Addressing Differences in Mortality Rates Between FDA and Sponsors

- FDA considers all valid scientific evidence in regulatory decision-making
- Rationale for FDA focus on the pivotal RCTs (AT population with updated data presented)
  - Highest quality data, verified by FDA
    - Covariate balance
- Inclusion of other datasets provides additional information and increases the evaluable sample size; however:
  - Inclusion of non-US RCTs
    - Shorter follow-up duration
    - Missing data
  - Inclusion of single arm registries
    - Can introduce bias and confounding
    - Data may not be poolable/exchangeable
    - May not help clarify the presence or magnitude of the potential late mortality signal

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Differences in Presented Mortality Rates between Companies and FDA

Cook Zilver DES

- FDA Analysis
  - AT population (accounted for secondary randomization but NOT crossover (31 patients))
  - No live cases (-5 patients)
  - Presented crude rates (and KM curves)
  - 5 year Mortality
    - 23.4% (52/222) DES
    - 14.0% (18/129) PTA
- Cook Analysis
  - mAT population (cross over and secondary randomization)
    - Initial DES sample size: 336 = 242 (primary) + 63 (secondary randomization) +31 (crossover)
  - Included live cases (+5 patients)
  - Presented KM rates
  - Mortality
    - 18.9% KM DES (n=57 dead)
    - 15.6% KM PTA (n=20 dead)
- Conclusion: Main difference in mortality data rates between FDA and Cook is presentation of AT population (FDA) vs mAT population (Cook)

BD/BARD Lutonix 035 DCB

- FDA Analysis
  - Included:
    - Levant 2 Pivotal RCT
  - 5 year mortality rate (19.9% DCB vs 12.7% PTA)
- BD/Bard Analysis
  - Included:
    - Levant 1 OUS RCT
    - Levant 2 Pivotal RCT
    - Levant Continued Access Registry
    - Levant Japan OUS RCT
  - Unclear how missing data was handled (from data presented)
  - Did not present mortality rates
- Conclusion: Pooling of data may have resulted in potentially different rates

Medtronic IN.PACT Admiral DCB

- FDA analysis
  - Presented crude rate at 5 years for AT population
    - 15.9% DCB vs 11.2% PTA
- Medtronic Analysis
  - Separate pivotal RCT analysis and pooled analysis of pivotal RCT and Japan RCT (3 year follow up)
  - KM rates for pivotal RCT
    - 15.7% DCB and 11.2% PTA
- Conclusion: Data are very similar (may be due to presentation of KM vs Crude rate with low missing data)

Phillips Stellarex DCB

- FDA Analysis
  - Pivotal RCT only
  - Crude rates presented
  - 3 year mortality rates
    - 10.9% DCB vs 13% (PTA)
- Phillips Analysis
  - Updated data was not provided to FDA
  - Mortality rates that were presented appeared to be pooled for pivotal RCT and EU RCT
  - KM Rates presented
  - 3 year mortality rates
    - 9.3% DCB vs 9.9% (PTA)
- Conclusion:
  - Missing data appears high
  - Follow up not complete
  - Differences are likely due to pooling of data

BSC Eluvia DES

- FDA Analysis
  - Since DES vs DES study with 2 year data, Eluvia data not included in FDA 5-year meta-analysis, but was included in cause of death assessment
  - Reported crude mortality rate for pivotal RCT only
    - 6.8% (Eluvia) vs 8.2% (Zilver)
- BSC Analysis
  - Combined MAJESTIC (single arm – 3 YR FU) and IMPERIAL (RCT – 2 YR FU available)
  - Pooled 2 year mortality:
    - 6.5% (DES) and showed against “FDA PTA Reference” (7.4%)
- Conclusion:
  - Limited long term data are available and study was PTX vs PTX
  - Reported 2 year mortality rates between FDA and BSC are similar for Eluvia

Overall Conclusions

- Data is still evolving
  - Missing data is being acquired
  - Follow up is continuing for some trials
- The appropriateness of pooling data from pivotal RCTs, OUS RCTs, and single arm registries is unclear
- FDA will continue to work with industry to resolve differences
- FDA believes our analysis is most appropriate and does not change overall conclusions.
- FDA appreciates panel comments on these topics