FDA Perspective on the Critical Cardiovascular Safety Issues in COPD Drug Development

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- This presentation is not intended to convey official US FDA policy, and no official support or endorsement by the US FDA is provided or should be inferred

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- I do not have any financial interest or conflict of interest with any pharmaceutical company

Critical CV Safety Issues in COPD Programs

- Class concerns
  - LAMA
  - LABA
- Safety database
  - size, number of events
  - missing data
- Generalizability of safety data
  - enrichment

Class Concerns

- Mechanism of Action
- LAMA potential concerns
  - increased HR
  - arrhythmias
- LABA potential concerns
  - increased HR, BP
  - arrhythmias
  - class labeling for potential CV effects

Class Concerns - LAMA

- Stroke, MI, Cardiovascular Death
  - Pooled analysis of 29 RCT with tiotropium (Nov 2007)
    - stroke RR 1.37 (95% CI: 0.73, 2.56)
    - FDA Drug Safety Communication (March 2008)
  - Meta-analysis tiotropium & ipratropium 17 RCT[1] (Sept 2008)
    - cardiovascular death, MI, or stroke RR 1.58 (95% CI: 1.21, 2.06)

- Overall mortality
  - RCT with tiotropium Respimat (FDA PADAC Mtg Nov 2009)
    - numerical imbalance in mortality favoring placebo
  - Meta-analysis tiotropium Respimat trials[2] (2011)
    - mortality RR 1.52 (95% CI: 1.06, 2.16)
    - request for withdrawal of tiotropium Respimat from market (EU)

[1] JAMA 2008; 300(12):1439-1450 359:1543-5 [2]BMJ 2011; 342:d3215

Class Concerns - LAMA

- RCT with tiotropium – UPLIFT[3] (October 2008)
  - mortality hazard ratio 0.89 (95% CI: 0.79, 1.02)
  - MI hazard ratio 0.73 (95% CI: 0.53, 1.0)
  - stroke hazard ratio 0.95 (95% CI: 0.70, 1.29)

- RCT with tiotropium HH and Respimat – Tiospir[4] (2013)
  - mortality tiotropium Respimat 2.5mcg NI to tiotropium HH
    - HR 1.0 (95% CI: 0.87, 1.14)
  - mortality tiotropium Respimat 5mcg NI to tiotropium HH
    - HR 0.96 (95% CI: 0.84, 1.09)

[3]NEJM 2008 [4] NEJM 2013;369:1491-50

Safety Database

- Adverse events of interest
  - potential for targeted approach
  - robust data collection – adjudication, standardized definitions
  - minimize missing data
- Adequacy of safety database
  - ICH not sufficient to assess CV risk
    - ICH: 1500 pts overall, 300 pts 6 months, 100 pts for 1 year
- Enrichment of patient population
  - difficult to evaluate risk if few events

Generalizability

- Questions raised on generalizability of safety data
- COPD clinical programs generally exclude patients with clinically significant cardiovascular conditions
- No limitation on patient population once product approved
- Enroll broader patient population

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Looking forward to today's discussion