PRODUCT REGISTRY REPORT

Compound(s): DRONEDARONE/MULTAQ®

Registry title: Individual management of patients with paroxysmal or persistent atrial fibrillation using Dronedarone: A prospective, non-interventional study (NIS) in German ambulatory care.

Original registry title: Individuelles Management von Patienten mit paroxysmalem oder persistierendem Vorhofflimmern unter Verwendung von Dronedaron: prospektive, nicht-interventionelle Studie (NIS) in der ambulanten Versorgung.

Registry number: DRONE_L_04949

Registry name: IMPULS

Registry initiation date [date first patient in (FPI)]: 02-Apr-2012

Registry completion date [last patient completed/last patient out (LPO)]: 31-Dec-2013

Registry design: Prospective, non-interventional study (NIS) to observe the use of dronedarone in patients with paroxysmal or persistent atrial fibrillation over a 12-months period

Report date: 21-Oct-2014

This registry was performed in compliance with the guidelines for Good Epidemiology Practice. This report has been prepared based on the publication 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Guidelines for reporting observational studies – Ann Intern Med. 2007'.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
ALT	Alanine Aminotransferase
AMG	Arzneimittelgesetz
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
CSG	Clinische Studien Gesellschaft mbH
CRA	Clinical Researc Associate
CRF	Case Report Form
CRO	Clinical Research Organisation
DCF	Data Clarification Form
DM	Data Management
DRG	Diagnosis-Related Group
DS	Drug Safety
ECG	Electrocardiogramm
EHRA	European Heart Rhythm Association
ES	Enrolled Set
ESC	European Society of Cardiology
FAS	Full Analysis Set
FU	Follow-up
GPT	Glutamate Pyruvate Transaminase
INR	International Normalized Ratio
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
PCI	Percutaneous Coronary Intervention
PV	Pharmacovigilance
PT	Preferred Term
QoL	Quality of Life
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SaS	Safety Set
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TIA	Transient Ischemic Attack
ULN	Upper Normal Value
VAS	Visual Analogue Scale

SYNOPSIS

Title of the registry:	Registry title: Individual management of patients with paroxysmal or persistent atrial fibrillation using Dronedarone: a prospective, non-interventional study (NIS) in German ambulatory care. Original registry title: Individuelles Management von Patienten mit paroxysmalem oder persistierendem Vorhofflimmern unter Verwendung von Dronedaron: prospektive, nicht-interventionelle Studie (NIS) in der ambulanten Versorgung. Registry number: DRONE_L_04949
Design:	IMPULS was a prospective multicenter non-interventional study (NIS) according to § 67 (6) German Drug Law ("Arzneimittelgesetz" (AMG)) to document the management/treatment of consecutive patients treated with Dronedarone. Patient Selection Either incident patients who began a treatment with Dronedarone or prevalent patients who were already treated with Dronedarone for no longer than a maximum of 3 months were eligible for inclusion. Only patients with paroxysmal or persistent atrial fibrillation (AF) and at least one cardiovascular risk factor (arterial hypertension, diabetes mellitus, previous stroke, transient ischemic attack (TIA), arterial embolism, left atrium diameter ≥ 50 mm) were to be enrolled in this study. Patients were required to give their informed consent to participate in the study. Patients were asked to complete quality of life (QoL) questionnaires (AF-QoL, SF36) at baseline and at their 3-month, 6-month and 12-month follow-up visits. Site Selection About 500 resident cardiologists, general practitioners and internists were planned to document approx. 1.500 consecutive patients. No diagnostic measures or treatment methods were stipulated, but remained in the sole responsibility of the participating physicians. At baseline and after approx. 6 and 12 months, respectively, the physicians had to document diagnostic and therapeutic parameters as assessed under routine treatment or as available from additional sources like e.g. hospital reports.
Objectives:	The essential objectives of this study were the patients' characteristics of subjects suffering from paroxysmal or persistent AF in terms of • Demographic characteristics (i.e. age group, sex) • Risk factors (i.e. arterial hypertension, diabetes mellitus, recent stroke, TIA, arterial embolism, left ventricular ejection fraction ≤ 40%) • Concomitant diseases • Diagnostic procedures • Surveillance of liver, kidney, lung and heart function • AF type and antiarrhythmic treatment pattern • Pharmacotherapy and other components of individual patient management • Tolerability and effectiveness of Dronedarone treatment in every day treatment • Increases of liver and kidney laboratory parameters (glutamate pyruvate transaminase (GPT), creatinine) and if such are ascertained, determination of concomitant medication • Patients' quality of life and affecting cofactors • Treatment changes and adjustments (in a qualitative and quantitative manner) and affecting cofactors • Treatment in accordance to European Society of Cardiology (ESC) guidelines [8] (August 2010) and affecting cofactors • Frequency and duration of hospitalizations • Costs of management of AF patients from the perspective of third-party payers and society
Treatment:	In this NIS only patients with the indication for a Dronedarone therapy were to be enrolled which comprised patients that had already been treated with Dronedarone for no longer than a maximum of 3 months or that started the treatment with Dronedarone at baseline. No specific

	procedures regarding diagnostics, therapy and assessments were stipulated. Treatment decisions by the investigators had to be made independently from study participation and had to follow the routine practice in agreement with the corresponding treatment guidelines and the summary of product characteristics (SmPC).
Scientific committee and members:	Scientific clinical lead: Prof. Dr. med. Andreas Götte Medical Director Medical Clinic II Cardiology and Internistic Intensive Care St. Vincenz-Krankenhaus GmbH Am Busdorf 2 33098 Paderborn PD Dr. med Ralph Bosch Cardiology Practice Asperger Straße 48 71634 Ludwigsburg
Publications (reference):	Not applicable
Introduction - Background/ rationale:	AF is the most common sustained cardiac arrhythmia occurring in approx. 1 % of the general population (10 % of all 80 years old people are suffering from AF). Over 6 million Europeans suffer from this arrhythmia and its prevalence is estimated to increase significantly within the next decades as the population ages [1, 2, 3]. AF is associated with a doubling of overall mortality and a fivefold increased risk of stroke [4, 5]. Clinical AF symptoms may vary from palpitations, dyspnea, syncopes and restricted loading capacity to significant impairment of quality of life [6]. On the other hand AF can also go unnoticed unless incidentally found or until complications occur [7]. According to the European Society of Cardiology (ESC) guideline for the management of AF [8] the following five types of AF can be distinguish based on the presentation and duration of the arrhythmia: first diagnosed, paroxysmal (self-terminating, < 7 days, usually ≤ 48 h), persistent (termination by cardioversion required, > 7 days), long-standing persistent (≥ 1 year), and permanent (accepted) AF. The initial therapy after onset of AF should always include adequate antithrombotic treatment and control of the ventricular rate. There are two different strategies for the treatment of AF: rate or rhythm control. Rate control is needed for most patients with AF unless the heart rate during AF is naturally slow. Rhythm control may be added to rate control if the patient is symptomatic despite adequate rate control, or if a rhythm control strategy is selected because of factors such as the degree of symptoms, younger age, or higher activity levels [9]. Permanent AF is managed by rate control unless it is deemed possible to restore sinus rhythm when the AF category is re-designated as 'long-standing persistent'. Paroxysmal AF is more often managed with a rhythm control strategy, especially if it is symptomatic and there is little or no associated underlying heart disease. If the ultimate goal is restoration and maintenance of the sinus rhythm, rate control medication should be continued throughout follow-up, unless continuous sinus rhythm is present. The goal is to control the ventricular rate adequately whenever recurrent AF occurs. Depending on the patient's course, the strategy initially chosen may prove insufficient and may then be supplemented by rhythm control drugs or interventions. It is likely that long-lasting AF renders maintenance of sinus rhythm more difficult [25 – 27] but clinical data on the usefulness and benefit of early rhythm control therapy are lacking. Nonetheless, it is likely that a window of opportunity to maintain sinus rhythm exists early in the course of management of a patient with AF. According to the ESC guidelines for the management of AF the choice of antiarrhythmic medication should be based on safety considerations and individual symptoms [8]. While the success of the therapy is measured primarily by electrocardiographic parameters other

	treatment aims such as reduction of cardiovascular mortality and morbidity as well as corresponding hospitalization periods have been disregarded in the past. Dronedarone which has market authorization since 2010 in Germany is a new drug (Multaq®) that has been shown to have a good antiarrhythmic effect in patients with paroxysmal or persistent AF [19] and to reduce cardiovascular mortality and hospitalizations [17, 20]. It is indicated only for clinically stable patients to maintain the sinus rhythm after successful cardioversion [28]. Dronedarone must not be given to patients with hemodynamic impairment, previous or current congestive heart failure, left ventricular systolic dysfunction, permanent AF when restoration of the sinus rhythm is no longer considered, or liver and lung toxicity related to previous treatment with Amiodarone. Patients who receive Dronedarone should be monitored carefully by regularly controlling the function of heart, kidneys, liver and lungs. In addition to the increasing epidemiological relevance the economic aspects of AF are of high interest. Since AF leads to the highest number of hospitalizations of all cardiac arrhythmic disorders [8] the resulting costs are considerable [30]. The average resource costs related to AF per patient and year are estimated at 827 €. The total costs add up to at least 660 million € per year [21, 22]. A cost-of-illness study in 5 European countries evaluated the average cost per patient at 1.000 – 3.000 € with hospitalizations and interventional procedures causing more than 70 % of the total costs per year [23]. AF patients are directly affected by their constrained quality of life caused directly and indirectly by AF which can already be detected even when the patients do not yet suffer from secondary diseases [24]. NIS investigating the use, the tolerability and safety as well as the therapy results of Dronedarone in the daily routine are yet to be performed after the market launch of Multaq® and the update of the SmPC due to new safety considerations. The real life patient population often differs from patient collectives in controlled clinical studies with regards to demographic characteristics, comorbidities and concomitant diseases. Data collected in NIS like IMPULS can complement the findings of pivotal studies. Sanofi-Aventis Deutschland GmbH, the sponsor of this NIS, together with the competence network AF investigated the current management of AF patients with at least one additional cardiovascular risk factor being initially treated with Dronedarone or having been treated with Dronedarone for no longer than 3 months, the quality of life during treatment and the resulting costs of outpatient treatment over the period of one year. The study was conducted with resident cardiologists or internists who are responsible for AF treatment decisions and who were selected to ensure the representativeness of the patients documented. Only patients with paroxysmal or persistent AF and at least one cardiovascular risk factor (arterial hypertension, diabetes mellitus, previous stroke, TIA, arterial embolism, left atrium diameter ≥ 50 mm) were to be enrolled in this study. Additional data on patient characteristics, treatment strategies and presciption patterns as well as on quality of life and hospitalizations were to be collected. The observational period of one year allowed to capture morbidity and mortality parameters under Dronedarone treatment as well as additional concomitant therapies. A target-performance comparison with the current treatment guidelines could be the basis for further therapy optimization of AF patients. On the one hand this observational study was planned to validate the results of the ATHENA study regarding effects on morbidity, mortality and hospitalization in the daily routine [29]. On the other hand real life data on the tolerability of Dronedarone and the medical treatment situation as well as the resulting costs should be collected. By using the disease-specific questionnaire AF-QoL which has been validated for the German language and cultural region differences in the quality of life in comparison to other instruments were to be captured. The collected data should give a picture of the health care situation and needs of patients with paroxysmal or persistent AF (and one additional cardiovascular risk factor) who are treated with Dronedarone. An additional health economic analysis should shed light AF-related costs.
Methodology:	(a) Site and patient selection:

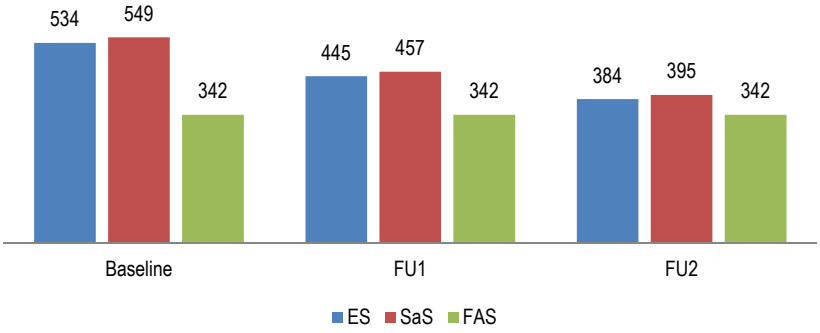
	About 500 resident cardiologists, general practitioners and internists were planned to document approx. 1.500 patients with paroxysmal or persistent AF and at least one cardiovascular risk factor (arterial hypertension, diabetes mellitus, previous stroke, TIA, arterial embolism, left atrium diameter ≥ 50 mm). A representative selection of sites was pursued regarding the geographic and medical specialists distribution all over Germany. The selection of study sites was based on previous experience regarding the willingness to participate in NIS and assisted by the competence network AF. Each site was planned to document the AF treatment and management of 3 consecutive patients upon enrolment at baseline and after 6 and 12 months, respectively. No site replacement methodology was implemented in this study. (b) Data collection: Each site was provided with an investigator site file containing an NIS contract, an observational plan, a patient identification list, a complete set of paper-based case report forms (CRF) including also quality of life questionnaires for 3 patients and each 3 adverse event (AE) and serious adverse event (SAE) report forms. Each patient planned to be enrolled in the study had to be informed by the physician about the objectives and the conduct of this observational study including also data transmission. Each patient willing to participate in the study should sign and date two informed consent forms one of which remained at the site. The other exemplar was handed out to the patient. Based on their patient records and other documentation routinely available at the sites the participating physicians documented demographic, anamnestic and clinical patient characteristics, AF and other treatments, resource use parameters and safety information in the CRFs. The completed CRFs were sent back to the sponsor to be entered into an Oracle clinical database. (c) Safety data collection: The AE/SAE management process is described in the SAE Mangement Plan (see annex) According to the observational plan, AEs and SAEs were recorded paper-based by the physician or a delegated person on the Adverse Event Form or on Serious Adverse Event Form of the CRF and were forwarded by fax to the clinical research organisation (CRO) Clinische Studien Gesellschaft mbH (CSG). The CSG DS (DS) Manager reviewed and managed the incoming AEs and SAEs. Completed CRFs were sent by the physician directly to the NIS Management Department of Sanofi-Aventis Deutschland GmbH, where a first review of CRFs regarding unreported hidden AEs/SAEs was performed. If potential, unreported AEs/SAEs were identified, the corresponding CRF documentation was sent immediately to CSG for case processing. If CRFs were sent to CSG first by mistake, review of the CRFs for AEs/SAEs and case processing was performed by the CSG DS Manager (for further details see PV Service for AE/SAE Management (SAE-Management Plan V 1.0, appendix 3.5). The CSG DS Department was responsible for the review of all AEs regarding causality (causality assessment was to be provided by the reporting physician), coding of AEs in the current MedDRA version and checking of labeling based on the SmPC. Processing of the cases (AEs and SAEs) in the CSG safety data base (Oracle AERS), including generation of case narratives, was done within a maximum of 24 hours or 1 business day, respectively. Case processing in the CSG safety database was performed for all AEs/SAE`s for which the reporter or Sanofi Pharmacovigilance Department considered a causal relationship to Multaq® or another Sanofi (SA)-/ Winthrop-/Zentiva product. All other AEs/SAE`s with no causal relationship to Multaq® treatment were reported as monthly listings to the Sanofi Pharmaocovigilance Department for notification by the CSG DS Manager. All AEs (serious and non-serious) reported by the physicians in this study are listed in this report in appendix 2.1.4. If no assessment of relationship between Multaq® or other SA-/ Winthrop-/Zentiva products and an AE/SAE was documented by the reporting physician, the relationship was considered "related" (worst case scenario). If no seriousness assessment of an AE/SAE was considered by the reporting physician, the case was considered as "serious" if the event fits the seriousness criteria or if the event was on the company`s list of medical important events (see appendix

	3.5). Notification of Sanofi Pharmacovigilance Department was performed on a daily basis via e2B in xml-format together with the original documentation (source documents). Immediate processing of any follow-up information and subsequent notification was done in the same way. According to the observational plan and in agreement with Sanofi Pharmacovigilance Department, only events were recorded in the CSG safety database, for which a causal relationship between Multaq® or any SA-/ Winthrop-/Zentiva products was assumed. (see appendix 2.1.4 Listing: "Related AEs/SAEs"). All other cases (unrelated) were notified to the Sanofi Pharmacovigilance Department and are listed in appendix 2.1.4 (Listing: Unrelated AEs/SAEs). The following variables were served for safety assessment: • Electrocardiogramm (ECG) findings • Liver function tests in general • ALT 3fold and more of upper normal value (ULN) (documented before treatment start, monitored monthly in the first 6 months after treatment start and after 9th and 12th month). • Serum creatinine test approx. 7 days after treatment start. • Individual symptoms • Frequency and type of AE • Discontinuation of Multaq® due to AEs (d) Data management (DM), review, validation: All DM processes are described in detail in the data mangement plan (DMP) (appendix 3.5). Sanofi-Aventis Deutschland GmbH was responsible for the distribution of study materials to the study sites including paper-based CRFs. The study site sent the completed CRFs to the NIS management department of Sanofi-Aventis Deutschland GmbH for a first check of completeness and hidden AEs. The reviewed CRFs were forwarded to CSG for further processing. The DS department of CSG checked the incoming CRFs immediately for hidden AEs. CSG was responsible for data entry into the clinical database by double data entry. All collected data were validated after the end of data capture by running discrepancy check programs in SAS. If an edit check failure required clarification from the study site, a data clarification form (DCF) was issued to the site investigator. DCFs were sent to the sites only once. If a DCF was returned with an unsatisfactory response, data was documented as incomplete, in exceptional cases a second DCF might have been issued. All discrepancies were closed/resolved in the Oracle Clinical Database before database closure. In cases which were not solvable by the investigator, the site had to comment the entries, mark them as 'irresolvable' and send the issue back to CSG DM. Irresolvable and incomplete issues were closed and commented by DM (closed – no resolution). Resolvable issues were closed and commented by the DM (closed - resolved comment: investigator consulted). Before database closure the data was validated according to the data validation document which is attached to the DMP. CSG was responsible for onsite monitoring at 15 study sites. During the monitoring visits source data verification was performed for pre-defined CRF parameters agreed upon by Sanofi-Aventis Deutschland GmbH. Each monitoring visit was documented in a monitoring visit report prepared by the clinical research associate (CRA) of CSG. The reviewed reports were sent to Sanofi Aventis Deutschland GmbH for approval. (e) Statistical considerations: This statistical analysis plan (SAP) provides a detailed description of statistical techniques to be used to perform the analysis of data from the IMPULS study (appendix 3.2.1) Costs of management of AF patients: Cost analyses were conducted from the third-party payers´ and societal perspectives. The third-party payers´ perspective includes direct inpatient and outpatient costs of treatment. The societal perspective includes additionally indirect costs due to sick leave.

	Cost analyses were based on the resource use documented in the study. Unit costs were derived from tariffs and other publicly available sources. Cost analyses were conducted for the reference year of 2012. Costs were not discounted as the patient-related observation period did not exceed 1 year. Patients' co-payments for drugs and inpatient treatments were not considered due to the chronic nature of disease. The following cost variables were analyzed: Direct costs: Inpatient costs: • Hospitalization in an acute treatment facility Calculation of case-related costs for hospitalizations was based on invoiced diagnosis-related groups (DRGs) corresponding to respective diagnoses (predefined in this study as well as documented as "other reasons" of hospitalization) using publicly available data („G-DRG V2013 Browser 2012 § 21 KHEntgG") • Inpatient rehabilitation Calculation of costs for inpatient rehabilitation was based on an average price of 118.72 € per treatment day in a rehabilitation clinic using data from the German Public Pension Fund Direct costs: Outpatient costs: • Outpatient treatment in an emergency unit Calculation of costs for outpatient treatment in an emergency unit was based on the Uniform Value Scale for outpatient services • Treatment initiation (Dronedarone) and monitoring Costs for initiation of outpatient Dronedarone therapy and its monitoring were calculated based on the Uniform Value Scale for outpatient services and on Dronedarone prescribing information and applied for each patient as long that the patient was treated with Dronedarone. Quarterly lump sums for the physician groups participating in the study as well as costs of international normalized ratio (INR) and ECG measurement are shown separately, as they are not related exclusively to Dronedarone therapy. • AF drug treatment / thromboprophylaxis Daily costs of a respective drug class or compound were estimated based on the prescriptions data from the Arzneimittelverordnungsreport and calculated as a cost of the various preparations in the respective group weighted with their prescriptions. For Class Ia antiarrhythmics the costs were calculated based on the largest pack of Prajmalin (only drug available for ATC-Code C01BA in the Lauer-Taxe), as the respective data was not available in the Arzneimittelverordnungsreport. Drug costs for follow-up (FU) 1 and 2 were calculated multiplying the respective daily costs with the number of treatment days documented. Dronedarone costs were applied in all patients for the duration of the study. In case of a therapy change, the costs of respective drugs instead of Dronedarone were used considering the mean duration of treatment with the respective drug class or compound based on the documented data. Indirect costs • Sick leave Calculation of costs for sick leave was based on average costs per sick leave day of 101.73 € using data from the Federal Statistical Office. Duration of hospitalization, number of days spent in intensive care unit, number of contacts with documenting physician (of these: not planned), number of contacts with an outpatient clinic and number of contacts with other specialists were analyzed in natural units.

RESULTS	
Participants (actual):	Participants (actual): A total of 161 resident cardiologists, general practitioners and internists throughout Germany took part in this study. In total, 641 patients were screened in the period from January 2012 until December 2013. All of these patients are assumed to have been treated with Dronedarone at least once. For 57 of these patients no date of patients´ informed consent or treatment start with Dronedarone was documented by the physicians. Therefore, these patients were excluded from analysis. A total of 50 of the remaining 584 patients did not meet the documentation criteria and were not considered for analysis. The rest of the patients (N = 534) met all target population criteria and therefore constituted the enrolled set (ES) for analysis. For 15 of all those patients that were not considered for analysis in the ES, however, at least one AE or SAE was reported by the physician or considered as AE/SAE by the DS manager (in case of suspected hidden events). Therefore, these patients were included in the safety set (SaS) for analysis resulting in a total of 549 patients in this analysis set. 342 patients of the ES who were treated with Dronedarone at least once and for whom a valid baseline value and valid follow-up values (6 and 12 months) for the quality of life questionnaire for patients with AF (AF-QoL) were available so that a change in the primary effectiveness variable (AF-QoL) could be analyzed constituted the full analysis set (FAS) (table 1). Table 1: Number of Patients by ES, SaS and FAS (see appendix 2.1.3 table 1.1) In figure 1 the number of patients in each analysis set at each stage of the study is depicted. Figure 1: Number of Patients by Visit – ES, SaS and FAS

Analysis Set	Specification	N	% of Screened
Screened	Screened	641	100.0
Screened	Excluded	57	8.9
Screened	Of these. included in SaS	10	1.6
Screened	Not meeting documentation criteria	50	7.8
Screened	Of these. included in SaS	5	0.8
ES	Baseline	534	83.3
SaS	Baseline	549	85.7
FAS	Baseline	342	53.4



Participant characteristics and primary analyses:

Demographic and Baseline Characteristics

In the SaS the median for the AF duration was 396 days. This median was used as a reference value for the stratification of the AF duration in the FAS and ES to illustrate the shifted distribution between below and above median.

Table 2: Number of Patients by Subgroup – FAS, ES

Subgroup	Parameter	n	% of patients
	FAS		
Age	<65 yrs.	134	39.18
Age	>=65 yrs.	208	60.82
Sex	Male	196	57.31
Sex	Female	146	42.69
AF Type	Missing	7	2.05
AF Type	Paroxysmal	244	71.35
AF Type	Persisting	91	26.61
AF Duration	Below median of SaS (=396 d)	185	55.39
AF Duration	Above median of SaS (=396 d)	149	44.61
	ES		
Age	<65 yrs.	180	33.71
Age	>=65 yrs.	354	66.29
Sex	Male	284	53.18
Sex	Female	250	46.82
AF Type	Missing	10	1.87
AF Type	Paroxysmal	387	72.47
AF Type	Persisting	137	25.66
AF Duration	Below median of SaS (=396 d)	262	51.07
AF Duration	Above median of SaS (=396 d)	251	48.93

(see appendix 2.1.3 table 1.2)

Table 3: Frequency of Obligatory Risk Factors – ES, FAS

Risk factor	n	% of patients
	ES	
Arterial hypertension	493	92.32
Diabetes mellitus	108	20.22
Stroke, TIA	37	6.93
Leftatrial diameter ≥ 50 mm	66	12.36
	FAS	
Arterial hypertension	321	93.86
Diabetes mellitus	80	23.39
Stroke, TIA	24	7.02
Leftatrial diameter ≥ 50 mm	47	13.74

(see appendix 2.1.3 table 3.1)

Table 4: Frequency of Additional Risk Factors – ES, FAS

Risk factor	n	% of patients
	ES	
Hyperthyreose	14	2.62
Vitium	115	21.54
Pathological alcohol consumption	6	1.12
	FAS	
Hyperthyreose	13	3.80
Vitium	60	17.54
Pathological alcohol consumption	4	1.17

(see appendix 2.1.3 table 3.2)

Table 5: Cardiac Anamnesis – ES, FAS

Disease	n	% of atients
	ES	
Coronary heart disease	117	21.91
Myocardial infarction	29	5.43
PCI	61	11.42
Bypass surgery	19	3.56
	FAS	
Coronary heart disease	74	21.64
Myocardial infarction	18	5.26
PCI	40	11.70
Bypass surgery	10	2.92

(see appendix 2.1.3 table 3.3)

Table 6: Previous Medical Events or Diseases – ES, FAS

Medical Event / Disease	n	% of patients
	ES	
TIA	26	4.87
Stroke	8	1.50
Peripheral arterial embolism	8	1.50
	FAS	
TIA	18	5.26
Stroke	5	1.46
Peripheral arterial embolism	3	0.88

(see appendix 2.1.3 table 3.4)

Table 7: Patients Demographics by Sex - FAS

Sex	$n_{(values)}$	$n_{(missing)}$	Min	Mean	SD	Max
			Age [years]			
Overall	342	0	33	66.28	9.74	85
Male	196	0	33	64.87	9.97	84
Female	146	0	38	68.17	9.12	85
			Height [cm]			
Overall	342	0	149	172.53	8.55	196
Male	196	0	160	177.46	6.09	196
Female	146	0	149	165.91	6.71	180

(see appendix 2.1.3 tables 2.2 and 2.3)

Table 8: Weight [kg] by Sex - FAS

Analysis Time Point	Sex	$n_{(values)}$	$n_{(missing)}$	Min	Mean	SD	Max
Baseline	Overall	341	1	54	84.47	14.52	147
FU1	Overall	338	2	53	84.94	15.58	176
FU2	Overall	337	5	55	85.41	15.81	170
Baseline	Female	146	0	54	78.16	13.86	125
FU1	Female	144	2	53	78.18	13.88	125
FU2	Female	143	3	55	79.31	15.26	152
Baseline	Male	195	1	62	89.19	13.18	147
FU1	Male	194	0	64	89.96	14.89	176
FU2	Male	194	2	64	89.9	14.7	170

(see appendix 2.1.3 table 2.4)

Table 9: BMI [kg/m^2] by Sex - FAS

Analysis Time Point	Sex	$n_{(values)}$	$n_{(missing)}$	Min	Mean	SD	Max
Baseline	Overall	341	1	18.93	28.35	4.27	48.00

FU1	Overall	338	2	19.03	28.47	4.65	60.19
FU2	Overall	337	5	19.03	28.68	5.08	64.93
Baseline	Female	146	0	18.93	28.39	4.71	42.76
FU1	Female	144	2	19.03	28.34	4.74	42.76
FU2	Female	143	3	19.03	28.85	5.70	64.93
Baseline	Male	195	1	20.45	28.33	3.93	48.00
FU1	Male	194	0	20.43	28.56	4.60	60.19
FU2	Male	194	2	19.58	28.55	4.58	58.82

(see appendix 2.1.3 table 2.5)

Primary Effectiveness Variables

AF-QoL Psychological Domain:

In the ES the psychological domain of AF-QoL increased by 10.74 points (baseline -> FU1) and by 14.15 points from baseline to FU2.

The AF-QoL psychological domain in the FAS shows an improvement by 12.06 points (baseline -> FU1) and increased by 16.02 points from baseline to FU2.

Table 10: AF-QoI Psychological Domain - FAS

Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Baseline	342	0.00	44.60	22.57	100.00	
FU1	342	0.00	56.66	21.66	100.00	
FU2	342	0.00	60.62	22.58	100.00	
FU1 - Baseline	342	-46.43	12.06 [9.85; 14.27]	20.81	78.57	< 0.0001
FU2 - Baseline	342	-46.43	16.02 [13.52; 18.52]	23.51	100.00	< 0.0001

(see appendix 2.1.1 table 2.1.2)

AF-QoL Physical Domain:

In the ES the physical domain of AF-QoL increased by 8.89 points (baseline -> FU1) and by 8.72 points from baseline to FU2.

The AF-QoL physical domain in the FAS shows an improvement by 10.34 points (baseline -> FU1) and increased by 10.86 points from baseline to FU2.

Table 11: AF-QoI Physical Domain - FAS

Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95%]	SD	Max	p-Value
Baseline	342	0.00	49.46	22.16	100.00	
FU1	342	3.13	59.80	20.50	100.00	
FU2	342	0.00	60.32	23.97	100.00	
FU1 - Baseline	342	-40.63	10.34 [8.27; 12.42]	19.49	78.13	< 0.0001
FU2 - Baseline	342	-43.75	10.86 [8.47; 13.24]	22.46	100.00	< 0.0001

(see appendix 2.1.1 table 2.2.2)

AF-QoL Sexual Domain:

In the ES the sexual domain of AF-QoL increased by 4.94 points (baseline -> FU1) and by 5.69 points from baseline to FU2.

The AF-QoL sexual domain in the FAS shows an improvement by 6.48 points (baseline -> FU1) and increased by 6.55 points from baseline to FU2.

Table 12: AF-QoI Sexual Domain - FAS

Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Baseline	342	0.00	61.82	27.05	100.00	
FU1	342	0.00	68.30	24.83	100.00	

FU2	342	0.00	68.37	26.65	100.00	
FU1 - Baseline	342	-83.33	6.48 [3.90; 9.06]	24.23	100.00	< 0.0001
FU2 - Baseline	342	-91.67	6.55 [3.56; 9.55]	28.19	100.00	< 0.0001

(see appendix 2.1.1 table 2.3.2)

Irrespective of the analyzed set (ES or FAS) the strongest improvement is shown in AF-QoL psychological domain showing and increased better individual feeling, self-satisfaction and complacence.

Regarding the ES the patients self-assessment and self-evaluation of health status EQ-5D VAS improved from baseline to FU1 by 8.79 points and from baseline to FU2 by 9.31 points.

In the FAS the patients self assessment of health status EQ-5D VAS improved by 10.79 points (baseline -> FU1) and from baseline to FU2 by 11.35 points.

Table 13: EQ-5D VAS - FAS

Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Baseline	341	10.00	62.26	17.13	95.00	
FU1	338	4.00	73.09	17.03	100.00	
FU2	336	20.00	73.88	17.32	100.00	
FU1 - Baseline	337	-62.00	10.79 [8.87; 12.70]	17.89	75.00	< 0.0001
FU2 - Baseline	335	-49.00	11.35 [9.35; 13.36]	18.65	76.00	< 0.0001

(see appendix 2.1.1 table 1.2)

Subgroup Sex (Female vs. Male):

AF-QoL Psychological Domain:

The AF-QoL psychological domain in the FAS shows an improvement by 13.39 points (baseline -> FU1) for male patients and increased by 10.27 points from baseline to FU1 for female patients, and from baseline to FU2 male patients show an increase by 17.00 points vs. 14.70 points for female patients.

Table 14: AF-QoI Psychological Domain by Sex - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Male	Baseline	196	0.00	46.43	22.87	100.00	
Male	FU1	196	0.00	59.82	21.33	100.00	
Male	FU2	196	0.00	63.43	22.37	100.00	
Female	Baseline	146	0.00	42.15	22.01	96.43	
Female	FU1	146	0.00	52.42	21.46	100.00	
Female	FU2	146	0.00	56.85	22.38	100.00	
Male	FU1 - Baseline	196	-46.43	13.39 [10.54; 16.25]	20.26	78.57	< 0.0001
Female	FU1 - Baseline	146	-46.43	10.27 [6.76; 13.79]	21.47	67.86	< 0.0001
Male	FU2 - Baseline	196	-35.71	17.00 [13.65; 20.36]	23.82	82.14	< 0.0001
Female	FU2 - Baseline	146	-46.43	14.70 [10.92; 18.48]	23.11	100.00	< 0.0001

(see appendix 2.1.1 table 2.1.2.1)

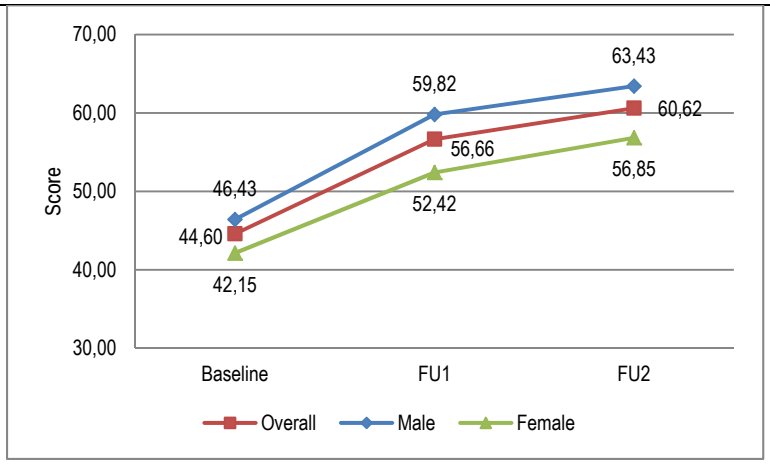


Figure 2: AF-QoI Psychological Domain Mean by Sex - FAS

AF-QoL Physical Domain:

The AF-QoL physical domain in the FASet shows an improvement by 9.45 points (baseline -> FU1) for male patients and increased by 11.54 points from baseline to FU1 for female patients, and from baseline to FU2 male patients show an increase by 10.25 points vs. 11.67 points for female patients.

Table 15: AF-QoI Physical Domain by Sex - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Male	Baseline	196	6.25	53.52	21.17	100.00	
Male	FU1	196	3.13	62.98	20.33	100.00	
Male	FU2	196	0.00	63.78	23.07	100.00	
Female	Baseline	146	0.00	44.01	22.34	100.00	
Female	FU1	146	9.38	55.54	20.03	100.00	
Female	FU2	146	6.25	55.67	24.44	100.00	
Male	FU1 - Baseline	196	-37.50	9.45 [6.89; 12.02]	18.23	62.50	< 0.0001
Female	FU1 - Baseline	146	-40.63	11.54 [8.09; 14.98]	21.06	78.13	< 0.0001
Male	FU2 - Baseline	196	-43.75	10.25 [7.23; 13.27]	21.46	78.13	< 0.0001
Female	FU2 - Baseline	146	-34.38	11.67 [7.77; 15.56]	23.80	100.00	< 0.0001

(see appendix 2.1.1 table 2.2.2.1)

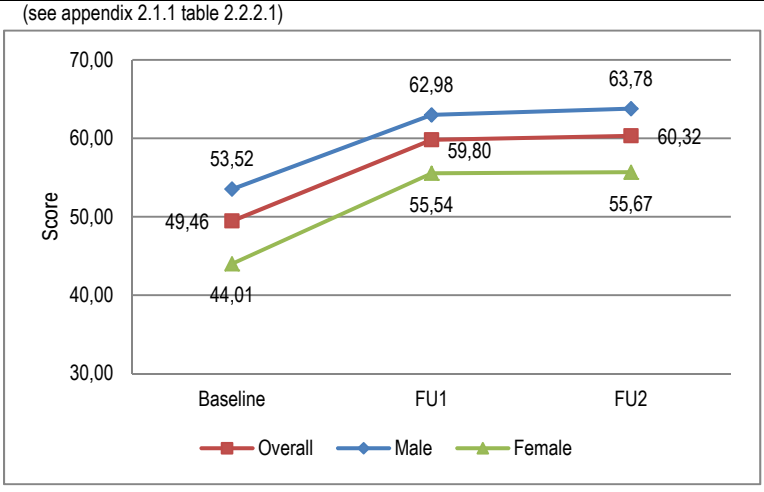


Figure 3: AF-QoI Physical Domain Mean by Sex - FAS

AF-QoL Sexual Domain:

The AF-QoL sexual domain in the FAS shows an improvement by 9.52 points (baseline -> FU1) for male patients and increased by 2.40 points from baseline to FU1 for female patients, and from baseline to FU2 male patients show an increase by 8.33 points vs. 4.17 points for female patients.

Table 16: AF-Qol Sexual Domain by Sex - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Male	Baseline	196	0.00	57.53	26.84	100.00	
Male	FU1	196	0.00	67.05	25.48	100.00	
Male	FU2	196	0.00	65.86	27.55	100.00	
Female	Baseline	146	0.00	67.58	26.34	100.00	
Female	FU1	146	0.00	69.98	23.92	100.00	
Female	FU2	146	8.33	71.75	25.09	100.00	
Male	FU1 - Baseline	196	-83.33	9.52 [6.10; 12.95]	24.30	100.00	< 0.0001
Female	FU1 - Baseline	146	-75.00	2.40 [-1.46; 6.26]	23.61	83.33	< 0.2219
Male	FU2 - Baseline	196	-91.67	8.33 [4.40; 12.26]	27.89	83.33	< 0.0001
Female	FU2 - Baseline	146	-91.67	4.17 [-0.50; 8.93]	28.50	100.00	< 0.0795

(see appendix 2.1.1 table 2.3.2.1)

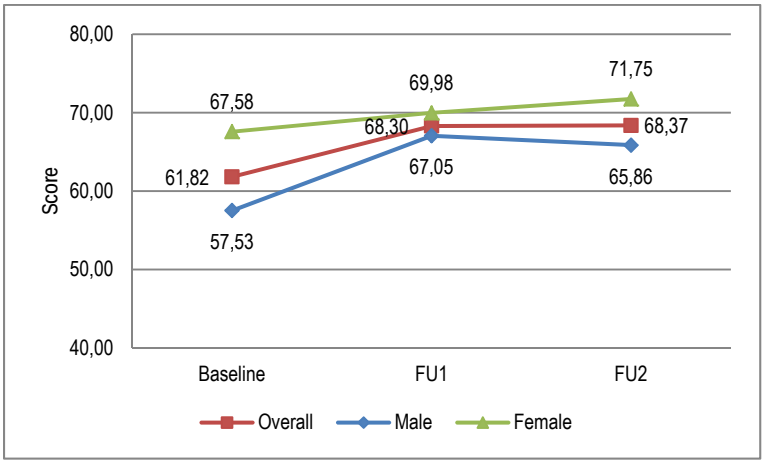


Figure 4: AF-Qol Sexual Domain Mean by Sex - FAS

In the psychological and sexual domain of AF-QoL, male patients show a stronger improvement than female patients, whereas in the physical domain of AF-QoL female patients show a stronger increase than male patients.

In the FAS the patients self assessment of health status EQ-5D VAS improved by 9.78 points (baseline -> FU1) for male patients vs. 12.18 for female patients, and from baseline to FU2 male patients show an increase by 11.45 points vs. 11.21 points for female patients.

Table 17: EQ-5D VAS by Sex - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Male	Baseline	196	10.00	63.71	16.39	92.00	
Male	FU1	196	4.00	73.49	17.27	99.00	
Male	FU2	194	20.00	75.35	16.68	100.00	
Female	Baseline	145	10.00	60.30	17.95	95.00	
Female	FU1	142	25.00	72.52	16.75	100.00	
Female	FU2	142	20.00	71.87	18.01	100.00	
Male	FU1 - Baseline	196	-62.00	9.78 [7.33; 12.23]	17.39	67.00	< 0.0001
Female	FU1 - Baseline	141	-40.00	12.18 [9.10; 15.27]	18.54	75.00	< 0.0001
Male	FU2 - Baseline	194	-49.00	11.45 [8.88; 14.03]	18.20	65.00	< 0.0001
Female	FU2 - Baseline	141	-39.00	11.21 [8.00; 14.43]	19.32	76.00	< 0.0001

(see appendix 2.1.1 table 1.2.1)

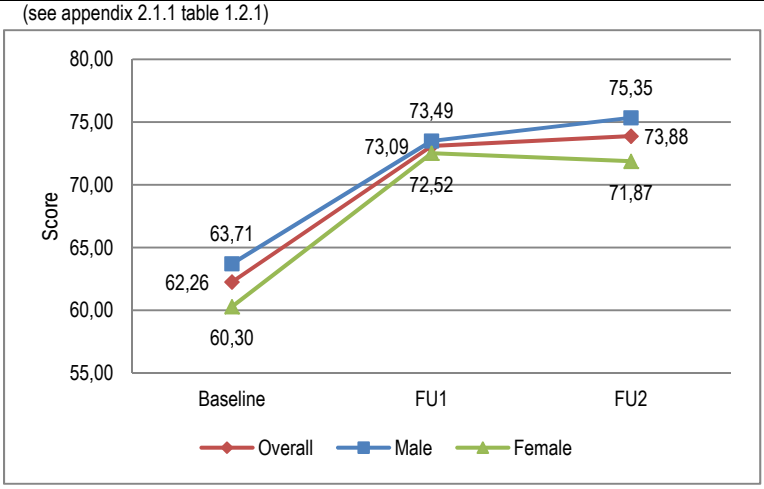


Figure 5: EQ-5D VAS Mean by Sex - FAS

Subgroup AF-Type (Paroxsysmal vs. Persisting):

AF-QoL Psychological Domain:

The AF-QoL pychological domain in the FAS shows an improvement by 11.70 points (baseline -> FU1) for patients with paroxsysmal AF and increased by 13.62 points from baseline to FU1 for patients with persisting AF, and from baseline to FU2 patients with paroxsysmal AFshow an increase by 16.16 points vs. 16.25 points for patients with persisting AF.

Table 18: AF-QoI Psychological Domain by AF-Type - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Paroxysmal	Baseline	244	0.00	45.62	22.72	100.00	
Paroxysmal	FU1	244	0.00	57.32	21.96	100.00	
Paroxysmal	FU2	244	0.00	61.78	22.39	100.00	
Persisting	Baseline	91	0.00	41.60	21.71	100.00	
Persisting	FU1	91	3.57	55.22	20.94	100.00	
Persisting	FU2	91	0.00	57.85	23.44	100.00	
Paroxysmal	FU1 - Baseline	244	-46.43	11.69 [8.92; 14.47]	22.02	78.57	< 0.0001
Persisting	FU1 - Baseline	91	-25.00	13.62 [9.97; 17.27]	17.51	57.14	< 0.0001
Paroxysmal	FU2 - Baseline	244	-46.43	16.16 [13.15; 19.16]	23.83	100.00	< 0.0001
Persisting	FU2 - Baseline	91	-42.86	16.25 [11.45; 21.05]	23.06	75.00	< 0.0001

(see appendix 2.1.1 table 2.1.2.2)

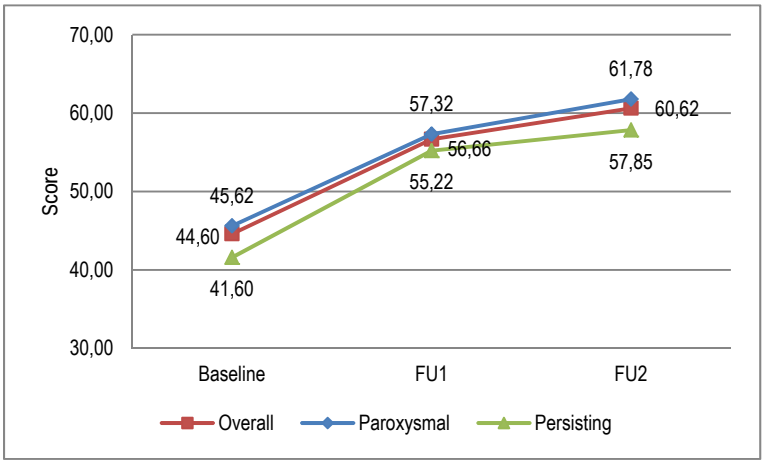


Figure 6: AF-QoI Psychological Domain Mean by AF-Type - FAS

AF-QoL Physical Domain:

The AF-QoL physical domain in the FAS shows an improvement by 9.34 points (baseline -> FU1) for patients with paroxsysmal AF and increased by 12.74 points from baseline to FU1 for patients with persisting AF, and from baseline to FU2 patients with paroxsysmal AF show an increase by 10.51 points vs. 11.57 points for patients with persisting AF.

Table 19: AF-QoI Physical Domain by AF-Type - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Paroxysmal	Baseline	244	0.00	51.09	22.36	100.00	
Paroxysmal	FU1	244	12.50	60.43	20.51	100.00	
Paroxysmal	FU2	244	0.00	61.60	23.89	100.00	
Persisting	Baseline	91	6.25	45.50	20.75	100.00	
Persisting	FU1	91	3.13	58.24	20.51	100.00	
Persisting	FU2	91	3.13	57.07	24.29	100.00	
Paroxysmal	FU1 - Baseline	244	-40.63	9.34 [6.80; 11.87]	20.10	78.13	< 0.0001
Persisting	FU1 - Baseline	91	-21.88	12.74 [9.06; 16.42]	17.69	62.50	< 0.0001
Paroxysmal	FU2 - Baseline	244	-43.75	10.51 [7.58; 13.45]	23.24	100.00	< 0.0001
Persisting	FU2 - Baseline	91	-37.50	11.57 [7.33; 15.82]	20.38	68.75	< 0.0001

(see appendix 2.1.1 table 2.2.2.2)

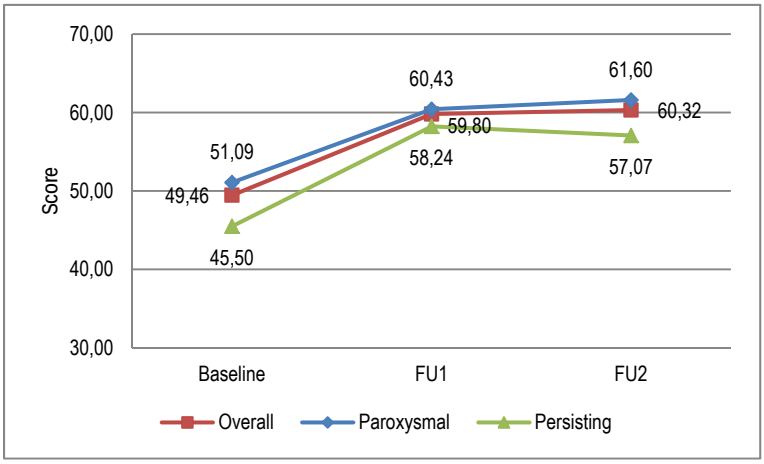


Figure 7: AF-QoI Physical Domain Mean by AF-Type - FAS

AF-QoL Sexual Domain:

The AF-QoL sexual domain in the FAS shows an improvement by 7.45 points (baseline -> FU1) for patients with paroxsysmal AF and increased by 4.95 points from baseline to FU1 for patients with persisting AF, and from baseline to FU2 patients with paroxsysmal AFshow an increase by 7.41 points vs. 4.85 points for patients with persisting AF.

Table 20: AF-QoI Sexual Domain by AF-Type - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95%]	SD	Max	p-Value
Paroxysmal	Baseline	244	0.00	62.67	27.65	100.00	
Paroxysmal	FU1	244	0.00	70.12	23.35	100.00	
Paroxysmal	FU2	244	0.00	70.08	25.83	100.00	
Persisting	Baseline	91	0.00	59.71	25.41	100.00	
Persisting	FU1	91	0.00	64.65	27.68	100.00	
Persisting	FU2	91	0.00	64.56	28.21	100.00	
Paroxysmal	FU1 - Baseline	244	-83.33	7.45 [4.28; 10.61]	25.09	100.00	< 0.0001
Persisting	FU1 - Baseline	91	-66.67	4.95 [0.40; 9.49]	21.84	50.00	< 0.0334
Paroxysmal	FU2 - Baseline	244	-91.67	7.41 [3.68; 11.14]	29.56	100.00	< 0.0001
Persisting	FU2 - Baseline	91	-91.67	4.85 [-0.21; 9.92]	24.31	66.67	< 0.0601

(see appendix 2.1.1 table 2.3.2.2)

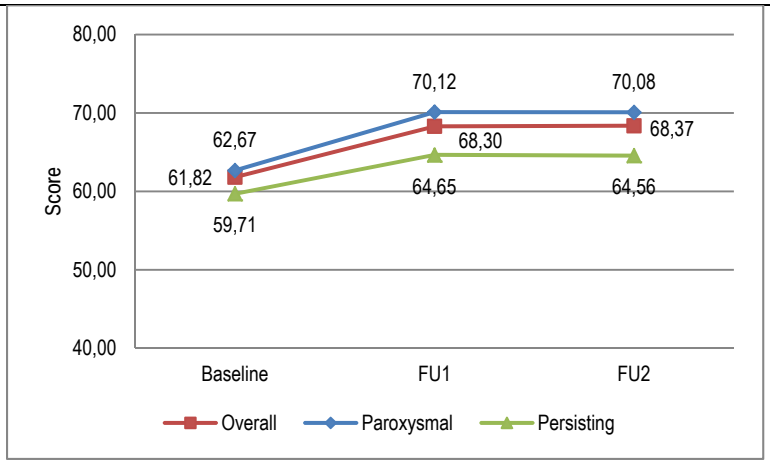


Figure 8: AF-Qol Sexual Domain Mean by AF-Type - FAS

In the psychological and physical domain of AF-QoL, patients with persisting AF show a stronger improvement than patients with paroxysmal AF, whereas in the sexual Domain of AF-QoL patients with paroxsysmal AF show a stronger increase than patients with persisting AF.

In the FAS the patients self assessment of health status EQ-5D VAS improved by 10.68 points (baseline -> FU1) for patients with paroxsysmal AF vs. 11.42 points for patients with persisting AF, and from baseline to FU2 patients with paroxsysmal AF show an increase by 10.42 points vs. 13.79 points for patients with persisting AF.

Table 21: EQ-5D VAS by AF-Type - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Paroxysmal	Baseline	243	19.00	62.01	16.88	95.00	
Paroxysmal	FU1	241	4.00	72.78	17.17	100.00	
Paroxysmal	FU2	239	20.00	72.79	17.32	100.00	
Persisting	Baseline	91	10.00	62.80	17.87	92.00	
Persisting	FU1	90	30.00	74.10	16.89	99.00	
Persisting	FU2	90	20.00	76.63	17.09	100.00	
Paroxysmal	FU1 - Baseline	240	-62.00	10.68 [8.38; 12.97]	18.07	75.00	< 0.0001
Persisting	FU1 - Baseline	90	-50.00	11.42 [7.73; 15.11]	17.61	67.00	< 0.0001
Paroxysmal	FU2 - Baseline	238	-40.00	10.42 [7.99; 12.86]	19.07	76.00	< 0.0001
Persisting	FU2 - Baseline	90	-49.00	13.79 [10.07; 17.51]	17.77	65.00	< 0.0001

(see appendix 2.1.1 table 1.2.2)

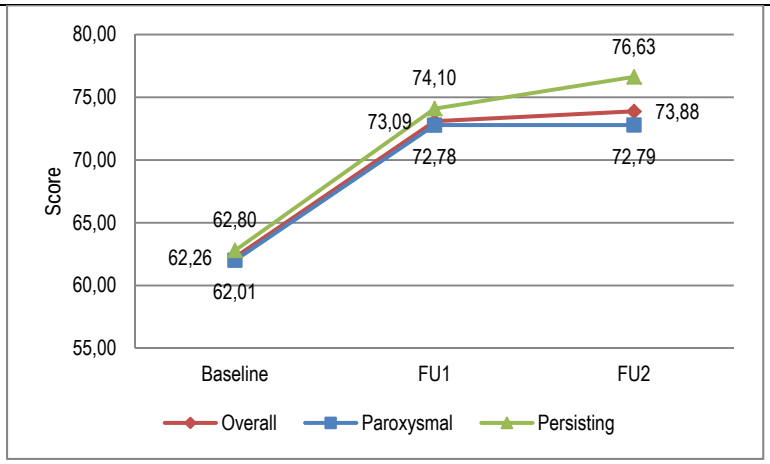


Figure 9: EQ-5D VAS Mean by AF-Type - FAS

Other analyses:

Secondary Effectiveness Variables

In order to analyze outcomes, SF-12 is a practical, reliable and valid measure of physical and mental health.

SF-12 Physical Summary Scale:

In the ES the SF-12 physical summary scale (German weights) improved by 3.62 points from baseline to FU1 and increased by 3.88 points from baseline to FU2.

This SF-12 physical summary scale (German weights) increased by 4.02 points from baseline to FU1 and improved by 4.34 points from baseline to FU2 regarding the FAS.

Table 22: SF-12 Physical Summary Scale - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Overall	Baseline	321	20.02	42.31	8.60	62.32	
Overall	FU1	321	23.90	46.17	7.92	63.62	
Overall	FU2	322	19.55	46.54	9.00	64.57	
Overall	FU1 - Baseline	305	-23.08	4.02 [3.05; 4.99]	8.63	27.14	< 0.0001
Overall	FU2 - Baseline	303	-20.08	4.34 [3.29; 5.39]	9.28	29.15	< 0.0001

(see appendix 2.1.1 table 3.2.1.2)

SF-12 Mental Summary Scale:

In the ES the SF-12 mental summary scale (German weights) improved by 3.92 points from baseline to FU1 and increased by 3.79 points from baseline to FU2.

This SF-12 mental summary scale (German weights) increased by 4.43 points from baseline to FU1 and improved by 4.82 points from baseline to FU2 regarding the FAS.

Table 23: SF-12 Mental Summary Scale - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Overall	Baseline	321	13.34	43.41	11.85	66.16	
Overall	FU1	321	12.48	47.90	10.02	62.64	
Overall	FU2	322	17.39	48.10	9.75	62.77	
Overall	FU1 - Baseline	305	-28.06	4.43 [3.26; 5.59]	10.33	37.40	< 0.0001
Overall	FU2 - Baseline	303	-28.59	4.82 [3.54; 6.10]	11.32	38.27	< 0.0001

(see appendix 2.1.1 table 3.2.2.2)

SF-12 German weights mental summary scale shows a stronger increase than the SF-12 German weights physical summary scale

By calculating the figures of mean of differences (FU1 –Baseline resp. FU2 – Baseline) you have to consider that both samples (FU1 resp. Baseline) do not necessarily include the identical cases, that means differences only can be calculated of the intersection set of both

samples.

Subgroup Sex (Female vs. Male):

SF-12 Physical Summary Scale:

In the FAS the SF-12 physical summary scale (German weights) improved by 3.64 points from baseline to FU1 for male patients vs. 4.51 points for female patients, and increased by 4.20 points from baseline to FU2 for male patients and by 4.53 points for female patients.

Table 24: SF-12 Physical Summary Scale by Sex - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Male	Baseline	183	20.02	43.81	8.31	62.32	
Male	FU1	184	25.63	47.31	7.70	60.31	
Male	FU2	184	23.22	48.00	8.35	64.57	
Female	Baseline	138	22.60	40.32	8.61	58.30	
Female	FU1	137	23.90	44.63	7.98	63.62	
Female	FU2	138	19.55	44.59	9.50	64.57	
Male	FU1 - Baseline	174	-15.55	3.65 [2.44; 4.85]	8.05	27.14	< 0.0001
Female	FU1 - Baseline	131	-23.08	4.51 [2.90; 6.13]	9.36	25.36	< 0.0001
Male	FU2 - Baseline	172	-18.56	4.20 [2.83; 5.57]	9.10	28.95	< 0.0001
Female	FU2 - Baseline	131	-20.08	4.53 [2.88; 6.18]	9.55	29.15	< 0.0001

(see appendix 2.1.1 table 3.2.1.2.1)

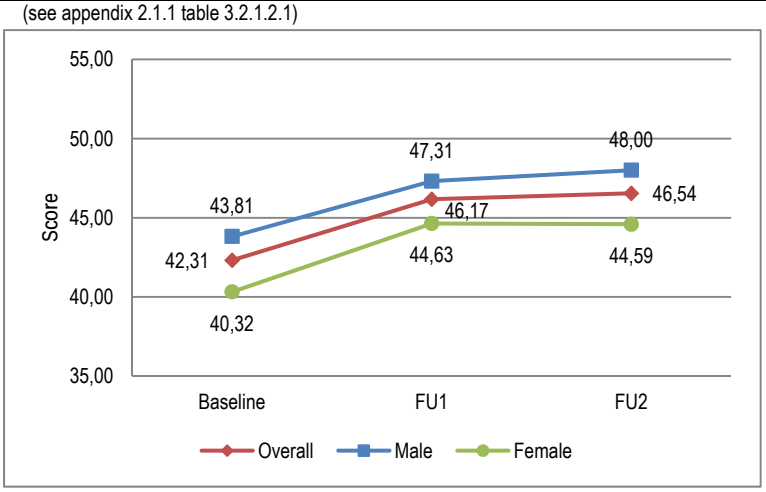


Figure 10: SF-12 Physical Summary Scale Mean by Sex - FAS

SF-12 Mental Summary Scale:

In the FAS the SF-12 mental summary scale (German weights) improved by 3.97 points from baseline to FU1 for male patients vs. 5.03 points for female patients, and increased by 4.11 points from baseline to FU2 for male patients and by 5.75 points for female patients.

Table 25: SF-12 Mental Summary Scale by Sex - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Male	Baseline	183	15.08	44.70	10.63	64.12	
Male	FU1	184	12.48	48.89	9.76	61.60	
Male	FU2	184	17.39	48.78	9.81	61.96	
Female	Baseline	138	13.34	41.70	13.14	66.16	
Female	FU1	137	19.92	46.58	10.25	62.64	
Female	FU2	138	20.14	47.20	9.62	62.77	
Male	FU1 - Baseline	174	-28.06	3.97 [2.58; 5.36]	9.30	30.19	< 0.0001
Female	FU1 - Baseline	131	-24.04	5.03 [3.03; 7.03]	11.56	37.40	< 0.0001

Male	FU2 - Baseline	172	-24.07	4.11 [2.58; 5.64]	10.18	38.27	< 0.0001
Female	FU2 - Baseline	131	-28.59	5.75 [3.57; 7.93]	12.63	37.32	< 0.0001

(see appendix 2.1.1 table 3.2.2.2.1)

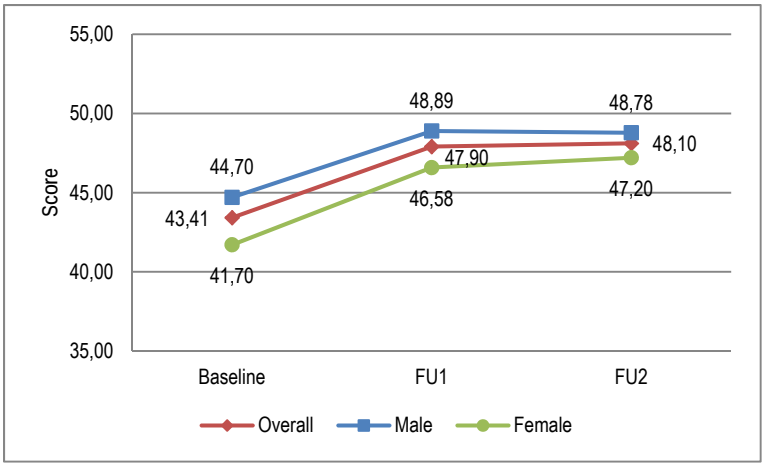


Figure 11: SF-12 Mental Summary Scale Mean by Sex - FAS

In general, female patients show a stronger improvement in the SF-12 Physical and SF-12 Mental Scale.

Subgroup AF-Type (Paroxsysmal vs. Persistent):

SF-12 Physical Summary Scale:

In the FAS the SF-12 physical summary scale (German weights) improved by 3.49 points from baseline to FU1 for patients with paroxsysmal AF vs. 5.27 points for patients with persistent AF, and increased by 4.07 points from baseline to FU2 for patients with paroxsysmal AF and by 4.85 points for patients with persistent AF.

Table 26: SF-12 Physical Summary Scale by AF-Type - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Paroxysmal	Baseline	226	22.60	43.14	8.16	58.30	
Paroxysmal	FU1	230	23.90	46.40	7.79	63.62	
Paroxysmal	FU2	230	19.55	47.07	8.92	64.57	
Persisting	Baseline	88	20.02	40.62	9.21	62.32	
Persisting	FU1	84	25.43	45.84	8.24	57.76	
Persisting	FU2	85	23.22	45.33	9.19	58.53	
Paroxysmal	FU1 - Baseline	216	-23.08	3.49 [2.34; 4.64]	8.59	25.36	< 0.0001
Persisting	FU1 - Baseline	82	-19.57	5.27 [3.33; 7.20]	8.79	27.14	< 0.0001
Paroxysmal	FU2 - Baseline	214	-18.56	4.06 [2.83; 5.30]	9.17	29.15	< 0.0001
Persisting	FU2 - Baseline	82	-20.08	4.85 [2.73; 6.97]	9.66	28.95	< 0.0001

(see appendix 2.1.1 table 3.2.1.2.2)

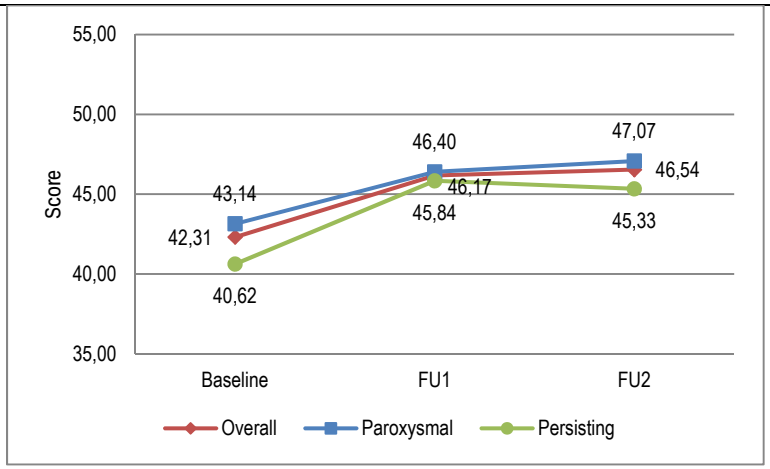


Figure 12: SF-12 Physical Summary Scale Mean by AF-Type - FAS

SF-12 Mental Summary Scale:

In the FAS the SF-12 mental summary scale (German weights) improved by 4.43 points from baseline to FU1 for patients with paroxysmal AF vs. 5.09 points for patients with persistent AF, and increased by 5.04 points from baseline to FU2 for patients with paroxysmal AF and by 4.52 points for patients with persistent AF.

Table 27: SF-12 Mental Summary Scale by AF-Type - FAS

Subgroup	Analysis Time Point / Difference	$n_{(values)}$	Min	Mean [CI 95 %]	SD	Max	p-Value
Paroxysmal	Baseline	226	13.34	43.47	12.31	66.16	
Paroxysmal	FU1	230	12.48	47.84	9.78	62.64	
Paroxysmal	FU2	230	17.39	48.20	9.76	62.77	
Persisting	Baseline	88	21.64	43.12	10.63	63.53	
Persisting	FU1	84	19.92	48.59	10.24	61.06	
Persisting	FU2	85	21.80	47.92	9.77	61.96	
Paroxysmal	FU1 - Baseline	216	-24.04	4.44 [3.02; 5.86]	10.61	37.40	< 0.0001
Persisting	FU1 - Baseline	82	-28.06	5.09 [3.01; 7.16]	9.46	29.86	< 0.0001
Paroxysmal	FU2 - Baseline	214	-28.59	5.04 [3.43; 6.66]	11.98	38.27	< 0.0001
Persisting	FU2 - Baseline	82	-17.65	4.52 [2.40; 6.64]	9.64	27.20	< 0.0001

(see appendix 2.1.1 table 3.2.2.2.2)

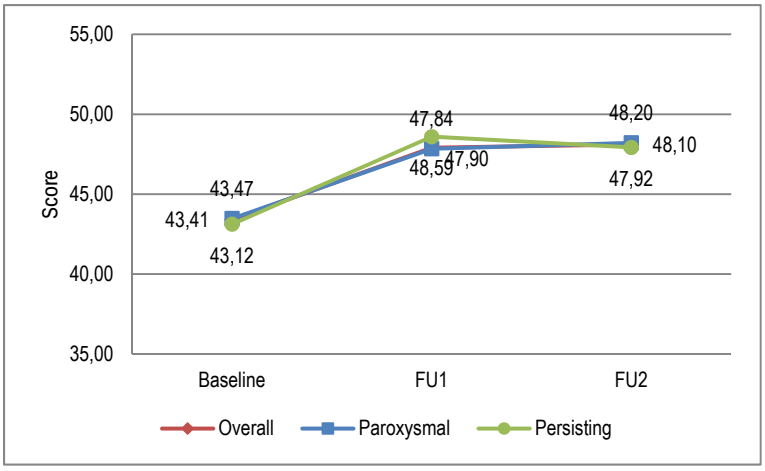


Figure 13: SF-12 Mental Summary Scale Mean by AF-Type - FAS

Patients with persistent AF show a stronger improvement in the SF-12 summary scales

(physical and mental) with one exclusion for a better outcome/increase regarding patients with paroxsysmal AF in the mental summary scale from baseline to FU2.

Table 28: ECG Findings by AF- and ECG-Type - SaS

Baseline				
AF Type	ECG Type	Rhythm	n	% of SaS patients
VHF				
Missing	RUHE EKG	VHF	7	1.3
Paroxysmal	MISSING	VHF	1	0.2
Paroxysmal	LANGZEIT EKG	ANDERER RHYTHMUS+SR PAROXYSMAL VHF	1	0.2
Paroxysmal	LANGZEIT EKG	VHF	43	7.8
Paroxysmal	LANGZEIT EKG	VHF+LOWN IVA; LOWN IIIA	1	0.2
Paroxysmal	RUHE EKG	VHF	143	26.0
Paroxysmal	RUHE EKG	VHF+VES LOWN II	1	0.2
Paroxysmal	RUHE EKG	VHF+VORHOFFLATTERN	1	0.2
Persisting	MISSING	VHF	1	0.2
Persisting	LANGZEIT EKG	VHF	11	2.0
Persisting	RUHE EKG	VHF	94	17.1
Total			304	55.4
Sinus and other rhythms				
Missing	MISSING		2	0.4
Missing	LANGZEIT EKG	ANDERER RHYTHMUS	1	0.2
Missing	RUHE EKG	ANDERER RHYTHMUS	1	0.2
Paroxysmal	MISSING		2	0.4
Paroxysmal	LANGZEIT EKG	ANDERER RHYTHMUS	15	2.7
Paroxysmal	LANGZEIT EKG	ANDERER RHYTHMUS+SR	1	0.2
Paroxysmal	LANGZEIT EKG	HV_RHYTHM+IES LOW IIIA	1	0.2
Paroxysmal	RUHE EKG		6	1.1
Paroxysmal	RUHE EKG	ANDERER RHYTHMUS	169	30.8
Paroxysmal	RUHE EKG	ANDERER RHYTHMUS+PM-STIMULATION	1	0.2
Paroxysmal	RUHE EKG	ANDERER RHYTHMUS+SINUSRHYTHMUS	4	0.7
Paroxysmal	RUHE EKG	ANDERER RHYTHMUS+SR	2	0.4
Paroxysmal	RUHE EKG	VH-FLATTERN	3	0.5
Persisting	MISSING		1	0.2
Persisting	LANGZEIT EKG		1	0.2
Persisting	LANGZEIT EKG	ANDERER RHYTHMUS	4	0.7
Persisting	RUHE EKG		1	0.2
Persisting	RUHE EKG	ANDERER RHYTHMUS	24	4.4
Persisting	RUHE EKG	ANDERER RHYTHMUS+SINUS RHYTHMUS	1	0.2
Persisting	RUHE EKG	ANDERER RHYTHMUS+SINUSRYTHMUS	1	0.2
Persisting	RUHE EKG	VH-FLATTERN	4	0.7
Total			245	44.6
Overall total			549	100.0
FU1				
AF Type	ECG Type	Rhythm	n	% of SaS patients
VHF				
Missing	RUHE EKG	SINUSRHYTHMUS+VHF PAROXYSMAL	1	0.2
Missing	RUHE EKG	VHF PERMANENT	1	0.2
Paroxysmal	MISSING	VHF PERMANENT	1	0.2
Paroxysmal	LANGZEIT EKG	SINUSRHYTHMUS+VHF PAROXYSMAL	3	0.7
Paroxysmal	LANGZEIT EKG	VHF	1	0.2
Paroxysmal	LANGZEIT EKG	VHF PAROXYSMAL	4	0.9
Paroxysmal	LANGZEIT EKG	VHF PERSISTIEREND	1	0.2
Paroxysmal	RUHE EKG	ANDERER RHYTHMUS+VHF PAROXYSMAL	3	0.7

	Paroxysmal	RUHE EKG	SINUSRHYTHMUS+VHF PAROXYSMAL	2	0.4
	Paroxysmal	RUHE EKG	VH-FLATTERN+VHF PAROXYSMAL	1	0.2
	Paroxysmal	RUHE EKG	VHF PAROXYSMAL	19	4.2
	Paroxysmal	RUHE EKG	VHF PERMANENT	5	1.1
	Paroxysmal	RUHE EKG	VHF PERSISTIEREND	7	1.5
	Persisting	MISSING	VHF LONG DUR PERSIST	1	0.2
	Persisting	MISSING	VHF PAROXYSMAL	2	0.4
	Persisting	LANGZEIT EKG	VHF LONG DUR PERSIST	1	0.2
	Persisting	LANGZEIT EKG	VHF PERSISTIEREND	3	0.7
	Persisting	RUHE EKG	SINUSRHYTHMUS+VHF PAROXYSMAL	2	0.4
	Persisting	RUHE EKG	VHF	2	0.4
	Persisting	RUHE EKG	VHF LONG DUR PERSIST	4	0.9
	Persisting	RUHE EKG	VHF PAROXYSMAL	7	1.5
	Persisting	RUHE EKG	VHF PERMANENT	7	1.5
	Persisting	RUHE EKG	VHF PERSISTIEREND	5	1.1
	Total			83	18.2
			Sinus rhythm		
	Missing	RUHE EKG	SINUSRHYTHMUS	6	1.3
	Paroxysmal	MISSING	SINUSRHYTHMUS	1	0.2
	Paroxysmal	LANGZEIT EKG	SINUSRHYTHMUS	28	6.1
	Paroxysmal	RUHE EKG	SINUSRHYTHMUS	218	47.7
	Persisting	LANGZEIT EKG	SINUSRHYTHMUS	9	2.0
	Persisting	RUHE EKG	SINUSRHYTHMUS	59	12.9
	Total			321	70.2
			Other rhythm		
	Paroxysmal	MISSING		27	5.9
	Paroxysmal	LANGZEIT EKG	VH-FLATTERN	1	0.2
	Paroxysmal	RUHE EKG		2	0.4
	Paroxysmal	RUHE EKG	ANDERER RHYTHMUS	3	0.7
	Paroxysmal	RUHE EKG	VH-FLATTERN	1	0.2
	Persisting	MISSING		19	4.2
	Total			53	11.6
	Overall total			457	100.0
			FU2		
	AF Type	ECG Type	Rhythm	n	% of SaS patients
			VHF		
	Missing	RUHE EKG	VHF	1	0.3
	Paroxysmal	MISSING	VHF PAROXYSMAL	1	0.3
	Paroxysmal	LANGZEIT EKG	ANDERER RHYTHMUS+VHF PERMANENT	1	0.3
	Paroxysmal	LANGZEIT EKG	SINUSRHYTHMUS+VHF PAROXYSMAL	4	1.0
	Paroxysmal	LANGZEIT EKG	VHF	2	0.5
	Paroxysmal	LANGZEIT EKG	VHF LONG DUR PERSIST	1	0.3
	Paroxysmal	LANGZEIT EKG	VHF PAROXYSMAL	2	0.5
	Paroxysmal	LANGZEIT EKG	VHF PERMANENT	2	0.5
	Paroxysmal	RUHE EKG	ANDERER RHYTHMUS+VHF	1	0.3
	Paroxysmal	RUHE EKG	SINUSRHYTHMUS+VHF PAROXYSMAL	4	1.0
	Paroxysmal	RUHE EKG	VHF	2	0.5
	Paroxysmal	RUHE EKG	VHF PAROXYSMAL	11	2.8
	Paroxysmal	RUHE EKG	VHF PERMANENT	10	2.5
	Paroxysmal	RUHE EKG	VHF PERSISTIEREND	9	2.3
	Persisting	MISSING	VHF LONG DUR PERSIST	1	0.3
	Persisting	MISSING	VHF PERMANENT	2	0.5
	Persisting	LANGZEIT EKG	VHF	1	0.3
	Persisting	LANGZEIT EKG	VHF PAROXYSMAL	4	1.0
	Persisting	LANGZEIT EKG	VHF PERMANENT	1	0.3

Persisting	RUHE EKG	VHF	1	0.3
Persisting	RUHE EKG	VHF LONG DUR PERSIST	1	0.3
Persisting	RUHE EKG	VHF PAROXYSMAL	7	1.8
Persisting	RUHE EKG	VHF PERMANENT	3	0.8
Persisting	RUHE EKG	VHF PERSISTIEREND	4	1.0
Total			76	19.2
		Sinus rhythm		
Missing	RUHE EKG	SINUSRHYTHMUS	4	1.0
Paroxysmal	MISSING	SINUSRHYTHMUS	1	0.3
Paroxysmal	LANGZEIT EKG	SINUSRHYTHMUS	27	6.8
Paroxysmal	RUHE EKG	SINUSRHYTHMUS	191	48.4
Persisting	MISSING	SINUSRHYTHMUS	1	0.3
Persisting	LANGZEIT EKG	SINUSRHYTHMUS	5	1.3
Persisting	RUHE EKG	SINUSRHYTHMUS	51	12.9
Total			280	70.9
		Other rhythm		
Missing	RUHE EKG	ANDERER RHYTHMUS	1	0.3
Paroxysmal	MISSING		20	5.1
Paroxysmal	RUHE EKG	ANDERER RHYTHMUS	4	1.0
Persisting	MISSING		14	3.5
Total			39	9.9
Overall total			395	100.0

(see appendix 2.1.1 table 4.1)

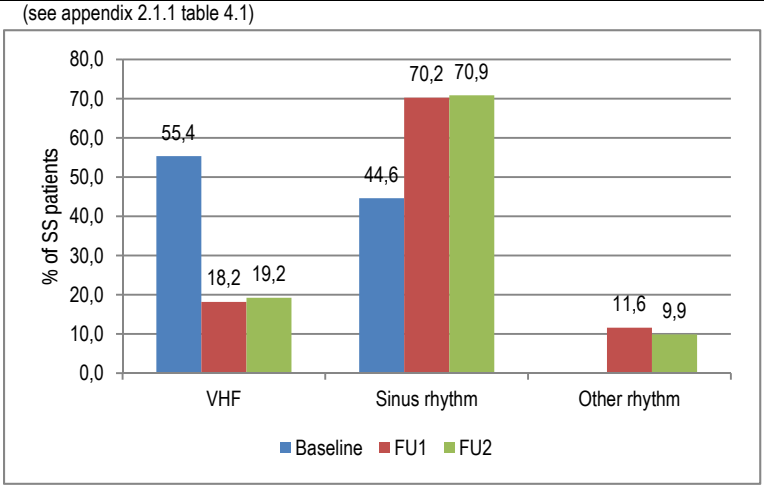


Figure 14: ECG Findings by AF- and ECG-Type - SaS

In appendix 2.1.1 table 4.2 the course of ECG outcomes throughout the 4 documentation time points is shown. In table 29 all patients that did not show an improvement under Dronedarone therapy according to ECG results are listed.

Table 29: ECG Findings by AF-Type and Analysis Time Point- SaS

AF Type	Trajectory	n	% of SaS patients
Missing	ANDERER RHYTHMUS->MISSING->VHF PERMANENT->ANDERER RHYTHMUS	1	0.18
Paroxysmal	ANDERER RHYTHMUS+PM-STIMULATION->ANDERER RHYTHMUS->MISSING->VHF PERMANENT	1	0.18
Paroxysmal	ANDERER RHYTHMUS->ANDERER RHYTHMUS->SINUSRHYTHMUS->VHF PERMANENT	1	0.18
Paroxysmal	ANDERER RHYTHMUS->MISSING->ANDERER RHYTHMUS+VHF PAROXYSMAL->VHF PERMANENT	1	0.18
Paroxysmal	ANDERER RHYTHMUS->MISSING->SINUSRHYTHMUS->VHF PERMANENT	1	0.18
Paroxysmal	ANDERER RHYTHMUS->MISSING->VHF PERMANENT->VHF	1	0.18

		PERMANENT		
	Paroxysmal	ANDERER RHYTHMUS->SINUSRHYTHMUS->SINUSRHYTHMUS->VHF PERMANENT	1	0.18
	Paroxysmal	ANDERER RHYTHMUS->SINUSRHYTHMUS->VHF PAROXYSMAL->VHF PERMANENT	1	0.18
	Paroxysmal	ANDERER RHYTHMUS->SINUSRHYTHMUS->VHF PERSISTIEREND->VHF PERMANENT	1	0.18
	Paroxysmal	VHF+VES LOWN II->VHF->VHF PAROXYSMAL->ANDERER RHYTHMUS+VHF PERMANENT	1	0.18
	Paroxysmal	VHF->ANDERER RHYTHMUS->VHF PERMANENT->MISSING	1	0.18
	Paroxysmal	VHF->MISSING->MISSING->VHF PERSISTIEREND	3	0.55
	Paroxysmal	VHF->MISSING->SINUSRHYTHMUS->VHF PERMANENT	1	0.18
	Paroxysmal	VHF->MISSING->SINUSRHYTHMUS->VHF PERSISTIEREND	1	0.18
	Paroxysmal	VHF->MISSING->VHF PERMANENT->MISSING	1	0.18
	Paroxysmal	VHF->MISSING->VHF PERMANENT->SINUSRHYTHMUS	1	0.18
	Paroxysmal	VHF->MISSING->VHF PERSISTIEREND->MISSING	1	0.18
	Paroxysmal	VHF->MISSING->VHF PERSISTIEREND->VHF PERMANENT	1	0.18
	Paroxysmal	VHF->SINUSRHYTHMUS->SINUSRHYTHMUS+VHF PAROXYSMAL->VHF PERMANENT	1	0.18
	Paroxysmal	VHF->SINUSRHYTHMUS->SINUSRHYTHMUS->VHF LONG DUR PERSIST	1	0.18
	Paroxysmal	VHF->SINUSRHYTHMUS->SINUSRHYTHMUS->VHF PERSISTIEREND	3	0.55
	Paroxysmal	VHF->SINUSRHYTHMUS->VHF PERMANENT->VHF PERMANENT	1	0.18
	Paroxysmal	VHF->SINUSRHYTHMUS->VHF PERSISTIEREND->MISSING	1	0.18
	Paroxysmal	VHF->VH-FLATTERN->VH-FLATTERN->VHF PERSISTIEREND	1	0.18
	Paroxysmal	VHF->VHF->VHF PERMANENT->SINUSRHYTHMUS	1	0.18
	Paroxysmal	VHF->VHF->VHF PERSISTIEREND->MISSING	3	0.55
	Paroxysmal	VHF->VHF->VHF PERSISTIEREND->VHF PERSISTIEREND	1	0.18
	Persisting	ANDERER RHYTHMUS->SINUSRHYTHMUS->VHF PERMANENT->VHF PERMANENT	1	0.18
	Persisting	ANDERER RHYTHMUS->SINUSRHYTHMUS->VHF PERSISTIEREND->MISSING	1	0.18
	Persisting	VHF->MISSING->SINUSRHYTHMUS->VHF PERMANENT	1	0.18
	Persisting	VHF->MISSING->SINUSRHYTHMUS->VHF PERSISTIEREND	1	0.18
	Persisting	VHF->MISSING->VHF LONG DUR PERSIST->MISSING	2	0.36
	Persisting	VHF->MISSING->VHF LONG DUR PERSIST->VHF PAROXYSMAL	1	0.18
	Persisting	VHF->MISSING->VHF PERMANENT->MISSING	3	0.55
	Persisting	VHF->MISSING->VHF PERMANENT->VHF PAROXYSMAL	2	0.36
	Persisting	VHF->MISSING->VHF PERSISTIEREND->MISSING	3	0.55
	Persisting	VHF->SINUSRHYTHMUS->SINUSRHYTHMUS->VHF PERSISTIEREND	2	0.36
	Persisting	VHF->SINUSRHYTHMUS->VHF LONG DUR PERSIST->SINUSRHYTHMUS	1	0.18
	Persisting	VHF->SINUSRHYTHMUS->VHF PAROXYSMAL->VHF LONG DUR PERSIST	1	0.18
	Persisting	VHF->SINUSRHYTHMUS->VHF PAROXYSMAL->VHF PERMANENT	1	0.18
	Persisting	VHF->SINUSRHYTHMUS->VHF PERSISTIEREND->SINUSRHYTHMUS	1	0.18
	Persisting	VHF->SINUSRHYTHMUS->VHF PERSISTIEREND->VHF PERMANENT	1	0.18
	Persisting	VHF->VHF->MISSING->VHF LONG DUR PERSIST	1	0.18
	Persisting	VHF->VHF->MISSING->VHF PERSISTIEREND	1	0.18
	Persisting	VHF->VHF->SINUSRHYTHMUS+VHF PAROXYSMAL->VHF PERMANENT	1	0.18
	Persisting	VHF->VHF->VHF PAROXYSMAL->VHF PERMANENT	1	0.18
	Persisting	VHF->VHF->VHF PERMANENT->MISSING	1	0.18
	Persisting	VHF->VHF->VHF PERSISTIEREND->MISSING	2	0.36
	Total		62	11.29
	(see appendix 2.1.1 table 4.2)			

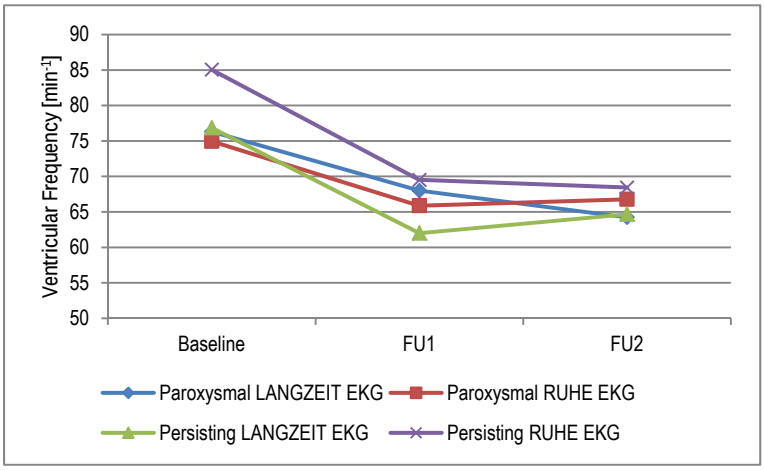


Figure 15: Ventricular Frequency Mean [min-1] by ECG-, AF-Type and Analysis Time Point- SaS

Table 30: Ventricular Frequency [min-1] by ECG-, AF-Type and Analysis Time Point- SaS

Analysis Time Point / Difference	AF Type	ECG_TYPE	n(values)	Min	Mean	SD	Max
Baseline	Missing	RUHE EKG	5	45	80.8	24.82	109
Baseline	Paroxysmal	MISSING	1	64	64		64
Baseline	Paroxysmal	LANGZEIT EKG	36	48	76.31	21.05	159
Baseline	Paroxysmal	RUHE EKG	301	42	74.95	21.17	151
Baseline	Persisting	MISSING	1	91	91		91
Baseline	Persisting	LANGZEIT EKG	7	62	76.86	11.82	96
Baseline	Persisting	RUHE EKG	103	47	85.05	25.19	180
ELAB3	Missing	RUHE EKG	3	54	61.67	11.59	75
ELAB3	Paroxysmal	MISSING	2	60	60	0	60
ELAB3	Paroxysmal	LANGZEIT EKG	28	57	70.54	11.4	105
ELAB3	Paroxysmal	RUHE EKG	182	42	65.85	12.9	159
ELAB3	Persisting	MISSING	1	63	63		63
ELAB3	Persisting	LANGZEIT EKG	4	50	73	29.42	116
ELAB3	Persisting	RUHE EKG	66	47	68	13.72	118
FU1	Missing	RUHE EKG	8	49	62.75	7.57	71
FU1	Paroxysmal	MISSING	2	74	77	4.24	80
FU1	Paroxysmal	LANGZEIT EKG	25	52	68	10.61	90
FU1	Paroxysmal	RUHE EKG	257	40	65.86	13.45	130
FU1	Persisting	MISSING	3	72	83.33	11.02	94
FU1	Persisting	LANGZEIT EKG	5	56	62	7.87	74
FU1	Persisting	RUHE EKG	81	43	69.51	14.69	120
FU2	Missing	RUHE EKG	6	50	68	11.51	81
FU2	Paroxysmal	MISSING	2	55	85	42.43	115
FU2	Paroxysmal	LANGZEIT EKG	29	46	64.24	11.62	95
FU2	Paroxysmal	RUHE EKG	219	39	66.77	11.81	120
FU2	Persisting	MISSING	2	55	80	35.36	105
FU2	Persisting	LANGZEIT EKG	6	49	64.67	15.21	90
FU2	Persisting	RUHE EKG	63	45	68.43	11.94	109
ELAB3 - Baseline	Missing	RUHE EKG	2	-43	-32	15.56	-21
FU1 - Baseline	Missing	RUHE EKG	5	-42	-18.6	24.12	16
FU2 - Baseline	Missing	RUHE EKG	3	-49	-18.33	38.59	25
ELAB3 - Baseline	Paroxysmal	LANGZEIT EKG	9	-32	-4.78	14.2	16
FU1 - Baseline	Paroxysmal	LANGZEIT EKG	7	-29	-6.14	14.94	16
FU2 - Baseline	Paroxysmal	LANGZEIT EKG	9	-21	-4.56	11.84	11
ELAB3 - Baseline	Paroxysmal	RUHE EKG	136	-86	-10.29	21.34	28

FU1 - Baseline	Paroxysmal	RUHE EKG	201	-89	-9.49	20.17	44
FU2 - Baseline	Paroxysmal	RUHE EKG	172	-90	-7.09	18.47	51
ELAB3 - Baseline	Persisting	RUHE EKG	47	-132	-20.55	26.78	15
FU1 - Baseline	Persisting	RUHE EKG	60	-127	-15.57	30.36	59
FU2 - Baseline	Persisting	RUHE EKG	47	-132	-18.17	26.51	15

(see appendix 2.1.1 table 4.3.1)

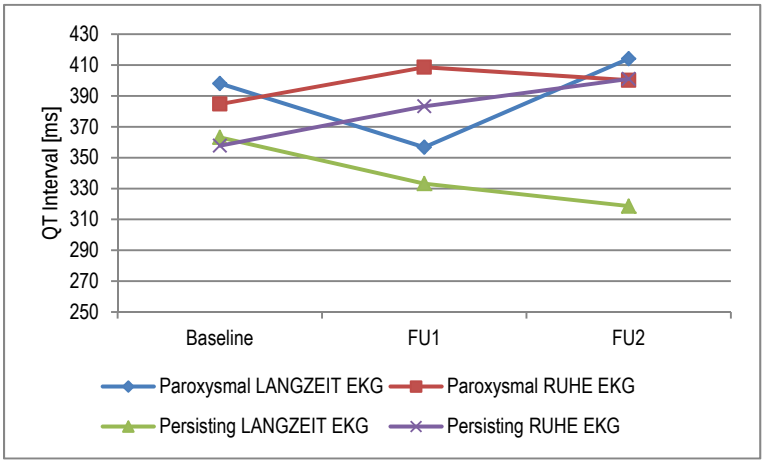


Figure 16: QT-Interval Mean [ms] by ECG-, AF-Type and Analysis Time Point- SaS

Table 31: QT-Interval [ms] by ECG-, AF-Type and Analysis Time Point- SaS

Analysis Time Point / Difference	AF Type	ECG_TYPE	$n_{(values)}$	Min	Mean	SD	Max
Baseline	Missing	RUHE EKG	7	0	369.14	166.41	496
Baseline	Paroxysmal	LANGZEIT EKG	41	34	398.05	72.72	546
Baseline	Paroxysmal	RUHE EKG	276	29	384.72	80.29	520
Baseline	Persisting	MISSING	1	400	400		400
Baseline	Persisting	LANGZEIT EKG	11	288	363.18	82.59	568
Baseline	Persisting	RUHE EKG	105	30	357.75	93.12	488
ELAB3	Missing	RUHE EKG	3	0	273.33	238.61	440
ELAB3	Paroxysmal	MISSING	1	460	460		460
ELAB3	Paroxysmal	LANGZEIT EKG	25	32	361.68	128.68	508
ELAB3	Paroxysmal	RUHE EKG	167	0	401.84	79.48	517
ELAB3	Persisting	MISSING	1	400	400		400
ELAB3	Persisting	LANGZEIT EKG	3	360	453.67	90.67	541
ELAB3	Persisting	RUHE EKG	62	40	394.79	82.13	515
FU1	Missing	RUHE EKG	7	0	356.14	160.41	460
FU1	Paroxysmal	MISSING	1	416	416		416
FU1	Paroxysmal	LANGZEIT EKG	20	29	356.75	124.75	508
FU1	Paroxysmal	RUHE EKG	218	0	408.59	77.96	620
FU1	Persisting	MISSING	3	346	373.67	24.09	390
FU1	Persisting	LANGZEIT EKG	5	42	333.2	169.33	448
FU1	Persisting	RUHE EKG	76	30	383.29	98.04	502
FU2	Missing	RUHE EKG	4	380	408.75	22.97	434
FU2	Paroxysmal	MISSING	1	451	451		451
FU2	Paroxysmal	LANGZEIT EKG	22	340	414.09	41.83	501
FU2	Paroxysmal	RUHE EKG	178	0	400.14	83.98	521
FU2	Persisting	MISSING	2	416	418	2.83	420
FU2	Persisting	LANGZEIT EKG	5	69	318.6	140.06	396
FU2	Persisting	RUHE EKG	55	37	401.02	61.38	474
ELAB3 - Baseline	Missing	RUHE EKG	3	-447	-149	258.27	10
FU1 - Baseline	Missing	RUHE EKG	6	-447	-25	258.21	366
FU2 - Baseline	Missing	RUHE EKG	4	-78	75.5	220.58	403

ELAB3 - Baseline	Paroxysmal	LANGZEIT EKG	11	-160	-6.55	51.88	26
FU1 - Baseline	Paroxysmal	LANGZEIT EKG	7	-39	6.29	23.33	28
FU2 - Baseline	Paroxysmal	LANGZEIT EKG	6	-36	-0.5	18.39	15
ELAB3 - Baseline	Paroxysmal	RUHE EKG	136	-114	22.77	51.07	344
FU1 - Baseline	Paroxysmal	RUHE EKG	169	-392	17.04	58.96	272
FU2 - Baseline	Paroxysmal	RUHE EKG	136	-320	14.3	61.88	366
ELAB3 - Baseline	Persisting	LANGZEIT EKG	1	20	20		20
FU1 - Baseline	Persisting	LANGZEIT EKG	1	128	128		128
FU2 - Baseline	Persisting	LANGZEIT EKG	1	-219	-219		-219
ELAB3 - Baseline	Persisting	RUHE EKG	48	-206	31.6	67.71	284
FU1 - Baseline	Persisting	RUHE EKG	60	-362	13.17	87.5	184
FU2 - Baseline	Persisting	RUHE EKG	43	-50	29.42	50.85	190

(see appendix 2.1.1 table 4.1.1)

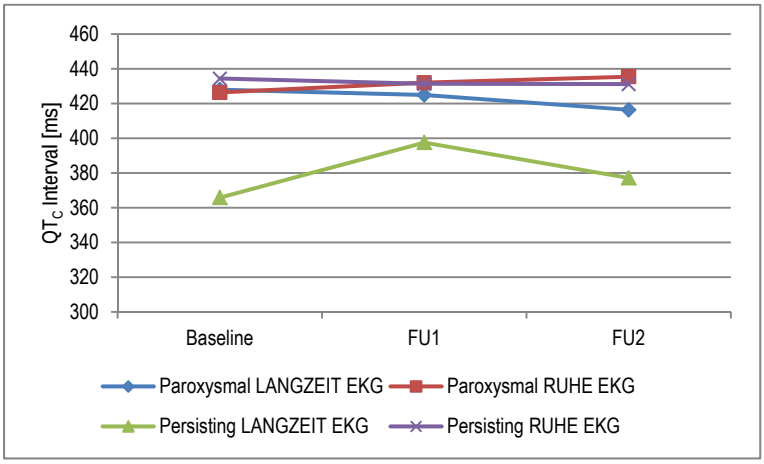


Figure 17: QT_C-Interval Mean [ms] by ECG-, AF-Type and Analysis Time Point- SaS

Table 32: QT_C-Interval [ms] by ECG-, AF-Type and Analysis Time Point- SaS

Analysis Time Point / Difference	AF Type	ECG_TYPE	$n_{(values)}$	Min	Mean	SD	Max
Baseline	Missing	LANGZEIT EKG	1	405	405		405
Baseline	Missing	RUHE EKG	1	574	574		574
Baseline	Paroxysmal	LANGZEIT EKG	21	314	427.95	38.46	484
Baseline	Paroxysmal	RUHE EKG	182	290	426.35	40.37	590
Baseline	Persisting	LANGZEIT EKG	7	52	365.86	147.4	497
Baseline	Persisting	RUHE EKG	66	349	434.39	29.37	496
ELAB3	Missing	RUHE EKG	1	0	0		0
ELAB3	Paroxysmal	MISSING	1	410	410		410
ELAB3	Paroxysmal	LANGZEIT EKG	12	340	417.33	73.98	621
ELAB3	Paroxysmal	RUHE EKG	110	0	429.73	50.28	496
ELAB3	Persisting	LANGZEIT EKG	2	335	387.5	74.25	440
ELAB3	Persisting	RUHE EKG	44	52	431.16	71.96	574
FU1	Missing	RUHE EKG	2	0	195	275.77	390
FU1	Paroxysmal	MISSING	2	195	328.5	188.8	462
FU1	Paroxysmal	LANGZEIT EKG	22	360	424.95	27.64	469
FU1	Paroxysmal	RUHE EKG	142	0	431.99	61.8	530
FU1	Persisting	MISSING	1	433	433		433
FU1	Persisting	LANGZEIT EKG	9	320	397.56	51.16	494
FU1	Persisting	RUHE EKG	52	320	431.35	32.26	530
FU2	Missing	RUHE EKG	2	450	454.5	6.36	459
FU2	Paroxysmal	MISSING	1	457	457		457
FU2	Paroxysmal	LANGZEIT EKG	20	330	416.4	36.89	470
FU2	Paroxysmal	RUHE EKG	131	316	435.46	34.51	529

FU2	Persisting	MISSING	1	405	405		405
FU2	Persisting	LANGZEIT EKG	6	295	377.17	62.52	429
FU2	Persisting	RUHE EKG	35	316	431.17	50.58	555
ELAB3 - Baseline	Missing	RUHE EKG	1	-574	-574		-574
FU1 - Baseline	Missing	RUHE EKG	1	-574	-574		-574
ELAB3 - Baseline	Paroxysmal	LANGZEIT EKG	3	-26	-7.33	17.62	9
FU1 - Baseline	Paroxysmal	LANGZEIT EKG	5	-19	-9.8	12.79	12
FU2 - Baseline	Paroxysmal	LANGZEIT EKG	5	-59	-26.8	19.42	-12
ELAB3 - Baseline	Paroxysmal	RUHE EKG	82	-99	4.49	33.12	144
FU1 - Baseline	Paroxysmal	RUHE EKG	96	-368	4.8	51.67	159
FU2 - Baseline	Paroxysmal	RUHE EKG	86	-100	5.84	39.05	175
ELAB3 - Baseline	Persisting	LANGZEIT EKG	1	10	10		10
FU1 - Baseline	Persisting	LANGZEIT EKG	2	8	9	1.41	10
FU2 - Baseline	Persisting	LANGZEIT EKG	1	-33	-33		-33
ELAB3 - Baseline	Persisting	RUHE EKG	30	-36	2.97	28.2	79
FU1 - Baseline	Persisting	RUHE EKG	37	-73	-3.51	32.19	64
FU2 - Baseline	Persisting	RUHE EKG	21	-79	-3.33	40.9	69

(see appendix 2.1.1 table 4.4.2)

Since there is no formal algorithm to calculate an European Heart Rhythm Association (EHRA) score based on the severity categories of the symptom items to be documented it was agreed with the scientific leader that only patients with EHRA symptom items in the lowest severity category are considered as “asymptomatic”. Patient with at least one symptom item of a higher severity category are considered as “symptomatic”. The results are shown in table 33 and table 34.

Table 33: EHRA Score by AF-Type and Analysis Time Point- FAS

AnalysisTime Point	AF Type	Symptomatology	n	% of Patients
Baseline	Missing	asymptomatic	1	0.29
Baseline	Paroxysmal	asymptomatic	1	0.29
Baseline	Persisting	asymptomatic	4	1.17
Baseline	Paroxysmal	not assessable	1	0.29
Baseline	Missing	symptomatic	6	1.75
Baseline	Paroxysmal	symptomatic	242	70.76
Baseline	Persisting	symptomatic	87	25.44
Total			342	100.00
FU1	Missing	asymptomatic	1	0.29
FU1	Paroxysmal	asymptomatic	23	6.73
FU1	Persisting	asymptomatic	14	4.09
FU1	Paroxysmal	not assessable	3	0.88
FU1	Persisting	not assessable	2	0.58
FU1	Missing	symptomatic	6	1.75
FU1	Paroxysmal	symptomatic	218	63.74
FU1	Persisting	symptomatic	75	21.93
Total			342	100.00
FU2	Missing	asymptomatic	2	0.58
FU2	Paroxysmal	asymptomatic	34	9.94
FU2	Persisting	asymptomatic	16	4.68
FU2	Missing	not assessable	1	0.29
FU2	Paroxysmal	not assessable	6	1.75
FU2	Persisting	not assessable	3	0.88
FU2	Missing	symptomatic	4	1.17
FU2	Paroxysmal	symptomatic	204	59.65
FU2	Persisting	symptomatic	72	21.05
Total			342	100.00

(see appendix 2.1.1 table 5.2.2)

Table 34: EHRA Score by AF-Type and Analysis Time Point- SaS

Analysis Time Point	AF Type	Symptomatology	n	% of Patients
Baseline	Missing	not assessable	2	0.36
Baseline	Missing	asymptomatic	1	0.18
Baseline	Missing	symptomatic	7	1.28
Baseline	Paroxysmal	not assessable	5	0.91
Baseline	Paroxysmal	asymptomatic	5	0.91
Baseline	Paroxysmal	symptomatic	385	70.26
Baseline	Persisting	asymptomatic	8	1.46
Baseline	Persisting	symptomatic	135	24.64
Total			548	100.00
FU1	Missing	not assessable	2	0.36
FU1	Missing	asymptomatic	1	0.18
FU1	Missing	symptomatic	7	1.28
FU1	Paroxysmal	not assessable	71	12.96
FU1	Paroxysmal	asymptomatic	32	5.84
FU1	Paroxysmal	symptomatic	292	53.28
FU1	Persisting	not assessable	25	4.56
FU1	Persisting	asymptomatic	18	3.28
FU1	Persisting	symptomatic	100	18.25
Total			548	100.00
FU2	Missing	not assessable	5	0.91
FU2	Missing	asymptomatic	1	0.18
FU2	Missing	symptomatic	4	0.73
FU2	Paroxysmal	not assessable	108	19.71
FU2	Paroxysmal	asymptomatic	39	7.12
FU2	Paroxysmal	symptomatic	248	45.26
FU2	Persisting	not assessable	49	8.94
FU2	Persisting	asymptomatic	14	2.55
FU2	Persisting	symptomatic	80	14.60
Total			548	100.00

(see appendix 2.1.1 table 5.1.2)

Table 35: EHRA Score by Categories, AF-Type and Analysis Time Point- FAS

Parameter	AF Type	Missing	Never	Rarely	Occasionally	Often
			Baseline			
Palpitation	Missing	0 (0%)	1 (14.3%)	2 (28.6%)	2 (28.6%)	2 (28.6%)
Miopia	Missing	0 (0%)	1 (14.3%)	0 (0%)	2 (28.6%)	4 (57.1%)
Fatigue	Missing	0 (0%)	1 (14.3%)	0 (0%)	4 (57.1%)	2 (28.6%)
Dizziness	Missing	0 (0%)	2 (28.6%)	3 (42.9%)	1 (14.3%)	1 (14.3%)
Pain	Missing	0 (0%)	2 (28.6%)	3 (42.9%)	1 (14.3%)	1 (14.3%)
Constriction	Missing	0 (0%)	2 (28.6%)	0 (0%)	4 (57.1%)	1 (14.3%)
Palpitation	Paroxysmal	1 (0.41%)	7 (2.87%)	131 (53.7%)	66 (27.0%)	39 (16.0%)
Miopia	Paroxysmal	1 (0.41%)	39 (16.0%)	130 (53.3%)	52 (21.3%)	22 (9.02%)
Fatigue	Paroxysmal	1 (0.41%)	56 (23.0%)	122 (50.0%)	42 (17.2%)	23 (9.43%)
Dizziness	Paroxysmal	1 (0.41%)	107 (43.9%)	109 (44.7%)	21 (8.61%)	6 (2.46%)
Pain	Paroxysmal	1 (0.41%)	127 (52.0%)	97 (39.8%)	14 (5.74%)	5 (2.05%)
Constriction	Paroxysmal	1 (0.41%)	116 (47.5%)	102 (41.8%)	20 (8.20%)	5 (2.05%)
Palpitation	Persisting	0 (0%)	9 (9.89%)	38 (41.8%)	25 (27.5%)	19 (20.9%)
Miopia	Persisting	0 (0%)	15 (16.5%)	37 (40.7%)	27 (29.7%)	12 (13.2%)
Fatigue	Persisting	0 (0%)	20 (22.0%)	47 (51.6%)	11 (12.1%)	13 (14.3%)
Dizziness	Persisting	0 (0%)	42 (46.2%)	37 (40.7%)	8 (8.79%)	4 (4.40%)
Pain	Persisting	0 (0%)	50 (54.9%)	36 (39.6%)	4 (4.40%)	1 (1.10%)
Constriction	Persisting	0 (0%)	42 (46.2%)	36 (39.6%)	11 (12.1%)	2 (2.20%)
			FU1			
Palpitation	Missing	0 (0%)	2 (28.6%)	3 (42.9%)	1 (14.3%)	1 (14.3%)

Miopia	Missing	0 (0%)	1 (14.3%)	2 (28.6%)	2 (28.6%)	2 (28.6%)
Fatigue	Missing	0 (0%)	2 (28.6%)	2 (28.6%)	3 (42.9%)	0 (0%)
Dizziness	Missing	0 (0%)	4 (57.1%)	1 (14.3%)	0 (0%)	2 (28.6%)
Pain	Missing	0 (0%)	4 (57.1%)	3 (42.9%)	0 (0%)	0 (0%)
Constriction	Missing	0 (0%)	4 (57.1%)	2 (28.6%)	1 (14.3%)	0 (0%)
Palpitation	Paroxysmal	0 (0%)	50 (20.5%)	115 (47.1%)	72 (29.5%)	7 (2.87%)
Miopia	Paroxysmal	0 (0%)	80 (32.8%)	104 (42.6%)	54 (22.1%)	6 (2.46%)
Fatigue	Paroxysmal	1 (0.41%)	80 (32.8%)	96 (39.3%)	50 (20.5%)	17 (6.97%)
Dizziness	Paroxysmal	1 (0.41%)	138 (56.6%)	76 (31.1%)	27 (11.1%)	2 (0.82%)
Pain	Paroxysmal	2 (0.82%)	161 (66.0%)	65 (26.6%)	15 (6.15%)	1 (0.41%)
Constriction	Paroxysmal	3 (1.23%)	162 (66.4%)	70 (28.7%)	8 (3.28%)	1 (0.41%)
Palpitation	Persisting	1 (1.10%)	24 (26.4%)	40 (44.0%)	23 (25.3%)	3 (3.30%)
Miopia	Persisting	1 (1.10%)	29 (31.9%)	36 (39.6%)	21 (23.1%)	4 (4.40%)
Fatigue	Persisting	1 (1.10%)	38 (41.8%)	29 (31.9%)	19 (20.9%)	4 (4.40%)
Dizziness	Persisting	2 (2.20%)	58 (63.7%)	22 (24.2%)	7 (7.69%)	2 (2.20%)
Pain	Persisting	1 (1.10%)	55 (60.4%)	32 (35.2%)	3 (3.30%)	0 (0%)
Constriction	Persisting	1 (1.10%)	55 (60.4%)	30 (33.0%)	4 (4.40%)	1 (1.10%)
			FU2			
Palpitation	Missing	1 (14.3%)	2 (28.6%)	1 (14.3%)	2 (28.6%)	1 (14.3%)
Miopia	Missing	0 (0%)	2 (28.6%)	2 (28.6%)	2 (28.6%)	1 (14.3%)
Fatigue	Missing	0 (0%)	3 (42.9%)	0 (0%)	3 (42.9%)	1 (14.3%)
Dizziness	Missing	0 (0%)	3 (42.9%)	1 (14.3%)	3 (42.9%)	0 (0%)
Pain	Missing	0 (0%)	4 (57.1%)	2 (28.6%)	0 (0%)	1 (14.3%)
Constriction	Missing	0 (0%)	5 (71.4%)	1 (14.3%)	1 (14.3%)	0 (0%)
Palpitation	Paroxysmal	2 (0.82%)	57 (23.4%)	109 (44.7%)	65 (26.6%)	11 (4.51%)
Miopia	Paroxysmal	3 (1.23%)	87 (35.7%)	91 (37.3%)	49 (20.1%)	14 (5.74%)
Fatigue	Paroxysmal	2 (0.82%)	85 (34.8%)	98 (40.2%)	38 (15.6%)	21 (8.61%)
Dizziness	Paroxysmal	4 (1.64%)	133 (54.5%)	75 (30.7%)	29 (11.9%)	3 (1.23%)
Pain	Paroxysmal	3 (1.23%)	174 (71.3%)	53 (21.7%)	13 (5.33%)	1 (0.41%)
Constriction	Paroxysmal	3 (1.23%)	168 (68.9%)	60 (24.6%)	12 (4.92%)	1 (0.41%)
Palpitation	Persisting	0 (0%)	26 (28.6%)	38 (41.8%)	23 (25.3%)	4 (4.40%)
Miopia	Persisting	0 (0%)	33 (36.3%)	31 (34.1%)	20 (22.0%)	7 (7.69%)
Fatigue	Persisting	0 (0%)	35 (38.5%)	29 (31.9%)	23 (25.3%)	4 (4.40%)
Dizziness	Persisting	3 (3.30%)	55 (60.4%)	20 (22.0%)	10 (11.0%)	3 (3.30%)
Pain	Persisting	0 (0%)	71 (78.0%)	13 (14.3%)	5 (5.49%)	2 (2.20%)
Constriction	Persisting	0 (0%)	67 (73.6%)	20 (22.0%)	3 (3.30%)	1 (1.10%)

(see appendix 2.1.1 table 5.4.2)

Physician evaluated general health

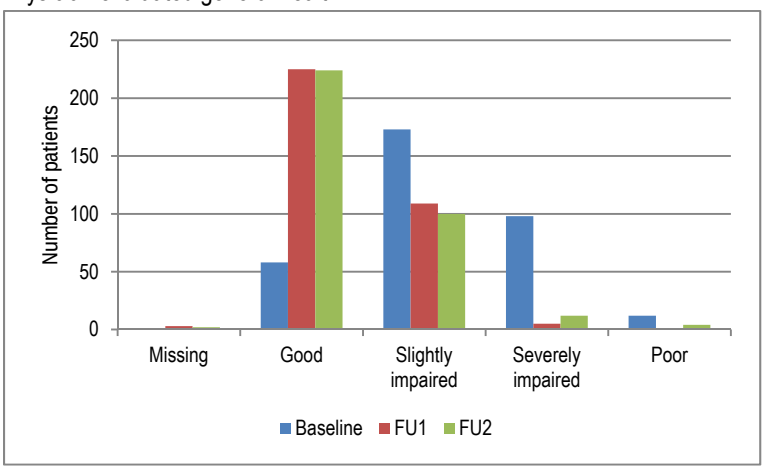


Figure 18: General Health Evaluation by Analysis Time Point- FAS

Table 36: General Health Evaluation by Analysis Time Point- SaS

Analysis time point	Missing	Good	Slightly impaired	Severely impaired	Poor
Baseline	2 (0.36%)	122 (22.22%)	274 (49.91%)	134 (24.41%)	17 (3.10%)
FU1	3 (0.66%)	287 (62.80%)	154 (33.70%)	10 (2.19%)	3 (0.66%)
FU2	3 (0.76%)	266 (67.34%)	106 (26.84%)	16 (4.05%)	4 (1.01%)

(see appendix 2.1.1 table 6.1.1)

Table 37: General Health Evaluation by Analysis Time Point- FAS

Analysis time point	Missing	Good	Slightly impaired	Severely impaired	Poor
Baseline	1 (0.29%)	58 (16.96%)	173 (50.58%)	98 (28.65%)	12 (3.51%)
FU1	3 (0.88%)	225 (65.79%)	109 (31.87%)	5 (1.46%)	
FU2	2 (0.58%)	224 (65.50%)	100 (29.24%)	12 (3.51%)	4 (1.17%)

(see appendix 2.1.1 table 6.1.3)

Table 38: General Health Evaluation by AF-Type and Analysis Time Point- SaS

Analysis time point	AF Type	Missing	Good	Slightly impaired	Severely impaired	Poor
Baseline	Missing	2 (16.67%)	3 (25.00%)	3 (25.00%)	3 (25.00%)	1 (8.33%)
Baseline	Paroxysmal	1 (0.25%)	91 (23.04%)	200 (50.63%)	90 (22.78%)	13 (3.29%)
Baseline	Persisting		28 (19.58%)	71 (49.65%)	41 (28.67%)	3 (2.10%)
FU1	Missing	2 (20.00%)	4 (40.00%)	4 (40.00%)		
FU1	Paroxysmal	69 (17.47%)	215 (54.43%)	106 (26.84%)	4 (1.01%)	1 (0.25%)
FU1	Persisting	22 (15.38%)	69 (48.25%)	44 (30.77%)	6 (4.20%)	2 (1.40%)
FU2	Missing	4 (40.00%)	4 (40.00%)	1 (10.00%)		1 (10.00%)
FU2	Paroxysmal	105 (26.58%)	196 (49.62%)	79 (20.00%)	14 (3.54%)	1 (0.25%)
FU2	Persisting	47 (32.87%)	66 (46.15%)	26 (18.18%)	2 (1.40%)	2 (1.40%)

(see appendix 2.1.1 table 6.1.2)

Table 39: General Health Evaluation by AF-Type and Analysis Time Point- FAS

Analysis time point	AF Type	Missing	Good	Slightly impaired	Severely impaired	Poor
Baseline	Missing		3 (42.86%)	1 (14.29%)	3 (42.86%)	
Baseline	Paroxysmal	1 (0.41%)	46 (18.85%)	133 (54.51%)	54 (22.13%)	10 (4.10%)
Baseline	Persisting		9 (9.89%)	39 (42.86%)	41 (45.05%)	2 (2.20%)
FU1	Missing		2 (28.57%)	5 (71.43%)		
FU1	Paroxysmal	2 (0.82%)	168 68.85%)	72 (29.51%)	2 (0.82%)	
FU1	Persisting	1 (1.10%)	55 (60.44%)	32 (35.16%)	3 (3.30%)	
FU2	Missing		4 (57.14%)	2 (28.57%)		1 (14.29%)
FU2	Paroxysmal	2 (0.82%)	163 (66.80%)	69 (28.28%)	9 (3.69%)	1 (0.41%)
FU2	Persisting		57 (62.64%)	29 (31.87%)	3 (3.30%)	2 (2.20%)

(see appendix 2.1.1 table 6.1.4)

Safety Variables

Frequency and Types of AEs

The following safety evaluations are based on the reconciled data sets provided by the Sponsor's DS Department ("line listing"[1]) and are focused on AEs and SAEs related to dronedarone treatment or another Sanofi/Wintrop or Zentiva product (adverse drug reactions (ADRs), serious adverse drug reactions (SADRs)).

Overall, 300 events[2] (related non-serious AEs and related SAEs), which occurred in 145 patients and which have been captured in the safety database and submitted to Sanofi-Aventis Deutschland GmbH by the DS Department of the CRO, were considered for analysis in this report (see appendix 2.1.4 Listing: "Related AEs / SAEs"). AEs which were unrelated, have been reviewed and analyzed with regards to safety aspects. These events were not considered for analysis in this report since a causal relationship to dronedarone treatment or another Sanofi/Wintrop or Zentiva product was denied by the reporter and Sanofi DS Department. These cases have continuously been reported to Sanofi Pharmacovigilance Department on a monthly basis and are listed in this report (see appendix 2.1.4 Listing: "Unrelated AEs /SAEs").

The relationship between the AEs and Multaq® or another Sanofi/Wintrop or Zentiva product (causality) was assessed by both, physicians (reporter) and DS Department of Sanofi-Aventis Deutschland GmbH (company).

In the opinion of the reporters, 182 events (AEs/SAEs) (of the total 300 reported events that were considered for analysis) were considered as "related" to Multaq®, 42 events were considered as "unrelated" and for 3 events the causality was "unknown". For the remaining 73 events no causality assessment has been provided by the reporters (see appendix 2.1.2).

In the opinion of the company, 281 AEs/SAEs (of the total 300 reported events that were considered for analysis) were considered as "related" to Multaq®. The remaining 19 events, which occurred in 9 patients, were considered as "unrelated" to treatment with Multaq. Out of these, 18 events were serious and 1 was non-serious (see appendix 2.1.2).

None of the reported AEs/SAEs were considered as "related" to another Sanofi/Wintrop or Zentiva product, nor by the reporters neither by the company.

In the following, only AEs/SAEs are analyzed for which a causality to therapy with Multaq® was assumed as per company assessment (related ADRs).

Related ADRs - Incidence, Severity, Causality, Outcome

The evaluation of all AE/SAE reports and case documents forwarded to Sanofi-Aventis Pharmacovigilance Department by the CRO`s DS Department showed, that 136 patients patients (25 % of all patients in the SaS) had at least one ADR causally related to Multaq® (related ADR) (table 40). Out of 281 individual ADRs recorded within this NIS a total of 165 ADRs were considered to be serious (SADR, related).

Table 40: Overview of the incidence of all ADRs related to Multaq®

Category	$n_{(Individual\ Events)}$	$n_{(patients)}$*	% of patients at risk
Any ADR	281	136	24.8
Non-serious ADRs	116	57	10.4
Serious ADRs	165	92	16.8

(see appendix 2.1.2 table 2.1)

As shown in table 41, most of the serious ADRs (SADR) occurred in the system organ class (SOC) "cardiac disorders" (94 SADRs in 80 patients), followed by "general disorders and administration site conditions" (23 SADRs in 17 patients), "investigations" (18 SADRs in 9 patients) and "respiratory, thoracic and mediastinal disorders" (11 SADRs in 8 patients). The residual SADRs are spreaded over the SOC "nervous system disorders" (7 SADRs in 7

[1] The reconciled line listing (see appendix 2) contains all ADRs and SAEs

[2] Including hidden AEs/SAEs

patients), “renal and urinary disorders” (4 SADRs in 4 patients), “gastrointestinal disorders” (3 SADRs in 3 patients) and “injury, poisoning and procedural complications” (2 ADRs in 2 patients). SADRs with the SOCs “neoplasms benign, malignant and unspecified (incl. cysts and polyps)”, “psychiatric disorders” and “vascular disorders” each occurred once.

Table 41: SADRs by Frequency according MedDRA SOC - SaS

SOC	Frequency of event	% of all SADRs
Cardiac disorders	94	57.0
General disorders and administration site conditions	23	13.9
Investigations	18	10.9
Respiratory, thoracic and mediastinal disorders	11	6.7
Nervous system disorders	7	4.2
Renal and urinary disorders	4	2.4
Gastrointestinal disorders	3	1.8
Injury, poisoning and procedural complications	2	1.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.6
Psychiatric disorders	1	0.6
Vascular disorders	1	0.6

(see appendix 2.1.2 table 3)

According to table 42, most of the non-serious ADRs occurred in the SOC “investigations” (30 ADRs in 21 patients), followed by “gastrointestinal disorders” (25 ADRs in 20 patients), “general disorders and administration site conditions” (19 ADRs in 18 patients) and “skin and subcutaneous tissue disorders” (12 ADRs in 9 patients). Other, less frequently ADRs occurred in the SOCs “nervous system disorders” (7 ADRs in 6 patients), “cardiac disorders” (6 SADRs in 6 patients), “respiratory, thoracic and mediastinal disorders” (6 ADRs in 6 patients), “psychiatric disorders” (3 ADRs in 3 patients), “metabolism and nutrition disorders” (3 ADRs in 2 patients), “musculoskeletal and connective tissue disorders” (2 ADRs in 2 patients). For the SOC “endocrine disorders”, “hepatobiliary disorders” and “immune system disorders” one ADR was reported for each.

Table 42: Non-serious ADRs by Frequency according MedDRA SOC - SaS

SOC	Frequency of event	% of all ADRs
Investigations	30	25.9
Gastrointestinal disorders	25	21.6
General disorders and administration site conditions	19	16.4
Skin and subcutaneous tissue disorders	12	10.3
Nervous system disorders	7	5.2
Cardiac disorders	6	6.0
Respiratory, thoracic and mediastinal disorders	6	5.2
Psychiatric disorders	3	2.6
Metabolism and nutrition disorders	3	2.6
Musculoskeletal and connective tissue disorders	2	1.7
Endocrine disorders	1	0.9
Hepatobiliary disorders	1	0.9
Immune system disorders	1	0.9

(see appendix 2.1.4)

In the following tables, all ADRs (281) are listed by frequency according to MedDRA Preferred Term (PT) (current version). With regard to all ADRs (165), which fulfilled the criterion “serious” (table 43), approximately the half of all SADRs (46.1%) was “atrial fibrillation”. The remaining SADRs occurred with a frequency of 4.8% (“drug ineffective”) and less.

Table 43: SADRs by frequency according to MedDRA PT Level - SaS

SADR (PT)	Frequency of event	% of all SADRs	% of Patients at risk
Atrial fibrillation	76	46.1	13.8
Drug ineffective	8	4.8	1.5
Cardiac failure	7	4.2	1.3
Dyspnoea	7	4.2	1.3
Alanine aminotransferase increased	3	1.8	0.5
Dizziness	3	1.8	0.5
Electrocardiogram QT prolonged	3	1.8	0.5
Syncope	3	1.8	0.5
Arrhythmia	2	1.2	0.4
Aspartate aminotransferase increased	2	1.2	0.4
Blood creatinine increased	2	1.2	0.4
Cardiac arrest	2	1.2	0.4
Chest discomfort	2	1.2	0.4
Condition aggravated	2	1.2	0.4
Gamma-glutamyltransferase increased	2	1.2	0.4
Ill-defined disorder	2	1.2	0.4
Interstitial lung disease	2	1.2	0.4
Left ventricular dysfunction	2	1.2	0.4
Palpitations	2	1.2	0.4
Tachyarrhythmia	2	1.2	0.4
Transaminases increased	2	1.2	0.4
Abdominal pain upper	1	0.6	0.2
Adverse event	1	0.6	0.2
Adverse reaction	1	0.6	0.2
Alveolitis	1	0.6	0.2
Anxiety	1	0.6	0.2
Bradyarrhythmia	1	0.6	0.2
Brain injury	1	0.6	0.2
Chromaturia	1	0.6	0.2
Chronic myeloid leukaemia	1	0.6	0.2
Creatinine renal clearance decreased	1	0.6	0.2
Diverticulum	1	0.6	0.2
Dyspnoea exertional	1	0.6	0.2
Fatigue	1	0.6	0.2
Feeling abnormal	1	0.6	0.2
General physical health deterioration	1	0.6	0.2
General symptom	1	0.6	0.2
Glomerular filtration rate decreased	1	0.6	0.2
Hepatic enzyme increased	1	0.6	0.2
Hypotension	1	0.6	0.2
International normalized ratio increased	1	0.6	0.2
Lumbar vertebral fracture	1	0.6	0.2
Nausea	1	0.6	0.2
Nocturia	1	0.6	0.2
Oedema	1	0.6	0.2
Oedema peripheral	1	0.6	0.2
Sudden death	1	0.6	0.2
Toxicity to various agents	1	0.6	0.2

Renal failure acute	1	0.6	0.2
Renal failure	1	0.6	0.2

(see appendix 2.1.4)

With regard to non-serious ADRs (116), „alanine aminotransferase increased“ was the most frequently reported ADR (9.5%), followed by „diarrhoea”, “nausea” (6.0%), “abdominal discomfort” and “dyspnoea” (4.3%).

Table 44: Non-serious ADRs by frequency according to MedDRA PT Level - SaS

ADR (PT)	Frequency of event	% of all ADRs	% of patients at risk
Alanine aminotransferase increased	11	9.5	2.0
Diarrhoea	7	6.0	1.3
Nausea	7	6.0	1.3
Abdominal discomfort	5	4.3	0.9
Dyspnoea	5	4.3	0.9
Drug intolerance	4	3.4	0.7
Hepatic enzyme increased	4	3.4	0.7
Drug ineffective	3	2.6	0.5
Headache	3	2.6	0.5
Liver function test abnormal	3	2.6	0.5
Malaise	3	2.6	0.5
Rash	3	2.6	0.5
Arrhythmia	2	1.7	0.4
Bradycardia	2	1.7	0.4
Gastrointestinal disorder	2	1.7	0.4
Heart rate decreased	2	1.7	0.4
Hyperhidrosis	2	1.7	0.4
Ill-defined disorder	2	1.7	0.4
Local swelling	2	1.7	0.4
Pruritus	2	1.7	0.4
Transaminases increased	2	1.7	0.4
Abdominal pain	1	0.9	0.2
Abdominal pain upper	1	0.9	0.2
Adverse event	1	0.9	0.2
Anxiety	1	0.9	0.2
Arthralgia	1	0.9	0.2
Aspartate aminotransferase increased	1	0.9	0.2
Autonomic nervous system imbalance	1	0.9	0.2
Blood alkaline phosphatase increased	1	0.9	0.2
Blood creatinine increased	1	0.9	0.2
Blood thyroid stimulating hormone increased	1	0.9	0.2
Discomfort	1	0.9	0.2
Dizziness	1	0.9	0.2
Drug eruption	1	0.9	0.2
Dry mouth	1	0.9	0.2
Dyspepsia	1	0.9	0.2
Dyspnoea exertional	1	0.9	0.2
Eczema	1	0.9	0.2
Electrocardiogram abnormal	1	0.9	0.2
Erythema	1	0.9	0.2
Fatigue	1	0.9	0.2
Full blood count abnormal	1	0.9	0.2
Gamma-glutamyltransferase	1	0.9	0.2

increased			
General physical health deterioration	1	0.9	0.2
Hypercalcaemia	1	0.9	0.2
Hyperlipidaemia	1	0.9	0.2
Hypersensitivity	1	0.9	0.2
Hyperuricaemia	1	0.9	0.2
Hypothyroidism	1	0.9	0.2
Insomnia	1	0.9	0.2
International normalized ratio increased	1	0.9	0.2
Liver disorder	1	0.9	0.2
Oedema peripheral	1	0.9	0.2
Pain in extremity	1	0.9	0.2
Palpitations	1	0.9	0.2
Sinus bradycardia	1	0.9	0.2
Skin exfoliation	1	0.9	0.2
Sleep disorder	1	0.9	0.2
Syncope	1	0.9	0.2
Tremor	1	0.9	0.2
Urticaria	1	0.9	0.2

(see appendix 2.1.4)

Discontinuation of Therapy with Multaq®

Out of 136 patients, for whom at least one non-serious ADR and/or SADR was documented, a total of 110 patients discontinued the therapy with Multaq® because of one or more adverse reaction(s).

When analyzed by treatment discontinuation (defined as permanent or temporary discontinuation or “drug withdrawal” due to ADR and/or SADR), most frequently the ADR “cardiac disorders” (80 events) led to withdrawal of Dronedarone (28.5 % of all ADRs (serious and non-serious) and 80,0 % of all reactions with this SOC). In the SOC “general disorders and administration site conditions”, a total of 39 events resulted in discontinuation (13.9% of all (S)ADRs and 92.9% of all reactions with this SOC), followed by the SOCs “investigations” (n=37, 13.2% of all (S)ADRs and 77.1% of all reactions with this SOC) and“gastrointestinal disorders (n=27, 9.6% of all (S)ADRs and 96.4% of all reactions with this SOC).

Table 45: Non-serious ADRs and SADRs leading to Withdrawal according to MedDRA SOC Level - SaS

(S)ADR (SOC level)	Frequency of event	% of all ADRs/SADRs	% of all ADRs/SADRs of SOC level
Cardiac disorders	80	28.5	80.0
General disorders and administration site conditions	39	13.9	92.9
Investigations	37	13.2	77.1
Gastrointestinal disorders	27	9.6	96.4
Respiratory, thoracic and mediastinal disorders	17	6.0	100.0
Skin and subcutaneous tissue disorders	11	3.9	91.7
Nervous system disorders	11	3.9	78.6
Renal and urinary disorders	4	1.4	100.0
Metabolism and nutrition disorders	3	1.1	100.0
Psychiatric disorders	3	1.1	75.0
Injury, poisoning and procedural complications	2	0.7	100.0
Musculoskeletal and connective tissue disorders	2	0.7	100.0
Endocrine disorders	1	0.4	100.0
Hepatobiliary disorders	1	0.4	100.0

Immune system disorders	1	0.4	100.0
Vascular disorders	1	0.4	100.0
Total	240	85.4	

(see appendix 2.1.4)

With regard to the most frequent ADRs (serious and non-serious) that led to discontinuation of therapy with Multaq®, the events according to PT-term are listed below.

Table 46: Non-serious ADRs and SADRs leading to Withdrawal according to MedDRA PT Level - SaS

SOC Term	PT Term	Frequency of event (n)	% of SaSpatients
Cardiac disorders		80	
	Arrhythmia	2	0.36
	Atrial fibrillation	60	10.38
	Bradyarrhythmia	1	0.18
	Bradycardia	2	0.36
	Cardiac failure	7	1.28
	Left ventricular dysfunction	2	0.36
	Palpitations	3	0.55
	Sinus bradycardia	1	0.18
	Tachyarrhythmia	2	0.36
General disorders and administration site conditions		39	
	Adverse event	1	0.18
	Adverse reaction	1	0.18
	Chest discomfort	2	0.18
	Condition aggravated	2	0.36
	Discomfort	1	0.18
	Drug ineffective	10	1.64
	Drug intolerance	4	0.73
	Fatigue	2	0.36
	Feeling abnormal	1	0.18
	General physical health deterioration	2	0.36
	Ill-defined disorder	4	0.73
	Local swelling	2	0.36
	Malaise	3	0.55
	Oedema	1	0.18
	Oedema peripheral	2	0.36
	Sudden death	1	0.18
Investigations		37	
	Alanine aminotransferase increased	12	2.19
	Aspartate aminotransferase increased	2	0.36
	Blood creatinine increased	3	0.55
	Blood thyroid stimulating hormone increased	1	0.18
	Creatinine renal clearance decreased	1	0.18
	Full blood count abnormal	1	0.18
	Gamma-glutamyltransferase increased	2	0.36
	Glomerular filtration rate decreased	1	0.18
	Heart rate decreased	1	0.18
	Hepatic enzyme increased	4	0.73
	International normalized ratio increased	2	0.36

	Liver function test abnormal	3	0.55
	Transaminases increased	4	0.73
Gastrointestinal disorders		27	
	Abdominal discomfort	5	0.91
	Abdominal pain	1	0.18
	Abdominal pain upper	2	0.36
	Diarrhoea	7	1.28
	Diverticulum	1	0.18
	Dry mouth	1	0.18
	Dyspepsia	1	0.18
	Gastrointestinal disorder	2	0.36
	Nausea	7	1.28
Respiratory, thoracic and mediastinal disorders		17	
	Alveolitis	1	0.18
	Dyspnoea	12	2.19
	Dyspnoea exertional	2	0.36
	Interstitial lung disease	2	0.36
Nervous system disorders		11	
	Autonomic nervous system imbalance	1	0.18
	Dizziness	4	0.73
	Headache	2	0.36
	Syncope	3	0.55
	Tremor	1	0.18
Skin and subcutaneous tissue disorders		11	
	Drug eruption	1	0.18
	Eczema	1	0.18
	Erythema	1	0.18
	Hyperhidrosis	2	0.36
	Pruritus	1	0.18
	Rash	3	0.55
	Skin exfoliation	1	0.18
	Urticaria	1	0.18

(see appendix 2.1.4)

Laboratory safety variables

Alanine Aminotransferase (ALT)

The analysis of laboratory values of the liver function, i.e. ALT values, showed that for 60 out of 549 patients (10.9 % of the safety population) increased ALT levels (≥3 fold reference limit) were documented (for details see appendix 2.1.2).

Table 47: ALT Analysis by Analysis Time Range - SaS

Analysis Time Range / Difference	$n_{(GPT\ values)}$	$n_{(patients)}$	ALT Value [U/l]			
			Min	Mean	SD	Max
1: before treatment start	592	455	0.20	26.46	15.42	117.00
2: up to 7 days after treatment start	149	140	0.25	31.05	22.35	122.00
3: 8 to 30 days after treatment start	256	214	0.26	29.95	19.31	133.00
4: 31 to 90 days after treatment start	443	298	0.27	28.71	17.11	139.20
5: 91 to 180 days after treatment start	510	342	0.17	26.59	14.50	116.00
6: more than 180 days after treatment start	665	352	0.17	27.24	15.40	108.00
Time range 1 - 2		99	-50.40	4.60	20.52	84.00
Time range 1 - 3		166	-46.20	2.31	18.60	112.00
Time range 1 - 4		247	-69.49	1.93	14.89	97.00

Time range 1 - 5	289	-75.00	-0.14	13.29	46.00
Time range 1 - 6	298	-84.33	0.54	15.12	77.00

(see appendix 2.1.2 table 5)

Table 48: Patients with ALT above 3-fold Reference Limit - SaS

	ALT Value [U/l]*					
Patient ID	before treatment start	up to 7 days after treatment start	8 to 30 days after treatment start	31 to 90 days after treatment start	91 to 180 days after treatment start	more than 180 days after treatment start
1011	65					
1092		94				
132			91	117	99	70; 130
1402				139.		
1473					60	
1491	63		87			
1533			77			
1542						72
1792		84				
1793	67					
1841			124			
1903		63				
2032	70					
2281	73					
241		87				
2471	73					
2703	59	63				57
2731	117	70				
2831	78					
303					71	
3062					99	
3151	84					
3152				61	99	
3153		105; 110				
3192				66		
332			72			
343					60	
3472	113				116	108
3543			133			
3552			96			
3581	58; 60					
3741		58				
3871			114; 64	76		
3872		114	63.6	76		
3881		107	64; 64			
3882		61				
4023	91					
4072						72
4211						74
4311	62	62				
4342						86
4352						60
4433	59			64		61
4521						78; 74; 132
4543					79	
4602	60			81		86; 101; 67
4603	106	122		110; 86	93; 70	70; 111

4611						80
4612				79		87
4613	92		90	101; 82; 82	61; 79; 71; 88	91; 86; 106; 90
4652			70; 101			
4713						89
4761						70
5242						77; 77
5243		96	84	102; 79	82	98; 76; 111
592	78					
802						61; 116; 86; 79
803	60			83		
841				125		
971	148			74		112

(see appendix 2.1.2 listing 1)

*All values are declared in U/l as documented in the CRFs. In case of ALT values provided by the physicians in units other than U/l (e.g µmol/l, µkat/l), transformation in U/l was performed by CSG. According to Sanofi-Guideline for Standardized Evaluation of NIS V3.0 , the following ranges were accepted:
Plausibility range: 0 – 150 U/l
Normal ranges: men: 0 – 23 U/l; women: 0 – 19 U/l
Values out of plausibility range were not considered for analysis.

Creatinine

The analysis of laboratory values of the renal function, i.e. creatinie values, showed that for none of the patients increased creatinine levels (≥2 fold reference limit) were documented (for details see appendix 2).

Table 49: Creatinine Analysis by Kidney Failure and Analysis Time Point – SaS

Kidney failure at baseline	$n_{(set)}$	$n_{(values)}$	$n_{(missing)}$	Creatinine Value [mg/dl]*			
				Min	Mean	SD	Max
Baseline							
overall	549	72	477	0.60	1.22	0.34	2.25
missing	6	2	4	0.92	1.06	0.20	1.20
yes	39	34	5	0.80	1.36	0.27	1.92
no	504	36	468	0.60	1.10	0.37	2.25
3-Month Period							
overall	549	385	164	0.46	1.02	0.26	1.90
missing	6	1	5	1.30	1.30		1.30
yes	39	30	9	1.04	1.39	0.23	1.75
no	504	354	150	0.46	0.98	0.24	1.90
FU1							
overall	457	335	122	0.50	1.02	0.25	1.88
missing	2	0	2				
yes	36	29	7	0.95	1.35	0.25	1.88
no	419	306	113	0.50	0.99	0.23	1.62
FU2							
overall	395	277	118	0.55	1.02	0.28	2.47
missing	2	0	2				
yes	32	25	7	0.70	1.34	0.41	2.47
no	361	252	109	0.55	0.99	0.25	2.10

(see appendix 2.1.2 table 6)

*All values are declared in mg/dl as documented in the CRFs. In case of creatinie values provided by the physicians in µmol/l, transformation in mg/dl was performed by CSG. According to Sanofi-Guideline for Standardized Evaluation of NIS V3.0, the following ranges were accepted:
Plausibility range 0.5 – 3.5 mg/dl
Normal ranges : men 0.67 – 1.36 mg/dl; women 0.57 – 1.17 mg/dl
Values out of plausibility range were not considered for analysis.

Blood Pressure

In the overall poplation the mean systolic blood pressure decreased by 2.5 mmHg (1.9 %) from baseline to FU2 and the mean diastolic blood pressure decreased by 2.3 mmHg (1.9 %).

Table 50: Blood Pressure Evaluation by Sex and Analysis Time Point – SaS

Analysis Time Point	Sex	$n_{(values)}$	$n_{(missing)}$	Blood Pressure [mm Hg]			
				Min	Mean	SD	Max
		Systolic					
Overall	Overall	1384	17	90	133.16	16.29	220
Baseline	Overall	538	11	90	134.54	17.09	220
FU1	Overall	455	2	98	132.51	15.54	187
FU2	Overall	391	4	90	132.04	15.92	209
Baseline	Female	254	3	90	135.31	18.22	220
FU1	Female	212	1	100	135	16.42	187
FU2	Female	184	2	90	133.37	17.68	209
Baseline	Male	284	7	90	133.84	16.02	190
FU1	Male	243	1	98	130.35	14.41	186
FU2	Male	207	2	90	130.85	14.11	180
Baseline	Missing	0	1				
		Diastolic					
Overall	Overall	1384	17	20	79.57	9.29	120
Baseline	Overall	538	11	20	80.7	9.63	117
FU1	Overall	455	2	50	79.27	9.13	120
FU2	Overall	391	4	50	78.37	8.82	110
Baseline	Female	254	3	54	80.82	9.37	117
FU1	Female	212	1	50	80.31	9.81	120
FU2	Female	184	2	50	78.98	9.13	103
Baseline	Male	284	7	20	80.59	9.88	110
FU1	Male	243	1	60	78.37	8.4	102
FU2	Male	207	2	52	77.84	8.52	110
Baseline	Missing	0	1				

(see appendix 2.1.3 table 2.6)

Resource use and cost analyses

Direct costs: Inpatient costs

At FU1, hospitalizations in an acute treatment facility were reported for 37 of 534 enrolled patients resulting in costs in the amount of 119,808.37 € (table 51). At FU2, hospitalizations in an acute treatment facility were reported for 30 of 534 enrolled patients resulting in costs in the amount of 93,865.75 € (table 52). Total costs of hospitalizations in an acute treatment facility at the end of the study were 213,674.12 € for enrolled patients.

Table 51: Costs of Hospitalization in an Acute Treatment Facility – FU1

Main diagnosis	n	% of Hospitalizations at FU1	Unit Costs	Costs of Hospitalization
Atrial fibrillation	20	54.05	2,785.57 €	55,711.31 €
Stroke or TIA	1	2.70	4,986.36 €	4,986.36 €
Acute coronary syndrome	1	2.70	5,176.43 €	5,176.43 €
Arterial embolism	0	0.00	6,167.01 €	0.00 €
Decompensated heart failure	2	5.41	3,771.47 €	7,542.94 €
Syncope	3	8.11	1,930.44 €	5,791.33 €
Ventricular arrhythmia	0	0.00	8,170.26 €	0.00 €
Non-fatal cardiac arrest	0	0.00	15,908.76 €	0.00 €
Adverse drug reactions	0	0.00	2,250.00 €	0.00 €
Other diagnoses	10	27.03	4,060.00 €	40,600.00 €
Total	37	100.00		119,808.37 €

Table 52: Costs of Hospitalization in an Acute Treatment Facility - FU2

Main diagnosis	n	% of Hospitalizations at FU2	Unit Costs	Costs of Hospitalization
Atrial fibrillation	22	73.33	2,785.57 €	61,282.44 €
Stroke or TIA	0	0.00	4,986.36 €	0.00 €
Acute coronary syndrome	2	6.67	5,176.43 €	10,352.86 €
Arterial embolism	0	0.00	6,167.01 €	0.00 €
Decompensated heart failure	0	0.00	3,771.47 €	0.00 €
Syncope	1	3.33	1,930.44 €	1,930.44 €
Ventricular arrhythmia	0	0.00	8,170.26 €	0.00 €
Non-fatal cardiac arrest	0	0.00	15,908.76 €	0.00 €
Adverse drug reactions	0	0.00	2,250.00 €	0.00 €
Other diagnoses	5	16.67	4,060.00 €	20,300.00 €
Total	30	100.00		93,865.75 €

A hospitalization in a rehabilitation clinic was reported for 5 of 534 enrolled patients at FU1. For 4 of these 5 patients length of stay was documented and amounted to a mean of 12.75 days. Costs for hospitalizations in a rehabilitation clinic at FU1 were 7,568.40 €. No hospitalizations in a rehabilitation clinic were documented at FU2 (table 53).

Table 53: Costs of Inpatient Rehabilitation

FU	n with Hospitalization in a Rehabilitation Clinic	n Reporting Duration of Hospitalization	Mean Days in Rehabilitation Clinic	SD	Average Cost per Day of Inpatient Rehabilitation	Mean Inpatient Rehabilitation Costs per Patient	Mean Inpatient Rehabilitation Costs for Patients with a Hospitalization in a Rehabilitation clinic
FU1	5	4	12.75	10.56	118.72 €	1,513.68 €	7,568.40 €
FU2	0	0	-	-	118.72 €	0.00 €	0.00 €
Total							7,568.40 €

Direct costs: Outpatient costs

At FU1, a visit in an emergency unit was documented for 5 of 534 enrolled patients resulting in costs in the amount of 77.98 €. At FU2, a visit in an emergency unit was documented for 1 patient of 534 enrolled patients resulting in costs in the amount of 15.60 €. Total costs of visits in an emergency unit at the end of the study were 93.58 € for enrolled patients (table 54).

Table 54: Costs of Outpatient Treatment in an Emergency Unit

FU	n with Outpatient Treatment in an Emergency Unit	Average Cost per Visit in an Emergency Unit	Costs of Outpatient Treatment in an Emergency Unit*
FU1	5	15.60 €	77.98 €
FU2	1	15.60 €	15.60 €
Total	6		93.58 €

*assuming one visit per patient

Costs of treatment initiation and monitoring for Dronedarone according to prescribing information amount to 5.53 € per patient for the first 6 months and to 3.48 € per patient for further 6 months (table 55).

Table 55: Dronedarone Initiation and Monitoring Costs

Cost Parameter	Unit Cost	Resource Use in First	Resource Use from	Resource Use from	Costs of Dronedarone	Costs of Dronedarone

		Treatment Year	Baseline to FU1	FU1 to FU2	Treatment Initiation and Monitoring from Baseline to FU1	Treatment Monitoring from FU1 to FU2
Basic quarterly lump sum for laboratory services	1.37 €	4	2	2	2.73 €	2.73 €
Creatinine	0.40 €	2	2	0	0.80 €	0.00 €
Alanine aminotransferase	0.25 €	11	8	3	2.00 €	0.75 €
Total					5.53 €	3.48 €

* Costs for ECG and INR are not considered separately, because they are not related exclusively to Dronedarone therapy

Costs of treatment initiation and monitoring with Dronedarone were 2,955.02 € from baseline to FU1 and 1,672.20 € from FU1 to FU2 for patients staying on Dronedarone (table 56).

Table 56: Dronedarone Initiation and Monitoring Costs for Patients Staying on Dronedarone

Timeframe	n on Dronedarone Therapy at Beginning of Timeframe	Costs of Dronedarone Treatment Initiation and Monitoring at Beginning of Timeframe - per Patient	Costs of Dronedarone Treatment Initiation and Monitoring at Beginning of Timeframe
Baseline to FU1	534	5.53 €	2,955.02 €
FU1 to FU2	480	3.48 €	1,672.20 €
Total			4,627.22 €

* Only patients at the end of FUwere considered, since exact treatment changes were not documented

Costs of Dronedarone medication amount to 560.66 € per patient per FU time frame for patients staying on Dronedarone (table 57).

Table 57: Costs of Dronedarone Medication per Patient

Dronedarone	Resource Use until FU1	Resource Use until FU2	Unit Cost	Dronedarone drug Costs until FU1	Dronedarone Drug Costs until FU2
Dronedarone	182.625	182.625	3.07 €	560.66 €	560.66 €

For patients switching during the study from Dronedarone to another AF medication, costs of this new medication were considered for the respective duration of treatment. No costs of Dronedaron were taken into account after switch.

Costs of AF drug treatment other than Dronedarone were 2,128.37 € at FU1 (table 58) and 2,121.22 € at FU2 (table 59) for all those patients switching from Dronedarone to another AF medication.

Table 58: Costs of AF Drug Treatment for Patients Having Switched from Dronedarone - FU1

Antiarrhythmic Treatment at FU1	n with Treatment Change	n Reporting Treatment Duration	Mean Duration of Treatment (Days) as Documented*	Mean Duration of Treatment (SD)	Mean Duration of Treatment (Days)*	Mean Costs per DDD	Costs per Treatment	Costs per Treatment for all Patients with Treatment Change	Mean Treatment Duration with Dronedarone (182.625 Days Minus Duration of New Antiarrhythmic Treatment)	Number of Days on Dronedarone for Patient Having Changed Treatment	Dronedarone Costs Not Accrued
Class Ia	0	-	-	-	0.00	0.91 €	0.00 €	0.00 €	182.63	0.00	0.00 €
Class Ic	7	7	53.29	58.61	53.29	0.76 €	40.47 €	283.30 €	129.34	905.35	2,779.41 €
Class II	25	25	632.32	1090.60	182.63	0.24 €	43.99 €	1,099.84 €	0.00	0.00	0.00 €
Class III Amiodarone	8	8	47.63	61.79	47.63	0.64 €	30.48 €	243.87 €	135.00	1079.96	3,315.48 €
Class III Sotalole	2	2	56.00	77.78	56.00	0.27 €	15.12 €	30.24 €	126.63	253.25	777.48 €
Class IV	4	4	122.00	86.27	122.00	0.34 €	41.08 €	164.33 €	60.63	242.50	744.48 €
Digitalis	8	2	3637.00	4887.50	182.63	0.21 €	38.35 €	306.79 €	0.00	0.00	0.00 €
Total	54							2,128.37 €			7,616.84 €

* if > 182.625 days were documented, the treatment duration was set to 182.625 days (rounded results shown)

Auxiliary calculation needed for table 60

Table 59: Costs of AF Drug Treatment for Patients Having Switched from Dronedarone - FU2

Antiarrhythmic Treatment at FU2	n with Treatment Change	n Reporting Treatment Duration	Mean Duration of Treatment (Days) as Documented*	Mean Duration of Treatment (SD)	Mean duration of Treatment (Days)*	Mean Costs per DDD	Costs per Treatment	Costs per Treatment for all Patients with treatment Change	Mean Treatment Duration with Dronedarone (182.625 Days Minus Duration of New Antiarrhythmic Treatment)	Number of Days on Dronedarone for Patient Having Changed Treatment	Dronedarone costs not accrued
Class Ia	3	3	20.67	17.90	20.67	0.91 €	18.84 €	56.52 €	161.96	485.87	1,491.61 €
Class Ic	14	13	50.92	81.20	50.92	0.76 €	38.67 €	541.40 €	131.705	1843.87	5,660.68 €
Class II	23	23	672.43	1061.70	182.63	0.24 €	43.99 €	1,011.85 €	0.00	0.00	0.00 €
Class III Amiodarone	8	8	87.88	56.99	87.88	0.64 €	56.24 €	449.95 €	94.745	757.96	2,326.94 €
Class III Sotalole	0	-	-	-	0.00	0.27 €	0.00 €	0.00 €	182.63	0.00	0.00 €
Class IV	1	1	2639.00	-	182.63	0.34 €	61.50 €	61.50 €	0	0.00	0.00 €
Digitalis	4	0	-		0.00	0.21 €	0.00 €	0.00 €	182.63	730.50	2,242.64 €
Total	53							2,121.22 €			11,721.86 €

* if > 182.625 days were documented, the treatment duration was set to 182.625 days (rounded results shown); if no treatment duration was documented, no costs for the respective drug were taken into account

Auxiliary calculation needed for table 60

Dronedarone treatment costs for enrolled patients were 291,774.93 € from baseline to FU1 and 257,394.34 € from FU1 to FU2 (table 60). These costs consider patients having switched from Dronedarone to another antiarrhythmic treatment during the FU periods.

Table 60: Costs of Dronedarone Treatment Considering Treatment Changes

Time		n on Dronedarone Therapy	Dronedarone Drug Costs until Next FU (not Considering Potential Treatment Changes) - per Patient	Dronedarone Drug Costs until Next FU (not Considering Potential Treatment Changes) - all Patients on Dronedarone	Patients with Change of Antiarrhythmic Treatment at Next FU*	Dronedarone Costs not Accrued*	Dronedarone Drug Costs until Next FU (Considering Patients with Treatment Switches)
1	Baseline to FU 1	534	560.66 €	299,391.77 €	54	7,616.84 €	291,774.93 €
FU1 to FU2		480	560.66 €	269,116.20 €	53	11,721.86 €	257,394.34 €
Total							549,169.28 €

*see table 58 and table 59

At FU1 and FU2 costs of thromboprophylactic treatment amounted to 644.53 € (table 61, table 62).

Table 61: Costs of Thromboprophylaxis - FU1

Thromboprophylaxis at FU1	n with Thromboprophylactic Treatment	n Reporting Treatment Duration	Mean Duration of Treatment (Days) as Documented*	Mean Duration of Treatment (SD)	Mean Duration of Treatment (Days)*	Mean Costs per DDD	Costs per Treatment
Thrombocyte function inhibitors	78	44	809.57	1048.80	182.63	0.04 €	7.31 €
Vitamin K antagonists	253	111	18907.00	554.16	182.63	0.17 €	31.05 €
Oral Factor IIa/Xa inhibitors	66	30	344.30	449.43	182.63	3.32 €	606.18 €
Total							644.53 €

* if > 182.625 days were documented, the treatment duration was set to 182.625 days (rounded results shown)

Table 62: Costs of Thromboprophylaxis - FU2

Thromboprophylaxis at FU2	n with Thromboprophylactic Treatment	n Reporting Treatment Duration	Mean Duration of Treatment (Days) as Documented*	Mean Duration of Treatment (SD)	Mean Duration of Treatment (Days)*	Mean Costs per DDD	Costs per Treatment
Thrombocyte function inhibitors	70	43	1142.50	1251.10	182.63	0.04 €	7.31 €
Vitamin K antagonists	214	92	18978.00	537.98	182.63	0.17 €	31.05 €
Oral Factor IIa/Xa inhibitors	58	28	439.32	484.17	182.63	3.32 €	606.18 €
Total							644.53 €

* if > 182.625 days were documented, the treatment duration was set to 182.625 days (rounded results shown)

Indirect costs: Sick leave

At FU1, for 66 of 101 employed patients, the number of days of sick leave was documented. This amounted to a mean of 3.65 days of sick leave per patient and resulted in mean costs of 371.31 € per patient. At FU2, for 55 of 95 employed patients, the number of days of sick leave was documented. This amounted to a mean of 5.65 days of sick leave per patient and resulted in mean costs of 571.71 € per patient (table 63). Total costs for sick leave were 55,950.34 € after one year for all those patients for whom a sick leave was documented.

Table 63: Costs of Sick Leave

FU	n Employed	n Reporting Sick Leave Days	Mean Days of Sick Leave	SD	Average Cost per Day of Sick Leave	Average Costs of Sick Leave per Patient	Costs of sick leave for all patients reporting sick leave days
FU1	101	66	3.65	7.96	101.73 €	371.31 €	24,506.25 €
FU2	95	55	5.62	21.06	101.73 €	571.71 €	31,444.09 €
Total							55,950.34 €

Total annual costs of AF management (third-party payers' perspective)

Total annual costs of AF management (third-party payers' perspective) after one year amount to 780,671.24 € or 1,461.93 € per patient, respectively (table 64).

Table 64: Total Annual Costs of AF Management (Third-Party Payers' Perspective)

Direct Costs	FU1	FU2	Total
Costs of hospitalization in an acute treatment facility	119,808.37 €	93,865.75 €	213,674.12 €
Costs of inpatient rehabilitation	7,568.40 €	0.00 €	7,568.40 €
Costs of outpatient treatment in an emergency unit	77.98 €	15.60 €	93.58 €
Costs of Dronedarone treatment initiation and monitoring	2,955.02 €	1,672.20 €	4,627.22 €
Costs of AF drug treatment and thromboprophylaxis			
Dronedarone	291,774.93 €	257,394.34 €	549,169.28 €
AF drug treatment (other than Dronedarone)	2,128.37 €	2,121.22 €	4,249.58 €
Thromboprophylaxis	644.53 €	644.53 €	1,289.06 €
Total annual costs of AF management (third-party payers' perspective)	424,957.61 €	355,713.63 €	780,671.24 €
Total annual costs of AF management (third-party payers' perspective) - per patient (N=534)	795.80 €	666.13 €	1,461.93 €

Taking all cost parameters into account, costs of AF drug treatment and thromboprophylaxis from the third-party payers' perspective represented 71 % of the total costs of AF management. Costs of hospitalization constituted 27 % of the total costs of AF management, whereas other cost parameters had a smaller quota (≤1 %) (figure 19).

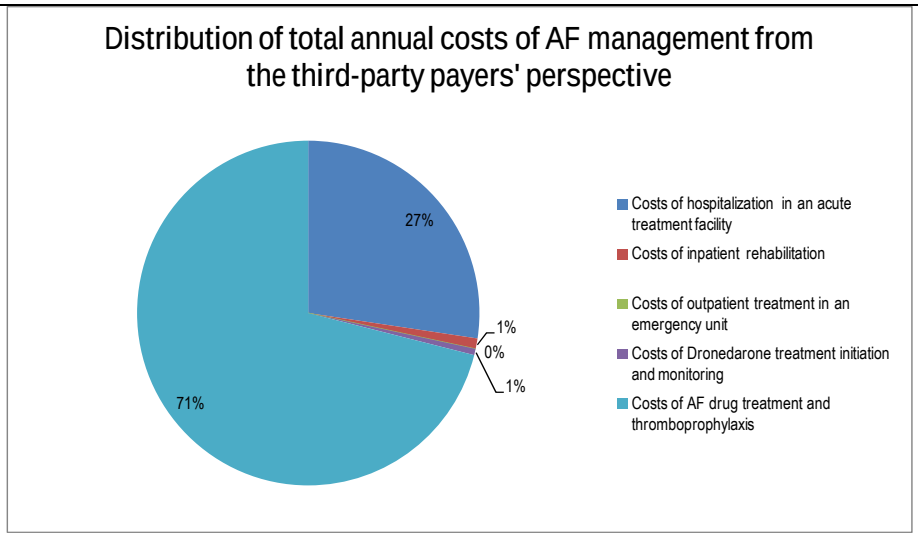


Figure 19: Distribution of Total Annual Costs of AF Management from the Third-Party Payers' Üerspective

Total annual costs of management of AF patients (societal perspective)

Annual costs for management of AF patients amounted to 836,621.58 € in total and 1,566.71 € per patient, respectively (table 65).

Table 65: Total Annual Costs of Management of AF Patients (Societal Perspective)

Total Annual Costs of AF Management	FU1	FU2	Total
Total direct costs	424,957.61 €	355,713.63 €	780,671.24 €
Total indirect costs			
Costs of sick leave	24,506.25 €	31,444.09 €	55,950.34 €
Total annual costs of AF management (societal perspective)	449,463.86 €	387,157.72 €	836,621.58 €
Total annual costs of AF management (societal perspective) - per patient (N=534)*	841.69 €	725.01 €	1,566.71 €

* considering that about 18 % of the patients enrolled in the study were employed

Taking all cost parameters into account, costs of AF drug treatment and thromboprophylaxis represented 66 % of the total costs of AF management. Costs of hospitalization constituted 25 % of the total costs of AF management, whereas other cost parameters had a smaller quota (≤7 %) (figure 20).

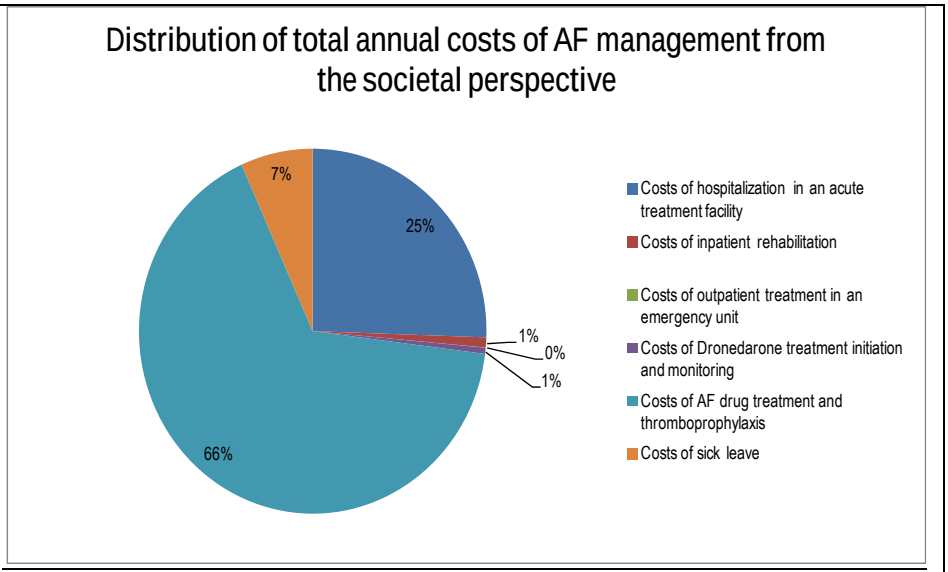


Figure 20: Distribution of Total Annual Costs of AF Management from the Societal Perspective

Other resource consumption during AF treatment

Duration of hospitalization:

Mean duration of hospitalization (SD) was 6.84 days (7.75) at FU1 (appendix 2.2 table 75) and 3.74 (4.71) days at FU2, respectively (appendix 2.2 table 76).

Number of days spent in intensive care unit:

Mean number of days spent in an intensive care unit (SD) was 5.00 days (4.00) at FU1 and 2.00 (0.82) days at FU2, respectively (appendix 2.2 table 77).

Number of contacts with documenting physician, of these: not planned:

Mean number of contacts with documenting physician (SD) was 3.78 (3.54) at FU1, whereas 0.47 (1.09) of those visits were not planned (appendix 2.2 table 78). At FU2 there were 4.58 (6.15) contacts of which 0.54 (1.34) were not planned (appendix 2.2 table 79).

Number of contacts with outpatient clinic:

Mean number of contacts with outpatient clinic (SD) was 0.10 (0.57) at FU1, and 0.40 (4.46) at FU2, respectively (appendix 2.2 table 80).

Number of contacts with other specialists:

At FU1, the mean number of contacts with other specialists (SD) ranged from 1.43 (0.50) for general practitioners to 2.00 (0.05) for endocrinologists (appendix 2.2 table 81). At FU2, the mean number of contacts (SD) with other specialists ranged from 1.36 (0.48) for general practitioners to 1.98 (0.12) for endocrinologists (appendix 2.2 table 82).

Discussions:	AF is the most common clinically relevant arrhythmia, affects 6 million individuals in Europe, resulting in significant morbidity and mortality, including 4- to 5-fold increased risk of stroke and a 3-fold increased risk of heart failure resulting in significant effects on quality of life (QoL). Ageing of the population and the accumulation of predisposing conditions will cause the prevalence of AF to rise by at least 2.5 fold by the year 2050 [2]. Treatment of AF is based in drug therapy and ablative strategies. The focused pharmacotherapy aimed at controlling both heart rate and rhythm to relieve AF syndromes. The question is which approach is preferable. The primary goals of pharmacotherapy in AF are to restore sinus rhythm, control heart rate and prevent stroke. Anti-arrhythmic drug therapy is limited by a relatively high recurrence rate and proarrhythmic side effects. Catheter ablation suppresses paroxysmal AF in the majority of patients without structural heart disease but is more difficult to achieve in patients with persistent AF or with concomitant cardiac disease. Stroke is a potential devastating complication of AF, requiring anticoagulation that harbors the risk of bleeding. AF is responsible for one-third of hospitalizations for cardiac rhythm disturbances and has a prevalence of 1% and is age-dependent with approx. 10% of patients > 80 years being affected in contrast to 0.1% of all individuals < 55 years [3]. Symptoms associated with AF are primarily caused by rapid and irregular heartbeat and include palpations, dizziness, anxiety, and reduced exercise capacity which result in severely impaired quality of life [31]. But one-third of patients exhibit no symptoms and are unaware of abnormal heart rhythm, preventing early detection. In a subgroup of patients the severity of symptoms decreases with the time owing to a transition from paroxysmal to permanent AF [2]. Recent in vitro and in vivo evidence provided significant towards a comprehensive understanding of structural and electrical mechanisms underlying AF on the molecular level [32]. Based on these data, interventional and pharmacological therapies targeting novel mechanisms and utilizing innovative modalities are currently developed and evaluated in pre-clinical and clinical studies [32, 33]. In recent years the pathophysiology of AF has been studies extensively. Correction of the underlying arrhythmia in AF may appear to be the best treatment option. However, rate control has bee shown to be at least as effective in improving mortality, stroke rate, AF symptoms and QoL [11]. Rate control has also been shown to be a more cost-effective strategy than rhythm control, with reduced medical resource requirements [34]. In the emergency setting, the priority is to maintain hemodynamic stability by urgently restoring sinus rhythm or controlling ventricular rate. Direct current cardioversion should be considered for AF patients who are hemodynamically unstable, or who show signs of myocardial ischemia or heart failure [35]. If AF has presented recently (<7 days) and the patient is hemodynamically stable, cardioversion with anti-arrhythmic drugs can be effective. If AF has been present for > 48 hours, artrial thrombus must be excluded and adequate anti-coagulation initiated. Class IC anti-arrhythmics are not recommended for elderly AF patients due to the risk of co-morbidities, such as coronary artery disease or left ventricular dysfunction. In these patients, and where arrhythmia has persisted for >1 week, a class III agent, such as Dronedarone may be preferred. In one trial in elderly AF patients, the newly introduced agent, Dronedarone, reduced AF recurrence versus placebo, and also had beneficial effects on cardiovascular mortality/morbidity, although the difference for all-cause death was statistically non-significant. Dronedarone therapy also lacked many of the side-effects associated with Amiodarone. Even with a variety of anti-arrhythmic drugs and repeated external cardioversions, only 39–63% of AF patients maintain sinus rhythm [12]. Rate control may therefore be a beneficial alternative strategy, especially in elderly patients. Rate control aims to achieve a resting heart rate of 60–80 beats/min (bpm) and avoid periods with an average heart rate over 1 h of >100 bpm. The benefits of rate versus rhythm control have been much discussed. Rhythm control does not reduce mortality; the two largest trials of rate versus rhythm control suggested that rhythm control may show a trend towards increased mortality [12] possibly due to anti-arrhythmic drug toxicity or inappropriate withdrawal of anti-coagulant therapy. Patient QoL is similar in rate and

	rhythm control groups [36, 37]. Rate control is less costly than rhythm control, involving fewer hospitalizations. In clinical practice, the decision between rate or rhythm control depends on multiple patient-specific factors including the severity of symptoms, hemodynamic effects, duration and frequency of AF episodes, underlying structural or endocrine disease, and the outcome of previous treatment regimes. Dronedarone is a new anti-arrhythmic drug that has been developed to provide rhythm and rate control in AF patients, with fewer side effects compared with Amiodarone [38]. Dronedarone is chemically related to Amiodarone but unlike Amiodarone, it does not possess the iodine part affecting thyroid function. Moreover the addition of a methyl sulphonyl group decreases its lipophilicity and shortens its plasma half-life, thought to reduce organ toxicity due to cumulative effects. Similar to Amiodarone, Dronedarone is a multichannel blocker that meets criteria of all four Vaughan Williams anti-arrhythmic drug classes: rate-dependent inhibition of the rapid Na^+ current (class I), alpha and beta-adrenergic receptor inhibition (class II), blockade of K^+ outward currents as the main mechanism of action (class III), and blockade of slow Ca^{2+} inward currents (class IV) [39, 40, 41]. Action potential duration is prolonged and heart rate is reduced. Dronedarone was approved in 2009 based on the results of the ATHENA trial (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Atrial Flutter) [29]. Dronedarone significantly reduced the incidence of hospitalization due to cardiovascular events or death in high-risk patients with AF. Dronedarone represents a valuable addition to the limited spectrum of anti-arrhythmic drugs and is currently recommended in patients with paroxysmal and persistent AF to achieve rate and rhythm control, excluding cases of severe or unstable congestive heart failure. IMPULS is a prospective multicenter NIS to document the management and treatment of consecutive patients treated with Dronedarone. Either incident patients who began a treatment with Dronedarone or prevalent patients who were already treated with Dronedarone for no longer than a maximum of 3 months were eligible for inclusion. Only patients with paroxsysmal or persistent AF and at least one cardiovascular risk factor (arterial hypertension, diabetes mellitus, previous stroke, transient ischemic attack, arterial embolism, left atrium diameter ≥ 50 mm) were to be enrolled in this study. Primary and secondary effectiveness variables: Change from baseline in AFQoL score: In the FAS the EQ-5D VAS improved by 10.79 points from baseline to FU1 and increased also by 11.35 points from baseline to FU2. This general tendency was almost identical in male and female patients and no relevant difference was seen in patients within persisting or paroxsysmal AF, respectively (paroxsysmal AF: baseline -> FU1 10.68, baseline -> FU2 10.42, persisting AF: baseline -> FU1 11.42, baseline -> FU2 13.79). Within the AF-Qol Psycholigical Domain male patients show an better improvement (baseline -> FU1 13.39, baseline -> FU2 17.00) than female patients (baseline -> FU1 10.27, baseline -> FU2 14.70), and no difference was seen in paroxsymal AF vs. persisting AF but also an improvement. Within the Physical Domain of AFQoL female patients (baseline -> FU1 11.54, baseline -> FU2 11.67) show a better increase than male patients (baseline -> FU1 9.45, baseline -> FU2 10.25), and patients with persisting AF show a better improvement than patients with paroxsysmal AF (12.74 vs. 9.34 from baseline -> FU1 and 11.57 vs. 10.51 from baseline -> FU2, respectively) Within the AF-QoL Sexual Domain male patients show a distinct improvement (more than twice) than female patients and patients with paroxsysmal AF show a clearly better increase than patients with persisting AF. The SF-12 Mental Summary Scale and SF-12 Physical Summary Scale show an increase in male and female patients with AF from baseline to FU1 and this improvement was kept till FU2 regardless the type of AF (paroxsysmal vs. persistent).

	Change and reversion from AF to sinus rhythm: At baseline 55.4 % of all patients in the SaS had shown a AF-rhythm and 45.6 % were classified in different rhythm or sinus rhythm. At FU1 patients with AF-rhythm were reduced up to 18.2 % (19.2 % at FU2) and patients with sinus rhythm increased up to 70.2 % (70.9 % at FU2). This impressive change and reversion by Dronedarone from AF to sinus rhythm from baseline to FU1 and FU2, respectively, is significant, by simultaneously improving AF-QoL. In addition the ventricular frequency was clearly reduced in patients with paroxsysmal and persistent AF while keeping the QT_C almost constant. The liver enzyme ALT was slightly increased (keeping normal ranges) within 30 days after baseline, after 6 months this slight increase disappeared. In 60 patients the liver enzyme ALT was increased beyond the normal range but this increase was also seen before baseline. The EHRA score improvement (symptomatic vs. asymptomatic) was seen from baseline to FU forward to FU2 by decreasing the numbers of patients with symptomatic EHRA score in paroxsysmal AF: N=242 -> N=218 -> N=204, and in persistent AF: N=87 -> N=75 -> N=72, respectively. 136 patients (25 % of all patients in the SaS) had at least one ADR causally related to Multaq® as assessed by company. Out of 281 individual ADRs reported in 136 patients 165 ADRs were considered to be serious (SADR, related) and 116 were considered to be non-serious (ADR, related). The most common side effects were “atrial fibrillation”, “gastrointestinal disorders” and “respiratory, thoracic and mediastinal disorders”. Most frequently, recurrence of AF was found to cause discontinuation (n=56 ADRs, 10.2 % of the safety population). Laboratory values (ALT, creatinine) were unremarkable and were within normal ranges for the majority of patients. Generally, no clinically significant abnormalities were detected for these parameters. Dronedarone treatment of patients with paroxysmal or persistent AF can be considered safe in the daily routine. The reported ADRs assessed related to therapy with Multaq® were as expected and described in the currently valid SmPC. In this prospective observational study the average annual cost of AF management per patient treated with Dronedarone amounted to about 1,450 € from the third-party payers‘ perspective and to about 1,550 € from the societal perspective when indirect costs incurred by sick leave were additionally considered. These results lie within the range reported by other researches for Germany (600 € – 7,700 € [21] and 827 € ±1,476 € [22] and for other European countries as well (1,010 € – 3,225 € [23], 450 € – 3,000 € [30]. In contrast to the cost analyses published by McBride 2009, in the present study no resource use regarding emergency transport, physical therapy and patient aids was documented [22]. Further, no resource use for outpatient care after hospitalization due to events (e.g. stroke, ACS) were documented in the study. These costs were therefore not considered for the cost analyses. Additionally, no resource use for initiation and monitoring of the other antiarrhythmic drugs than Dronedarone were considered. Thus, the estimated total costs of AF management could be underestimated. The most important cost factors in the present study are drug costs (71 % and 66 % of total costs from the third-party payers‘ and societal perpective, respectively) and costs of hospitalizations (28 % and 26 % of total costs, respectively). In the other cost analyses the costs of hospitalizations were the most cost driver amounting for 44% in Germany [22] and for 50--70% of direct costs in the other countries [30]. As the hospitalization rates were comparable in the analysis published by McBride [22] and in the present study (11% vs. 13% (considering the settings “acute treatment facility” and “rehabilitation clinic”)), different cost units applied for inpatient treatment with the respective main diagnosis could be one of the reasons for the different weight of the inpatient costs in the total AF-costs. Unit costs used by McBride [22] are generally lower. This could be due to an earlier base year (2004 by McBride vs. 2012 in the present study) and other methods of

	identification of the relevant DRGs; no detailed information about that is reported in the respective publication. Further, in the present study only patients starting a Dronedarone treatment were included. Cost analysis of McBride was conducted before Dronedarone was available in the German market. Therefore older and cheaper medications were considered. Additionally their costs were estimated using data from the year 2004. These facts can explain the differences of the drug costs between both cost studies for German AF-patients. Summarizing, the average annual cost per patient with AF treated with Dronedarone of about 1,500 € are comparable with the average annual cost per patient with AF from other cost studies for Germany and other European countries and indicate high economic burden of AF for the health care systems. Reducing the frequency of hospitalizations in patients suffering from AF would lead to reduced health care expenditures in this indication.
Conclusions:	Dronedarone shows a positive risk-benefit ratio by improving the AF-QoL score in all categories, by reversion from AF to sinus rhythm, simultaneously keeping the QT_C almost constant, and reducing the ventricular frequency, and by improving the EHRA-score. The reported ADRs or assessed laboratory data related to therapy with Multaq® were as expected and described in the currently valid SmPC. Dronedarone can be considered safe in the daily routine.
Date of report:	21-Oct-2014