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Quick Pulse

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FDA Panel Recommends Approval of New Drug for Atrial Fibrillation

Silver Spring, MD
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The FDA's Cardiovascular and Renal Products (Cardio-Renal) Advisory Committee voted 10 to 3 to recommend that the FDA approve Sanofi-Aventis's Multaq (dronedarone) to treat atrial fibrillation or atrial flutter. The question never was efficacy, just safety, and the panel agreed that dronedarone should not be used in unstable heart failure patients or patients with liver disease. Several panel members also cautioned that dronedarone needs more study and should not totally replace amiodarone until there are more data.

Sanofi-Aventis is seeking approval of Multaq, given 400 mg BID with meals, "for rhythm and rate control in patients with either a recent history of or current non-permanent atrial fibrillation (AFib) or atrial flutter (AFL) with associated risk factors. Multaq has been shown to decrease the combined risk of cardiovascular (CV) hospitalization or death." The company has stated that inappropriate patients for dronedarone would be: "Patients with symptoms of heart failure at rest or with minimal exertion within the last month or patients hospitalized for heart failure within the last month."

The FDA appeared inclined to grant approval even before the panel met, so the panel's positive vote makes approval likely. However, there are still serious safety concerns, and the label is not likely to be as broad as the company might like. A claim for reduction in death appears unlikely.

In opening remarks to the panel, Dr. Norman Stockbridge, director of the FDA's Division of Cardiovascular and Renal Drug Products in the Center for Drug Evaluation and Research (CDER), laid out the key dilemma facing the Agency: "The case today is going to be pretty interesting. No one seems to dispute that the drug delays atrial fibrillation…but we have two morbidity/mortality studies that give very different results…We have result A, thought we understood it. Then, we did something different and got result B. Along the way we discovered the hypothesis for result A was changed…You, on the committee, have to help us decide whether the new story is plausible – more than plausible, whether you find it compelling. And if it is compelling, we need your help in drawing a line that identifies patients very likely to get result B."

Sanofi-Aventis's original explanation for the ANDROMEDA failure was due to ACE inhibitor/ARB use, but that didn't hold up on further analysis. At the panel meeting, the company experts argued that this trial failed due to the stability – or instability – of the heart failure patients, not the severity of their disease.

There were 13 voting members on the panel – 5 cardiologists, 2 nephrologists, 2 pulmonologists, a biostatistician, a patient advocate, a toxicologist, and a

consumer representative – as well as a non-voting industry representative. The FDA had 11 questions for the panel, but asked for a vote only on one: Should dronedarone be approved to treat AFib? And the panel voted overwhelmingly that it should be approved. In fact, as soon as the panel began discussing the first question – the reason for the ANDROMEDA trial failure – it was clear that the panel accepted the company's explanation for that failure and was likely to recommend approval, provided there are post-marketing studies, a characterization of who might and might not benefit, and boxed warnings. FDA officials, too, were talking almost as if approval were a done-deal.

Yet, the panel also clearly wanted dronedarone to be used responsibly. Dr. Stockbridge asked, "Would you expect to see an advertisement that says: 'It's more than AFib'?" The panel unanimously said ***no***, they did not want that to happen. The benefit is a reduction in AFib-related hospitalization, they agreed. Biostatistician Dr. James Neaton from the University of Minnesota summed up the sentiment, "I go back to the unmet need for drugs that do more than reduce hospitalization for AFib recurrence, and I don't think the data here are real convincing on that, so I would hate to see advertising or a claim for that."

BACKGROUND

An estimated 2.2 million Americans have AFib. It is the most common sustained arrhythmia in the U.S., affecting 6% of people >age 65. The overall incidence of AFib increases with each decade of age. The number of patients with AFib is expected to increase 2.5-fold over the next 50 years. AFL is similar to AFib with respect to risk factors, symptoms, and prognosis.

The primary goal in the management of AFib has been the restoration and maintenance of sinus rhythm. Even in asymptomatic patients, it was believed that patients fared better if they spent more time in sinus rhythm than in AFib, perhaps by reducing the risk of stroke. Although electrical cardioversion could restore sinus rhythm, AFib recurrence was ~75% without an anti-arrhythmic drug. However, Class I anti-arrhythmic drugs are associated with an increased risk of CV death, so their use is limited. Amiodarone and sotalol are now used, but long-term treatment has been associated with a high risk of end-organ toxicity, including thyroid abnormalities, hepatic toxicity, neuropathy, pulmonary fibrosis, and skin discoloration. Dofetilide is considered efficacious for rhythm control but is seldom used because of a high rate of torsade de pointes.

Because of the toxicity of rhythm control drugs, rate control started to get more attention, and physicians began prescribing digoxin, beta blockers, and/or the ACE inhibitors verapamil and diltiazem for AFib. The AFFIRM and RACE studies demonstrated a trend for a better survival and a reduction in ischemic strokes and CV hospitalizations with rate control vs. rhythm control.

Although rhythm and rate control may reduce symptoms, it is not clear that either approach has any meaningful favorable impact long-term. AFib/AFL patients remain at increased risk of CV death and hospitalization.

Dronedarone was first submitted to the FDA in June 2005, and the FDA turned it down because of adverse events and increased mortality in high-risk patients (NYHA Class II-IV) in the ANDROMEDA trial. ANDROMEDA was stopped early because of an excess of mortality (25 vs. 12), hospitalization for heart failure (39 vs. 31), and hospitalization for CV causes (71 vs. 50).

Regulatory history of dronedarone:

- June 2005: NDA filed based on DAFNE, EURIDIS, ADONIS, EROTA, and ANDROMEDA trials.
- August 2006: FDA finds dronedarone not approvable. The unfavorable risk:benefit was "largely because of adverse outcomes in ANDROMEDA."
- July 2008: Sanofi-Aventis did an additional study, ATHENA, resubmitted dronedarone with the results of that study, and the FDA granted priority review.
- February 2009: New DIONYSOS data provided to FDA, showing dronedarone not as effective as amiodarone but more tolerable.
- March 18, 2009: Cardio-Renal advisory committee recommends approval.
- April 30, 2009. The FDA action (PDUFA) date for a decision on dronedarone. The FDA is not expected to wait for the new FDA Commissioner to be confirmed and take office to make a decision.

Deaths in ANDROMEDA Trial

Deaths	Placebo n=2,327	Dronedarone n=2,301
Any deaths	12	25 (p=0.03)
Cardiovascular	9 (3%)	23 (8%)
Heart failure	2	10
Arrhythmia	2	6
Presumed CV	3	5
Myocardial infarction	2	0
Other	0	3
Non-cardiovascular	3 (1%)	1 (<1%)

Deaths by ARB/ACE Inhibitor Use in ANDROMEDA Trial

Death	Placebo	Dronedarone
Not on ACE-I/ARB at baseline	1 of 50	6 of 36
ACE-I/ARB maintained	10 of 267	10 of 274
ACE-I/ARB discontinued	1 of 12	9 of 19
Total	12 of 329	25 of 329

Hospitalizations or Death in ATHENA Trial

Adverse event	Placebo n=2,327	Dronedarone n=2,301
Primary endpoint: Any CV hospitalization or death	917 patients	734 patients (p<0.05)
Primary secondary endpoint: All cause death	139 deaths	116 deaths (Nss, p=0.176)
CV hospitalizations	859 patients	675 patients
Death as first event	58 patients	59 patients
Death at any time during study	134 patients	115 patients
Categories of CV hospitalizations		
Any	859	675
AFib or supraventricular arrhythmia	457	296
Worsened heart failure	92	78
Unstable angina or MI	61	48
Stable angina or atypical chest pain	41	45
TIA or stroke	35	28
ICD or pacemaker	29	32
Arterial procedures	31	27
12 less common categories	113	121

THE COMPANY PERSPECTIVE

Briefing documents

In its briefing documents, Sanofi-Aventis contended: "In addition to demonstrating efficacy on rhythm and rate in AFib and AFL, dronedarone was shown to provide clinical benefit on cardiovascular hospitalizations or death in a large clinical trial including patients with recent history of or current AFib/AFL. This benefit was consistent across all subgroups evaluated. Since none of the existing anti-arrhythmic drugs have ever demonstrated efficacy on morbidity/mortality outcomes, dronedarone represents a new advance in the management of patients with atrial fibrillation/flutter, addressing an important unmet clinical need for patients and physicians. This supports the proposed indication for dronedarone."

Three doses of dronedarone were tested – 400 mg BID, 600 mg BID, and 800 mg BID – and 400 mg BID was chosen because it "was associated with the greatest efficacy and least toxicity." That dose showed both rate and rhythm control.

The company offered three possible explanations for the differing results in ANDROMEDA and ATHENA.

1. **The clinical stability of the patients differed.** Both trials enrolled patients with low ejection fraction and/or with NYHA Class II-III heart failure, but ANDROMEDA patients had been hospitalized recently for worsening heart failure, while "such unstable patients" were excluded from ATHENA. "Analyses of ANDROMEDA and ATHENA subgroups with a low ejection fraction or with Class III heart failure indicated that these subgroups responded differently in the two trials…(suggesting) that clinical instability was an important determinant of the effect of dronedarone but that ejection fraction or functional class did not influence response to the drug in clinically stable patients…These findings suggest that clinically stable patients with moderate-to-severe left ventricular dysfunction (LVD) or with moderate-to-severe symptoms of heart failure would benefit from treatment with dronedarone, since they showed the greatest absolute benefit from treatment."
2. **Use of ACE-I/ARBs**, though analyses have indicated that the differential use of ACE inhibitors and ARBs in a small proportion of ANDROMEDA patients could not account for the increase in risk observed in the ANDROMEDA trial.
3. **Small number of events over a short period of time in ANDROMEDA**. "However, since the clinically unstable patients enrolled in ANDROMEDA have not been evaluated in any subsequent trial, this possibility cannot be objectively evaluated…As a precautionary measure, Multaq is contraindicated in patients with worsening congestive heart failure (CHF) or hospitalized for CHF within the last month."

Sanofi-Aventis has conducted numerous trials of dronedarone, including DAFNE, EURIDIS, ADONIS, EROTA, and DIONYSOS, in addition to ANDROMEDA and ATHENA. All showed efficacy. Only ANDROMEDA raised any safety questions.

DIONYSOS, which was initiated at the request of European regulators, was a randomized, double-blind, head-to-head comparison with amiodarone in 504 AFib patients followed for at least six months. It found that dronedarone was better tolerated than amiodarone but less effective in reducing the recurrence of AFib. The primary endpoint was AFib recurrence or premature study drug discontinuation for intolerance or lack of efficacy. Recurrences of AFib were reported to be more frequent in the dronedarone group vs. amiodarone, but premature drug discontinuations due to intolerance were higher with amiodarone.

Presentation to the panel

Richard Gural, PhD, head of regulatory affairs for Sanofi-Aventis, claimed there is a medical need for a new drug like dronedarone, asserting, "There is an unmet medical need for drugs that improve morbidity/mortality beyond reducing recurrences of atrial fibrillation." He then reviewed the pharmacokinetics of dronedarone and the Phase II/III clinical development program.

Dr. Gerald Naccarelli, an electrophysiologist from Hershey Medical Center, discussed the unmet medical need for dronedarone. He pointed out that AFib/AFL is associated with a 2-fold increase in the risk of death, a 2- to 3-fold increase in the risk of CV hospitalization, a 4.5-fold increase in the risk of stroke, and worsening heart failure or adverse atrial and ventricular remodeling. He noted that the AFFIRM trial showed that control of AFib may not reduce the risk of death or CV hospitalization and that current treatments for AFib/

AFL have not been shown to reduce the risk of death or hospitalization. He speculated that dronedarone could influence mortality and morbidity by affecting both rate and rhythm and preventing the recurrence of AFib/AFL.

Dr. Milton Packer, a cardiologist from the University of Texas Southwestern Medical Center at Dallas, reviewed the effect of dronedarone on major CV events in the ANDROMEDA and ATHENA trials. He noted that amiodarone is commonly used off-label for AFib/AFL: "In general there is no favorable or unfavorable effect of amiodarone – a neutral effect – on morbidity and mortality in large scale trials...Because amiodarone is not associated with an increased risk of death, amiodarone is currently regarded as the first choice anti-arrhythmic drug in the management of non-permanent AFib in patients with heart failure, especially in those with Class III-IV symptoms, even though it is not FDA-approved for this indication."

Dr. Packer noted that amiodarone and dronedarone do not necessarily have the same effects on CV events, "In every single measure, there is a reduction in systolic and diastolic blood pressure that is generally seen starting about the first week and maintained through follow-up. And the magnitude of effect is consistent across all the studies. And there is an effect of 2-3.5 mmHg."

➢ **ANDROMEDA trial** – focused on patients with the highest possible risk of a major CV event. The trial was stopped early by the data safety monitoring board (DSMB) because of a higher mortality rate with dronedarone. He suggested 3 possible explanations for these results:

- **A chance finding**, a false positive result.
- **Due to difference in background medication use**. Increases in serum creatinine may have led to differential use of RAAS agents (ACE inhibitors or ARBs). Adjustment for use of ACE-I/ARBs did not alter the effect of dronedarone. "I don't think this is the explanation…If one looks at the effect of dronedarone vs. placebo, there is still an increase in risk (with dronedarone)…So part of the briefing documents raises this, but I don't think this is a credible explanation."
- **A deleterious effect of dronedarone in recently unstable patients** who were hospitalized for decompensated heart failure and who did not have non-permanent AFib. He said the trial enrolled only patients with recent clinical instability, and 11.3% of trial patients had permanent AFib/AFL, 20.3% had long-standing AFib/AFL, 6.7% had recent onset AFib/AFL, and 61.7% had no past or current AFib/AFL. A post hoc analysis found dronedarone did not increase the risk in patients with non-permanent AFib.

Post Hoc Analysis of Risk of Deaths in ANDROMEDA Trial

Type of AFib/AFL	Placebo death	Dronedarone death
No past or current	3.1%	5.6%
Long-standing	7.6%	18.0%
Recurrent (<6 months) onset of recurrence – arrhythmia not terminated	0	6.9%
Recent (<6 months) onset or recurrence – arrhythmia terminated	5.6%	4.2%

➢ **ATHENA trial –** focused on patients likely to receive the drug in clinical practice. Dr. Packer said, "Event rates in this trial were not meeting expectations, particularly for purposes of mortality, so the sponsor decided to enrich the likelihood of a CV event by moving the age bar from 70 to 75 and requiring everyone in the study to be at least 70, and if you had no CV risk factors, at least 75 years old …The major distinction between ATHENA and ANDROMEDA was the exclusion of NYHA Class IV heart failure patients in ATHENA."

Dr. Packer said the trial protocol was changed to include more patients because it appeared the mortality effect, which was the reason for doing the trial, would not be met with the original trial size, "The agreement with the FDA…was to increase the sample size from 3,700 to 4,300…The whole purpose was to achieve a total of 260 deaths – the number not for a mortality advantage but the number needed to rule out a 50% increase in the risk of death."

ATHENA All-cause Mortality and CV Hospitalization

Measurement	Placebo n=2,327	Dronedarone n=2,301	Relative risk reduction
All-cause mortality	139	116	16%
All-cause mortality or CV hospitalization	917	734	24%

Dr. Packer concluded, "In the ATHENA population this drug (dronedarone) is not associated with an increased risk of death…The mortality results of ATHENA are discordant with those of ANDROMEDA." He also reassured the committee that "no matter how you analyze these data…the results are the same. The results are not changed…And the results of ATHENA on all-cause mortality or all-cause hospitalizations …found a significant reduction in risk in the dronedarone group vs. placebo…All of the effect on hospitalization was for CV hospitalizations – a 26% reduction for CV reasons and no decrease or increase for the risk of non-CV reasons."

How can patients who will benefit from dronedarone (ATHENA-like) and not be harmed be identified? Dr. Packer said, "It is not feasible to ask physicians to distinguish between NYHA Class II and Class III heart failure patients or between patients with an LVEF of 34% vs. 36%." He summed up:

1. ATHENA demonstrated that dronedarone reduces the combined risk of all-cause mortality or CV hospitalization in patients with recent history or recent onset AFib, and all subgroups, including patients with NYHA Class III heart failure and LVEF <35% showed benefit.
2. The effects of dronedarone in ATHENA differed "dramatically" from those in ANDROMEDA.

3. Differences between the 2 trials may have been due to:
   a. "Imprecision of the estimates of risk due to frequent interim monitoring of a small number of events in ANDROMEDA."
   b. Lack of overlap in types of patients enrolled.

Dr. Packer's Approach to Reconciliation of ATHENA and ANDROMEDA Results

Type of patients	Dronedarone appropriateness
Non-permanent AFib	Dronedarone can be appropriately used in these patients
No symptoms of CHF	
EF >35%	
Class II CHF	
EF ≤35%	Should dronedarone be prohibited in all of these patients? Can dronedarone be used in a specific subset of these patients?
Class III CHF	
Class IV CHF	Dronedarone can be used effectively and safely in a specific subset of these patients (i.e., ATHENA-like patients)
No past or current AFib	
Permanent AFib	

Proposed Selection Criteria for AFib Patients Treated with Dronedarone

Type of patients	ATHENA-type patients	ANDROMEDA-type patients
	Appropriate use	Inappropriate use
No symptoms of CHF	If clinically stable during the past month	
EF >35%		
EF ≤35%	If clinically stable during the past month	If hospitalized for heart failure or class IV symptoms within the last month
Class II CHF		
Class III CHF		
Class IV CHF		If hospitalized for heart failure or Class IV symptoms within the last month
No past or current AFib		
Permanent AFib		

Dr. Paul Chew of Sanofi-Aventis reviewed the safety of dronedarone in AFib/AFL trials. Dr. Chew concluded, "We believe the identified and characterized safety risks are manageable and able to be handled with labeling." He said drug interactions with beta blockers, digoxin, and statins are "manageable."

Dr. A. John Camm, an electrophysiologist from St. George's University of London, U.K., and chairman of the European Society of Cardiology's Committee on AFib guidelines, which are in the process of being updated, said the identified benefits of dronedarone include:

- Prolongation of time to first CV hospitalization or death – a 24% risk reduction in ATHENA, consistent across all major subgroups.

Adverse Events with Dronedarone in Pooled Analysis of 5 Trials

Adverse event	Placebo n=2,875	Dronedarone n=3,282
GI	20.8%	24.1%
Diarrhea	5.8%	9.0%
Nausea	3.1%	4.9%
Vomiting	1.1%	2.0%
Blood creatinine increased	1.1%	4.0%
Renal failure	0.5%	0.6%
Acute renal failure	0.2%	0.6%
Bradycardia	1.0%	3.3%
QT prolongation	0.5%	1.3%
Sinus bradycardia	0.5%	1%
Hypothyroidism	0.2%	0.6%
Hyperthyroidism	0.4%	0.3%
Abnormal thyroid function test	<0.1%	0
Insomnia	1.5%	1.5%
Tremor	0.6%	0.6%
Sleep disorder	0.1%	0.3%
Interstitial lung disease	<0.1%	<0.1%
Pulmonary fibrosis	<0.1%	<0.1%
Pneumonitis	<0.1%	<0.1%
Any hepatic treatment-emergent adverse event	2.5%	2.9%
Any serious treatment-emergent adverse event	1.0%	0.9%
Any hepatic treatment-emergent adverse event leading to discontinuation	0.2%	0.3%
Hy's Law patients (ALT >3xULN + bilirubin >2xULN)	0.06%	0.1% *

* The rate with amiodarone 600 mg/200 mg with 155 patient-years is 0.65%

- Numerical reduction of all-cause mortality – not statistically significant, but it is very unlikely that dronedarone is associated with an increased mortality. Exploratory analyses show marked reductions of all-cause death, CV hospitalization, CV death, and sudden cardiac death.

Comparison of Dronedarone and Other AFib Drugs

Drug	Potential adverse effects	Dronedarone
Flecainide and propafenone	Ventricular tachycardia Conversion to AFL with rapid conduction Aggravation/provocation of heart failure	Low risk of ventricular tachycardia No report of AFL with rapid conduction No increased heart failure in stable patients
Dofetilide	Torsades de pointes	Low risk of Torsades de pointes (1 case reported)
Sotalol	Torsades de pointes Bradycardia Aggravation/provocation of heart failure Exacerbation of asthma/COPD	Low risk of Torsades de pointes (1 case reported) Low incidence of significant bradycardia No increased heart failure in stable patients Little observed effect on pulmonary disease
Amiodarone	Photosensitivity, pulmonary toxicity, GI upset, bradycardia, hepatic toxicity, thyroid dysfunction, eye complications	Lower incidence of amiodarone-like side effects

Dr. Camm admitted dronedarone does have safety issues, but the "benefit:risk for dronedarone in the treatment of appropriate patients is uniquely positive." Safety issues are:

- GI side effects – occur early and are manageable.
- Increased serum creatinine – is well characterized, not due to renal toxicity, and managed easily.
- Drug/drug interactions can be managed – e.g., reducing the dose of digoxin and some statins.
- Multi-organ toxicities are noticeably less than with amiodarone, but will be further studied post-approval.
- Recently "unstable" heart failure patients must be avoided.

What does dronedarone mean for the patient? Dr. Camm said:

- Little pro-arrhythmic risk.
- Could be initiated outpatient.
- No deleterious impact on oral anticoagulation management.
- Potential for better compliance and adherence.
- Decreased AFib and CV hospitalization.

Appropriate Patients for Dronedarone

Appropriate patients – Excellent benefit:risk	Inappropriate patients – Poor benefit:risk
Recent history of AFib or current non-permanent AFib in patients with associated CV risk as recruited in the ATHENA trial	Symptoms of heart failure at rest or with minimal exertion, or hospitalization for heart failure within the last month, as recruited in the ANDROMEDA trial

THE FDA PERSPECTIVE

Briefing documents

In briefing documents the FDA prepared for the panel in advance of the meeting, the lead FDA reviewer, Dr. Abraham Karkowsky, recommended approval of dronedarone to "delay recurrence of symptomatic events and decrease hospitalization for AFib, in a population likely to have recurrence of AFib… (But) no mortality claim should be granted…(And) individuals with NYHA Class III or IV heart failure should be precluded from its use. The tricky issue is how to control those whose heart failure transitions into NYHA Class III from less severe degrees of heart failure."

Dr. Karkowsky told the panel, "It does not appear that the mortality excess, as observed in the ANDROMEDA study can be explained by a model in which subjects had asymptomatic creatinine increases which provoked discontinuation of ACE-I or ARB treatment and only then resulted in cardiac decompensation. All events which provoked discontinuation of the ACE-I/ARB treatment appear to be acute exacerbations of either renal or cardiac disease at the time these drugs were discontinued."

Among Dr. Karkowsky's other concerns and comments were:

- **Definition of CV death** – "The broad outline of what constitutes a CV death appears somewhat arbitrary and in some cases irrelevant to events that would likely be preventable in this population. It is unclear if the new analysis of cause-specific mortality events adds clarity to any benefit of dronedarone or the results merely allow for a second attempt at defining a mortality benefit."
- **ATHENA not convincing** – "The results of the ATHENA study with respect to CV outcomes are so discrepant with the results from the ANDROMEDA study, that caution should be exercised in asserting dronedarone as having a mortality benefit."
- **Reasons for AFib/AFL hospitalizations unclear** – "CV hospitalizations…(are) driven entirely by the AFib/AFL hospitalization. The underlying reason the subjects were hospitalized for AFib/AFL is unclear."
- **Dronedarone is a useful anti-arrhythmic for AFib but hasn't shown a mortality benefit** – "I find the (trial) results…consistent with the conclusion that dronedarone is a useful anti-arrhythmic to delay recurrence of symptoms associated with the underlying arrhythmia and to prevent atrial fibrillation hospitalizations….(but not that) dronedarone prevents other morbid or mortal outcomes."
- **Approval should be limited to AFib and not include atrial flutter.**
- **A new trial – DIONYSOS – suggests dronedarone is less effective than amiodarone.** This conclusion is based on top-line data; the Agency has not yet reviewed the complete results.

Dr. Karkowsky did not buy Sanofi-Aventis's explanation for the excess deaths in ATHENA, which he said would suggest this sequence of events: "First, the subject would have an asymptomatic creatinine elevation leading to the discontinuation of the ACE-I/ARB and only then would the patient be at risk for cardiac decompensation or death…(But) among those who died, there were few subjects whose creatinine increases were unrelated to either a cardiac or renal insult. The percentage of subjects who were treated with dronedarone who died was substantially higher whether they were not treated with ACE-I/ARBs at baseline or discontinued from these medications."

Other FDA reviewers, Dr. Gail Moreschi and Valeria Freidlin, PhD, were also skeptical about dronedarone. They raised several issues, including:

- **Secondary endpoints.** Since the main secondary endpoint was not met, other secondary endpoints – e.g., CV death – "should not be tested at all."
- **The reliability of the CV death classifications.** "The nominal p-value of only p=0.03 for CV mortality (in ATHENA)…is inconclusive and may be due to data dredging."

- **Safety concerns.** "These reviewers are concerned regarding the safety of dronedarone…There is a continuum in patients with AFib/AFL; they go in and out of congestive heart failure. We feel that the safety of dronedarone presents a problem that the label alone may not be able to cover."
- **Insufficient rhythm/rate control.** "The prior studies… for rhythm and rate control did establish that patients stay in normal sinus rhythm a little longer than placebo, but their heart rate on dronedarone when exercising is not within the ACC Guidelines."
- **Efficacy.** Although the composite of death from any cause or CV hospitalization was highly statistically significant, "the efficacy of the prevention of death from any cause was not established…The composite endpoint was driven mostly by…CV hospitalizations. Note that the need to hospitalize these patients varies from physician to physician and country to country."
- **Concerns with ATHENA trial.** "The patients in… ATHENA…were not as sick as those in the prior ANDROMEDA study."
- **Side effects.** "GI disorders, QT prolongation, increased serum creatinine suggest that patients on dronedarone will go into heart failure (and)…may not do well if on dronedarone…If approved, (dronedarone) will be utilized chronically. We do not know if ultimately patients will develop the side effects as seen with amiodarone or if they will develop the endocrine, teratogenicity, and carcinogenicity problems as seen in the animal models."
- **Dosing.** Exposure is elevated in elderly patients and Asian males raising questions about safety in those populations of the proposed dose.

FDA presentation to the panel

Dr. Karkowsky cautioned that "dronedarone, even though it looks a lot like amiodarone, may not be an analog of amiodarone." He offered several points for the panel to consider about dronedarone:

- **Biopharmaceutical issues.**
  - Poor bioavailability.
  - Interacts with P-gp and can increase digoxin exposure 2.5-fold.
  - ~90% cannot be accounted for.
  - At least 30 metabolites, nearly all unidentified.
- **Toxicology issues.**
  - Mutagenic in one *in vitro* model.
  - Suggestion of drug-related tumors in animal models.
  - Teratogenic in at least 1 model species.
- **Pharmacology issues.**
  - Potentially a negative inotrope.
  - Would likely prolong cardiac repolarization.

NYHA Class and Risk of Death in ANDROMEDA Trial

Patient group	Placebo	Dronedarone
NYHA Class		
Class II	4.2%	5.6%
Class III	3.8%	9.6%
Class IV	0	17%
Wall motion index at baseline		
0.3-0.7	0	10.7%
0.8-0.9	5.2%	9.2%
1.0-1.1	7.4%	1.3%
1.1-1.2	4.1%	9.4%

On ANDROMEDA, Dr. Karkowsky noted, "The sponsor's early hypothesis was that mortality in ANDROMEDA was a consequence of early discontinuation of ACE-I/ARB as a consequence of dronedarone's ability to inhibit creatinine secretion…This hypothesis requires that an asymptomatic serum creatinine increase provoked the discontinuation of ACE-I/ARB…(However,) deaths do not appear to be related to ACE-I or ARB status during the study…The increased mortality...in ANDROMEDA…cannot be attributed to an inappropriate discontinuation of ACE-I or ARB."

On ATHENA, Dr. Karkowsky's criticisms included:

- The statistical analysis plan was submitted after the interim look, and the secondary endpoints were re-arranged at that time, with CV hospitalization placed higher in the hierarchy of secondary endpoints than CV mortality."
- Prior to the statistical change, all-cause mortality was not statistically different comparing dronedarone to placebo (p=0.24).
- All-cause mortality was not significant; therefore, additional analyses are exploratory in nature.
- CV mortality before the protocol change was less with dronedarone (p=0.03).

Comparison of Patients in ANDROMEDA and ATHENA Trials

Measurement	ANDROMEDA	ATHENA
Patient population	Recently hospitalized or clinic visit for heart failure requiring at the minimum IV diuretics	Elderly population with history of AFib/AFL and normal sinus rhythm
Age	70	72
Male	76%	55%
Median wall motion index	0.9	Unknown
LVEF	Unknown	Mean 57%
NYHA Class 0	0	70%
NYHA Class I	0	8%
NYHA Class II	39%	17%
NYHA Class III	58%	5%
NYHA Class IV	3%	0

- "Nearly all the effect" on CV hospitalizations was due to AFib hospitalizations. The case reports did not capture whether patients were hemodynamically unstable, had an exacerbation of heart failure, or were admitted for anti-coagulation. "It is unclear why these patients were hospitalized for AFib."

Dr. Karkowsky questioned whether cause-specific measurements clarify or allow for a second statistical look. He also cited cases where an event was classified as CV with placebo while a relatively similar event was classified as not CV in a dronedarone patient, "Errors in classification add a…form of uncertainty. All-cause mortality includes events not likely to be altered by the use of an anti-arrhythmic drug…CV mortality is only an exploratory analysis, there are potential errors in the characterization of events, and the results are inconsistent with the ANDROMEDA study."

FDA Summary of Dronedarone Trial Deaths

Measurement	Placebo	Dronedarone
ANDROMEDA		
Overall deaths	3.7%	8.1%
Adjudicated CV deaths	2.8%	7.7%
Adjudicated as death due to worse heart failure	1%	3%
ATHENA		
Categorized as death due to worse heart failure	0.3%	0.6%

So, how did the FDA interpret the discrepancies? Dr. Karkowsky said, "There are two studies with remarkably different outcomes. Both studies contribute data points to risk based on heart failure patients. If not for the results of the ANDROMEDA study, subgroup analyses would offer comfort. In the presence of the ANDROMEDA results, there has to be an inflection point to negative mortality outcomes based on degree of heart failure. Small numbers in the trials for the population or in subgroups of populations make the conclusions less reliable, both for risk and for comfort."

He concluded with a question, saying that three trials suggest "a benefit in delay of recurrent of AFib. The ANDROMEDA study suggests subjects with heart failure have an adverse outcome. The ATHENA study suggests no overall adverse mortality outcome in patients without severe heart failure and a decrease in AFib hospitalization. Where is the cross-over point?"

Panel Questions for FDA Reviewers and Company Experts

ANDROMEDA findings could be chance. Both Dr. Sanjay Kaul (a cardiologist from Cedars-Sinai Heart Institute in Los Angeles) and Dr. Neaton, a biostatistician, agreed with the company experts that the negative mortality findings in the ANDROMEDA trial could be due to "a play of chance."

FDA reviewer Dr. Karkowsky said the ANDROMEDA trial results continue to bother him, despite the findings in ATHENA, "If I didn't have ANDROMEDA, I would have come to a different conclusion and a different recommendation. With ANDROMEDA, if you can't discount it or make it go away by some method, you are stuck with a population for which you know it is (harmful) and one population where you suspect it may be useful."

Dr. William Calhoun, a pulmonologist from the University of Texas Medical Branch in Galveston, added, "It seems to me that ANDROMEA has generated a great deal more heat and smoke than light."

Heart failure instability vs. severity. Dr. Packer argued that ***stability*** is more important in excluding patients from dronedarone than heart failure ***severity***. He said physicians have experience in managing beta blockers in heart failure patients, and dronedarone is a similar situation – use is beneficial and safe in stable heart failure patients but should be avoid in acutely unstable heart failure patients, "There is one other class of drugs that, as clinicians, we say is okay to be given in patients with Class III heart failure as long as they are clinically stable and not okay if they are currently clinically unstable, and that is beta blockers…The analogy here is very similar to beta blockers…For beta blockers in heart failure, we treat some awfully sick patients, but we make sure they are clinically stable before initiating therapy…If you are clinically unstable, you have to stabilize before starting therapy with a beta blocker."

Dr. Robert Temple, director of the FDA's Office of Medical Policy and director of the FDA's Office of Drug Evaluation, CDER, appeared to find this argument interesting and important. Dr. Temple asked Dr. Karkowsky for his opinion of Dr. Packer's argument. Dr. Karkowsky said, "Whether it was instability or the degree of heart failure, I can't tell from the data I have."

Composite primary endpoint. The FDA's Dr. Temple said, "It was overwhelmingly expected that the (beneficial) effect would be driven by hospitalizations, (but) it seemed irresponsible not to include death in the (primary) endpoint…We have asked that any drug with an arrhythmia claim provide reasonable assurance that they are not rubbing people out."

Asked for his view of the hospitalization finding, Dr. Karkowsky responded, "There was an overwhelming effect on hospitalizations."

Change in the ATHENA statistical plan. *Asked about criticisms of the ATHENA trial because there was an interim analysis and a subsequent change in the statistical analysis method*, the FDA's Dr. Temple said, "We do have a continuing problem with late modifications, and we are urging everyone to do it earlier. Even though everyone says, 'Don't worry; it was blinded,' we really want it done earlier." Dr. Packer, a Sanofi-Aventis expert speaker, said, "The statistical plan was in the original protocol. The only reason there was a 'late submission' (change) was at the request of the FDA, which said, 'You have three secondary endpoints. If you want a claim for any secondary endpoint, you have to create a hierarchy, so please submit a modified statistical plan that specifies the hierarchy.' That was it. That was the only change in the statistical plan. It is important for the committee not to have the impression the sponsor knew anything going on… other than to respond to an FDA request."

PUBLIC WITNESSES

All three public witnesses supported approval of dronedarone.

Susan Levy, National Association of Medical Directors. She supported approval of dronedarone because so many elderly people have AFib.

James Baranski, CEO, National Stroke Association. "The physician side can be summed up in four words: 'Big problem, few options'…Of the 780,000 strokes, about 15% are the result of AFib, and an estimated 6 million stroke survivors are desperately, desperately seeking any alternative to prevent recurrent stroke." He compared the current AFib medications to the subprime loans and the banking situation, "'Toxic assets' keeps popping up in my head...From the patient perspective this seems like a toxic asset question. There has to be another solution."

Melanie True Hills, StopAfi.org, a patient advocacy website sponsored by Sanofi-Aventis and others. She said she is an AFib survivor herself, "I had a surgical procedure that cured my AFib and gave me back my life…After being cured, I couldn't stand on the sidelines and watch as others suffered… What is taking the FDA so long? I'm hearing that over and over from patients having trouble with amiodarone...Believe me the AFib community is far from unbiased over this…The AFib community is asking you, 'Won't you please give us options? Won't you please give us solutions? Won't you please give us our lives back?'"

FDA QUESTIONS TO THE PANEL

QUESTION 1a. Sanofi-Aventis now believes that adverse effects in ANDROMEDA were related to clinical instability of the ANDROMEDA population. Does the committee find this explanation plausible? Are the differences in cause of death consistent with the sponsor's hypothesis? YES

Panel comments included:

- *Dr. A. Michael Lincoff, a cardiologist and vice chairman for clinical research at the Cleveland Clinic:* "I think it is reasonable, and the data support the idea that this patient population was unstable, and that is a potentially good explanation for the mortality difference, especially with the lack of a mortality hazard in a less sick patient population in ATHENA."
- *Dr. Sidney Wolfe, director of the Health Research Group of Public Citizen and the panel's consumer representative:* "Blaming the patient as a cause is reasonable in this case. These people were clearly sicker…We do have a negative inotrope, but maybe because of their condition, they were more susceptible to a negative inotrope."
- *Dr. Robert Harrington, a cardiologist from Duke University and the panel chair:* "This may well represent a deleterious effect of the drug in a clinically unstable population."
- *Dr. Calhoun, a pulmonologist:* "(The) idea that this may be a false positive is something we can't discount… However, in that patient safety is really paramount, we have to treat this as a real finding."
- *Dr. Black, a nephrologist:* "The only plausible explanation is chance, or this is a patient population at risk, and we have to be careful when we use it."

QUESTION 1b. In ATHENA, during the specified period of follow-up, there were 135 deaths on placebo (5.8%) and 115 deaths on dronedarone (5.0%, relative risk=0.86). Are these results compatible with mortality in ANDROMEDA when you compare: confidence limits, populations enrolled, and patient management? YES

Panel comments included:

- *Dr. Neaton, a biostatistician:* "The goal was to rule out 50% higher mortality, and they achieved that…which speaks for itself. Even when you include ANDROMEDA ...(the relative risk of mortality) would be 1.17-1.18, so from a statistical point of view, they are not dissimilar. They look different in the two populations, but I think we have a situation where the sponsors have done what they set out to do – rule out a mortality risk >50%...The data here suggest that, from a statistical point of view, these (six trials) are poolable…Another way of looking at this is each of these studies is essentially providing an

estimate, some more reliable than others, of the same effect." (He explained that a relative risk <1.20 would be considered similar.)

- *Dr. Kaul, a cardiologist:* "I agree, but I am concerned that the point estimates are in two different directions. Typically, the point estimates don't change that much… So, that is bothersome to me." He said he would call these distinctly different results.
- *Dr. Darren McGuire, a cardiologist from the University of Texas Southwestern Medical Center in Dallas:* "I think they are comparable…Beta blockers are deleterious in acutely unstable (heart failure) patients and beneficial in the stable patients…I think we have a lot of plausible mechanistic explanations, all of them completely theoretical but certainly compatible with the results of the two trials."
- *Dr. Lewis Nelson, a toxicologist from New York University School of Medicine:* "It is obvious these are two separate patient populations…One thing I'm a little concerned about is a third patient population we haven't looked at…We really don't know what that risk:benefit is in that group, and when the drug is marketed more widely, we know it is dangerous in patients who are quite ill…It has some benefit in patients with moderate degrees of illness…The other patient population may be very large, depending on how the drug is generalized once it is approved."
- *Panel chair:* "While the label may say one thing, the usage may be much broader, and we may not have information about that group."
- *The FDA's Dr. Stockbridge:* "Are you reassured that in ATHENA people who presumably are not unstable but who were the sickest appeared to do best?"
- *Dr. Nelson:* "There are a lot of other issues not touched on, such as people will be on this for 20-30-50 years, and there are no long-term safety studies. We discussed pulmonary toxicity, which is a risk apart – amiodarone (which causes pulmonary toxicity) often doesn't manifest for quite a long time, and we don't know mechanistically why amiodarone causes that. This drug is structurally very similar. I think we can feel comfortable the thyroid effect won't occur...but there are a lot of issues. So, even though there might be some short-term risk:benefit, as it progresses over time, all bets are off…There are thousands of reasons people have AFib…The benefit may change, but the risk is persistent. The risk to a 75-year-old may not be any different than the risk to a 20-year-old except the 20-year-old will be on it for life."
- *FDA's Dr. Temple:* "You are worried that it will be used by patients at lower risk?…I gather the company is planning to do longer-term pulmonary studies, and we will be interested in that…There are ways to track a cohort and look for pulmonary fibrosis, and we will talk to the company about that."
- *Dr. Black:* "I would be tempted to use this *before* a patient gets AFib."

QUESTION 2. ATHENA's planned enrollment was 4,300, but the actual enrollment was 4,637. Why? The panel generally agreed this protocol change was not a problem.

The panel dissenters were the most vocal:

- *FDA's Dr. Karkowsky:* "(I am comfortable with that)… but I have no information to add…It seemed reasonable what they did, but there is always that question when things occur late after an interim look. Although you think everyone is honest, it is still uncomfortable…I see why they did that, but it could be something else."
- *Dr. Emil Paganini, a nephrologist from Chesterland OH:* "I agree with Dr. Stockbridge that adding the additional patients could indicate something sinister."
- *Dr. Kaul:* "The addition of more patients wouldn't change the primary endpoint, but it could affect secondary endpoints, such as cardiovascular mortality."

QUESTION 3. Some analyses categorized hospitalizations and deaths as cardiovascular or non-cardiovascular. Please comment on:

a. The categories of events that were considered CV or non-CV. Insufficient data for a CV death benefit claim.

b. The adequacy of the information on the case report form to support categorization. Insufficient since the deaths weren't adjudicated

The panel went further arguing that there should not be any mention of CV death in the label even though it is part of the combined endpoint. Their concern was that the mention of CV death as a part of a positive combined endpoint would mislead people into thinking there was a CV benefit when there isn't.

Panel comments included:

- *Dr. Lincoff:* "The way the CV deaths were adjudicated, I feel very strongly we cannot make conclusions based on CV death…That categorization is flawed, intrinsically. There is insufficient information collected in this trial. No statement can be made on CV death…I don't think the form provides enough information, and even if it had, the right way to do this if you want a statement on CV death is to adjudicate the deaths."
- *FDA's Dr. Temple:* "We would normally put the nature of the combined endpoint somewhere in the label. That's part of what you do when you win on a combined endpoint. Ordinarily, that is what we would do, without a p-value. It seems odd not to put it in."

- *Dr. Lincoff:* "That is very interesting. I understand the rationale, but we don't have enough information about some of the components to definitively say there is an effect. I think the reason this needs consideration is that there was another trial that suggested ***increased*** mortality."
- *Panel chair:* "We frequently use composite endpoints, and death just seems like it should always be in there…I feel uncomfortable arguing against (putting CV death in the label), but I think there might be a special situation here."
- *FDA's Dr. Temple:* "The composite endpoint was driven largely by CV hospitalization, sort of downplaying the mortality component. It is fairly obvious you are going to say something about the mortality endpoint. It was there, not necessarily to win but to show something."

QUESTION 4a. In ATHENA, is the effect on CV hospitalizations more than an effect on symptomatic AFib (AFib leading to hospitalization)? Unanimously NO

Panel member comments included:

- Dr. McGuire said he believes the effect is not limited to symptomatic AFib.
- *Dr. Lincoff:* "I don't know if the mechanism is anything but AFib…but I do believe there are important cause of hospitalization other than just AFib."
- *Dr. Wolfe, consumer rep:* "I think that, at least from my perspective…it is almost entirely accounted by AFib hospitalizations. And we don't have a clue what the AFib hospitalizations were like except (in the trial) someone ticked off AFib, and this is unfortunate."
- *Dr. Kaul, cardiologist:* "The overall hazard ratio is 0.75, and for the AFib indication it is 0.63, and for non-AFib it is 0.86. So, the answer is yes, its effect on CV hospitalization is driven by the effect on AFib-induced hospitalization."
- *Dr. Neaton, a biostatistician:* "It seems to me the answer is it is primarily driven by AFib hospitalization, but in ATHENA we see a modest effect that is maybe significant on other hospitalization besides AFib."
- *FDA's Dr. Stockbridge:* "The direction in the label will say something about the composite endpoint. It will say the composite was essentially all CV hospitalization and then say what exactly about whether CV hospitalization was mostly or largely AFib-related?"
- *Panel chair Dr. Harrington:* "You'd say in the CV hospitalizations, which is a composite endpoint, that the effect is largely driven by a reduction in hospitalization for AFib, and you can provide the data on the other CV components."
- *FDA's Dr. Stockbridge:* "Would you expect to see an advertisement that says: 'The effect on hospitalization – it's more than AFib'"?
- *Dr. Lincoff:* "What we have is evidence it (dronedarone) reduces hospitalization related to AFib. That is a reasonable claim. That pathophysiologically fits."
- *Panel chair:* "You are seeing a reduction in hospital related AFib. And you don't know which came first."
- *Dr. Temple:* "You take some reassurance in the finding of excess of heart failure hospitalizations."
- *Dr. Neaton:* "I go back to the unmet need for drugs that do more than reduce hospitalization for AFib recurrence, and I don't think the data here are real convincing on that. So I would hate to see an advertisement or claim for that."

QUESTION 4b. In ATHENA, are the study results on CV hospitalizations applicable to U.S. practice? Mixed answers

QUESTION 4c. While heart failure hospitalization trended lower on dronedarone (3% vs. 4%), other potential signs of worsening heart failure trended adversely – peripheral edema (6% vs. 5%), fatigue (5% vs. 4%), and dyspnea (5% vs. 4%). How do you reconcile these findings? The panel agreed that these are small differences and that the harder endpoint of CV hospitalization is lower in favor of the drug.

Panel comments included:

- *Dr. Wolfe:* "We have this idea that it (dronedarone) is a negative inotrope, and it might be that when it is related to heart failure. The heart failure itself, even though the cases are different, the severity is more."
- *Panel chair Dr. Harrington:* "That is a theme from a number of you – this notion that if the drug were to be approved and marketed, understanding its effects in LVEF or heart failure patients…is going to have to be worked out…so certainly more investigation is going to be warranted."

QUESTION 5. Is there an effect of dronedarone on atrial flutter? YES

QUESTION 6. The secondary endpoints were arranged to be analyzed sequentially. The first secondary endpoint was all-cause mortality, which trended non-significantly (p=0.25) lower on dronedarone. Thus, one is not entitled to evaluate subsequent endpoints of CV hospitalization alone (RR=0.75, p<0.01) or CV death (RR=0.70, p=0.037). However, there was no possibility of getting a claim for all-cause mortality (too broad to be meaningful). Can you

ignore all-cause mortality because it should never have been in the analysis plan, and if so, is there a reasonable basis for a claim on CV death? NO

The FDA's Dr. Stockbridge clarified the issue: "The question here is whether someone is tied to an analysis plan that we may have bought into but which doesn't really make a lot of sense. It was not a sensible thing to stick all-cause mortality in as the first secondary endpoint. If they thought it was only worth talking about because it was reassuring that overall it would carry the day on all-cause mortality, it shouldn't have been a named secondary endpoint at all. There isn't any likelihood, any plausibility, that a drug really affects all-causes of mortality. So, we weren't going to give them an all-cause mortality claim even if they appeared to earn it. If that is true, why is the chain broken by this endpoint? I'd say the same thing about the CV hospitalization thing. We were going to look at that whether it was part of the formal analysis or not, and if it drove the overall analysis, as it did, that is going to be the major claim they get at the end of the day, so that should not have been in their either."

Panel comments included:

- *Dr. Neaton:* "They probably should get a claim for CV mortality that is very different from what you laid out. If we were in a different situation where there was more cohesive evidence across the studies, and we were confident in the classification, I probably would be inclined to go along with the idea that a sequential (analysis) plan was illogical in the first place, and we should look at the data and make common sense conclusions."
- *Dr. Lincoff:* "I think they (Sanofi-Aventis) were trying to counter the impression of ANDROMEDA, so I understand why they prioritized that endpoint…There have been a lot of trials that didn't try to adjudicate death where you assume most of the deaths are CV-related… You lost power, but so what?...You get a claim for mortality – not all-cause mortality – but mortality."
- *FDA's Dr.* Temple: "It is very common to have all-cause mortality be an endpoint…but we try to look at subgroups and see if all the action is in CV mortality…and my bias is, you put down CV mortality if that is where all the action is because you are misleading people otherwise… That is outside the statisticians. It is clinicians fooling around…I would have put CV hospitalization as my first secondary endpoint because that is where all the action is."
- *Panel chair:* "So, it is still most appropriate for sponsors and investigators to lay their nickel down in terms of a sequential testing plan…hopefully, with logic…but it would be reasonable for you and us to peel back the onion a bit and try to find the predominant effect?"
- *Dr. Temple:* "It is sort of permission for us to noodle around."
- *Dr. Calhoun:* "I agree the CV death claim is on shaky ground, that it does not look to be a robust outcome, but there probably is important information in CV hospitalization…It is focusing too much on process and not outcome."
- *Dr. Kaul:* "I reiterate that the quality of the data regarding CV death are suspect to me, and the original…analysis on CV death fails to include a risk ratio of 1, so to me that should be the basis for any decision we make here."
- *Panel chair:* "And there is some concern about the robustness of the CV death endpoint."

QUESTION 7. If you favored a mortality claim in the previous question, are placebo-controlled trials still ethical in this setting? NO

QUESTION 8. Have dose and regimen been adequately studied? If not, does further study need to be done prior to approval? NO, dosing studies, subgroup studies, PK and PD studies all need to be done.

Panel comments included:

- *Dr. Nelson:* "I don't think it has been adequately studied, or if it was done, it was not presented and well documented. Many levels of study need to be done, most obviously dose ranging. At least the relationship between a dose and a blood level. It seems incomprehensible every single human being can get the same dose. We all have different metabolism…We know bioavailability differs dramatically among people – men, women, Japanese, etc. So, I think we need a lot more data…I also think we need (more) drug interaction studies…This is critical information, and I don't see how, without good quality data, the drug could be let out on its own and given to people on a broad scale…I don't know that it has to be done in a large randomized clinical trial, but I think there has to be good PK and PD data on what we can expect with a given type of human, not a 74-year-old white man…And we need to be able to semi-quantify what a given drug will give on blood level…I just think we have such limited data from these studies…This is a drug with really serious potential side effect issues."
- *Dr. Wolfe:* "This is a drug that killed a lot of people in the first trial, so there is a huge amount of concern…In the real world, there is no question you will have in-between patients…I think there is a huge dilemma here largely, if not entirely, caused by the ANDROMEDA study…We know this drug is toxic in certain circumstances and has killed people. And we know off-label use is ***guaranteed***…I am very concerned about that both in terms of, not so much the dosing but the kinds of people getting dosed."

- Dr. Paganini suggested studying it in acute kidney injury patients.
- *Dr. Black:* "It is late in the game to ask for these things …We haven't seen pulmonary toxicity yet."

QUESTION 9. Who should not receive dronedarone? For each such restriction, please indicate:

a. How *important* it is to restrict use.

b. How *feasible* it is to restrict use.

Use should be restricted in unstable heart failure patients, and there is precedent for this with beta blockers.

Panel comments included:

- *Dr. Lincoff:* "We will never be able to set aside ANDROMEDA. We have to operate on the assumption that ANDROMEDA is real…Probably to start, there should be a cutoff EF, probably 35% to get this."
- *Dr. Krantz:* "I agree. With ANDROMEDA, to not call it out as a potential source of risk is a little risky. It is not like we haven't had drugs like TZD and metformin that we can't use in heart failure…and I think it is feasible to restrict use."
- *Panel chair:* "Perhaps clinical instability is a marker of when not to treat (with dronedarone)…(We might) extend that to patients with heart failure until we have more data and are sure."
- *Dr. Calhoun:* "I was reassured that new onset heart failure during treatment still did better while on active therapy vs. placebo…So, it seems to me that, though post hoc and lots of potential problems with that data, it is reassuring enough to me that I wouldn't restrict it so much...I would be amenable to restrictions on acuity."
- *Dr. Wolfe:* "On using hospitalization as a criterion: the variability around the country on what threshold doctor A uses vs. doctor B is such that I don't think that is reliable."
- *Dr. Kaul:* "The whole premise in ATHENA was to overcome the adverse mortality in ANDROMEDA…but when you combine all the trials, so far I'm not sure, personally, a clinically unacceptable increase in mortality has been excluded…The efficacy appears very modest on normal sinus rhythm and rate control, and the population does not represent the AFib patients in my practice…I'm struggling to find the proper role for this drug in practice …This drug was designed to have fewer side effects than amiodarone…and I'm not sure superior efficacy has been shown…There is a possibility of a quality of life advantage…I don't think this should be given to patients with NYHA Class III or EF <35%. For those patients, amiodarone should be the treatment of choice, and this could be considered if they are intolerant to amiodarone."

QUESTION 10. How concerned are you about adverse effects of dronedarone on renal function, bradycardia, QT prolongation, heart failure, and other safety issues? The panel mostly repeated earlier comments. The biggest concerns were patients with unstable heart failure, liver problems, or structural heart disease.

Panel comments include:

- *Dr. McGuire:* "Defibrillator thresholds – we need to know that…and I would like the issue with Coumadin interactions addressed, not necessarily before approval… ALT has been elevated, and I think we should hold the label to that exclusion if approved…I'm just concerned about cumulative toxicity. The primary advantage was supposed to be reduction in amiodarone toxicity, and that hasn't been demonstrated – one year (of data) is not sufficient, though I don't see a signal that concerns me… We all learned about amiodarone toxicity at a time when it was used at 800 mg/day or 400 mg/day, and it is dose- and time-dependent…At 200 mg/day I'm comfortable (with the amiodarone safety). As a patient, I'm not entirely comfortable, but I think I would be…I would like to see amiodarone at 200 mg to put this safety concern in a clinical context."
- *FDA's Dr. Temple:* "The amiodarone pulmonary toxicity can be seen in <1 year. I am a little puzzled about the (panel's) enthusiasm for amiodarone…Amiodarone is fantastic at preventing AFib, but it isn't very good at preventing death because it does things that kill you… **You wouldn't get me on long-term amiodarone**…I must say I was struck by the modest effect (of dronedarone) in delaying AFib in the two earlier studies and somewhat surprised in the reduction in hospitalizations...but that is what they found. We and others have found decreased hospitalization to be something of value. If people don't think it is of value, I would like to hear more."
- *Dr. Black:* "On amiodarone – cardiologists are afraid of it…I wouldn't start it or change it on a patient. Am I biased against amiodarone? Is my concern about the toxicity reasonable?...(Dronedarone) would replace amiodarone…You wouldn't have pulmonary toxicity, and you wouldn't have a thyroid (problem)…And it would be better tolerated…(Dronedarone) has shown that it probably is not killing people…I think the ANDROMEDA patients shouldn't get this drug. That's just common sense. This is a drug which, overall, is going to be helpful …You could put this drug as something for people who can't tolerate amiodarone."
- *Dr. Lincoff:* "This drug (dronedarone) would certainly be used…If there were a less toxic alternative to amiodarone, it would be used…But if a patient were high risk, then we would preferentially use amiodarone."

- *Dr. Krantz, a cardiologist:* "QT prolongation is not a big concern. I think digoxin and Coumadin are concerns… The question is whether this (dronedarone) is the same as amiodarone on structural heart disease…Amiodarone is the only safe drug for structural heart disease. I don't think we can say that for this drug yet…I agree amiodarone is not safe, but it is the best we have, and we have to be cautious in that context."
- *Panel chair:* "There needs to be more work done here. This should not be a wholesale abandonment of a pretty good drug (amiodarone) that has been worked out over a fair amount of time with a dosing regimen that is now pretty well tolerated in favor of something where we have a lot of uncertainty."

QUESTION 11. Should dronedarone be approved to treat patients with non-permanent AFib? After the vote, please comment on whether you believe the claim should be any broader or narrower than ATHENA's primary endpoint.
VOTE: 15 YES, 3 NO

(*The NO votes were Drs. Nelson and Wolfe and the patient advocate.*)

Panel comments included:

- YES – *Dr. Krantz, cardiologist:* "This is a nice advantage for our patients…I do have some significant concerns on LVEF and heart failure and suggest a boxed label on that. I do not think the indications should be very broad …I think we should be fairly circumspect."
- YES – *Dr. McGuire, cardiologist:* "This is a great step forward in AFib management…I would not be in support of a claim for mortality. The label should be for prevention of CV hospitalization, driven primarily by AFib. I would be in favor of explaining the claim for reduction in AFib recurrence…I think there should be duration labeling and drug interactions with digoxin and Coumadin …I'd consider a black box on NYHA Class III-IV."
- NO – *Dr. Sid Wolfe, consumer advocate:* "(I voted no) partly because of the FDA's statement that 'the safety of dronedarone presents a problem the label may not be able to cover.' It doesn't work as well as amiodarone…And it was (not tested) in real world…patients…There definitely should be a black box (if it is approved). The company already said it would do a Medication Guide, but with this drug we clearly need a black box warning."
- YES – *Dr. Lincoff, cardiologist:* "I think this is an incremental agent with an attractive side effect profile, though it may not be as effective as amiodarone, it is still a useful addition to the armamentarium. I also agree the claim should be for CV hospitalization, not mortality."
- YES – *Panel chair Dr. Harrington, cardiologist:* "I would like to make sure the claim is narrow in scope and that we are very careful about the (instructions about use) in heart failure patients in the labeling. I also would support ***not*** including the mortality claim at all in the label …I would ***not*** include a claim for CV death…I think a number of things need to be done postmarketing, including (studies in) ethnic minorities, comparisons vs. amiodarone, more long-term data. So, a cautious yes."
- YES – *Dr. Paganini, nephrologist:* "I think it is a little less effective than amiodarone, but it is an alternative medication…I think it should be strictly restricted to the less sick population (EF >35% especially)."
- YES – *Dr. Black, nephrologist:* "I agree the restrictions should be tight…We need more information on tolerability vs. amiodarone."
- NO – *Patient advocate Robert Dubbs from West Palm Beach FL:* "I'm not sure the verbiage that can be added would overcome the deleterious effects and differentiation among the patients who would take it."
- YES – *Dr. Calhoun, pulmonologist:* "The differential safety profile looks just marginally cleaner for dronedarone vs. amiodarone, and that provides a little impetus… The patients who are like the ANDROMEDA patients should clearly be excluded, and the label needs to (explain that)."
- YES – *Dr. Kaul, cardiologist:* "A very cautious yes… The claims should be reducing CV hospitalizations… Specifically, a claim for a tolerability advantage over amiodarone should not be allowed. And the sponsor should be encouraged to do a larger long-term study vs. amiodarone. Amiodarone should remain the treatment of choice for patients with structural heart disease."

Dr. Temple reminded the panel that the FDA does not issue black box warnings, just boxed warnings, but he noted, "We are very sympathetic about what people are saying about (the warnings)."

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