Implementation of CV Risk Assessment – Regulatory requirements.

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Diabetes – used to be an attractive area for industry

- Pandemic increase of incidence and prevalence
- Medical need for new and better treatments
- Accepted surrogate (HbA1C)
- Predictive Phase 2 – glycemic control demonstrated
- Clear development guidelines – ICH recommended at least 1500 subjects, 300-600 for 6 months and 100 for 1 year.
New draft guidance from FDA February 2008

- Phase 3 trial data for at least 2,500 subjects exposed to the investigational product.
- 1,300 - 1,500 a year or more
- 300-500 for 18 months or more

Since most of development programs were larger than the ICH minimum, this guidance had some, but not dramatic, effects on size, length and cost of Phase 3 programs.

Advisory committee July 2008 and Guidance for Industry December 2008

- Upper bound of two-sided 95% CI for CV HR less than 1.8 for approval

Consequences?
- Need to present data on more than 120 adjudicated events.
- CV mortality, MI and stroke, could potentially include hospitalization for ACS.
- Restricting to MACE with an incidence of 1.5% in the traditional populations enrolled, this translates into 8-9,000 patient years.

This is a major increase in development program size and cost.
Advisory committee July 2008 and Guidance for Industry December 2008

- Upper bound of two-sided 95% CI for HR less than 1.3 to remain on the market

- Consequences?
  - Need to present data on more than 600-700 adjudicated events.
  - CV mortality, MI and stroke, uncertainty around other endpoints.
  - Restricting to MACE with an incidence of 2-3% in higher risk populations, this translates into 25,000 to 30,000 patient years.

This is what has traditionally been seen in outcome studies with approved drugs, e.g. antihypertensives, statins or antiplatelets.

Suddenly T2D does not look like such an attractive area to invest in.

Taspoglutide Phase 3 program:
Over 6,000 patients

4062 patients exposed to taspoglutide corresponding to 2785 patient years

<table>
<thead>
<tr>
<th>Study name</th>
<th>Patient population</th>
<th>Comparator</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-emeurge1</td>
<td>Inadequately controlled on diet &amp; exercise (monotherapy)</td>
<td>Placebo</td>
<td>373</td>
</tr>
<tr>
<td>t-emeurge2</td>
<td>Inadequately controlled with metformin, TZD, or metformin + TZD (add-on)</td>
<td>Exenatide BID</td>
<td>1189</td>
</tr>
<tr>
<td>t-emeurge3</td>
<td>Inadequately controlled with pioglitazone + metformin (add-on)</td>
<td>Placebo</td>
<td>326</td>
</tr>
<tr>
<td>t-emeurge4</td>
<td>Inadequately controlled with metformin (add-on)</td>
<td>Sitagliptin, Placebo</td>
<td>666</td>
</tr>
<tr>
<td>t-emeurge5</td>
<td>Inadequately controlled on metformin + SU; SU withdrawn at pre-randomization (add-on)</td>
<td>Insulin glargine</td>
<td>1049</td>
</tr>
<tr>
<td>t-emeurge6</td>
<td>Inadequately controlled with SU ± metformin (add-on)</td>
<td>Pioglitazone</td>
<td>760</td>
</tr>
<tr>
<td>t-emeurge7</td>
<td>Inadequately controlled with metformin (add-on) (high BMI)</td>
<td>Placebo</td>
<td>305</td>
</tr>
<tr>
<td>t-emeurge8</td>
<td>Patients with higher CV risk (add-on)</td>
<td>Placebo</td>
<td>2000</td>
</tr>
</tbody>
</table>

Doses: PPS – 10 mg QW, or 10 mg QW for 4 weeks followed by 20 mg QW (t-emeurge 1, 2, 3, 4, 5, 6).
Doses: PPS – one dose: 10 mg QW for 4 weeks, followed by 20 mg QW (t-emeurge 7, 8).
Advisory committee July 2008 and Guidance for Industry December 2008

• Upper bound of two-sided 95% CI less than 1.3

• What will the situation be when one or more products demonstrate CV outcomes benefit?
  - Will these treatments (for ethical reasons) have to be used as the new base treatment, with further reductions in event rates?
  - Or will they have to be used as comparators - making the probability of success less than today?
  - Moving the goal-post will further reduce the attraction of diabetes for industry.

EMA Guideline January 2010 – a few quotes

Any new glucose-lowering agent should show at least neutral or beneficial effects on associated CV risk factors.

The goal of treatment is to reduce the risk of diabetic complications, not just to lower HbA1c.

The effects of the tested product on LDL and HDL cholesterol should be specifically documented in type 2 diabetes.

It is expected that the development programme provides sufficient data supporting the lack of a drug-induced excess cardiovascular risk both from a clinical and regulatory perspective.
What is sufficient?

Both extremes might be problematic – or not, if everyone is happy.

HbA1c is no longer sufficient for approval

*Evidence demonstrating the lack of a CV risk is mandated*

**Summary of FDA/EMA Guidance:**
- Sponsors will need to show [pre-approval](#) that the upper bound of 2-sided 95% CI for the risk ratio of the incidence of CV events is <1.8 using the meta-analysis of Phase 2/3 trials (FDA), and “as far as possible, exclude that the new drug increases the risk of macrovascular complications, e.g. cardiovascular disease” (EMA).
- Long term studies (at least 18–24 months (EMA) or minimum 2 years (FDA). Number of patients not clear.

**Consequences for Pharma:**
- Substantial increase in the size, length and cost of pivotal T2D packages
  - Event driven pivotal trials – cost increase 2–3X for PhIII; in the range of $500–700 million
  - Given the cost & time – this investment must deliver evidence of positive benefit
  - Neutral / equivocal data will be punished by the market (cf Zetia and ENHANCE)
  - All risk is back loaded but investment is front loaded
ALECARDIO: Development of a dual ppar agonist

- Double-blind, placebo-controlled, randomized, international study
- Event-driven outcome study

Treatment period
≥ 2.5 years and ≥ 950 events

<table>
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<tr>
<th>Standard care (diabetes and other CV risk factors)</th>
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<tbody>
<tr>
<td>Aleglitazar 150 µg/day</td>
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<tr>
<td>Placebo</td>
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</tbody>
</table>

Follow-up period
4 weeks

Conclusions

- Questions exist over the role of HbA1c as a surrogate vs. risk marker
  - HbA1c potentially no longer a commercially valid surrogate for approval
  - HbA1c may lose value as a target for type 2 diabetes drug discovery
  - Outcomes likely needed at/near launch

- Pharma will switch to “safe-bet” targets
  - Targets will need a “reason to believe” that they reduce CV risk prior to Phase III investment; this will impact size, length and cost of Phase II
  - Targets with “just” glucose reduction will not be investable – and will drop out of the pipeline
  - Novel targets that do not impact classical surrogates will become less attractive
  - Role of biotech and small-pharma may change (investment required for Phase II much greater – focus on early development)

- Regulators, industry and academia must continue to identify and validate predictive benefit markers / panels
  - More accurate markers of modifiable risk in T2D to improve efficiency of compound selection
  - Molecular segmentation of diabetes (i.e. greater focus on PHC in primary care) eg targeted approval for selected niche diabetic populations

Available at: http://clinicaltrials.gov/ct2/show/NCT01042769 (accessed 01.07.11).