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Vernakalant NDA 22034 Resubmission

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"FDA Overview of Cardiovascular Safety"

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"Safety of Ibutilide or Electrical Cardioversion in Patients with Atrial Fibrillation or Flutter"

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FDA Overview of Cardiovascular Safety

Cardiovascular and Renal Drugs Advisory Committee Meeting

December 10, 2019

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Medical Officer

Presentation Agenda

- Regulatory history
- Mechanistic considerations: Vaughan-Williams Class
- Clinical Cardiovascular Safety
  - Re-integration of controlled clinical trials
  - SPECTRUM observational registry
- Pre-infusion checklist
  - Will this identify subjects at risk?
- Safety of alternative therapies
  - Ibutilide (approved for the rapid conversion of AFib)
  - Electrical cardioversion (ECV)
- Conclusions

Vernakalant Regulatory History – 1

- 2006: Original submission of NDA 22034
  - 375 treated subjects
  - 8 serious adverse events
  - 1 death
- 2008: Approvable letter
  - Risk appeared excessive with respect to benefit
  - Another controlled study requested with entry criteria resulting in <1% risk of serious cardiovascular adverse events
- 2009: ACT V was initiated
  - Planned 474 subjects enrolled (2:1)

Vernakalant Regulatory History – 2 Investigational New Drug Application (IND) Placed on Clinical Hold in 2010

- 2010: Pulseless electrical activity and cardiogenic shock at the end of first vernakalant infusion
  - Subject at low baseline risk (only hypertension; left ventricular hypertrophy)

- Intravenous (IV) vernakalant IND was placed on full clinical hold

Vernakalant Regulatory History – 3 on Clinical Hold Since 2010

- 2014-2016: applicant failed to identify a new dosing strategy that would be effective without causing the negative inotropic effects

- 2019: NDA resubmitted
  - Interim controlled safety data
  - SPECTRUM

What is Vernakalant?

Applicant's position:
"Vernakalant IV, an atrial-selective ion channel blocker, has a differing mechanism of action that mitigates some of the main safety concerns of other anti-arrhythmic treatments." (2016 SPECTRUM Protocol, Synopsis)
"Vernakalant is a multichannel blocker of certain potassium channels, an atypical class III antiarrhythmic." (2019, risk management module of NDA)
"BRINAVESS is an antiarrhythmic drug that acts preferentially in the atria by prolonging atrial refractoriness and slowing impulse conduction in a rate-dependent fashion… Because of its atrial preferential actions, vernakalant does not readily fit in the Vaughan Williams anti-arrhythmic drug classification, which is based on ventricular activity." (2019, Proposed label)

Vernakalant is a Non-selective Ion Channel Blocker – Affects Ventricles As Well As Atria

	I_{Na-P}	I_{Na-L}	I_{Kr}	I_{to}	I_{kur} (atrial)	I_{KACh} (atrial)
IC_{50} (μM) at ≤ 1 Hz	13	14	7.2	20	3.2	10

Sponsor data. IC_{50} values shown are the lowest for each current. A safety margin <30-fold is likely to have clinical effects (Redfern et al. Cardiovasc Res. 2003 Apr 1;58(1):32-45.)

- All channels blocked at therapeutic concentrations
- All channels blocked with indistinguishable potency

Vernakalant Channel Blocking Profile Is Similar to Flecainide (Known Class IC)

	Channels blocked with similar potencies						
	I_{Na-P}	I_{Na-L}	I_{Kr}	I_{to}	I_{Ca-L}	I_{Kur} (atrial)	I_{KAch} (atrial)
Vernakalant[applicant]	✓	✓	✓	✓	✓	✓	✓
Flecainide[1,2,3,4,5,6]	✓	✓	✓	✓	✓	✓	✓

[1]Guo D and Jenkinson s. J Pharmacol & Toxicological Meth. 2019, 99:106575.
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Vaughan-Williams Classification of Sodium Channel Blockers

- Class I antiarrhythmic drugs
  - Prolong the QRS and are negative inotropes
  - Three subclasses defined by dissociation constant from channel:

Sub-classes	Kinetics[1,2,3]	Dissociation constant[3]
1A (procainamide)	Intermediate	1-10 seconds
1B (mexiletine)	Fast	< 1 second
1C (flecainide)	Slow	> 10 seconds

[1]Frumin H, Kerin N and Rubenfire M. *J Clin Pharmacol*. 1989, 29: 387.
[2]Mittchell L. *Drugs for Arrhythmias*. Merck Manuals.
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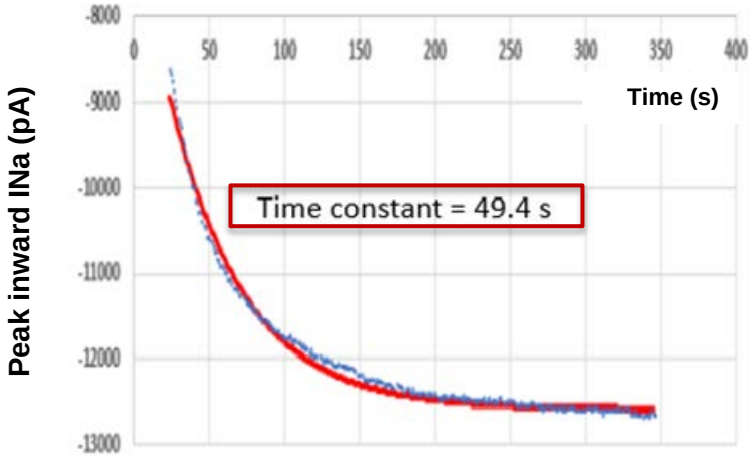
Vernakalant Dissociates Slowly From the Sodium Channel

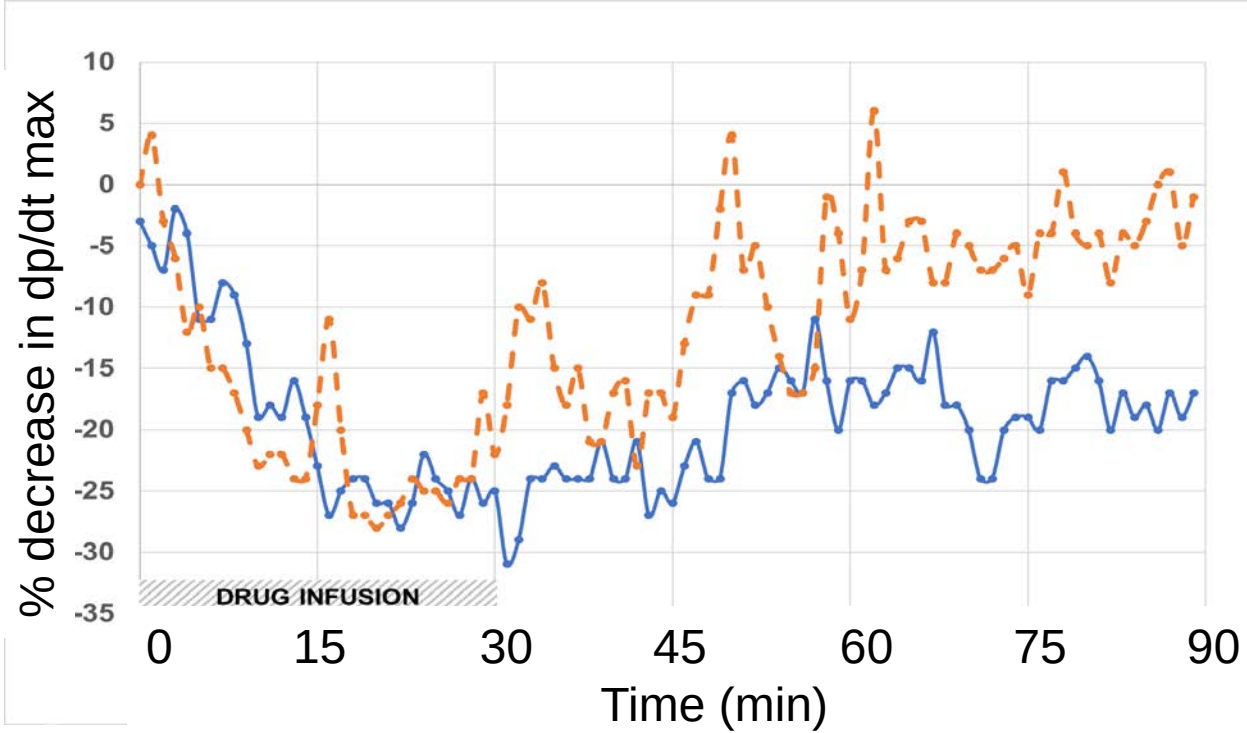
- Class IC definition: dissociation time constant greater than 10 seconds
- Vernakalant's calculated dissociation time constant is 49.4 seconds

RSD1205
(vernakalant and its diastereomers)



Source: sponsor

2014 Canine Contractility Study – Assessed as dp/dt

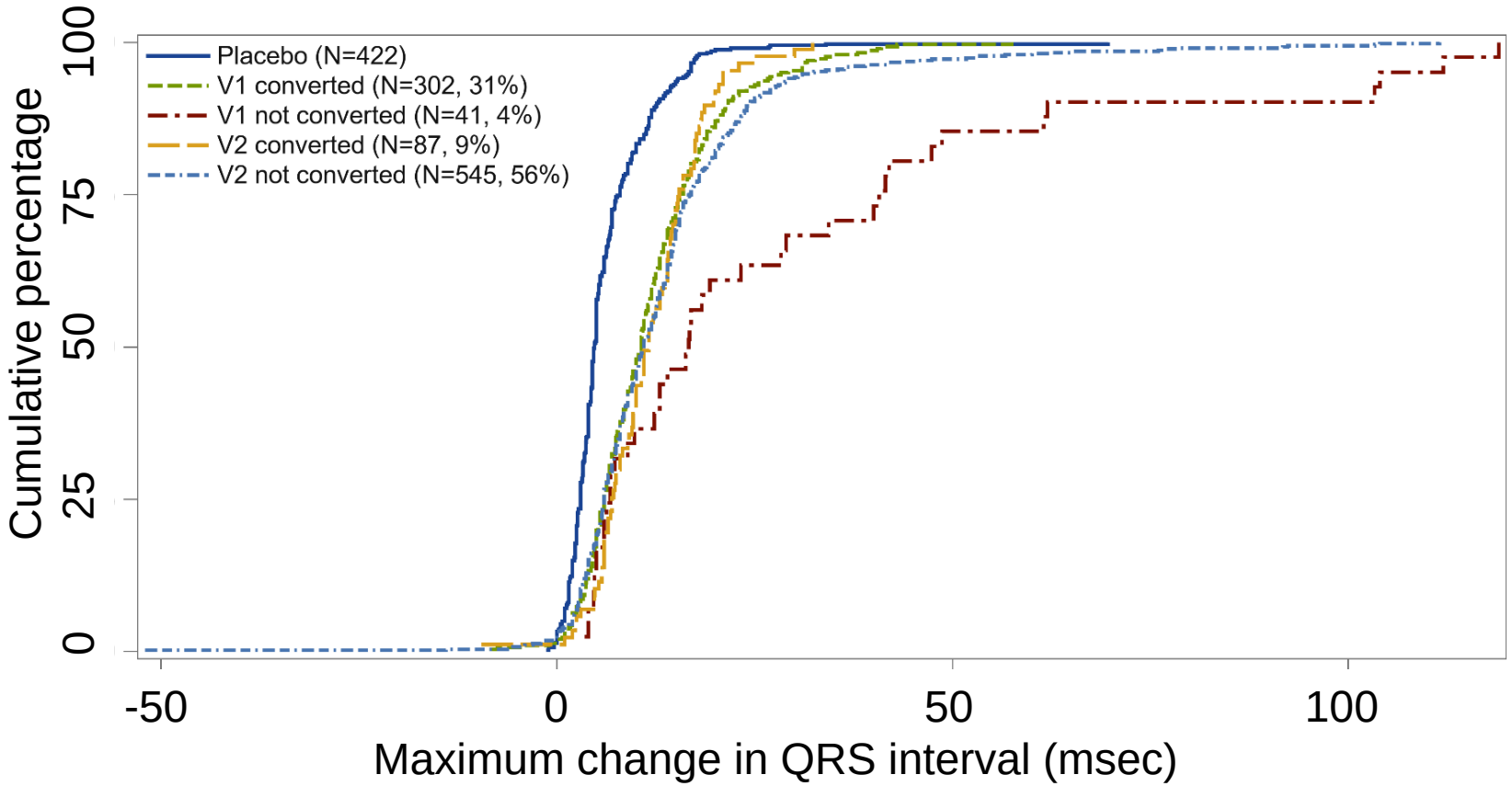


	Dog Exposure	Therapeutic C_{max}
IV Vernakalant (n=8)	~1800 ng/ml	4300 ng/ml
IV Flecainide (n=4)	~700 ng/ml	200-1000 ng/ml

Canine Deaths

- 2012 dog hemodynamic study (N=11)
  - One of 6 dogs given IV vernakalant after induction of cardiac dysfunction with 3-5 weeks of rapid ventricular pacing died on-study:
    - Increase in electrocardiogram (ECG) QRS duration
    - Rapid decreases in blood pressure (BP), heart rate (HR), and cardiac output (CO); dog lost consciousness
    - Regained consciousness, but HR and BP fell precipitously again; dog could not be recovered
- 2014 dog contractility (dp/dt) study (N=8)
  - The only dog that received IV vernakalant after one week of rapid atrial pacing was found dead in its cage within 2 hours of vernakalant administration.

Vernakalant Prolongs the QRS Interval in Humans



Vernakalant arm stratified by # of doses and outcome of conversion

Summary – Mechanistic Considerations

- Vernakalant is:
  - A Vaughan-Williams Class IC agent
  - A negative inotrope that prolongs the QRS
  - Not atrial specific (affects ventricles and atria)
  - Similar to flecainide

- Vernakalant would be expected to cause serious cardiovascular events such as:
  - Hypotension
  - Bradycardia
  - Ventricular arrhythmias
  - Possible death

Vernakalant Safety:
Controlled Clinical Trials

IV Vernakalant-related serious adverse events were consistent with the safety profile of a Vaughan-Williams Class IC antiarrhythmic drug

Serious adverse event of interest – 0-2 hours post-dose	Placebo (N=459)	Vernakalant (N =1073)
Hypotension	0	9 (0.8%)
Arrhythmia	0	16 (1.5%)
Atrial Flutter	0	3 (0.3%)
Bradycardia	0	6 (0.6%)
Ventricular arrhythmia	0	5 (0.5%)
Conduction disturbance	0	3 (0.3%)
Vernakalant-related death	0	2 (0.2%)

Data source: all patients population from the integrated safety data for phase 2/3 clinical studies

A subset of patients were identified with a greater risk for vernakalant-related adverse effects but could not be prospectively identified

- Subjects who did not convert to sinus rhythm and who did not receive the second dose (N=43, 4%) had worse outcomes as follows:
  - Higher incidence (26%) of SAEs within 2 hours post-dose
  - Marked increase in QTcF (>30 msec) and QRS intervals (~20 msec)[a]
  - 32% had systolic BP decrease ≥ 20%
  - 16% had systolic BP decrease ≥ 20% and to < 90 mmHg
- No demographic or disease-specific characteristics were found to prospectively identify most of these subjects

[a] Placebo-adjusted increase at peak

Summary – Controlled Clinical Trial Safety - 1

- Vernakalant prolongs the QRS interval in clinical trials
- Vernakalant causes adverse effects consistent with its Vaughan-Williams Class IC sodium channel blockade
- Most patients who will do poorly with vernakalant cannot be prospectively identified
  - Harm caused cannot be reliably predicted

Summary – Controlled Clinical Trial Safety - 2

- Reliable risk mitigation for serious cardiovascular adverse events could not be achieved on the basis of demographic characteristics
  - Harm cannot be prevented through risk mitigation

- In ACT V, serious hypotension without bradycardia occurred that was unresponsive to pressors for 40 minutes
  - When harm occurs – in some cases, it cannot be treated

Vernakalant Safety:
SPECTRUM

Overview of SPECTRUM

- Observational registry for patients who received vernakalant IV in 6 western European countries
  - N = 1778
  - 2,009 vernakalant treatment episodes
  - 79% prospective and 21% retrospective patients
- Data were largely collected through medical chart abstraction

Incidence of Serious Adverse Events of Special Interest Within 2 hours Post-dose: SPECTRUM versus Controlled Clinical Trials

Serious adverse event grouping	SPECTRUM (N=2,009)	Clinical Trials (N = 1,073)
Hypotension	4 (0.2%)	9 (0.8%)
Arrhythmia	18 (0.9%)	16 (1.5%)
Bradycardia	7 (0.3%)	6 (0.6%)
Ventricular arrhythmia	2 (0.1%)	5 (0.5%)
Conduction disturbance	4 (0.2%)	3 (0.3%)
Vernakalant-related deaths	0 (0.0%)	2 (0.2%)

SPECTRUM results are not reassuring

- SPECTRUM limitations:
  - Potential selection bias (enrollment based on physician discretion)
  - Unknown whether all subjects who may have been eligible for vernakalant treatment were actually screened for enrollment
  - Non-consecutive enrollment (21% of screened subjects not enrolled)
  - Retrospective enrollment (21%)
- SPECTRUM safety results were consistent with clinical studies:
  - Incidence of serious adverse events of interest lower than observed in clinical studies, but…
  - Underreporting of adverse events could not be ruled out in SPECTRUM

Vernakalant Safety:

Pre-infusion Checklist

Problematic Pre-infusion Checklist Questions/Statements

- **Labeled Contraindications:**
  - **Low baseline blood pressure?**
  - **Low baseline heart rate?**
  - **Long QT interval?**
  - **Heart failure or known moderate to severe left ventricular dysfunction?**
- **Has the patient received an intravenous rhythm control antiarrhythmic drug (class I and class III) within 4 hours prior to or within 4 hours following, BRINAVESS administration?**
- **Use of IV BRINAVESS with beta-blockers is not recommended within 2 hours prior to, or 2 hours after, administration.**

The proposed pre-infusion checklist will not reliably predict which subjects will experience cardiovascular serious adverse events with vernakalant.

Safety of Ibutilide or Electrical Cardioversion in Patients with Atrial Fibrillation or Flutter

Cardiovascular and Renal Drugs Advisory Committee Meeting
December 10, 2019

Daniel Woronow, MD, FACC
Medical Officer
Division of Pharmacovigilance
Office of Surveillance and Epidemiology

Purpose

- Review available evidence from medical literature and postmarket case reports to determine if there is a substantial risk of death or severe hypotension with
  - Ibutilide Pharmacological Cardioversion (PCV) or
  - Electrical Cardioversion (ECV)

NO CONCLUSIVE EVIDENCE that ECV or Ibutilide PCV causes

- Non-embolic fatalities, or
- Severe hypotension

in patients meeting the ACT V study enrollment criteria such as absence of

- History of heart failure (HF)
- Significant valvular stenosis
- Acute coronary syndrome within the preceding 30 days
- Clinically significant illness

ACT V Study

- Initiated by the Sponsor to address FDA's concerns regarding the safety of intravenous vernakalant with respect to serious drug-induced hypotension, bradycardia, and arrhythmias
- Primary objective was to evaluate the safety of vernakalant injection in subjects with AFib and no evidence or history of HF
- **INCLUSION/EXCLUSION CRITERIA FOR ACT V STUDY WERE MORE RESTRICTIVE THAN IBUTILIDE OR ECV STUDIES**

ECV Preferred over PCV

- American College of Cardiology/American Heart Association Guidelines (2014):
  - ECV is preferred [over PCV] in patients with
    - decompensated HF
    - ongoing myocardial ischemia
    - **hypotension**

    These are ACT V Exclusion Criteria and proposed Vernakalant Contraindications
  - There are NO patient subgroups for whom a PCV strategy is preferred over ECV
- ECV used more commonly than PCV among surveyed US cardiologists, emergency physicians, and hospitalists regarding acute management of AFib (Funk, 2015)

Ibutilide Premarketing Phase II/III Studies

Treatment-Emergent Medical Events With Frequency of More Than 1% and Higher Than That of Placebo

Event	Placebo N=127		All Ibutilide N=586		Absolute Risk Difference
	Patients		Patients		%
	n	%	n	%	
CARDIOVASCULAR					
Sustained polymorphic VT	—	—	10	1.7	**1.7**
Non-sustained monomorphic VT	1	0.8	29	4.9	**4.1**
Non-sustained polymorphic VT	—	—	16	2.7	**2.7**
QT segment prolonged	—	—	7	1.2	**1.2**
Bradycardia	1	0.8	7	1.2	**0.4**
Bundle branch block	—	—	11	1.9	**1.9**
Atrioventricular block	1	0.8	9	1.5	**0.7**
Hypotension	2	1.6	12	2.0	**0.4**

IMPORTANTLY, there were NO deaths in these studies.
Instances of sustained polymorphic Ventricular Tachycardia (VT) were **all treated successfully**.

Ibutilide Postmarketing Randomized Controlled Trials (RCTs)

	Volgman 1998	Reisinger 2004	Zhang 2005	TOTAL Ibutilide
Country	US (Rush-Presbyterian-St. Luke's)	Austria	China	-
Ibutilide treatment arm	N=60	N=106	N=41	N=207
Ventricular arrhythmia requiring intervention	1 (1.7%) Polymorphic VT **treated successfully**	0	0	1 (0.5%)
Hypotension	0	0	0	0
Death	0	0	0	0

Ibutilide Postmarket Case Reports Assessment of Fatal Outcomes

- FDA Adverse Event Reporting System (FAERS) database searched
  - Ibutilide and Outcome of Death
  - Since US market approval in 1995 to September 2019
- 14 reports *(after excluding 2 reports because of insufficient information to determine a causal association)*
- The 14 reports were heavily confounded and included patients with
  - "Do Not Resuscitate" orders
  - patients meeting ACT V exclusion criteria

ECV Safety in RCTs Comparing ECV to PCV

	Bellone 2012	Chen 2013	de Paola 2003	Mattioli 1998	Total, ECV
Country	Italy	China	Brazil	Italy	-
ECV treatment arm	N=121	N=59	N=67	N=34	N=281
Ventricular arrhythmia requiring intervention	none reported	none reported	none reported	none reported	none reported
Hypotension	none reported	none reported	none reported	none reported	none reported
Mechanical respiratory assistance or pulmonary edema	none reported (1 hypoxia, no mechanical assistance reported)	none reported	none reported	none reported	none reported (1 hypoxia, no mechanical assistance reported)
Death	**0**	**0**	**0**	**0**	**0**

ECV Observational Studies that include Respiratory or Pulmonary Edema Adverse Events

	Botkin 2003	Burton 2004	Davarashvili 2018
Country	**US, Loyola, Chicago**	**US, multihospital**	**Israel**
Study method	retrospective observational, outpatient ECV, AFib & atrial flutter	retrospective observational, consecutive ED-ECV patients, AFib	retrospective observational, consecutive ECV patients, AFib
ECV procedures	N=532	N=388	N=1696
HF related baseline characteristics	44% average left ventricular ejection fraction (LVEF)	INCLUDED unstable and hypotensive patients	*within total patient population:* • 42% with aortic stenosis, moderate or severe • 13% with LVEF ≤ 40%
Ventricular arrhythmia requiring intervention	none reported	2 (0.5%)	none reported
Hypotension	none reported	0	none reported
Mechanical respiratory assistance or pulmonary edema	2 (0.4%) intubations	no intubations	No intubations reported 66 (3.9%) developed pulmonary edema
Death	0	0	no ECV deaths reported *(9 deaths of unreported causes within 30 days of ECV)*

No Conclusive Evidence of Non-Embolic Fatalities with ECV

33,177 total ECV procedures
• 58 total publications containing ECV survival information
• 2 “non-sudden cardiac death[s]” reported in Euro Heart Survey Registry study among **712** ECV procedures - Insufficient information to determine a causal association
• NO conclusive evidence that Death is a substantial risk with ECV among patients treated for the rapid conversion of atrial arrhythmias to sinus rhythm

Summary

Ibutilide PCV
Literature review did not identify any instances of ibutilide-related death during index hospital inpatient/outpatient stays among patients who otherwise could have been enrolled in ACT V
ECV
ECV is generally successful in rapidly converting AFib to sinus rhythm
ECV literature review did not identify any deaths causally related to ECV despite most of these studies including patients with more severe baseline comorbidities than in the ACT V study
ECV related serious adverse events (AEs) that are non-transient, and not self-limited occur uncommonly or rarely, despite most of these ECV studies including patients with more severe baseline comorbidities than in the ACT V study

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Vernakalant NDA 22034 Resubmission

FDA Conclusions

Preston M. Dunnmon, MD, MBA, FACP, FACC

FDA Conclusions - 1

Vernakalant

- Is a Vaughan-Williams Class IC antiarrhythmic
- Is not atrial-specific (affects ventricles and atria)
- Prolongs the QRS, markedly so in some subjects
- Is a negative inotrope in dogs and in humans
- Has caused deaths in dogs and in humans

FDA Conclusions - 2

Vernakalant

- Is similar to flecainide
  - in dogs, vernakalant's negative inotropic effect is as large as that observed with IV flecainide but does not recover during 90 minutes of post-dosing observation
  - in humans, adverse events are similar (hypotension, bradycardia, ventricular arrhythmias, atrial flutter, conduction disturbances, and death)

FDA Conclusions - 3

- The proposed pre-infusion checklist will not reliably predict which subjects will experience cardiovascular SAEs with vernakalant

- SPECTRUM results are not reassuring regarding vernakalant's cardiovascular safety

FDA Conclusions - 4

- Vernakalant has induced harm that cannot be reliably:
  - Predicted
  - Prevented
  - Treated (in some cases)
- In contrast to vernakalant, ECV and ibutilide PCV can cause adverse events that are transient or treatable
- We believe the benefit risk profile of vernakalant is unfavorable for the proposed indication


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BACK-UP SLIDES SHOWN

Patient “A” Clinical Course

- Echo/ECG documented PEA – 40 minute pulseless resuscitation
- Encephalopathy (never regained consciousness)
- Renal failure requiring dialysis
- Recurrent AFib during dialysis
- Hepatic failure
- Rhabdomyolysis
- Coagulopathy
- Aspiration
- Sepsis
- Death - hypovolemic shock (ischemic/necrotizing colitis and resultant uncontrollable GI bleeding)

Echo Day	LVEF	RVEF	MR
D1 (AFib 156 bpm)	44%	WNL	Mild
D1 (CPR)	0	0	0
D1 (SR post ECV)	25%	NR	NR
D2 (AFib 96bpm)	40%	WNL	Mild
D19 (SR 88 bpm)	49%		Mild
D 23	78%	WNL	Severe
Day 28: Death			

Divergent Assessments of Patient A

Applicant:

"The follow-up echocardiogram showing left ventricular hypertrophy, a left atrial size of 50 mm and mitral regurgitation suggests long standing mitral regurgitation secondary to left ventricular dysfunction and an ejection fraction of 25%. With normal coronary anatomy, the most likely etiology is alcohol cardiomyopathy and long-standing hypertension. It is very unusual to develop either renal failure, liver failure, or rhabdomyolysis or coagulopathy after cardiac resuscitation suggesting that he had a very prolonged state of inadequate circulation."

FDA:

This subject's rapid recover of left ventricular function following his vernakalant-induced, 40-minute, pulseless arrest does not support the applicant's explicit assessment that alcoholic cardiomyopathy was to blame, or the implicit idea that an alcoholic cardiomyopathy could have been identified by either ACT V exclusion criteria or the proposed pre-infusion checklist that could have or should have kept this person from being dosed with vernakalant.

Postmarket Serious Hypotension

- Patient “B” with no history of cardiac disease presented with new and recent-onset AFib. He received Brinavess 318 mg IV (one dose only) and experienced the following at times post-infusion:
  - 5 min: itching, clammy, diaphoresis
  - 10 min: SBP fell 130 to 80 mmHg while in AFib with HR 100-130
  - 12 min: 500 cc NS bolus
  - 15-25 min: sweating, clammy, SBP 70-80, HR 100 (AFib). Second 500 cc NS bolus
  - 25 min: deterioration of hemodynamic status, very clammy, tonic-clonic seizures, loss of consciousness, no carotid pulse, arrest called, and chest compressions initiated
  - 27 min sinus brady @ 40-50/min, narrow QRS, SBP @ 80/min, consciousness recovered

- Echocardiograms (all by same experienced “highly competent” sonographer) showed:
  - Echo 1: 30 minutes post drug infusion LVEF “low normal”
  - Echo 2: 90 minutes post drug patient now awake in “good stable condition clinically,” LVEF < 20%
  - Echo 3: 300 minutes (5 hours) post drug, normal echo with normal LV systolic function, troponins negative

Additional ECV Deaths
Unlikely or Unclear Causal Association

32 additional deaths: could not determine to be related to the ECV procedure

- (Guédon-Moreau, 2007) **3 (0.4%) deaths** ……. among **684** ECV procedures
  - Lethal brain hemorrhage in a patient on both LMWH and warfarin
  - 86-year-old patient with hypertrophic cardiomyopathy who died of HF one day after ECV
  - 78-year-old patient with valvular cardiomyopathy who died one month after ECV
- (Hellman, 2018) **4 (0.1%) deaths** of unreported causes within 30 days ……. among **4356** ECV procedures
- (Steinberg, 2015) **14 (1.4%) deaths** within 30 days…… among **1017** ECV procedures
  - 5 from HF
  - 2 from respiratory failure
  - 2 from septic shock
  - 5 cause not available
- (Gallagher, 2008) **9 (0.3%) unexpected deaths** within 28 days after attempted ECV……. **2522 ECV** procedures
  - 2 attributed to pulmonary embolism. These patients were older than the population mean.
- (Grönberg, 2010) **1 (0.01%) death** due to aortic dissection 24 hours after ECV... among **6906** ECV procedures
- (El-Am, 2019) **1 (0.7%) death**, patient with **amyloidosis** who developed left hemiplegia the same night following successful ECV and died 5 days later …….. among **148** ECV procedures

Above studies all Observational

Sensitivity Analysis

- The 6 studies from the previous slide are included in the 33,177 total ECV procedures previously mentioned
- Irrespective of causal association or patient comorbidities, there are 43 total deaths combining studies by Pisters, Davarashvili, Guédon-Moreau, Hellman, Steinberg, Gallagher, Grönberg, and El-Am
- This calculates to 43/33,177=**0.13**%, which represents all deaths, maximum follow-up of 30 days, **irrespective of causal relationship, and irrespective of patient comorbidities**
- **There is no conclusive evidence that any of these deaths are causally related to ECV**

ECV Publications Compared with Vernakalant Clinical Trials

Although we found NO deaths conclusively caused by ECV, if we extend our analysis to ECV deaths IRRESPECTIVE of causal association, there remains a very low number of deaths with ECV compared with Vernakalant clinical trials.
ECV study follow-up times are up to 30 days.

	Vernakalant Clinical Trials		58 ECV publications
AE Grouping	Placebo (N=459)	Vernakalant (N=1073)	ECV (N=33,177)
Deaths	1 (0.2%)	8 (0.7%)	43 (0.13%)