Phase 3 and 4, Pre- and Post-Marketing Continuum Models for Cardiovascular Safety with Diabetic Drugs

Statistical issues: Pharmaceutical Perspective

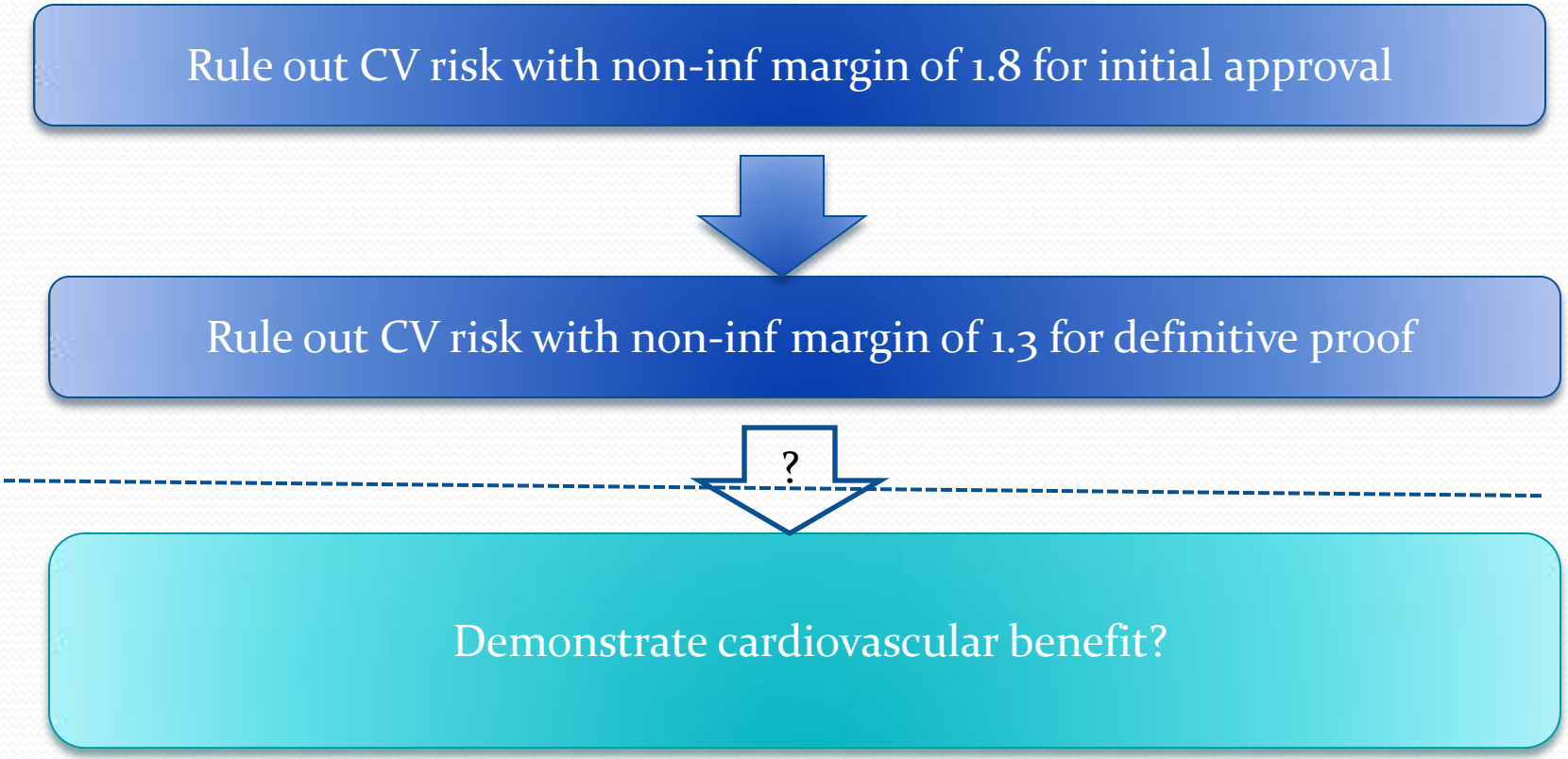
Disclaimer

- Fred Yang, PhD is an employee of GlaxoSmithKline, and possesses stock in this company.

- Dr. Yang is the sole author of this presentation, and takes full responsibility for its content. The presentation represents the personal opinion of the author and does not represent assertions or opinions of GlaxoSmithKline.

FDA guideline

Outline of the CV safety/efficacy evaluation



Key considerations

- Cohort
- Design
- Endpoint
- Follow-up

Statistics, (Meta-) analysis, sample size, analysis population, etc.

Cohort (A.K.A. Population)

Outcome study examples

	Event Rate	Key consideration	Note
General T2DM population	Low (e.g.: ≤1%?)	How long/large it would be?	Typical short term Phase IIIa population
High risk / multi. risk factors population	Moderate (e.g.: 1% -3%?)	Generalizability?	Most outcome study population
ACS population	High (e.g.: 3+%?)	Too late to show benefit/detect difference? Generalizability??	Selected outcome studies

* May also apply to Phase III studies?

Design: Overall Phase III (IV) Program

	Diabetes indication	Rule out RR of 1.8	Rule out RR of 1.3	Demonstrate superiority
Traditional multiple Phase III studies (duration ≤ 1yr)	Straight forward	Many (!!!) studies Need outcome study?	Unachievable? Need outcome study!	Impossible?
Hybrid: • **Traditional Phase 3 studies + mid-size outcome studies specifically address CV events** • **Multiple mid-term studies: e.g., 2-3 yrs duration/ Meta-analysis across studies with similar designs** • **May/May not be able to rule out RR of 1.3?**				
Large Outcome study	Indicated population ? Comparator?	Through interim analysis? Multiple comparison?	Another interim analysis? Multiple comparison?	Final analysis? Multiple comparison?

Design and Meta-analysis

- Studies included in the analysis:
  - Similar: design, population, etc.
- Comparators included in the studies
  - Placebo control
  - Active control: same as placebo?
    - Different types of active control --- are they the same?
- Data and Analysis
  - Consistency in data collection / endpoint adjudication
  - Analysis
    - Stratification by study
    - Consistency across studies/comparators

Endpoint: MACE (+)?

- Endpoint selection: Cardiovascular safety vs. Cardiovascular efficacy
  - Would MACE alone be sufficient to demonstrate safety?
  - Would MACE(+) be too noisy for signal detection?
    - Assay sensitivity/specificity

  Role of general CV safety evaluation

- Event identification and adjudication
  - Event identification / data collection:
    - Investigator identify / SMQ look through
    - Process and timing
  - Independent adjudication

Follow-up and data analysis

treatment discontinuation & study discontinuation

- Patients need to be followed up even after treatment discontinuation: Consent form/ 3rd parties/ etc.
- Data analysis

	PROs	CONs
ITT approach: include all events	Complete as overall safety even off treatment	May introduce additional noise
Per protocol approach: exclude events post treatment discontinuation	Drug specific effect during treatment	May miss signal post treatment

Summary

- The evaluation of cardiovascular safety in diabetes drug development requires comprehensive consideration on
  - Cohort: Patient Population Selection
  - Design: Overall Program
  - Endpoint: MACE+ Selection & Data Collection
  - Follow-up: Operation & Data Analysis

Thank you very much

Back ups

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Cohort: Outcome study examples

Examples of Historical Outcome Studies

	RECORD N=4437	ADVANCE N=11,140	ACCORD N=10,251	VADT N=1,791	PROactive N=5,238	BARI 2D N=2,368
Key inclusion criteria	Age 40–75 No major CV events in last 3 months	Age 55+ hist. of major macro/micro-vascular disease or 2+ risk factors	Age 40–79 with CV disease or 55–79 with 2+ CV risk factors	Age 40+ with no CV events within 6 months	Age 35–75 with history of CV disease	Age 25+ with diagnosis of CHD
Prior CVD	21%	32%	35%	40%	100%	100%
Event Rate / Year	~1.45%	~2.1%	~2.2%	~4.2%	~3.6%	~4.7%

Examples of Ongoing Outcome Studies

	Sitagliptin N~14000	Saxigliptin N ~12000	Liraglutide N~8800	Bydureon N~9500	Alogliptin N~5400
Key inclusion criteria	Age 50+ CV history	Age 40+ Previous CV history /risk factors	Age 50+ Concurrent / risk factors	Age 18+ CV history / risk factors	Age 18-90 ACS

Design: Outcome study

- Non-inferiority (safety) /Superiority (efficacy)
  - Non-inf →superiority
- Simple Large Trial (SLT) or Long Study (LS)

	Non-inf w/ margin 1.3	Superiority w/ risk ↓ 20%	Non-inf w/ margin 1.2 then superiority w/ risk ↓ 20%
# of events required	~625	~850	~1250
Total sample size needed (3% event rate, 90% power, 1:1 randomization)			
SLT (1 yr accrual /2 yr total duration)	~13700	~21500	~28500
LS (2 yr accrual/6 yr total duration)	~4350	~6700	~9000