EMA EFPIA workshop
Break-out session no. 4

Modelling to guide Regulatory Guidelines and decision making during development

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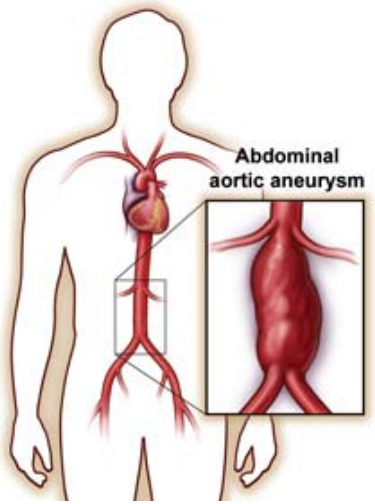
Assessment of opportunities within a new disease area

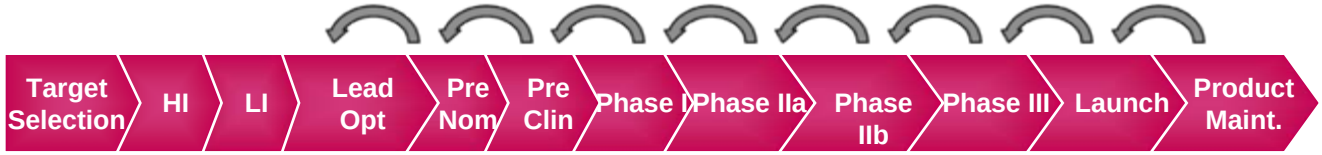
- Important to have a clear strategy on how to develop compounds before entering into a new disease area.
- In some disease areas, the regulatory requirements in terms of Guidelines might be unclear.
- Modelling can bring important value to highlight the link between Regulatory requirements and the feasibility of developing new drugs.



AAA- Abdominal aortic aneurysm

- High incidence of AAA in subjects with risk factors (male, age, smoking, Caucasian)
- There is currently no treatment for patients with diagnosed AAA.
- Watchful waiting is the approach used. Once the AAA reach a critical diameter of 50-55 mm surgery is performed (open or endovascular)
- Screening programmes under build-up in England, Wales and Sweden. Medicare covers screening for subjects at risk in the US.

Objectives of the M&S work



To determine if it is feasible to design a Clinical program for a new compound vs AAA by addressing the key questions:

1)Under what Regulatory requirements on the primary Phase III endpoint is it feasible to design and run a Phase III programme?

2)What would be a suitable Phase II endpoint and what would level of effect would we need to see to merit an investment in Phase III?

3)What would a Phase II design look like to enable efficient decision making and is it possible to run such a study with a reasonable number of subjects and study length?

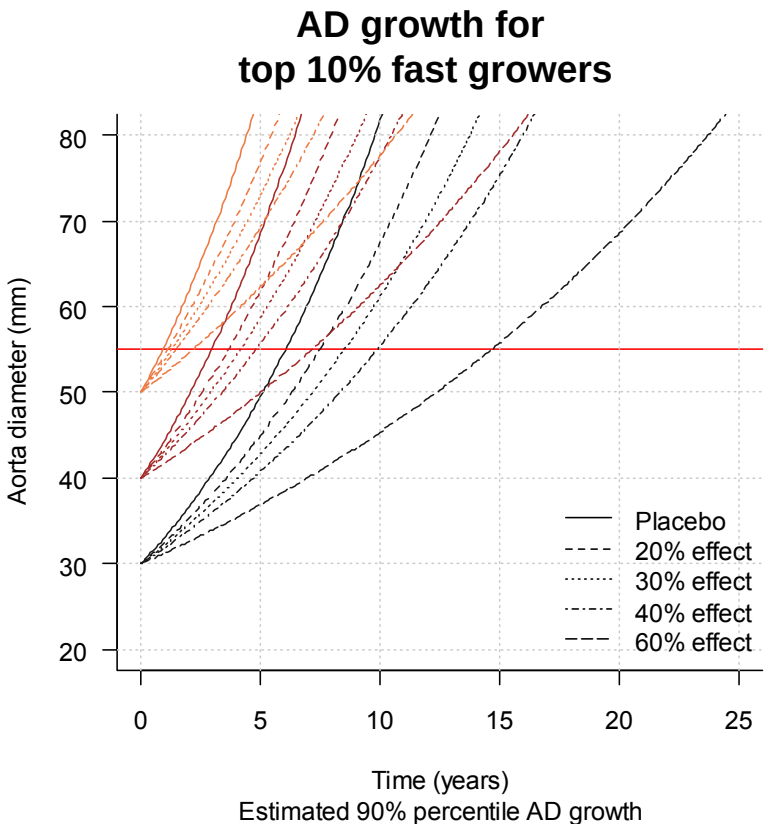
Efficacy endpoints explored in different phases

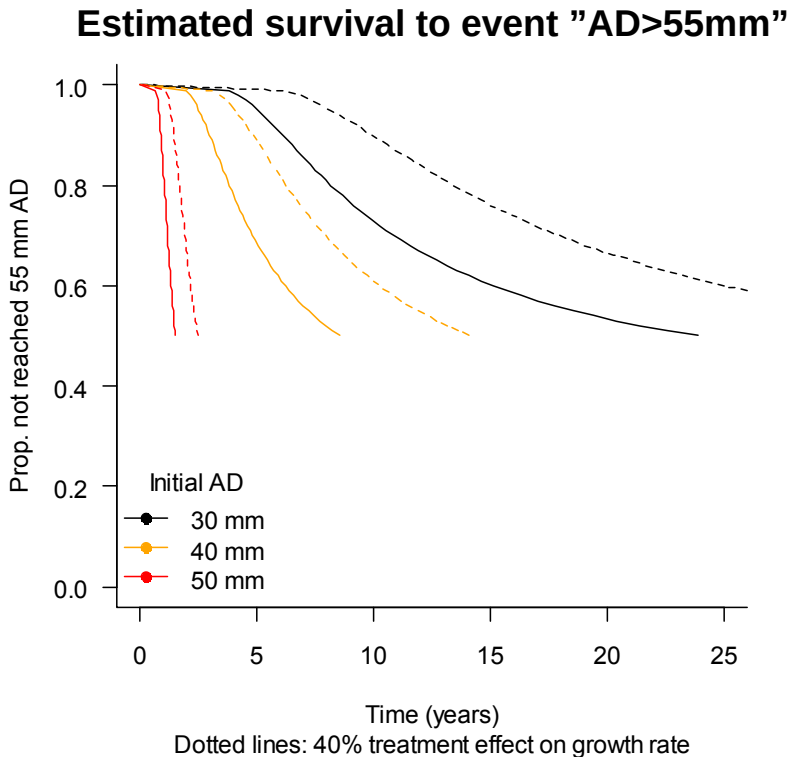
Pre-clinical	Phase II	Phase III
Aneurysm diameter (AD)	Aneurysm diameter (AD) Stiffness (i.e safety) (Aorta volume)	**A)** Aneurysm diameter (AD) as a surrogate endpoint (with extension considering events on composite endpoint & safety) **B)** Time to event for composite endpoint of: • CV mortality, Rupture, Surgical intervention & AD >55mm (with extension on safety) **C)** Time to event for: •CV mortality, Rupture

- No general acceptance that specific animal models predict effect on human aneurysms.

- AD is the best known predictor of rupture rate.
- Clinical management of disease based on AD.

Establishing a link between phase II and III endpoints





- Events in Phase III driven by individuals with the highest growth rate.
- Link between AD growth and time to event requires knowledge about variability between individuals in AD growth.
- Hazard for event “AD>55mm” varies over time, especially for small initial aneurysms.
- Sample size in Phase III strongly dependent on disease status of patients, study length and effect size

Derived from data in Verdulaki (1998)

Clinical feasibility of Phase III

		Phase 3 endpoint		
		A) AD as surrogate + extension on composite/safety	**B)** Composite + extension on safety	**C)** CV mortality /rupture
Effect of compound (30-60 % reduction in AD growth)	Small ADs (30-40 mm) ≈ 60-70% of patients	Depending on regulatory requirements	Depending on effect size	Too low event rate
	Large ADs (>40 mm) ≈ 30-40% of patients	Depending on regulatory requirements	Depending on effect size	Too low event rate

Colors based on clinical feasibility with "definition" of feasibility: N< ≈ 6000, time of study < 4 years

Conclusion:

- Regulatory requirements of Phase III endpoint will determine if clinical development in Phase III is feasible.

Regulatory Interaction

- Plans for seeking Regulatory feedback exists, but not initiated yet (will likely be part of discussions around new compound).

- Relevant questions to discuss:

Phase II:

1) Endpoint: What would be a suitable endpoint in Phase II to establish the smallest efficasious dose and use for dose-selection in Phase III?

Phase III:

2) Endpoint: What would be a suitable endpoint in Phase III as a basis for registration?
3) Patients: What stages of disease would be relevant to study (for what indication & label claims)?
4) Patients: What would be a relevant population wrt gender/ethical background/smoking (screening programs do not cover the whole population)?
5) Benefit/risk: What is a suitable way forward to ensure the overall CV safety in order to characterize risk-benefit?

Conclusions & Summary

- Regulatory requirements of Phase III endpoint will determine if clinical development in Phase III is feasible.
- Important to evaluate more precise ways to measure AD to decrease sample size and study length in Phase II(a).

<u>Internal impact:</u>

- M&S results well received by Senior Management.
- Investment decisions within AAA could be taken – including initiation of external collaborations.
- The evaluation of Clinical feasibility have been the starting point for several activities.
- MeMo-study
- Access to screening database
- Health economic evaluation

BOS4 : Position statement and associated questions

- M&S is important, not only in individual drug projects, but also to understand a disease area and how the Regulatory requirements determines the feasibility for clinical development of a new compound.
- At what stage of development is it suitable to have industry-Regulatory interactions?
- What should be the requirements of M&S work in such a situation?
- Is there a potential for collaboration across companies?

- M&S can help guide the development of future Regulatory Guidelines in terms of suitable endpoints in clinical trials (early & late stage) and requirements for registration and label claims.
- How to facilitate discussions, based on M&S, between industry and Regulatory agencies regarding new Guidelines?
- What should be the requirements of M&S work in such a situation?

BACK-UP

Phase III :
Sample size estimation to show effect on composite endpoint

Sample size/arm for different treatment effects on AD growth and initial ADs.

	Study length		
1.5 year accrual	**3 years**	**4 years**	**5 years**
In AD 30 mm			
20%	>8,000	3,200	1,000
30%	>8,000	1,850	525
40%	>8,000	1,625	350
In AD 35 mm			
20%	3,750	860	520
30%	2,300	410	210
40%	1,850	275	130
In AD 40 mm			
20%	720	670	510
30%	350	175	160
40%	220	95	80

Assumptions

- Accrual: 1.5 years (40% 0 - 6 months (uniform); 30% 6 - 12 months (uniform); 30% 12 - 18 months (uniform)
- Drop out : 2.5% / 6 months
- Simulation based on a piece wise exponential survival model with 6 months intervals with constant hazard.

- Sample size strongly dependent on disease status of patients, study length and effect size.