect to the ability to inhibit the efflux of two PGP probe substrates, 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

Consequently, dronedarone may inhibit the efflux of PGP substrates, thereby increasing the plasma exposure of these compounds.

2.4.1.5 *In vivo studies with medications that are likely to be administered in AF/AFL patients and that serve as metabolic or transporter probes (substrates/inhibitors/ inducers)*

In several clinical PK/PD studies, administration of dronedarone at dosages equivalent to or greater than the proposed clinical dosage showed interactions that were generally not clinically significant. Results from these studies are summarized in Table 21; most studies were conducted in healthy male subjects.

Table 21: Summary of Drug Interaction Findings

PK/PD Effects of Dronedarone on Concomitant Medications	**Metabolic (other)**
Drugs not Affected by Dronedarone	
Losartan	CYP2C9 substrate
Drugs Affected by Dronedarone	
Digoxin	PGP substrate
Metoprolol, Propranolol	CYP2D6 substrates
Levonorgestrel, ethinylestradiol, nisoldipine, simvastatin, verapamil	CYP3A substrates
Warfarin	CYP2C9 substrate
Theophylline	CYP1A2 substrate
PK/PD Effect of Drugs on Dronedarone	
Drugs Affecting Dronedarone	
Rifampin	CYP3A inducer
Grapefruit juice, ketoconazole, verapamil, diltiazem, nifedipine	CYP3A inhibitors
Drugs not Affecting Dronedarone	
Pantoprazole	Decreases gastric pH
Simvastatin, nisoldipine	CYP3A substrates
Losartan, warfarin	CYP2C9 substrates

Dosage Adjustment for Dronedarone

No definitive dosage adjustments can be recommended for dronedarone because alternative dosage schedules have not been evaluated with respect to exposure-response. It should also be noted that dronedarone is available in only one tablet strength and the tablet is not scored therefore the only way to adjust dosage is by interval adjustment.

In the pivotal clinical trials most comedications used in AF/AFL therapy were allowed; these medications included diuretics, beta-blockers, digitalis, calcium antagonists, ACE inhibitors, angiotensin-II receptor antagonists, statins, coronary vasodilators, and oral anti-coagulants. Overall, there did not appear to be evidence of clinically significant adverse events due to comedication, suggesting that dronedarone can be given with most comedications, if appropriate caution is observed.

Based on the study results, the only proposed contraindication is with potent CYP3A inhibitors, such as ketoconazole. This proposal is reasonable based on the observed

results (> 5-fold increase in dronedarone exposure). Based on the drug interaction results some drugs are not recommended for coadministration with dronedarone due to the following:

- unacceptable lowering of dronedarone exposures (strong CYP inducers, such as rifampin, St John's Wort)
- potential development of proarrhythmia (Class I or class III anti-arrhythmic) and drugs that prolong the QT interval (inducing torsades de pointes).

Additionally, caution should be exercised for most drugs (e.g. beta blockers, calcium antagonists) to be used in combination with dronedarone for the treatment of AF/AFL due to potential PD interactions.

Dosage Adjustment for Concomitant Medications

The majority of drugs evaluated in the drug interaction studies and drugs likely to be used with dronedarone follow schedules that allow for titration, therefore, dosage can be modified accordingly when given with dronedarone. Additionally, appropriate caution should be exercised due to the potential PD interactions.

Reviewer Note on Dosage Adjustments during dronedarone therapy

Overall, the proposed drug interaction guidelines are acceptable with minor modifications which will be addressed in labeling (see Labeling Section of Review).

2.4.1.6 **Mechanistic basis for PD drug-drug interactions between dronedarone and comedications**

There is a potential for additive to synergistic pharmacodynamic effects between dronedarone, an anti-arrhythmic agent, and other drugs used in patients with cardiac disease. For dronedarone this interaction is enhanced due to its putative effects on all four classes of Vaughan Williams' classification. Therefore, caution should be exercised when dronedarone is combined with several agents, even if a clinically significant PK or PD interaction was not observed in the reported drug-drug interaction studies.

2.4.2 Unaddressed Potential Drug Interactions (Drugs that may be affected in inhibition of renal tubular secretion)

In a renal function study seeking to elucidate the effect of dronedarone on serum creatinine, dronedarone inhibited renal tubular secretion (Study PDY5487). This finding suggests that drugs predominantly eliminated by renal tubular secretion may have increased exposure when given with dronedarone. Dronedarone also inhibits the organic cation transporter and may affect drugs eliminated by this pathway. It is noted that the applicant cautioned against the concomitant use of ACE inhibitors with dronedarone in ANDROMEDA because of a concern for decreased renal function. This caution was issued prior to completion of PDY5487 that demonstrated the apparent decline in renal function was transient and not likely to alter the exposure of ACEs. As was shown in the PM analyses of DAFNE and PDY5487, serum creatinine rises initially when dronedarone therapy is initiated but decreases upon discontinuation of dronedarone. Appropriate precautionary language should be included in the label to address the potential interaction between dronedarone and the previously mentioned drugs.

2.5 What are the General Biopharmaceutics Characteristics of Dronedarone Formulations?

2.5.1 BCS Information

The applicant reports that dronedarone is a member of BCS 2, which are drugs with low solubility and high permeability. Solubility information was provided to support the claim of low solubility (see Dissolution), but limited to no permeability information was included in the application. The absolute bioavailability information (F < 20 %) suggests that dronedarone is a not a high permeability drug; it is unclear if the relatively high recovery of radioactivity as metabolites (90 %) in the mass balance study confers high permeability on dronedarone. Overall, the data do not suggest that dronedarone is a high permeability compound; additional *in vitro* or *in vivo* information is needed to accurately identify dronedarone BCS type (BCS 2 vs. BCS 4). The BCS type does not have a significant impact on the current application, apart from dissolution.

2.5.2 Relative bioavailability information

The relative bioavailability information provided for the TBM (prototype) formulation was adequate. The prototype formulation, 2E3, was used in the pivotal clinical trials and this formulation had comparable bioavailability to the 2E2 formulation used in the Phase 2 dose ranging study and other critical clinical pharmacology studies (Table 22). Two additional formulations were developed: 2E4 for stability studies and 2E5 the market formulation; neither of these two formulations was administered to humans but dissolution information is available on the formulation.

Table 22: Dronedarone geometric mean ratios (based on $^{12}C/^{13}C$ ratio) and associated 90 % confidence intervals under fasted conditions (2E3 vs. 2E2)

Mean (CV%) $^{12}C/^{13}C$ Ratio	Phase III tablet +^{13}C-dronedarone	Phase II tablet +^{13}C-dronedarone	Ratio [90% CI]	Within-subject SD
C_{max} (ng/mL)	0.77 (37)	0.69 (29)	1.09 [0.95 – 1.26]	0.19
AUC_{last} (ng.h/mL)	0.78 (17)	0.82 (8)	0.94 [0.88 – 1.00]	0.08
AUC (ng.h/mL)	0.82 (15)*	0.85 (8)	0.95 [0.88 – 1.02]*	0.09

Phase III (1x400mg tablet) + ^{13}C-dronedarone (4x100mg capsules): treatment A
Phase II (2x200mg tablets) + ^{13}C-dronedarone (4x100mg capsules): treatment B a: n=11

The 2E5 intended for marketing formulation has the same qualitative and quantitative compositions as the reference 2E3 formulation; the only difference between the two formulations is minor punch marking on 2E5. This minor difference does not appear likely to alter the *in vivo* performance of the formulations, and *in vitro* dissolution information suggests the formulations have comparable quality.

Food Effect Information

As indicated previously, food increases dronedarone exposure by approximately 2- to 5-fold (Table 23); overall, there was a small difference between dronedarone exposures obtained with a high fat meal vs. low fat meal.

Table 23: Dronedarone geometric mean ratios and associated 90 % confidence intervals under fed and fasted conditions

Parameters (units)	Low fat meal / fasted	Fat-rich meal / fasted	Fat-rich meal / low fat meal
C_{max} (ng/ml)	3.15 [2.28 - 4.36]	4.59 [3.32 - 6.35]	1.46 [1.05 - 2.01]
AUC_{inf} (ng.h/ml)	2.34 [1.99 - 2.75]	3.06 [2.60 - 3.61]	1.31 [1.11 - 1.54]

n = 9

In the pivotal clinical studies and clinical pharmacology studies, dronedarone was typically given in the fed state (shortly before or after a meal) at breakfast and dinner for BID administration. Meal types were not standardized in the pivotal trial suggesting that patients received meals of different fat content. Since the clinical effectiveness and safety data were obtained in the fed state and there is limited information in the fasted state (low exposure) to support safety and effectiveness, dronedarone should be given in the fed state.

In sum, dronedarone should be given in the fed state, either shortly before or after a meal; the fat content of the meal is not critical.

Reviewer Note on Food Effect with different dronedarone formulations
Several different dronedarone formulations were developed by the applicant in an attempt to optimize bioavailability while minimizing the effect of food. Initial formulations were greatly affected by food; in some instances (early capsule formulations), when food was present, dronedarone exposure was increased more than 10-fold relative to the fasted state. Ultimately, a tablet formulation containing 10 % pluronic acid, was found to have an acceptable bioavailability profile.

2.5.4 Dissolution

The applicant developed an acceptable dissolution methodology for dronedarone tablets to ensure *in vivo* performance and quality of Multac tablets. The proposed dissolution method and specification are as follows.

Applicant's Proposal
Dissolution methodology
Apparatus: paddle at 75 rpm; Medium: 1000 ml of pH 4.5 phosphate buffer

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's Recommendation
Dissolution methodology
Applicant's proposal is acceptable.

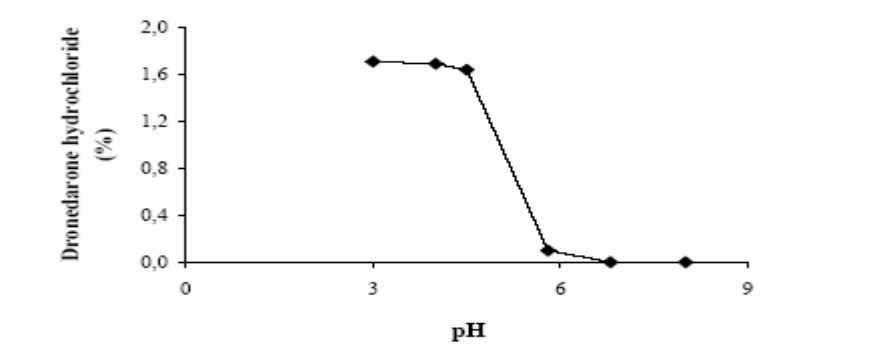
Dissolution specification

- Not less than 25 % and not more than 50 % dissolved within 30 minutes
- Q = 80 % in 90 minutes

Reviewer Notes on Methodology

As shown in Figure 13, dronedarone is most soluble at pHs between 3 and 5; subsequent studies indicated that solubility is optimal (maintenance of sink conditions) at pH 4.5.

Figure 13: Dronedarone solubility in aqueous solution at 25^{O} C in phosphate buffer systems



Testing in various buffer systems at pH 4.5 demonstrated that the phosphate buffer was acceptable for dissolution. Upon addition of surfactant, the overall dissolution rate did not improve, however there was an indication that inter-individual variability was decreased (Table 24). It should be noted that there was a limit as to how much surfactant could be added before precipitation occurred. The applicant elected not to include surfactant in subsequent dissolution testing.

Table 24: 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)

The applicant also adequately evaluated the effect of different dissolution apparatus and rotation speeds on dronedarone dissolution.

Reviewer Comments on Methodology

Based on the information provided, the proposed methodology is acceptable; the method may be limited by the overall poor dissolution profile of dronedarone that is related to dronedarone solubility. However, the applicant has not adequately evaluated the discriminatory ability of the dissolution method when different manufacturing conditions, such as varying temperature and pressure conditions are employed.

Reviewer Comment on Specification

Based on the poor solubility profile of dronedarone and its putative BCS 2 designation, the setting of a two-point dissolution specification is reasonable, per Dissolution

Guidance. As mentioned previously, dronedarone may belong to BCS 4 rather than BCS 2, based on its apparently low *in vivo* permeability. The Dissolution Guidance dose not offer specific recommendations regarding the setting of dissolution specifications for low solubility/low permeability compounds, BCS 4. However, an approach similar to that for BCS 2 appears reasonable, because the drug solubility characteristics have the greatest impact on drug dissolution. Irrespective of BCS designation, 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, 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 the following specification is appropriate:

- Not less than 25 % and not more than 50 % is dissolved within 30 minutes
- Q = 80 % in 90 minutes

2.6 What Analytical Methods were used in the Dronedarone Development Program?

Overall, the performance of the bioanalytical methods used to identify and measure dronedarone levels was acceptable, per Bioanalytical Guidance. The analytical methods used in the clinical pharmacology and efficacy/safety studies are summarized in Table 25.

The assays satisfy the criteria (per Bioanalytical Guidance) for accuracy precision, and specificity. Sample stability was also demonstrated under various conditions including long-term storage, freeze-thaw, sample-handling, sample transport and with autosampler. Generally low, mid and high QC samples were present and these QC samples were adequate with respect to their relevant values to points on the standard curve.

Table 25:- Summary of bioanalytical studies associated with clinical pharmacology studies and efficacy/safety clinical studies (per Applicant)

Methods Report (Report Location)	Analytes	Type of Method	Calibration Range[a] (ng/mL)	Precision CV%		Accuracy A%[b]		Matrix (Anticoagulant)	Clinical Studies
				Within run	Between run	Within run	Between run		
DOS0124 (Sec. 5.3.1.4)	dronedarone	LC-UV	5 to 1000	Better than 8.5%	Better than 10.3%	92 to 95%	90 to 97%	Plasma (lithium heparinate)	TDU2164
	SR35021	LC-UV	5 to 1000	Better than 10%	Better than 9%	93 to 99%	94 to 98%		
DOH0020 (Sec. 5.3.1.4)	dronedarone	LC-UV	5 to 1000	3.9 to 5%	5.9 to 9.4%	98 to 104%	95 to 101%	Plasma (CDP)	INT2631, INT2634, INT2931, TDR2394, TDU2164
	SR35021	LC-UV	5 to 1000	3.1 to 5.5%	5.7 to 8%	97 to 106%	96 to 104%		
DOH0072 (Sec. 5.3.1.4)	dronedarone	LC-UV	5 to 1000	-	Better than 7.1%	-	106 to 111%	Plasma (CDP)	TDR2395, PDY2399, PDY2400, PDY2402, PDY2945, ACT2771, ACT2401, BEX2770, INT2636
	SR35021	LC-UV	5 to 1000	-	Better than 9.2%	-	96 to 108%		
DOH0048 (Sec. 5.3.1.4)	dronedarone	LC-UV	10 to 1000	Better than 14.7%	Better than 6.6%	86 to 107%	89 to 100 %	Blood (CDP)	ACT2771
DOH0036 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 50	1.3 to 4.8%	1.9 to 6.4%	-9.3 to -2%	-9.9 to -3.6%	Plasma (CDP)	INT3353, POP2769, TDU3007, PDY2399, PDY2400
	SR35021	LC-MS/MS	0.5 to 50	1.5 to 4.1%	1.7 to 4.3%	5.7 to 8.1%	3.9 to 9.6%		
DOH0151 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 50	3.8 to 11.2%	4.7 to 10.8%	-2.91 to 8.0%	-2.1 to 0.8%	Plasma (CDP)	INT3561, INT3683, INT4074, INT4442, TDR3549, PDY3828, DRI3550
	SR35021			5.5 to 13.3%	4.8 to 14.3%	-6.3 to –0.3%	-2.6 to 0.5%		
DOH0203 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 50	Better than 5.9%[c]		Better than 7.4%[c]		Plasma (CDP)	
	SR35021			Better than 16.8%[c]		Better than 9.5%[c]			
	SR35021			Better than 6.96%[c]		Better than 9.48%[c]			
	^{13}C-SR33589			Better than 5.97%[c]		Better than –4.19%[c]			
	^{13}C-SR35021			Better than 5.59%[c]		Better than –14.5%[c]			

Methods Report (Report Location)	Analytes	Type of Method	Calibration Range[a] (ng/mL)	Precision CV%		Accuracy A%[b]		Matrix (Anticoagulant)	Clinical Studies
				Within run	Between run	Within run	Between run		
DOH0239 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 300	Better than 8.37%[c]		Better than 9.49%[c]		Plasma (lithium heparinate)	INT4695, INT4880, INT4881, INT4886, LTS3841, EFC4788/ADONIS, DRI3151, INT4882, TDU4899
	SR35021			Better than 6.70%[c]		Better than –10.7%[c]			
DOH0292 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 300	Better than 9.08%[c]		Better than 3.04%[c]		Plasma (lithium heparinate)	INT4880, INT5189, EFC4788/ADONIS EFC4508/ERATO, EFC4966/ANDROMEDA
	SR35021			Better than 7.99%[c]		Better than 6.30%[c]			
DOH0309 (Sec. 5.3.1.4)	dronedarone	LC-MS/MS	0.5 to 300	Better than 4.07%[c]		Better than 6.38%[c]		Plasma (lithium heparinate)	LIN2890, INT3560, INT4884, POP2896, EFC3153/EURIDIS
	SR35021			Better than 4.15%[c]		Better than –11.4%[c]			

CV=coefficient of variation

[a] expressed as non salified compound

[b] A% = (Mean found / theoretical value)*100 for DOH0020 and DOH0072 and A% = ((Observed conc. – Expected conc)/Expected conc.)*100 for DOH0036 and DOH0238

[c] Total

3 Detailed Labeling Recommendations

Based on the Clinical Pharmacology and Biopharmaceutics Review, the following changes were made to the applicant's original labeling proposal. These changes apply to the Clinical Pharmacology and Dosage and Administration sections of the label.

The applicant's proposed labeling is acceptable with the noted recommendations (please refer to the sections of attached label.

4 Appendices

4.1 Proposed labeling with revised text (reviewer recommended)

MULTAC®
(dronedarone HCl)
TABLETS

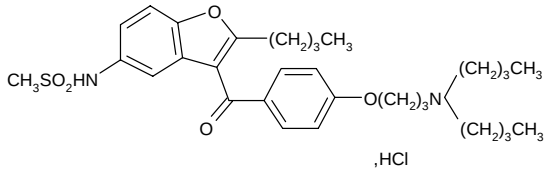
DESCRIPTION

MULTAC (dronedarone HCl) is an antiarrhythmic drug with effects from all four classes of the Vaughan Williams' classification.

Dronedarone HCl is a benzofuran derivative with the following chemical name: N-{2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl]benzofuran-5-yl} methanesulfonamide, hydrochloride.

Dronedarone HCl is a white fine powder that is practically insoluble in water and freely soluble in methylene chloride and methanol.

Its empirical formula is $C_{31}H_{44}N_2O_5S$, HCl with a relative molecular mass of 593.2. Its structural formula is:



MULTAC is provided as tablets for oral administration.

Each tablet of MULTAC contains 400 mg of dronedarone (expressed as base).

The inactive ingredients are:

Core of the tablets: hypromellose, starch, crospovidone, poloxamer 407, lactose monohydrate, colloidal silicon dioxide, magnesium stearate.

Coating / Polishing of the tablets: hypromellose, polyethylene glycol 6000, titanium dioxide, carnauba wax.

CLINICAL PHARMACOLOGY

Mechanism of Action

In animals, dronedarone prevents atrial fibrillation or restores normal sinus rhythm depending on the model used. It also prevents ventricular tachycardia and ventricular fibrillation in several animal models. These effects most likely result from its electrophysiological properties belonging to all four Vaughan-Williams classes. It is a multichannel blocker inhibiting the potassium currents (including $I_{K(Ach)}$, I_{Kur}, I_{Kr}, I_{Ks}) and thus prolonging cardiac action potential and refractory periods (Class III), the sodium currents (Class Ib), the calcium currents (Class IV) and it non-competitively antagonizes adrenergic activities (Class II).

Pharmacodynamic Properties
In animal models, dronedarone reduces the heart rate. It prolongs Wenckebach cycle length and AH-, PQ-, QT- intervals; with no marked effect on QTc-, HV- and QRS-intervals. It increases effective refractory periods of the atrium, atrio-ventricular node and ventricle with no reverse-use dependency.
Dronedarone slightly decreases arterial blood pressure and myocardial contractility (dP/dt max) with no change in left ventricular ejection fraction and reduces myocardial oxygen consumption.
Dronedarone has vasodilatory properties, more pronounced in coronary arteries (related to the activation of nitric oxide pathway) than in peripheral arteries.
Dronedarone displays antiadrenergic effects; it reduces alpha-adrenergic blood pressure response to epinephrine and beta1 and beta2 responses to isoproterenol.
In healthy humans, a moderate prolongation of the PR- and QTc-intervals was observed at 400 mg twice daily and above. No QTc value above 500 msec was observed, even at 1600 mg twice daily.

Pharmacokinetics
The pharmacokinetics of dronedarone in patients with atrial fibrillation is consistent with that in healthy subjects.

Absorption
The absolute oral bioavailability of dronedarone following administration of MULTAC is unknown; however following single dose (800 mg) administration of a dronedarone capsule formulation the absolute oral bioavailability of dronedarone (given with food) is 15 %. Concomitant intake of food increases dronedarone bioavailability by approximately 2- to 5- fold. After oral administration in fed conditions, peak plasma concentrations of dronedarone and the main circulating metabolite (N-debutyl metabolite) are reached within 3 to 6 hours. The steady state mean dronedarone C_{max} is 84-147 ng/mL and the exposure of the main N-debutyl metabolite is similar to that of the parent compound. The pharmacokinetics of dronedarone and its N-debutyl metabolite both deviate moderately from dose proportionality: a 2-fold increase in dose results in an approximate 2.5- to 3.0- fold increase with respect to C_{max} and AUC. After repeated administration of 400 mg twice daily, steady state is reached within one week of treatment and the mean accumulation ratio for dronedarone ranges from 2.6 to 4.5.

Distribution
The *in vitro* plasma protein binding of dronedarone and its N-debutyl metabolite is > 98 % and not dependent on drug concentration. Both compounds bind mainly to albumin. After intravenous (IV) administration the volume of distribution associated with the terminal elimination phase (Vz) ranges from 2500 to 3440 L.

Metabolism
Dronedarone is extensively metabolized, mainly by the CYP3A enzyme. The major metabolic pathway includes N-debutylation to form the main circulating active metabolite, SR35021, followed by oxidation, oxidative deamination to form the inactive

propanoic acid metabolite, followed by oxidation, and direct oxidation. SR35021 exhibits pharmacodynamic activity but is 3 to 10-times less potent than dronedarone.

Excretion/Elimination
After oral administration, approximately 6 % of the labelled dose is excreted in urine mainly as metabolites (no unchanged compound excreted in urine) and 84 % is excreted in feces mainly as metabolites. After IV administration the plasma clearance of dronedarone ranges from 130 to 150 L/h. Following IV administration the terminal elimination half-life of dronedarone is between 13 and 19 hours. After oral administration dronedarone apparent terminal half-life is approximately 25 to 30 hours and SR35021 apparent terminal half-life is approximately 20 to 25 hours. In patients, dronedarone and its metabolite are completely eliminated from the plasma within 2 weeks after the end of a 400 mg twice daily- treatment.

Special Populations
Liver Impairment
The effect of hepatic impairment on the pharmacokinetics of dronedarone has not been assessed (See PRECAUTIONS). Liver impairment is expected to significantly modify dronedarone pharmacokinetics because dronedarone is extensively cleared by hepatic processes.

Renal Impairment
The effect of renal impairment on dronedarone pharmacokinetics has not been assessed. Renal impairment is not expected to modify the pharmacokinetics of dronedarone because no unchanged compound was excreted in urine and only approximately 6% of the dose was excreted in urine as metabolites.

Gender
In female healthy subjects and in female patients, dronedarone and its N-debutyl metabolite exposures are increased by 1.3- to 1.9- fold.

Race
Pharmacokinetic differences due to race were not formally assessed. However, based on a cross study comparison, Asian males (Japanese) had 2-fold higher exposure than Caucasian males. The pharmacokinetics of dronedarone in Blacks have not been characterized

Geriatric Patients
In healthy subjects and in patients aged 65 years old and above, dronedarone and the SR35021 exposures are increased by 1.2- to 1.5- fold relative to younger subjects (under 45 years old).

Drug Interactions (See CONTRAINDICATIONS, PRECAUTIONS, Drug Interactions)

Dronedarone is mainly metabolized by CYP 3A. Coadministration of drugs that inhibit CYP 3A are expected to increase dronedarone exposure and those that induce CYP 3A to decrease its exposure. Since dronedarone is a CYP 3A (moderate), CYP 2D6 (weak) and P-glycoprotein (strong) inhibitor, the exposure of drugs primarily metabolised by CYP 3A or CYP 2D6, or transported by P-glycoproteins may be increased when these drugs are given with dronedarone. This could increase or prolong the therapeutic activity and/or adverse effects of these drugs (See CONTRAINDICATIONS and PRECAUTIONS). Dronedarone has no or limited potential to inhibit CYP 2C9, CYP 2C19 and CYP 1A2 enzymes.

Interaction studies were performed with dronedarone and other drugs/products commonly used for pharmacokinetic interactions or likely to be coadministered. The results of these studies follow.

CYP 3A4 inhibitors

Repeated doses of ketoconazole (200 mg daily), a strong CYP 3A4 inhibitor, resulted in a 17- to 25- fold increase in dronedarone exposure. The effects of coadministration with moderate CYP3A inhibitors, diltiazem, verapamil, nifedipine and grapefruit juice were not as great as with ketoconazole. Repeated doses of diltiazem (240 mg twice daily), verapamil (240 mg once daily) and nifedipine (20 mg twice daily) resulted in an increase in dronedarone exposure of 1.7-, 1.4-, and 1.2- fold, respectively. Repeated doses of double strength 300 ml grapefruit juice three times daily resulted in a 3- fold increase in dronedarone exposure. The N-debutyl metabolite exposure was not significantly changed by any of these CYP3A4 inhibitors.

CYP 3A4 inducers

Rifampicin (600 mg once daily) decreased dronedarone exposure by 80 % with no major change in its active metabolite exposure.

CYP 3A4 substrates

Repeated doses of dronedarone (400 mg twice daily) increased verapamil exposure by 1.4- fold, and nisoldipine exposure by 1.5- fold. Dronedarone (400 mg twice daily) increased simvastatin, a sensitive CYP3A substrate, and simvastatin acid exposure by 4-fold and 2- fold, respectively. This finding suggests that dronedarone is a moderately potent CYP3A inhibitor. No decreases in ethinylestradiol and levonorgestrel were observed in healthy subjects receiving dronedarone (800 mg twice daily) concomitantly with oral contraceptives.

CYP 2D6 substrates

Dronedarone 400 mg or 800 mg twice daily increased metoprolol exposure by 1.6- and 2.3- fold, respectively. Dronedarone (800 mg once daily) increased propranolol exposure by 1.3- fold.

CYP 2C9 substrates

Dronedarone (600 mg twice daily) increased S-warfarin exposure by 1.2- fold. No interaction was observed between dronedarone and losartan.

P-glycoprotein substrates
Dronedarone (400 mg twice daily) increased digoxin exposure by 2.5- fold.

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

Drugs eliminated by renal tubular secretion
Dronedarone has the potential to increase the exposure of drugs eliminated by renal tubular secretion because dronedarone inhibits this pathway.

CLINICAL STUDIES

Maintenance of sinus rhythm

The efficacy of dronedarone in maintaining sinus rhythm in patients with a prior episode of atrial fibrillation (AF) or atrial flutter (AFL) was provided primarily by two randomized, double-blind, multi-national clinical trials, EURIDIS and ADONIS. Additional data on maintenance of sinus rhythm in recently converted AF patients are available from the double-blind, placebo-controlled, dose-ranging study, DAFNE.

In EURIDIS and ADONIS, a total of 1237 patients were randomized in an outpatient setting and treated with either dronedarone 400 mg twice daily (n=828) or placebo (n=409) and followed for 12 months. Patients had at least one electrocardiographic (ECG)-documented AF/AFL episode during the last 3 months and were in sinus rhythm for at least one hour. The primary endpoint for both studies was time to first documented AF/AFL recurrence. Detection of AF/AFL recurrences was based on a centralized review of transtelephonic ECG monitoring (TTEM) and 12-lead ECG. Time to symptomatic first recurrence and mean ventricular rate during first recorded AF/AFL recurrence were assessed as secondary endpoints.

Patients were to be excluded from participation in case of arrhythmia due to an acute condition known to cause AF/AFL, history of *torsade de pointes*, bradycardia < 50 bpm, PR-interval ≥ 0.28 sec, second degree atrio-ventricular block or higher without a permanent pacemaker implanted, or NYHA class III or IV congestive heart failure.

Patients ranged in age from 20 to 88 years, with the majority being Caucasian (97%), male (69%) patients. The most common comorbidities were hypertension (56.8%) and structural heart disease (41.5%) including coronary heart disease (21.8%).

Associated concomitant medications at baseline were those commonly prescribed in AF/AFL patients including oral anticoagulants, beta-blocking agents, angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, chronic antiplatelet agents, diuretics, statins, digitalis, and calcium antagonists.

In the pooled data from EURIDIS and ADONIS as well as in the individual trials, dronedarone consistently delayed the time to first recurrence of AF/AFL as compared to placebo, as shown in table 1 and in figure 1 below. Dronedarone lowered the risk of first AF/AFL recurrence during the 12-month study period by 25%. The median time from randomization to first AF/AFL recurrence in the dronedarone group was 116 days, i.e. 2.2-fold longer than in the placebo group (53 days). The majority (60%) of first recurrences were symptomatic. Dronedarone also delayed the time to symptomatic first recurrence of AF/AFL in both studies ($p = 0.0003$) as shown in figure 2 below. With dronedarone 400mg twice daily, the rate of patients with no symptomatic first recurrence of AF/AFL at one year was 62.3 %.

Table 1: Time from Randomization to First AF/AFL Recurrence within 12 Months – All Randomized and Treated Patients (Pooled EURIDIS and ADONIS Data)

	EURIDIS		ADONIS		Pooled	
	Placebo (N=201)	Dronedarone 400 mg BID (N=411)	Placebo (N=208)	Dronedarone 400 mg BID (N=417)	Placebo (N=409)	Dronedarone 400 mg BID (N=828)
Number of patients with endpoints	155	272	146	246	301	518
Median time in days (95% CI)	41 ([16;87])	96 ([61;133])	59 ([22;96])	158 ([80;252])	53 ([23;81])	116 ([89;150])
Relative risk (95% CI[a])	0.784 [0.644;0.955]		0.725 [0.590;0.890]		0.753 [0.653;0.868]	
Log-rank's test (p-value)	0.01383		0.0017		0.00007	

[a] Determined from Cox regression model.
CI: Confidence Interval

Figure 1: Kaplan-Meier Cumulative Incidence Curves from Randomization to First AF/AFL Recurrence within 12 Months – All Randomized and Treated Patients (Pooled ADONIS and EURIDIS data)

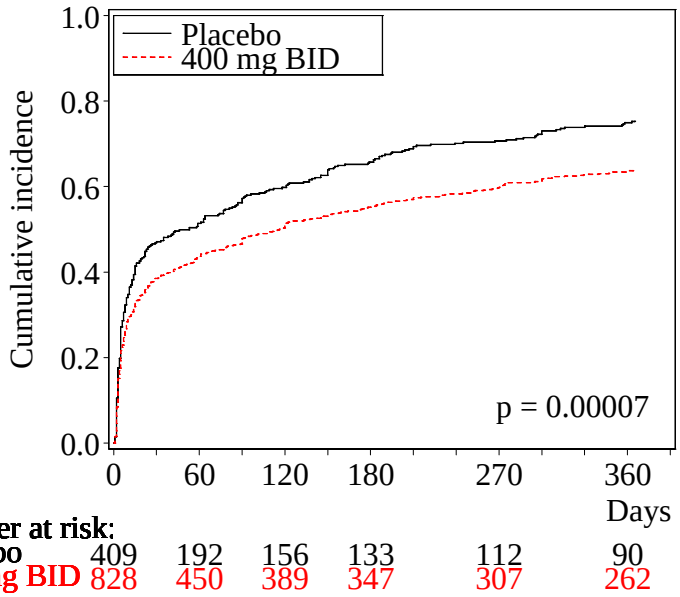
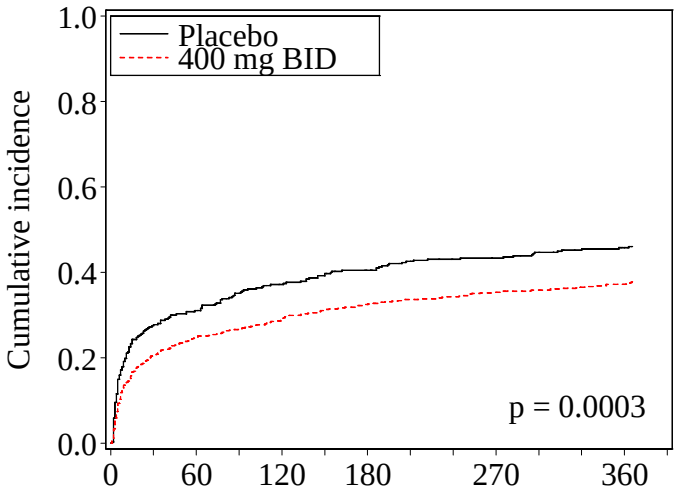


Figure 2: Prentice Cumulative Incidence Curve from Randomization to symptomatic first Recurrence of AF/AFL – All Randomized and Treated Patients (Pooled EURIDIS and ADONIS data)



Number at risk:						
Placebo	409	192	156	133	112	90
400 mg BID	828	450	389	347	307	262

In DAFNE where dronedarone was started before conversion, the median time to AF recurrence, as measured by TTEM and 12 lead ECG, was 60 days in the 400 mg twice daily dronedarone group, compared to 5 days in the placebo group. Dronedarone 400 mg twice daily lowered by 55% (p = 0.001) the risk of first recurrence of AF compared to placebo during the 6 months study period.

Control of Ventricular Rate

The efficacy of dronedarone in the control of ventricular rate was demonstrated in patients with symptomatic permanent (lasting over 6 months) AF in the ERATO study, a double-blind, placebo-controlled 6-month clinical trial. One hundred and seventy-four patients (174) were randomized and treated with either dronedarone 400 mg twice daily (85 patients) or placebo (89 patients), in addition to conventional therapy including beta-blockers (49%), digitalis (37.4%), and/or calcium antagonists (18.4%). The primary endpoint of the study was the change from baseline in mean ventricular rate on Day 14. A secondary assessment of the same endpoint was made at 4 months. Other secondary endpoints were maximal exercise duration and ventricular rate at maximal exercise and at submaximal exercise (50% of maximal exercise at baseline).

Patients were to be excluded from participation in case of arrhythmia due to an acute condition known to cause AF/AFL, history of *torsade de pointes*, bradycardia < 50 bpm, PR-interval ≥0.28 sec, second degree atrio-ventricular block or higher without a permanent pacemaker implanted, or NYHA class III or IV congestive heart failure.

Patients ranged in age from 31 to 86 years, with the majority being Caucasian (99%), male (69%) patients. The most common comorbidities were hypertension (49%) and structural heart disease (39%).

At day 14 dronedarone decreased mean ventricular rate as compared to placebo as summarized in the table 2 below, ($p < 0.0001$). This effect was independent of background rate control therapies and maintained for 4 months after treatment initiation with a mean decrease from baseline equal to 8.8 bpm ($p < 0.0001$). Under intake of beta-blockers, digitalis, and calcium antagonists with heart rate lowering effects, the mean decrease of ventricular rate and the 95% CI were 14.9 bpm, [-20; -10], 11.5 bpm, [-17; -6.4]) and 5.05 bpm, [-11; 0.92], respectively. A decrease of ventricular rate was also observed during submaximal and maximal exercise at day 14 without changing the exercise duration (see the table 2 below).

Table 2: ERATO: Change from Baseline in Heart Rate (bpm) at day 14 Measured by 24 hour Holter and Heart Rate at Submaximal and Maximal Exercise Test - All Randomized Patients

			Placebo (N=89)	Dronedarone 400 mg BID (N=85)
24 hour Holter heart rate (bpm)	Baseline D14	Mean (SEM) Mean (SEM)	90.6 (1.5) 90.2 (1.5)	86.5 (1.4) 76.2 (1.4)
	Change from baseline [a]	Mean [95%CI] [b]	0.7 [-1.9;3.3]	-11.0 [-13.5;-8.5]
	Treatment effect [a]	Mean [95%CI] [b] p-value(b)	-11.7 [-14.8;-8.5] 22×10^{-14}	
Heart rate (bpm) at submaximal exercise	Baseline D14	Mean (SEM) Mean (SEM)	131.6 (2.9) 130.0 (2.9)	124.6 (2.3) 103.3 (2.3)
	Change from baseline [a]	Mean [95%CI]	-2.2 [-6.7;2.4]	-25.6 [-30.1;-21.1]
	Treatment effect(a)	Mean [95%CI] p-value	-23.4 [-28.9;-17.9] 25×10^{-15}	
Heart rate (bpm) at maximal exercise	Baseline D14	Mean (SEM) Mean (SEM)	162.4 (3.6) 159.6 (3.7)	152.6 (2.9) 129.7 (3.1)
	Change from baseline [a]	Mean [95%CI]	-2.9 [-8.0;2.3]	-27.4 [-32.5;-22.3]
	Treatment effect [a]	Mean [95%CI] p-value	-24.5 [-30.8;-18.3] 1×10^{-12}	

(a) Change from baseline and treatment effect (difference between dronedarone 800 mg and placebo groups) are adjusted for baseline heart rate value, age and type of baseline standard treatment (beta-blocker, heart rate lowering calcium antagonist, digitalis)
(b) Following multiple imputation technique using Rubin's rule[4 (4.7%) dronedarone and 2 (2.2%) placebo patients had missing data at baseline and were evaluated on Day 14, and 5 (5.9%) dronedarone and 5

(5.6%) placebo patients were evaluated at baseline and had missing data on Day 14, 1 (1.2%) dronedarone patient had missing data at baseline and on Day 14]

In the pooled data from EURIDIS and ADONIS, patients treated with dronedarone 400mg twice daily had lower mean ventricular rates at the time of first recurrence (103.4 bpm) as compared to placebo patients (117.1 bpm) (TTEM method, $p < 0.0001$).

In DAFNE, the 400 mg twice daily dronedarone group had lower mean ventricular rates at the time of first AF recurrence compared to placebo (89.7 bpm versus 102.9 bpm, $p = 0.0047$).

INDICATIONS AND USAGE
MULTAC is indicated for rhythm and rate control in patients with atrial fibrillation or atrial flutter, to maintain normal sinus rhythm or to decrease ventricular rate.

CONTRAINDICATIONS
MULTAC is contraindicated in patients with:
History of hypersensitivity reactions to dronedarone or any of its excipients,
Second- or third- degree AV block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker),
Bradycardia < 50 bpm,
Pregnancy (Category X, see PRECAUTIONS – Pregnancy) and lactation,
Coadministration with strong CYP3A4 inhibitors, such as ketoconazole, itraconazole, cyclosporine, clarithromycin, erythromycin, nefazodone and ritonavir (See PRECAUTIONS – Drug Interactions).

WARNINGS
In ANDROMEDA, a clinical trial in patients with a recent episode of severe congestive heart failure (CHF) (NYHA class III and IV), dronedarone has not been shown to be more effective than placebo for preventing cardiovascular hospitalizations or death and this trial was prematurely discontinued due to an unfavourable imbalance in deaths.

PRECAUTIONS
General
Electrolytes imbalance
Since antiarrhythmic drugs may be ineffective or may be arrhythmogenic in patients with hypokalemia, any potassium or magnesium deficiency should be corrected before instituting and during dronedarone therapy.

Serum creatinine monitoring
An increase in serum creatinine with dronedarone 400 mg twice daily was consistently observed in both healthy subjects as well as in patients. This increase occurred within 3 to 5 days of treatment initiation; values remained stable during treatment and returned to

baseline within 14 days after treatment discontinuation. In a specific study in healthy subjects, this increase was shown to be related to inhibition of creatinine secretion at the tubular level, with no effect on glomerular filtration or on renal blood flow. In most patients with AF/AFL, the maximal increase from baseline was < 30% with a mean change from baseline ranging from 10 to 15 %. Therefore it is recommended to monitor serum creatinine values intensively during the period of treatment initiation and periodically throughout therapy. If an increase in serum creatinine is observed, clinical judgment should be made regarding the continued use of dronedarone. by assessing the potential risks and benefits of dronedarone therapy, taking into account that this increase may be expected with dronedarone. Additionally, caution should be exercised when administering dronedarone with drugs that are eliminated by tubular secretion (see PRECAUTIONS, Drug Interactions).

Liver impairment
Given that dronedarone is highly metabolized by the liver and the impact of liver impairment has not been assessed in any clinical trial, it should be contraindicated in patients with severe hepatic impairment and used with great caution in patients with moderate hepatic impairment.

Renal impairment
Dronedarone has not been studied in patients with severe renal impairment. However, because it is minimally excreted via the kidney, no particular precaution is needed.

Information For Patients
Patients should be advised to remain under the care of a physician when using dronedarone. If a dose is missed, patients should take the next dose at the regularly scheduled time and should not double the dose. Therapy with dronedarone should be initiated and maintained at the recommended dosage.
Before taking the drug, patients should be advised to inform their physician of any history of proarrhythmia or predisposing conditions such as uncorrected hypokalemia. Dronedarone may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John’s wort.

Dronedarone should be administrated during or shortly after a meal. Patients should however be warned not to take dronedarone concomitantly with grapefruit juice.

Laboratory Tests
An asymptomatic serum creatinine increase may be observed with dronedarone and was shown to be related to inhibition of renal tubular secretion (see PRECAUTIONS - General).

Drug Interactions
Dronedarone is primarily metabolized by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6. Therefore, dronedarone has the potential for interactions with inhibitors and inducers of CYP 3A, as well as substrates of CYP 3A and CYP 2D6. It also has the

potential to inhibit P-glycoproteins transport. (See CLINICAL PHARMACOLOGY - Drug Interactions.)

Ketoconazole and other potent CYP 3A4 inhibitors
Concomitant use of ketoconazole as well as other potent CYP 3A inhibitors such as itraconazole, ritonavir, cyclosporin, clarythromycin, erythromycin, nefazodone is contraindicated (see CONTRAINDICATIONS).

Grapefruit juice
As grapefruit juice increases dronedarone exposure, patients should be warned to avoid grapefruit juice beverages while taking dronedarone.

Rifampicin and other potent CYP 3A inducers
Rifampicin and other potent CYP3A4 inducers such as pentobarbital, carbamazepine, phenytoin, St John's Wort should not be used concomitantly with dronedarone because they decrease dronedarone exposure.

Calcium antagonists
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.

Statins which are CYP 3A4 substrates
As high doses of statins increase the risk of myopathy, concomitant use of statins which are CYP3A substrates should be undertaken with caution and patients monitored for clinical signs of muscular toxicity. *In patients taking these statins concomitantly with dronedarone, therapy should be started or adjusted to the lowest dose of the statin. Alternatively treatment with another statin that is not a CYP3A4 substrate should be considered.*

Beta- blockers
Due to the pharmacokinetic interaction and possible pharmacodynamic interaction, betablockers should be used with caution concomitantly with dronedarone.

Class I or III antiarrhythmics
Coadministration of class I or class III antiarrhythmic drugs with dronedarone is not recommended because of potential risk of proarrhythmia.

Drugs prolonging the QT interval (inducing *torsades de pointes*)
Coadministration of these drugs with dronedarone is not recommended.

Drugs eliminated by renal tubular secretion
Dronedarone has the potential to increase the exposure of drugs eliminated by renal tubular secretion because dronedarone inhibits this pathway.

Digoxin

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.

In clinical trials, patients treated with dronedarone received a variety of concomitant medications including diuretics, beta-blockers, digitalis, calcium antagonists (including those with heart rate-lowering effects), angiotensin converting enzyme inhibitors and angiotensin-II receptor antagonists, statins, coronary vasodilatators, antidiabetic agents, chronic antiplatelet therapy, and oral anticoagulants without evidence of clinically significant adverse interactions.

Carcinogenicity, Mutagenicity, Impairment of Fertility
In animals, there was no increased incidence of tumors considered relevant for humans. Dronedarone had no genotoxic effects, based on one *in vivo* micronucleus test in mice and four in vitro tests: the Ames test with or without metabolic activation, a DNA repair test on rat hepatocytes, a gene mutation assay on hamster fibroblasts and a cytogenetic study of human lymphocytes.
Dronedarone was not shown to alter fertility in animal studies up to 100 mg/kg/day.

Pregnancy
Pregnancy Category X (See CONTRAINDICATIONS.)
MULTAC was shown to be teratogenic in the rat and is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

MULTAC can cause fetal harm when administered to pregnant women. Dronedarone caused marked effects on embryo-fetal development in rats at 100 mg/kg/day such as increased post-implantation losses, reduced fetal and placental weights, various external, visceral and skeletal malformations in most fetuses. At lower dosages, up to 50 mg/kg/day (corresponding to 4.5 times the recommended human therapeutic dose), dronedarone had no effects on the litters (with the exception of a transient minor effect on the bodyweight gain of the pups from D1 to D4 post-partum). Dronedarone had no effects on the mothers up to 30 mg/kg/day. On the contrary, in rabbits, the high dose level (200 mg/kg/day) did not induce any effects to fetuses.

Labor and Delivery
It is not known whether the use of dronedarone during labor or delivery has any immediate or delayed adverse effects. In peri- and post-natal development studies in the rat, at doses up to 50 mg/kg/day, dronedarone induced no effect on the duration of gestation or on parturition.

Nursing Mothers
Dronedarone and its metabolites are excreted in rat milk. Nursing in lactating rats administered dronedarone was associated with minor reduced body-weight gain in the

offspring. It is not known whether this drug is excreted in human milk. Therefore, when dronedarone therapy is indicated, the mother should be advised to discontinue nursing.

Pediatric Use
Safety and efficacy in children below the age of 18 years have not been established. Therefore use in these patients is not recommended.

Geriatric Use
Of the total number of subjects in clinical studies of dronedarone, 50.7% were 65 and over. Clinical experience has not identified differences in response between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS
The safety of dronedarone 400mg twice daily was assessed in four placebo controlled studies , EURIDIS and ADONIS conducted for 12 months, and DAFNE and ERATO conducted for 6 months. In these studies, a total of 1681 patients were randomized and treated either with dronedarone twice daily (n = 1117) or placebo (n = 564). Nine hundred eighty nine (989) of the patients receiving dronedarone received the 400 mg twice-daily dose. Two hundred and eighty three (283) patients were treated with dronedarone 400 mg twice daily for 1 year and 661 patients were treated for 6 months. Because clinical trials are conducted under widely varying conditions, adverse reaction-rates observed in the clinical trial cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. However, as these studies were placebo-controlled studies, the medical importance of the observed emergent adverse events during these studies should be considered.
Overall, there were more treatment- emergent adverse events with dronedarone 400mg twice daily (67%) compared to placebo (60%). The most frequent adverse reactions observed in these 4 studies were diarrhea, serum creatinine increased, upper respiratory infection and back pain. Diarrhea was usually mild to moderate and did not lead to dronedarone discontinuation except in rare cases (0.4%).
Twenty-eight events occurred at a rate of ≥ 1% and were ≥ 0.5% more than the corresponding placebo rate (table 3). Conversely a total of 9 events occurred at a rate of ≥ 1% with the placebo rate ≥ 0.5% more than that of dronedarone.

Table 3 – Number of patients with incidence of adverse events ≥ 1 % and difference versus placebo of ≥ 0.5% in four placebo-controlled studies in patients with AF/AFL

Organ Class Preferred term	Placebo (N=564)	Dronedarone 400 mg BID (N=989)
Gastrointestinal Disorders		
Diarrhea	4.1	6.7
Nausea	3.0	3.9
Any abdominal pain (a)	2.8	4.0
Vomiting	0.7	1.7
Infections and Infestations		
Nasopharyngitis	3.2	3.7
Upper respiratory tract infection	1.1	2.9
Bronchitis	0.9	1.9
Urinary tract infection	0.4	1.5
Nervous System Disorders		
Paraesthesia	0.7	1.3
Investigations		
Blood creatinine increased	0.2	2.2
Blood creatine phosphokinase increased	0.9	1.5
Gamma-glutamyltransferase increased	0.4	1.2
Cardiac Disorders		
Bradycardia	1.4	2.6
Cardiac failure congestive	0.7	1.3
General Disorders and Administration Site Conditions		
Any oedema (b)	4.1	4.8
Asthenia/fatigue (c)	2.8	3.7
Non-cardiac chest pain	0.5	1.5
Musculoskeletal and Connective Tissue disorders		
Back pain	1.6	3.3
Arthralgia	1.6	3.1
Pain in extremity	0.9	2.1
Joint swelling	0.2	1.3
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.4	2.2
Epistaxis	0.5	1.7
Skin and Subcutaneous Tissue Disorders		
Any rash (d)	1.6	3.8
Eczema	0.0	1.0
Psychiatric Disorders		
Anxiety	0.5	1.1
Depression	0.4	1.1

Organ Class Preferred term	Placebo (N=564)	Dronedarone 400 mg BID (N=989)
Ear and Labyrinth Disorders Vertigo	0.2	1.3

(a) Groups together 'abdominal pain lower', 'abdominal pain' and 'abdominal pain upper' preferred terms
(b) Groups together 'oedema' and 'oedema peripheral' preferred terms
(c) Groups together 'asthenia' and 'fatigue' preferred terms
(d) Groups together: rash, rash erythematous, photosensitive rash, rash maculo-papular, rash pruritic, heat rash, rash macular, rash papular preferred terms

Heart failure occurred more frequently in older patients.
In addition the following events that may be of clinical interest were reported with dronedarone 400 mg twice daily: photosensitivity reaction (0.4 %), anemia (0.7 %), acute renal failure (0.2 %) and sudden death (0.5 %).
No *torsades de pointes* were reported in clinical studies.

OVERDOSAGE
No case of overdosage has been reported.
In the event of overdosage, the patient's cardiac rhythm and blood pressure should be monitored in addition to general supportive measures. Treatment should be supportive and based on symptoms.
It is not known whether dronedarone and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).
There is no specific antidote available.

DOSAGE AND ADMINISTRATION
The recommended dosage is 400 mg twice daily (800 mg daily).
MULTAC should be taken as one tablet with or shortly after the morning meal and one tablet with or shortly after the evening meal.
Treatment with MULTAC can be initiated in an outpatient setting.

Switch to MULTAC from Class I or Class III antiarrhythmic therapy:
Treatment with MULTAC can be initiated as soon as amiodarone therapy is stopped. An ECG should be performed in these patients about 4 hours after drug administration. It is recommended that all other Class I and III antiarrhythmics be withdrawn for at least 5 plasma half-lives before starting treatment with MULTAC.

HOW SUPPLIED
MULTAC 400 mg tablets are provided as white film- coated tablets for oral administration, oblong- shaped, engraved with a double wave marking on one side and "4142" code on the other side in:

bottles of 60 tablets, NDC 0024-4142-60
bottles of 180 tablets, NDC 0024-4142-18
bottles of 500 tablets NDC 0024-4142-50
box of 10 blisters (10 tablets per blister) NDC 0024-4142-50

Special Handling and Storage conditions
Store at up to 25°C (77°F) [see USP controlled room temperature].

Store in the original package.

Manufactured by:
Sanofi Winthrop Industrie
Ambares
33565 Carbon Blanc Cedex
France

Distributed by:
Sanofi-Synthelabo Inc.
New York, NY 10016

MULTAC® is a trademark of Sanofi-Synthelabo Inc.

Made in France

4.2 Individual Study Reviews

List of Studies in NDA 21-913

Study Report ID	Study Title or Description	Reviewed?
	Bioavailability	
PPK2397	Assessment of food effect on pharmacokinetic parameters of a single dose (800 mg) of SR33589B and assessment of absolute bioavailability	No
ALI3179	Effect of Fat Content on the Bioavailability of an Oral Administration of Two 400 mg Tablets of SR33589B Containing 5% of Pluronic F127.	No
ALI3180	Effect of fat content on the bioavailability of an oral administration of two 400 mg tablets of SR33589B containing 10% of Pluronic F127.	Yes
BDR2889	Relative bioavailability of four different formulations after a single oral dose of 800 mg of SR33589B under fasting and non- fasting conditions in healthy male subjects.	No
GAR3144	Relative bioavailability of three different formulations after a single oral dose of 800 mg of SR33589B under fasting and non fasting conditions in healthy male subjects.	No
GAR3585	Relative bioavailability of four different formulations after a single oral dose of 800 mg of SR33589B under fasted and fed conditions in healthy male subjects.	No
BDR4680	Relative bioavailability between the dronedarone tablets used in phase II studies and those prepared for phase III studies after single oral administration to young healthy subjects. Open, randomized, crossover and single center study.	Yes
	Healthy Subject Pharmacokinetic and Initial Tolerability Study Reports	
TDU2163	Single ascending dose tolerability study of SR33589B administered orally to healthy volunteers.	No
TDU2164	Single ascending dose tolerability study of SR33589B administered intravenously to healthy volunteers.	No
BEX2770	Excretion balance, pharmacokinetics, metabolite profile, and identification after a single PO and i.v. (by infusion) dose of SR33589B using 14C and 13C- labeled compounds in healthy male subjects.	Yes
TDU3007	Study on the tolerability of SR33589B given as a single ascending dose administered intravenously in healthy male subjects.	Yes
TDU4899	Study of the safety and pharmacokinetics or (SR33589B) in single oral administration in Japanese young male healthy subjects.	Yes
TDR2395	Study on the tolerability of SR33589B given as single and multiple oral doses in healthy male subjects under non fasted conditions.	Yes
LIN2890	Dose proportionality study after oral single and twice daily (BID) repeated (for 10 days) administrations of 200 mg, 400 mg, 800 mg dronedarone in healthy young male subjects - Randomized, open- labeled, non placebo-controlled, three- treatment, three- period crossover study.	Yes
TDR3549	Study on the tolerability of SR33589B given twice daily as repeated ascending oral doses in healthy male subjects.	Yes
	Patient Pharmacokinetic and Initial Tolerability Study Reports	
TDR2394	Repeated ascending dose tolerability study of SR33589B administered orally to patients with premature ventricular beats.	No
	Intrinsic Factor Pharmacokinetic Study Reports	
POP2769	Pharmacokinetic profile of SR33589 and its metabolite SR35021 after single and repeated oral administration of 800 mg SR33589B in healthy young male and elderly male and female subjects.	Yes
POP2896	Pharmacokinetics and safety of dronedarone after repeated oral doses for 10 days in patients with moderate hepatic impairment in comparison with healthy matched subjects- non- randomized, non- placebo-controlled, open-labeled, 2 parallel- groups study.	No
	Drug-Drug Interaction Study Reports	
INT2631	Assessment of plasma levels of single dose of warfarin administered alone or following administration of a repeated dose of SR33589B in healthy male volunteers.	No
INT2634	Evaluation of the effect of repeated oral doses of SR33589B on steady-state plasma digoxin concentrations in healthy volunteers.	No
INT2636	Pharmacokinetic and pharmacodynamic effects of single and repeated oral	Yes

	doses of SR33589B and of propranolol given alone or coadministered in healthy male subjects.	
INT2931	Tolerability of ascending oral doses of SR33589B Co-administered with a stable dose of 80 mg of propranolol in healthy male subjects.	No
INT3353	Study on the interaction between a single oral dose of warfarin and repeated oral doses of SR33589B in healthy male subjects.	Yes
INT3560	Pharmacokinetic interaction of repeated oral 40 mg o.d. pantoprazole on repeated oral 400 mg bid dronedarone in healthy young male subjects - Open- labeled, non placebo-controlled, randomized, 2- treatment, 2- period crossover study.	Yes
INT3561	Influence of repeated oral doses of ketoconazole [inhibitor of cytochrome P450 3A4 (CYP3A4)] on the pharmacokinetic profile of dronedarone in healthy male subjects.	Yes
INT3683	Influence of repeated oral doses of Rifampicine (inducer of Cytochrome P450 3A4) on the pharmacokinetic profile of Dronedarone in healthy male subjects.	Yes
PDY3828	Dose escalation study tolerability and pharmacokinetic effects of Dronedarone on top of Metoprolol in healthy male volunteers.	Yes
INT4074	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.	Yes
INT4442	Interaction between repeated oral doses of dronedarone and a single oral dose of simvastatin in healthy male subjects.	Yes
INT4695	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.	Yes
INT4880	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.	Yes
INT4881	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.	Yes
INT4882	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	Yes
INT4884	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.	Yes
INT4886	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.	Yes
INT5189	Pharmacokinetic interaction of repeated oral 400 mg BID dronedarone for 10 days on repeated oral 0.25 mg OD Digoxin in healthy young male subjects - Randomized, double- blind, placebo- controlled, two- sequence, two-treatment, crossover study.	Yes
INT	Theophylline	Yes
	Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Study Reports	
POH0051	Population Pharmacokinetic Analysis on the pool of EURIDIS & ADONIS (European and American- Australian trials in atrial fibrillation or flutter patients for the maintenance of sinus rhythm) and ANDROMEDA (Antiarrhythmic trial in congestive heart failure and left ventricular dysfunction) studies.	Yes
PDY5487	Effect of dronedarone on renal functions in healthy male subjects - Randomized, double- blind, placebo- controlled, two- by- two crossover in sequential groups study.	Yes
	Renal function	No
PDY2399	Hemodynamic study of patients with normal left ventricular function following I.V. infusion of 3 doses of SR33589B or I. V. amiodarone.	No
PDY2400	Study of the electrophysiological and hemodynamic characteristics of	No

	SR33589B administered intravenously to patients with impaired left ventricular function.	
ACT2401	Study of the safety and the pharmacodynamic effects of SR33589B administered orally for one month to patients with left ventricular dysfunction.	No
PDY2402	Study of the electrophysiological and hemodynamic characteristics of SR33589B administered orally for one month at the doses 400mg and 800mg versus Amiodarone (400mg) to patients with normal or impaired left ventricular function.	No
SPH, LPH and DOH studies	**Reports of Bioanalytical and Analytical Methods for Human Studies (n = 15)**	Yes (partially)
	Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials	
LPH0006	In Vitro Characterisation of the Binding of [14C]- SR33589 to Human Plasma Proteins.	Yes
LPH0021	In Vitro Characterisation of the Binding of [14C]- SR35021 to Human Plasma Proteins.	Yes
MIH0006	Assessing the potential for Co- administered drugs to inhibit the N-debutylation of SR33589B using human liver microsomes in vitro.	No
MIH0007	Assessing the potential for SR33589B or amiodarone to inhibit cytochrome P450 (CYP) enzymes using human liver microsomes in vitro.	Yes
MIH0037	Investigating the Potential for SR35021 to Inhibit Cytochrome P450 (CYP) Enzymes Using Human Liver Microsomes in vitro.	Yes
MIV0144	Regulation of the expression of cytochrome P450 gene subfamilies IA, IIA and IIIA by SR33589B in primary cultures of human hepatocytes.	Yes
MIV0158	SR33589B metabolism using human hepatic models.	Yes
MIV0159	Identification of main cytochrome P450 isozymes involved in SR33589B metabolism by human liver microsomal fractions.	Yes
MIV0281	Role for CYP3A4 in the hepatic metabolic clearance of SR33589B, using primary cultures of human hepatocytes.	No
AIV0062	In vitro investigation of SR33589B trans- epithelial transport polarisation and inhibitory potency towards the active efflux of vincristine and digoxine using Caco- 2/TC-7 cells monolayers.	Yes
	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication	
DRI3550	Dose-ranging study of the efficacy and safety of Dronedarone for the maintenance of sinus rhythm in patients undergoing cardioversion for atrial fibrillation.	Yes (PM consult)
EFC4508	Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO).	No
EFC3153	EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maIntenance of Sinus rhythm (EURIDIS).	No
EFC4788	American- Australian- African trial with DronedarONe In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm (ADONIS).	No
	Other Study Reports	
ACT2771	Efficacy of the intravenous formulation of SR33589B (dronedarone) in patients with a sustained episode of atrial fibrillation at the dose 80 mg versus placebo.	No
PDY2945	Study of the efficacy of Dronedarone (SR33589B) in the suppression of inducible ventricular tachycardia.	No
DRI3151	Placebo- controlled dose- finding safety and tolerability study in patients with an implantable cardioverter defibrillator (ICD).	No
LTS3841	Long- term tolerability and efficacy estimation study in patients with an implantable cardioverter defibrillator (ICD).	No
EFC4966	ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity DecreAse (ANDROMEDA).	No

4.2.1 Dose proportionality study after oral single and twice daily (BID) repeated (for 10 days) administrations of 200 mg, 400 mg, 800 mg dronedarone in healthy young male subjects - Randomized, open- labeled, non placebo- controlled, three-treatment, three-period crossover study (LIN2890)

PROTOCOL #	LIN2890
INVESTIGATOR	Dr Nicolas Fauchoux
STUDY SITE	Biotrial Rue Jean- Louis Bertrand Technopole Atalante Villejean 35000 Rennes, France
STUDY PERIOD	06 May 2004 to 15 Sep 2004

Objectives (per applicant):

- To assess the deviation from dose proportionality of dronedarone and of its N-debutyl metabolite SR35021 pharmacokinetics after 200 mg, 400 mg, and 800 mg single and BID repeated oral doses of dronedarone for 10 days.
- To assess the clinical and biological tolerability [including blood pressure (BP), heart rate (HR), and electrocardiogram (ECG)] of 200 mg, 400 mg, and 800 mg single and repeated oral doses of dronedarone for 10 days.

Study Design

This was a randomized, open-labeled, non placebo-controlled, three-treatment, three-period crossover study. There was a washout of 14 days between periods. Healthy male subjects, aged between 18 to 40 years were enrolled. Doses were as follows: 200 mg (2 x 100 mg tablets), 400 mg (1 x 400 mg tablet) and 800 mg (2 x 400 mg tablets). All doses were given as a single dose on Day 1, BID from Day 5 to Day 13, and only in the morning on Day 14. Dronedarone was given orally in fed conditions (standard meal). Details of the standard meal were not provided.

Subject Demographics

Subject demographics are presented in Table 26.

Formulation (2E3 Formulation)

- Dronedarone 100 mg tablets, batch number CL-04600
- Dronedarone 400 mg tablets, batch number CL-04530

Pharmacokinetics

The following pharmacokinetic measures were determined:

- Day 1: Cmax, tmax, AUC_{0-12h}, AUClast, AUC, $t_{1/2z}$, CL/F, Vz/F (for dronedarone only), and metabolic ratio, Rmet, (SR35021 AUC_{0-12}/dronedarone AUC_{0-12}).
- Day 14: Cmax, tmax, AUC_{0-12h}, $t_{1/2}z$, CL/F, Vz/F (for dronedarone only), and Rmet; accumulation ratio, Rac, calculated from AUC_{0-12h} and Cmax.

Pharmacokinetic sampling times

PK samples for assays of dronedarone and its metabolite SR35021 were collected as follows:

- before dosing (T0) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72 and 96 hours after dosing on Day 1 and Day 14
- before morning dosing (T0) for trough determinations on Days 6, 7, 8, 9, 10, and 12.

Table 26: Subject Demographic Data

Parameter (Unit)	Statistics / Category	Overall Subjects (N = 21)
Age (years)	N Mean (SD) Min-Max	21 28.3 (6.4) 19-40
Weight (kg)	N Mean (SD) Min-Max	21 71.67 (9.34) 54.0-89.0
Height (cm)	N Mean (SD) Min-Max	21 178.2 (6.5) 168-192
BMI (kg/m^2)	N Mean (SD) Min-Max	21 22.56 (2.88) 19.0-28.7
Gender	Male (N,%)	21 (100)
Race	Caucasian (N,%) Black (N,%) Other (N,%)	18 (85.7) 2 (9.5) 1 (4.8)

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in Table 27.

Table 27: Performance of Dronedarone and SR35021 Assays (DOH0309)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day precision	CV data were not provided	Cannot be assessed
Between day accuracy	The majority of QC samples were within 15 % of the nominal concentrations	Acceptable
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day precision	CV data were not provided	Cannot be assessed
Between day accuracy	The majority of QC samples were within 15 % of the nominal concentrations	Acceptable
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

*The validation report for the assay included precision measurements (CV < 5 %) and chromatograms that suggest that the assay was precise and specific

Results

Subject Disposition (Patients contributing PK data)

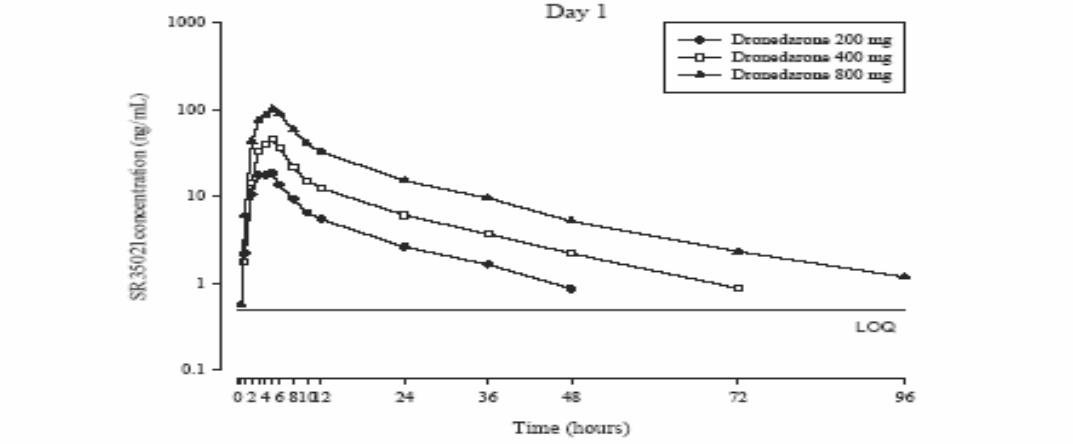
Data from several subjects were excluded from the PK analyses for various reasons; the main reasons for exclusions were absence of PK assessments and incomplete PK assessments. Exclusion of these data appears reasonable. Despite these exclusions there were a sufficient number of subjects to facilitate statistical analysis of PK data ($n \geq 16$ for each condition).

Reviewer Note on Figures and Tables
It should be noted that Study Day 5 and Day 14 correspond to the first and tenth days of BID dosing respectively.

Plasma Concentrations

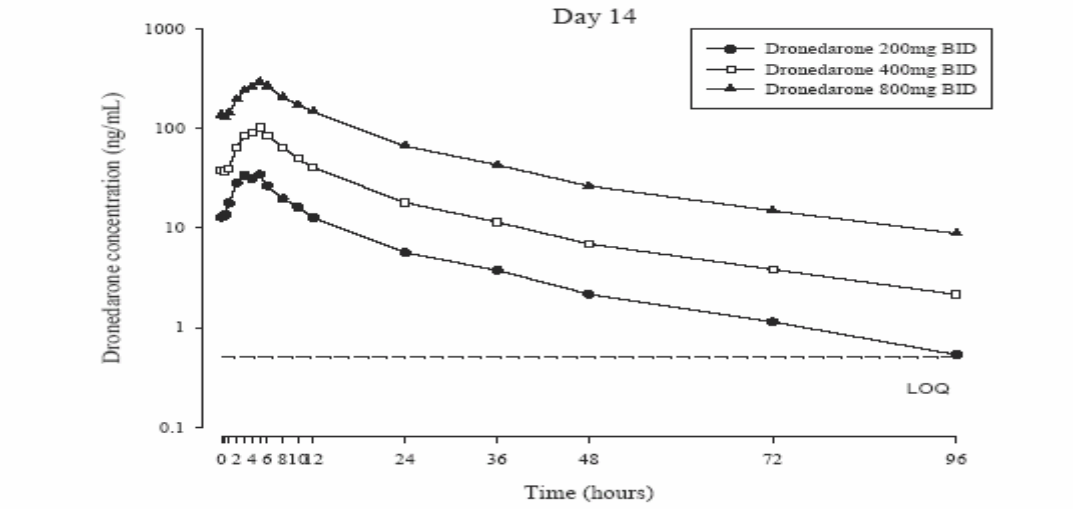
The dronedarone plasma concentration-time profile on Day 1 is depicted in Figure 14.

Figure 14: Mean dronedarone plasma concentration-time profile on Day 1



The dronedarone plasma concentration-time profile on Day 14 is depicted in Figure 15.

Figure 15: Mean dronedarone plasma concentration-time profile on Day 14



Both Day 1 and day 14 profiles depict a biphasic elimination of dronedarone after Cmax is reached. The Day 1 and 14 plasma concentration-time profiles of the dronedarone metabolite are depicted in Figure 16 and Figure 17, respectively.

Figure 16: Mean SR35021 plasma concentration-time profile on Day 1 following dronedarone administration

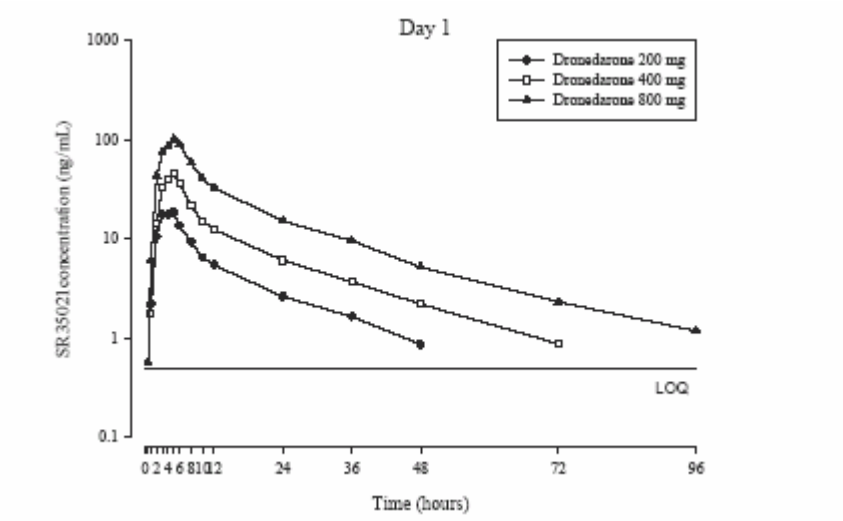
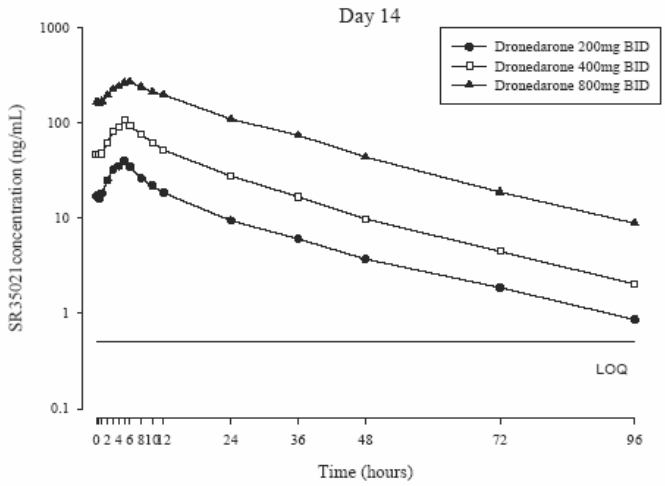


Figure 17: Mean SR35021 plasma concentration-time profile on Day 14 following dronedarone administration



Dronedarone and SR35021 PK measures on Day 1 and Day 14 are presented in Table 28.

General Observations

- Dronedarone and SR35021 plasma concentrations increased with dose in a greater than dose proportional manner over the 200 to 800 mg dosage
- Day 14 concentrations were greater than Day 1 concentrations, indicating accumulation occurred
- Tmax was independent of Day or dronedarone dose
- Day 1 $t_{1/2}$ (< 20 hr) appeared shorter than Day 14 $t_{1/2}$ (> 29 hr), and Day 1 $t_{1/2}$ was dose-dependent

Table 28: Dronedarone and SR35021 PK Measures in Healthy Males Following Single and Multiple Dose Administration (200, 400 and 800 mg BID)

PK Parameters		Dronedarone			SR35021		
		200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]	200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]
C_{max} (ng/mL)	Day 1	23.1 (38)	67.2 (36)	162 (40)	20.8 (21)	49.5 (25)	109 (29)
	Day 14	40.3 (30)	111 (17)	298 (13)	41.2 (27)	107 (22)	282 (21)
t_{max} [a] (h)	Day 1	3 [2; 5]	3 [2; 5]	3 [2; 6]	5 [2; 5]	5 [3; 6]	5 [3; 6]
	Day 14	5 [2; 5]	5 [3; 6]	5 [2; 6]	5 [2; 6]	5 [3; 8]	5 [3; 4 8]
AUC_{0-12} (ng.h/mL)	Day 1	111 (24)	310 (28)	846 (27)	123 (19)	275 (23)	668 (24)
	Day 14	276 (23)	798 (19)	2510 (12)	325 (21)	882 (17)	2680 (20)
$t_{1/2z}$ (h)	Day 1	9.81 (33)	17.6 (56)	19.6 (33)	16.2 (28)	19.2 (24)	21.9 (22)
	Day 14	26.9 (32)	30.0 (29)	31.2 (32)	23.5 (14)	21.1 (16)	20.4 (8)
AUC (ng.h/mL)	Day 1	160 (27)	474 (33)	1310 (26)	237 (23)	545 (22)	1360 (20)
CL/F [d] (L/h)	Day 1	1350 (29)	937 (35)	669 (38)	-	-	-
	Day 14	765 (25)	517 (18)	324 (13)	-	-	-
Vz/F [d] (L)	Day 1	18000 (24)	21000 (31)	17900 (33)	-	-	-
	Day 14	29400 (34)	22800 (41)	14500 (31)	-	-	-

Numbers rounded at 3 significant figures.
[a] median value [Min–Max]
[b] n = 14 at Day 14
[c] n = 16 at Day 14
[d] CL_{0-12}/F and Vz_{0-12}/F at Day 14

Dose Proportionality Assessment

As shown in Table 13 there was a slightly greater than proportional increase in plasma exposure on Day 1 and Day 14 with increasing dose (pooled data from three dronedarone doses):

- Day 1: for a two-fold in increase in dose exposure increased more than 2.6-fold
- Day 14: for a two-fold in increase in dose exposure increased more than 2.7-fold

This finding suggests that dronedarone may exhibit non-linear PK. The source of the non-linearity is not known; however, non-linearity does not appear due to saturable elimination because half-life was comparable for all dronedarone regimens (~ 30 hours on Day 14).

Table 29: Dose-proportionality Estimations Following Single and Multiple Dose Administration of Dronedarone 200, 400 and 800 mg Doses

Ratio estimates for dose proportionality at Days 1 and 14

PK Parameters		Ratio Estimate	90% CI
Dronedarone			
C_{max} (ng/mL)	Day 1	2.62	[2.39 – 2.88]
	Day 14	2.77	[2.62 – 2.93]
AUC[a] (ng.h/mL)	Day 1	2.86	[2.67 – 3.06]
	Day 14	3.06	[2.92 – 3.20]
SR35021			
C_{max} (ng/mL)	Day 1	2.24	[2.10 – 2.38]
	Day 14	2.59	[2.46 – 2.73]
AUC[a] (ng.h/mL)	Day 1	2.37	[2.27 – 2.48]
	Day 14	2.82	[2.71 – 2.93]

a: AUC_{0-12} at Day 14.

Accumulation Assessment

The accumulation ratios for the various dronedarone regimens are summarized in Table 30.

Table 30: Accumulation Ratio Summary for BID Dosing

Accumulation ratio summary

PK Parameters		R_{ac} Estimate	95% CI
Dronedarone			
C_{max} (ng/mL)		1.84	[1.65, 2.04]
AUC_{0-12} (ng.h/mL)		2.72	[2.52, 2.94]
SR35021			
C_{max} (ng/mL)	200 mg	1.96	[1.72, 2.23]
	400 mg	2.15	[1.87, 2.47]
	800 mg	2.66	[2.33, 3.03]
AUC_{0-12} (ng.h/mL)	200 mg	2.62	[2.36, 2.91]
	400 mg	3.21	[2.87, 3.60]
	800 mg	4.07	[3.65, 4.53]

The applicant pooled accumulation ratio (R_{ac}) data for the three dronedarone doses, rather than calculating R_{ac} for separate doses. The approximate ratios (based on linear scale AUCs) for each dose were 200 mg ~ 2.49, 400 mg ~ 2.57 and 800 mg ~ 2.97. Thus, numerically, there appears to be an increasing degree of accumulation with increasing dose; this trend was also observed for the metabolite.

Metabolic Ratio

The metabolic ratio, SR35021/Dronedarone for AUC and Cmax on Days 1 and 14 are presented in Table 12

Table 31: Mean (CV %) metabolic ratio of Cmax and AUC

Dose		200 mg n = 17	400 mg n = 16 [b]	800 mg n = 17 [c]
R_{met} C_{max}	Day 1	0.996 (34)	0.795 (32)	0.724 (31)
	Day 14	1.08 (28)	0.973 (20)	0.944 (15)
R_{met} AUC[a]	Day 1	1.55 (25)	1.22 (26)	1.08 (19)
	Day 14	1.22 (24)	1.12 (17)	1.07 (17)

[a] AUC on Day 1 and AUC_{0-12} on Day 14
[b] n = 14 at Day 14
[c] n = 16 at Day 14

Based on Day 1 AUC and Cmax data, more metabolite was formed at lower doses than at higher doses, suggesting saturation in metabolism may occur (non-linear PK). On Day 14, numerically the same trend was observed, but differences were not as great as on Day 1.

Steady State Assessment

Based on a visual inspection of the data (Figure 18 and Figure 19) following the 400 mg BID dose, dronedarone and SR35021 steady-state is achieved by Day 9, which corresponds to 4 days of BID dosing. There appeared to be a dose effect with respect to time to reach steady state. The applicant's statistical analyses revealed that dronedarone steady-state is achieved within 3 to 4 days and SR35021 steady-state is achieved within 4 to 5 days. Overall the findings suggest that steady state is reached within 6 days of dosing (~ 1 week).

Figure 18: Dronedarone Ctrough vs. Time

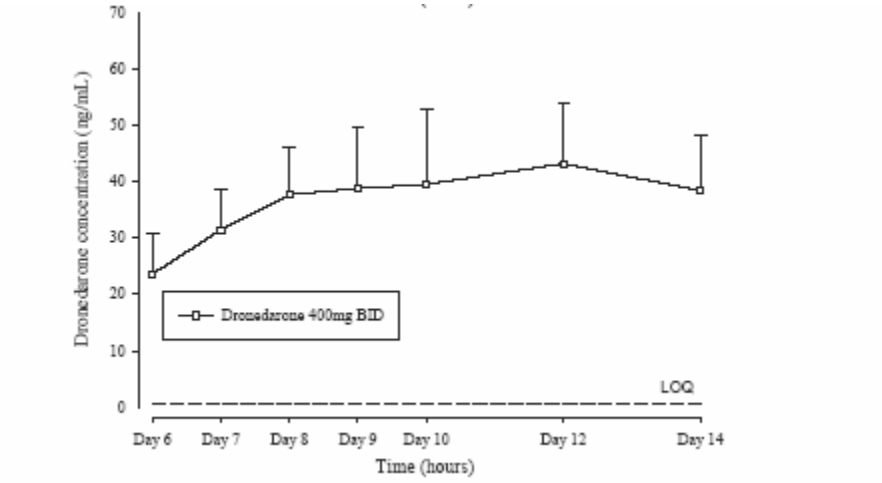
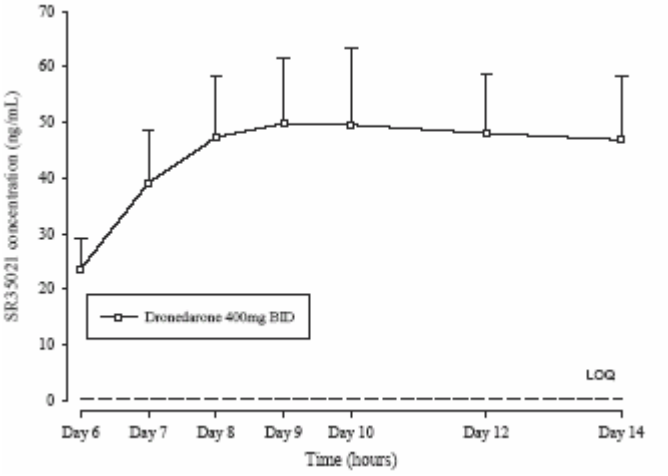


Figure 19: SR35021 Ctrough vs. Time



Applicant's Safety Summary

No deaths or serious adverse events (SAEs) occurred during the study. The most common treatment emergent adverse event in all dronedarone dose groups was asthenia (23.5%). Two subjects were withdrawn from treatment because of AEs: one due to a moderate urticaria occurred 4 days after completing the period 1 treatment with dronedarone 800 mg; and one due to a severe myalgia on Day 10 of period 3 treatment with dronedarone 800 mg. Both events resolved after drug discontinuations. Regarding ECG parameters, no prolongation of QTc > 500 ms was recorded. Two subjects in the 800 mg treatment period experienced both prolonged QTc intervals > 450 ms and changes from baseline in delta QTc > 60 ms. The overall clinical and laboratory tolerability of dronedarone 200 mg, 400 mg, and 800 mg single and BID administrations in this study was good.

Recommendations/Conclusions

The following PK information generated in Study LIN2890 is acceptable for labeling purposes, as appropriate. It should be noted that PK were not determined in the fasted state

1. Steady-state dronedarone and SR35021 concentrations were reached within 6 days.
2. Dronedarone appears to exhibit non-linear PK as shown by:
   - Cmax and AUC_{0-12} of dronedarone and SR35021 increased more than dose-proportionally, for a two fold increase in dose, plasma exposure increased > 2.6 times
   - The amount of metabolite formed appeared to be dose dependent: the lower the dose, the more metabolite formed. This finding suggests that there is a saturable first pass effect.
3. The accumulation ratio (based on AUC ratios) was approximately 2.7 across the 200 mg to 800 mg dose range; the accumulation ratio for the 400 mg dose was ~ 2.6
4. Dronedarone $t_{1/2}z$ increased significantly from 200 mg to 800 mg and from Day 1 to 10.

Mean (CV %) Dronedarone PK Measures following 400 mg Dronedarone Dose in Healthy Subjects

PK Measure	Single 400 mg Dose	Day 10 Multiple 400 mg BID Dose (steady state)
AUC (ng·h/mL)	310 (24)	798 (19)
Cmax (ng/mL)	67.2 (36)	111 (17)
Half-life (h)	17.6 (56)	30 (29)
Tmax (h)^	3 (2 to 5)	5 (3 to 6)

^ Tmax reported as median and (range)

4.2.2 Excretion balance, pharmacokinetics, metabolite profile, and identification after a single p.o. and i.v. (by infusion) dose of SR33589B using 14 C And 13 C- labeled compounds in healthy male subjects (BEX2770)

PROTOCOL #	BEX2770
INVESTIGATOR	Philip T. Leese, M. D.
STUDY SITE	Innovex Inc., 11250 Corporate Avenue, Lenexa, Kansas 66219.
STUDY PERIOD	October to December 1996

Objectives (per applicant)

- To determine the pharmacokinetics of ^{14}C relative to unchanged SR33589B (dronedarone) in blood and plasma; the balance excretion (mass balance) of ^{14}C in urine, feces and expired air; the metabolite profile in urine, feces and plasma; and the identification of metabolites in selected samples after single oral (p.o.) or single intravenous (i.v.) doses.
- To assess clinical and biological safety and tolerability of dronedarone.

Study Design

This was an open-label, single dose, parallel group study in healthy male volunteers. Twelve subjects enrolled: n = 6, single oral dose six and n = 6, single intravenous dose. A single 800 mg dronedarone dose was given orally: 400 mg as ^{13}C- dronedarone and 400 mg as ^{14}C-dronedarone. A single 40 mg dronedarone dose was given intravenously: 20 mg of dose was ^{13}C-dronedarone and 20 mg ^{14}C- dronedarone. The IV dose was given as a 60-minute infusion. The study proceeded for seven days post-dose or until urinary and excretion radioactivity criteria were met (< 0.1 % of dose and < 0.5 % of dose for urine and feces, respectively).

Subject Demographics

The subject demographics are summarized in Table 32.

Table 32: Demographic Characteristics of Subjects in BEX2770

Demographic characteristic	Oral SR33589B (n=6)	Intravenous SR33589B (n=6)
Age (years)		
Mean (SD)	60.5 (6.2)	56.2 (7.4)
Range	50.0 - 69.0	51.0 - 68.0
Weight (kg)		
Mean (SD)	79.1 (9.5)	87.2 (10.1)
Range	70.7 - 95.6	75.2 - 100.1
Height (cm)		
Mean (SD)	174.2 (5.1)	177.6 (5.6)
Range	165.8 - 181.0	167.6 - 183.0

It should be noted that all subjects were > 50 years, which may affect drug disposition, if an age effect exists for dronedarone.

Formulation

- Dronedarone capsules, 200 mg, ^{13}C- labeled dronedarone; batch No. DPJ 134
- Dronedarone capsules, 200 mg, ^{14}C- labeled dronedarone with 179.01 m Ci (6.63 MBq); batch No. DPJ 134
- Dronedarone solution, 0.33 mg/mL; batch No. DPJ 137.
- Dronedarone solution, 0.33 mg/mL with 60.6 m Ci (2.24 MBq) of ^{14}C-labeled dronedarone; batch No. DPJ 137.

Bioanalytical Assay

Liquid scintillation counting was used to determine radioactivity in the different matrices. Blood concentrations of dronedarone and its N-debutyl metabolite, SR35021, in plasma was determined by a validated electrospray LC-MS/MS. Metabolite profiling and quantification was conducted by HPLC with fraction collection, followed by liquid scintillation counting. The metabolite structures were elucidated using tandem mass spectrometry with electrospray ionization following HPLC. All assays performed in an acceptable manner.

Pharmacokinetic Methods

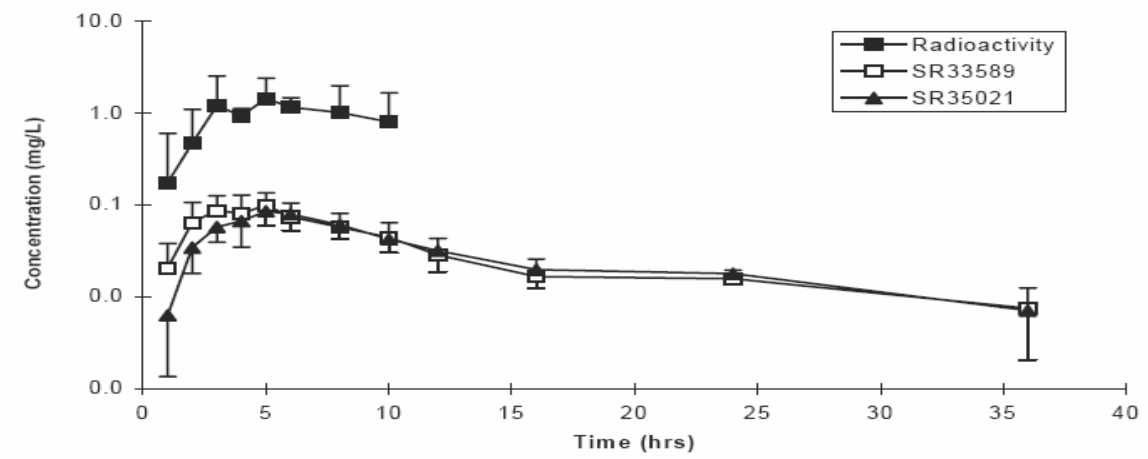
The pharmacokinetics (PK) of total radioactivity, dronedarone and SR35021 and metabolites in plasma, urine, feces and expired air were determined, as appropriate. No formal statistics were performed on the PK measures.

Results

Oral and IV Plasma Pharmacokinetics

The mean (± SD) plasma concentration-time profiles of radioactivity, SR33589 (dronedarone) and SR35021 following oral administration of 800 mg dronedarone are shown Figure 20.

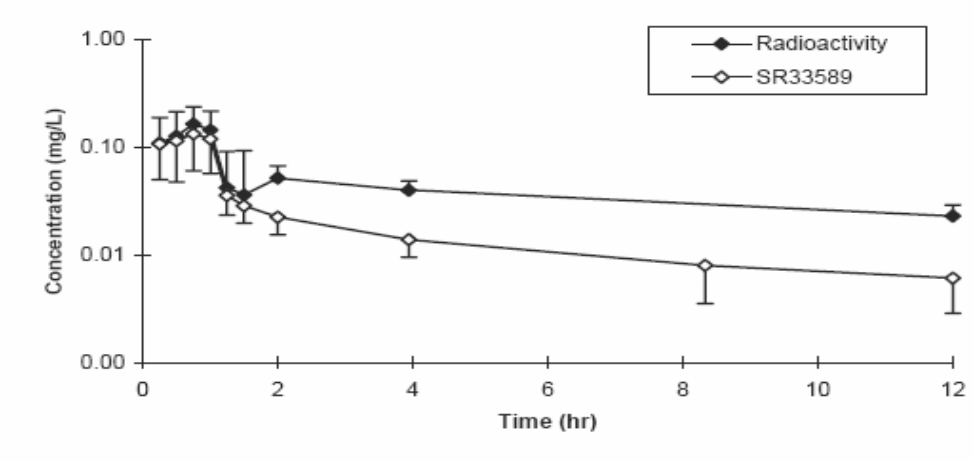
Figure 20: Plasma concentration-time profiles of total radioactivity, dronedarone and SR35021 following oral administration of radiolabeled dronedarone



The profiles suggest that dronedarone is extensively metabolized, as the total radioactivity exceeds that of non-labeled dronedarone and its known metabolite, SR35021.

The mean (± SD) plasma concentrations of radioactivity and dronedarone following intravenous administration of 40 mg dronedarone is shown in Figure 21.

Figure 21: Plasma concentration-time profiles of total radioactivity and dronedarone following intravenous administration of radiolabeled dronedarone



The profile obtained after IV administration indicates:

- dronedarone is extensively metabolized
- the primary metabolite, SR35021 is not formed, suggesting SR35021 is formed mainly during first pass metabolism after oral administration

The mean (SD) plasma PK measures of total radioactivity, dronedarone and SR35021 following oral administration of 800 mg (6.63 MBq) of ^{14}C-droendarone are shown in Table 33.

Table 33: PK measures for dronedarone, SR35021 and total radioactivity following oral dronedarone administration

Parameter (units)	Oral Group		
	Radioactivity [a,b]	SR33589 [a]	SR35021 [a]
C_{max} (mg/L)	1.75 (1.06)	0.10 (0.04)	0.09 (0.02)
t_{max} (h)	4.5 [c] (3 to 6) [d]	4.5 [c] (3 to 6) [d]	5.5 [c] (5 to 6) [d]
$t_{1/2}$ (h)	ND [e]	18.84 (4.01)	18.49 (2.57)
AUC_{0-t} (mg*h/L)	19.86 (29.85)	1.11 (0.41)	1.08 (0.34)
t (h)	11.0 (2.0)	36.0 (7.6)	40.8 (6.6)
AUC (mg*h/L)	ND	1.58 (0.39)	1.46 (0.34)
%(Extrapolated AUC /AUC)	ND	18.35 (6.54)	18.46 (4.43)

[a] Mean (±SD)
[b] Radioactivity is expressed as mg-equivalents where appropriate
[c] Median of all subjects
[d] Range for t_{max} from all subjects
[e] Not determined

The applicant notes that a terminal elimination half-life for plasma radioactivity could not be determined due to the rapid decline of plasma concentrations of radioactivity.

The mean (SD) plasma pharmacokinetic parameters of radioactivity and dronedarone following IV administration of 40 mg radiolabeled dronedarone are shown in Table 34.

Table 34: PK Measures for dronedarone and total plasma radioactivity following IV administration of radiolabeled dronedarone

Parameter (units)	Intravenous Group	
	Radioactivity [a,b]	SR33589 [a]
C_{max} (mg/L)	0.17 (0.07)	0.14 (0.07)
t_{max} (h)	0.83 [c] (0.75 to 1.0) [d]	1.0 [c] (0.75 to 1.25) [d]
$t_{½}$ (h)	11.76 (5.78)	10.97 (5.21)
AUC_{0-t} (mg*h/L)	0.65 (0.32)	0.35 (0.15)
t (h)	17.33 (8.26)	17.33 (6.02)
AUC (mg*h/L)	0.95 (0.44)	0.49 (0.19)
%(Extrapolated AUC/AUC)	34.01 (8.56)	25.65 (11.48)

[a] Mean (±SD)
[b] Radioactivity is expressed as mg-equivalents where appropriate
[c] Median of all subjects
[d] Range for t_{max} from all subjects

Total Recovery of Radioactivity

The mean recovery of radioactivity in urine, feces and expired air following IV and oral administration are summarized in Table 35 and Table 36. The data indicate that recovery was relatively high (> 80 %) following both administration routes.

Table 35: Mean recovery of radioactivity in urine, feces and expired air following oral administration

Excretion (% of dose)			
Urine	Feces	Expired air	Total
5.8 ± 1.2	83.9 ± 5.1	0.0 ± 0.0	89.7 ± 4.7

Table 36: Mean recovery of radioactivity in urine, feces and expired air following IV administration

Excretion (% of dose)			
Urine	Feces	Expired air	Total
8.3 ± 1.9	74.5 ±7.8	0.0 ± 0.0	82.8 ± 8.4

The recovery was maximal within 180 hours for oral administration and 300 hours for IV administration.

Metabolites and metabolite profiling

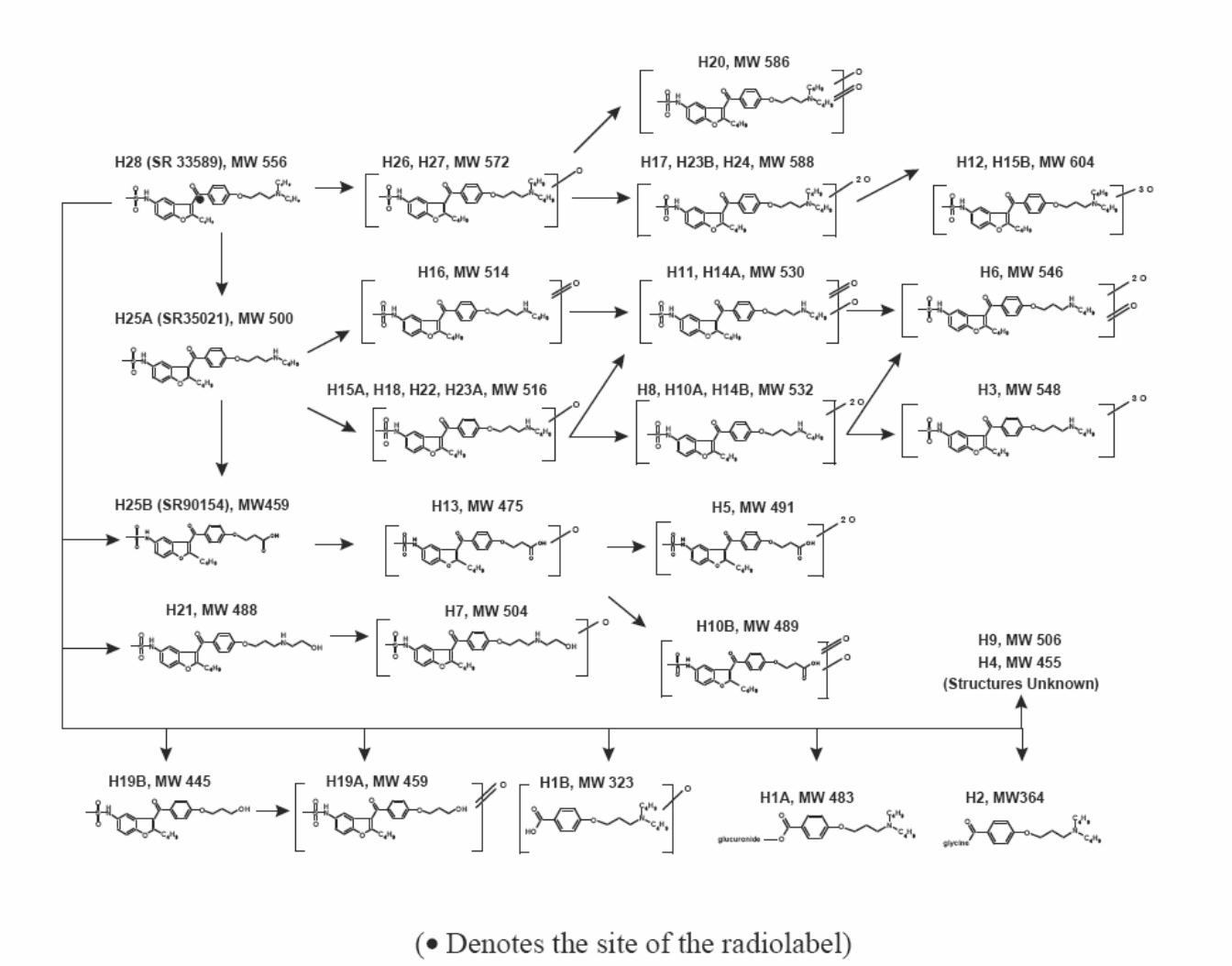
Thirty-four putative metabolites were noted in urine or feces. Structural information was obtained on 32 of these metabolites. Most of the metabolites excreted in urine and feces could be organized into one of three major groups based on structure. These groups included the:

- N-debutylated metabolite and oxygenated metabolites
- Propanoic acid metabolite and oxygenated metabolites of this metabolite
- Metabolites resulting from the direct oxygenation of dronedarone.

Many of the excreted metabolites, from each of the major metabolite groups, were also observed in plasma through 12 hours after dosing.

The characterized pathways of dronedarone metabolism are shown in Figure 11.

Figure 22: Metabolic pathways of dronedarone



Metabolites accounted for the majority (> 70 %) of the radioactivity recovered in the urine and feces following both oral and IV administration. The applicant indicates that plasma from subjects receiving the intravenous dose of dronedarone was not analyzed for metabolites due to the low amounts of radioactivity at all time points. Metabolites were not detected in blood samples.

Relative Amounts of Metabolites in Urine, Feces and Plasma after Oral Administration

The relative amounts of dronedarone metabolites in the different matrices are summarized in Table 37, (HU is for urine) and Table 38, (HF is for feces) and Figure 23 (HP is for plasma). In general, individual metabolites accounted for < 5 % of the radioactive dose.

Reviewer Note on Metabolite Identification

The applicant reported that some of the chromatographic peaks could not be resolved. In other instances some metabolites were not detected in extracted urine samples by radio chromatography, but were observed with LC-MS detection. The peaks that could not be resolved

were primarily the N- debutylated metabolite (SR35021) and the propanoic acid metabolite (SR90154); these peaks were identified as HP25A and HP25B (in plasma), respectively. Consequently, these metabolites were quantified together because they were not resolved from each other by radio chromatography. This approach is acceptable as quantitative assessment is not critical in this mass balance study.

Table 37: Dronedarone metabolites in urine

HU1 (A,B)	HU2, 3	HU4	HU5	HU6	HU7	HU8	HU9	HU10 (A,B)	HU11
7.3 (0.8)	5.7 (0.8)	3.6 (0.6)	3.5 (0.5)	2.0 (0.6)	0.9 (0.4)	1.1 (0.3)	1.1 (0.5)	2.1 (0.6)	10.7 (1.5)
HU12	**HU13**	**HU14 (A,B)**	**HU15 (A,B)**	**HU16**	**HU17**	**HU18**	**HU19 (A,B)**	**HU20**	**HU21**
NQ	21.7 (2.0)	1.9 (0.4)	4.1 (0.8)	1.3 (0.3)	2.6 (0.6)	1.4 (0.4)	3.8 (0.7)	NQ	1.2 (0.6)
HU22	**HU23 (A,B)**	**HU24**	**HU25 (A,B)**	**HU26**	**HU27**	**HU28**	**Total**		
NQ	2.0 (0.7)	NQ	1.9 (0.8)	0.8 (0.3)	NQ	NQ	**80.8 (3.6)**		

[a] Expressed as a percent of urinary radioactivity (0 - 168 hours)
NQ - Not quantifiable, but detected by LC-MS/MS

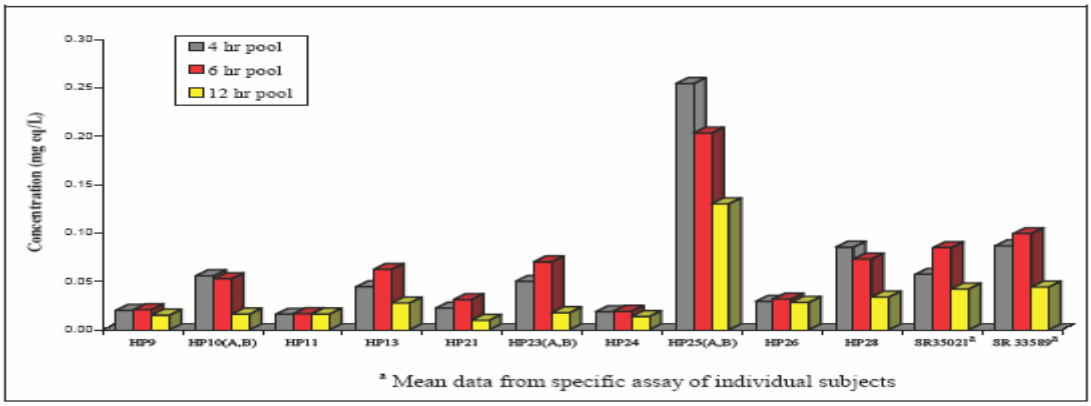
Table 38: Dronedarone metabolites in feces

HF1 (A,B)	HF2, 3	HF4	HF5	HF6	HF7	HF8	HF9	HF10 (A,B)	HF11
ND	ND	ND	ND	ND	0.7 (0.1)	1.0 (0.1)	ND	10.5 (0.5)	5.4 (1.1)
HF12	**HF13**	**HF14 (A,B)**	**HF15 (A,B)**	**HF16**	**HF17**	**HF18**	**HF19 (A,B)**	**HF20**	**HF21**
2.8 (0.4)	18.5 (1.1)	3.1 (0.8)	3.7 (0.9)	0.3 (0.1)	0.9 (0.1)	0.6 (0.1)	NQ	0.7 (0.1)	1.9 (0.5)
HF22	**HF23 (A,B)**	**HF24**	**HF25 (A,B)**	**HF26**	**HF27**	**HF28**	**Total**		
0.4 (0.1)	6.5 (2.1)	1.4 (0.5)	4.4 (0.7)	0.4 (0.2)	0.4 (0.05)	6.3 (2.3)	**70.2 (4.6)**		

[a] Expressed as a percent of fecal radioactivity (0 - 216 hours)
ND, Not detectable
NQ - Not quantifiable, but detected by LC-MS

The applicant notes that the numbering of metabolites in urine and feces is the same; for example, HU2 corresponds to HF2.

Figure 23: Mean plasma concentrations of dronedarone, SR35021 and metabolites at 4, 6 and 12 hours post dose



Applicant's safety summary
All subjects completed the study. There were no discontinuations for any reason. The most frequent adverse events were headache and increases in hepatic enzymes. The elevations of AST and GGT of up to 2.5 times the upper limit of the reference range, observed in three subjects, were considered clinically relevant by the investigator. Cardiac monitoring suggested no arrhythmogenic effects of dronedarone, and there were no significant findings in vital signs monitoring or in physical examinations.

Recommendations/Conclusions
The following information from Study BEX2770 is acceptable for labeling, as needed

- The total recovery of radioactivity was 90 % after oral administration. Approximately 6% and 84% of the administered oral dose of ^{14}C- dronedarone was excreted in urine and feces, respectively. In urine, unnamed metabolites HU11 (~ 11 %) and HU13 (~ 22 %) contributed the most to total radioactivity; whereas in feces, unnamed metabolites HF10 (11 %) and HF13 (19 %) contributed the most to total radioactivity. In plasma, SR35021 and SR95014 (existed as unresolved peak) contributed the most to total radioactivity. Generally all other individual metabolites contributed < 5 % to total radioactivity.
- The total recovery of radioactivity was ~ 83 % following IV administration; ~ 8% and 75% of the administered intravenous dose was excreted in urine and feces, respectively.
- Dronedarone was extensively metabolized to a variety of different metabolites that were excreted in urine and feces; dronedarone was only observed in low amount in feces and non-existent in urine.
- The metabolites formed in feces, urine and plasma were similar
- Major pathways of dronedarone metabolism included: 1) N-debutylation, followed by oxidation, 2) N- dealkylation to form the propanoic acid metabolite, followed by oxidation, and 3) direct oxidation of dronedarone. Mono- and multiple hydroxylated metabolites were also observed, along with metabolites containing a ketone moiety.

4.2.3 Pharmacokinetic profile of SR33589 and its metabolite SR35021 after single and repeated oral administration of 800 mg SR33589B in healthy young male and elderly male and female subjects (POP2769)

PROTOCOL #	POP2769
INVESTIGATOR	Dr. Wolfgang Tetzloff
STUDY SITE	IPHAR - Institut für Klinische Pharmakologie GmbH - Arnikastrasse 4 - D - 85635 Höhenkirchen-Siegertsbrunn - Germany
STUDY PERIOD	August 1997 to January 1998

Objectives (per applicant):

- Provide estimates of pharmacokinetic parameters of SR33589 (dronedarone), and its N-debutyl metabolite, SR35021, after single and repeated doses in healthy subject population subgroups (elderly males, elderly females and young males), and to test for a gender effect in elderly healthy subjects.
- To assess the tolerability of dronedarone in healthy elderly subjects in comparison to healthy young male subjects, after single and repeated doses in fed conditions.

Study Design

This was a double-blind, randomized and placebo-controlled study that enrolled elderly male, elderly female and young male subjects. On Day 1 each subject received an oral dose of dronedarone 800 mg or placebo. Following a two day wash-out period, a once daily dose of 800 mg dronedarone or placebo was given for 14 days from Day 4 to Day 17 inclusive, under fed conditions.

Subject Demographics

Subject demographics are summarized in Table 39.

Table 39: Subject Demographic Data (Study POP2769)

Age Group	Statistic	Placebo Group			SR33589B Group		
		Age (years)	Height (cm)	Weight (kg)	Age (years)	Height (cm)	Weight (kg)
Elderly female (n = 17)	n	4	4	4	13	13	13
	Mean	72	160	59	69	161	61
	SD	6.5	5	7.5	3.3	5.3	8.5
	Minimum	66	153	48.8	65	150	47
	Maximum	80	165	66.1	74	167	73.7
Elderly male (n = 19)	n	5	5	5	14	14	14
	Mean	70	176	79	69	175	76
	SD	5.1	5.0	7.0	3.3	6.5	9.3
	Minimum	65	169	71.6	65	163	60.7
	Maximum	77	182	89.8	74	186	94
Young male (n = 18)	n	5	5	5	13	13	13
	Mean	29	186	82	28	181	74
	SD	4.8	3.6	11.3	4.8	5.9	7.8
	Minimum	23	182	66.2	21	173	61.8
	Maximum	36	192	91	38	195	85.7

Formulation

- Dronedarone capsules: 200 mg strength, batch number 96-00365
- Placebo capsules: batch number 96-00247

Pharmacokinetic (PK) sampling times

PK blood samples were collected according to the following schedule:

- Study Day 1 and Day 17: blood samples were taken before drug administration and 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours after drug administration.
- Predose blood samples were obtained on Days 7, 9, 11, 13, 15.

Pharmacokinetics

The following dronedarone and SR35021 pharmacokinetic measures were determined: Cmax, $AUC_{0\text{-}24h}$ AUC_{last} and AUC after single dose; Cmin after repeated dose; and accumulation ratio (Rac) after 14-day dosing. ANOVA was used to test for age, gender, and time effects on the PK measures.

Bioanalytical Assay

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in Table 40.

Table 40: Performance of Dronedarone and SR35021 Assays (DOH0036)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV were < 8 % for all quality control samples	Satisfactory
Accuracy	QC samples were between -7 and – 3 of the nominal concentrations	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity*	Chromatograms were not provided	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV were < 8 % for all quality control samples	Satisfactory
Between day Accuracy	QC samples were between -4 and -2 % of the nominal concentrations	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity*	Chromatograms were not provided	Cannot be assessed

* Chromatograms were not provided, however, assay validation report includes chromatograms that indicate assay is specific

Results

Dronedarone Pharmacokinetics

Dronedarone plasma concentration-time profiles in young males and elderly subjects following single (Day 1) and 14 days of repeated dose administration (Study Day 17) are depicted in Figure 24. SR35021 plasma concentration-time profile in young males and elderly volunteers following single (Day 1) and repeated administration (Day 17) are depicted in Figure 25.

The key comparisons for this study are as follows:

1. Elderly male vs. young male adults to evaluate the age effect (in males)
2. Elderly female vs. elderly males to evaluate the gender effect (in elderly subjects)

The absence of a young healthy female group does not allow one to determine if a gender effect occurs in young adults.

Figure 24: Mean dronedarone plasma concentration-time profile in elderly males and females and young males on Day 1 and Study Day 17 following 800 mg dronedarone once daily administration

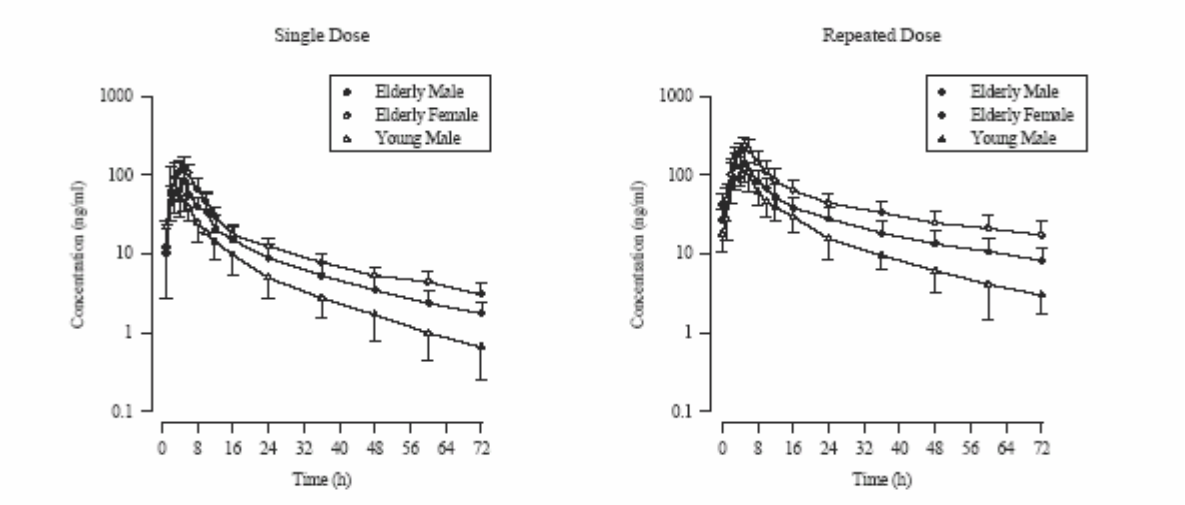
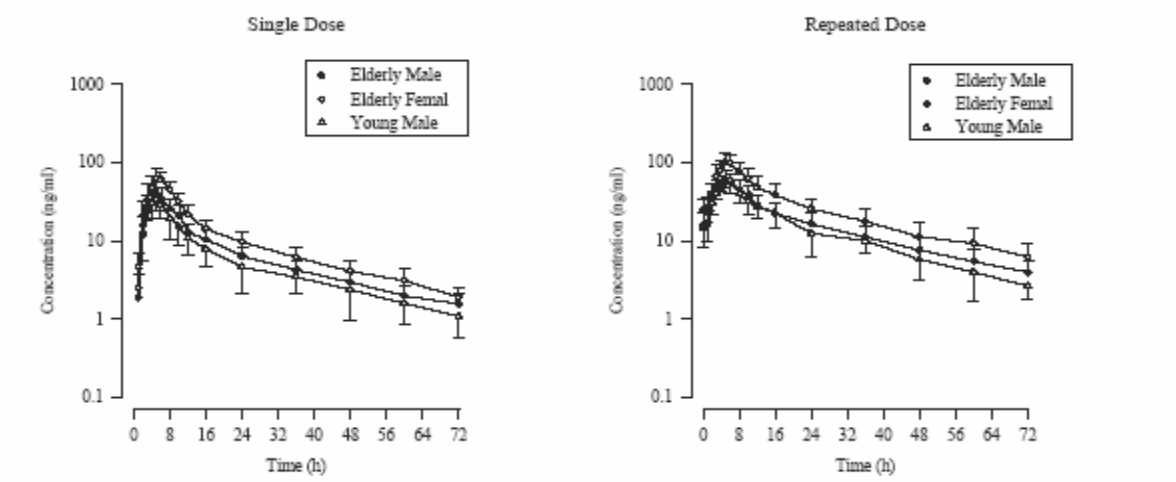


Figure 25: Mean SR35021 plasma concentration-time profile in elderly males and females and young males on Day 1 and Study Day 17 following 800 mg dronedarone once daily administration



Dronedarone PK measures in young males and elderly subjects are summarized in Table 15.

General PK Observations

- Tmax was comparable among the three study groups and was comparable on Day 1 (following single dose) and Study Day 17 (following 14 days of multiple dosing).
- Approximately 2.3-fold accumulation occurred on multiple dosing in all subject groups
- Half-life on Day 1 was shorter than on Day 17; additionally, elderly subjects had significantly longer half-life than younger subjects

Table 41: Dronedarone PK measures in healthy males and elderly adults and females following single and multiple dose administration (800 mg QD)

Parameter	Statistic	Young Male		Elderly Male		Elderly Female	
		Day 1	Day 17	Day 1	Day 17	Day 1	Day 17
C_{max} (ng/ml)	Mean	76	130	89	168	142	241
	SD	29	37	27	55	38	62
	CV%	38%	28%	30%	33%	27%	26%
t_{max} (h)	Mean	3.00	4.67	4.67	3.83	4.75	4.83
	SD	1.28	1.15	2.06	1.19	1.42	0.83
	CV%	43%	25%	44%	31%	30%	17%
AUC_{0-24h} (ng.h/ml)	Mean	511	1139	679	1520	1035	2393
	SD	171	318	228	508	303	702
	CV%	33%	28%	34%	33%	29%	29%
R_{ac}	Mean	N/A	2.35	N/A	2.31	N/A	2.35
	SD		0.66		0.72		0.46
	CV%		28%		31%		19%
C_{min} (ng/ml)	Mean	N/A	14.6	N/A	23.2	N/A	39
	SD		6.4		10.4		12.3
	CV%		44%		45%		32%
AUC_{last} (ng.h/ml)	Mean	609	N/A	874	N/A	1335	N/A
	SD	200		308		350	
	CV%	33%		35%		26%	
AUC (ng.h/ml)	Mean	628	N/A	936	N/A	1473	N/A
	SD	205		323		383	
	CV%	33%		35%		26%	
$t_{½}$ (h)	Mean	17.9	24.1	24.3	38.1	28.8	44.6
	SD	4.2	7.2	5.4	10.1	9.8	13.9
	CV%	23%	30%	22%	26%	34%	31%

N/A: Not applicable

Exposure comparisons (Cmax, Cmin and AUC) between elderly subjects and between elderly subjects and young males are summarized in Table 16 and Table 17.

Table 42: Comparison of Cmax and Cmin between elderly subjects and young male subjects

Parameter	Elderly Male vs. Young Male			Elderly Female vs. Elderly Male		
	Ratio	95 % CI	90 % CI	Ratio	95 % CI	90 % CI
C_{max}	1.23	[0.99 , 1.52]	[1.02 , 1.47]	1.54	[1.24 , 1.92]	[1.29 , 1.85]
C_{max} N	1.26	[0.98 , 1.63]	[1.02 , 1.56]	1.23	[0.95 , 1.58]	[0.99 , 1.51]
C_{min} (RD)	1.61	[1.13 , 2.28]	[1.20 , 2.15]	1.75	[1.23 , 2.47]	[1.31 , 2.33]

N: Normalized to 70 kg body weight
RD: Repeated Dose

Table 43: Comparison of AUC between elderly subjects and young male subjects

Parameter	Elderly Male vs. Young Male			Elderly Female vs. Elderly Male		
	Ratio	95% CI	90% CI	Ratio	95% CI	90% CI
AUC_{0-24h}	1.33	[1.04 , 1.69]	[1.08 , 1.62]	1.56	[1.22 , 1.99]	[1.28 , 1.91]
AUC_{0-24h}N	1.37	[1.05 , 1.79]	[1.09 , 1.71]	1.24	[0.95 , 1.62]	[0.99 , 1.55]
AUC_{last} (Day 1)	1.44	[1.10 , 1.88]	[1.16 , 1.80]	1.55	[1.18 , 2.02]	[1.24 , 1.93]
AUC (Day 1)	1.50	[1.15 , 1.95]	[1.20 , 1.87]	1.59	[1.22 , 2.08]	[1.28 , 1.99]

N: Normalized to 70 kg body weight
Day 1: Single Dose

Age and Gender Effect (Table 16 and Table 17)

1. ***Elderly Male vs. Young Male***

- Based on the point estimate and associated 90 % confidence interval (CI), Cmax, weight normalized Cmax and Cmin are ~ 25 % higher in elderly males than young males
- The weight normalized data suggest that the difference in Cmax is not only due to weight differences between the two groups
- AUC data show a similar trend as observed with Cmax data

2. Elderly Female vs. Elderly Male

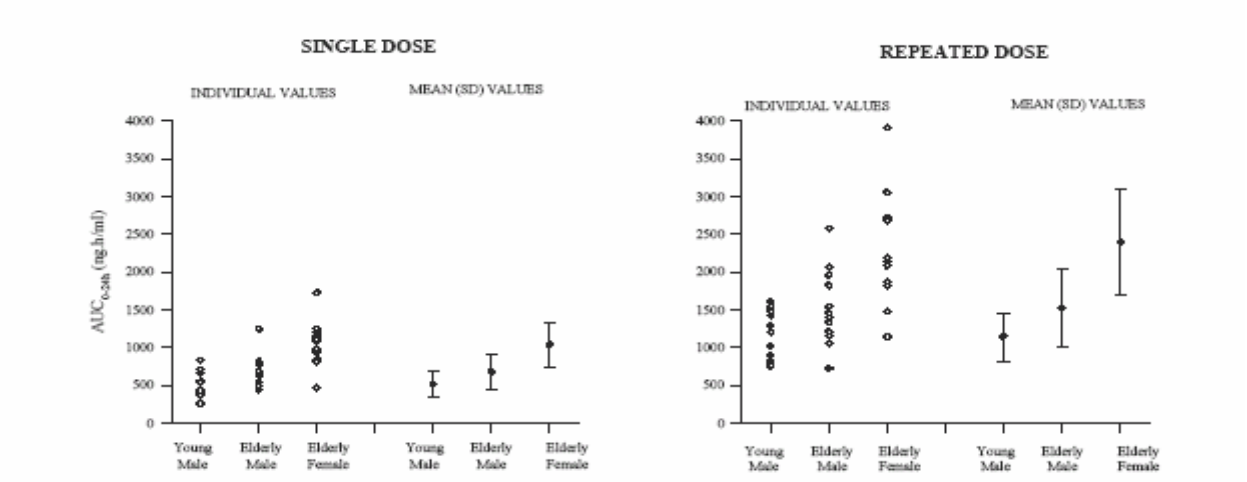
- Based on the point estimate and associated 90 % CI, Cmax and AUC of elderly females is ~ 50 % higher than elderly males.
- Weight normalization eliminates the statistical difference in exposure between the two groups; however, elderly females still tend to have higher (~ 25 %) numerical dronedarone exposure than elderly males

3. Elderly Female vs. Young Male

Assuming that the observed age (males) and gender (elderly subjects) are additive, female subjects will have exposures that are ≥ 50 % that of young males.

The individual and mean dronedarone PK measures following single and multiple dose administration in young males and elderly volunteers is shown in Figure 26.

Figure 26: Individual and Mean dronedarone AUC in young males and elderly volunteers following administration of 800 mg dronedarone



The preceding plots indicate that the female subjects exhibited the highest degree of inter-patient variability. Additionally, the figures and preceding table demonstrate that single dose PK differ from multiple dose PK; time dependent dronedarone PK have been observed in other PK studies and may be due to time-dependent metabolic processes.

The reason for the observed age and gender effects is unclear. Dronedarone is cleared primarily by metabolism, rather than by the renal pathway; thus, typical decline in renal function with age does not account for the differences.

Reviewer Note: Clearance Data Generated to Facilitate Group Comparisons

This reviewer generated weight normalized and non-normalized apparent oral clearance (CL/F) data to facilitate group comparisons and evaluate the effect of weight on CL/F. All subjects received the same dose, thus the AUC values are reflective of CL/F since CL/F= Dose/AUC. CL/F data (Day 17) are summarized in Table 44.

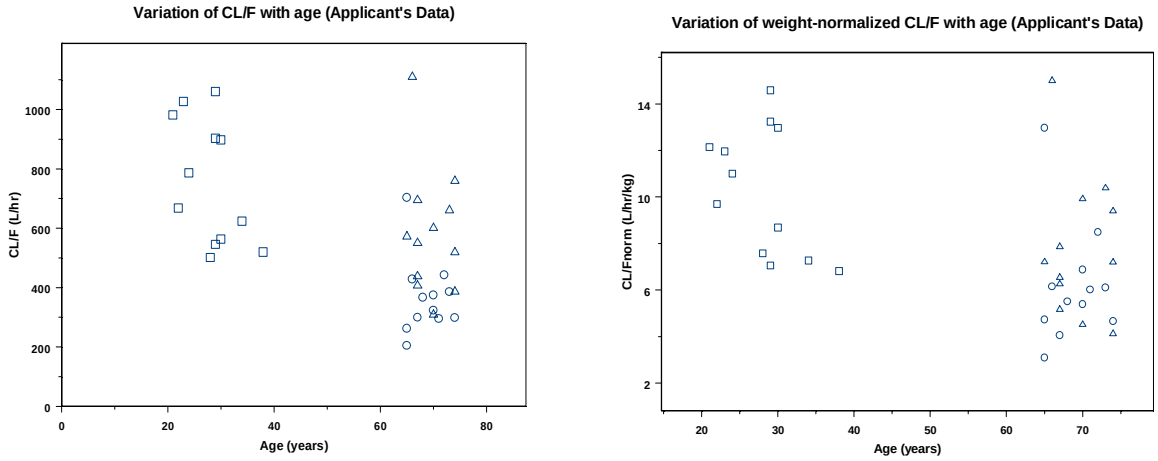
Table 44: Mean steady state apparent oral clearance in young males and elderly subjects

	Young Males	Elderly Males	Elderly Females
	Applicant	Applicant	Applicant
CL/F (L/hr)	755 ± 210	586 ± 213	365 ± 127

Clearance Information (Reviewer Generated)

In the following plots (Figure 27) squares represent young adult males, triangle represent elderly males and oblong symbols represent elderly females.

Figure 27: Variation of non-normalized and body weight normalized clearance with age



The preceding plots demonstrate that:

- overall, the individual CL/Fs of young males are greater than that of elderly subjects, suggesting that an age effect exists
- the individual CL/Fs of elderly males and females overlap to a great extent, suggesting that the apparent gender effect in the elderly, may not be clinically significant

Reviewer's Note on Activity (Applicant's Findings)

The study report included limited information on dronedarone activity. According to the applicant, despite a significant difference in plasma concentration between strata, no obvious difference in PK/PD linear relationship was detected for QTc among population strata.

Applicant's Safety Summary

Single dose administration of dronedarone did not lead to study discontinuation. All adverse events were of either mild or moderate intensity, and the subjects recovered without sequelae. During the multiple dose phase, six (four on dronedarone and two on placebo) subjects were withdrawn from the study as a direct result of the adverse event. Some of the AEs were cardiac (e.g. asymptomatic non-sustained ventricular tachycardia, atrial fibrillation and sinus bradycardia

and accelerated idioventricular rhythm. However, occurrence of cardiac events occurred in an equal number of elderly females, elderly males, and young males following repeated doses.

Recommendations/Conclusion
The following findings from Study POP2769 are acceptable for labeling:

- Dronedarone PK are affected by age: elderly males have approximately 30 % higher dronedarone exposure than young males receiving 800 mg dronedarone after correcting for weight differences. The CL/F of elderly males is ~ 20 % lower than that of young males.
- Dronedarone PK are affected by gender: elderly females have approximately 23 % higher dronedarone exposure than elderly males receiving 800 mg dronedarone after correcting for weight differences. The CL/F of elderly females is ~ 40 % lower than that of elderly males.
- Potentially elderly female subjects may have dronedarone exposure that is ≥ 50 % of that in young male subjects
- From this study it is unclear if the gender effect will exist for young subjects because young female subjects were not included in this study.

Due to nonlinear PK, the quantitative values obtained in this study (800 mg) may differ from that at the proposed clinical dose (400 mg); however, the results can be expected to be qualitatively similar at both doses.

Labeling Comments
The gender differences (elderly female vs. elderly male) observed in this study do not appear to warrant dosing adjustments, as the difference in exposure is relatively small (~ 25 %) and statistically insignificant after correcting for body weight. The highest potential difference occurs between healthy males and elderly females, however, the maximal difference is approximately 50 %, which does not appear to warrant dose adjustments based on the limited dronedarone exposure-response information.

In sum, neither age nor gender differences will require dosage adjustment.

4.2.4 Effect of fat content on the bioavailability of an oral administration of two 400 mg tablets of SR33589B containing 10% pluronic F12 (ALI3180).

PROTOCOL #	ALI3180
INVESTIGATOR	Dr. Wolfgang Tetzloff
STUDY SITE	iphar, Institut für Klinische Pharmakologie GmbH, Arnikastrasse 4, 85635 Höhenkirchen- Siegertsbrunn, Germany.
STUDY PERIOD	April 1997 to June 1997

Objectives (per applicant):

- To assess the effect of fat content of a morning meal on the bioavailability of two 400 mg tablets of SR33589B containing 10% pluronic F127, compared to results obtained when the tablets were given under fasted conditions.
- To assess clinical and biological tolerability.

Study Design

This was an open-label, non-placebo controlled, single-group, cross-over study. Each subject received three different treatments. Dronedarone was given under each of the following treatment conditions: fasted, immediately after a low fat meal, and immediately after a fat-rich meal. There was a wash-out period of at least seven days between treatments. The meal compositions are in the Appendix. The high fat meal was acceptable as it is consistent with the FDA-recommended high-fat meal composition.

Subject Demographics

Subject demographics are presented in Table 45.

Table 45: Subject Demographic Data

Characteristics	Parameters	Values
Age (years)	Mean	31.1
	SD	6.5
	Minimum	24.0
	Maximum	39.0
Height (cm)	Mean	181.9
	SD	3.6
	Minimum	177.0
	Maximum	188.0
Weight (kg)	Mean	77.5
	SD	6.7
	Minimum	68.5
	Maximum	88.5

n = 9

Pharmacokinetic sampling times

PK samples for assays of dronedarone and its metabolite SR35021 were collected at 0h (before administration), 1h, 2h, 3h, 4h, 5h, 6h, 8h, 10h, 12h, 16h, 24h, 36h, and 48h after each drug administration.

Formulation

Dronedarone 400 mg tablets containing 10% pluronic F127, batch No. D005680/96-00494.

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in Table 27.

Table 46: Performance of Dronedarone and SR35021 Assays (DOH0036)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.991$	Satisfactory
Between day Precision	CV was < 8.0 %	Satisfactory
Accuracy	QC samples were between +0.6 and -2.2 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 0.5 to 50 ng/mL range; $R^2 > 0.991$	Satisfactory
Between day Precision	CV was < 6.0 %	Satisfactory
Accuracy	QC samples were between +0.7 and -0.4 of nominal concentration	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

*The validation report for the assay included chromatograms that suggest the assay was specific

Pharmacokinetics

The following dronedarone pharmacokinetic measures were determined after each treatment: Cmax, tmax, and AUClast.

Statistical methods

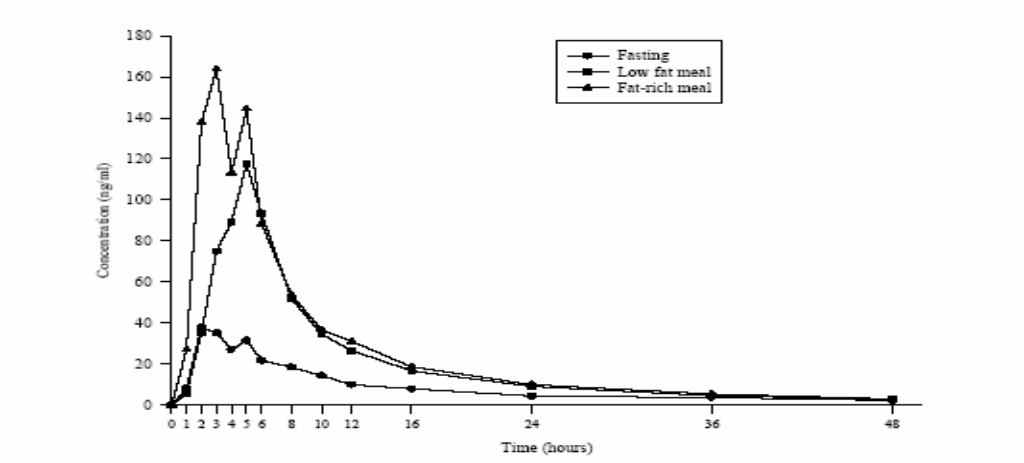
Standard pharmaco-statistical methods were used to evaluate the food effect. The fasted treatment was the reference treatment and test treatments were the high fat and low fat meals.

Results

Dronedarone Pharmacokinetics

The mean dronedarone plasma concentration-time profiles in the fasted and fed conditions (low fat and high fat meals) are shown in Figure 28.

Figure 28: Mean dronedarone plasma concentration-time profile under fasted and fed conditions



Dronedarone PK measures under the three treatment conditions are presented in Table 47.

Table 47: Dronedarone PK measures in healthy males following single dose administration under fasted and fed conditions

Parameters (units)	Statistics	Administration		
		Fasted	Low fat meal	Fat-rich meal
C_{max} (ng/ml)	Mean	42.92	128.29	192.40
	Median	40.00	120.80	173.40
	SD	21.50	50.26	90.88
	CV%	50	39	47
t_{max} (h)	Mean	3.67	4.67	3.89
	Median	5.00	5.00	5.00
	SD	1.58	1.00	1.36
	CV%	43	21	35
AUC_{last} (ng.h/ml)	Mean	416.35	975.61	1274.37
	Median	416.00	964.59	1179.63
	SD	106.59	252.08	329.89
	CV%	26	26	26

n = 9

Geometric mean ratios and associated 95% CI of the main dronedarone PK measures are presented in Table 11.

Table 48: Dronedarone geometric mean ratios and associated 90 % confidence intervals* under fed and fasted conditions

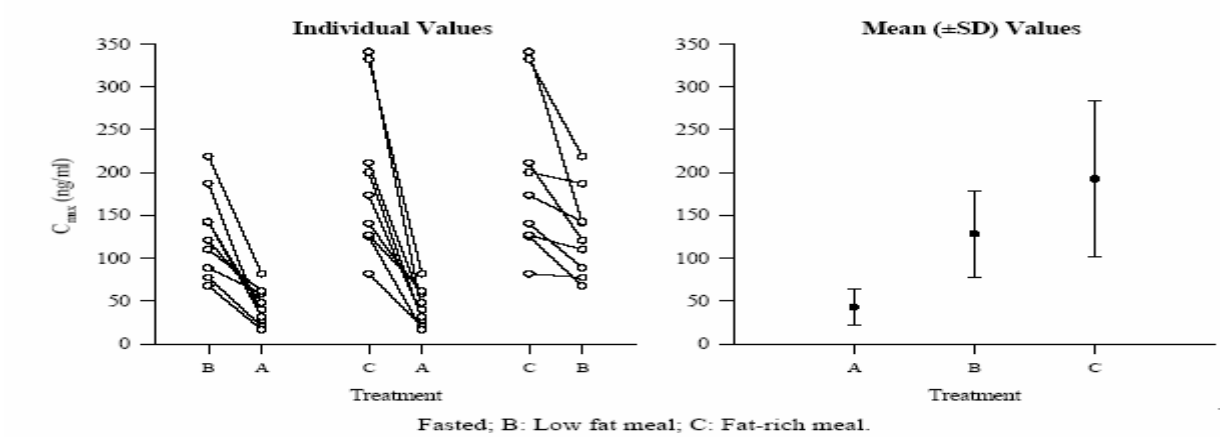
Parameters (units)	Low fat meal / fasted	Fat-rich meal / fasted	Fat-rich meal / low fat meal
C_{max} (ng/ml)	3.15 [2.28 - 4.36]	4.59 [3.32 - 6.35]	1.46 [1.05 - 2.01]
AUC_{last} (ng.h/ml)	2.34 [1.99 - 2.75]	3.06 [2.60 - 3.61]	1.31 [1.11 - 1.54]

n = 9

* Typically, 90 % confidence intervals are preferred over 95 % confidence intervals for regulatory evaluations.

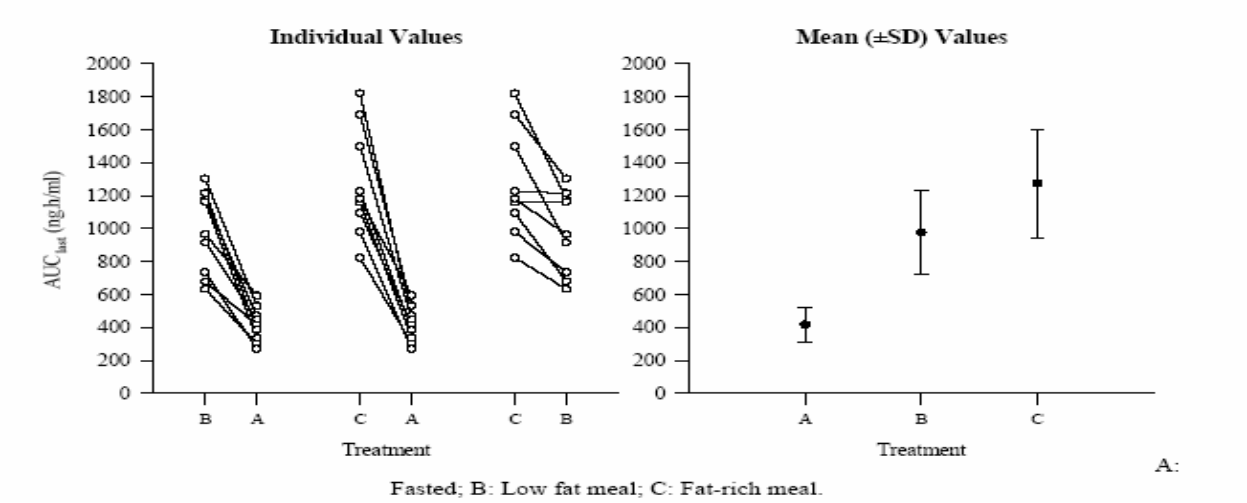
The data in Table 11 demonstrate that food increases dronedarone BA relative to the fasted state; additionally, increasing fat content increases bioavailability. It is noted that two subjects had far greater food effects than the other subjects (Figure 29 and Figure 30). The reason for this finding is unclear; without these two subjects the difference in food effect between the high fat meal and low fat meal may not have reached statistical significance and the food effect data would be less variable.

Figure 29: Individual and mean Cmax values under fasted and fed conditions



Fasted; B: Low fat meal; C: Fat-rich meal.

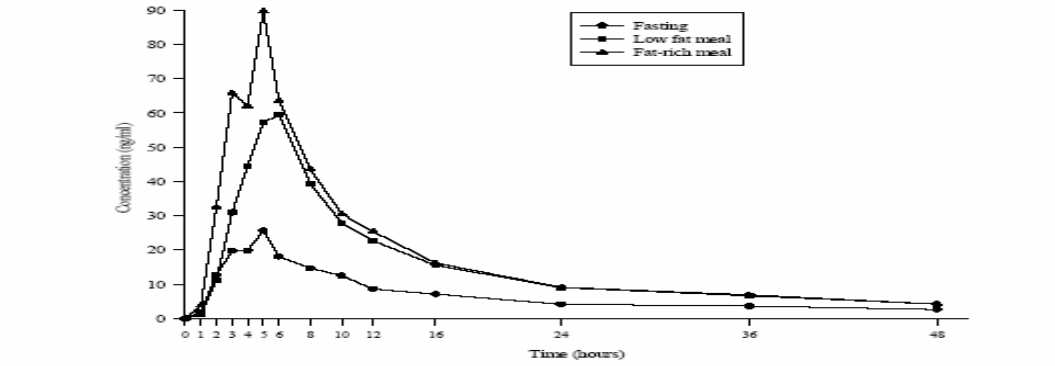
Figure 30: Individual and mean AUC values under fasted and fed conditions



SR35021 Pharmacokinetics

The mean SR35021 plasma concentration time profile under fasted and fed conditions is depicted in Figure 31.

Figure 31: Mean SR35021 plasma concentration-time profile under fed and fasted conditions



SR35021 PK measures in the study are shown in Table 49.

Table 49: SR30521 PK measures in healthy males following single dose administration of dronedarone under fasted and fed conditions

Parameters (units)	Statistics	Administration		
		Fasted	Low fat meal	Fat-rich meal
C_{max} (ng/ml)	Mean	26.43	62.99	98.71
	Median	27.30	69.40	81.60
	SD	9.49	17.33	39.74
	CV%	36	28	40
t_{max} (h)	Mean	4.56	5.56	4.56
	Median	5.00	6.00	5.00
	SD	0.88	0.53	0.88
	CV%	19	9	19
AUC_{last} (ng.h/ml)	Mean	329.44	724.34	868.94
	Median	344.95	732.69	811.80
	SD	83.87	170.65	221.37
	CV%	25	24	25

n = 9

Geometric mean ratios and associated 95% CI of the main dronedarone PK measures are presented in Table 50.

Table 50: SR30621 Geometric mean ratios and associated confidence intervals under fasted and fed conditions

Parameters (units)	Low fat meal / fasted	Fat-rich meal / fasted	Fat-rich meal / low fat meal
C_{max} (ng/ml)	2.44 [1.96 - 3.05]	3.70 [2.97 - 4.62]	1.51 [1.21 - 1.89]
AUC_{inf} (ng.h/ml)	2.22 [2.00 - 2.45]	2.65 [2.39 - 2.93]	1.20 [1.08 - 1.32]

n = 9

The SR35021 PK data indicate that food increases SR35021 bioavailability to a similar degree as observed with dronedarone.

Applicant's Safety Summary

Three subjects reported adverse events:

- Subject A had a serious adverse event (calcaneus fracture), due to an accident, not related to the study drug
- Subject B had a short lasting episode of diarrhea
- Subject C had two short lasting episodes of non-sustained asymptomatic ventricular tachycardia.

The serious adverse event required hospitalization and conservative therapy whereas the other events resolved spontaneously.

Laboratory tests, vital signs, electrocardiograms, and telemetric evaluations showed no clinically relevant changes from baseline.

Recommendations/Conclusions

The following PK information generated in Study ALI3180 is acceptable for labeling purposes, as appropriate.

1. Food (low fat meal and high fat meal) increases dronedarone bioavailability on average by approximately 4-fold (3.15 to 4.59) at the 800 mg dronedarone dose level.
2. The high fat meal had only a slightly greater effect on bioavailability (~ 40 % increase) than the low fat meal, suggesting that dronedarone may be administered with low or high fat meals.
3. Food did not significantly prolong drug absorption; the median Tmax was 5 hr under fasted and fed conditions.

APPENDIX to Study ALI3180

Composition of Meals

Standard rich fat meal.

Food item	Calories	Fat (g)	Carbohydrates (g)	Protein (g)
2 eggs (scrambled)	203	16.2	1.2	12.2
2 slices white bread toasted	128	1.8	23.4	4.2
1 teaspoonful butter	36	4.1	Trace	0.0
1 tablepoonful jelly	55	Trace	14.1	Trace
2 strips of bacon	70	6.2	0.2	3.2
4 oz hash brown potatoes	72	0.1	16.4	1.8
8 oz of whole milk	157	8.9	11.4	8.0
TOTAL		**37.3**	**66.7**	**29.4**
TOTAL CALORIES	**718,10**	**335,70**	**266,80**	**117,60**

Standard low fat meal.

Food item	Protein [g]	Fat [g]	Carbohydrate [g]	
120 g yoghurt (0.3%)	5.28	0.12	5.04	
2 rolls (100g)	7.6	1.2	47.8	
40 g honey	0.1	-	30.04	
25 g jam	0.15	-	16.5	
5 g margarine	0.2 g	4 g	-	
2 cups decaffeinated coffee				
TOTAL	**13.33**	**5.32 (4.5%)**	**99.38**	
TOTAL CALORIES	**54.65**	**49.48 (9.7%)**	**407.49**	**Σ511.62**

4.2.5 Relative bioavailability between the dronedarone tablets used in phase II studies and those prepared for phase III studies after single oral administration to young healthy subjects (BDR4680)

PROTOCOL #	BDR4680
INVESTIGATOR	Emmanuel Krupka, M.D.
STUDY SITE	LARIME, Z.A. des Greffières, Rue Auguste Perret, 17140 Lagord, France
STUDY PERIOD	July to August 2001

Objectives (per applicant):

- to evaluate, after single oral administration, in fasted conditions, the relative bioavailability between the oval shaped phase III tablets (Formulation A) and the round shaped phase II tablets (Formulation B)
- to assess the safety of the treatment with dronedarone

Study Design

This was an open-label, two-period, randomized study in healthy subjects. There were two different treatment groups, corresponding to the two dronedarone tablets; each tablet was given with labeled* dronedarone capsules. Subjects received a single 800 mg dose: dronedarone 400 mg via tablet + dronedarone 400 mg via capsules. Treatments were given in the fasted condition and there was a 7-day washout period between treatments.

*** Rationale for use of labeled dronedarone**

An internal marker, ^{13}C-labeled dronedarone, was co-administered as a capsule with each of the tablets; this co-administration provides lower within-subject variability by using adjusted pharmacokinetic (PK) parameters based on the ratio of $^{12}C/^{13}C$, i.e., unlabeled versus labeled dronedarone.

Subject Demographics

Subject demographics are presented in Table 51.

Formulation

- Test product: 400 mg ^{12}C-dronedarone Phase III tablet (2E3 formulation); batch number: CL- 03936
- Internal marker: 100 mg ^{13}C- dronedarone capsules; batch number: CL- 04269
- Reference product: 200 mg ^{12}C-dronedarone Phase II tablet (2E2 formulation); batch number: 99- 02753

Pharmacokinetic Sampling

PK blood samples were collected before dosing and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours after dronedarone administration.

Pharmacokinetic Measures

The following PK measures were estimated

- dronedarone and SR35021: Cmax , tmax , AUClast , AUC, $t_{1/2}z$
- ^{13}C- dronedarone and ^{13}C- SR35021: Cmax, tmax , AUClast, AUC, $t_{1/2}z$
- dronedarone $^{12}C/^{13}C$ and SR35021 $^{12}C/^{13}C$ ratios: Cmax , AUC last and AUC

Table 51: Subject Demographic Data

Parameter (unit)	Statistics/ Category	Total (N=12)
Age (yrs)	N	12
	Mean	27.4
	SD	5.1
	Min	19
	Max	34
Weight (kg)	N	12
	Mean	72.02
	SD	6.20
	Min	61.4
	Max	80.4
Height (cm)	N	12
	Mean	176.9
	SD	6.8
	Min	163
	Max	186
Body mass index (kg/m2)	N	12
	Mean	22.9
	SD	1.9
	Min	19
	Max	26
Gender	Male	12 (100%
	Female	0 (0%)
Race	Caucasian	12 (100%)
	Black	0 (0%)
	Asian	0 (0%)
	Other	0 (0%)

Bioanalytical Method

The concentrations of dronedarone, SR35021 and their ^{13}C isotopes were determined using a validated Electrospray Liquid LC/MS method (DOH0238). The assay performance was acceptable as shown in Table 52 and
Table 53.

Table 52: ^{12}C Dronedarone and SR35021 Assay Performance

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV data were not provided	Cannot be assessed
Accuracy	Relative bias data were not provided. The concentrations of QC samples were within 15 % of nominal concentration	Acceptable
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.996$	Satisfactory
Between day Precision	CV data were not provided	Satisfactory
Accuracy	Relative bias data were not provided. The concentrations of 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 demonstrate assay specificity

Table 53: Dronedarone and SR35021 Assay Performance

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.995$	Satisfactory
Between day Precision	CV data were not provided	Satisfactory
Accuracy	Relative bias data were not provided. The concentrations of QC samples 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 0.5 to 50 ng/mL range; $R^2 > 0.998$	Satisfactory
Between day Precision	CV data were not provided	Satisfactory
Accuracy	Relative bias data were not provided. The concentrations of 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 demonstrate assay specificity

Statistical methods

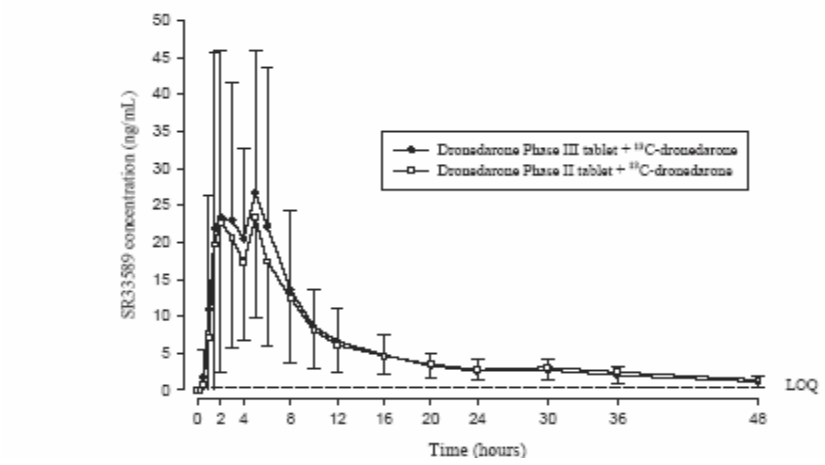
Standard pharmaco-statistical methods were used to determine the relative bioavailability of the 2E3 tablet formulation (test) to the 2E2 formulation (reference).

Results

Dronedarone Pharmacokinetics

The mean plasma concentration-time profiles of dronedarone obtained after administration of each formulation are presented in Figure 32.

Figure 32: Mean dronedarone plasma concentration-time profiles following administration of 2E3 and 2E2 dronedarone formulations



Dronedarone PK measures are presented Table 54. Geometric mean ratios and associated 90 % CI of the main dronedarone PK measures are presented in Table 55.

Table 54: Dronedarone PK measures (based on dronedarone) in healthy males following single dose administration under fasted conditions

Mean (CV%) Parameters	Phase III tablet +^{13}C-dronedarone	Phase II tablet +^{13}C-dronedarone	Ratio [90% CI] or p value	Within-subject SD[a]
C_{max} (ng/mL)	40.0 (66)	32.0 (59)	1.22 [0.95 – 1.56]	0.34
t_{max} (h)[b]	3 [1.5 – 6]	2 [1.5 – 5]	p = 0.899	-
AUC_{last} (ng.h/mL)	287 (58)	273 (53)	1.02 [0.85 – 1.22]	0.24
$t_{1/2}$ (h)	19.2 (48)	16.0 (29)	p = 0.370	-
AUC (ng.h/mL)	324 (58)[c]	307 (55)	1.09 [0.95 – 1.26][c]	0.18

Phase III (1x400mg tablet) + ^{13}C-dronedarone (4x100mg capsules): treatment A
Phase II (2x200mg tablets) + ^{13}C-dronedarone (4x100mg capsules): treatment B
a: for log-transformed parameters, b: median values [min – max], c: n=11

Table 55: Dronedarone geometric mean ratios (based on ^{12}C/^{13}C ratio) and associated 90 % confidence intervals under fasted conditions

Mean (CV%) ^{12}C/^{13}C Ratio	Phase III tablet +^{13}C-dronedarone	Phase II tablet +^{13}C-dronedarone	Ratio [90% CI]	Within-subject SD
C_{max} (ng/mL)	0.77 (37)	0.69 (29)	1.09 [0.95 – 1.26]	0.19
AUC_{last} (ng.h/mL)	0.78 (17)	0.82 (8)	0.94 [0.88 – 1.00]	0.08
AUC (ng.h/mL)	0.82 (15)[a]	0.85 (8)	0.95 [0.88 – 1.02][a]	0.09

Phase III (1x400mg tablet) + ^{13}C-dronedarone (4x100mg capsules): treatment A
Phase II (2x200mg tablets) + ^{13}C-dronedarone (4x100mg capsules): treatment B a: n=11

The PK data indicate the following:

- there is greater within subject variability using dronedarone alone, vs. the ratio of labeled dronedarone
- there is no significant difference in exposure between treatments (CIs include 1) using either analysis method

Overall, the two formulations have similar bioavailability in terms of dronedarone exposure.

Reviewer Note on SR35021

The applicant provided SR35021 PK information, but the data are not included in this review as they do not impact the BE evaluation.

Applicant's Safety Summary

No serious AEs (SAEs), deaths, or discontinuations occurred during this study. There was one treatment emergent AE reported, asthenia (system organ class: body as a whole). Other AEs of note included:

- orthostatic change in heart rate
- five subjects had a QTc-interval change (changes ranged from 30 to 38 ms) but the changes were isolated, and in all cases values stabilized on subsequent measurements. No QTc > 450 ms were reported.

Recommendations/Conclusions

The following PK information generated in Study BDR4680 is acceptable, as appropriate:

- The Phase 2 (2E2) and Phase 3 (2E3) tablets have similar bioavailability
- The use on an internal marker ^{13}C-dronedarone decreases dronedarone inter-subject PK variability

4.2.6 Assessment of food effect on pharmacokinetic parameters of a single dose (800 mg) of SR33589B and assessment of absolute bioavailability (PPK2397)

PROTOCOL #	PPK2397
INVESTIGATOR	J.M Kroodsma
STUDY SITE	U-Gene Research, Bolognalaan 40, 3584 CJ Utrecht, The Netherlands
STUDY PERIOD	June – August, 1995

Objectives (per applicant)

- To assess the influence of food intake on oral absorption of dronedarone (SR33589B)
- To assess the bioavailability of the compound and, the overall tolerability and pharmacodynamic effects of dronedarone

Reviewer's Note

Study PPK2397 does not contribute relevant biopharmaceutical information to the NDA with respect to the to-be-marketed (TBM) tablet. However, the study is being reviewed for its qualitative value as related to estimation of absolute bioavailability (BA).

Study Design

A randomized, open label and three treatment period study design was adopted. Healthy male subjects received dronedarone under the following conditions:

- 800 mg orally under fed conditions
- 800 mg orally under fasted conditions
- 60 mg IV infusion under fasted conditions

Subject Demographics

Subject demographics are presented in Table 56.

Table 56: Subject Demographic Data (Study PPK2397)

Characteristic	Parameter	Fasted → Fed → i.v. (n = 6)	Fed → Fasted → i.v. (n = 6)
Age (years)	Mean	25.0	27.3
	SD	3.4	6.5
	Minimum	21.0	20.0
	Maximum	30.0	39.0
Weight (kg)	Mean	75.3	73.7
	SD	5.4	7.3
	Minimum	68.4	65.6
	Maximum	80.8	83.2
Height (cm)	Mean	186.2	183.3
	SD	4.6	6.1
	Minimum	179.0	179.0
	Maximum	193.0	195.0

Reviewer Note on Subjects

All 12 subjects completed the study. The CYP2D6 status of subjects was recorded: three of the 12 subjects (# 4, 5, and 8) were poor metabolizers.

Formulation

- 100 mg dronedarone capsules, batch number L062J
- 1 mg/mL solution (ampoules), batch number L184T

Pharmacokinetic sampling times

Extensive blood sampling was conducted during (IV infusion) and following administration of dronedarone (oral and IV). Blood samples were collected from predose (10 minutes before dose) and up to 72 hours post dosing. Blood sampling times are reported in this study's Appendix.

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated HPLC-UV method. The assay performance was acceptable as illustrated in Table 57.

Table 57: Performance of Dronedarone and SR35021 Assays (DOH0020)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 5 to 1000 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV for QC samples were < 10 %	Satisfactory
Accuracy	QC samples were between -5 % and +1 % of the nominal concentrations	Satisfactory
LLOQ	3 ng/ml	Satisfactory
Specificity	Chromatogram was provided	Satisfactory
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.999$	Satisfactory
Between day Precision	CV for QC samples were < 8.0 %	Satisfactory
Between day Accuracy	QC samples were between -4 % and +4 % of the nominal concentrations	Satisfactory
LLOQ	2 ng/mL	Satisfactory
Specificity	Chromatogram was provided	Satisfactory

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined for dronedarone and SR35021:

- Oral administration- Cmax, tmax, AUC_{0-t}, AUC, $t_{1/2}$, and F
- IV administration, Cmax, AUC_{0-t}, AUC, $t_{1/2,}$ CL_T and Vd

The food effect was assessed using standard pharmaco-statistical analyses, where the fasted treatment served as reference and fed treatment as the test. Absolute BA was assessed for the fasted and fed states.

Pharmacodynamics

The following electrocardiogram (ECG) interval changes were assessed: HR PR, QRs and QT.

Reviewer Note

The ECG data were not reviewed in detail because they do not impact the absolute BA findings.

Results

Dronedarone Pharmacokinetics

The dronedarone plasma concentration-time profile following IV infusion and oral administration of dronedarone are depicted in Figure 33 and Figure 34, respectively.

Figure 33: Mean dronedarone plasma concentration-time profile following 60 mg IV dronedarone given by 60-minute infusion

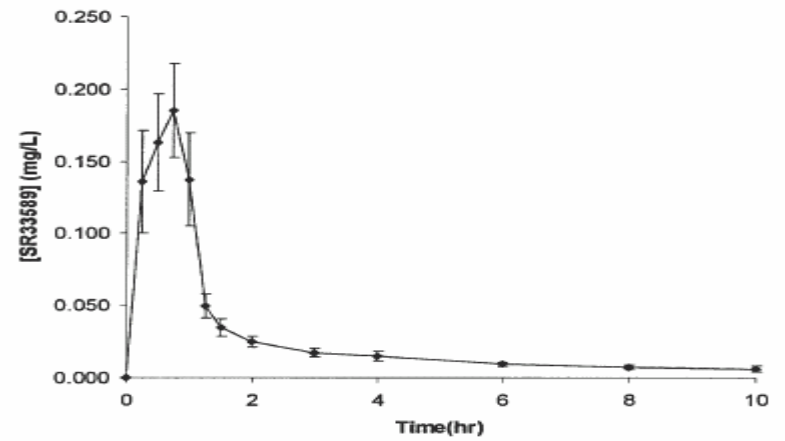
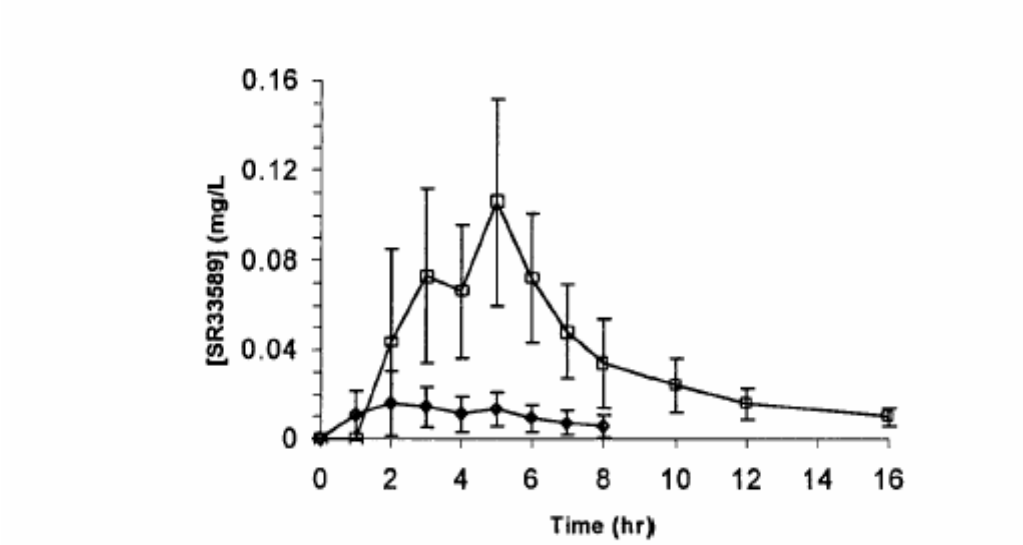


Figure 34: Mean dronedarone plasma concentration-time profile following oral administration of 800 mg dronedarone under fed (squares) or fasted (box) conditions



The mean dronedarone PK measures obtained after oral and IV administration are presented in Table 58.

IV Pharmacokinetics

After Cmax was achieved, dronedarone was rapidly cleared from the blood and widely distributed (Vz > 1500 L) following IV administration. Plasma concentration-time data exhibited high inter-patient variability during and at the end of the infusion; the reason for this finding is unclear. It should be noted that metabolite could not be detected following IV administration, suggesting that the metabolite is primarily formed during first pass or presystemic metabolism.

Table 58: Dronedarone PK Measures following 60 mg dronedarone IV infusion and 800 mg dronedarone oral (fed and fasted)

Parameter (units)	Intravenous Fasted	Oral Fasted	Oral Fed	90% CI (Oral Fed / Oral Fasted)	p-value
C_{max} (mg/l)	0.189 (0.034)	0.020 (0.012)	0.120 (0.043)	442 - 900	0.0001
t_{max} (h)	0.67 (0.12)	2.7 (1.3)	4.3 (1.1)	NPT	0.001
AUC_{0-t} (mg/l*h)	0.288 (0.051)	0.108 (0.097)	0.644 (0.282)	481-1169	0.0001
AUC (mg/l*h)	0.350 (0.054)	0.219 (0.209)†	0.721 (0.327)‡	----------	----------
$t_{½}$ (h)	7.5 (3.4)	9.3 (9.5)†	8.9 (6.1)	NPT	0.31
$Vd\lambda_z$ (l)	1837 (713)	----------	----------	----------	----------
Cl_t (l/h)	176 (34)	----------	----------	----------	----------
F (%)	----------	4 (4)†	15 (6)‡	----------	----------

†n=6, ‡n=11
NPT - non-parametric test

Oral Pharmacokinetics (Fed vs. Fasted)

Overall, food increased the exposure of dronedarone relative to the fasted state. There was an approximately 6-fold increase in mean AUC_{0-t} and Cmax in the fed state; additionally food increased Tmax by ≥ 1 hr. Data obtained in the fasted state were highly variable (CV > 50 % for all PK measures).

Absolute Bioavailability

Dronedarone exhibited relatively low absolute bioavailability (BA): 4 % in the fasted state and 15 % in the fed state. The reliability of the absolute BA estimate in the fasted state is unclear because the extrapolated fraction of the total AUC exceeded 40 % for some subjects. Typically, BA evaluations are conducted in the fasted state to minimize the effect of extrinsic factors, such as food, on formulation performance. For dronedarone, a BA assessment in the fed state appears reasonable because food appears to decrease variability relative to the fasted state and may yield more readily interpretable results. However, because the dronedarone food effect is formulation dependent the applicability of these BA results (with capsule) in the fed state to the TBM tablet formulation is unclear. It should also be noted that dronedarone was administered at a supra-therapeutic dose, 800 mg, in this study. Dronedarone exhibits nonlinear kinetics that affect the extent of absorption, therefore the absolute BA findings will be dose dependent. Due to the stated differential food effect (tablet vs. capsule) and dose dependent extent of absorption (therapeutic dose = 400 mg vs. study dose = 800 mg) the quantitative absolute BA information obtained with the capsule at the 800 mg dose should not be extrapolated to the TBM tablets that will be administered at 400 mg. In sum, the absolute BA information is not acceptable for labeling.

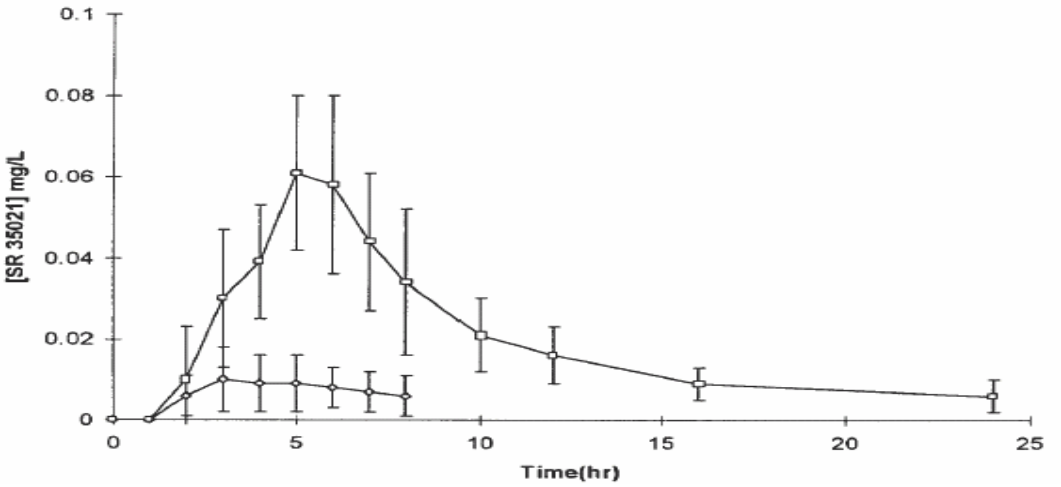
Reviewer Comment on Assay Sensitivity (impact on half-life estimation)

The reported LOQ in this study was ~ 5 ng/mL; this value exceeds that for the LC/MS/MS assays that were developed later on in the dronedarone program. The limited sensitivity of the assay used in the current study may have impacted the PK estimates; for example, the half-life reported in this study was < 10 hours whereas in later studies the half-life was > 20 hours. It is noted that the half-life could not be determined for six of the 12 subjects in the fasted state and one subject in the fed state.

SR35021 Pharmacokinetics

The mean SR35021 plasma concentration-time profiles in the fed and fasted state are depicted in Figure 35.

Figure 35: Mean SR35021 plasma concentration-time profile following oral administration of 800 mg dronedarone under fed (square) and fasted (diamond) conditions.



As noted previously, SR35021 levels were not measurable following IV administration. Following oral administration SR35021 was detectable in most patients, however; two subjects had concentrations equal to LOQ within 4 hours after drug administration.

The mean SR35021 PK measures are summarized in Table 59.

Table 59: SR35021 PK Measures in Healthy Males following 800 mg dose

Parameter (units)	Oral Fasted	Oral Fed	90% CI (Oral Fed / Oral Fasted)	p-value
C_{max} (mg/l)	0.016 (0.005)	0.065 (0.019)	293 - 761	0.0001
t_{max} (h)	4.1 (1.1)	5.8 (1.1)	NPT	0.016
AUC_{0-t} (mg/l*h)	0.082 (0.047)	0.497 (0.192)	459 - 994	0.0001
AUC (mg/l*h)	† NC	0.638 (0.327)‡	----------	---------
$t_{½}$ (h)	† NC	14.1 (8.8)‡	NP	NP

†n=2, ‡n=8
NPT - non-parametric test
NC - not calculated
NP - not performed (sample size too small)

Dronedarone Pharmacodynamics (PD)

Dronedarone PD data are summarized in Table 60 and Table 61. The PD data were not reviewed in detail because they do not impact the absolute BA information. In brief there were statistically significant differences in HR, PR and QT between the fed and fasted conditions; the differences were mainly observed at 2 hrs post dose. However, there was no clear trend, in that fed conditions did not consistently have a greater change in ECG measures than fasted conditions. Assuming similar baseline ECG values prior to dronedarone administration, the difference between fed and fasted conditions do not appear clinically significant (differences < 10 %).

Table 60: Dronedarone PD after oral administration under and fed and fasted conditions

Parameter (units)	Time (hours)	Fasted†	Fed†	Treatment p-value‡
HR (bpm)	2	55	64	0.007
	4	55	59	ns
	8	62	59	ns
	24	58	57	ns
PR (ms)	2	169	161	0.005
	4	167	172	ns
	8	158	174	0.001
	24	165	166	ns
QRS (ms)	2	93	92	ns
	4	93	93	ns
	8	92	92	ns
	24	93	92	ns
QT (ms)	2	394	369	<0.001
	4	395	378	0.015
	8	384	383	ns
	24	389	392	ns
QTc (ms)	2	375	378	ns
	4	375	373	ns
	8	386	380	ns
	24	378	379	ns

† Adjusted mean value

Table 61: Dronedarone PD after oral administration (fasted conditions) and IV administration

Parameter (units)	Time (hours)	Oral†	Intravenous†	Treatment p-value‡
HR (bpm)	2	55	55	ns
	4	55	53	ns
	8	61	58	ns
	24	58	57	ns
PR (ms)	2	169	179	0.001
	4	167	169	ns
	8	159	159	ns
	24	165	165	ns
QRS (ms)	2	93	93	ns
	4	93	92	ns
	8	92	91	ns
	24	92	90	ns
QT (ms)	2	398	390	ns
	4	398	397	ns
	8	383	390	ns
	24	390	386	ns
QTc (ms)	2	376	373	ns
	4	377	374	ns
	8	386	383	ns
	24	379	375	ns

† Adjusted mean value

Applicant's Safety Summary

Generally oral and IV dronedarone were well tolerated. However, local tolerability following IV administration was poor, leading to a serious adverse event in one patient.

Recommendations/Conclusions

Overall this reviewer does not recommend including results from Study PPK2397 in product labeling because:

- Absolute bioavailability information was obtained at the 800 (fed or fasted) vs. 400 mg (proposed) dose and dronedarone exhibits dose-dependent PK
- dronedarone exhibits a formulation dependent food-effect, which alters PK in fed state

However, if absolute BA information is deemed critical for product labeling the above limitations should be included. Overall, the following findings from the study may have qualitative utility:

1. metabolite is not formed following IV dronedarone administration suggesting the metabolite is formed pre-systemically
2. food increases dronedarone exposure
3. absolute BA of dronedarone is approximately 15 % in fed conditions following administration of capsule at 800 mg dose level.

APPENDIX to STUDY PPK2397

Blood sampling time in Study PPK2397

Intravenous Route				Oral Route (Fed and Fasted)		
Time of Sampling	Sample	Sample Number		Time of Sampling	Sample	Sample Number
T0-10min	1st sample	P0		T0-10min	1st sample	P0
T0+15min	2nd sample	P1				
T0+30min	3rd sample	P2				
T0+45min	4th sample	P3				
T1h (end of infusion)	5th sample	P4		T1h	2nd sample	P1
T1h+15min	6th sample	P5		T2h	3rd sample	P2
T1h+30min	7th sample	P6		T3h	4th sample	P3
T2h	8th sample	P7		T4h	5th sample	P4
T3h	9th sample	P8		T5h	6th sample	P5
T4h	10th sample	P9		T6h	7th sample	P6
				T7h	8th sample	P7
T6h	11th sample	P10		T8h	9th sample	P8
T8h	12th sample	P11		T10h	10th sample	P9
T10h	13th sample	P12		T12h	11th sample	P10
T12h	14th sample	P13		T16h	12th sample	P11
T16h	15th sample	P14		T24h	13th sample	P12
T24h	16th sample	P15		T36h	14th sample	P13
T48h	17th sample	P16		T48h	15th sample	P14
T72h	18th sample	P17		T72h	16th sample	P15

4.2.7 In vitro characterization of the binding of [^{14}C]-SR33589B to human plasma proteins (LPH0006).

PROTOCOL #	LPH0006
STUDY SITE	Sanofi-Synthelabo Research, Willowburn Avenue, Alnwick Northumberland, England, NE66 2JH
STUDY PERIOD	August - December 2002

Study Description

Equilibrium dialysis was used to determine the plasma protein binding of radiolabeled dronedarone in natural plasma, human serum albumin (HSA) and α1-acid glycoprotein (AAG). The following dronedarone concentrations were evaluated: 25, 50, 500, 5000, and 50,000 ng base/mL. Liquid scintillation counting was used to measure total radioactivity. Two additional experiments were conducted in conjunction with the protein binding evaluation:

1. Stability of [^{14}C]-dronedarone was studied in each matrix and dialysate by HPLC and radiochemical detection
2. Protein concentration in the dialysate was measured to ensure the exclusion of protein by the equilibrium dialysis membrane.

The protein concentration experiment was not reviewed in detail because standard equilibrium dialysis membranes are expected to exclude proteins.

Reviewer Note on Experimental Design

The study procedures were acceptable. According to the applicant, a previous study showed that ultra-filtration was not suitable for the determination of the protein binding of [^{14}C] - dronedarone due to high non-specific binding to the ultra-filtration devices. As a result equilibrium dialysis was used to determine protein binding.

Materials

- Test substance: dronedarone (dronedarone hydrochloride salt) ^{14}C in carbonyl function. The specific radioactivity was 3.65 MBq/mg base (98.8 µCi/mg base).
- Frozen plasma from six healthy male individuals was obtained from Biochemed Pharmacologicals, USA.

RESULTS

Plasma Protein Binding

The results for the dronedarone plasma protein binding are summarized in Table 62. Dronedarone was over 99 % bound at all concentrations examined (25 – 50000 ng/mL nominal concentration) and the degree of binding appeared independent of dronedarone concentration. At the clinically relevant concentration (Cmax ~ 200 ng/mL), binding of [^{14}C] - dronedarone to proteins in plasma was 99.7 % (Table 63). Generally, binding to purified human serum albumin (HSA) appeared independent of concentration; this independence was obvious at 40 mg/mL (physiological conditions), but not clear at the 2 mg/mL HSA concentration. The degree of binding to α1-acid glycoprotein (AAG) at physiological concentrations appeared largely independent of drug concentration. These data indicate that [^{14}C]-dronedarone was extensively bound to HSA and AAG, and these two proteins appear to account for the majority of binding in plasma.

Table 62: Mean Percent* of Dronedarone bound in plasma and purified plasma proteins

Nominal Concentration (ng/mL)	Plasma (n = 2)	HSA 40 mg/mL (n = 2)	HSA 2mg/mL (n = 2)	AAG (n = 4; mean ± SD)
25	99.73	98.82	81.88	77.56 ± 4.67
50	99.73	98.94	82.04	82.07 ± 5.30
500	99.70	98.93	72.29	81.83 ± 7.67
5000	99.72	98.68	80.17	87.21 ± 2.02
50000	99.71†	98.40	92.18	88.58 ± 1.88

† n = 1 due to cell blockage

* n refers to the number of experiments conducted with pooled plasma samples from six healthy male subjects.

Reviewer Comment

The sample size for the experiments presented in Table 62 is inappropriate because it may not reflect experimental variability. Ideally the number of experiments should be > 2; however, the results from the individual plasma samples (Table 63) suggest low inter-subject variability, which can be assumed to be equivalent or higher than inter-experimental variability. Consequently, the results from the protein binding study are acceptable, despite the low number of replicates. It is noted that the data provided from the two replicates (plasma and HSA) were similar.

Table 63: Mean percent ^{14}C-dronedarone bound in plasma at 200 ng/mL dronedarone concentration

Individual identity number	Percent bound Mean ± SD (n = triplicate measurements)
N17890	99.73 ± 0.019
N17895	99.70 ± 0.054
N17899	99.72 ± 0.025
N19471	99.79 ± 0.0010
N19472	99.75 ± 0.044
N19474	99.74 ± 0.054
Mean	99.74
s.d.	0.030

Equilibrium Constants

The equilibrium dissociation constant for the binding of dronedarone to HSA and AAG are presented in Table 64.

Table 64: Apparent equilibrium dissociation constants for the binding of dronedarone to purified HSA and AAG

	K_D	95% confidence interval	% CV
HSA	9.11	9.06; 9.15	0.23
AAG	0.62	0.48; 0.80	13.71
HSA (2 mg/mL)	1.16	0.60; 2.28	33.62

The apparent dissociation constants (K_D) for binding of dronedarone to purified HSA and AAG were obtained by assuming a single binding site per protein molecule. Based on these K_D values, dronedarone had a significantly higher affinity (lower K_D) for AAG than HSA (physiological concentrations). However, due to the greater physiological

concentration of HSA, and hence, greater capacity, binding was approximately three times greater to HSA as shown in Table 62.

Non-Specific Binding (Recovery of radioactivity)

The recovery of radioactivity data in plasma, HSA and AAG are presented in Table 65.

Table 65: Percent of Radiolabeled dronedarone recovered from equilibrium dialysis cells

	Recovery							
Nominal Concentration	Plasma		HSA		AAG		AAG (repeated experiment)	
	Initial	Total	Initial	Total	Initial	Total	Initial	Total
25	90.3	93.4	87.4	99.9	18.8	80.7	23.2	97.0
	95.1	98.3	89.0	100	17.8	85.1	20.6	102
50	91.2	94.5	79.8	92.0	22.0	104	26.6	103
	94.8	97.3	86.3	99.4	23.8	105	33.8	106
500	92.3	95.4	85.1	96.3	19.1	81.9	29.6	93.3
	80.3	82.3	85.9	96.1	20.1	78.6	29.2	96.0
5000	93.2	96.0	88.8	98.1	22.1	96.0	18.9	95.3
	94.5	97.4	79.7	88.3	20.4	95.6	19.3	92.5
50000	91.6	95.5	76.6	84.4	16.0	94.7	16.6	92.7
	-†	-†	91.4	99.6	16.2	92.7	17.5	105

† no data due to cell blockage

Initial recovery of radioactivity was generally > 80% from experiments with plasma and HSA demonstrating a low level of non-specific binding in these experiments. However, initial recovery was lower in matrices containing a lower protein concentration (AAG). The initial low recovery appeared due to non-specific binding to the cells, because the recovered amount increased significantly by washing with methanol. The initial recovery results with AAG were similar in the first and repeated experiments, but, the total recovery in the repeated experiment was almost complete vs. ~ 81 % in the first experiment. The reason for the variability in AAG results is unclear and should have been explored further by the applicant.

Reviewer Comment

The limited initial recovery with AAG suggests the protein binding results for AAG may not be reliable because radiolabeled dronedarone may have had a greater affinity for the dialysis cells than AAG thereby not accurately reflecting dronedarone-AAG binding. The applicant should have attempted to optimize the equilibrium dialysis conditions to minimize non-specific binding.

[^{14}C]- dronedarone radiochemical stability

The radiochemical purity of [^{14}C]-dronedarone in retentate and dialysate samples are shown in Table 66 and Table 67.

Table 66: Radiochemical Purity (Stability) of radiolabeled dronedarone (initial 5 µg/mL [^{14}C]-dronedarone concentration) in retentate samples

Matrix	Replicate	% Of Total Radioactivity	
		[^{14}C]-SR33589	Impurity
Plasma	1	101.09	0.37
	2	99.67	-
HSA	1	98.75	1.74
	2	97.34	1.46
Alpha-1-acid glycoprotein	1	88.24	8.49
	2	92.74	7.26

Table 67: Radiochemical purity (Stability) of radiolabeled dronedarone (initial 5 µg/mL [^{14}C]-dronedarone concentration) dialysate samples

Matrix	Replicate	% Of Total Radioactivity	
		[^{14}C]-SR33589	Impurity
Plasma	1	75.53	22.46
	2	66.79	25.03
HSA	1	90.57	8.83
	2	88.58	10.52
Alpha-1-acid glycoprotein	1	90.19	8.42
	2	91.69	7.32

Generally, the retentate samples had high radiochemical purity (> 90 %), whereas the dialysate samples were not as pure. The implications of the lack of radiochemical purity for each of the matrices are discussed as follows:

Plasma

In plasma, dialysate impurities constituted approximately 24% of total radioactivity, with [^{14}C] - dronedarone representing ~ 70 % radioactivity. These data suggest that potentially up to 30 % of the radioactivity in the dialysate may be due to radiochemical impurities and not radiolabeled dronedarone. Consequently, differential binding of radiochemical impurities to plasma proteins, compared to [^{14}C] - dronedarone, could result in an overestimation (approximately 30 %) of free fraction using total radioactivity calculations. The applicant notes that this potential overestimation was not accounted for in estimates of fractional binding of [^{14}C] - dronedarone.

HSA

The radiochemical purity of radiolabeled-dronedarone in retentate from HSA was approximately 98%. However, in dialysates, radiolabeled-dronedarone accounted for only 90% of the total radioactivity, which would result in a small overestimation of free fraction. This difference is also sufficiently small to have limited impact on estimation of the dissociation constant.

AAG

Radiochemical purity was approximately 90% in both retentate and dialysate. Since the dialysate composition of radioactive components reflects that in the retentate, there was no impact on the estimation of the free fraction or dissociation constant

Protein Concentration

There was no protein in the dialysate, whereas the retentate had a significant amount of protein (Table 68); this finding indicates that the dialysis membrane functioned appropriately.

Table 68: Protein concentration in dialysate and plasma retentate

	Total protein concentration (g/L)	
Replicate no.	Dialysate	Retentate
1	0	61
2	0	62

Recommendations/Conclusions

The lack of radiochemical purity in the plasma and HSA samples warrants cautious interpretation of all protein binding calculations. Additionally, the initial low and variable total recovery with AAG indicates that experimental conditions were not optimized in this plasma protein binding assessment. Assuming the worst case scenario with respect to radiochemical impurity, enrichment of radiochemical impurities in plasma dialysate will result in a 30% overestimation of the free fraction in plasma. Consequently, the estimate of fu in this study (0.26 ± 0.03%; n = 6 healthy male subjects) could be adjusted to 0.19% if a correction for radiochemical impurities is applied. Similarly, in experiments with HSA a 10% overestimation of fu would occur. With these caveats the following conclusions can be drawn from the protein binding experiments:

- Binding of [^{14}C]- dronedarone to plasma proteins is greater than 99 % and not concentration-dependent over the 25 to 50000 ng/mL concentration range.
- HSA is the major binding protein, with approximately three times more drug bound to HSA than AAG. These two proteins appear to account for the majority of the plasma protein binding of dronedarone.

4.2.8 In vitro characterization of the binding of ^{14}C-SR35021 to human plasma proteins (LPH0021)

PROTOCOL #	LPH0021
STUDY SITE	Sanofi-Synthelabo Research, Willowburn Avenue, Alnwick Northumberland, England, NE66 2JH
STUDY PERIOD	July - August 2001

Study Description

Equilibrium dialysis was used to determine the plasma protein binding of radiolabeled dronedarone in natural plasma, human serum albumin (HSA) and α1-acid glycoprotein (AAG). The following SR35021 concentrations were evaluated: 25, 50, 500, 5000, and 50,000 ng base/mL. Liquid scintillation counting was used to measure total radioactivity. Two additional experiments were conducted in conjunction with the protein binding evaluation:

1. Stability of [^{14}C]-SR35021 was studied in each matrix and dialysate by HPLC and radiochemical detection
2. Protein concentration in the dialysate was measured to ensure the exclusion of protein by the equilibrium dialysis membrane.

The protein concentration experiment was not reviewed in detail because standard equilibrium dialysis membranes are expected to exclude proteins.

Materials

- Test substance: SR35021 hydrochloride salt, ^{14}C in carbonyl function. The specific radioactivity was 3.79 MBq/mg
- Frozen plasma from six healthy male individuals was obtained from Biochemed Pharmacologicals, USA.

RESULTS

Plasma Protein Binding

The results for the SR35021 plasma protein binding are summarized in Table 69. SR35021 was over 98 % bound at all concentrations examined (25 – 50000 ng/mL nominal concentration) and the degree of binding appeared independent of SR35021 concentration. At the clinically relevant concentration (Cmax ~ 200 ng/mL), binding of [^{14}C]-SR35021 to proteins in plasma was 98.2 % (Table 69). Binding to purified human serum albumin (HSA) appeared independent of concentration at the 40 mg/mL HSA concentration (physiological conditions). The degree of binding to α1-acid glycoprotein (AAG) at physiological concentrations appeared dependent on drug concentration; binding of SR35021 appeared to decrease with increasing SR35021 concentration. However, the exact nature of this concentration dependence was not clear except at the extreme ends of the tested SR35021 concentrations (Binding was ~ 73 % at 25 ng/mL and ~ 30 % at 50000 ng/mL). Nevertheless, the AAG and HSA data indicate that [^{14}C]-SR35021 was extensively bound to HSA and AAG, and these two proteins appear to account for the majority of binding in plasma.

Table 69: Mean percent of ^{14}C-SR35021 bound in human plasma, HSA and AAG

Nominal [^{14}C]-SR33589 (ng/mL)	Plasma	HSA (41 mg/mL)	α_1-Acid Glycoprotein (0.6 mg/mL)
25	98.473	94.548	73.350
50	98.512	95.066	56.493
500	98.255	95.296	61.479
5000	98.618	94.611	69.140
50000	98.633	95.197	29.807

Table 70: Mean SD percent ^{14}C-SR35021 (200 ng/mL) protein bound in plasma from healthy male subjects

Individual identity number	Percent bound Mean ± s.d. (n = triplicate measurements)
N17890	97.97 ± 0.0198
N17895	97.98 (n = 2)
N17899	97.66 ± 0.349
N19471	98.54 ± 0.123
N19472	98.71 ± 0.0144
N19474	98.42 ± 0.0144
Mean	98.21
s.d.	0.40

Equilibrium Constants

The equilibrium dissociation constant for the binding of SR35021 to HSA and AAG are presented in Table 71.

Table 71: Calculated dissociation constants for the binding of ^{14}C-SR35021 to purified HSA and AAG

	K_D* (μM)	95% confidence interval	% CV
HSA (41 mg/mL)	30.23	29.67; 30.82	0.84
AAG	3.85	2.67; 5.66	19.80

* n = 1 binding site per molecule

The apparent dissociation constants (K_D) for binding of SR35021 to purified HSA and AAG were obtained by assuming a single binding site per protein molecule. Based on these K_D values, SR35021 had a significantly higher affinity (lower K_D) for AAG than HSA (physiological concentrations). However, due to the greater physiological concentration of HSA, and hence, greater capacity, binding was approximately six times greater to HSA as shown in Table 69.

Non-Specific Binding (Recovery of radioactivity)

The recovery of radioactivity data in plasma, HSA and AAG are presented in Table 72. Initial recovery of radioactivity was > 80% from experiments with plasma and HSA demonstrating a low level of non-specific binding in these experiments. However, initial recovery was lower in matrices containing a lower protein concentration (e.g. for AAG). The initial low recovery appeared due to non-specific binding to the cells, because the recovered amount increased significantly by washing with methanol.

Table 72: Recovery of radioactivity in plasma, AAG and HSA

Nominal Concentration	Recovery							
	Plasma		HSA		AAG		AAG (repeated experiment)	
	Initial	Total	Initial	Total	Initial	Total	Initial	Total
25	93.2	95.4	83.5	97.2	31.0	96.7	19.6	90.0
	91.8	94.4	84.5	98.2	21.2	90.6	19.5	95.8
50	87.2	91.1	85.4	98.3	21.4	94.0	22.1	85.5
	84.1	87.3	84.1	99.7	22.4	101	15.9	83.5
500	77.9	80.8	82.4	94.4	25.3	84.2	25.7	84.6
	84.8	88.1	84.9	95.7	27.7	95.3	33.3	93.4
5000	90.7	95.6	71.7	78.3	51.8	95.8	54.9	92.3
	93.0	97.8	90.9	99.2	55.5	96.4	62.3	96.7
50000	90.3	94.8	90.8	95.0	68.0	87.7	74.3	94.0
	91.7	96.0	94.5	99.2	76.7	98.2	77.9	98.3

The initial recovery results with AAG were similar for the first and repeated experiments,

Reviewer Comment

The limited initial recovery with AAG suggests the protein binding results for AAG may not be reliable because radiolabeled SR35021 may have had a greater affinity for the dialysis cells than AAG thereby not accurately reflecting SR35021-AAG binding. The applicant should have attempted to optimize the equilibrium dialysis conditions to minimize non-specific binding.

[^{14}C]- SR35021 radiochemical stability

The radiochemical purity of [^{14}C]-SR35021 in retentate and dialysate samples are shown in Table 73 and Table 74.

Table 73: Purity (Stability) of SR35021 (initial concentration was 5 µg/mL of [^{14}C]-SR35021) in retentate samples

Matrix	Replicate	% Of Total Radioactivity	
		[^{14}C]-SR35021	Impurity
Plasma	1	98.74	-
	2	98.90	-
HSA	1	97.52	1.57
	2	97.70	-
Alpha-1-acid glycoprotein	1	95.06	3.54
	2	93.07	6.57

Table 74: Purity (Stability) of SR35021 (initial concentration was 5 µg/mL of [^{14}C]-SR35021) in dialysate samples

Matrix	Replicate	% Of Total Radioactivity	
		[^{14}C]-SR35021	Impurity
Plasma	1	82.27	15.66
	2	82.16	16.79
HSA	1	89.10	9.68
	2	89.91	9.39
Alpha-1-acid glycoprotein	1	92.62	6.38
	2	92.11	6.26

Generally, the retentate plasma and HSA samples had higher radiochemical purity (> 92 %) than their respective dialysate samples. The implications of the lack of radiochemical purity for each of the matrices are discussed as follows.

Plasma

In plasma, dialysate impurities constituted approximately 16 % of total radioactivity, with [^{14}C] - SR35021 representing ~ 80 % radioactivity. These data suggest that potentially up

to 20 % of the radioactivity in the dialysate may be due to radiochemical impurities and not radiolabeled SR35021. Consequently, differential binding of radiochemical impurities to plasma proteins, compared to [^{14}C] - SR35021, could result in an overestimation (approximately 20 %) of free fraction using total radioactivity calculations. The applicant notes that this potential overestimation was not accounted for in estimates of fractional binding of [^{14}C] - SR35021.

HSA

The radiochemical purity of radiolabeled-SR35021 in retentate from HSA was approximately 98%. However, in dialysates, radiolabeled-SR35021 accounted for only 90% of the total radioactivity, which would result in a small overestimation of free fraction. This difference is also sufficiently small to have limited impact on estimation of the dissociation constant.

AAG

Radiochemical purity was approximately 93 % in both retentate and dialysate. Since the dialysate composition of radioactive components reflects that in the retentate, there was no impact on the estimation of the free fraction or dissociation constant

Protein Concentration

There was no protein in the dialysate whereas the retentate had a significant amount of protein (Table 75); this finding indicates that the dialysis membrane functioned appropriately.

Table 75: Protein concentration in dialysate and plasma retentate

	Total protein concentration (g/L)	
Replicate no.	Dialysate	Retentate
1	0	61
2	0	62

Recommendations/Conclusions

The lack of radiochemical purity in the plasma and HSA samples warrants cautious interpretation of all protein binding calculations. Additionally, the initial low recovery with AAG indicates that experimental conditions were not optimized in this plasma protein binding assessment. Assuming the worst case scenario with respect to radiochemical impurity, enrichment of radiochemical impurities in plasma dialysate will result in a 20% overestimation of the free fraction in plasma. Consequently, the estimate of fu in this study (1.79 ± 0.4 %; n = 6 healthy male subjects) could be adjusted to 1.52 % if a correction for radiochemical impurities is applied. Similarly, in experiments with HSA a 10% overestimation of fu would occur. With these caveats the following conclusions can be drawn from the protein binding experiments:

- Binding of [^{14}C]- SR35021 to plasma proteins is greater than 98 % and not concentration-dependent over the 25 to 50000 ng/mL concentration range.
- HSA is the major binding protein, with approximately six times more drug bound to HSA than AAG. These two proteins appear to account for the majority of the plasma protein binding of SR35021.

4.2.9 Effect of dronedarone on renal functions in healthy male subjects - Randomized, double-blind, placebo-controlled, two-by-two crossover in sequential groups study (PDY5487)

PROTOCOL #	PDY5487
INVESTIGATOR	Pr Jerome Biollaz
STUDY SITE	Hôpital de Beaumont, Avenue de Beaumont, 29, 1011 Lausanne - CHUV – Vaud, Switzerland
STUDY PERIOD	June to November 2003

Objectives (per applicant)

- to evaluate the effect of dronedarone on the creatinine clearance and on the glomerular filtration rate compared to placebo.
- to elucidate the mechanism of action of repeated doses of dronedarone on the renal blood flow and renal cationic transport compared to placebo
- to assess the clinical and biological tolerability of dronedarone
- to assess plasma concentration profile of dronedarone and SR35021 on the last day of treatment

Study Design

This was a randomized, placebo-controlled, double-blind, two-by-two crossover study in healthy male subjects. There was a 14-day washout between periods. Two sequential dose groups were planned*:

- Group 1 (first dose level)
  - Treatment A = placebo for seven days
  - Treatment B = dronedarone 400 mg twice daily (BID) for seven days
- Group 2 (second dose level)
  - Treatment A = placebo for seven days
  - Treatment B = dronedarone 800 mg BID for seven days

*According to the applicant, an interim analysis indicated that the second dose level of the study was not required because results were conclusive from the first dose level and did not need to be confirmed by a higher dose.

Reviewer's Note

The 400 mg BID dose is the proposed clinical dose, thus this study provides relevant information. However, information at a higher dose or alternative doses would be useful to determine if there is an exposure (concentration)-response (effect on renal function) or dose-response relationship; evaluating this relationship would facilitate dose adjustments, if needed.

Subject Demographics

Subject demographics are presented in Table 76.

Formulations

- Dronedarone (2E3 formulation), 400 mg tablet; batch number: CL-03936
- Placebo Matching tablet; batch number: CL-03812
- Sinistrin, Inutest vials containing 5g/20mL provided by Fresenius Kabi Austria GmbH (Graz, Austria); batch number 21 3063

- Para-amino-hippurate (PAH), Sodium PAH vials containing 2 g/10 mL provided by Clinalfa, Merck Biosciences AG (Läufelfingen, Switzer land); batch number AC 0465 and AC 0349

Table 76: Subject Demographic Data for Study PDY5487

Parameter (Unit)	Statistics/ Category	Total (N=12)
Age (year)	N	12
	Mean	25.8
	SD	5.1
	Min	19
	Max	38
Height (cm)	N	12
	Mean	179.3
	SD	7.3
	Min	169
	Max	192
Weight (kg)	N	12
	Mean	67.65
	SD	9.16
	Min	55.5
	Max	87.8
BMI (kg/m^2)	N	12
	Mean	20.98
	SD	1.62
	Min	19.0
	Max	24.6
Gender	Male (N, %)	12 (100)
Race	Black (N,%)	6 (50)
	Caucasian (N,%)	5 (41.7)
	Other (N,%)	1 (8.3)

Pharmacokinetics

Plasma concentrations of dronedarone and SR35021 were assessed before treatment on Day -1, before dosing on Day 6 and Day 7, then post dosing at 2, 3.5 and 5 h on Day 7. Due to the limited sampling, a formal PK analyses was not conducted, however, plasma concentrations were provided.

Pharmacodynamics

Primary

The primary PD criteria were based on the following urinary clearance evaluations on Day -1 and Day 7 and 14 Days after the last study drug was administered. Samples were collected at the 1 hour 30 minutes time point to estimate.

- renal creatinine clearance (CLcr)
- glomerular filtration rate (GFR) measured as renal sinistrin clearance

Secondary

The secondary PD criteria were the GFR estimated by systemic sinistrin clearance and the following urinary measurements on Day -1, Day 7 and Day 14. Samples were collected at the 1 hour 30 minutes time point.

- urinary flow rate (UFR)
- effective renal plasma flow (ERPF) using renal para-aminohippurate (PAH) clearance
- renal blood flow (RBF) = ERFP/(1- Hematocrit)
- filtration fraction (FF) = renal sinistrin clearance/RBF

- renal cationic transport by renal N^1-methylnicotinamide (NMN) clearance
- renal clearance ratio of creatinine over sinistrin
- renal clearance ratio of NMN over PAH.

Additionally, the following PD measurements were obtained from 24 h urine collections on Day -2, Day 6 and Day 13 (recovery: 13 days after the last study drug administration):

- renal creatinine clearance
- UFR (mL/24h)
- Osmolality
- sodium and potassium excretion

Pharmacodynamic Analyses

PD measures were log transformed prior to analysis. Standard pharmaco-statistical analyses were used to determine if dronedarone affected the PD measures, where Day 6 or 7 data were compared to baseline data.

Reviewer Comment on PD Measures and Analyses

The selected PD measures have been used to varying degrees to assess renal function. This review focuses on the CLcr, because this is the most commonly used parameter in clinical pharmacology assessments of renal function.

Bioanalytical methods

Dronedarone and SR35021 concentrations were determined using a validated liquid chromatography- tandem mass spectrometry (LC-MS/MS) method (DOH0309). The assay performance was acceptable as illustrated in Table 77 .

Table 77: Performance of Dronedarone and SR35021 Assays (DOH0309)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.998$	Satisfactory
Between day Precision	CV data were not provided	Cannot be assessed
Accuracy	All QC samples were within 10 % of the nominal concentrations	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity*	Chromatograms were not provided	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.997$	Satisfactory
Between day Precision	CV data were not provided	Satisfactory
Between day Accuracy	All QC samples were within 10 % of the nominal concentrations	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity*	Chromatograms were not provided	Cannot be assessed

* The validation report for DOH0309 includes chromatograms and CV measures that indicate the assay is specific and precise

Results

Pharmacokinetics

The mean dronedarone and SR35021 plasma concentrations are presented in Table 78. Comparison of Day 6 and 7 plasma concentrations suggests that dronedarone and SR35021 reached steady state by Day 7. Plasma concentrations obtained in this study are consistent with previous PK data at this dose level.

Table 78: Mean (CV%) dronedarone and SR35021 plasma concentrations observed from Day - 1 to Day 7 during repeated oral administrations of dronedarone 400 mg BID in fed conditions (n = 12)

Mean (CV%) Concentrations	Day -1	Day 6	Day 7			
	0h30	0h00	0h00	2h00	3h30	5h00
Dronedarone (ng/mL)	<LOQ	34.3 (25.6)	30.3 (36.5)	69.2 (58.5)	110 (44.3)	80.5 (38.8)
SR35021 (ng/mL)	<LOQ	32.5 (27.6)	31.1 (31.6)	39.2 (30.0)	61.1 (22.9)	63.4 (20.7)

Pharmacodynamics

The estimates of urinary clearance measures on Day -1 and Day 7 following placebo or dronedarone 400 mg are summarized in Table 79 and Table 80

Table 79: Estimated D7/D-1 ratio of geometric mean renal clearances by treatment and between treatments

Parameter	Placebo D7/D-1 (%)	Dronedarone D7/D-1 (%)	(Day 7/Day -1)Dronedarone/ (Day 7/Day 1)Placebo Ratio		P-value
			Estimate (%)	95 % CI	
Sinistrin	1.35	-2.11	-3.42	[-20.41, 17.21]	0.7229
Creatinine	4.91	-13.66	-17.70	[-31.68, -0.85]	0.0405
Creatinine over sinistrin	3.42	-11.80	-14.72	[-20.72, -8.25]	<.0001
PAH	0.06	-5.72	-5.77	[-22.47, 14.51]	0.5471
NMN	-0.86	-17.74	-17.02	[-31.58, 0.65]	0.0581
NMN over PAH	-1.11	-12.75	-11.76	[-19.35, -3.45]	0.0068

P-value is the significance level of the hypothesis test: (Day7/Day-1) dronedarone/(Day7/Day-1) placebo ratio equals 1

Table 80: Estimated Day 7 geometric mean renal clearances by treatment and estimate of treatment ratio of Day 7 geometric mean clearances

Parameter	Placebo on Day 7 Estimate	Dronedarone on Day 7 Estimate	Dronedarone / Placebo Ratio on Day 7		P-value
			Estimate (%)	95% CI (%)	
Sinistrin (mL/min)	107.0	98.5	-8.01	[-19.82, 5.53]	0.2311
Creatinine (mL/min)	149.0	119.4	-19.86	[-29.78, -8.54]	0.0012
Creatinine over sinistrin	1.39	1.21	-12.81	[-17.21, -8.16]	<.0001
PAH (mL/min)	514.3	485.1	-5.68	[-17.87, 8.32]	0.4046
NMN (mL/min)	431.0	368.3	-14.56	[-25.50, -2.02]	0.0247
NMN over PAH	0.84	0.76	-9.24	[-14.86, -3.26]	0.0032

P-value is the significance level of the hypothesis test: Day7 dronedarone/placebo ratio equals 1

General Observations

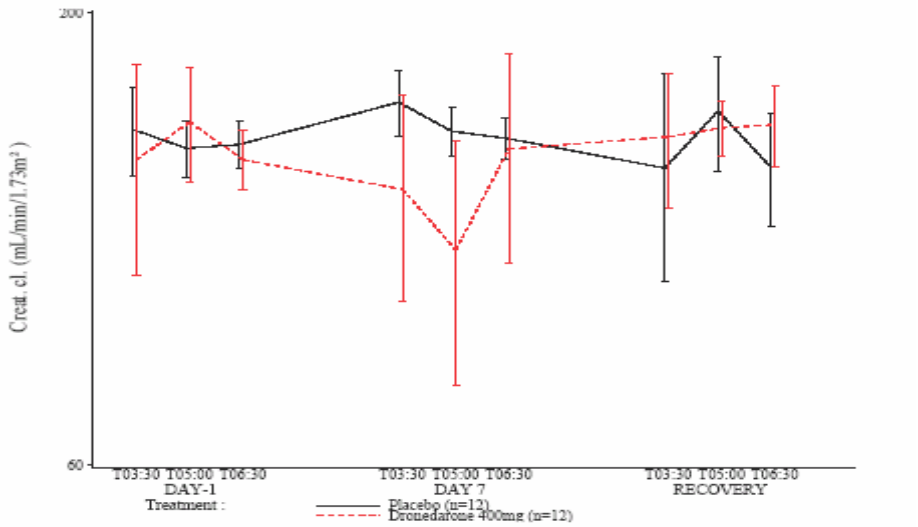
After 7 days of 400 mg BID dronedarone:

- Renal sinistrin clearance was not affected by dronedarone

- Renal creatinine clearance was significantly decreased relative to baseline and was significantly lower than placebo on Day 7
- Dronedarone did not affect the renal PAH clearance
- A significant decrease of renal NMN clearance was observed as well as a significant change in the NMN/PAH ratio
- Ratio of creatinine to sinistrin was lower for the dronedarone group than placebo, but the difference appears due to creatinine

The renal creatinine clearance values on the various study days are depicted in Figure 36 and summarized in Table 81.

Figure 36: Change in creatinine clearance^ in placebo and dronedarone groups



^the lower curve (red color) is for dronedarone and the upper curve (black color) is for placebo

Table 81: Renal Creatinine clearance by treatment and day

Treatment	Day	n	Geometric Mean	95% CI Lower	95% CI Upper	Min	Max
Placebo	Day -1	12	141.99	131.59	153.22	119.14	171.72
	Day 7	12	148.82	141.24	156.81	130.38	179.36
	Recov	12	137.37	124.41	151.68	102.95	176.66
Dronedarone 400mg	Day -1	12	138.26	127.55	149.88	102.95	162.24
	Day 7	12	119.38	105.63	134.91	73.61	148.93
	Recov	12	145.82	134.55	158.04	119.39	171.72

The creatinine clearance data indicate that placebo did not impact the creatinine clearance values. In contrast, dronedarone 400 mg BID decreased mean creatinine clearance by ~ 20 mL/min over a seven day-period; however, this decrease was recovered within 14 days after dronedarone was discontinued. This finding suggests that the effect of dronedarone on CLcr is reversible upon drug discontinuation in healthy subjects with normal renal function. The potential limitations of this study with respect to clinical utility include:

- it is unclear if this finding is applicable to patients with decreased renal function
- the time course for loss and gain of renal function could not be determined
- the study was conducted for a relatively short period of time.

The outlined limitations can be addressed using information from long-term trials, such as the pivotal trials or dose-ranging study.

There was a non-significant 4.75 % decrease in 24-hr creatinine clearance based on Day 6/Day-2 ratios (Table 82).

Table 82: Estimated Day6/Day-2 ratio of renal 24-hour creatinine clearances by treatment and between treatments

Parameter	Placebo D6/D-2 (%)	Dronedarone D6/D-2 (%)	$(Day\ 6/Day\ -2)_{Dronedarone}$ / $(Day\ 6/Day\ -2)_{Placebo}$ Ratio		P-value
			Estimate (%)	95% CI (%)	
Creatinine renal clearance	-7.87	-12.25	-4.75	[-17.96, 10.58]	0.5111

It is noted that the 24-hr CLcr finding was different from that for CLcr; the reason for this difference is unclear, but may be related to the lack of control of diet, exercise and other factors over the 24-hour period. For a practical perspective, the acute CLcr values are more readily attainable clinically and appear more reliable.

The impact of dronedarone administration on measures of renal function (PD measures) is summarized in Table 4.

Table 83: Impact of dronedarone administration on measures of renal function

Component	Estimates	Dronedarone vs. placebo	Comment
Renal Sinistrin	GFR	↔	No effect
CLcr	Renal function	↓	
CLcr/CL sinistrin	Renal tubular secretion of creatinine	↓	interferes
PAH	Renal Blood flow and tubular organic anion transporter (OAT)	↔	No effect on RBF
NMN renal clearance	Tubular organic cation transporter (OCT)	↓	May impact organic cations eliminated renally
24-hr creatinine clearance	Overall renal function	↔	Findings are inconclusive due to study design
Electrolytes (UFR, Na, K ions)	Excretion and osmolality	↔	No effect on physiological processes

Discussion: Interpretation of PD results

In brief, the PD findings suggest that dronedarone decreases renal function by interfering with tubular secretion of creatinine. However, this interference does not appear to significantly alter overall renal function as evidenced by the minimal impact on GFR, renal blood flow and other measures of renal function. Some investigators indicate that an apparent decrease in creatinine clearance alone does not necessarily signify a worsening of renal function. In light of the findings from the current study and the observations reported by other investigators, it is reasonable to conclude that dronedarone's impact on renal function may not be clinically significant. However, the label should include the findings from this study that suggest there may be potential increase in serum creatinine.

The decrease in the function of OCT suggests that dronedarone may affect the elimination of organic cation that are renally excreted; thus, there is a potential for drug-drug interactions to occur between dronedarone and such compounds.

Applicant's Safety Summary
No deaths, serious adverse events (SAEs) or AEs leading to treatment discontinuation occurred during the study. There were no significant changes in any laboratory test results. Additionally, no safety concerns in vital signs or ECG were noted. Headache was the most common treatment emergent AE in both treatment groups.

Recommendations/Conclusions
This study provides some insight into the short-term impact of dronedarone administration on renal function as assessed by PD measures. The overall clinical utility of this study is unclear because the time course was not well-defined and the study was conducted for a relatively short period of time. However, the study provides information on dronedarone drug-drug interaction potential with drugs with certain characteristics. The analysis should be repeated using information from long-term clinical trials; the Pharmacometric Reviewer has conducted this analyses. Despite the limitations of the current study, the following information from the study is useful for labeling as appropriate.

Relative to placebo, dronedarone at 400 mg BID for seven days in healthy subjects
1. significantly decreased the renal creatinine clearance; however, the decreased renal creatinine clearance returned to baseline level after study drug discontinuation (within 14 days). The mechanism of decreased creatinine clearance appears to be by partial inhibition of creatinine tubular secretion
2. did not alter GFR, renal blood flow or organic anion transport
3. appeared to inhibit the renal tubular organic cation transporter; this finding should be confirmed via an *in vivo* study with a renally excreted organic cation

Labeling
In light of the increase in serum creatinine, the applicant has proposed labeling that includes the following:
- precautionary language on the need to monitor serum creatinine during therapy
- use clinical judgment to determine if dronedarone use is warranted, if large increases in serum creatinine are observed.

Overall the applicant's labeling proposal appears adequate.

4.2.10 Study of the safety and pharmacokinetics of SR33589B in single oral administration in Japanese young male healthy subjects (TDU4899)

PROTOCOL #	TDU4899
INVESTIGATOR	Dr. Takanori Tanaka
STUDY SITE	Osaki Clinic, 5-7-13 Kitashinagawa, Shinagawa-ku, Tokyo, 141-0001, Japan
STUDY PERIOD	March – June 2002

Objectives (per applicant):

- To investigate the safety of SR33589B (dronedarone) after single oral dose administration to Japanese young male healthy subjects in fed and fasted conditions.
- To investigate the pharmacokinetic (PK) parameters of dronedarone and SR35021 (N-debutyl derivative) after single oral dose administration of dronedarone to Japanese young male healthy subjects in fed and fasted conditions.

Study Design

This was a randomized, placebo-controlled, double-blind, three-treatment and three-period study. A single 100, 200, 400 or 1200 mg dronedarone dose was given in the fed state. Additionally, some subjects received an 800 mg dose under fed and fasted conditions (crossover) to evaluate the food effect. Dronedarone was given orally in fed conditions (standard meal). Details of the standard meal are provided in the Appendix.

Subject Demographics

Subject demographics are presented in Table 84.

Table 84: Subject Demographic Data (Study TDU4899)

Parameter (unit)	Statistics		dronedarone					Total (N=40)
		Placebo (N=10)	100 mg (N=6)	200 mg (N=6)	400 mg (N=6)	800 mg (N=6)	1200 mg (N=6)	
Age (yrs)	N Mean (SD) Min - Max	10 22.3(1.8) 20-25	6 21.0(1.5) 20-23	6 22.3(1.8) 20-25	6 22.5(2.1) 20-26	6 23.5(2.3) 20-26	6 23.5(1.5) 21-25	40 22.5(1.9) 20-26
Weight (kg)	N Mean (SD) Min - Max	10 61.49(6.67) 50.1-74.8	6 62.20(4.59) 57.6-68.2	6 62.88(5.41) 54.7-68.5	6 58.95(6.23) 52.7-69.4	6 60.00(6.08) 55.6-70.0	6 59.72(3.11) 55.4-63.9	40 60.94(5.44) 50.1-74.8
Height (cm)	N Mean (SD) Min - Max	10 172.96(7.61) 160.2-184.8	6 173.97(6.20) 167.8-184.8	6 174.27(3.12) 170.3-178.5	6 173.73(4.97) 164.9-178.4	6 168.22(4.37) 160.6-173.2	6 171.95(3.86) 166.4-177.2	40 172.56(5.57) 160.2-184.8
BMI (kg/m^2)	N Mean (SD) Min - Max	10 20.57(1.86) 18.4-23.9	6 20.57(1.04) 18.9-22.0	6 20.72(1.96) 18.2-23.2	6 19.50(1.33) 18.1-22.0	6 21.18(1.68) 19.1-23.3	6 20.18(0.83) 19.0-21.5	40 20.47(1.53) 18.1-23.9

Formulation (2E3 Formulation*)

- Dronedarone 100 mg tablets, batch number CL-04600
- Dronedarone 400 mg tablets, batch number CL-04530
- Placebo 100 mg tablet, batch number CL-04601
- Placebo 400 mg tablet, batch number CL-03812

*The 2E3 formulation is adequately linked to the to-be-marketed tablet formulation

Pharmacokinetics

The following pharmacokinetic (PK) measures were determined for dronedarone and SR35021: t_{lag}, C_{max}, t_{max}, AUC_{last}, AUC_{0-24}, $t_{1/2Z}$, R_{met}, AUC, CL/F (only for SR33589), Vz/F

(only for SR33589), Ae_{0-24}, fe_{0-24}, and CL_{R0-T}. Standard pharmaco-statistical methods were used to evaluate the food effect. The test group was the fed treatment and the reference group was the fasted treatment. Dose proportionality, dose effects and metabolic ratio were also evaluated.

Pharmacokinetic sampling times

- Blood samples were collected before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 168 hours after drug administration
- Urine samples were collected over the following time intervals: 12 hours prior to dosing (H-12) to just prior to dosing (H0), time of dosing (H0) to 12 hours post dosing (H12), and 12 hours post dosing (H12) to 24 hours post dosing (H24)

Bioanalytical methods

Dronedarone and SR35021 plasma concentrations were determined using a validated LC-MS/MS method. The assay performance was acceptable as illustrated in Table 85.

Table 85: Performance of Dronedarone and SR35021 Assays (DOH0239)

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 300 ng/mL range; $R^2 > 0.992$	Satisfactory
Between day Precision	CV data were not provided	Cannot be assessed
Accuracy	QC samples were all within 15 % of the nominal concentrations for the low and medium QC samples. The majority of QC samples were within 15 % of nominal concentration (26 out of 30 samples)	Satisfactory
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the ng/mL range; $R^2 > 0.994$	Satisfactory
Between day Precision	CV data were not provided	Cannot be assessed
Between day Accuracy (relative error)	QC samples were all within 15 % of the nominal concentrations for the low and medium QC samples. The majority of QC samples were within 15 % of nominal concentration (27 out of 30 samples)	Satisfactory
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

* Chromatograms and CV % were provided in the validation report that indicate assay is specific and precise

Urine concentrations of dronedarone and SR35021 were determined using the method for plasma adapted to urine; however, this method was not validated. Due to the lack of validation of the urine assay, the reliability of the urine results is unknown.

Reviewer's Note on Applicant's reported urine results

According to the applicant the fraction of the dose of dronedarone excreted unchanged in the urine was less than 0.5 % for the highest dose administered. Per protocol, no further evaluation of urine samples or PK analyses would be conducted if fe_{0-24} was < 1 %. Consequently, urinary PK parameters were not presented in this report.

Results

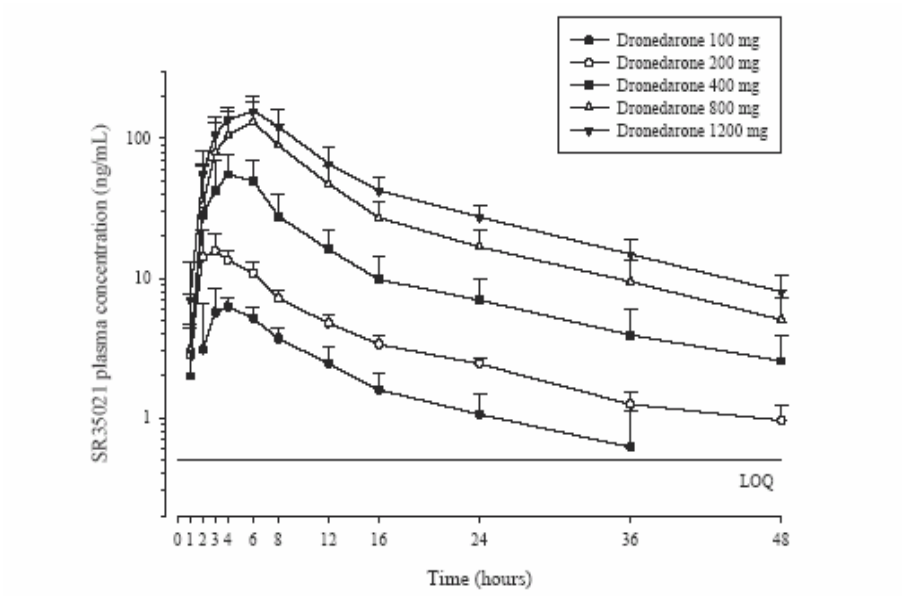
Subject Disposition (Patients contributing PK data)

Thirty-nine out of the 40 subjects completed the study; one patient in the placebo group discontinued the study for personal reasons.

Dronedarone Pharmacokinetics

The dronedarone plasma concentration-time profiles are depicted in Figure 37.

Figure 37: Mean dronedarone plasma concentration-time profile following administration of dronedarone single doses (100 to 1200 mg single doses)



After achieving Cmax plasma levels declined according to a biphasic elimination.

Mean dronedarone PK measures following administration of single dronedarone doses are summarized in Table 86.

Table 86: Mean (CV %) PK parameters of dronedarone (SR33589) after single dronedarone doses (100 to 1200 mg) in fed conditions

PK Parameter	SR33589B Dose (mg)				
Mean (CV%)	100 mg	200 mg	400 mg	800 mg	1200 mg
t_{lag} (h)[a]	0.8	0.0	0.5	0.5	0.0
C_{max} (ng/mL)	12.2 (43)	28.3 (42)	122.5 (58)	302.3 (36)	394.2 (33)
t_{max} (h)[a]	3.0	2.0	3.0	3.0	5.0
t_{last} (h)[a]	16	36	48	48	48
AUC_{last} (ng.h/mL)	62 (44)	168 (27)	701 (47)	2225 (37)	3430 (32)
$t_{1/2z}$ (h)	5.0 (40)	11.4 (20)	11.9 (17)	12.4 (14)	12.4 (12)
AUC (ng.h/mL)	67 (44)	178 (25)	712 (55)	2307 (37)	3573 (32)
CL/F (L/h)	1717 (37)	1201 (33)	663 (37)	388 (35)	366 (31)
Vz/F (L)	10808 (11)	19018 (22)	10963 (33)	6923 (39)	6518 (35)

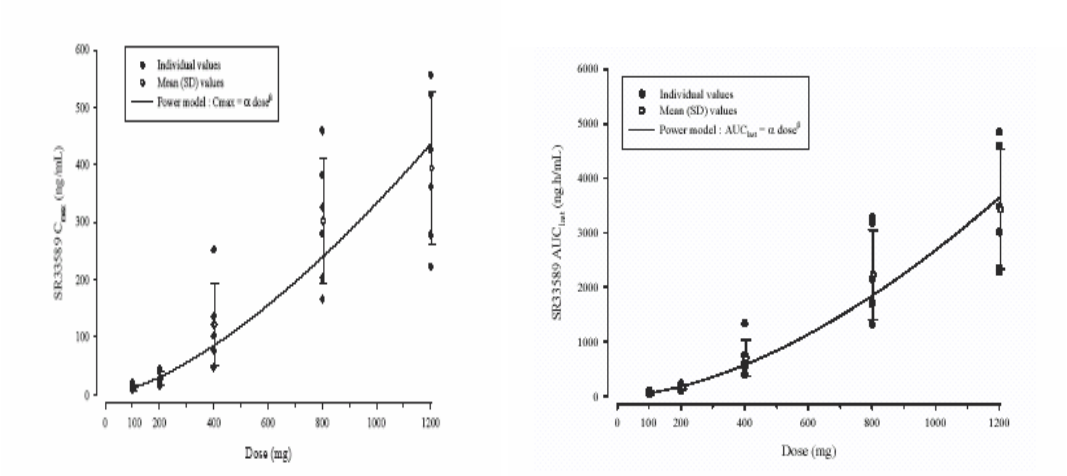
[a] : Median value.

The applicant reports that terminal half-life could not be accurately estimated in the 100 mg dose group due to insufficient quantifiable concentration. A significant dose effect was found for Tmax ($p = 0.0335$), but dose did not appear to affect the half-life.

Dose Proportionality (Assessment of PK Linearity)

Dronedarone Cmax, AUClast and AUC increased with the administered dose in a supra-proportional manner (Table 86 and Figure 38). This finding of supra-proportional increases in exposure with dose is consistent (of similar magnitude) with that observed in other studies. The existence of nonlinearity is supported by the varying CL/F values across the 100 to 1200 mg dose range (CL/F range: 366 to 1717 L/h).

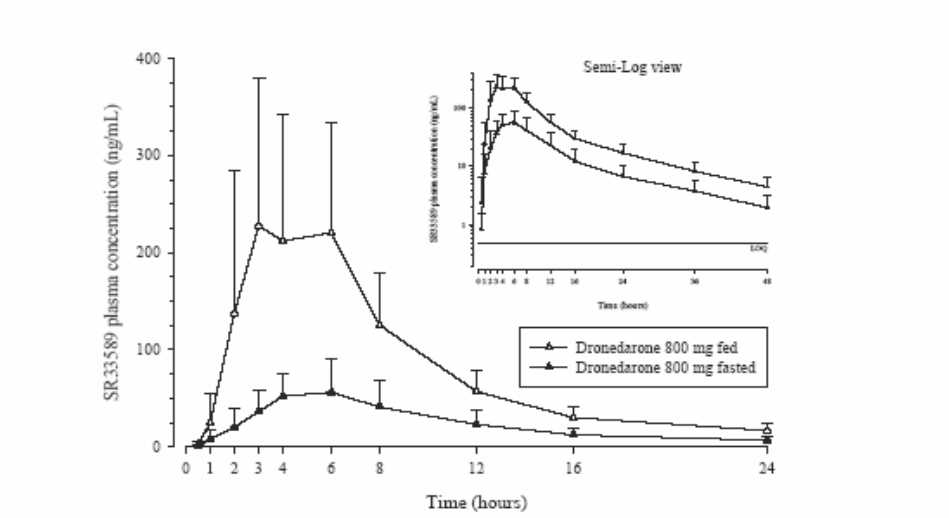
Figure 38: Individual and mean Dose-Response Plots (Cmax and AUC)



Food Effect

The dronedarone plasma concentration-time profiles of dronedarone under fed and fasted conditions are depicted in Figure 39.

Figure 39: Mean dronedarone plasma concentration-time profiles under fed and fasted conditions (800 mg dronedarone administered)



The food effect findings at the 800 mg dose level are summarized in Table 87.
Relative to the fasted state, dronedarone Cmax, AUClast, and AUC were significantly increased by food. Food effects of similar magnitude have been observed in other studies.

Table 87: Mean (CV %) PK parameters of dronedarone observed after a single 800 mg oral administration of dronedarone in fed and fasted conditions

PK Parameter Mean (CV%)	Fed Conditions	Fasted Conditions	Ratio Estimates[b] and 90% CI
C_{max} (ng/mL)	302.3 (36)	62.6 (51)	5.0 [4.24 –5.88]
t_{max} (h)[a]	3.0	4.5	p=0.460
AUC_{last} (ng.h/mL)	2225 (37)	666 (52)	3.5 [3.10 –3.95]
$t_{1/2z}$ (h)	12.4 (14)	13.4 (25)	p=0.679
AUC (ng.h/mL)	2307 (37)	707 (51)	3.4 [3.05 –3.84]

[a] : Median value,
[b] : Ratio fed / fasted, p-value for difference between regimens.

SR35021 exposure was also increased by food (Table 88 and Figure 40).

Figure 40: Mean SR35021 plasma concentration-time profile following dronedarone (800 mg) administration (fed and fasted conditions)

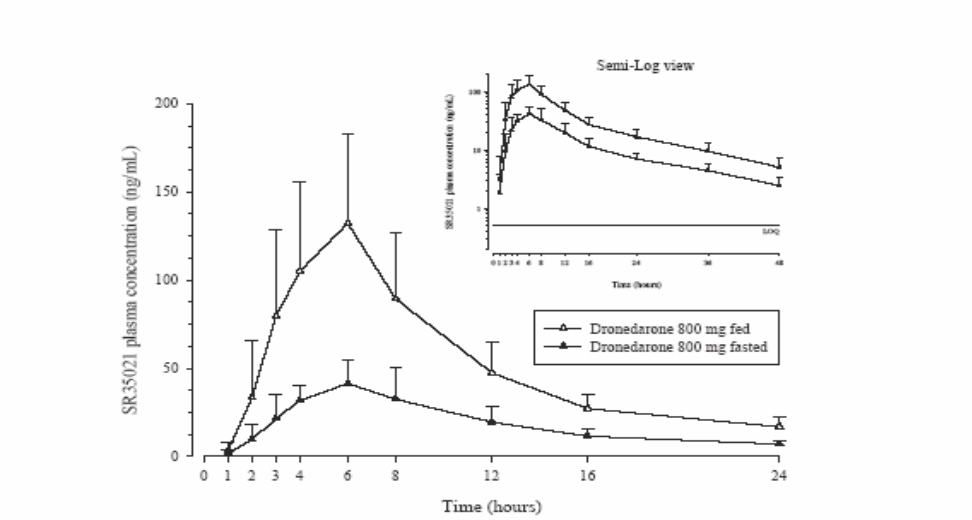


Table 88: Mean (CV %) PK parameters of SR35021 observed after dronedarone administration (800 mg) under fed and fasted conditions

PK Parameter Mean (CV%)	Fed Conditions	Fasted Conditions	Ratio Estimates[b] and 90% CI
C_{max} (ng/mL)	141.0 (29)	42.9 (29)	3.3 [2.79 –3.84]
t_{max} (h)[a]	6.0	6.0	p = 0.133
AUC_{last} (ng.h/mL)	1471 (32)	545 (28)	2.7 [2.43 –2.94]
$t_{1/2z}$ (h)	13.8 (17)	16.2 (27)	p = 0.112
AUC (ng.h/mL)	1575 (32)	607 (27)	2.6 [2.30 –2.87]

[a] : Median value, [b] : ratio Fed/Fasted, p-value for difference between regimens

Metabolic Ratio (SR35021 Pharmacokinetics)

Per the applicant's analyses plan, if a dose-by-compound interaction was absent the metabolic ratio (Rmet) was not evaluated. A dose-by-compound interaction was not

detected for Cmax; in contrast, the Rmet based on AUC decreased as dose increased (Table 89). This finding suggests that a saturable metabolic pathway exists.

Table 89: Metabolic Ratios for AUC and Cmax

PK Parameter	Dose-by-Compound p-value	Contrast	Ratio Estimate and 95% CI
(R_{met}) for C_{max}	0.284	SR35021/SR33589	0.53 [0.47 –0.60]
(R_{met}) for AUC	< 0.0001	SR35021/SR33589 100 mg	1.39 [1.14 –1.70]
		SR35021/SR33589 200 mg	1.14 [0.92 –1.42]
		SR35021/SR33589 400 mg	0.99 [0.79 –1.23]
		SR35021/SR33589 800 mg	0.69 [0.57 –0.85]
		SR35021/SR33589 1200 mg	0.64 [0.52 –0.78]

Applicant's Safety Summary

The tolerability of single oral doses of dronedarone up to 1200 mg was generally satisfactory in Japanese young male healthy subjects. All treatment-emergent adverse events (TEAE) were mild. There were no subjects who discontinued study drug due to TEAEs, and no serious AEs (SAEs) were reported. However, PR- interval (PR) prolongation and low-degree atrio-ventricular (AV) block were observed in 4 out of 6 subjects who received active drug at the 1200 mg dose. These observations appeared to be due to the pharmacological effects of the drug. No torsades de pointes were reported. There appeared to be some dose response with respect to (TEAEs) and no AEs were reported in the placebo group.

Recommendations/Conclusions

The following PK information generated in Study TDU4899 is acceptable for labeling purposes and cross-study or –population comparisons, as appropriate. In general the findings from Study TDU4899 appear quantitatively and qualitatively similar to those in other dronedarone studies.

- Dronedarone absorption is increased in the presence of food relative to the fasted state; the increase in exposure is approximately 3.5-fold for AUC and 5-fold for Cmax
- Dronedarone and SR35021 exhibited similar PK profiles, although the exposure of dronedarone was approximately twice as great as SR35021
- Supra-dose proportional PK were observed for parent drug and metabolite over the 100 to 1200 mg dose range. The relative increase of Cmax, AUClast and AUC estimated as function of a 2- fold increase of the dose, were between 2.5 and 4.2 with parent drug and between 2.4 and 3.3 with metabolite.
- The metabolic ratio based on AUC decreases when the dose increases: Rmet = 1.4 at 100 mg and Rmet = 0.6 at 1200 mg.

APPENDIX to Study TDU4899

Standard Breakfast Meal

MENU	Intake Volume (g)	Energy (Kcal)	Nutritive Value			
			Water (g)	Protein (g)	Lipids (g)	Carbohydrate (g)
Roll bread	105.0	293.0	36.8	9.2	5.4	51.9
Butter	8.0	60.0	1.3	0.0	6.5	0.0
Strawberry jam	14.0	37.0	4.4	0.1	0.0	9.4
Boiled egg	50.0	76.0	38.0	6.0	5.1	0.4
Apple juice	160.0	67.0	141.1	0.3	0.0	18.2
Total	337.0	533.0	221.6	15.6	17.0	79.9

4.2.11 Study on the tolerability of SR33589B given as a single ascending dose administered intravenously in healthy male subjects (TDU3007).

PROTOCOL #	TDU3007
INVESTIGATOR	Dr. W. Tetzloff
STUDY SITE	iphar, Institut für Klinische Pharmakologie GmbH, Arnikastrasse 4, D - 85635 Höhenkirchen- Siegertsbrunn, Germany
STUDY PERIOD	May to August 1997

Objectives (per applicant)

- To assess the local and general tolerability of single intravenous doses of SR33589B in healthy male subjects
- To evaluate the effect of single intravenous doses of dronedarone on electrocardiogram parameters, and to assess the pharmacokinetic profile of SR33589 and its N- debutyl metabolite, SR35021, after single intravenous administration.

Reviewer's Note

This review focuses on dronedarone pharmacokinetics; the efficacy information will not be reviewed in detail because IV administration is not being considered in this NDA.

Study Design

This was a randomized, placebo-controlled, double-blind, parallel group and ascending dose study. A thirty minute dronedarone infusion was given to healthy male volunteers. Each subject received a single intravenous administration of either dronedarone (10, 20, 40, 60 or 80 mg) or placebo.

Subject Demographics

Subject demographics are presented in Table 90.

Formulation (2E3 Formulation)

- Dronedarone solution for IV infusion, vials containing 4 mg/ml batch No. 96-00681
- Placebo solution for IV infusion, batch No. 96-00683

Pharmacokinetic blood sampling times

Blood samples were collected before the infusion (T0) and at 10, 20, 30 (= end of infusion), 40 , and 50 minutes, and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after drug administration.

Pharmacokinetics

The following pharmacokinetic measures were determined:
Dronedarone: Cmax, tmax, Cend , AUClast, AUC, $t_{½}$, CL and Vz
SR35021: Cmax, tmax, AUClast, $t_{½}$, and AUC

Table 90: Subject Demographics in Study TDU3007

Characteristics (units)	Dose (n)	Mean ± SD	Minimum	Maximum
Age (years)	10 mg (n = 3)	27.7 ± 6.0	22	34
	20 mg (n = 3)	34.3 ± 6.0	28	40
	40 mg (n = 6)	30.8 ± 6.2	23	37
	60 mg (n = 6)	33.8 ± 4.9	25	38
	80 mg (n = 6)	32.5 ± 5.2	23	38
	Placebo (n = 8)	31.9 ± 6.1	22	39
Height (cm)	10 mg (n = 3)	75.9 ± 2.7	72.9	78.2
	20 mg (n = 3)	77.7 ± 5.9	72.0	83.8
	40 mg (n = 6)	79.7 ± 8.7	67.9	88.9
	60 mg (n = 6)	79.5 ± 6.1	69.4	84.9
	80 mg (n = 6)	79.2 ± 6.2	69.5	86.0
	Placebo (n = 8)	75.5 ± 4.4	69.4	82.8
Weight (kg)	10 mg (n = 3)	183.3 ± 7.2	175	188
	20 mg (n = 3)	178.7 ± 7.5	170	183
	40 mg (n = 6)	182.3 ± 4.9	176	188
	60 mg (n = 6)	179.8 ± 4.6	172	186
	80 mg (n = 6)	178.8 ± 6.4	168	184
	Placebo (n = 8)	178.9 ± 6.3	173	190

Bioanalytical Methods

Plasma concentrations of dronedarone and SR35021 were analyzed by a validated LC/MS/MS method. The assay performance was acceptable as shown in Table 91.

Table 91: Performance of Dronedarone and SR35021 Assays

Parameter	Measure	Reviewer Comment
	Dronedarone Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.996$	Satisfactory
Between day precision	CVs were < 7 %	Cannot be assessed
Between day accuracy	The QC samples were within 5 % of the nominal concentrations	Acceptable
LLOQ	0.5 ng/ml	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed
	SR35021 Assay	
Linearity	The assay was linear over the 0.5 to 50 ng/mL range; $R^2 > 0.996$	Satisfactory
Between day precision	CV data were not provided	Cannot be assessed
Between day accuracy	The QC samples were within 3 % of the nominal concentrations	Acceptable
LLOQ	0.5 ng/mL	Satisfactory
Specificity	Chromatograms were not provided*	Cannot be assessed

*The validation report included chromatograms that demonstrate assay specificity

Pharmacodynamics (Activity)

Changes in electrocardiogram measures such as PR and QTc prolongation, and the number of abnormal transition ST-T changes were determined.

Results

The plasma concentration time profiles for dronedarone following IV administration are depicted in Figure 41.

The pharmacokinetic parameters of dronedarone after single intravenous administration of dronedarone (10 to 80 mg) are summarized in Table 92. These data indicate that:

- Dronedarone exhibits approximately linear kinetics following IV administration over the 10 to 80 mg dose range
- The volume of distribution with dronedarone doses ≥ 40 mg is ~ 2500 to 3500 L

Figure 41: Mean dronedarone plasma concentration time profile following IV administration (30 minute infusion)

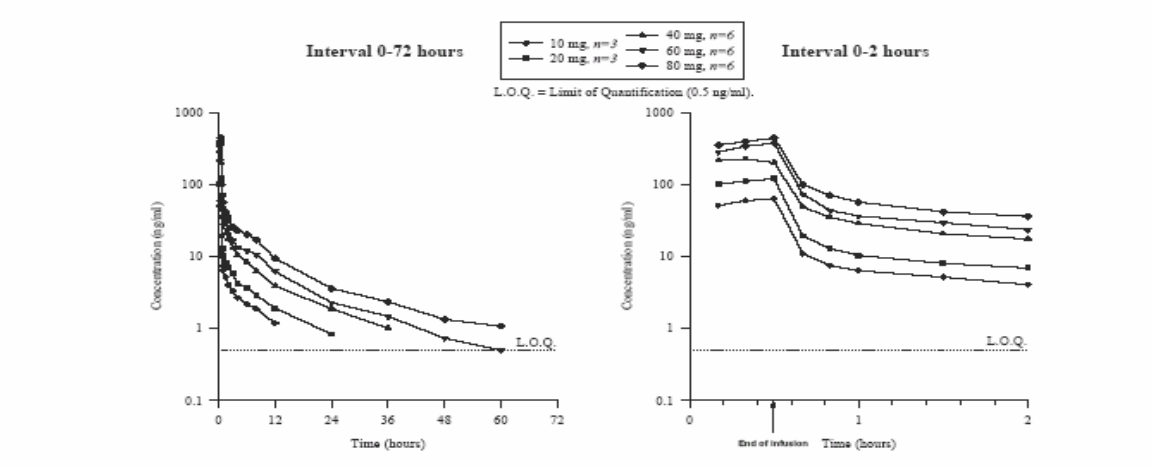


Table 92: Dronedarone PK Measures Following IV Administration

Parameters (units)	Statistics	Dose (mg) of dronedarone administered				
		10 (n = 3)	**20** (n = 3)	**40** (n = 6)	**60** (n = 6)	**80** (n = 6)
C (ng/ml)	Mean	63.0	120.4	253.0	374.2	470.1
	SD	9.4	24.3	46.5	112.3	127.2
	CV%	15	20	18	30	27
t (h)	Mean	0.50	0.45	0.33	0.44	0.44
	SD	0.00	0.09	0.15	0.09	0.09
	CV%	0	20	44	20	20
C_{end} (ng/ml)	Mean	63.0	98.9	200.3	373.2	441.1
	SD	9.4	47.1	35.4	111.4	151.0
	CV%	15	48	18	30	34
AUC_{last} (ng.h/ml)	Mean	62.0	127.5	287.5	433.1	619.2
	SD	7.5	22.7	55.9	52.5	137.0
	CV%	12	18	19	12	22
$t_{½}$ (h)	Mean	6.9	10.5	13.0	15.8	18.4
	SD	1.8	1.6	3.1	3.3	3.3
	CV%	25	15	24	21	18
AUC (ng.h/ml)	Mean	70.7	136.2	299.2	448.4	638.2
	SD	6.2	24.5	57.3	52.7	142.2
	CV%	9	18	19	12	22
V_z (l)	Mean	1398	2240	2500	3104	3436
	SD	240	237	149	812	808
	CV%	17	11	6	26	24
CL (l/h)	Mean	142	150	138	136	132
	SD	13	30	25	19	34
	CV%	9	20	18	14	26

The plasma concentration time profile of SR35021 following administration of dronedarone is depicted in Figure 42. Pharmacokinetic parameters of SR35021 for the three highest doses of dronedarone in the healthy male subjects are shown in Table 93. The pharmacokinetic parameters

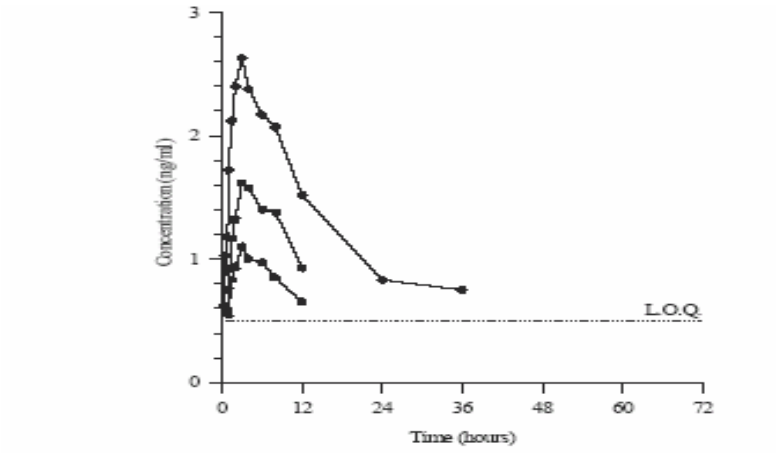
of SR35021 after single intravenous administration of the 10 and 20 mg doses could not be assessed due to low plasma concentrations.

Table 93: SR35021 PK measures following IV dronedarone administration

Parameters	Statistics	Dose (mg) of dronedarone administered		
		40 (n = 6)	**60** (n = 6)	**80** (n = 6)
C max (ng/ml)	Mean ± SD	1.2 ± 0.4	1.7 ± 0.7	2.8± 0.3
t max (h)	Mean SD	3.08 ± 1.56	4.00 ± 2.00	3.00 ± 0.63
AUClast (ng.h/ml)	Mean SD	13.2 ± 4.5	28.5 ± 15.7	52.5 ± 9.8
t½ (h)	Mean SD	21.4 N/A	29.8 N/A	26.1* 6.7
AUC (ng.h/ml)	Mean	32.7	69.1	75.7 ± 15.4*

*: n = 3
N/A: not applicable; n = 2

Figure 42: SR35021 Plasma Concentration Time Profile following IV Administration of Dronedarone



Applicant's Activity Highlights

According to the applicant, the exploratory activity analysis of the ECG parameters PR-interval and QTc showed a prolongation of these parameters, which is consistent with the expected electrophysiological profile of dronedarone after administration of dronedarone. There was a significant increase from baseline in the maximum PR- interval and maximum QTc within the 40 to 80 mg dose groups. There was also an increase in the maximum QTc in comparison to placebo at the 20 and 40 mg dose levels.

Reviewer's Note on Activity

As noted previously, this review focuses on the PK data rather than the PD or activity data because IV administration is not currently being considered. However, the activity findings tend to support the applicant's use of dronedarone as an anti-arrhythmic agent.

Applicant's Safety Highlights

Half of the subjects complained of injection site reactions or local pain. The highest incidence was at the 40 mg and 60 mg dose levels (five of six and four of six subjects, respectively). Only one subject complained of local reactions when placebo was administered. The systemic tolerability was good, laboratory tests, vital signs, electrocardiograms, and telemetric evaluations showed no clinically relevant deviations from baseline.

Conclusions/Recommendations

The following findings from Study TDU3007 are appropriate for labeling as appropriate

- After intravenous administration, Cmax and AUC of SR33589 increase in a dose-proportional manner over the 10 to 80 mg dronedarone dose range; this finding suggests that dronedarone exhibits linear kinetics following IV administration. The linearity was supported by the relative constant clearance over the studied dose range: CL = 132- 150 L/h
- The accuracy of the half-life estimates for the lower doses (10 and 20 mg was unclear) due to the low plasma concentrations observed in the terminal phase relative to LOQ. Based on the higher doses the mean $t_{1/2}$ following IV administration is ~ 13 to 18 hours. The volume of distribution estimates may have also been affected by the lack of assay sensitivity. Using the highest studied doses the Vz is ~ 2500 – 3500 L
- SR35021 was only measurable for the 40 mg dose of dronedarone and above. SR35021 appeared to exhibit dose proportional kinetics with respect to Cmax, but the increase of AUC last was more than dose proportional.

4.2.12 Study on the tolerability of SR33589B given as a single and multiple oral doses in healthy male subjects under non fasted conditions (TDR2395).

PROTOCOL #	TDR2395
INVESTIGATOR	Dr. W. Tetzloff
STUDY SITE	iphar, Institut für Klinische Pharmakologie GmbH, Arnikastrasse 4, D - 85635 Höhenkirchen- Siegertsbrunn, Germany
STUDY PERIOD	March to August 1996

Objectives (per applicant)

- to evaluate the tolerability of SR33589B (dronedarone) after single (one day) and multiple oral doses of 400 mg, 600 mg, 800 mg or 1000 mg twice daily, and 800 mg, 1200 mg, 1600 mg or 2000 mg once daily given for 14 days under fed conditions in healthy male subjects.
- to evaluate the pharmacokinetics and pharmacodynamics of dronedarone after single and multiple dosing.

Reviewer Note

This review focuses on the 14-day multiple dose PK and PD information: other studies address the single dose data and 7-day PK information is comparable to 14-day PK information.

Study Design

This was an ascending dose, double-blind, randomized, placebo-controlled (at each dose level) sequential group study. The following dronedarone doses were administered: 400, 600, 800 or 1000 mg twice daily, and 800, 1200, 1600 or 2000 mg once daily. Treatments lasted for 15 days: one single dose (Day 2) followed by 14-days of repeated dose (Days 5 to 18). There was a wash-out period on Days 3 and 4.

Subject Demographics

Subject demographics are presented in Table 94. Only male Caucasian subjects participated in the study. The total number of subjects included in the study was 52. Eight subjects withdrew from the study prematurely. The number of subjects who completed the study per treatment group was: placebo 11, dronedarone 800 mg QD six, dronedarone 400 mg BID six, dronedarone 1200 mg QD six, dronedarone 600 mg BID five, dronedarone 1600 mg QD six and dronedarone 800 mg BID four.

Formulation (2E3 Formulation)

- Dronedarone 200 mg capsules; batch number M304S
- Dronedarone placebo capsules; batch number M274G

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 94: Subject Demographics in Study TDR2395

Parameter (units)	Treatment Group	n	Mean	SD	Minimum	Maximum
Age (years)	Placebo	12	31.4	4.4	25	38
	800 mg o.d.	9	29.1	5.5	22	39
	400 mg b.i.d.	7	29.4	5.4	25	38
	1200 mg o.d.	6	29.8	4.7	23	36
	600 mg b.i.d.	6	25.7	2.4	23	29
	1600 mg o.d.	6	28.7	4.1	24	35
	800 mg b.i.d.	6	27.3	5.4	21	33
Weight (kg)	Placebo	12	74.0	6.8	67.5	88.4
	800 mg o.d.	9	78.2	6.3	68.9	88.6
	400 mg b.i.d.	7	75.3	5.5	67.8	85.4
	1200 mg o.d.	6	76.4	6.3	65.2	84.0
	600 mg b.i.d.	6	73.9	5.9	65.1	82.6
	1600 mg o.d.	6	74.9	1.4	72.8	76.9
	800 mg b.i.d.	6	76.0	4.1	71.3	81.2
Height (cm)	Placebo	12	179.5	4.5	173	186
	800 mg o.d.	9	180.7	6.7	172	192
	400 mg b.i.d.	7	177.9	8.6	171	195
	1200 mg o.d.	6	180.7	4.8	175	189
	600 mg b.i.d.	6	180.5	5.2	175	189
	1600 mg o.d.	6	178.7	4.1	173	185
	800 mg b.i.d.	6	180.0	4.6	173	185

Pharmacokinetics

The following dronedarone and SR35021 pharmacokinetic measures were determined: $AUC_{0\text{-}12h}$ (for BID regimens), $AUC_{0\text{-}24h}$ (for QD regimens), Cmax, Cmin and tmax of dronedarone and SR35021 after single dose (Day 2) administration and 7-days (Day 11) and 14-days (Day 18) repeated dose administration.

Bioanalytical Methods

Plasma was assayed for dronedarone and its N-debutyl metabolite, SR35021, using HPLC method with UV detection. The assay performance was acceptable:

- limit of quantification was 5 ng/ml for both compounds
- CV < 10 % for SR35021 and CV < 11 % for dronedarone
- Relative bias between -3 to 2 % of nominal concentration for SR35021 and relative bias between -1 to 5 % of nominal concentration for dronedarone
- Chromatograms were not provided, but assay validation report includes chromatograms indicating assay specificity

Pharmacodynamics (Activity)

Activity: The effect of dronedarone on the electrocardiogram parameters: HR, PQ, QRS, QT and QTc intervals and T-wave amplitude. Exercise tests were conducted to assess a possible anti-adrenergic effect of dronedarone on dynamic, exercise induced tachycardia.

Analyses

Pharmacokinetics

The applicant conducted several standard pharmaco-statistical analyses to evaluate:

- Dose, day and dose by day effects (ANOVA).

- Time to reach steady state by comparing Study Day 18 versus Day 11 $AUC_{0\text{-}tobs}$ values, and plasma concentrations before treatment during the repeated dose phase of the study.
- Dose proportionality (power model)
- Regimen comparison- BID vs. QD (Log Regression)

Activity (Pharmacodynamics)

Several activity measurements were determined under resting and exercise conditions:

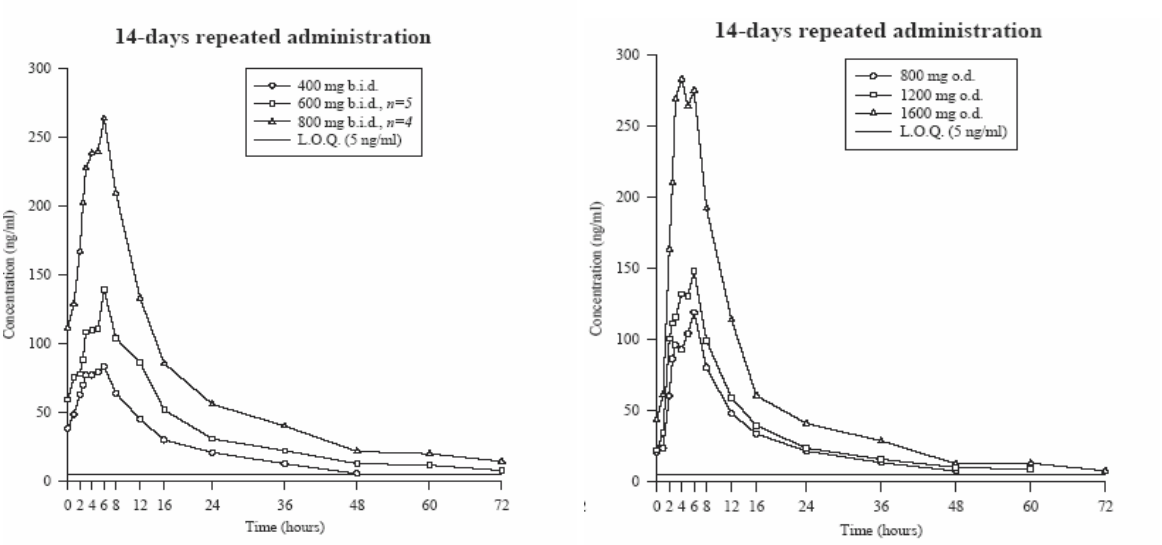
- Resting conditions
  - ECG changes from baseline and changes from Day 1 for the daily mean and the daily pretreatment (T0) values (ANOVA).
  - Analyses of the data from the multiple dose phase of the study (mixed effects modeling)
  - Daily maximum change for Days 2 and 18.
  - Dronedarone dose group compared with placebo group (ANOVA)
- Exercise tests
  - ECG and vital sign changes from pre to post-exercise
  - Daily mean for each subject was calculated.
  - Changes from Day 1 for the daily mean and the daily mean pretreatment (T0) values (mixed effects modeling)

Results

Dronedarone PK

The plasma concentration time profiles for dronedarone following single and multiple dose oral administration are depicted in Figure 43 (BID and QD).

Figure 43: Mean dronedarone plasma concentration-time profiles following BID and QD dronedarone dosing



Reviewer Note: Data available for PK analyses

It should be noted that not all subjects completed the study; therefore the number of subjects in each dose group was ≤ 6 (as shown in left panel of preceding figure). This review includes PK data from subjects who completed the study (14 days of dosing) and single dose data are presented for comparisons.

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 95.

Table 95: Dronedarone PK measures following administration of various dronedarone dosages

Parameter (units)	Dose Administered					
	400 mg BID	600 mg BID[a]	800 mg BID[b]	800 mg QD	1200 mg QD	1600 mg QD
14-Days Repeated Dose						
Cmax (ng/ml)	92.6 (28.8)	155.6 (71.5)	277.2 (59.3)	126.0 (35.3)	176.4 (87.7)	353.0 (164.3)
tmax (h)	4.85 (1.62)	4.80 (1.79)	5.13 (1.75)	5.50 (1.22)	4.58 (1.63)	4.33 (2.25)
Cmin (ng/ml)	37.5 (16.5)	53.3 (12.2)	106.3 (23.4)	20.1 (10.6)	21.7 (10.7)	39.1 (13.3)
$AUC_{0\text{-}12h}$ (ng.h/ml)	768.6 (270.5)	1201.0 (401.5)	2346.8 (594.9)	N/A	N/A	N/A
$AUC_{0\text{-}24h}$ *(ng.h/ml)	1537.2 (541.0)	2402.0 (803.0)	4693.6 (1189.8)	1294.2 (457.9)	1617.7 (853.7)	3033.4 (1180.1)
$T_{1/2}$ (h)	21.56 (9.96)	28.29 (6.19)	23.97 (4.45)	20.31 (3.03)	24.98 (13.56)	29.90 (21.76)

†For BID regimen, *$AUC0\text{-}_{24h}$ was estimated by 2 x AUC0-12h or BID regimen
n = 6 except for [a]n = 5, [b]n = 4
N/A = not applicable

Table 96: Dronedarone PK measures following single dose administration of dronedarone at different doses

Parameter (units)	Dose Administered					
	400 mg b.i.d.	600 mg b.i.d.[a]	800 mg b.i.d.[b]	800 mg o.d.	1200 mg o.d.	1600 mg o.d.
Single Dose						
C_{max} (ng/ml)	33.3 (11.1)	64.3 (19.1)	77.1 (30.5)	76.2 (34.8)	154.3 (72.0)	211.0 (34.4)
t_{max} (h)	3.67 (1.21)	3.10 (1.64)	4.38 (1.89)	4.92 (1.69)	5.26 (1.40)	5.17 (1.60)
AUC† (ng.h/ml)	183.2 (74.5)	303.7 (66.0)	395.7 (143.9)	514.2 (211.4)	1163.1 (481.4)	1497.0 (236.3)
AUC_{last} (ng.h/ml)	188.6 (83.2)	329.4 (77.9)	474.0 (231.9)	539.0 (221.1)	1288.4 (590.5)	1654.8 (181.2)

n = 6 except for [a]n = 5, [b]n = 4

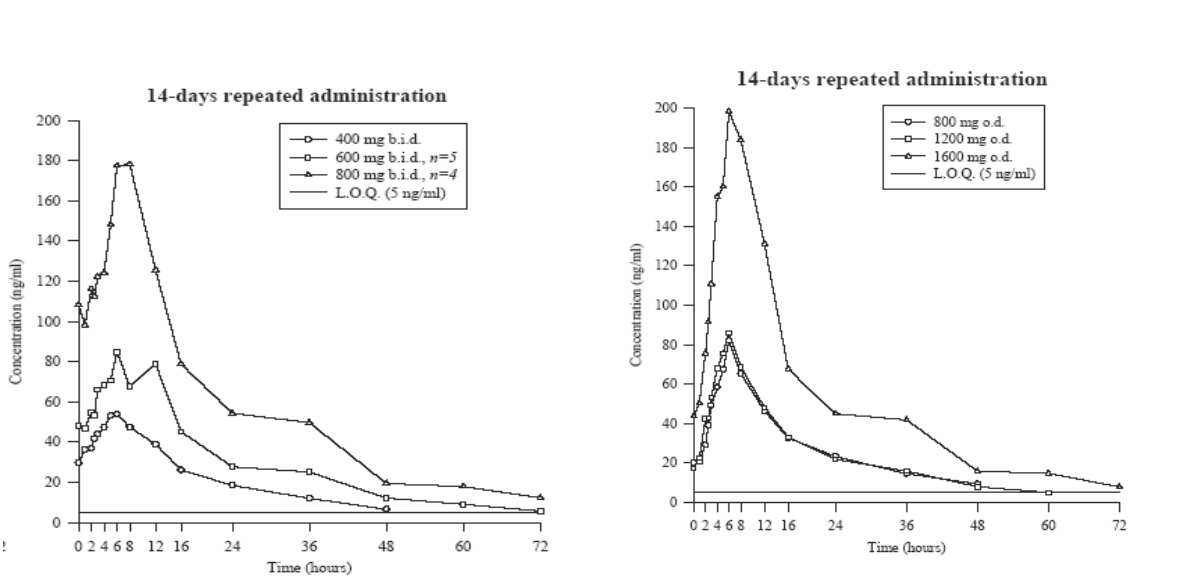
The following general observations can be made from the PK data:

- Tmax comparable across all dosage (mean and median ~ 5 hr)
- For the same total daily dose, as expected Cmin for BID dosing higher than QD dosing
- There is approximately 3 – 4 fold accumulation (14 Days vs. 1 Day, single Dose)
- Greater than proportional increases in exposure with increasing dose

SR35021 PK

The plasma concentration time profiles for dronedarone following single and multiple dose oral administration are depicted in Figure 44 (BID and QD).

Figure 44: Mean SR35021 plasma concentration time profile following administration of dronedarone



The mean (SD) PK parameters of SR35021 after repeated administration of dronedarone 400, 600 or 800 mg BID and 800, 1200 or 1600 mg QD are shown in Table 97 .

Table 97: SR35021 PK Measures Following Administration of various dronedarone doses

Parameter (units)	Dose Administered					
	400 mg BID	600 mg BID[a]	800 mg BID[b]	800 mg QD	1200 mg QD	1600 mg QD
Single Dose						
C_{max} (ng/ml)	27.8 (10.7)	33.8 (9.4)	47.7 (17.2)	53.6 (21.9)	84.2 (45.1)	135.6 (62.9)
t_{max} (h)	5.00 (1.55)	4.40 (1.52)	4.50 (1.73)	5.50 (0.84)	5.42 (1.43)	5.42 (1.43)
$AUC_{\dagger}$ (ng.h/ml)	156.0 (50.7)	204.7 (40.6)	265.8 (103.6)	442.5 (210.9)	744.1 (316.2)	1213.7 (602.5)
AUC_{last} (ng.h/ml)	181.0 (76.7)	230.9 (75.3)	382.5 (215.7)	497.7 (261.0)	935.4 (444.8)	1451.9 (773.2)
14-Days Repeated Dose						
C_{max} (ng/ml)	60.7 (18.4)	92.4 (37.7)	192.7 (77.8)	86.5 (33.8)	87.1 (45.9)	211.7 (160.8)
t_{max} (h)	5.85 (0.42)	6.40 (3.29)	4.75 (3.95)	5.83 (0.41)	5.83 (0.41)	6.00 (1.26)
C_{min} (ng/ml)	29.0 (13.0)	40.4 (6.4)	83.4 (21.0)	18.7 (10.1)	17.1 (8.6)	39.2 (17.7)
$AUC_{0\text{-}12h}$ (ng.h/ml)	533.8 (172.1)	815.4 (254.7)	1711.2 (575.7)	N/A	N/A	N/A
$AUC_{0\text{-}24h}$ * (ng.h/ml)	1067.6 (344.2)	1630.8 (509.4)	3422.4 (1151.4)	1030.2 (453.1)	1082.2 (546.0)	2531.2 (711.6)

* For BID regimens, $AUC_{0\text{-}24}$ was calculated by $AUC_{0\text{-}12}$ x 2

The SR35021 PK exhibited similar trends as dronedarone and will not be addressed further in this review, as the PK assessment for SR35021 has been addressed in other studies.

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, as appropriate.

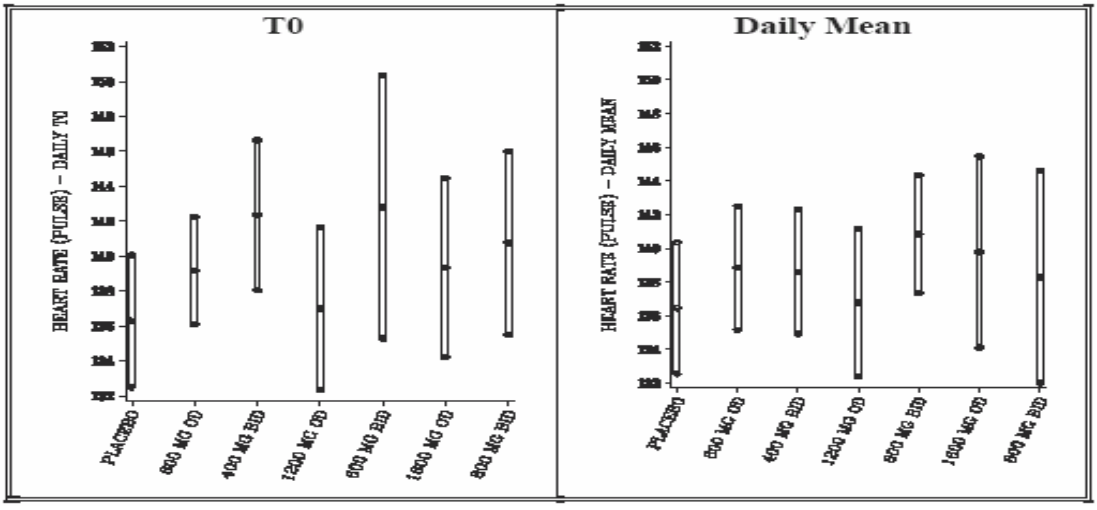
Reviewer Note
PD information was included for resting and exercise conditions. This review will focus on daily mean PD values, rather than values at specific time points, such as T0 because they had lower variability than PD measures obtained at T0 or other specific time points. Additionally, only PD data from the multiple dose phase were considered as they are the most clinically relevant. The most consistent results were obtained from the exercise tests.

Synopsis of Resting Conditions
In general, the PD data were highly variable; salient findings are summarized as follows.

- Heart Rate (HR): compared to placebo, the 1200 mg QD dose decreased the daily mean HR by -8.6 bpm (95 % confidence interval boundaries, -13.08, -3.24)
- PR Interval: compared to placebo, the 600 mg BID, 1200 mg QD and 1600 mg QD doses increased the mean PR interval; the maximal mean increase was 22.6 ms
- QT interval: compared to placebo, the 600 and 800 mg BID and 1200 and 1600 mg QD doses increased QT; the range of increase was 33 to 50 ms
- QTc interval: compared to placebo, the 1600 QD and 800 BID doses increased QTc by approximately 16 ms
- QRS interval: there were no differences for any of the treatments groups compared to placebo
- T-wave amplitude: compared to placebo, the 600 mg BID, 1600 mg BID, and 800 mg BID decreased the mean T-wave amplitude

Exercise Tests
The mean baseline values in exercise tests were variable among doses; however, the variability was minimized by correcting for baseline values. The variability in data is illustrated in the heart rate values at baseline for T0 and overall daily mean (Figure 45). TDD equals total daily dose.

Figure 45: Mean Heart Rate at T0 and overall daily mean with 95 % confidence interval at baseline



HR

The changes in heart rate during the exercise test are summarized in Figure 46 and Table 98.

Figure 46: Change in Daily Heart Rate as a function of dose during exercise test

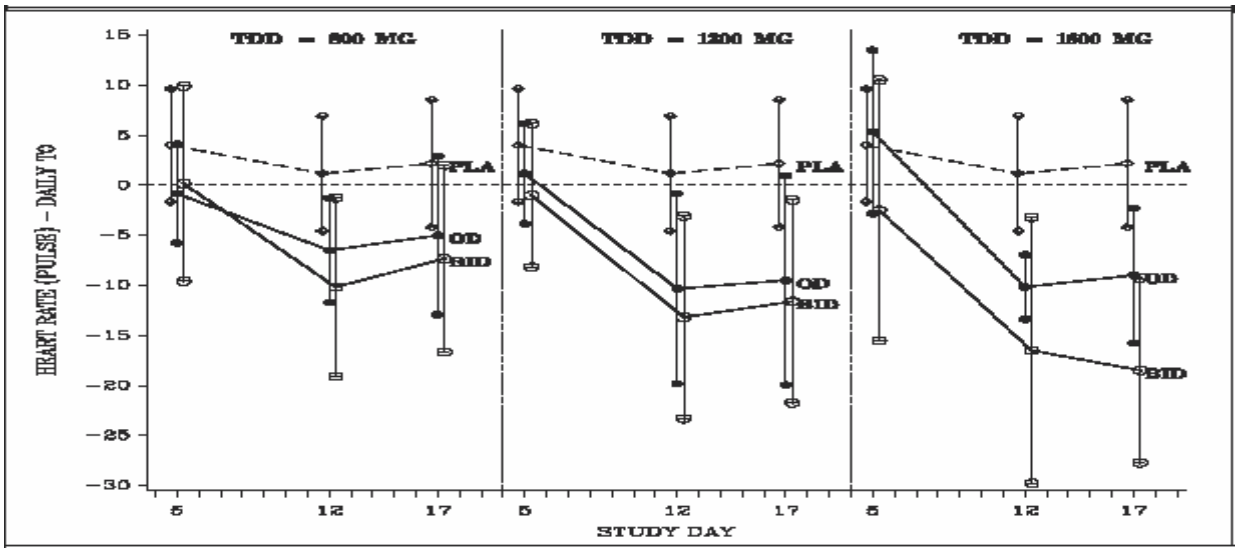


Table 98: Pairwise Comparisons (Day 12 to Day 17) of Heart Rate obtained during Exercise Test for Various dronedarone doses

Drug Dose vs. Placebo			QD vs. BID		
Dose (mg) Regimen	**Mean (95% CI)**	**p-value**	**Dose (mg) Regimen**	**Mean (95% CI)**	**p-value**
800 QD	-7.43 (-15.39, 0.53)	0.066	800 QD vs. 400 BID	3 (-6.05, 12.05)	0.506
400 BID	-10.43 (-18.39, -2.47)	0.012	1200 QD vs. 600 BID	2.48 (-7.01, 11.98)	0.599
1200 QD	-11.6 (-19.56, -3.64)	0.005	1600 QD vs. 800 BID	7.92 (-2.2, 18.04)	0.121
600 BID	-14.08 (-22.54, -5.63)	0.002	**TDD vs. Placebo**		
1600 QD	-11.27 (-19.22, -3.31)	0.007	800 TDD	-8.93 (-15.48, -2.39)	0.009
800 BID	-19.18 (-28.34, -10.03)	<0.001	1200 TDD	-12.84 (-19.54, -6.14)	<0.001
			1600 TDD	-15.22 (-22.15, -8.3)	<0.001

The HR comparisons indicate that all tested dronedarone dosages, apart from 800 mg QD, lowered HR to a greater extent than placebo. Additionally, administration of dronedarone as a daily divided dose produced a numerically greater decrease in HR than a single dose; this finding suggests that once twice daily dosing may be more effective than once daily dosing in controlling or decreasing HR. There also appeared to be a linear dose-response, as greater HR reduction was obtained with increasing dose. This bradycardic effect during exercise may be related to the antiadrenergic (Class II) properties of the drug.

PR Interval

The changes in PR during the exercise test are summarized in Figure 47 and Table 99.

The PR interval comparisons indicate that BID dronedarone dosages prolonged PR to a greater degree than placebo. There were no differences between BID and QD regimens, but in general administration of dronedarone as daily divided dose produced a numerically greater increase in PR interval than a single dose. This finding suggests that twice daily dosing may be more

effective than once daily dosing in increasing the PR interval or affecting a change in an electrophysiological (EP) parameter. There also appeared to be a linear dose-response with respect to BID dosing but not with QD dosing. The PR effect was probably related to the Class II and/or Class IV effects of the drug.

Figure 47: Change in post-exercise PR interval followiong dronedarone administration

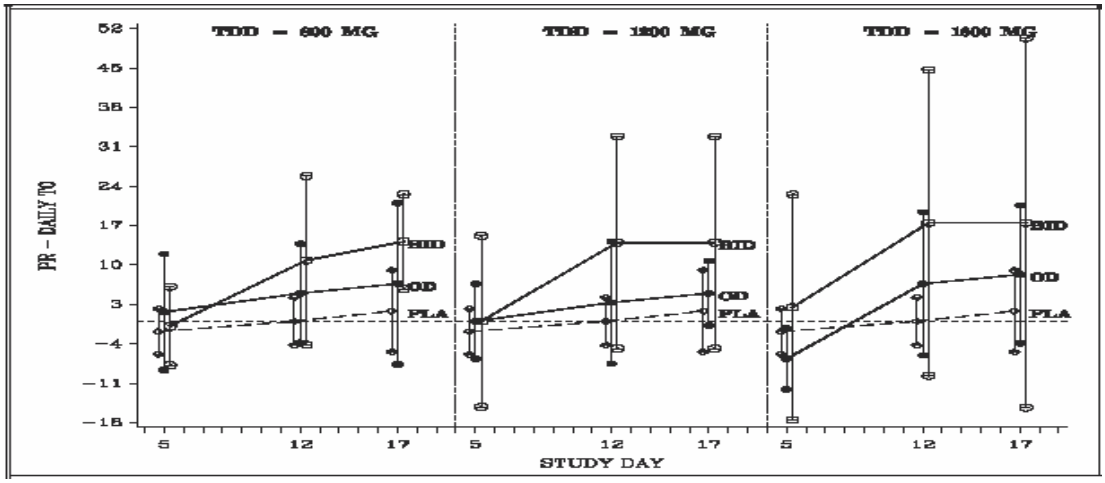


Table 99: Pairwise Comparisons (Day 12 to Day 17) of PR interval obtained during Exercise Test for Various dronedarone doses

Drug Dose vs. Placebo			QD vs. BID		
Dose (mg) Regimen	**Mean (95% CI)**	**p-value**	**Dose (mg) Regimen**	**Mean (95% CI)**	**p-value**
800 QD	4.92 (-6.36, 16.2)	0.382	800 QD vs. 400 BID	-6.67 (-19.5, 6.17)	0.299
400 BID	11.59 (0.31, 22.87)	0.044	1200 QD vs. 600 BID	-9.83 (-23.29, 3.63)	0.147
1200 QD	3.26 (-8.02, 14.54)	0.562	1600 QD vs. 800 BID	-10 (-24.35, 4.35)	0.166
600 BID	13.09 (1.1, 25.08)	0.033	**TDD vs. Placebo**		
1600 QD	6.59 (-4.69, 17.87)	0.244	800 TDD	8.26 (-1.02, 17.54)	0.079
800 BID	16.59 (3.61, 29.57)	0.014	1200 TDD	8.17 (-1.32, 17.67)	0.089
			1600 TDD	11.59 (1.77, 21.41)	0.022

QT Interval

The changes in QT interval during the exercise test are summarized in Figure 48 and Table 100.

Figure 48: Changes in QT interval during the exercise test

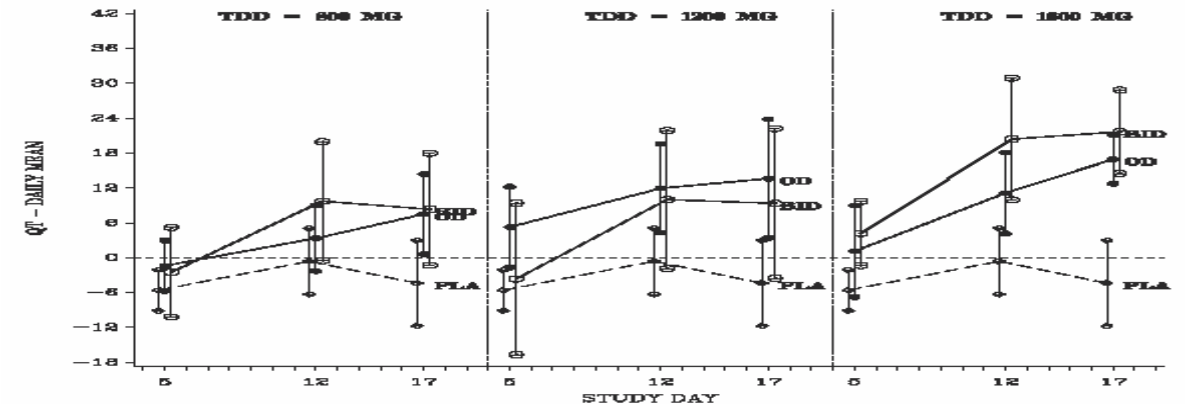


Table 100: Pairwise Comparisons (Day 12 to Day 17) of QT interval obtained during Exercise Test for Various dronedarone doses

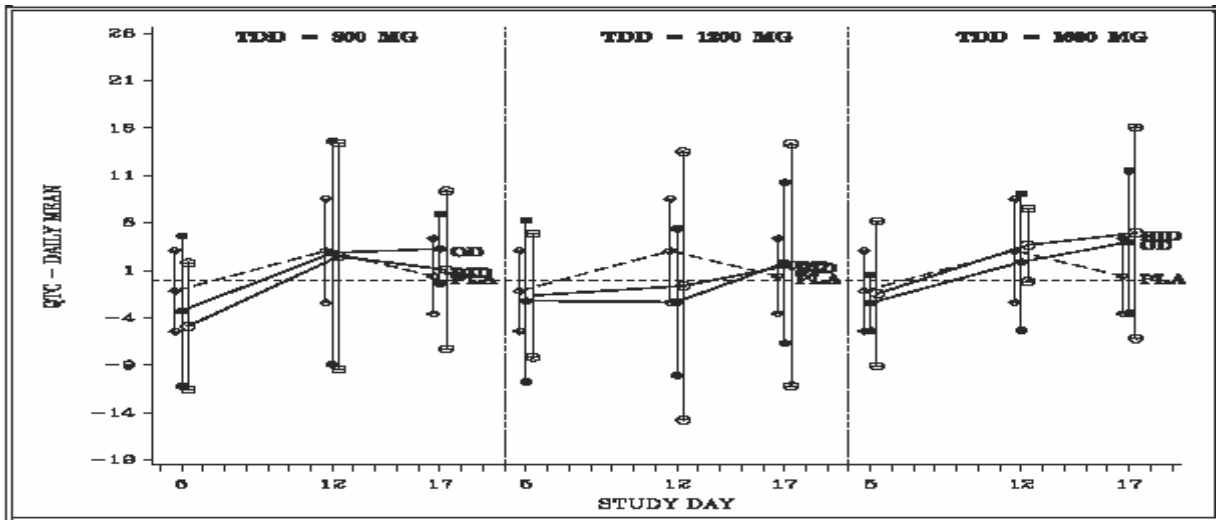
Drug Dose vs. Placebo			QD vs. BID		
Dose (mg) Regimen	**Mean (95% CI)**	**p-value**	**Dose (mg) Regimen**	**Mean (95% CI)**	**p-value**
800 QD	7.92 (0, 15.84)	0.050	800 QD vs. 400 BID	-3.61 (-12.62, 5.4)	0.422
400 BID	11.53 (3.61, 19.45)	0.005	1200 QD vs. 600 BID	3.11 (-6.34, 12.56)	0.509
1200 QD	15.28 (7.36, 23.2)	<0.001	1600 QD vs. 800 BID	-7.01 (-17.09, 3.06)	0.167
600 BID	12.17 (3.75, 20.58)	0.006	**TDD vs. Placebo**		
1600 QD	16.53 (8.61, 24.45)	<0.001	800 TDD	9.72 (3.21, 16.24)	0.005
800 BID	23.54 (14.43, 32.65)	<0.001	1200 TDD	13.72 (7.05, 20.39)	<0.001
			1600 TDD	20.03 (13.14, 26.93)	<0.001

The QT interval comparisons indicate that all tested dronedarone dosages increased QT interval relative to placebo. Additionally, administration of dronedarone as daily divided doses tended to produce a numerically greater increase in QT interval than a single dose; this finding suggests that once twice daily dosing may be more effective than once daily dosing in increasing the QT interval or affecting a change in an electrophysiological (EP) parameter. There also appeared to be a linear dose-response with respect to both the BID and QD dosing regimens. The QT prolongation is probably related to the Class III effects of dronedarone.

QTc Interval

The changes in QTc interval during the exercise test are summarized in Figure 49 and Table 101.

Figure 49: Changes in QTc interval during the exercise test



The QTc interval comparisons indicate that all tested dronedarone dosages have similar effects on the QTc interval as placebo.

Table 101: Pairwise Comparisons (Day 12 to Day 17) of QTc interval obtained during Exercise Test for Various dronedarone doses

Drug Dose vs. Placebo			o.d. vs. b.i.d.		
Dose (mg) Regimen	Mean (95% CI)	p-value	Dose (mg) Regimen	Mean (95% CI)	p-value
800 o.d.	1.34 (-6.08, 8.76)	0.716	800 o.d. vs. 400 b.i.d.	1.29 (-7.15, 9.73)	0.758
400 b.i.d.	0.05 (-7.37, 7.47)	0.989	1200 o.d. vs. 600 b.i.d.	-0.73 (-9.58, 8.12)	0.868
1200 o.d.	-1.99 (-9.41, 5.43)	0.590	1600 o.d. vs. 800 b.i.d.	-1.37 (-10.8, 8.07)	0.771
600 b.i.d.	-1.26 (-9.15, 6.62)	0.748	TDD vs. Placebo		
1600 o.d.	1.22 (-6.20, 8.64)	0.741	800 TDD	0.70 (-5.41, 6.8)	0.818
800 b.i.d.	2.59 (-5.95, 11.12)	0.543	1200 TDD	-1.63 (-7.87, 4.62)	0.601
			1600 TDD	1.90 (-4.56, 8.36)	0.554

QRS and T-wave Amplitude

Dronedarone administration did not alter the QRS or T-wave amplitude relative to placebo as shown in Table 102 and Table 103.

Table 102: Pairwise Comparisons (Day 12 to Day 17) of QRS interval obtained during Exercise Test for Various dronedarone doses

Drug Dose vs. Placebo			o.d. vs. b.i.d.		
Dose (mg) Regimen	Mean (95% CI)	p-value	Dose (mg) Regimen	Mean (95% CI)	p-value
800 o.d.	-1.36 (-5.8, 3.08)	0.539	800 o.d. vs. 400 b.i.d.	-1.18 (-6.23, 3.87)	0.638
400 b.i.d.	-0.18 (-4.61, 4.26)	0.936	1200 o.d. vs. 600 b.i.d.	-3.03 (-8.32, 2.27)	0.254
1200 o.d.	-1.15 (-5.59, 3.29)	0.603	1600 o.d. vs. 800 b.i.d.	1.39 (-4.26, 7.03)	0.621
600 b.i.d.	1.88 (-2.84, 6.59)	0.425	TDD vs. Placebo		
1600 o.d.	2.6 (-1.84, 7.04)	0.243	800 TDD	-0.77 (-4.42, 2.88)	0.673
800 b.i.d.	1.21 (-3.89, 6.32)	0.633	1200 TDD	0.36 (-3.37, 4.1)	0.844
			1600 TDD	1.91 (-1.96, 5.77)	0.324

Table 103: Pairwise Comparisons (Day 12 to Day 17) of T-wave amplitude obtained during Exercise Test for various dronedarone doses

Drug Dose vs. Placebo			o.d. vs. b.i.d.		
Dose (mg) Regimen	Mean (95% CI)	p-value	Dose (mg) Regimen	Mean (95% CI)	p-value
800 o.d.	30.37 (-91.45, 152.19)	0.616	800 o.d. vs. 400 b.i.d.	-45.28 (-183.86, 93.3)	0.512
400 b.i.d.	75.65 (-46.17, 197.47)	0.216	1200 o.d. vs. 600 b.i.d.	40.14 (-105.2, 185.48)	0.579
1200 o.d.	41.28 (-80.54, 163.09)	0.497	1600 o.d. vs. 800 b.i.d.	37.5 (-117.44, 192.44)	0.627
600 b.i.d.	1.14 (-128.32, 130.6)	0.986	TDD vs. Placebo		
1600 o.d.	10.72 (-111.1, 132.54)	0.859	800 TDD	53.01 (-47.18, 153.2)	0.291
800 b.i.d.	-26.78 (-166.93, 113.37)	0.701	1200 TDD	21.21 (-81.36, 123.77)	0.678
			1600 TDD	-8.03 (-114.04, 97.98)	0.879

Systolic and Diastolic Blood Pressure

Relative to placebo, there were statistically significant decreases in:

- Systolic blood pressure (SBP) at 1200 and 1600 mg once daily doses
- Diastolic blood pressures (DBP) at 1200 mg QD and 600 mg BID doses

There was no dose-response relationship for either of the BP decreases. The observed effect may be related to the vasodilator properties of dronedarone.

Figure 50: Change in systolic blood pressure during Exercise Test

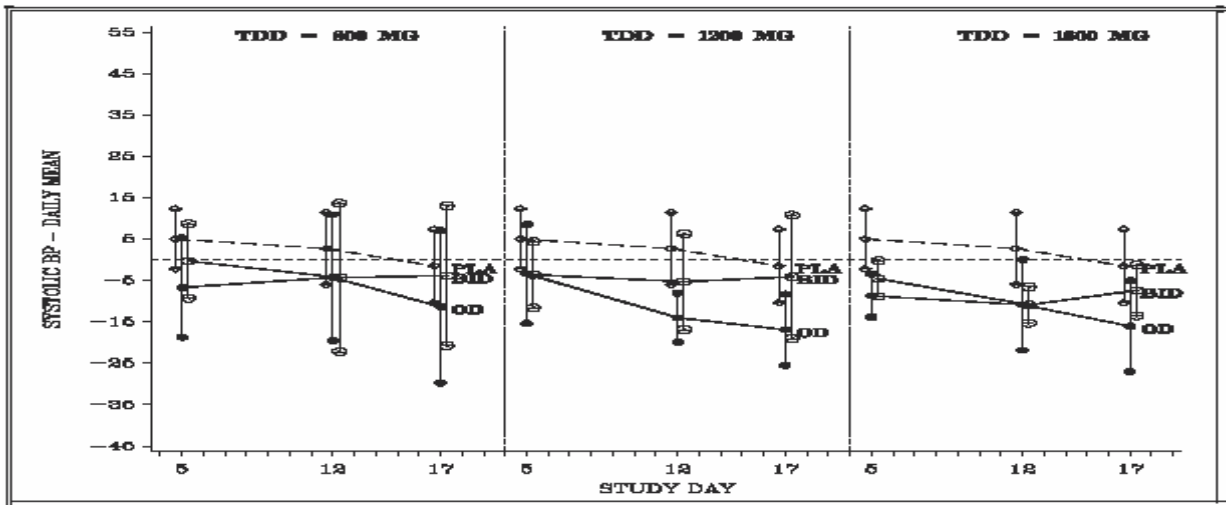
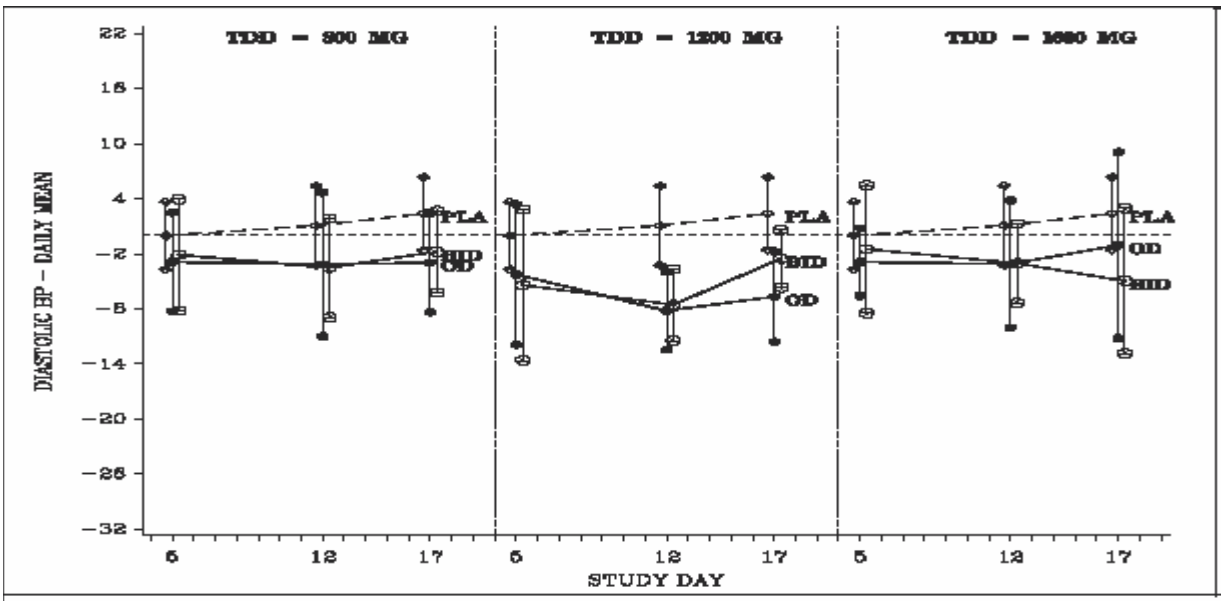


Figure 51: Change in diastolic blood pressure during Exercise Test



Applicant's Safety Analyses

According to the applicant, the investigator unblinded the study before the planned time due to relatively high incidence of adverse events (AEs); consequently, this study was stopped before initiation of the 2000 mg daily dose. Three subjects discontinued the study due to the incidence of severe AEs. The investigator indicated that these three subjects recovered from non-sustained asymptomatic monomorphic ventricular tachycardia without the need of corrective therapy and the relationship to study drug was unknown. Additionally, these severe AEs may have been

related to the prolonged telemetry (three weeks) performed in this study. Three additional subjects were discontinued from the study due to non-serious AEs: two were low degree AV block and the other due to having rash erythematous. Other alterations in ECG or clinical laboratories that were outside the normal range were not considered clinically relevant. No torsades de pointes or sustained episodes of ventricular arrhythmia were reported.

Conclusions/Recommendations
The following findings from Study TDR2395 are acceptable. The main limitation of this study is the lack of information at doses lower than the proposed clinical dose, 400 mg BID. Only one of the dosages evaluated in this study, 400 mg BID, appears clinically relevant, however the additional doses help potentially define the exposure-response relationship.

Pharmacodynamics

- Dronedarone produced a significant bradycardic effect during the exercise test, with a clear dose-response relationship: relative to placebo, the 400 mg dosage decreased heart rate by about 10 bpm. At rest, the bradycardic effect was less clear.
- Dronedarone altered some key electrophysiological measures, particularly during the exercise test. At rest, relatively high doses (1200 and 1600 mg QD) were required to demonstrate a difference between dronedarone and placebo. Two major findings from EP evaluation were:
    1. A dose-response (PR and QT interval) relationship was observed over the 400 mg to 800 mg BID range and 800 to 1600 mg QD range respectively
    2. There was a trend showing that BID dosing had a greater effect than QD dosing on the EP parameters
- Dronedarone caused decreases in 1) SBP at the 1200 and 1600 mg QD dose and 2) DBP at the 1200 mg QD dose and the 600 mg BID dose. There was no clearly dose-related effect in the BP changes.

Overall, the PD effects indicate that dronedarone possesses anti-arrhythmic activity (prolongation of cardiac repolarization) and an ability to decrease heart rate.

Pharmacokinetics
The pharmacokinetics of dronedarone have been fully characterized in other studies; PK data from Study TDR2395 can be used for comparative purposes, but are not needed for product labeling. Some PK highlights from this study are as follows:

- Steady-state was obtained within seven days of repeated administration
- Mean accumulation ratios (Rac) for dronedarone and SR35021 ranged between 1.5 and 3.6 for the QD administration and between 3.4 and 7.6 for the BID administration.
- There was a greater than dose proportional increase in exposure: For a doubling of the dose in the range of doses studies, AUC and Cmax for both SR33589 and SR35021 increased by approximately 2 - 3 fold (slightly greater than proportional).
- For both dronedarone SR35021, tmax (range 3 – 6 hours) appeared independent upon dose regimen, dose level or the day of observation.

4.2.13 Assessing the potential for SR 33589B or amiodarone to inhibit cytochrome P450 (CYP) enzymes using human liver microsomes in vitro (MIH0007)

PROTOCOL #	MIH0007
AUTHOR	William Brian
STUDY SITE	Sanofi Research Division, Malvern, PA, USA
STUDY PERIOD	November 1995

Objectives (per applicant):
To determine if dronedarone inhibits human liver CYP enzymes *in vitro*

Reviewer Note
Although amiodarone was evaluated in this study, this review focuses on the dronedarone results.

Experimental Conditions (Method)
Reagents and compounds were obtained from commercially available sources or as gifts from various companies. Human liver microsomes were obtained from Association of Human Tissue Users (Tucson, AZ).

Reviewer Note on Characteristics of Liver Donors
The majority of the donors used ethanol, tobacco or other CYP enzyme inducer which may have altered the metabolism results quantitatively. However, the use of a control group as reference renders the results useful.

The following CYP probe substrates and inhibitors were used:

Enzyme	Substrate	Inhibitor	Comment
CYP1A2	Phenacetin, 10 µM	furafylline	Acceptable
CYP2C9	Tolbutamide, 50 µM	sulfaphenazole	Acceptable
CYP2C19	Mephenytoin, 100 µM	papaverine	*Inhibitor is not a preferred or acceptable inhibitor, but has been used in literature
CYP2D6	Bufuralol, 50 µM	quinidine sulfate	Acceptable
CYP2E1	Chlorzoxazone, 100 µM	diethyldithiocarbamate	Acceptable
CYP3A4	Nifedipine, 20 µM	ketoconazole	Acceptable

Standard *in vitro* drug-drug interaction conditions were used for the experiment including presence of NADPH generating system and termination of reaction using methods determined for each assay. It is noted that expected concentrations for dronedarone were 0.2 µM based on a single oral dose of 1000 mg. Therefore the conditions for the initial study where dronedarone concentration was 50 µM, do not appear clinically relevant. However, use of the supra-therapeutic concentration is acceptable. The inhibition potential was further characterized by determining the Ki for a given enzyme, if needed. HPLC was used to quantify drug concentrations.

RESULTS
The study results are presented in Table 104. At the 50 µM dronedarone concentration, dronedarone did not affect the enzyme activity of CYP1A2, CYP2C19 or CYP2C9. For CYP2E1, the reliability of the result was unclear because the degree of inhibition (ranged

form 61 to 100 %) did not correlate with the amount of CYP2E1 activity in microsomal preparations. Dronedarone produced greater than 30 % inhibition in the activity of CYP3A4 and 2D6 relative to control group. Consequently, the Ki and type of inhibition for CYP 3A4 and 2D6 were determined. Ki values are summarized in Table 105 and Table 106.

Table 104: Effects of Dronedarone and Amiodarone on CYP Enzymes

CYP	Donor Date	Control[a]	SR33589B[a]	Amiodarone[a]	Inhibitor[a]
CYP1A2[c]	21-Jan-94	216	226 (105)[b]	217 (100)[b]	16 (7)[b]
	9-Jan-94	155	125 (81)	101 (65)	12 (8)
	23-May-94	173	131 (76)	125 (72)	22 (13)
CYP2C9[d]	7-Jan-94	130	110 (85)	108 (83)	10 (8)
	23-May-94	97	81 (84)	79 (81)	11 (12)
	15-Jun-94	87	71 (82)	75 (85)	—
CYP2C19[e]	21-Jan-94	78, 103[i]	84 (107)	86 (83)	16, 33 (21, 32)
	7-Jan-94	33, 35[i]	29 (89)	30 (86)	8, 8 (26, 23)
	28-May-94	38, 39[i]	40 (105)	36 (93)	10, 8 (26, 21)
CYP2D6[f]	7-Jan-94	39	14 (36)	28 (73)	11 (28)
	23-May-94	30	11 (36)	21 (70)	9 (29)
	3-Mar-94	48	12 (25)	30 (62)	7 (15)
CYP2E1[g]	20-May-93	515	312 (61)	235 (46)	146 (28)
	23-May-94	726	735 (101)	378 (52)	236 (32)
	21-Jan-94	1696	1197 (71)	779 (46)	401 (24)
CYP3A4[h]	21-Feb-94	469, 443[i]	258 (55)	486 (110)	26, 26 (6, 6)
	9-Jan-94	392, 419[i]	256 (65)	365 (87)	35, 37 (9, 9)
	23-May-94	327, 311[i]	183 (56)	311 (100)	24, 25 (7, 8)

Values are means of duplicate incubations.

[a] rates are expressed as pmol/mg/min

[b] Rates expressed as % of control values

[c] inhibitor was furafylline

[d] inhibitor was sulfaphenazole

[e] inhibitor was papaverine

[f] inhibitor was quinidine sulfate

[g] inhibitor was diethyldithiocarbamate

[h] inhibitor was ketoconazole

[i] inhibition by SR 33589B or amiodarone was examined in separate experiments; first and second values correspond to experiments with SR 33589B and amiodarone, respectively

— inhibitor was inadvertantly ommitted from reaction mixtures

Table 105: Apparent Ki values for Dronedarone and Amiodarone for bufuralol 1'—hydroxylation (CYP2D6 activity determinant)

	Apparent Ki Values (μM)	
Microsomal Preparation	SR 33589B	Amiodarone
HL 7-Jan-94	4.2	48.2
SD	0.3	4.5
HL 23-May-94	7.2	43.0
SD	0.8	5.0
HL 3-Mar-94	3.5	21.0
SD	0.3	2.5

*Values determined using SAAM II kinetics software package.
SD, Standard deviation

Table 106: Apparent Ki values for Dronedarone for nifedipine oxidation (CYP3A4 activity determinant)

Microsomal Preparation	Apparent Ki Values (μM)
HL 9-Jan-94	36.4
SD	2.9
HL 23-May-94	37.3
SD	3.2
HL 21-Feb-94	48.6
SD	3.3

*Values determined using SAAM II kinetics software package.
SD, Standard deviation

Conclusions

The following findings from Study MIH0007 are acceptable for labeling

- Dronedarone does not significantly inhibit the activity of CYP1A2, CYP2C9, CYP2C19 and CYP2E1 in human liver microsomes. Therefore clinically, dronedarone is not expected to inhibit the metabolism of compounds metabolized by these enzymes
- The I/Ki (assuming dronedarone concentration of 0.2 µM) value for CYP3A4 inhibition (I/Ki: 0.004 to 0.005) suggests that dronedarone is unlikely to inhibit the metabolism of drugs metabolized by CYP3A4. This conclusion can be evaluated in the context of in vivo drug-drug interaction results.
- The I/Ki (assuming dronedarone concentration of 0.2 µM) value for CYP2D6 inhibition (I/Ki: 0.028 to 0.057) suggests that dronedarone is unlikely to inhibit the metabolism of drugs predominantly metabolized by CYP2D6. This conclusion can be evaluated in the context of in vivo drug-drug interaction results.

APPENDIX

Characteristics of Human Liver Donors

Microsomal Preparation	Sex	Age (years)	Cause of Death	Known Drug Use or Medications
21-Feb-94	Female	43	Intracranial Bleed	NA
20-May-93	Male	18	Intracranial Bleed	None
9-Jan-94	Female	42	Cardiac Arrest	Tobacco/ Ethanol
23-May-94	Female	27	Closed Head Injury	Tobacco/ Ethanol
7-Jan-94	Male	41	Cranial Injury	None
3-Mar-94[a]	Female	2[b],6[c]	[b] Drowning [c] Seizure Disorder	[b] None [c] Phenobarbital
21-Jan-94	Male	43	Severe Head Injury	Tobacco/ Ethanol/ Dilantin
28-May-94	Unknown	<10	Unknown	None

NA, not available
[a] Microsome preparation is a mixture of two individuals;
[b] first individual;
[c] second individual.

4.2.14 Assessing Investigating the Potential for SR35021 to Inhibit Cytochrome P450 (CYP) Enzymes Using Human Liver Microsomes in vitro (MIH0037)

PROTOCOL #	MIH0037
AUTHOR	William Brian
STUDY SITE	Sanofi Research Division, Malvern, PA, USA
STUDY PERIOD	March – August, 1999

Objectives (per applicant)
To determine if SR35021 inhibits human liver CYP enzymes *in vitro*

Experimental Conditions (Method)
Reagents and compounds were obtained from commercially available sources or as gifts from various companies. Human liver microsomes were obtained from GENTEST, Inc. (Woburn, MA).

The following CYP probe substrates and inhibitors were used:

Enzyme	Substrate	Inhibitor	Comment
CYP1A2	Phenacetin, 10 µM	furafylline	Acceptable
CYP2A6	Coumarin, 1 µM	pilocarpine	Acceptable
CYP2C9	Tolbutamide, 200 µM	sulfaphenazole	Acceptable
CYP2C19	Mephenytoin, 75 µM	Tranylcypromine	Inhibitor is neither a preferred nor acceptable inhibitor, per Guidance. Compound has been used in literature and appears to be non-specific
CYP2D6	Bufuralol, 20 µM	quinidine sulfate	Acceptable
CYP2E1	Chlorzoxazone, 75 µM	diethyldithiocarbamate	Acceptable
CYP3A4	Nifedipine, 30 µM	ketoconazole	Acceptable

Standard *in vitro* drug-drug interaction conditions were used for the experiment including presence of NADPH generating system and termination of reaction using methods determined for each assay. It is noted that expected concentrations for SR35021 were 0.54 µM based on a single oral dose of 1600 mg. In the initial study, the SR35021 concentration was 200 µM, which is a supra-therapeutic concentration. In a subsequent study, the type of inhibition and apparent Ki values were determined. HPLC was used to quantify drug concentrations.

RESULTS
The results for SR35021 inhibition potential are summarized in Table 107. At a supra-therapeutic concentration, 200 µM, SR35021 significantly inhibited (defined as > 30% inhibition relative to control values), CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 oxidation. The relative degree of inhibition that would be obtained using lower, more clinically relevant SR35021 concentrations (~0.2 µM) is unclear. It is noted that selective inhibitor for a given enzyme produced numerically lower inhibition (measured as percent control) than SR35021, suggesting that at the high concentrations, SR35021 is as potent as the selective inhibitors.

Table 107: Effect of SR35021 on CYP isoform-selective substrate oxidation rates in human liver microsomes

Probe Assay	Human Liver	Percent of Control	
		SR35021	Selective Inhibitor
CYP1A2[a]	HG6	**6.53**	**12.2**
Phenacetin	HG56	**6.30**	**14.1**
O-deethylation	HG89	**9.04**	**10.2**
CYP2A6[b]	HG30	**<LOQ**	**46.8**
Coumarin	HG56	**<LOQ**	**44.2**
7-hydroxylation	HG66	**<LOQ**	**50.8**
CYP2C9[c]	HG6	**<LOQ**	**5.82**
Tolbutamide	HG23	**<LOQ**	**6.32**
methylhydroxylation	HG56	**<LOQ**	**16.2**
CYP2C19[d]	HG30	**<LOQ**	**16.5**
Mephenytoin	HG43	**<LOQ**	**17.2**
4'-hydroxylation	HG56	**<LOQ**	**16.9**
CYP2D6[e]	HG3	**<LOQ**	**<LOQ**
Bufuralol	HG23	**<LOQ**	**<LOQ**
hydroxylation	HG56	**<LOQ**	**21.0**
CYP2E1[f]	HG42	**32.6**	**60.9**
Chlorzoxazone	HG70	**32.0**	**57.0**
hydroxylation	HG89	**29.2**	**52.2**
CYP3A4[g, h]	HG30	**3.81**	**5.45**
Nifedipine	HG42	**4.50**	**6.77**
oxidation	HG70	**4.77**	**5.21**

Selective inhibitors were: [a] furafylline (100 μM); [b] pilocarpine (50 μM); [c] sulfaphenazole (50 μM); [d] tranylcypromine (100 μM); [e] quinidine (10 μM); [f] diethyldithiocarbamate (100 μM); [g] ketoconazole (1 μM); [h] data for CYP3A4 selective inhibition from a later experiment
<LOQ: data was below the LOQ of the assay (LOQ = 0.025 μM for CYPs 2A6, 2C9 and 0.05 μM for CYPs 2C19, 2D6)
Bolded values indicate > 30% inhibition (< 70% of control values)

Reviewer's Note

According to the applicant, addition of the isoform selective inhibitors to reaction mixtures resulted in significant inhibition relative to control reaction mixtures, confirming the ability of these CYP assays to show inhibition. Although, this statement is accurate, the suitability of the 2E1 assay systems is unclear because this system yielded greater than 50 % inhibition, which is expected for a known selective inhibitor.

Apparent Ki estimations and Inhibition Type

The type of inhibition and apparent Ki values are summarized in Table 108. Using the current CPB guidelines (I/Ki < 0.1 is unlikely to yield clinically significant inhibition), for drug-drug interaction potential, therapeutic concentrations of SR35021 are unlikely to inhibit the metabolism of compounds metabolized by any of the studied CYP enzymes. The applicant depicted the likelihood of SR35021 causing drug-drug interactions in Figure 52; the thresholds depicted in the figure are consistent with current FDA CPB guidelines.

The type of inhibition model was evaluated by the applicant, and the applicant's analyses appeared acceptable.

Table 108: Type of Inhibition and Ki values for SR35021

CYP Isoform	Model Type Observation	Mean Apparent Ki (µM)	I/Ki*
CYP1A2	mixed inhibition model best fit the data from two microsome preparations while the competitive model best fit the data for the third preparation	30.6	0.0065
CYP2A6	mixed- type inhibition model best fit the data from all three microsome preparations.	32.7	0.0061
CYP2C9	mixed- type inhibition model best fit the data from all three microsome preparations.	18.3	0.0109
CYP2C19	mixed- type inhibition model best fit the data for all three microsome preparations.	11.2	0.0179
CYP2D6	the competitive inhibition model best fit the data for all three microsome preparations.	4.37	0.0458
CYP2E1	the competitive model best fit the data for all three microsome preparations.	45.2	0.0044
CYP3A4	the competitive inhibition model best fit the data in two microsome preparations while the mixed-type model best fit the data in the third preparation.	8.12	0.0246

* I/Ki values determined using an I value of 0.2 µM

Figure 52: Dependence of I/Ki on SR35021 plasma concentrations for individual CYP isoforms

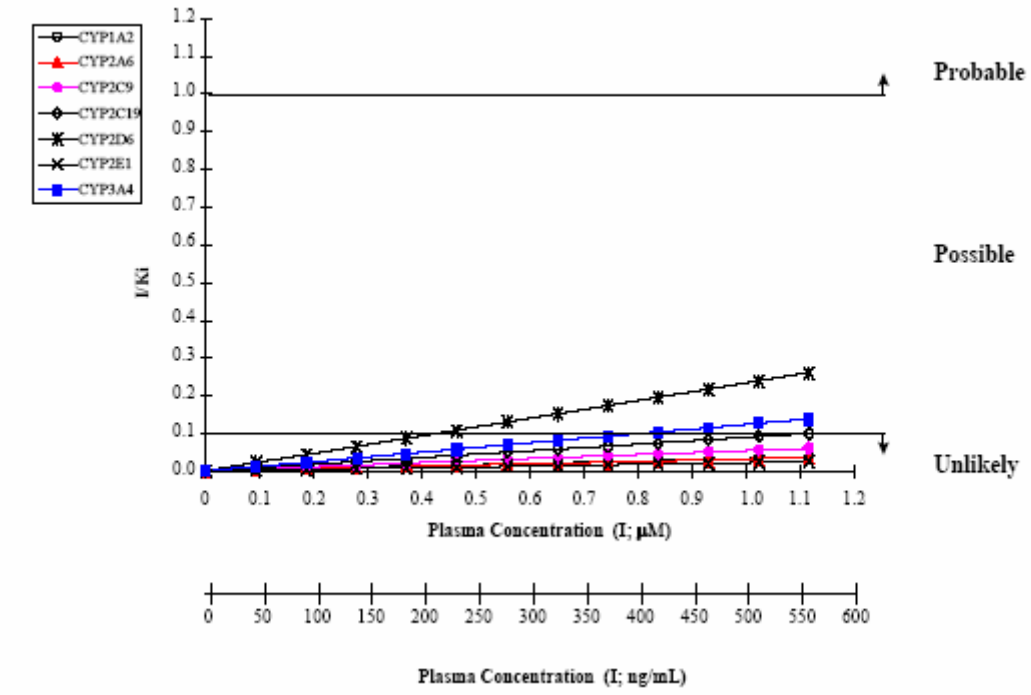


Figure 52 shows that a SR35021 concentration > 0.4 µM will be necessary to result in possible inhibition of CYP2D6; for the remaining enzymes a concentration > 0.8 will be required for possible inhibition. At the proposed clinical dose of 400 mg BID the SR35021 concentration is < 0.2 µM, thus SR35021 is unlikely to inhibit metabolism of any enzymes.

Conclusions

The following findings from Study MIH0037 are suitable for labeling

- At therapeutic concentrations, SR35021 is unlikely to cause inhibition of the major CYP enzymes. The validity of this conclusion will be evaluated during the review of in vivo drug interaction studies.
- The mechanism of enzyme inhibition by SR35021 is varied including competitive and mixed competitive

APPENDIX
Characteristics of Liver Donors

Liver Code	Gender	Age	Smoker	Race	Medical History
HG3	Female	30	N/A	Causasian	Dopamine, Lidocaine
HG6	Male	16	No	Causasian	N/A
HG23	Male	25	No	Causasian	Mannitol, Decadron
HG30	Female	28	No	Causasian	Rocephin, Zantac, Decadron, Dopamine, Atrophine, Lidocaine
HG42	Female	48	No	Causasian	N/A
HG43	Female	23	Yes	Causasian	Decadron, Lasix, Mannitol, Narcan, Dilantin, Ancef, Pavulon, Pitressin
HG56	Female	57	N/A	Causasian	N/A
HG66	Female	36	No	Causasian	Dopamine, Pitressin, DDAVP
HG70	Female	61	No	Causasian	Pitressin, Dopamine, Tagamet, Cardizem, Insulin, Aspirin
HG89	Female	71	N/A	Causasian	Ancef, Dopamine, Calan, Digoxin, Zoloft, Ativan

4.2.15 Identification of main cytochrome P450 isozymes involved in SR33589B metabolism by human microsomal fractions (MIV0159)

PROTOCOL #	MIV0159
STUDY DIRECTOR	G. Fablre
STUDY SITE	Sanofi Recherche, France
STUDY PERIOD	April – August 1992

Study Design

Standard procedures for *in vitro* metabolism studies were used. Human hepatic microsomal fractions were obtained from 15 organ donors (see Appendix for characteristics of donors). The incubation system contained drugs, microsomal fractions (2 mg/mL) and NADPH. The drug concentrations were: 1) Dronedarone, 5 µM and 2) CYP enzyme substrates and inhibitors, 0.1 to 200 µM. HPLC was used to determine the concentration of compounds. Table 109 summarizes the CYP enzymes and substrates evaluated in this study.

Table 109: CYP450 Enzyme substrates and inhibitors (per Applicant's report)

Cytochrome P450 isoform or gene subfamily	Substrates	Inhibitors
P450IA1	7-ethoxyresorufin	α-naphthoflavone
P450IA2	7-methoxycoumarin	
P450IIB	d-benzphetamine	
P450IID	debrisoquine	quinidine
P450IIIA	nifedipine	ketoconazole
Non specific		SKF-525A

Reviewer Note on Study Design Limitations

The evaluation of substrate status does not meet current FDA guidelines. It is noted that this study was conducted in 1992, when *in vitro* drug metabolism information was not well-advanced in terms of knowledge of CYP classes and their subfamilies or specific CYP substrates and inhibitors.

Compounds

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

Results

Determination of Dronedarone CYP Substrate Status by Chemical Inhibition

The metabolism of dronedarone in the presence and absence of specific CYP enzyme inhibitors is summarized in Table 110. The results with the inhibitors suggest:

- Ketoconazole inhibits the metabolism of dronedarone
- Quinidine, α-naphthoflavone, and SKF-525A do not significantly inhibit the metabolism of dronedarone

Table 110: Metabolism of dronedarone in the presence of CYP enzyme inhibitors

Inhibitor	Metabolite "1"	Metabolite "8"	SR 33589
None	0.64	0.68	3.51
α-Naphthoflavone			
20 μM	TP	0.97	3.07
200 μM	TP	0.31	4.86
Quinidine			
20 μM	0.43	0.65	3.26
200 μM	0.21	0.27	3.73
Ketoconazole			
20 μM	0	0	5.13
200 μM	0	0	5.62
SKF-525A			
20 μM	0.42	0.60	3.60
200 μM	0.11	0.19	4.49

TP = technical problem
Results are expressed in μM eq. SR 33589

Based on current drug-drug interaction information and guidelines the following conclusions may be drawn from the inhibition experiment:

- Dronedarone is a CYP3A substrate
- Dronedarone is not a CYP2D6 substrate
- Dronedarone is not a CYP1A2 substrate (α-naphthoflavone is a CYP1A2 inhibitor, not a CYP1A1 inhibitor).

Dronedarone Metabolism and Metabolites

Eight metabolites were observed during the metabolism studies. The metabolites were numbered sequentially, based on their elution characteristics (retention time); some of the metabolites, such as M6, are considered minor derivatives. It should be noted that the numbering of metabolites (based on *in vitro* studies) is not clear, therefore the metabolites will be referred to by name in this report, rather than number, when possible.

From previous studies, three of these metabolites have been identified; these metabolites are depicted in Figure 12. SR34871 (M5) is O-dealkylated dronedarone; SR35021 (M8) is N-debutylated dronedarone and SR 33580 is the sulfonamide hydrolyzed dronedarone. The kinetics of dronedarone metabolism in the absence and presence (n = two donors) of the hepatic microsomal system were also evaluated (Figure 54). The profiles indicate that dronedarone is rapidly converted to three main metabolites in the hepatic microsomal system. Metabolites 1 and 8 appear at a similar rate and are considered the major metabolites. Metabolites 1 and 5 are O-dealkylated derivatives of SR35021 and dronedarone, respectively.

Figure 53: Dronedarone metabolites identified by HPLC

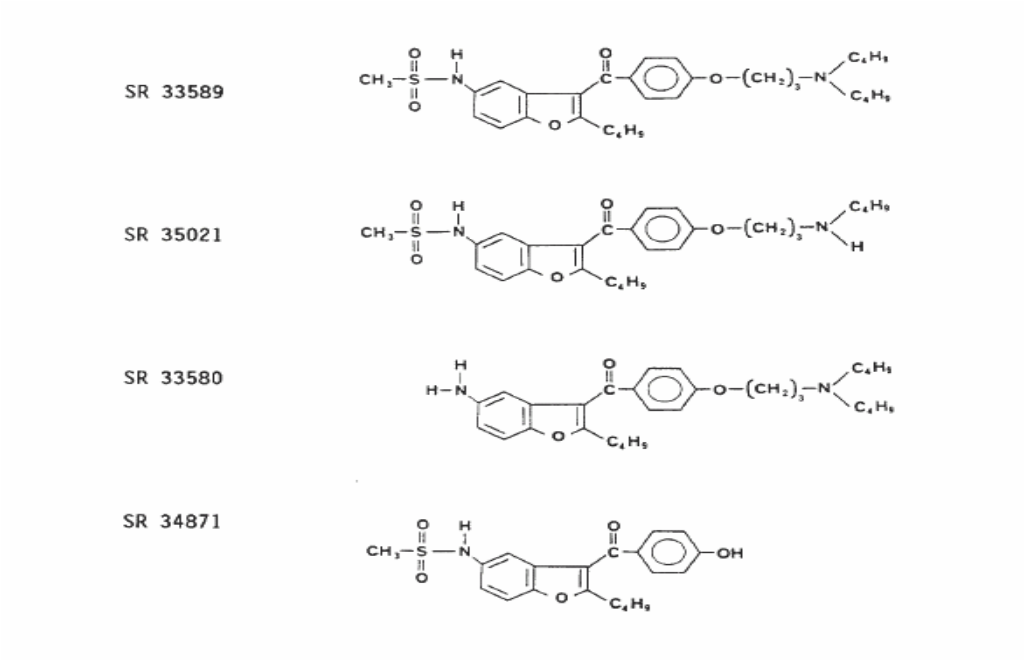
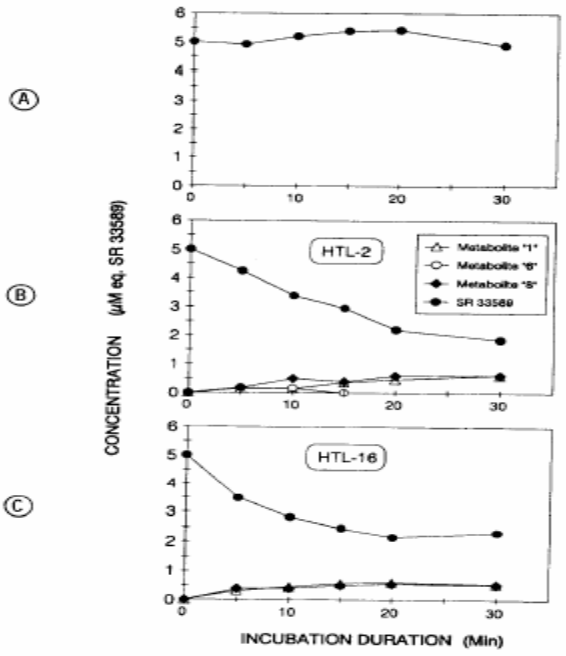


Figure 54: Kinetic profile of dronedarone metabolism



<u>Dronedarone metabolism in the presence of CYP substrates</u>

One of the CYP1A2 substrates, ethoxyresorufin, appeared to alter dronedarone metabolism, whereas phenacetin, the other CYP1A2 substrate did not alter dronedarone metabolism. The CYP substrates for the 2A6 (coumarin), 2B6 (benzphetamine), 2D6

(debrisoquine), and 3A (nifedipine and erythromycine) did not alter dronedarone metabolism (Table 111). The studied CYP2D6 substrate, d-benzphetamine, is not one of the preferred or acceptable probe substrates per current FDA guidelines, although some literature articles cite d-benzphetamine as a CYP2B6 substrate.

Table 111: Dronedarone metabolites in the presence of various CYP enzyme substrates

Substrate	Metabolite "1"	Metabolite "8"	SR 33589
None	0.64	0.68	3.51
7-Ethoxyresorufin			
20 µM	0	0.15	3.80
200 µM	0	0.15	4.51
Phenacetin			
20 µM	0.59	0.81	3.20
200 µM	0.59	0.73	3.10
7-Methoxycoumarin			
20 µM	0.64	0.92	3.40
200 µM	0.59	1.24	2.68
Coumarin			
20 µM	0.53	0.81	2.95
200 µM	0.43	1.11	2.68
d-Benzphetamine			
20 µM	0.53	0.76	3.50
200 µM	0.48	0.45	3.73
Debrisoquine			
20 µM	0.64	1.01	3.07
200 µM	0.59	0.97	2.61
Nifedipine			
20 µM	TP	0.42	3.58
200 µM	TP	0.08	5.68
Erythromycine			
20 µM	0.43	0.34	3.06
200 µM	0.11	0.08	3.73

TP = technical problem

Results are expressed in µM eq. SR 33589

The potential for selected CYP inhibitors and substrates to alter the metabolism of dronedarone and SR35021 was evaluated at different drug concentrations (Figure 55 and Figure 56).

Figure 55: Variation of dronedarone concentration with CYP inhibitor concentration in microsome

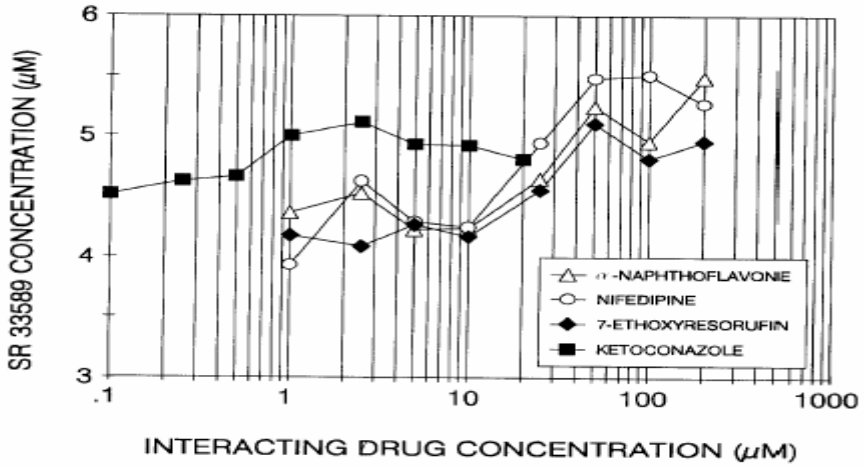
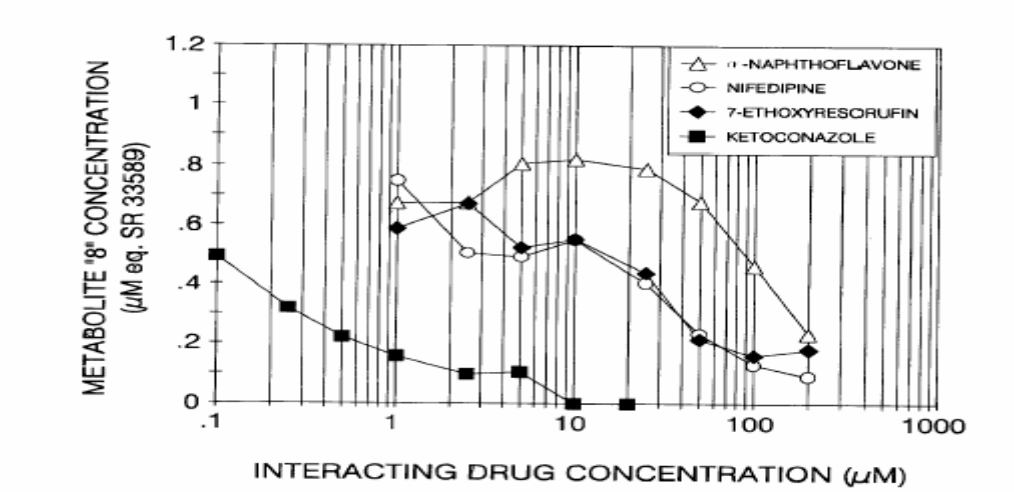


Figure 56: Variation of SR35021 concentration with CYP inhibitor concentration in microsome



The profiles in Figure 55 and Figure 56 suggest the following:

- The metabolism of dronedarone to SR35021 decreased over the 0.1 to 10 µM ketoconazole concentration range, and SR35021 is not formed at ketoconazole concentrations ≥ 10 µM.
- The metabolism of dronedarone to SR35021 is not impacted significantly by nifedipine, naphthoflavone or ethoxyresorufin at concentrations < 10 µM, but dronedarone metabolism is decreased when the concentrations of these drugs are between 20 and 100 µM. Therapeutic concentrations of the studied drugs are < 20 µM, thus, the *in vitro* concentrations that resulted in inhibition of dronedarone metabolism are unlikely to be achieved *in vivo*.

Overall these findings suggest that dronedarone is primarily metabolized to SR35021 by CYP3A and to a lesser extent by the studied CYP pathways.

Recommendations/Conclusions

The major deficiency in this study is:

Not all currently known CYP pathways were explored; the study could not determine if dronedarone is a CYP2C8, CYP2C9, CYP2C19, CYP2A6 or CYP2E1 substrate. The lack of information on these CYP enzymes can be included in the labeling, if the *in vivo* drug interaction information or other *in vitro* studies do not adequately address this deficiency. Alternatively, the applicant can conduct the relevant *in vitro* studies.

In spite of this deficiency, Study MIV0159 provides the following relevant metabolism information that is acceptable for labeling and other purposes:

- Dronedarone is metabolized by CYP3A to an N-dealkylated moiety, SR35021; this metabolite and dronedarone can undergo further metabolism
- Dronedarone is neither a CYP2D6 nor CYP1A2 substrate

APPENDIX

Caucasian human	Sex	Age	Cause of death
H(HL-1)m ; 070887-14	M	29	Autolysis (Gunshot)
H(HL-2)m ; 070887-19	M	30	Head injury (traffic accident)
H(HL-6)f ; 070887-16	F	20	Autolysis (Gunshot)
H(HL-9)m ; 070887-6	M	32	Head injury (traffic accident)
H(HL-10)m; 070887-15	M	46	Aneurysm rupture
H(HL-12)m; 070887-7	M	22	Head injury (traffic accident)
H(HL-16)m; 070887-5	M	20	Head injury (traffic accident)
H(HL-23)m; 070887-4	M	26	Head injury (traffic accident)

Caucasian human	Sex	Age	Pathology
H(HTL-2)m ; 211287-3	M	54	Pancreatic carcinoma
H(HTL-3)m ; 130887-1	M	51	Colon carcinoma
H(HTL-4)m ; 211287-1	M	36	Stomach carcinoma
H(HTL-5)m ; 211287-4	M	64	Sigmoide cancer
H(HTL-8)m ; 211287-9	M	63	Rectum carcinoma
H(HTL-12)m; 211287-6	M	56	Hepatocarcinoma
H(HTL-16)f; 211287-13	F	41	Pancreatic carcinoma

4.2.16 SR33589B metabolism using human hepatic models (MIV0158)

PROTOCOL #	MIV0158
STUDY SITE	Sanofi Recherche, France
STUDY PERIOD	April – August 1992

Study Design
Standard procedures for *in vitro* metabolism studies were used. Human hepatic microsomal fractions and primary cultures of hepatocytes were obtained from 15 organ donors (see Appendix for characteristics of donors). Incubation conditions were: incubation for 30 minutes in a system containing drugs, microsomal fractions (2 mg/mL) and NADPH. Dronedarone concentrations of 5 to 100 µM were evaluated. The glucuronidation pathway was explored using the SR34871 metabolite in the presence of 3 mM UDP-GA and Brij 58; SR34871 was selected because it had the greatest propensity towards undergoing glucuronidation. HPLC was used to determine the concentration of compounds.

Compound
Dronedarone hydrochloride salt; batch numbers DJ 07-51-5 and GD-07-11-3

Results
The kinetics of biotransformation of dronedarone, SR35021 and SR34871 are illustrated in Figure 57.

In the microsomal system the following metabolites were formed:
- Three metabolites from dronedarone
- Two metabolites from SR35021
- One metabolite from SR34871.

In another experiment, SR34871 formed the glucuronide metabolite in the presence of UDP-GA.

The identified metabolites were further characterized by MS and metabolic pathways were proposed for dronedarone and its metabolites (Figure 58, Figure 59, and Figure 60).

Metabolite Characterization
The following results were obtained when dronedarone metabolites were added to a medium containing dronedarone that had been incubated with human hepatocytes for 24-hours:
- S34871 was present in negligible amounts and co-eluted with one of the major dronedarone metabolites
- SR35021 was detected as a minor derivative
- Addition of ß-glucuronidase led to disappearance of a metabolite with a retention time of 6.5 minutes with a concomitant appearance of a derivative exhibiting chromatographic characteristics similar to that of SR34871
- Addition of saccharo-1,4-ß-lactone, a specific ß-glucuronidase inhibitor, inhibited the hydrolysis of the glucuronide derivative

- Several hydroxylated compounds of SR35021 and dronedarone were detected. Additionally, an acid derivative of dronedarone was observed that was obtained by a N-dealkylation process

Figure 57: Kinetics of biotransformation of dronedarone and its metabolites by human hepatic microsomal fractions

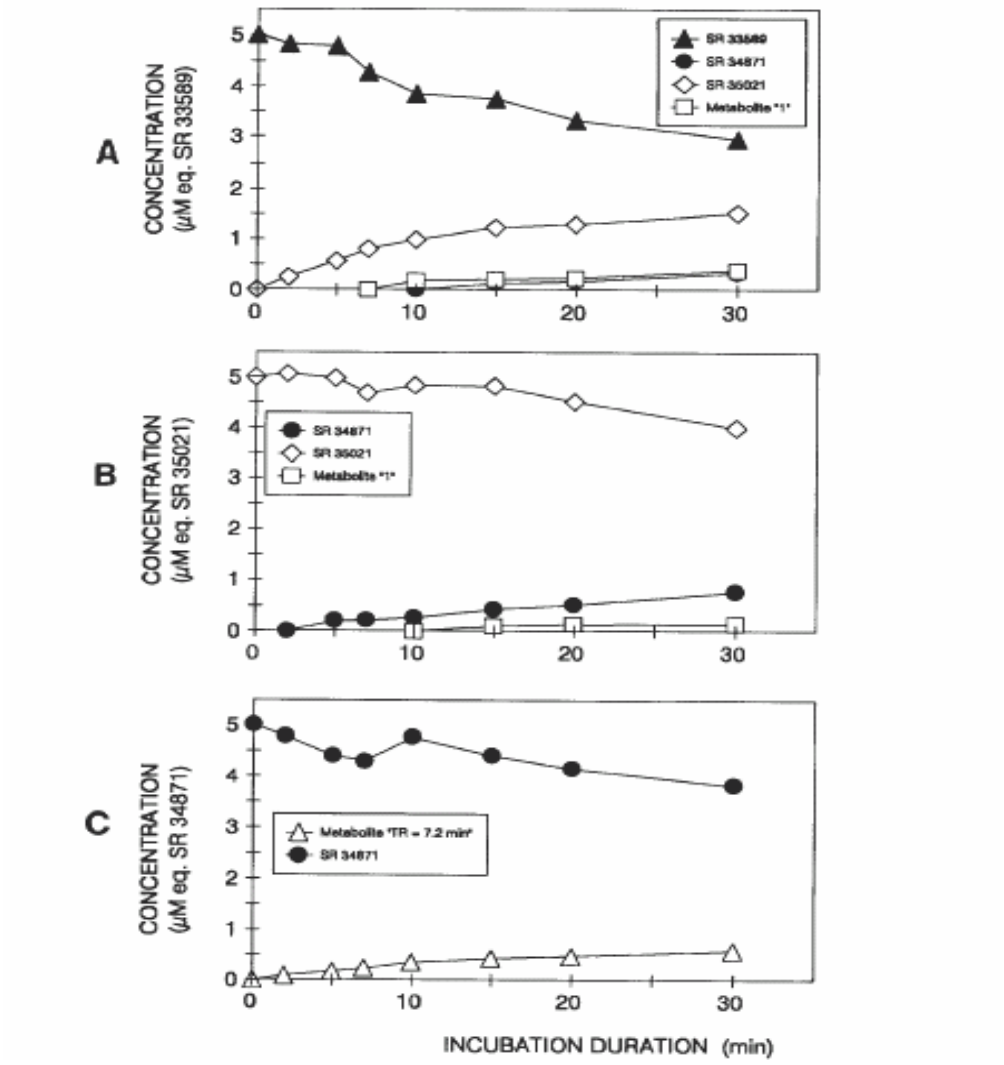


Figure 58: Proposed dronedarone metabolic pathway

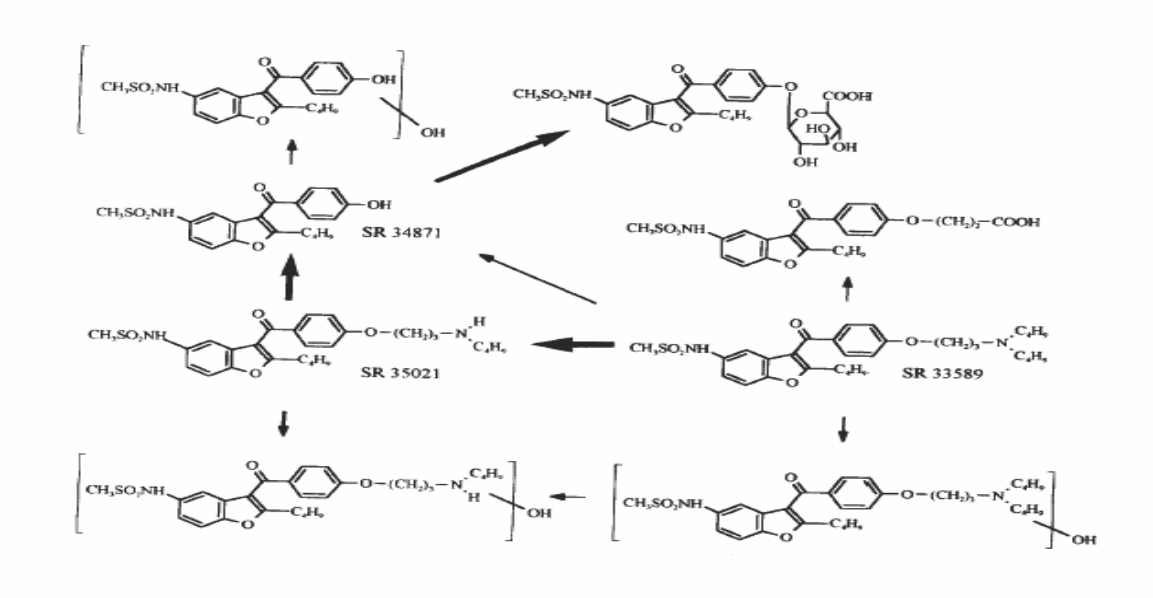


Figure 59: Proposed SR35021 metabolic pathway

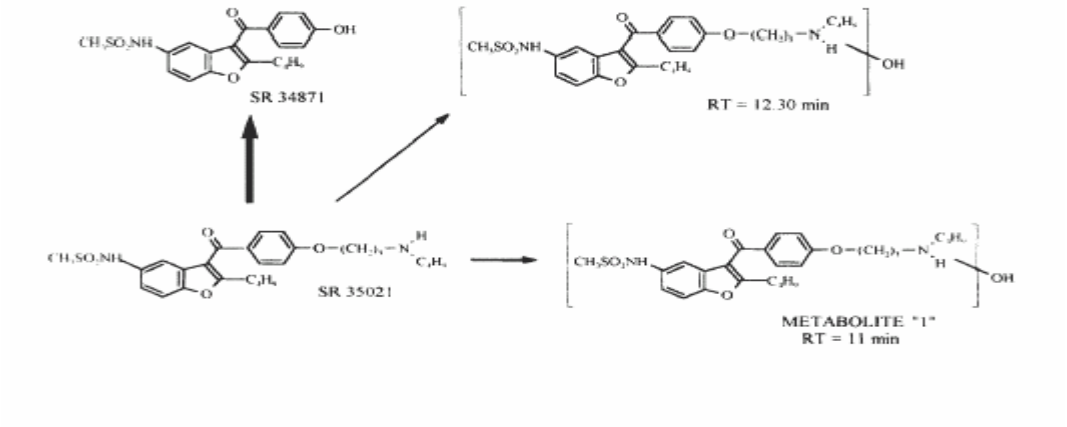
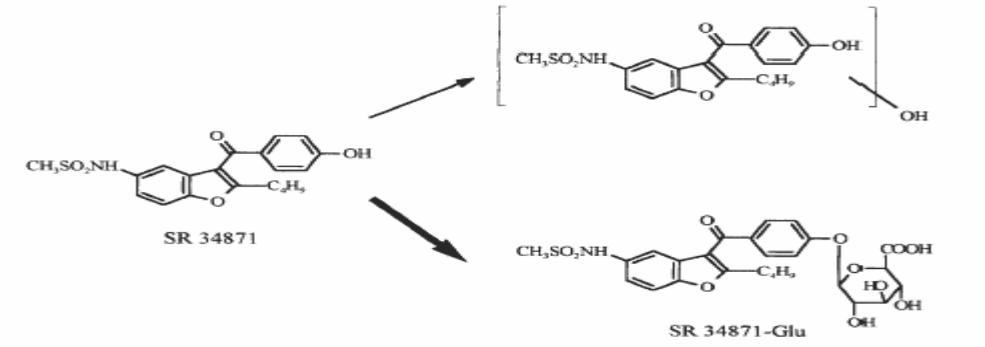


Figure 60: Proposed SR34871 metabolic pathway



Recommendations/Conclusions

The following information form Study MIV0158 is acceptable for labeling, as appropriate:

Dronedarone forms several metabolites when incubated with a human hepatocyte system; these metabolites include

- SR35021- formed by N-debutylation
- SR34871- formed by O-dealkylation of SR35021
- Acid derivative formed by dealkylation
- Numerous hydroxylated dronedarone and SR35021 derivatives

These metabolites are likely to be formed *in vivo.*