# Overview of Key Issues in Cardiac Safety Drug Development in Diabetics

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# Disclaimer

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# Overview of Presentation

- December 2008 diabetes cardiovascular guidance
- Implementing the December guidance
- Trial design considerations and challenges
- How to obtain product-specific advice

# Diabetes Cardiovascular Guidance

## Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

July 2008 advisory committee meeting documents:
www.fda.gov/ohrms/dockets/ac/cder08.html#EndocrinologicMetabolic

Guidance:
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

# Diabetes Cardiovascular Guidance

- Final guidance published December 2008
- Reaffirms HbA1c as the primary efficacy endpoint for glucose reduction
- Notes vulnerability of patients with diabetes to cardiovascular disease
- Asks sponsors to demonstrate that new therapies for type 2 diabetes do not unacceptably increase cardiovascular risk

# Diabetes Cardiovascular Guidance

- Independent committee should prospectively and blindly adjudicate major cardiovascular events
- Phase 2/3 design should permit a pre-specified meta-analysis of major cardiovascular events
- Trials should include patients at increased risk for cardiovascular disease
- Trial duration(s) should be longer than 6 months to obtain enough events and provide long-term data

# Diabetes Cardiovascular Guidance

| UPPER BOUND OF 95% CI FOR RISK RATIO | CONCLUSION |
|---|---|
| >1.8 | Inadequate to support approval |
| >1.3 but <1.8* | Postmarketing trial(s) needed to show definitively <1.3 |
| <1.3* | Postmarketing cardiovascular trial(s) generally not necessary |

CI=confidence interval
*with a reassuring point estimate

# Why 1.8 and 1.3?

- The smaller the excluded risk, the more events needed, and the larger the scope of the development program
- The 1.3 goal-post has been used in other settings for excluding cardiovascular risk (e.g., COX-2 inhibitors)
- The 1.3 goal-post is feasible, but meeting pre-approval would significantly delay new drug availability
- Willing to tolerate additional uncertainty (capped at 1.8) at approval because of benefits from glycemic control

# Power Considerations

- Power to rule out harm in a non-inferiority trial is determined by type 1 error, the margin, and the expected number of primary events

| Number of Primary Events Needed | | | |
|---|---|---|---|
| **Non-Inferiority Margin** | **Power** | | |
| | **80%** | **85%** | **90%** |
| 1.8 | 90 | 105 | 125 |
| 1.3 | 455 | 525 | 615 |
| Assumes logrank statistic, 1:1 randomization, and true hazard ratio = 1 | | | |

From Todd Sahlroot, FDA Biostatistician

# Power Considerations

| Annual Event Rate (Drug) | Annual Event Rate (Comparator) | Total Sample Size to Rule Out Increased Risk of 1.2 or 1.3 | |
|---|---|---|---|
| | | 1.2 | 1.3 |
| 2% | 2% | 16,500 | 8,000 |
| 2% | 1.75% | >100,000 | 34,000 |
| 3% | 3% | 11,200 | 5,400 |
| 3% | 2.8% | 29,300 | 10,100 |

α=0.05; 90% power; 5-year trial; 2-year recruitment

From Joy Mele, FDA Biostatistician

# Diabetes Cardiovascular Guidance

- Applies even if no known cardiovascular signal
  - Purpose is to identify off-target toxicity
  - Non-clinical studies use healthy animals, limiting conclusions regarding cardiovascular safety
  - Few events, as occurs in prior diabetes programs, yield inconclusive data on cardiovascular safety

# Diabetes Cardiovascular Guidance

Currently, the 1.8 and 1.3 criteria do not apply to:

- Most insulins
- Fixed-dose combination products, provided
  - The components do not increase risk
  - No pharmacological basis for an interaction between components

# Minimum Patient Exposures

- Cardiovascular 1.8 criterion should be assessed on ≥1,300-1,500 patients with ≥1 year exposure
  - Chronically used therapies
  - High-risk patients may have an event soon independent of intervention - many early events may bias to non-inferiority if follow-up is short
- Scope of phase 3 may be increased to address other safety concerns unique to the drug at hand

# Program Flexibility - Some Examples

Sponsors have proposed:

- A superiority trial to show cardiovascular benefit
- A dedicated trial in patients with recent acute coronary syndrome to show cardiovascular safety
- A standard phase 2/3 program plus a dedicated cardiovascular safety trial
- Substudies for glycemic efficacy within a dedicated cardiovascular safety trial

# Cardiovascular Trials Design Considerations

- Typically randomize patients to drug vs. placebo as add-on to background anti-diabetic medication(s)
- Can include renally-impaired patients and obtain other long-term data (e.g., pancreatitis, fractures)
- Type 1 error should be controlled if interim analyses are conducted

# Cardiovascular Trials Design Considerations

- Use structured case report forms to ensure critical cardiovascular data are captured
- Estimate event rates conservatively and design trials as event-driven
- Treat cardiovascular risk factors and HbA1c to current standards-of-care

# Cardiovascular Endpoints

- The Division is standardizing definitions
- Traditional MACE primary endpoint
  - Cardiovascular death
  - Non-fatal myocardial infarction
  - Non-fatal stroke
- Tension between additional components improving feasibility vs. biasing towards non-inferiority
  - Hospitalization for unstable angina
  - Hospitalization for heart failure
  - Revascularization

# Cardiovascular Trial Design: Challenges

- Deteriorating glycemic control over time
- Differential use of rescue medication
- Cardiovascular effects of active comparators
- Safeguarding trial integrity if interim analyses

# Common Proposals that are Unacceptable

- Performing multiple looks to see if 1.8 has been met without controlling type 1 error
- Choosing a primary MACE endpoint that is too broad

# Efficiently Implementing the Guidance

- Waiver for expedited reporting for components of the primary endpoint
- Limit the events analyzed in cardiovascular trials
  - e.g., adverse events of interest, serious adverse events, withdrawal due to adverse events
- Use few centralized laboratory tests
- Test for non-inferiority and superiority without alpha penalty in the same trial using the same test result

# Seeking Product-Specific Advice

- End-of-phase 2 meeting is the ideal time to discuss proposed plans for cardiovascular assessment
- Sponsors already in phase 3 should submit meeting requests or detailed plans with questions

# Summary

- Patients with diabetes have increased cardiovascular risk
- Sponsors should demonstrate that new therapies for type 2 diabetes do not unacceptably increase cardiovascular risk
- Cardiovascular data should be reliably collected, analyzed
- There is a 2-step approach to ruling out cardiovascular harm
- The end-of-phase 2 meeting is the ideal time to discuss proposed plans for cardiovascular assessment

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