Requirements from regulatory agencies and post marketing surveillance

Assessment of Cardiovascular Dugs for the treatment of ischemic heart disease

- Acute coronary syndromes: STEMI - NSTEMI
- Chronic stable angina: 1. risk factors, 2. anti-anginals

Assessment of Drug Efficacy in ACS

- Mortality
- Cardiovascular Mortality
  - Discharge
  - 30 days
  - 3 months
  - 1 year
- Reinfarction
- Sudden death

Assessment of Cardiovascular Dugs for the treatment of chronic ischemic heart disease

- Chronic stable angina: 1. risk factors, 2. anti-anginals

  ✓Risk factors: events, surrogate end points

  ✓Anti-anginals: inducible ischemia parameters, GTN consumption

Cardiovascular Risk factors
Lipids

- Approval based on effect on lipid profile
  - Short term efficacy
  - Long term safety
- Approval based on MACE

Cardiovascular Risk factors
Blood pressure

- Approval based on effect on blood pressure reduction
  - Short term 12 weeks vs placebo
  - Short term 12 weeks vs comparator
  - Long term 52 weeks safety study
  - Adequate patient groups
- Approval based on MACE

Assessment of efficacy in CSA

- Drugs: secondary prevention – anti-ischemic

- Mortality ?
- Morbidity?
- Degree of ischemia

Assessment of inducible myocardial ischemia

- Exercise ECG
- Holter monitoring
- Myocardial perfusion scintigraphy
- Stress echo

Assessment of efficacy for anti-anginals

- Exercise time during ETT
- Time to 1 mm ST segment depression
- HRQoL
- Number of episodes of angina
- No of GTN tablets used

- RRP to 1 mm ST
- RPP at peak exercise

Assessment of efficacy of antianginals

Study designs

- Rx vs Placebo
- Rx vs Beta blockers
- Rx+ beta-blockers vs other antianginals + beta-blockers

Assessment of anti-anginal drugs

Treatment of stable angina has not been subjected to the same scrutiny by large randomized trials as has, for example, that of myocardial infarction and unstable angina. Thus, although much has been achieved in comparing the symptomatic benefit of different modalities of treatment, there is relative paucity of information about their prognostic effects.

Antianginal drugs have classically been aimed to reduce myocardial oxygen demand and/or increase blood flow to ischaemic area. However, other therapeutic approaches with novel mechanisms of action are currently under investigation, which may reinforce the emphasis that should be placed on the need of reassuring pharmacodynamic and safety databases.

The clinical profile drugs fro stable angina needs to be studied in an acute stress testing setting, i.e. with provocation of anginal attacks due to cardiac ischaemia, which is assumed to represent the conditions of normal practice. Valid data are only likely to be obtained if sufficient account is taken of such factors as the pronounced placebo effect in angina pectoris, the substantial variation in the nature and severity of symptoms, and the subjective character of 'chest pain'.

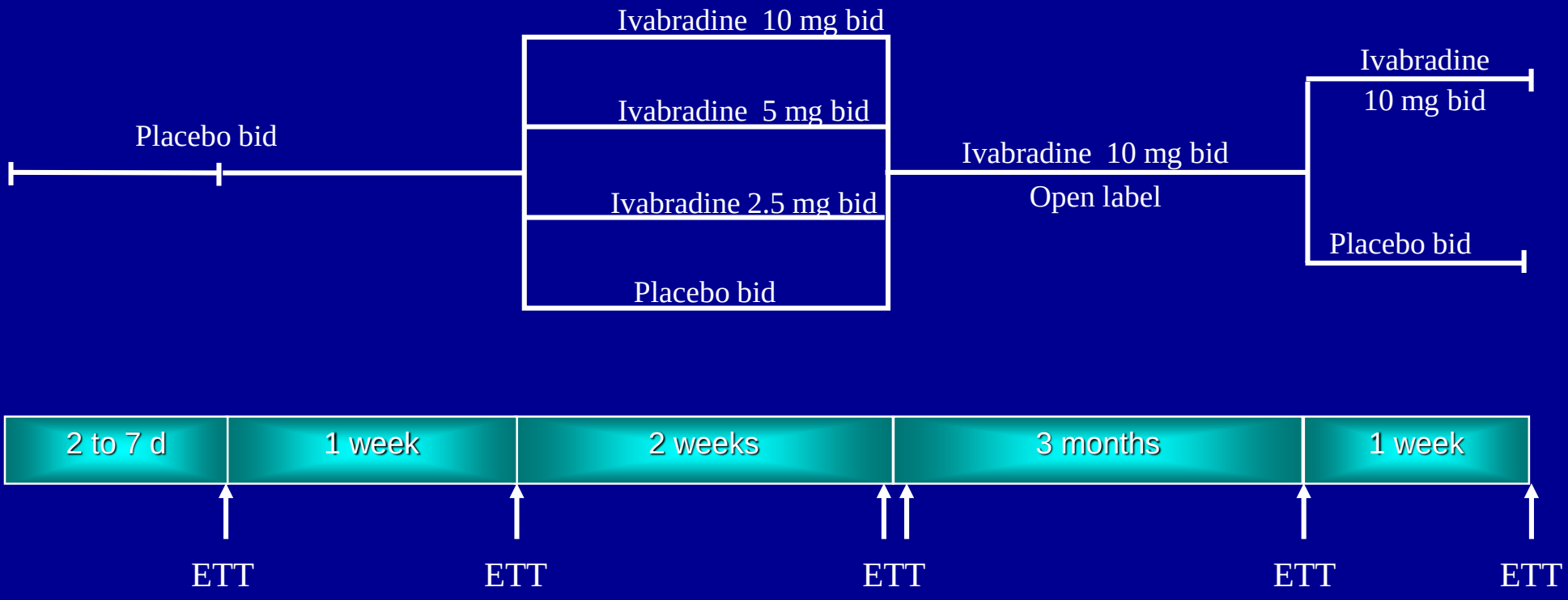
Assessment of anti-anginal drugs

Criteria of efficacy

As the assessment of the effect of antianginal drugs based on clinical measurements alone is as yet considered too unreliable because of the possible influence of uncontrolled variables, it has become accepted that measurements of exercise capacity using standardised exercise testing should be, in spite of an intrinsic amount of variability, the major criteria of efficacy, In addition to its more objective character, it is assumed that improved exercise capacity may accounts for the patient benefit in terms of reduction of symptoms. Moreover, exercise testing provides evidence that the relief of angina and increased exercise capacity are mediated by an anti-ischaemic effect. In addition, clinical evidence of symptomatic improvement in terms of anginal pain and HRQoL (Health-Related Quality of Life) should also be provided in the major therapeutic trials.

Example of a development plan of a drug approved for the treatment of chronic stable angina

Ivabradine and exercise-induced myocardial ischemia



ETT: Exercise tolerance test

Borer JS, et al. *Circulation.* 2003;107:817-823.

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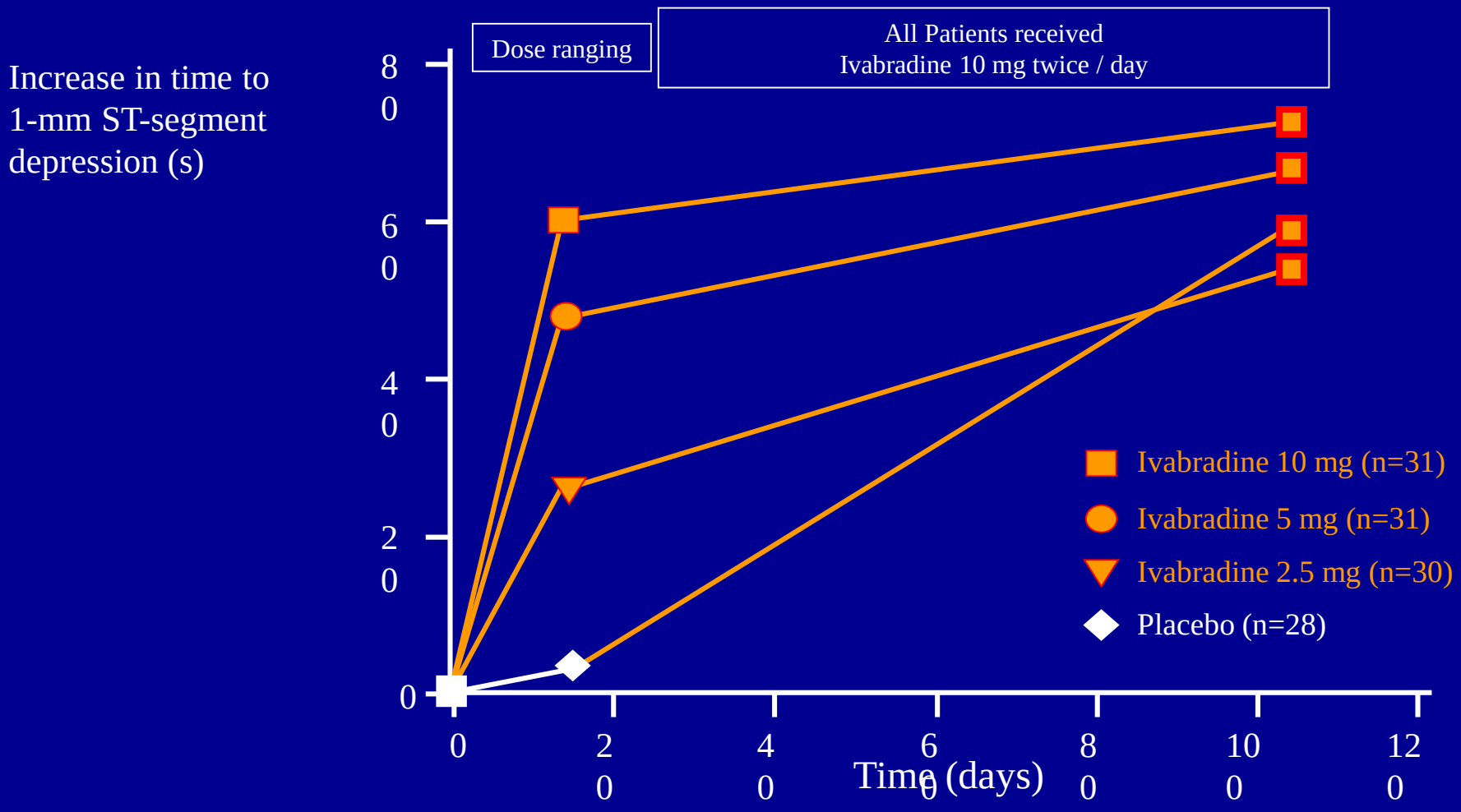

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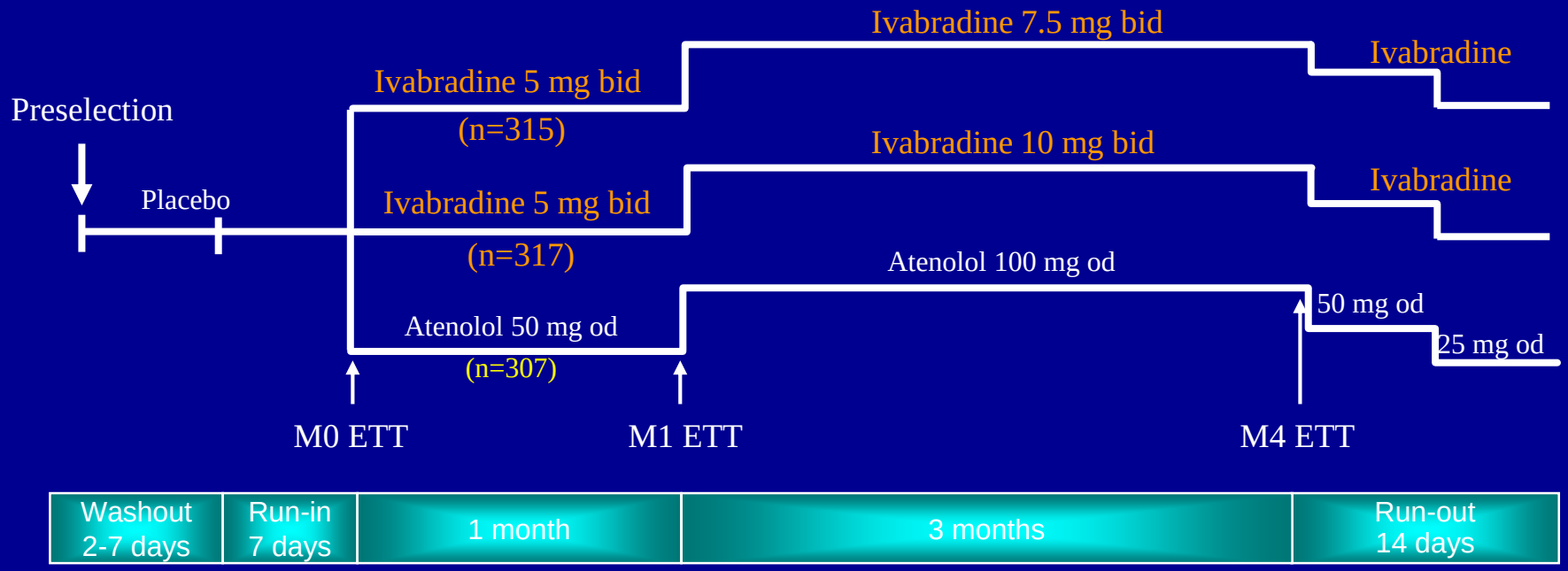

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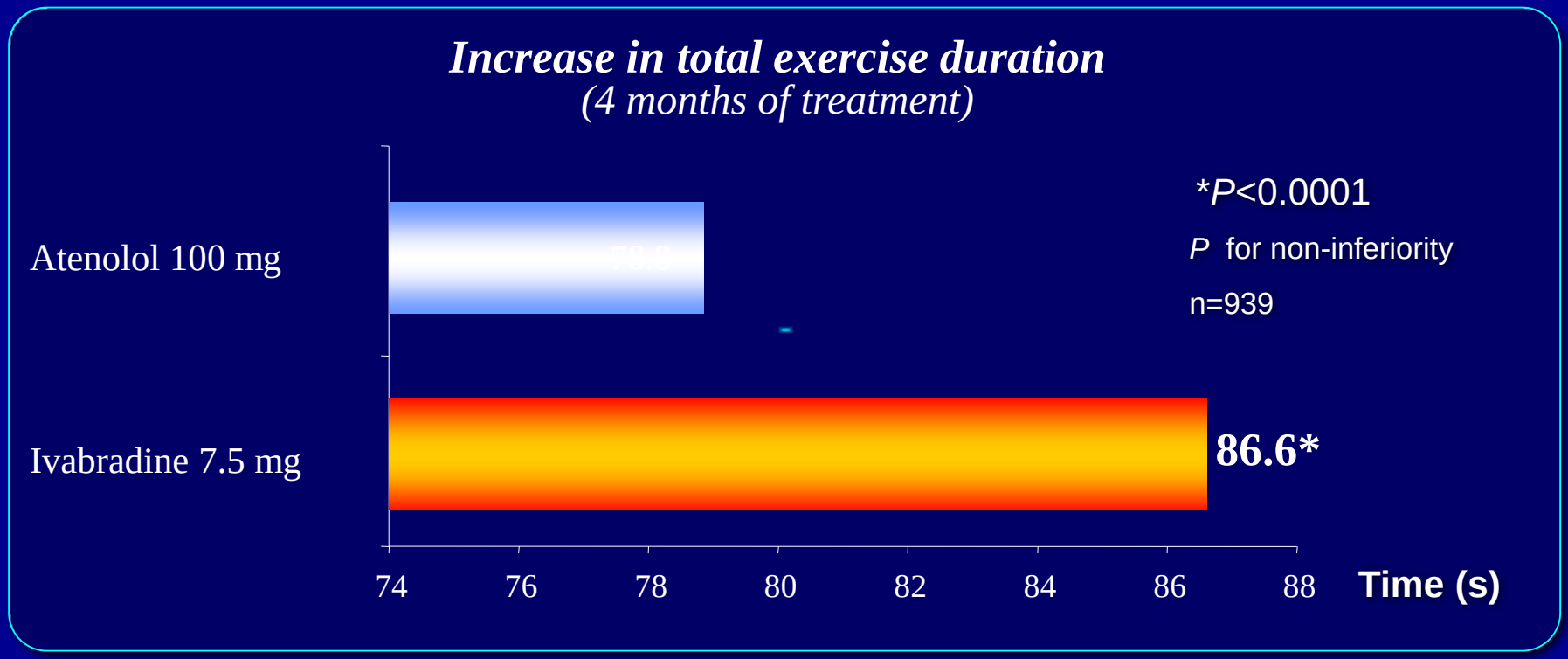

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 May 2014
EMA/280865/2014

Review of Corlentor/Procoralan started

- No benefit in overall mortality/morbidity
- Increased mortality in patients with angina

Studies for approval of therapeutic agents for the treatment of heart failure

Selection of patients

- **AHF**

  Patients hospitalised because of HF should be randomised within a reasonable time in order to be able to adequately assess efficacy

- **CHF**

  -LVD alone will not suffice.

  -Patients should exhibit a wide range of severity of CHF.
  Alternatively the information can be gathered by separate studies in different patient subsets

  -Patients should be in stable conditions, however a shorter period from the acute event and randomisation may be considered in patients with more severe forms of HF

  -It is advisable to exclude patients within 3 months from a MI and with a short (<3 months) duration of the disease

Selection of patients

- **AHF**

  Patients hospitalised because of HF should be randomised within a reasonable time in order to be able to adequately assess efficacy

  Patients needing optimisation of background Rx

  Patients already maximal Rx

- **HHF**

  Patients included at discharge after an unplanned hospitalisation for HF

- **CHF**

  -LVD alone will not suffice.

  -Patients should exhibit a wide range of severity of CHF. Alternatively the information can be gathered by separate studies in different patient subsets

  -It is advisable to exclude patients within 3 months from a MI and with a short (<3 months) duration of the disease

Criteria to assess efficacy

- AHF

  -In Hospital and 4 wks mortality

  -Depending on the indications claimed, long term mortality and duration of hospitalisation

  -Improvement in haemodynamic state and symptoms (categorical composite)

  -Relief of other manifestations of AHF including need of inotropic support and vasodilators

- CHF

  -Mortality, morbidity

  -Primary composite

Cardiovascular mortality

- Since no correlation exists between short term improvement in clinical symptoms and/or exercise capacity and mortality, many drugs are likely to require a trial which includes survival amongst its primary objectives before requesting an approval regardless of the claim being sought

- If the investigational drug belongs to a *new pharmacological class* or when *agents of the same class* have been associated with detrimental effects, a prospective, RCT aimed at assessing survival is requested

- Distinction should be made between a) sudden death b) death due to acute deterioration of clinical status c) death due to chronic progression of CHF

Composite end points

May be appropriate but should include selected aspect of cardiovascular morbidity along with overall mortality. They all should be clinically relevant

- Hospitalisations for HF
- Causes of hospitalisation (co-morbidities, non adherence etc)
- Worsening Heart Failure without Hospitalization
- No. of hospitalisations/year
- Patient journeys
- Recurrent morbid events

Secondary end points

- Exercise tolerance: 6MWT seems to correlate better than Maximal exercise test (with or without gas exchange analysis) with the clinical effect of the drug
- Haemodynamic data: are insufficient to demonstrate benefit but may be useful to elucidate the mechanism of action
- Neuroendocrine status: data may be included but they can be only be accepted as supportive
- Physical signs and renal function: can be accepted as supportive only
- Symptoms: the effect on symptoms should always be coupled with data on mortality and morbidity
- QOL: supportive only

Safety aspects

- Hypotension
- End organ consequences (Heart, CNS, kidney)
- Effect on cardiac rhythm
- Pro-ischaemic events

Regulatory requirements in clinical trials

What constitutes meaningful change

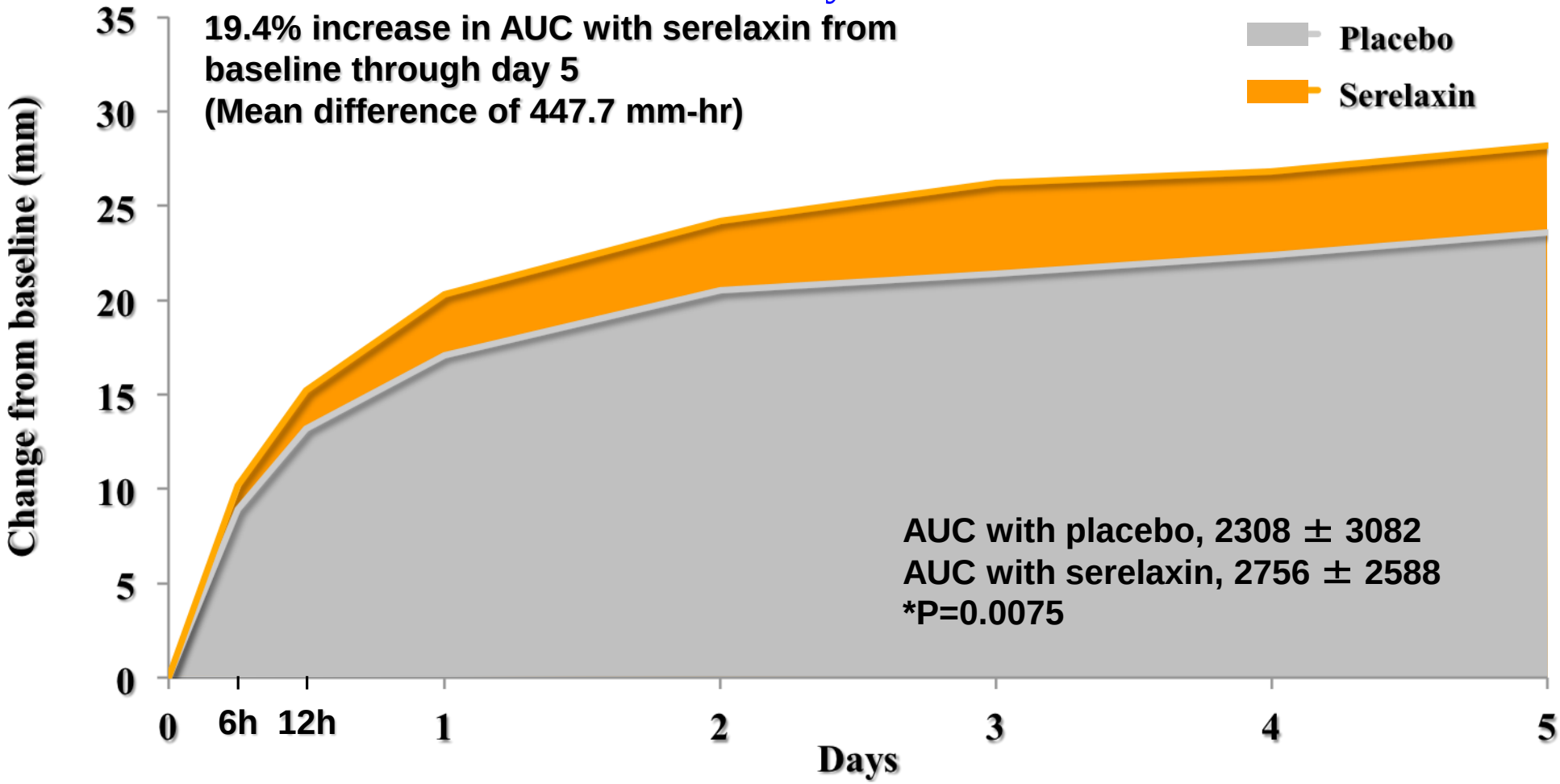
Meaningful change

- Any change in a primary end point that correlates with an improvement in mortality/morbidity
- A change in a primary end points that significantly improves QOL in end stage disease patients

Dyspnoea in AHF

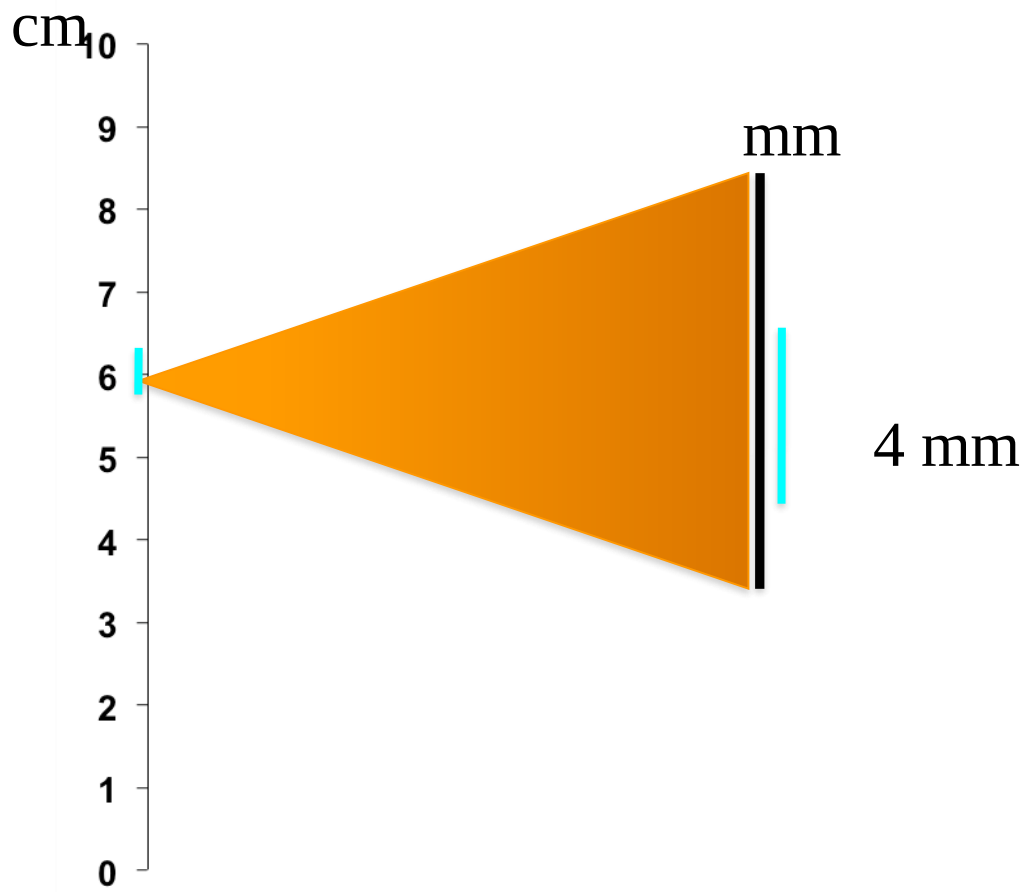
Significant Improvement of VAS AUC Endpoint

Effect evident early and maintained



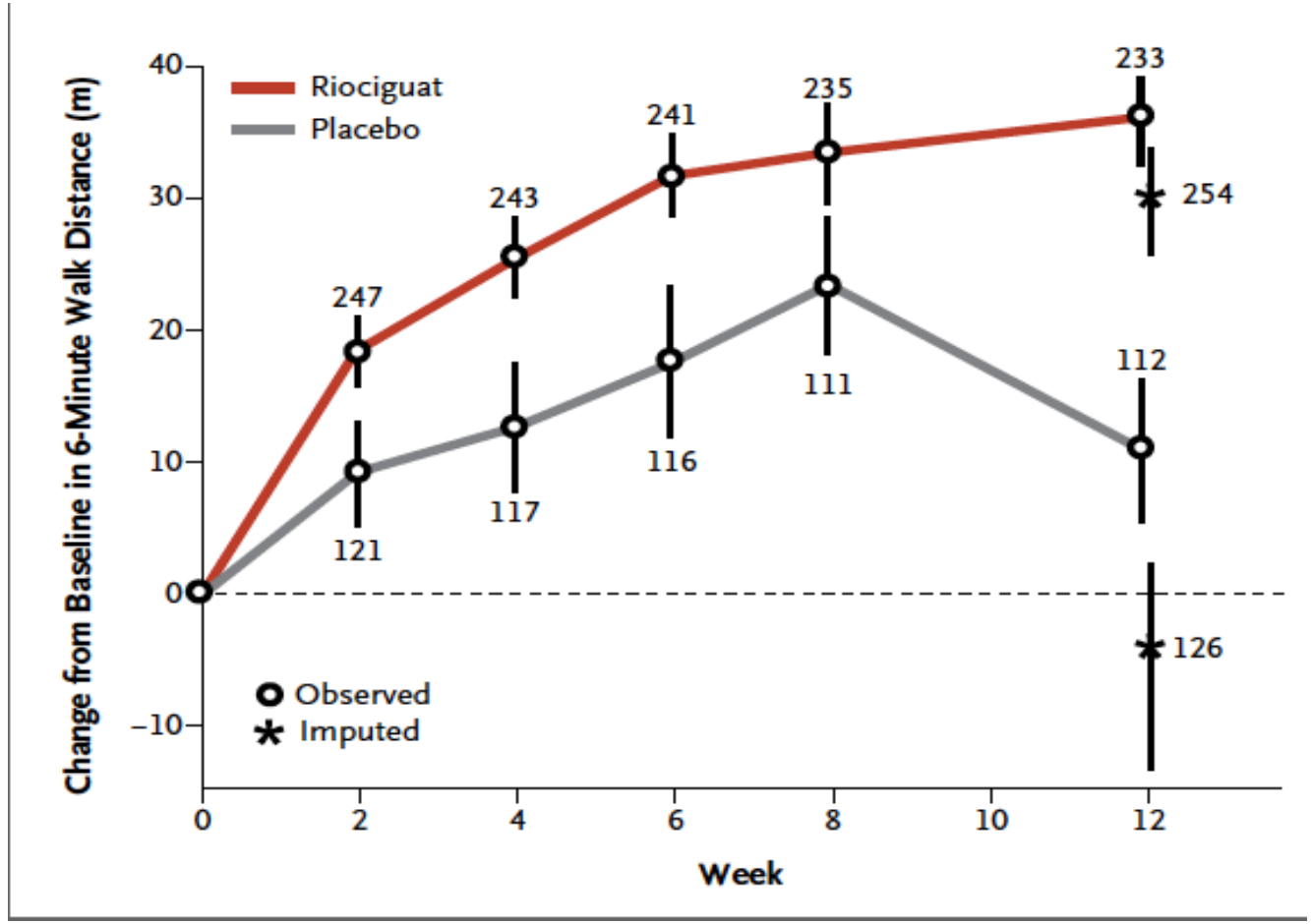
* P-value is based on a two-sided two sample t-test for serelaxin versus placebo comparing area under the curve (AUC, mm-hours) of change from baseline of dyspnea visual analog scale (VAS) from baseline to Day 5.

Absolute value of changes in VAS scale



Exercise capacity

Riociguat in pulmonary arterial hypertension



Ghofrani et al N Engl J Med 2013; 369: 4

Macitentan on exercise capacity and on Mortality-Morbidity end points

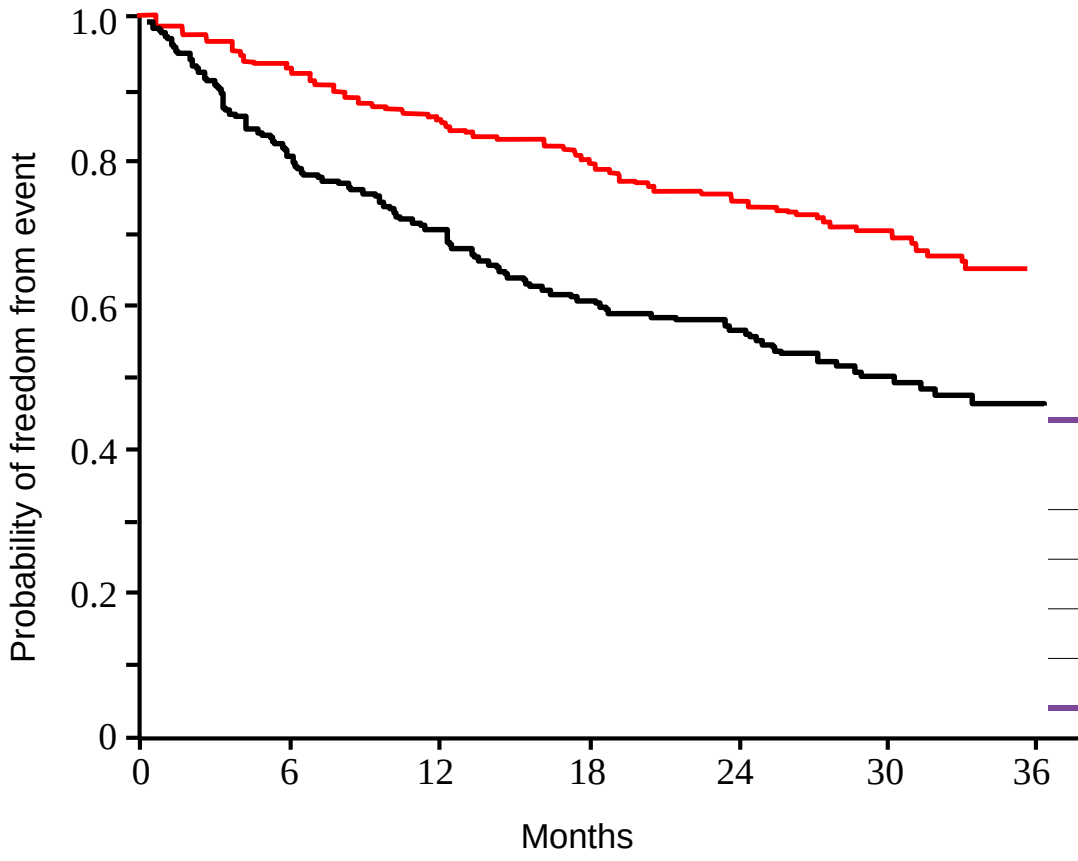
6-MWT

+ 7.4 m macitentan

- 9.4 m in Placebo

-(treatment effect 16.8 m; 97.5% CI, −2.7 to 36.4; P=0.01)

Macitentan on exercise capacity and on Mortality-Morbidity end points



6-MWT

+ 7.4 m macitentan

- 9.4 m in Placebo

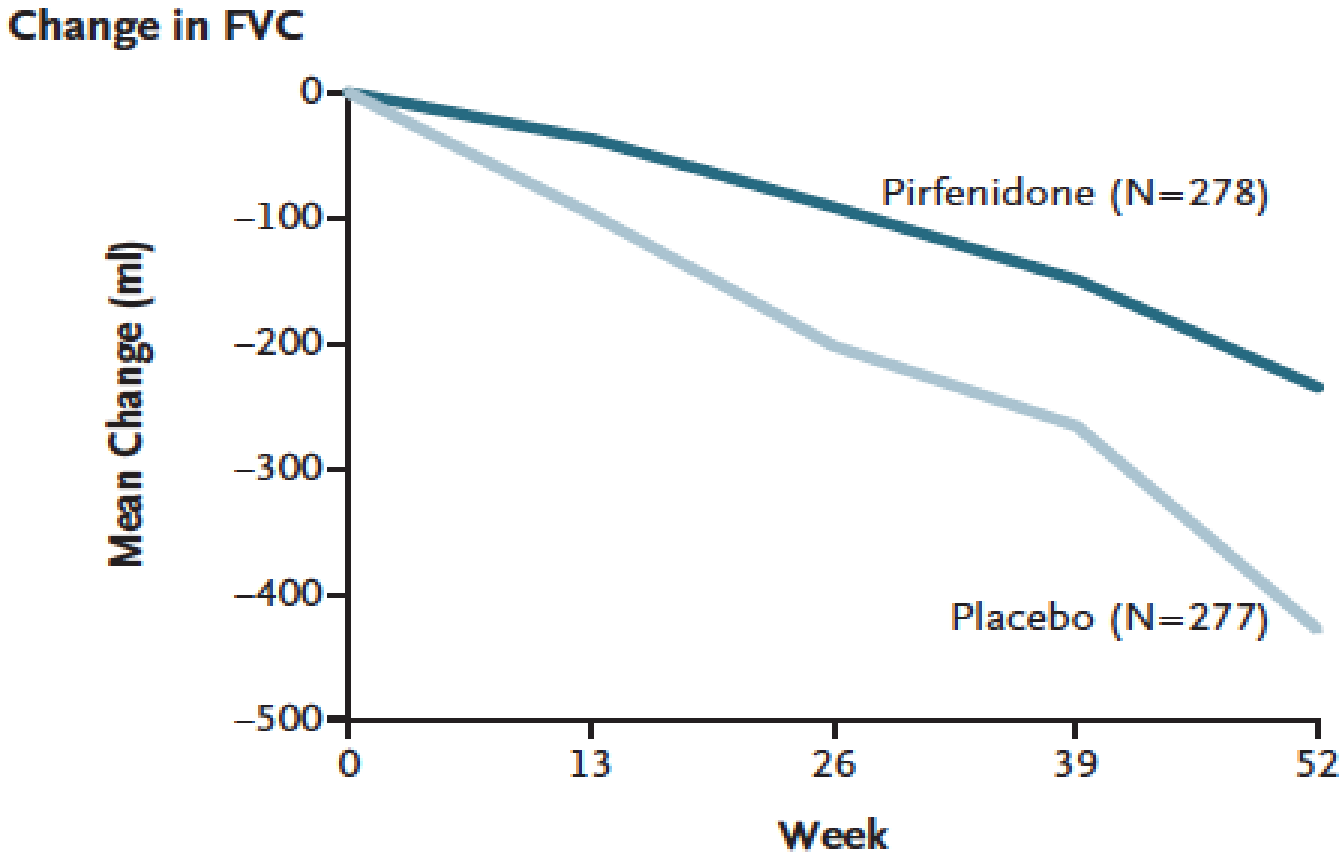
-(treatment effect 16.8 m; 97.5% CI, −2.7 to 36.4; P=0.01)

Macitentan 10 mg

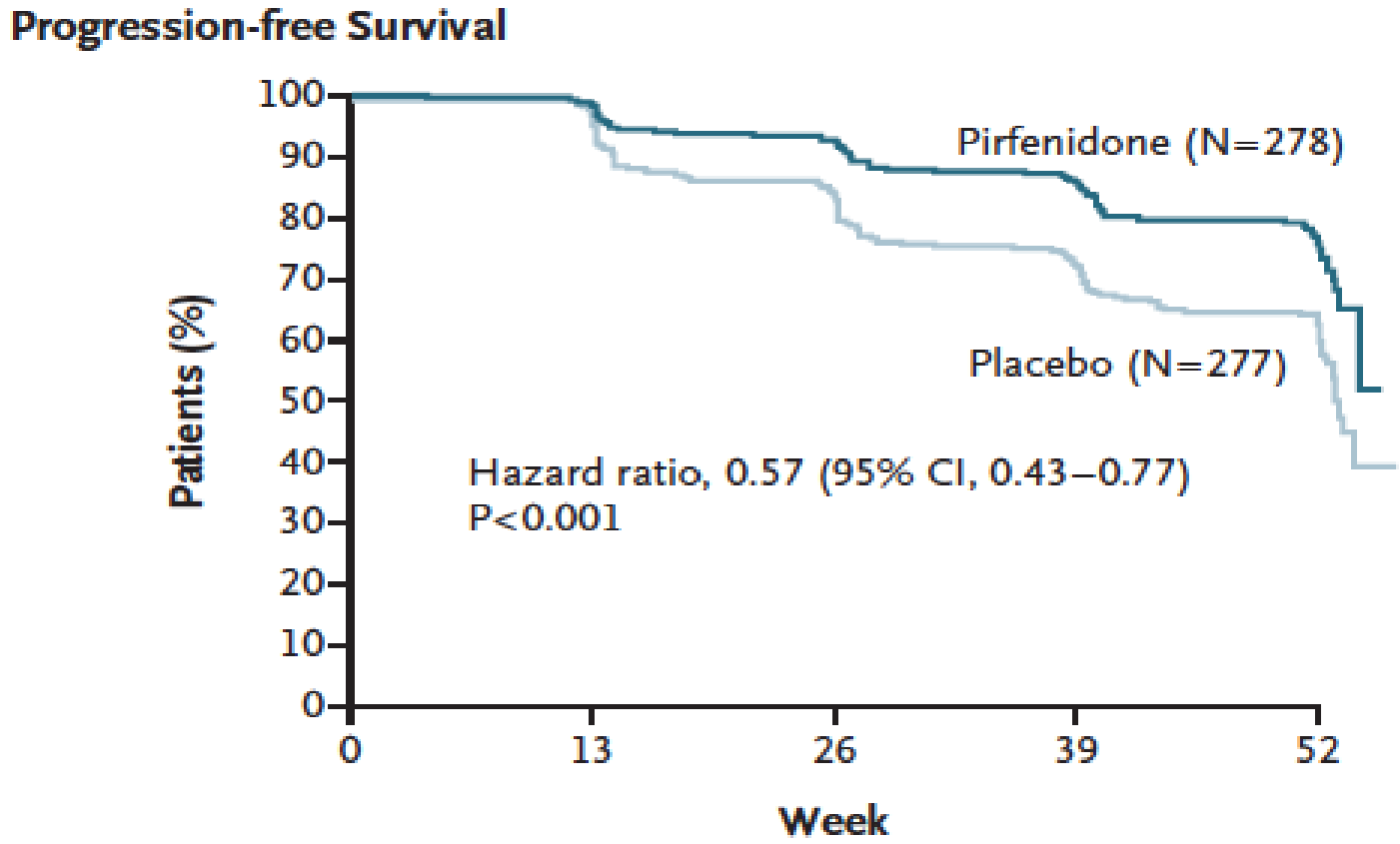
Placebo

	Placebo (n=250)	Macitentan (n=242)
Number of M/M Events	116	76
Hazard ratio (HR)		0.55
97.5% CI of HR		0.392, 0.762
p-value		< 0.0001

Pirfenidone in pulmonary fibrosis



Pirfenidone in pulmonary fibrosis



How to define a meaningful change

- Change in a parameter that correlates with mortality and/or morbidity or that has a clinical relevance
- No fixed value
- Has to be related to baseline function
- Attenuation of the decline in function
- Must be significantly related to the disease
- Must have a biological plausibility

Scientific background: The clinical trial programme in the pre-authorisation phase

- Focused on efficacy
- Safety is a secondary endpoint, generally underpowered and not pre-specified

Clinical trial limitations:

small sample size

Drug name	*No. Exposed to product in USA during testing*	*Approximate exposure prior to withdrawal*
Terfenadine	5.000	7.500.000
Fenfluramine	340	6.900.000
Dexfenfluramine	1.200	2.300.000
Mibefradil	3.400	600.000
Bromfenac	2.400	2.500.000

Friedman MA et al., JAMA 1999; 281:1728-1734

Challenge Faced by Regulatory Authorities at Marketing Approval:

How to ensure that life-saving therapies are available in a timely fashion

while

Still guarantee that medicines are safe

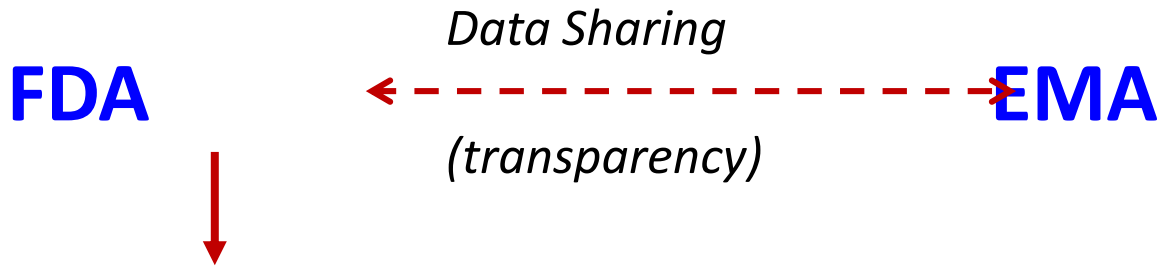
What we do not know at time of approval

Full safety profile including adverse drug reactions which are:

- Rare.
- Delayed (long latency).
- From chronic exposure.
- Due to cumulative effects.
- Medication error/off-label use.
- Associated with abuse/misuse.
- Associated with populations not studied in trials

  (e.g. children, elderly, pregnancy, co-morbidities).

Tools for monitoring and assessing risk-benefit profile



Publicly available PhV Database (**FAERS**)

Risk Evaluation and Mitigation Strategies (REMS)

Drug Safety Initiatives:
- Critical Path Initiatives
- Sentinel (**Mini-Sentinel**)

Drug Safety Consortia:
- iSAEC
- CSRC
- HESI

Publicly available PhV Database (**EudraV**)

Risk Management Plans (RMP):
- **PASS/PAES** (New PhV Legislation)

Drug Safety Initiatives:
- Encepp
- IMI (Innovative Medicines Initiatives)

Drug Safety Consortia:
- SOS
- EU-ADR
- ARITMO
- Safeguard

PASS
Post-authorization safety study:
definition

Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, **confirming the safety profile of the medicinal product**, or **measuring the effectiveness of risk management measures**.

Post-authorization safety study: objectives

- to quantify potential or identified risks
- to evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (i.e. pregnant women, specific age groups, patients with renal or hepatic impairment)
- to provide evidence about the absence of a risk
- to assess patterns of drug utilisation that add knowledge on the safety of the medicinal product (i.e. indications, dosage, co-medication, medication errors)
- to measure the effectiveness of a risk minimisation activity.

PASS: triggering factors

- PASS initiated, managed or financed by a MAH
  - Pursuant to an obligation imposed by a competent authority
    - as a condition to the granting of the marketing authorisation, or after the granting of a marketing authorisation if there are concerns about the risks of the authorised medicinal product **(category 1)**
    - as part of a marketing authorization granted under exceptional circumstances **(category 2)**
  - Voluntarily/required
    - studies required in the risk management plan to investigate a safety concern or evaluate the effectiveness of risk minimisation activities **(category 3)**
    - any other PASS **(category 4)**

Post-authorisation efficacy studies

Delegated Regulation to determine situations for a PAES:

In order to determine the situations in which post-authorisation efficacy studies may be required […] the Commission may adopt […] delegated acts" (Article 22a of Directive 2001/83/EC and 10b of Regulation (EC) No 726/2004)

PAES – Practical aspects

- Exceptional tool for 'standard' marketing authorisations
- Context: efficacy evaluation
- Identified concern - burden of proof with regulators
- Justified on a case-by-case basis
- Goal: address well-reasoned scientific concerns with direct impact on the maintenance of the marketing authorisation
- Design: appropriate to answer the scientific question – focal point: supplementing efficacy data

The Sibutramine experience

- ✓ 1997 sibutramine approved for weight loss by FDA labelled warning re BP and heart rate increases
- ✓ 2002 EMA requires CV outcomes trial (SCOUT)
- ✓ 10,744 overweight/obese with CV disease and/or diabetes over 3.4 years

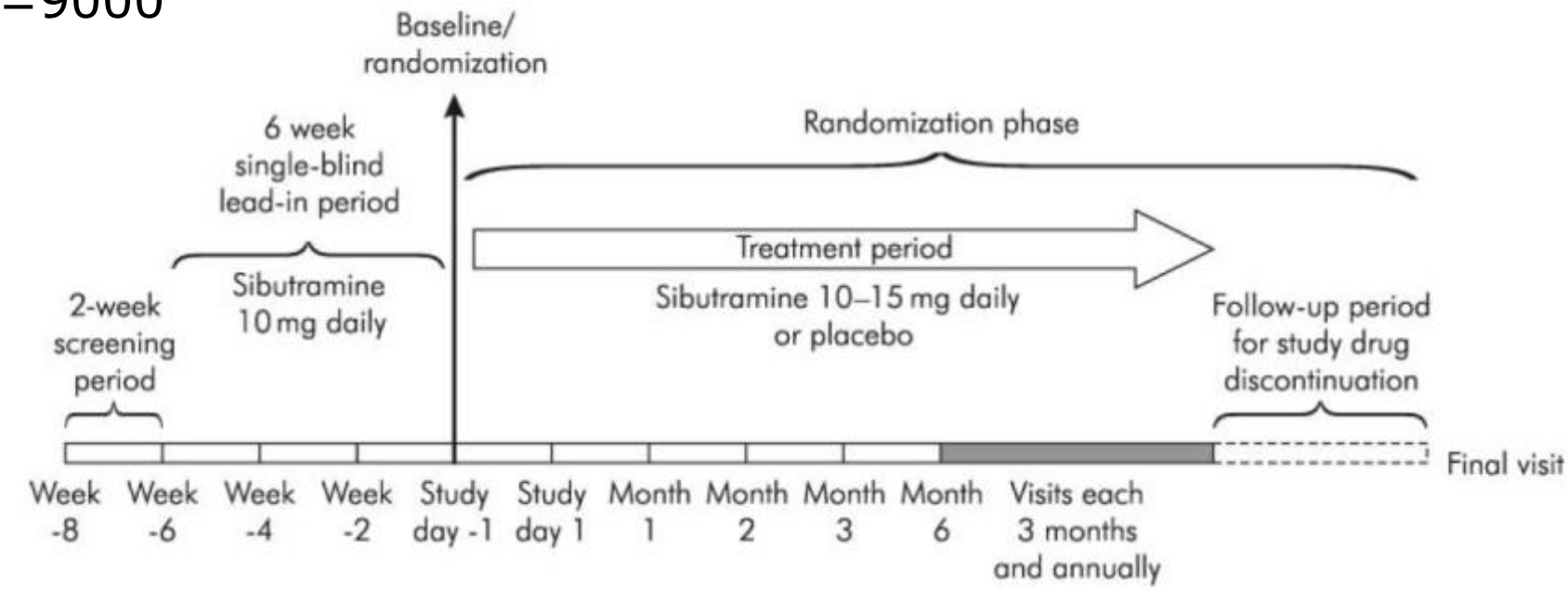
sibutramine

SCOUT (Sibutramine Cardiovascular Outcome Trial) requested by CHMP at the time of MAA to define risk-benefit profile in overweight high-risk cardiovascular patients

age ≥55, standard WHO BMI criteria + CVE or T2DM & add CVRF

1EP composite of MI, stroke, resuscitated cardiac arrest, CV death

N=9000

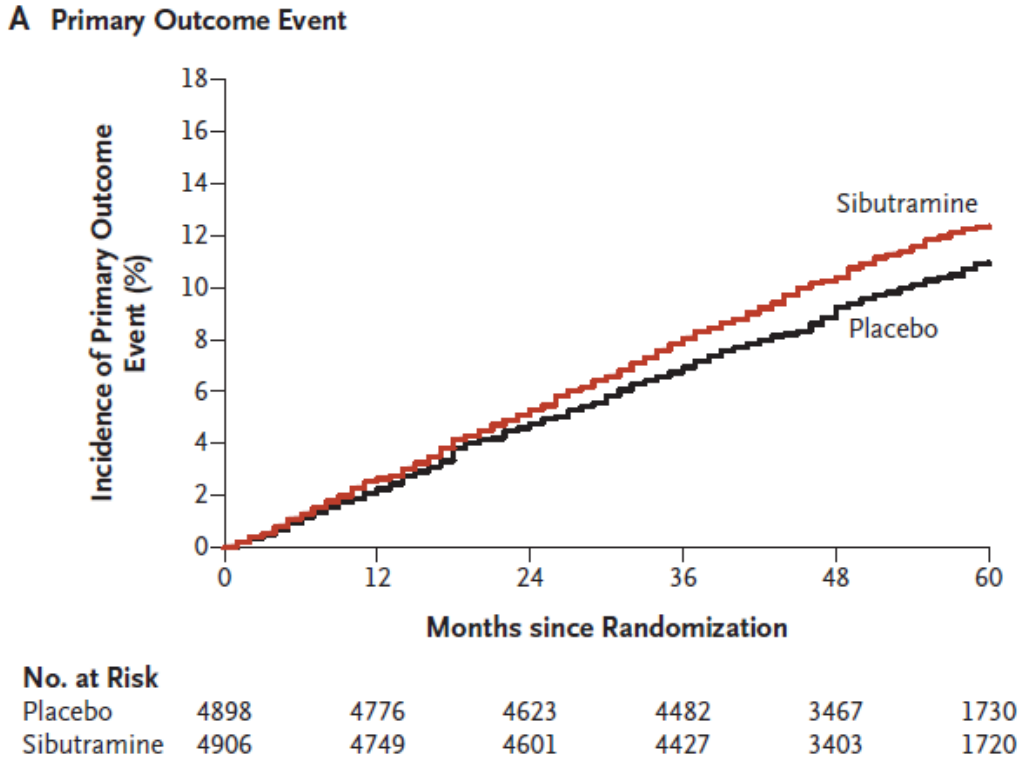


sibutramine

ESTABLISHED IN 1812 SEPTEMBER 2, 2010 VOL. 363 NO. 10

Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects

W. Philip T. James, M.D., D.Sc., Ian D. Caterson, M.D., Ph.D., Walmir Coutinho, M.D., D.Sc., Nick Finer, M.B., B.S., Luc F. Van Gaal, M.D., Ph.D., Aldo P. Maggioni, M.D., Christian Torp-Pedersen, M.D., Ph.D., Arya M. Sharma, M.D., Ph.D., Gillian M. Shepherd, B.Sc., Richard A. Rode, Ph.D., and Cheryl L. Renz, M.D., for the SCOUT Investigators*



- interim analysis found 16% increased risk of CV events such as MI and stroke compared with placebo-treated patients (HR 1.161 [95% CI 1.029–1.311]; p=0.016)

The Sibutramine experience

1997 sibutramine approved for weight loss by FDA
labelled warning re BP and heart rate increases

2002 EMA requires CV outcomes trial (SCOUT)

10,744 overweight/obese with CV disease and/or diabetes over 3.4 years

	sibutramine	placebo	
non-fatal MI	4.1%	3.2%	P=.02
non-fatal stroke	2.6%	1.9%	P=.03
CV death	4.5%	4.7%	
primary composite	**11.4%**	**10.6%**	**P=.02**

⇓

hazard ratio 1.16 (95% CI 1.03 to 1.31)

published NEJM Sept 2, 2010
drug withdrawn by FDA, EMA etc. soon after

CONCLUSIONS

Often, the Benefit/Risk balance of a medicinal product cannot be fully identified until after a drug is on the market and has been used by a large, diverse group of patients over time.

Clinical trials conducted before approval may be too small, too short, based on surrogate endpoints….. to detect all possible risks(…and efficacy).

Studies based on post marketing surveillance need to be defined at the time of MAA (case by case basis)