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
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