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EPIDEMIOLOGY STUDY PROTOCOL

Concomitant Use of Dronedarone and Digoxin (or Statins) and the Risk of Digitalis Intoxication (or Rhabdomyolysis and Myopathy)

-- A Post-marketing Cohort Study Using the US LabRx Database

Dronedarone (SR33589)

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Report type: Version 3.0 (final)

This study will be conducted in accordance with sanofi-aventis standard operating procedures for epidemiologic studies

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Date: August 31, 2010

STUDY SYNOPSIS

Drug name:	Dronedarone (MULTAQ®)
Title:	Concomitant use of dronedarone and digoxin (or statins) and the risk of digitalis intoxication (or rhabdomyolysis and myopathy)-- a post-marketing cohort study using the US LabRx database
Background:	This study is part of pharmacovigilance action to further evaluate dronedarone's potential interactions with digoxin and statins.
Objective(s):	To evaluate the possibility of dronedarone increasing the dose-related adverse events of the following concomitantly used drugs: digoxin (digitalis intoxication) and statins (rhabdomyolysis and myopathy).
Study design:	Retrospective cohort study
Study Population:	The study population will be patients aged 18 years and older with a diagnosis of atrial fibrillation (AF) or flutter (AFL) who filled a prescription of digoxin (or statins) since the launch of dronedarone in the US, identified from the LabRx® database. Cohort entry date will be defined as the date of the first prescription of digoxin (or statins) dispensed after July 21, 2009, the launch date of dronedarone in the US. Excluded from the cohort will be patients with the following conditions at cohort entry date: 1) less than six months of enrolment period; 2) a diagnosis of the outcome of interest within the last six months. Separate cohort will be identified according to each clinical outcome of interest.

Exposure measurement:	Exposure will be defined as on-drug treatment or off-drug treatment and categorized into the following three groups: 1) concomitant use of digoxin (statins) and dronedarone, 2) concomitant use of digoxin and amiodarone, and 3) digoxin (or statins) alone as the reference group, i.e. digoxin (or statins) without concomitant use of either dronedarone or amiodarone. The concomitant use of digoxin (or statins) and dronedarone (or amiodarone) will be defined as the treatment period during which a patient is on both of the drugs. Digoxin (statins) alone will be defined as the treatment period during which a patient is on digoxin (statins), but not on dronedarone or amiodarone. The treatment duration on digoxin (or statins) alone will begin accumulating on the first day of digoxin (or statins) prescription and continue with the subsequent continuous digoxin (or statins) prescriptions until: 1) a prescription for dronedarone overlapping the digoxin (or statins) days supplied, or 2) the end of the digoxin (or statins) days supplied (in addition to a grace period of up to 30 days, to account for non-adherence), 3) the occurrence of the outcome, 4) the enrollment end of membership, 5) the end of the observation period, whichever comes first. Likewise, the treatment duration of the concomitant use of digoxin (or statins) and dronedarone (or amiodarone) will begin on the first day of overlapping days supplied for digoxin (or statins) and dronedarone (or amiodarone) and will finish with the end of overlap of the days supplied for digoxin (or statins) and dronedarone (o amiodarone) (in addition to a grace period of up to 30 days) or the other endpoints, whichever comes first. The average daily dose of digoxin (or statins) will be adjusted for in the analysis. If a statistically significant association of interaction is observed, further analysis will be performed to check dose-response relationship.
Outcome(s) of interest:	Digitalis intoxication and rhabdomyolysis /myopathy are the outcomes of interest which will be analyzed separately. Digitalis intoxication will be defined as patients with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes 972.1 or E942.1. A secondary analysis will be conducted among the patients who had a claim of the above ICD-9 codes plus at least one laboratory testing claim and/or hospitalization within 30 days. Rhabdomyolysis and myopathy will be defined by an algorithm based on the ICD-9 codes, lab testing, and/or hospitalization that have been validated in a published study.

Covariates:	Covariates in the multivariate analyses will include age at baseline, gender, cohort entry date, duration of AF/AFL, congestive heart failure (CHF), diabetes, hypertension, stroke, myocardial infarction, and dose of digoxin (or statins). The major medications that are known to have potent interactions with digoxin or statins will additionally be adjusted as potential confounders, while for rhabdomyolysis and myopathy, chronic renal failure will also be adjusted for.
Statistical analysis:	Descriptive statistical analysis will be conducted to characterize the study participants. Cox proportional hazards regression modeling will be used to provide estimates of the relative hazard of the outcome of interest associated with concomitant use of digoxin (statins) and dronedarone, concomitant use of digoxin (or statins) and amiodarone, using digoxin (statins) alone as the reference group. Dose-response relationship with cumulative dose and treatment duration will be estimated if a positive association is observed.
Timelines:	The interim study reports will be submitted annually in December, 2010 to 2014. The final study report will be submitted in December 2016 at the latest. The study observation period will be from July 20, 2009 (the launch date of dronedarone in the US to the latest date of available data by August 31 of each year in the yearly study report.

TABLE OF CONTENTS

LIST OF TABLES **6**

LIST OF FIGURES **6**

ABBREVIATIONS **7**

1 INTRODUCTION **8**

2 STUDY OBJECTIVE(S) **8**

3 METHODS **8**

3.1 STUDY DESIGN 8

3.1.1 Source population(s)/database(s) used 9

3.2 STUDY POPULATION 9

3.3 EXPOSURE MEASUREMENT 9

3.4 OUTCOME(S) OF INTEREST 11

3.5 COVARIATE(S) 11

3.6 SAMPLE SIZE 12

3.7 STATISTICAL ANALYSIS 12

4 CONFIDENTIALITY AND ETHICAL CONSIDERATIONS **12**

5 STUDY TIMELINES **12**

6 REFERENCES **13**

7 TABLES AND FIGURES **14**

8 APPENDICES **17**

LIST OF TABLES

Table 1 Distribution of gender, age, and region of patients in the LabRx as of 2008 and in the US general population in 2005 14
Table 2 Age distribution in AF/AFL Patients in the LabRx (1/1985-3/2008)..... 15
Table 3 Estimated sample size 16

LIST OF FIGURES

N/A

ABBREVIATIONS

AF	Atrial fibrillation
AFL	Atrial flutter
CHF	Congestive heart failure
CPT	Current Procedural Terminology
GCP	Good Clinical Practice
GPE	Global Pharmcovigilance & Epidemiology
ICD-9	International Classification of Diseases, Ninth Revision
ICH	International Conference on Harmonization
ILD	Interstitial lung disease
NDC	National drug code
OR	Odds ratio
RMP	Risk Management Plan

1 INTRODUCTION

Dronedarone (MULTAQ®), like amiodarone, is a multi-channel blocker displaying antiarrhythmic properties of all four Vaughan-William's classes. Although structurally related to amiodarone, dronedarone shows different relative effects on individual ion channels, and its structure was modified with the intent to eliminate the non-cardiovascular effects of amiodarone. Dronedarone has been shown to be effective for reduction of the risk of cardiovascular hospitalization or death in patients with AF/AFL at the dose of 400 mg BID. The efficacy and safety of dronedarone have been evaluated in a comprehensive non-clinical testing program and extensive comprehensive clinical program in compliance with the International Conference on Harmonization (ICH) Good Clinical practice (GCP) guidelines.

The continuous assessment of all potential risks of dronedarone during its development has identified risk of drug-drug interactions with potent CYP3A4 inhibitors (such as ketoconazole). Dronedarone may have potential interactions with CYP3A4 substrates (such as some statins), and digitalis (such as digoxin). Although managed appropriately during clinical trials, the potential risks of these interactions need to be monitored in dronedarone users in the real life setting.

In order to further identify and evaluate dronedarone's potential interactions with frequently co-prescribed drugs, sanofi-aventis proposes epidemiologic studies using automated databases as part of the Risk Management Plan. They are done in addition to routine pharmacovigilance practices to ensure that the identified and potential risks are minimized in the real life setting, both in the US and in Europe. Using a US automatic claims database, LabRx, this epidemiologic study will be conducted once the number of dronedarone users is large enough to allow for analyses with sufficient statistical power.

2 STUDY OBJECTIVE(S)

The goal of this study is to provide safety information about dronedarone use in the US. The objectives of this study are to evaluate the possibility of dronedarone increasing the dose-related adverse events of the following concomitantly used drugs: digoxin (digitalis intoxication) and statins (rhabdomyolysis and myopathy).

3 METHODS

3.1 STUDY DESIGN

A retrospective cohort study is designed using information from a US claims database which will allow more facile implementation and explanation of the results among cohort of digioxin (statins) users and digoxin (statins) plus dronedarone users than a case-control study.

3.1.1 Source population(s)/database(s) used

The data source will be LabRx® (United HealthCare), an integrated medical and prescription-claims database augmented with laboratory data and linked to medical records and the National Death Index. As of January 2008, LabRx® consisted of seven-year data (since May 2000) and about 44 million unique members from 50 US states. This provides over 15 million covered lives (active patients) per year. If necessary, patients can be contacted to collect more information. About 30 million members' records (69%) contain at least one medical claim, about 27 million of them (61%) contain at least one prescription claim, and about 8 million records (19%) have at least one lab result (data provided by i3 Pharma Informatics on January 28, 2008 http://www.i3global.com/Businesses/i3PharmaInformatics/).

In general, LabRx database is representative of the US general population in terms of age, gender and region distributions (see Table 1). Since LabRx is an employment-based private insurance claims database, it has a lower proportion of patients aged 65+ years (6% in the LabRx vs. 12% in the US population). However, because of its large size, the number of subgroups in the database is large enough to allow for the studies with sufficient power. Our preliminary analysis identified 253,511 AF/AFL patients from January 1985 through March 2008 in the LabRx database, among which 127,516 patients (50.3%) were 65+ years old (see Table 2)

3.2 STUDY POPULATION

Separate study cohort will be identified according to the study objectives and the outcome of interest. To evaluate potential interaction of dronedarone and digoxin, patients aged 18 years and older with a diagnosis of AF/AFL (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes: 427.3X) who filled a prescription of digoxin since the launch of dronedarone in the US, will be identified from the LabRx® database. Likewise, to evaluate potential interaction of dronedarone and statins, we will identify patients aged 18 years and older with a diagnosis of AF/AFL who filled a prescription of statins since the launch of dronedarone. Cohort entry date will be defined as the date of the first prescription of digoxin (or statins) dispensed after July 21, 2009, the launch date of dronedarone in the US. The study observation period will be from July 21, 2009 to the latest date of available data by August 31 of each year in the yearly study report. Excluded from the cohort will be patients with the following conditions at cohort entry date: 1) less than six months of enrolment period in the managed care organization (UnitedHealthCare); 2) a diagnosis of the outcome of interest (prevalent cases) within the last six months.

3.3 EXPOSURE MEASUREMENT

Exposure will be defined as on-drug treatment or off-drug treatment. To identify exposure, all prescriptions for digoxin (or statins), dronedarone, and amiodarone will be identified and treatment episodes calculated. Statins of interest include atorvastatin, simvastatin, lovastatin, and pravastatin. Fluvastatin and rosuvastatin will not be considered for the potential interaction with dronedarone because they are not metabolized or only weakly metabolized by CYP3A4 and are not P-gp substrates.

Exposure will be categorized into the following three groups: 1) concomitant use of digoxin (statins) and dronedarone, 2) concomitant use of digoxin (or statins) and amiodarone, and 3) digoxin (or statins) alone as the reference group, i.e. digoxin (or statins) without concomitant use of either dronedarone or amiodarone. The concomitant use of digoxin (or statins) and dronedarone (or amiodarone) will be defined as the treatment period during which a patient is on both of the drugs. Digoxin (or statins) alone will be defined as the treatment period during which a patient is on digoxin (or statins), but not on dronedarone or amiodarone. Amiodarone is included as part of exposure of interest because it is one of the major drugs that are identified to have potent interactions with digoxin (or statins) as a multi-channel blocker displaying antiarrhythmic properties of all four Vaughan-William's classes.

The treatment duration or follow-up time on digoxin (or statins) alone will begin accumulating on the first day of digoxin (or statins) prescription and continue with the subsequent continuous digoxin (or statins) prescriptions until: 1) a prescription for dronedarone (or amiodarone) overlapping the digoxin (or statins) days supplied, or 2) the end of the digoxin (or statins) days supplied (in addition to a grace period of up to 30 days, to account for non-adherence), 3) the occurrence of the outcome, 4) the enrollment end of membership, 5) the end of the observation period, whichever comes first. The follow-up time of the concomitant use of digoxin (or statins) and dronedarone (or amiodarone) will be defined using the same methodology as described above. It will however begin on the first day of overlapping days supplied for digoxin (or statins) and dronedarone (or amiodarone) and will finish with the end of overlap of the days supplied for digoxin (or statins) and dronedarone (o amiodarone) (in addition to a grace period of up to 30 days) or the other endpoints, whichever comes first. Prescriptions will be treated as continuous if they are not interrupted by a break of greater than 30 days. If a gap of greater than 30 days occurred, patients may still contribute follow-up time (defined as a separate treatment episode) to digoxin (or statins) alone or the concomitant medications as appropriate, until they are right-censored at the first occurrence of: 1) the outcome, 2) the enrollment end of membership, and 3) the end of the observation period.

Given that digoxin (or statins) may be administered at a lower dose when used in combination with dronedarone than the use of digoxin (or statins) alone, and the drug interaction effect may be dose-related, the average daily dose of digoxin (or statins) will be adjusted for as a covariate in the analysis. It will be calculated as the total quantity prescribed divided by the total days supplied. If a statistically significant association of interaction is observed, further analysis will be performed to check dose-response relationship. For statins, the analyses will be conducted at equally effective doses which will address the effect of dose with the same cholesterol lowering effect. Based on published literature comparing statins efficacy, the following equally effective doses will be used in the secondary analysis for statins: atorvastatin 10mg, simvastatin 20mg, lovastatin 40mg, and pravastatin 40mg[1-2].

Both un-adjusted and adjusted odds ratios will be calculated using Cox proportional hazards regression modeling (see Section 3.7).

3.4 OUTCOME(S) OF INTEREST

Digitalis intoxication and rhabdomyolysis /myopathy will be analyzed separately as the outcomes of interest. Digitalis intoxication will be defined as patients with ICD-9 codes 972.1 and/or E942.1 that have been used in published studies[3-5]. Given that these codes have not been validated, a secondary analysis will be performed among the patients who had a claim of the above ICD-9 codes plus at least one laboratory testing claim and/or hospitalization within 30 days.

Rhabdomyolysis and myopathy will be defined by an algorithm based on the ICD-9 codes, lab testing, and/or hospitalization that have been validated in a published study[6]. Specifically, the patients who meet one of the following four criteria based on the ICD-9 codes, lab testing/Current Procedure Terms (CPT) codes, and/or hospitalization will be identified and defined as cases:

1) any code of myoglobinuria (ICD-9 code 791.3) or rhabdomyolysis (ICD-9 code 728.88);
2) a primary code of "other disorders of muscle" (ICD-9 code 728.89);
3) a secondary code of "other disorders of muscle (ICD-9 code 728.89) plus any serum creatine kinase (CK) test (CPT codes: 82550, 82552, 82553, 82554, 80012, 80016, 80018, 80019) within 7 days of hospitalization/admission for the ICD-9 code 728.89;
4) a secondary code of "other disorders of muscle (ICD-9 code 728.89) plus hospital discharge code for acute renal failure (ICD-9 code 584.x).

3.5 COVARIATE(S)

The following covariates will be adjusted for in the multivariate analyses: age at baseline, gender, cohort entry date, duration of AF/AFL, congestive heart failure (CHF) history, diabetes history, hypertension history, stroke history, myocardial infarction history, and dose of digoxin (or statins). The major medications that are known to have potent interactions with statins or digoxin will additionally be adjusted for as potential confounders. For digitalis intoxication, the medications will be those with potent interactions, including arbutamine, atazanavir, calcium chloride, calcium gluceptate, calcium gluconate, and saquinavir. The drugs with interaction that are generally considered to be moderate (e.g. aspirin) or mild (e.g. acetaminophen) will not be considered[7]. For the outcome of rhabdomyolysis and myopathy, the major medications will include erythromycin, clarithromycin, azithromycin, fusidic acid, warfarin, dicoumarol, nefazodone, ketoconazole, itraconazole, cholestyramine, mibefradil, digoxin, gemfibrozil, cyclosporine, chlorzoxazone, and vitamins niacin[8]. History of renal failure (except for acute renal failure) will also be adjusted for the outcome of rhabdomyolysis and myopathy.

The history of the medical conditions will be defined as a diagnosis in the baseline period based on the ICD-9 codes (codes to be provided). The count of the number of diagnoses of AF/AFL in the baseline period will be used as a surrogate for the duration of AF/AFL since the accurate information is not available in the LabRx database. All medications will be identified using the National Drug Code (NDC) directory. Maintained by the Food and Drug Administration (FDA), NDC is a code-set that serves as a universal product identifier for human drugs and biologics. The directory consists of prescription and a few selected over-the-counter drugs that are in commercial distribution in the United States. The products have been listed in accordance with the Drug

Listing Act and applicable Code of Federal Regulations for submitting drug product information to the FDA (see: http://www.fda.gov/cder/ndc/).

3.6 SAMPLE SIZE

We calculated sample size based on the likelihood ratio test in the context of a Cox proportional hazards regression analysis. The preliminary analysis of the last five-year data in the LabRx suggested that there might be about 44,000 participants for the cohort of digoxins and about 86,000 participants for the cohort of statins during the next 5-year cohort accrual period (07/2009-06/2014). With these figures, the study would be able to rule out a hazard ratio of 1.42 for the outcome of digitalis intoxication, and a hazard ratio of 1.61 for the outcome of rhabdomyolysis and myopathy with the assumptions of 0.05 alpha level (type I error), 80% statistical power (type II error), 17.1% prevalence of dronedarone use in the study population (the sponsor's prediction), 1.1% baseline incidence rate for the outcome of digitalis intoxication[9], and 0.3% baseline incidence rate for the outcome of rhabdomyolysis and myopathy[10-11]. For a 4-year cohort accrual period (07/2009-06/2013), we estimate that the study would be able to rule out a hazard ratio of 1.51 with over 32,000 participants for the outcome of digitalis intoxication, and a hazard ratio of 1.69 with over 70,000 participants for the outcome of rhabdomyolysis and myopathy with the same assumption. For a 3-year cohort accrual period (07/2009-06/2012), we estimate that the study would be able to rule out a hazard ratio of 1.59 with over 25,000 participants for the outcome of digitalis intoxication, and a hazard ratio of 1.77 with over 58,000 participants for the outcome of rhabdomyolysis and myopathy with the same assumption (see Table 3).

3.7 STATISTICAL ANALYSIS

Descriptive statistical analysis will be performed to characterize the study participants. Cox proportional hazards regression modeling will be used to provide estimates of the relative hazard of the outcome of interest associated with concomitant use of digoxin (statins) and dronedarone, and concomitant use of digoxin (statins) and amiodarone, using digoxin (statins) alone as the reference group. If a statistically significant association of interaction is observed, further analysis will be done to estimate dose-response relationship with cumulative dose and treatment duration.

4 CONFIDENTIALITY AND ETHICAL CONSIDERATIONS

Patient confidentiality will be maintained throughout the study. Patient records on the database are anonymous. Patient identifying details are replaced by codes, which cannot be broken by the researchers. There is no need to collect any additional data directly from patients currently. Therefore, no informed consent is required.

5 STUDY TIMELINES

The interim study reports will be submitted annually in December, 2010 to 2014. The final study report will be submitted in December 2016 at the latest. It is estimated that the LabRx database may not provide sufficient statistical power until 2014 for any event of interest to rule out a

hazard ratio of 1.5. However, the sponsor will check the number of incident of digitalis intoxication and rhabomyolysis /myopathy, the number of potential study participants, patients who received prescriptions of dronedarone and digoxin (or statins), and statistical power based on the above identified number of events and dronedarone users each year. Provided that 336 or more events are captured for any outcome(s) of interest before 2014 which will be sufficient to rule out at least a hazard ratio of 1.5, the final data analysis and study report for the particular outcome(s) will be initiated immediately.

6 REFERENCES

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7 TABLES AND FIGURES

Table 1 Distribution of gender, age, and region of patients in the LabRx as of 2008 and in the US general population in 2005

Attributes	LabRx	US Population (2005)*
Male	50%	49%
US Region	Total Lives (%)	Total Lives (%)
Northeast	22%	19%
North Central	30%	22%
South	30%	36%
West	18%	23%
Age Group	Total Lives (%)	Total Lives (%)
00-20	28%	27%
21-39	32%	29%
40-64	34%	32%
65+	6%	12%

*Statistical abstract, US Census

Table 2 Age distribution in AF/AFL Patients in the LabRx (1/1985-3/2008)

Age (yrs)	N	%
18-29	3,705	1.5
30-49	36,089	14.2
50-64	86,431	34.1
>65	127,516	50.3
Total	253,741	100.0

Table 3 Estimated sample size

Outcome	Incidence in literature	Size of cohort*		Hazard Ratio
Digitalis intoxication	1.1%9	3 years	25,000	1.59
		4 years	32,000	1.51
		5 years	44,000	1.42
Rhabdomyolysis /myopathy	0.3%10-11	3 years	58,000	1.77
		4 years	70,000	1.69
		5 years	86,000	1.61

Given alpha=0.05 (two-sided), statistical power = 80%, prevalence of dronedarone in the cohort = 17.1%, baseline event rate = 1.1% for digitalis intoxication, and 0.3% for rhabdomyolysis /myopathy, and right censoring rate = 30%

*Estimated based on the preliminary results of the available LabRx data as of August 31, 2010

8 APPENDICES

N/A