INFORMATIVE CENSORING IN A RARE DISEASE

A case study in PAH

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IN BRIEF

- The indication and context
- Composite endpoints in relation to the GRIPHON Selexipag pivotal study
- Informative censoring
- Joint frailty modeling
- Simulation study
- Regulatory challenges
- Conclusions

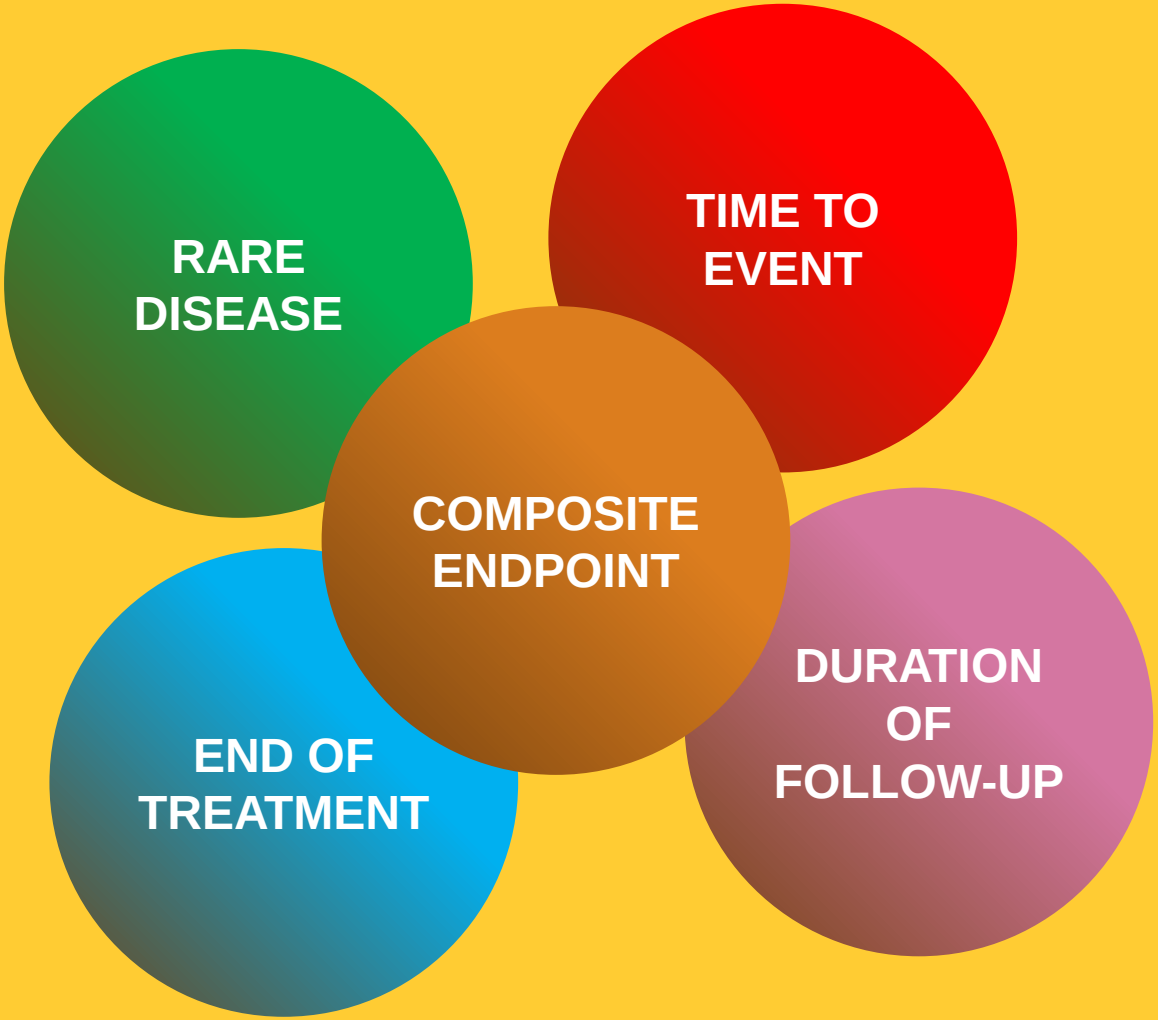
PULMONARY ARTERIAL HYPERTENSION (PAH)

PARADIGM SHIFT IN CLINICAL ENDPOINTS

- Pulmonary arterial hypertension is a severe **rare disease** with poor prognosis despite available treatments [Galiè 2015].
- Current patient management strategies support combining therapies that target the *endothelin*, *nitric oxide*, and *prostacyclin* pathways.
- Most PAH studies had previously considered short-term endpoints as change in 6MWD or in hemodynamic parameters to measure treatment benefit (e.g. at week 12).
- Since the outcome study SERAPHIN [Pulido, 2014], the Guidelines suggest using a long-term endpoint such as time to clinical worsening [Hoeper 2013], i.e. a composite endpoint made up of *softer* (e.g. decrease in 6MWD from baseline) and *harder* components (e.g. lung transplantation, death).
- As a composite, time to clinical worsening is defined as time from randomization to the first occurrence of any one of the components, up to end of treatment.

THE CONTEXT

STATISTICAL ELEMENTS OF THE STUDY DESIGN

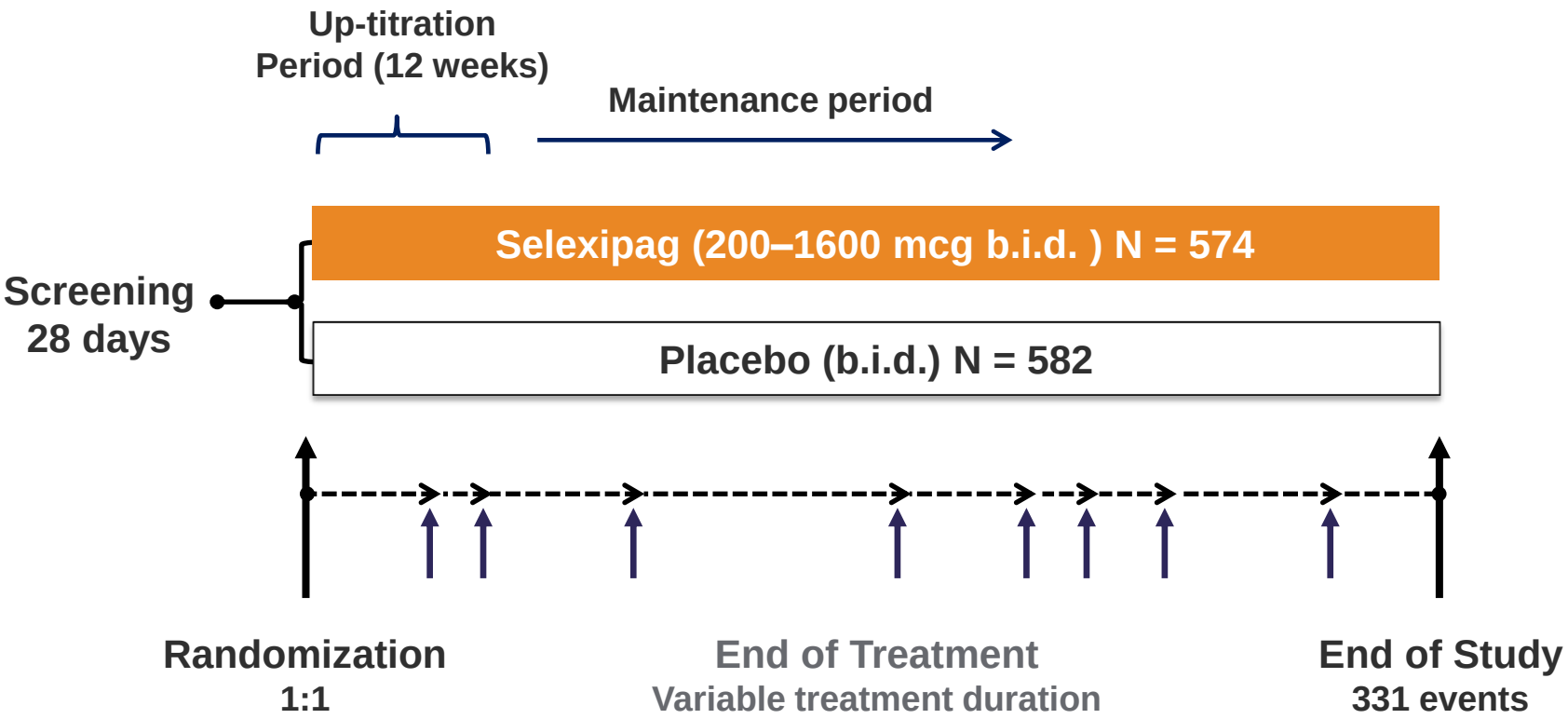


COMPOSITE ENDPOINTS AND THEIR CHALLENGES

- The use of composite endpoints is widespread in clinical development and particularly in cardiovascular indications (e.g. CV MACE) and in oncology (e.g. PFS).
- The advantage sought with composites in a rare disease is the higher event rate, which leads to potentially smaller sample sizes.
- There are obvious challenges: **all** components should
  - provide strong evidence of efficacy
  - be clinically relevant
  - be evaluated with unbiased assessments
  - be of similar importance

- The components are in fact *competing risks*, and dependent competing risk problems often make time to first occurrence of component event analysis difficult to interpret.

MOTIVATING EXAMPLE: THE GRIPHON EVENT-DRIVEN STUDY



The largest controlled study conducted in symptomatic PAH
80% of patients treated with at least one approved PAH medicine

Sitbon, NEJM 2015

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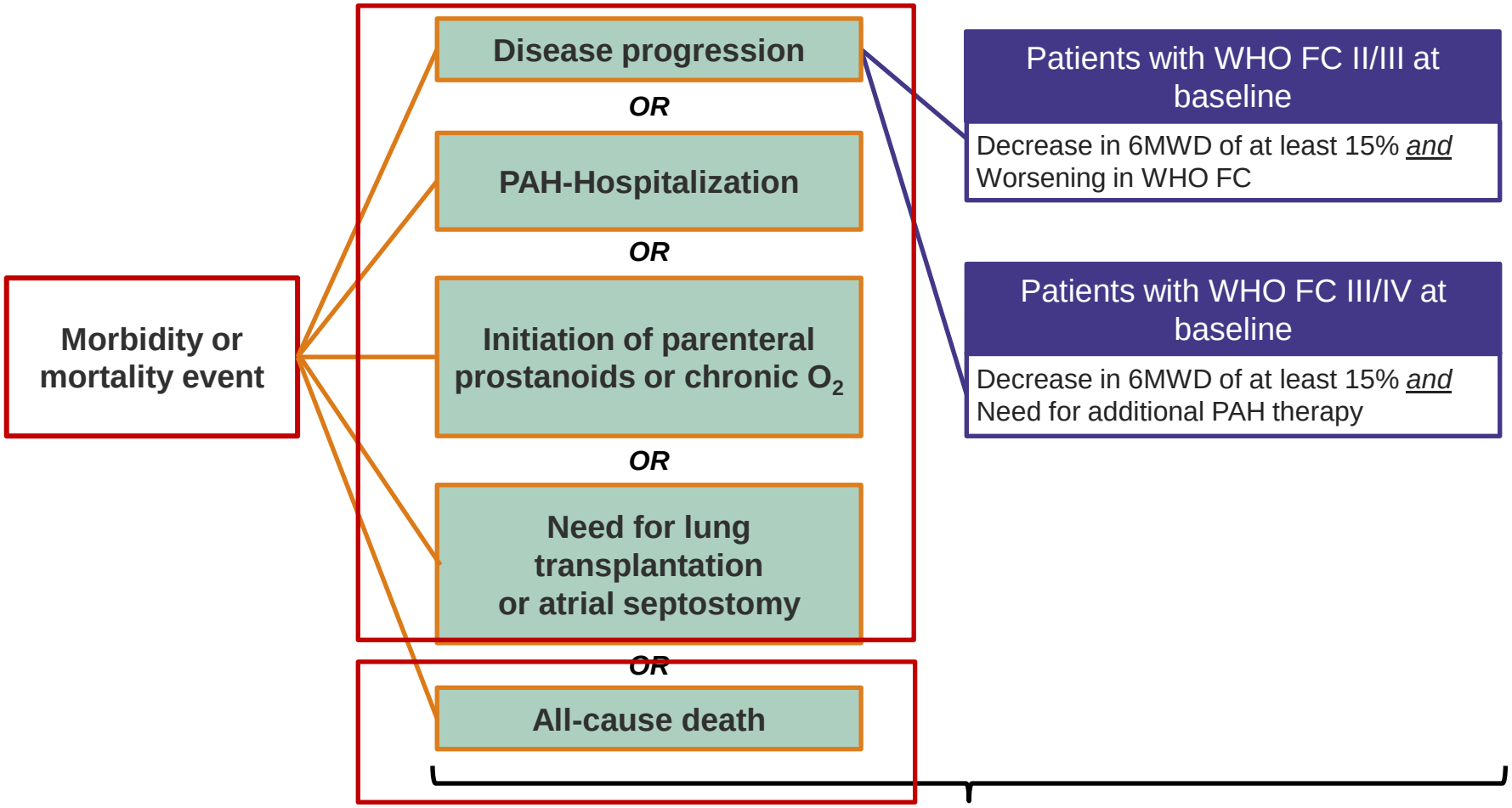
MOTIVATING EXAMPLE: THE GRIPHON STUDY

PRIMARY: TIME TO FIRST MORBIDITY OR MORTALITY EVENT *UP TO EOT*



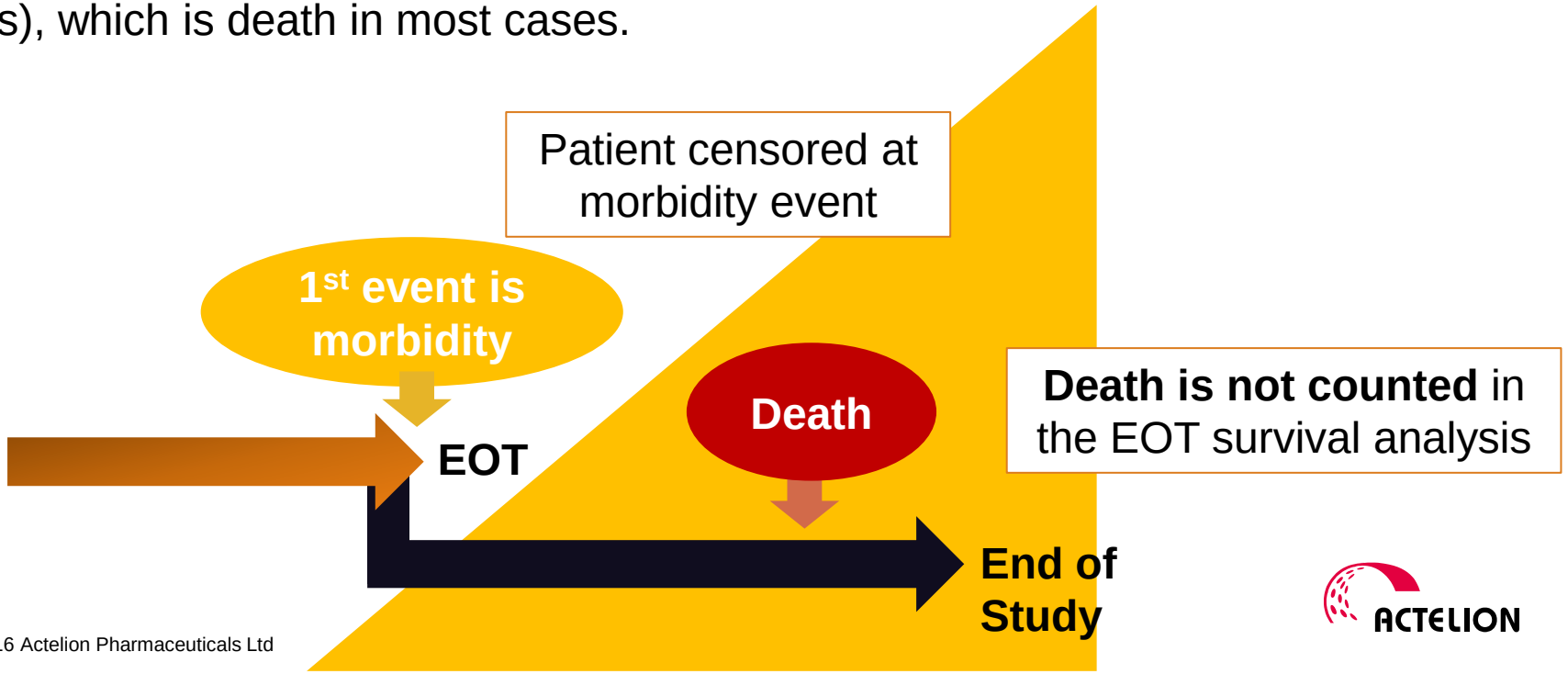
WHAT IS INFORMATIVE CENSORING (IC)

- When *data from patients without follow up beyond end of treatment is not independent of the underlying disease process, therefore introducing bias* [Clark, 2003]
- *Censoring patients when they discontinue treatment … is often likely to be informative … more likely to occur with patients who are at a higher risk of progression/death than with those who are at risk but not censored* [Denne 2013]
- The potential that censoring could be informative is a concern and could invalidate certain statistical analyses or render them less robust, e.g. Kaplan-Meier estimation [Campigotto 2014]
- So it is difficult, if not impossible, in a rare disease context such as PAH, to assess differences in mortality using the standard, conventional survival analysis inference procedures in the presence of IC [DeMets 2012]
- **What methodology could be used to understand this phenomenon?**

MOTIVATING EXAMPLE:

"SPLITTING" THE COMPOSITE ENDPOINT ONTO TWO COMPONENTS

- Let's assume there are only one fatal (death) and one non-fatal (morbidity) components in the composite endpoint.
- The **first** event triggers end of treatment (EOT) and induces **informative censoring** onto the **second** event.
- As the study was highly significant for the primary endpoint (**HR=0.6, 99%CI=[0.46,0.78]**), the first event censors (informatively) the subsequent one(s), which is death in most cases.



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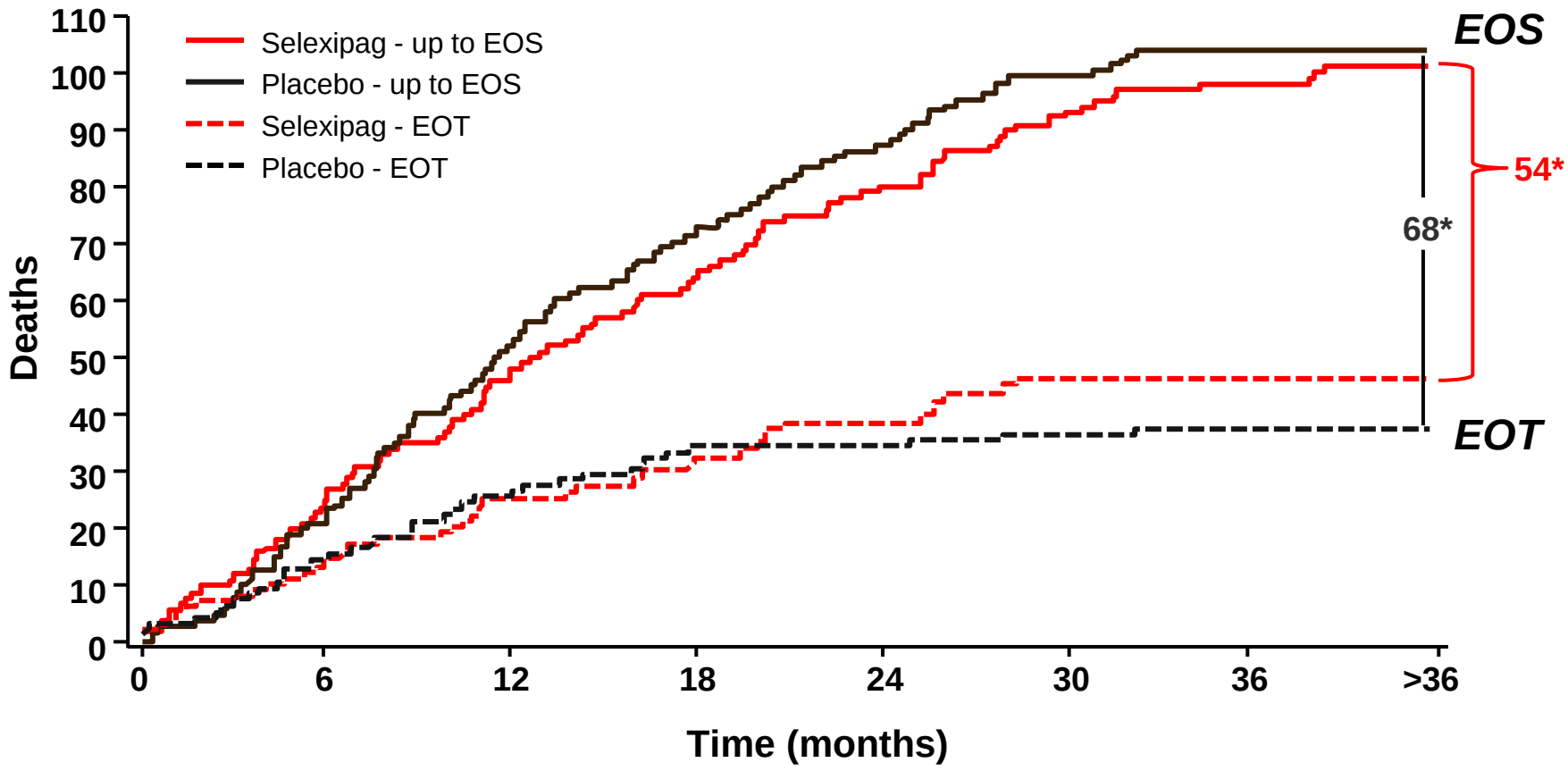
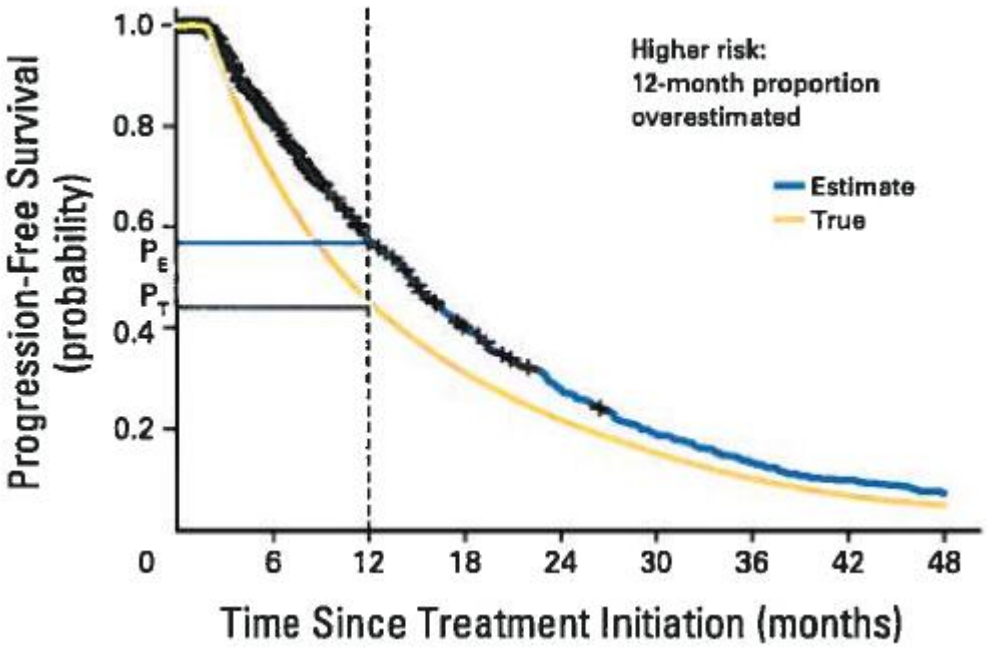
DEATH AT EOT IS UNDERESTIMATED IN BOTH GROUPS, MORE SO IN THE PLACEBO GROUP



*Cumulative number of deaths “excluded” (i.e. informatively censored) up to EOS by treatment arm

IMPACT OF INFORMATIVE CENSORING ON ESTIMATION

- The KM estimation of time to an event can be biased in presence of IC.
- The direction of the bias depends on whether those which are excluded from the estimation are at a lower of higher risk of the event/death relative to the ones who remain.
- In the PAH setting, people with a Morbidity event tend to be at higher risk of death.
- There is little empirical data so far to show the magnitude of the bias due to IC [Campigotto, 2014]



INCREASED RISK OF DEATH AFTER MORBIDITY INDEPENDENT OF TREATMENT

- Indeed the censoring (whether from a primary morbidity event or discontinuation of treatment) occurs more often in patients that are at a higher risk of death.
- These patients are more in placebo and they are censored earlier in placebo, as treatment with Selexipag is highly efficacious.
- This biases any analysis of survival alone after EOT and standard statistical methods are not helpful.

	From randomization up to EOT + 7		From EOT + 7 up to EOS	
Treatment	Follow-Up (Years)	Deaths per patient year	Follow-Up (Years)	Deaths per patient year
Placebo	795.93	0.046	305.46	0.223
Selexipag	843.93	0.055	235.31	0.229

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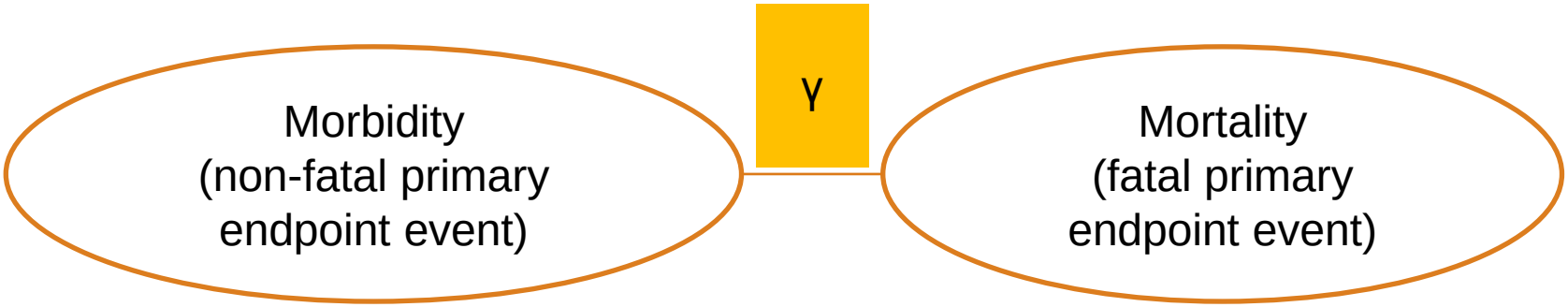
SIMULATIONS USING JOINT FRAILTY MODELLING

TWO SURVIVAL PROCESSES CONNECTED BY A FRAILTY TERM



- Morbidity and mortality are *competing risks* that lead to multiple, correlated, observations in the same patient: the *frailty* γ parameter defines this correlation
- A proportional hazards model with Weibull distributed event times and gamma frailty term γ is used to generate the fatal and non-fatal event times (premature discontinuations are taken as non-fatal events)
- The assumptions include *one* hazard-ratio between treatments for fatal events and *one* for non-fatal events.
- An acceleration model for the time to death process after the occurrence of the non-fatal event is additionally imposed to model the process beyond first event.

SIMULATIONS RESULTS USING FRAILTY (1)

ONE EXAMPLE SCENARIO: HR_{FATAL}=1, $HR_{NON\text{-}FATAL}$=0.58

ALL OTHER PARAMETERS SET BY REFLECTING THE STUDY DESIGN AND DATA

	Simulated Data		Observed Study Data	
Event type	Selexipag (n = 574)	Placebo (n = 582)	Selexipag (n = 574)	Placebo (n = 582)
Death as primary endpoint	25	17	28	18
Deaths up to EOT+7	43	37	46	37
Deaths between EOT and EOT+7	18	19	18	19
Deaths up to EOS	99	104	100	105
Non-fatal events	257	314	257	312

SIMULATIONS RESULTS USING FRAILTY (2)

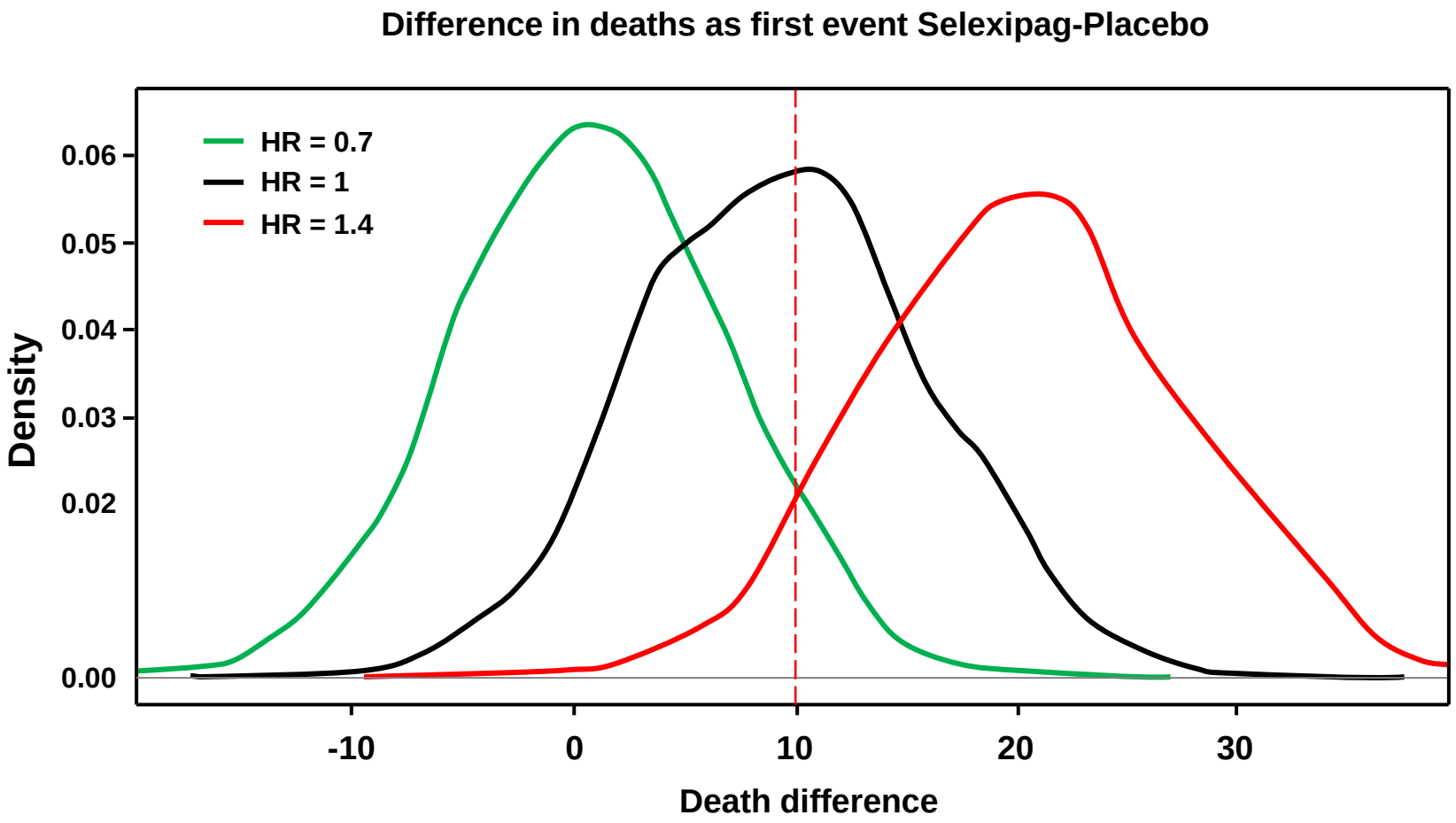
ACROSS SCENARIOS: VARYING THE HR_{FATAL}

- By increasing the HR_{fatal} towards detrimental effect of the treatment, the likelihood of differences between counts becomes more likely.

- Under an assumption of neutrality, a difference of 10 deaths in counts is likely to occur.

Assumed true HR	Selexipag Deaths as first event	Placebo Deaths as first event	Probability difference in deaths as first event is ≥ 10
Observed	28	18	
0.7	19	18	6%
1.0	25	17	44%
1.1	30	18	59%
1.2	33	18	72%
1.3	36	18	85%
1.4	39	18	93%

SIMULATIONS RESULTS USING FRAILTY (3)



from EPAR: […] *the imbalance in deaths is consistent with the assumption of a neutral effect on PAH mortality and reduction of non-fatal events.*

THE REGULATORY CHALLENGE

INTERPRETATION OF THE TIME TO INDIVIDUAL EVENTS

- Competing risks and informative censoring are not an easily explainable phenomena to the layman. IC is not typically acknowledged across Regulatory Divisions.
- Much work has been done to clarify and (also visually) quantify IC.
- Differences in counts in our experience are what draws attention, so it was a statistical challenge to bring it back to likelihoods and probabilities via simulations.
- Ultimately, in the Selexipag EPAR [April 2016]: […] *death rates up to EOT are biased by informative censoring. Informative censoring occurs when events are not counted in the analysis due to reasons related to the study design. […] If the censoring would be non-informative (i.e. if morbidity and mortality events would be independent from one another), the ratio of the event rates (censoring event rate ratio, CERR) would be expected to be 1.0.*

IN CONCLUSION

- Composite endpoints help… but sometimes create extra work, where clarifications are needed, possibly up-front.
- Any imbalances that occur beyond a first event need to be put into the context of competing risks and informative censoring.
- It is very important to educate all on this challenge, first and foremost us statisticians.
- It is of the utmost importance in cases where IC could arise, to minimize the risk of IC by observing all patients beyond EOT and continue the data collection up to study closure [DeMets, 2012].
- It should be considered at the design stage, to what extent is increased efficiency to be gained from adding a component to a composite, in those cases where the treatment effect on this component is not as strong as it is on the original endpoint. Ideally all relevant components should be included.

Thank you for your attention

Thank you goes to Professor L.J. Wei and Team at the Harvard T.H. Chan School of Public Health

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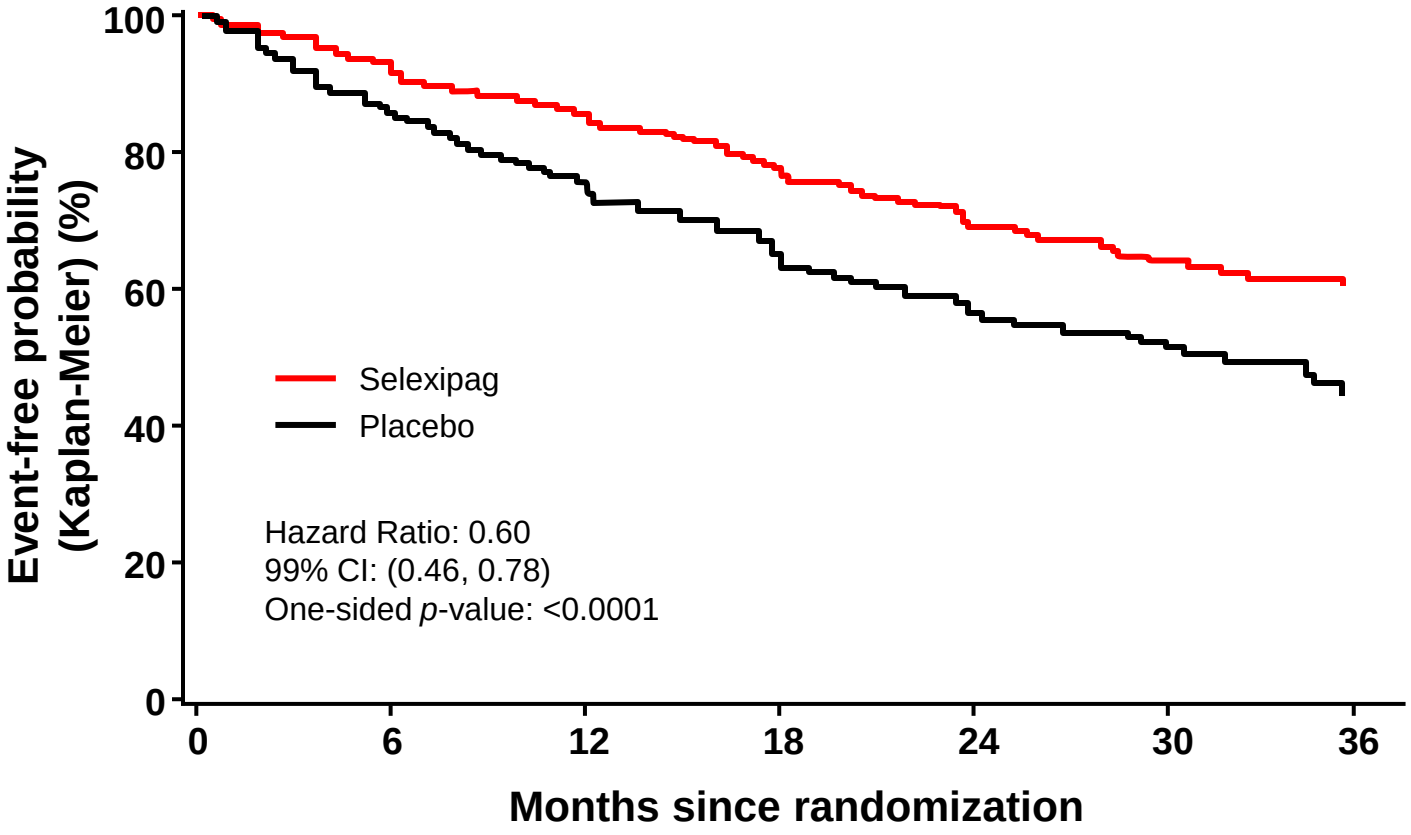
BACK-UPS

PRIMARY ENDPOINT

SELEXIPAG SIGNIFICANTLY REDUCES THE RISK OF A MORBIDITY / MORTALITY EVENT



Time to first M/M event up to EOT

PAIRED DEPENDENT PROCESSES WITH FRAILTY

UP TO END OF TREATMENT, UNDER NEUTRALITY

Hazard function for non-fatal event in Selexipag treatment group

$$h_1(t) = \nu \frac{p_1}{\lambda_1} \left(\frac{t}{\lambda_1} \right)^{p_1 - 1}$$

Hazard function for non-fatal event in placebo treatment group

$$h_1(t) = \nu \frac{p_1}{\lambda_2} \left(\frac{t}{\lambda_2} \right)^{p_1 - 1}$$

Common hazard function for fatal event in both treatment and placebo group, having assumed **neutrality**

$$h_2(t) = \nu^{\alpha} \frac{p_2}{\lambda_F} \left(\frac{t}{\lambda_F} \right)^{p_2 - 1}$$

where γ is the frailty random variable shared by these hazard functions, $\gamma_i \sim_{\text{i.i.d.}} \Gamma(1, \theta)$.

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