Clinical endpoints for VT/VF suppression in Patients with ICDs: Living longer and feeling better

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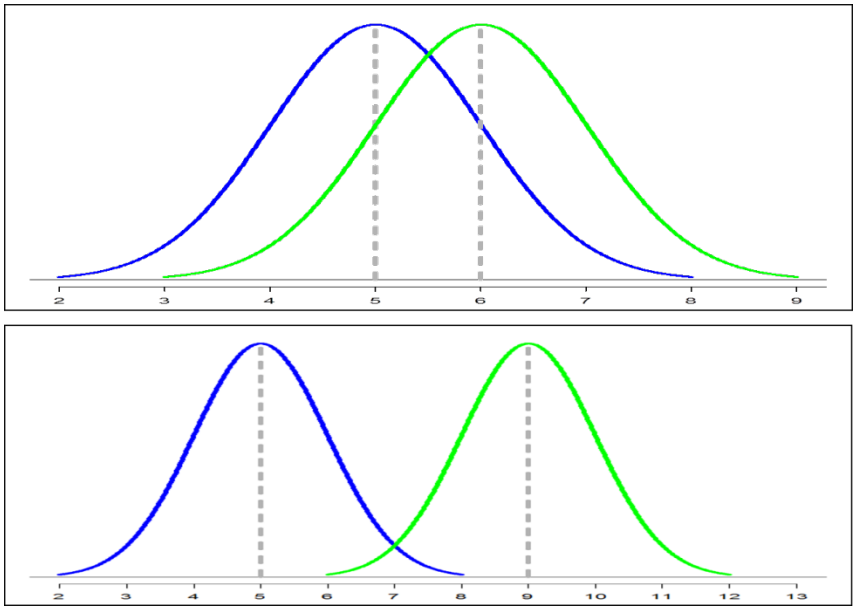
US Regulatory Approval Requirements

Efficacy



Safety

- Exposure sufficient to identify important drug side effects (ICH E1)
- Safety outcomes that justify approval in a benefit-risk assessment based on the Efficacy benefit demonstrated

Clinical Endpoints for ICD Therapies of VT/VF: A multiverse of VT/VF & patient phenotypes

- The underlying heart disease
  - Ischemic heart disease
  - Idiopathic nonischemic cardiomyopathies
  - Genetic diseases
    - HCM
    - Muscular dystrophies
    - Channelopathies
  - Congenital heart diseases

- The arrhythmia
  - Monomorphic VT
  - Polymorphic VT
  - VF

- The patient
  - Preserved left ventricular function
  - Depressed left ventricular function
  - Hypoxic versus not hypoxic
  - Cyanotic versus not cyanotic

More Permutations: Drug and ICD Effects

- Potential drug effects
  - Metabolic blockade
    - Energetics
    - Contractile machinery
  - Channel effects
  - Negative inotropy
  - Cytopenias
  - Lung effects
  - Liver effects
  - Thyroid effects
- ATP
  - Often minimally symptomatic
  - No effect of LVSF
- Shocks
  - Painful
  - Poor QoL
  - Troponin leaks, stunning
- ATP & Shocks
  - Increased frequency may reflect worsening of underlying disease

Azimilide: SHEILD-1

- N=633 (P, 75 mg, 125 mg), follow-up 1 year
- Demographics
  - Mean LVEF 35%
  - ~4 shocks per year in placebo arm
  - 91% of subjects were NYHA Classes I or II
  - AEs leading to discontinuation > 35% subjects
- Two co-primaries
  - Composite: All cause shocks + symptomatic ATP
  - All cause shocks
- Other analyses
  - CV-related ER visits
- Prespecified clinical outcomes
  - None

SHIELD-1 Co-Primary Endpoint Results

End-Point Treatment	N	n (%)	Total Events	HR 95% CI	P
All-cause shocks + sATP					
Placebo	214	124 (58)	1459		
Azimilide 75 mg	220	114 (52)	665	0.43 (0.26, 0.69)	0.0006
Azimilide 125 mg	199	100 (50)	737	0.53 (0.34, 0.83)	0.0053
All-cause shocks					
Placebo	214	113 (53)	613		
Azimilide 75 mg	220	106 (48)	472	0.72 (0.47, 1.10)	0.13
Azimilide 125 mg	199	91 (46)	480	0.83 (0.55, 1.24)	0.36

N, number of patients randomized; n (%), number (%) of patients who experienced at least 1 event.

Dorian et al. Circulation. 2004;110:3646-3654.

SHIELD-1 Secondary Endpoint: All appropriate ICD therapies - shocks or ATP (Adjudicated ICD-terminated VT/VF events)

End-Point Treatment	N	n (%)	Total Events	HR 95% CI	P
All Appropriate ICD Therapies-cause shocks + sATP					
Placebo	214	136 (63)	3936		
Azimilide 75 mg	220	136 (61)	2849	0.52 (0.30, 0.89)	0.017
Azimilide 125 mg	199	111 (55)	1436	0.53 (0.22, 0.65)	0.0004

N, number of patients randomized; n (%), number (%) of patients who experienced at least 1 event.

Dorian et al. Circulation. 2004;110:3646-3654.

SHIELD-1 Editorial

The Shocking Story of Azimilide

- Primary goal of AAD therapy: palliation
- ATP termination of arrhythmias – mild if any symptoms not impacting QoL
- No psychosocial endpoints (few deaths, no syncope or pre-syncope reported as AEs)
- Composite of shocks and ATP may not be useful

Hanna IR, Langberg JJ. Circulation 2004;110:3624-3626.

Azimilide: SHIELD-2

- Event driven (330 target) N~890, 12 months,
- Placebo vs Azimilide 75 mg, LVEF < 40%
- Primary composite endpoint: time to first (TTF)
  - unplanned CV hospitalization, or
  - CV emergency department visit, or
  - CV death
- Secondary endpoints:
  - TTF all-cause shock
  - TTF time to the first outpatient visit resulting in a change in ICD programming or to medication as a result of the ICD findings

Robinson VM et al. American Heart J. ttp://dx.doi.org/10.1016/j.ahj.2016.10.025

Eleclazine: TEMPO

- Dose ranging Phase 2 study for ~313 subjects with ICD or CRT-D
- Primary Outcome:
  - Total number of appropriate ICD interventions (ATP or shock) through Week 24
- Secondary Outcomes
  - Appropriate ICD interventions (ATP or shock) through EoS
  - Change in PVC frequency/48 hours
  - Change in NSVT frequency/48 hours
  - VT/VF occurrences (treated or untreated) through Week 24
  - Electrical storm through wk 24 and EoS
  - Inappropriate ICD int4erventions through wk 24 and EOS
  - TTF CV hospitalization, ER visit, CV death
  - Changes in LV systolic and diastolic function by echo at wks 12 and 24

ClinicalTrials.gov Identifier: NCT02104583

Outcomes for living longer and/or feeling better

- Clinical outcomes or clinical surrogates
  - Death
  - Aborted sudden death (appropriate ICD shocks, or freedom from appropriate shocks)
  - ER visits
  - Hospitalizations
  - TTF time to the first outpatient visit resulting in a change in ICD programming or to medication as a result of the ICD findings
  - Impact on worsening HF
  - Days alive and out of hospital
  - QoL and resource utilization
- Important/supportive but not sufficient
  - Delivered ICD therapies dominated by ATP (VT) reductions

2009 EHRA/HRS Consensus: Efficacy Endpoints of Ablative therapies for VT

- Minimum follow-up duration of 6–12 months for assessment of recurrent VT
- Minimum follow-up duration of 1 year for assessment of mortality.
- VT recurrence is defined as any episode of VT of at least 30 s duration or that requires ICD intervention
- Reporting of the following measures of efficacy is required
  - Spontaneous recurrence of any sustained VT
  - Freedom from VT in the absence of antiarrhythmic drug therapy.
  - Death

Aliot EM et al. Heart Rhythm, Vol 6, No 6, June 2009

Conclusions

- ICD delivered therapy endpoints may be useful in Phase 2 dose ranging and can be supportive of clinical endpoints in phase 3
- The lesson of SHIELD-1: reduction of ATP dominated ICD therapies delivered is not sufficient to justify approval of an AAD with important toxicities
- In most circumstances, non-mortality (non-shock) benefits must be reproducible (two trials)
- Efficacy benefit shown must justify safety cost