What level and types of CV safety data acquisition should be considered to sufficiently characterize a drug's benefit/risk assessment by the end of Phase 3 development?

Cardiac Safety Research Consortium
Thursday, March 6th, 2014

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Disclosures (2013 to the present)

- Funding – all comes from the NIH
- Speakers bureaus, stock, patents – none
- Consulting activities: Safety monitoring boards, steering committees, and end point committees for: Ardea Biosciences, Astra-Zeneca, Chelsea Therapeutics, Dendreon, Forest Research, Roche Inc, Shire LLC, St. Jude's Medical, Takeda Development Center, Teva Neurosciences

Benefit-to-Risk Relation for Pulmonary Drugs: Intrinsic Difficulties in Determination during Development

- Pathophysiological links between pulmonary drug and CV events may not always be overt
- Assessment of symptom relief for COPD or other chronic lung disorders requires relatively short-term RCTs (≤ 6 months)
- Phase 2 and 3 trials are powered and designed to test effect on a primary efficacy variable
  - Nearly always underpowered to detect difference in incidence of CV SAEs
  - Dose-response for the pulmonary benefit and for CV risk may differ – testing may occur at doses not likely to elucidate CV risk
- Population might not be characterized or stratified for intrinsic (baseline) CV risk, confounding post-hoc evaluation
- Detection and characterization of CV event may be sub-optimal

Benefit-to-Risk Relation for Pulmonary Drugs

- For drugs for pulmonary indications, the benefits and CV risks are qualitatively dissimilar;
  - Benefit to risk judgment is subjective (e.g., how much reduction in dyspnea or COPD exacerbations offsets an irreversible CV event?)
  - To define relative benefit, an RCT is required
    - The pulmonary condition requiring benefit is present in 100% of study population. Therefore, a relatively small sample is required to demonstrate comparative benefit (e.g., relief of dypsnea) with acceptably narrow confidence intervals ***BUT***
    - Clinically relevant population often has moderate intrinsic CV risk; therefore, the point estimate for absolute risk from the efficacy RCT may have too few CV events and relatively wide CIs

Mechanistic Findings that Could Incur Concerns During Phase 1 and 2 Development for a Pulmonary Drug

Finding	Cardiovascular Concern
Anti-natriuretic properties	Hypertension, heart failure
Moderate increases in blood pressure	Increased risk of stroke, heart failure, and myocardial infarction
Alterations in coagulation, platelet function	Thrombosis (deep venous, arterial, pulmonary embolism), coronary disease
Metabolic aberrations - lipids, glucose	Enhance atherosclerosis
ECG abnormalities	Arrhythmias, sudden death, embolic stroke (AF)

Cardiovascular Parameters that Could/Should be Obtained in Phase 2 Development*

- Clinical heart rate
- Clinical blood pressure
- 24 hour heart rate (and arrhythmia assessment)
- ECG interpretation (conduction abnormalities and QTc)

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***piggy-backed to dose ranging trials in target population**

What Should be Understood by End of Phase 3 in COPD and other serious disorders?

- Assuming that benefits have been defined by adequately controlled studies, a hierarchy of CV risks should be considered
  - General likelihood of CV death or major irreversible morbid CV event
    - MI, CVA
  - General likelihood of debilitating but reversible CV event
    - E.g., Unstable angina, heart failure
  - Likelihood of developing pathophysiology directly and unequivocally underlying such events
    - E.g., accelerated thrombogenesis, malignant arrhythmias, accelerated atherosclerosis, myocardial dysfunction, hypertension, salt/water retention

Background Risk of the Target Population Matters – Low Risk MACE rate < 0.003)

- Number of patients needed to demonstrate non-inferiority assuming type 1 error = 0.05 and 90% power:

Non-inferiority margin	Group n_k sample size for $n_1 = n_2$
30%	57,479 (total = 114,958)
50%	20,693 (total = 41,386)
100%	5,174 (total = 10,348)

Adapted from Borer J et al Eur Heart J

Background Risk of the Target Population Matters – High Risk
MACE rate = 0.05

- Number of patients needed to demonstrate non-inferiority assuming type 1 error = 0.05 and 90% power:

Non-inferiority margin	Group n_k sample size for $n_1 = n_2$
30%	3,616 (total = 7232)
80%	1,302 (total = 2,604)
100%	326 (total = 652)

Adapted from Borer J et al Eur Heart J 2007

Patients with COPD and other chronic lung disorders are moderate CV risk but have high mortality rates (UPLIFT as an example)

Cardiac event	Tiotropium (n = 2896)	Placebo (n = 3006)	Relative Risk (95% CI)
All (per 100 pt-years)	**3.56**	**4.21**	**0.84 (0.73-0.98)**
Angina	0.51	0.36	1.44 (0.91-2.26)
Atrial fibrillation	0.74	0.77	0.95 (0.68-1.33)
Congestive heart failure	0.29	0.48	0.59 (0.37-0.96)
Myocardial infarction	0.69	0.97	0.71 (0.52-0.99)
'Cardiac failure'	0.61	0.48	1.25 (0.84-1.87)
'Coronary artery d.'	0.21	0.37	0.58 (0.33-1.01)

UPLIFT mortality (792/5,993 or 13.2% over 4 years) Most common causes: Lower respiratory infections, cancer, respiratory failure, cardiovascular disorders

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Celli B et al. *Am J Respir Crit Care Med* 2009; 180:948-955.
Tashkin DP et al . N Engl J Med 2008; 359: 1543-1554.

Cardiovascular Event Assessment in the Roflumilast Development Program (for COPD)

- Non-cardiovascular deaths (all deaths not meeting CV categories below)
- Non-fatal CV events (myocardial infarction and stroke)
- Cardiovascular Deaths
  - Death due to myocardial infarction
  - Death due to stroke
  - Death due to heart failure
  - Death due to arrhythmia
  - Death, sudden etiology unknown
  - Other CV deaths (vascular emergencies)

White WB, Cooke G, Kowey PR, et al. *Chest* 2013; 144:758-765.

Cardiovascular Adjudication Committee MACE* Analysis

COX Proportional Hazard Model

	Event Rates		Hazard Ratio and 95% CI		
Event Category	Roflumilast n = 6563 events (%)	Placebo n = 5491 events (%)	Hazard ratio	95% CI	p-value
Non-fatal MI	11 (0.2)	22 (0.4)	0.55	[0.26, 1.14]	0.109
Non-fatal Stroke	6 (0.1)	12 (0.2)	0.41	[0.14, 1.17]	0.097
CV Death	35 (0.5)	42 (0.8)	0.76	[0.49, 1.20]	0.245
Composite*	52 (0.8)	75 (1.4)	0.66	[0.46, 0.94]	0.024

White WB, Cooke G, Kowey PR, et al. *Chest* 2013; 144: 758-765.

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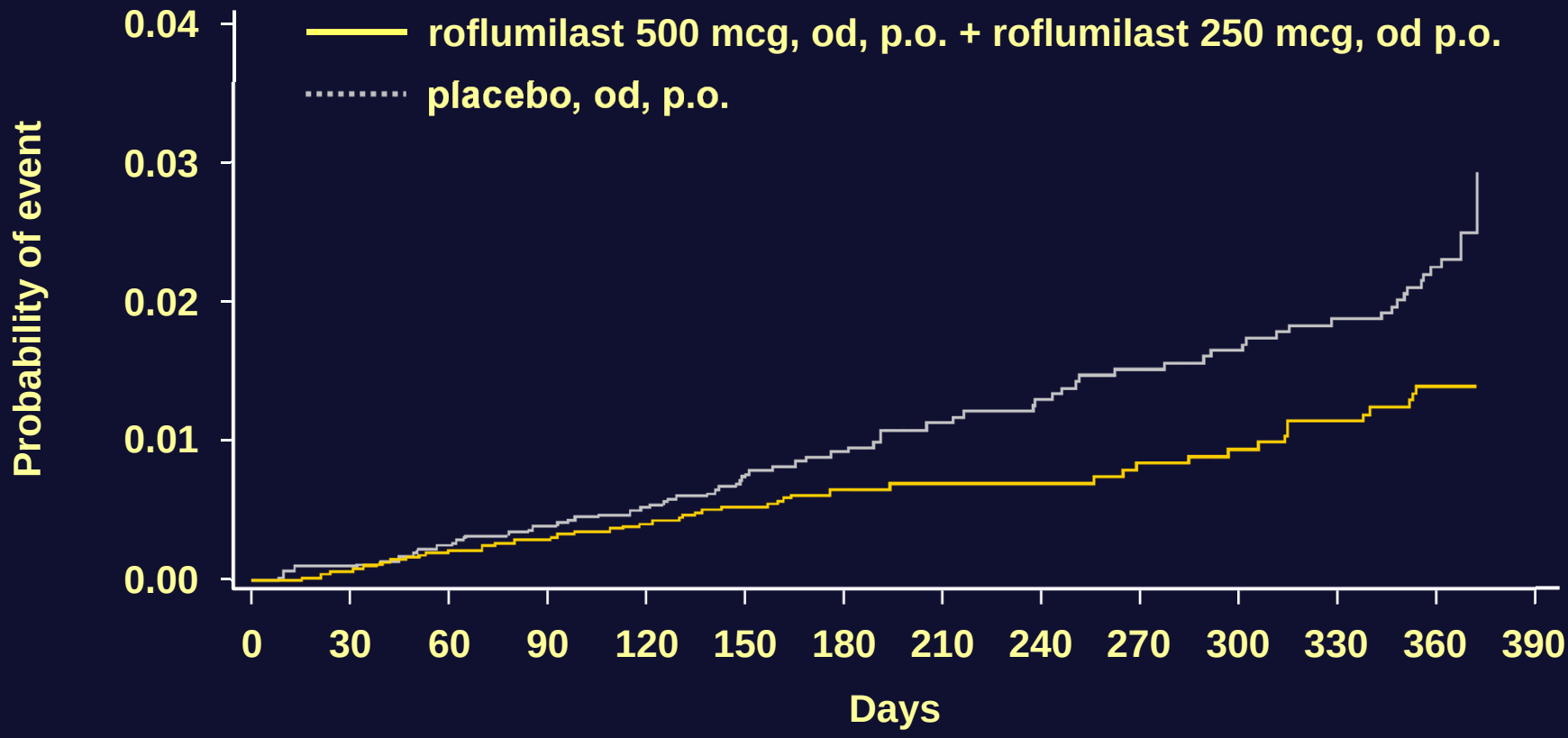
* MACE – Major Adverse Cardiovascular Events (CV death, non-fatal MI, nonfatal stroke)

Time to Onset of First MACE*



White WB, Cooke G, Kowey PR, et al. *Chest* 2013; 144: 758-765.

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Major adverse cardiovascular event: CV death, non-fatal MI, non-fatal stroke

COPD Safety Pool

All-Cause Mortality – Fatal Case Findings

Categories Used to Classify Patients' *Primary* Cause of Death	Fatal Cases for COPD Safety Pool		
	placebo (N=5491) (n=86*)	rof500 / rof250 (N=6563) (n=91*)	Relative Risk
	n (%)	n (%)	RR (95% CI)
Cardiovascular	**42 (0.77)**	**35 (0.53)**	**0.76 (0.49, 1.20)**
Death due to myocardial infarction	3 (<0.1)	4 (<0.1)	- †
Death due to stroke	4 (<0.1)	3 (<0.1)	-
Sudden death due to arrhythmia	2 (<0.1)	1 (<0.1)	-
Sudden death, etiology unknown	26 (0.47)	22 (0.34)	-
Death due to congestive heart failure	4 (<0.1)	2 (<0.1)	-
Other cardiovascular deaths	3 (<0.1)	3 (<0.1)	-
Non-cardiovascular	**40 (0.73)**	**52 (0.79)**	**1.09 (0.40, 1.25)**
Insufficient data	**4 (<0.1)**	**4 (<0.1)**	*

*** Number of patients with fatal events (COPD safety pool)**

† Event number too small to calculate RR

Endpoint Adjudication Committee Charter
(William B. White , MD, Dr. Peter Kowey, MD, and Glen Cooke, MD)

COPD Safety Pool

All-Cause Mortality Non-Cardiovascular Descriptions

Categories Used to Classify Patients' *Primary* Cause of Death	Fatal Cases in COPD Safety Pool	
	Placebo (N=5,491)	Roflumilast (N=6,563)
Non-cardiovascular deaths	n (%)	n (%)
Infection (incl. pneumonia)	7 (0.1)	7 (0.1)
Respiratory failure	21 (0.4)	23 (0.4)
Neoplasm	9 (0.2)	14 (0.2)
Injury (trauma)	2 (<0.1)	2 (<0.1)
Surgery (complications)	0 (0.0)	1 (<0.1)
Diabetes	0 (0.0)	1 (<0.1)
Suicide	0 (0.0)	3 (<0.1)
Gastrointestinal disorder	1 (<0.1)	1 (<0.1)
Total	40 (0.7)	52 (0.8)

* Number of patients with fatal events (COPD safety pool)

† Event number too small to calculate RR

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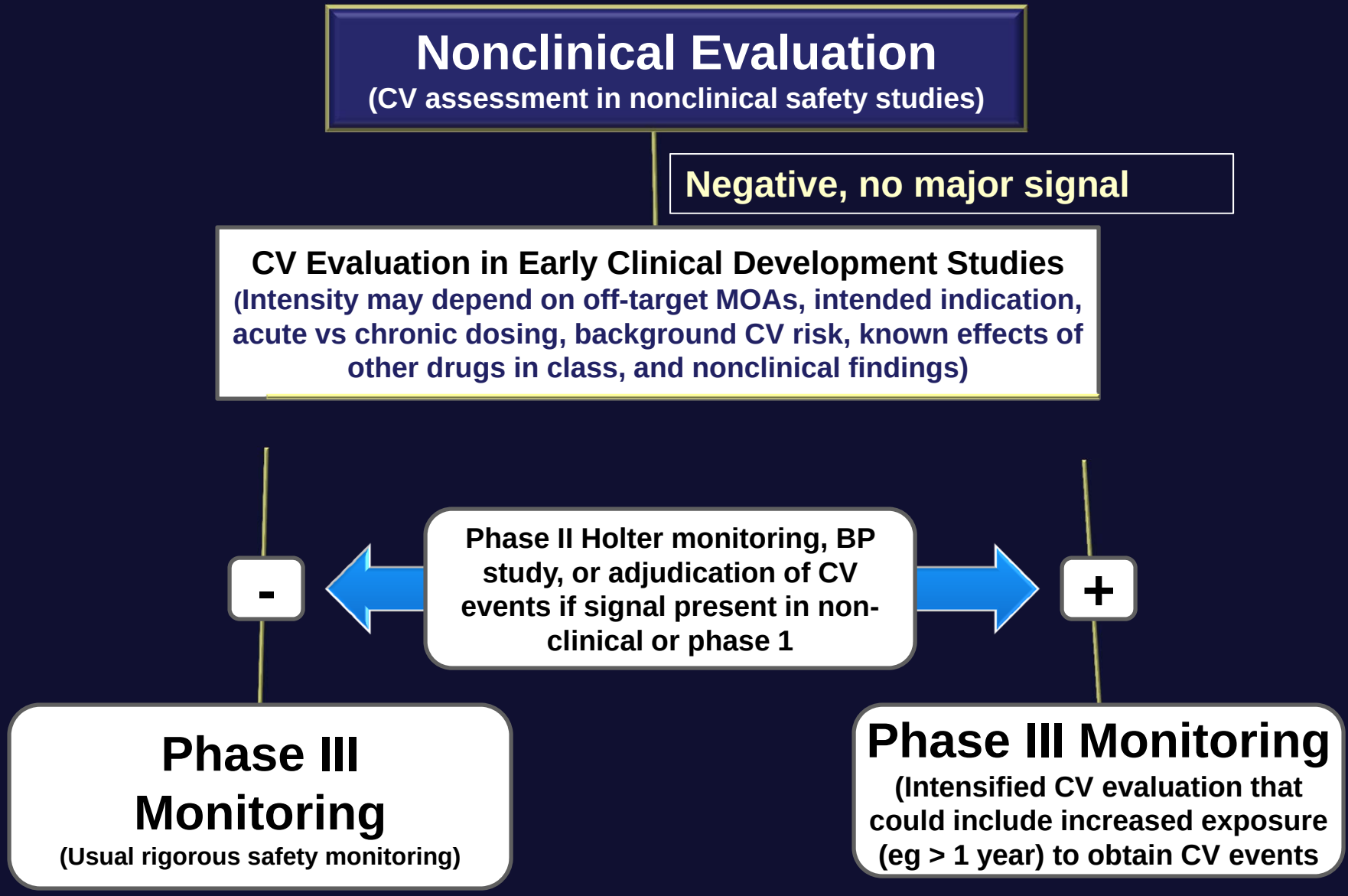
Pulmonary Drug Development Processes



Summary and Recommendations

- Explore safety “surrogates” early in development (phase I-II)
  - To identify obvious CV pathophysiological concerns for intensive clinical outcome studies
  - To eliminate from further development drugs with apparent major safety concerns
- Design development program to enable pooling of safety data (phase III)
  - Common, protocol-mandated definitions of events and procedures to obtain data (to be discussed today)
  - Prespecified statistical analyses to define point estimate and upper bound of confidence interval to define absolute risk for the risk:benefit determination
- Possible to refine labeling post-approval with consecutive-patient data registries from first dose or through pragmatic clinical trials that are amenable to data pooling