Our first experience with a EMA Adaptive Licensing pilot project

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London 15th October 2015

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Adaptive Licensing: for which medicine

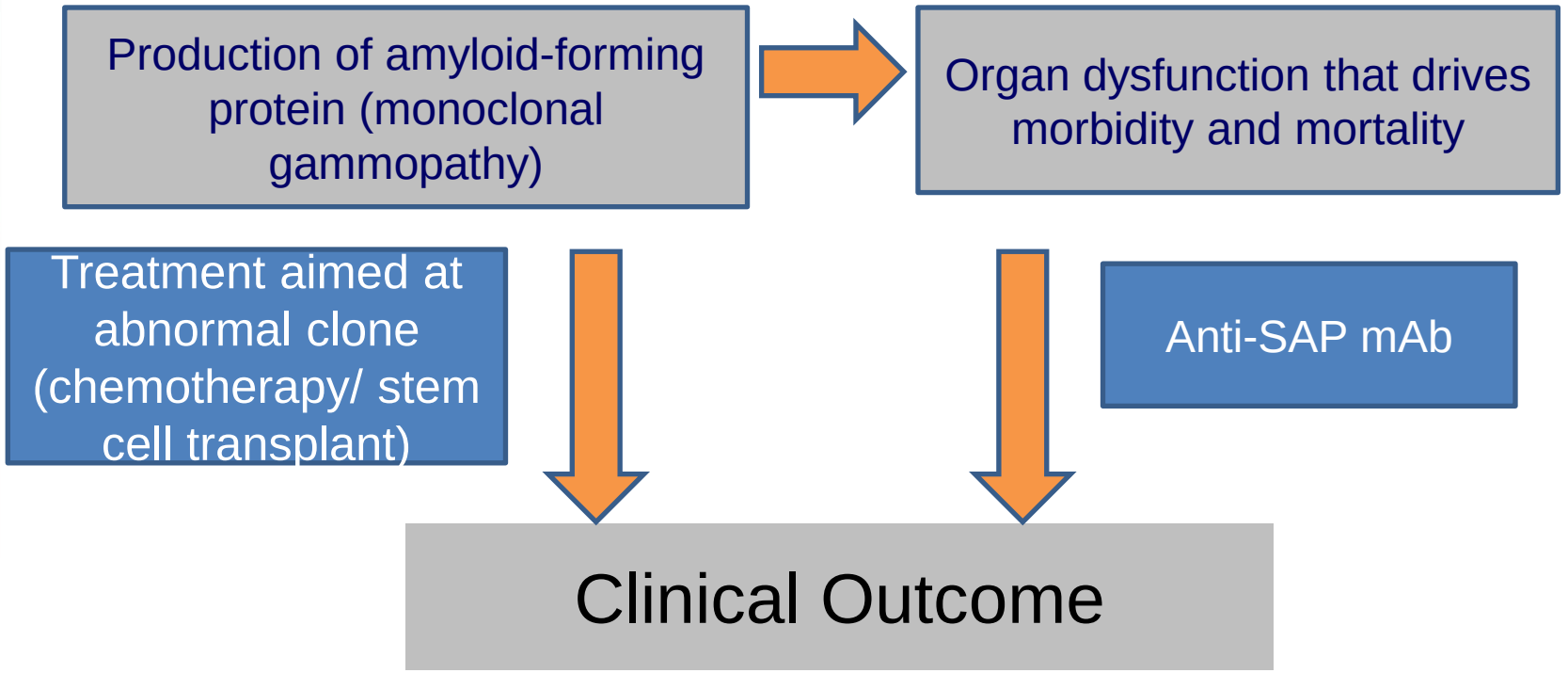
- Life threatening or severe condition that justifies early access
- Ability to clearly define a (sub) population which anticipates the best benefit risk balance for the initial study
- Ability to define a robust surrogate endpoint
- Ability to restrict access to this population in the initial marketing setting
- Availability of the ‘expansion’ populations

Case study:
GSK2315698 (small molecule SAP* depleter) and GSK2398852 (anti-SAP mAb)

- Investigational medicines for the treatment of systemic amyloidosis (AL amyloidosis)
- Disease caused by amyloid deposition in key organs
  - Amyloid accumulation leads to progressive organ failure
  - Heart and kidney prognostically most important
- Anti-SAP mAb binds to Serum Amyloid P component (SAP) decorating amyloid fibrils = drug target
  - GSK2315698 depletes SAP in plasma (leaves some bound to fibrils)
  - GSK2398852 anti-SAP mAb binds to SAP
    - complement and macrophage clearance of amyloid restores organ function enabling treatment of underlying cause

Case study:
GSK2315698 (small molecule SAP* depleter) and GSK2398852 (anti-SAP mAb)

- The anti-SAP approach has the potential to improve functional status and therefore the ability to tolerate and receive other therapies addressing the underlying production of amyloid-forming protein
- Anti-SAP treatment taken together with therapy addressing AL production has the potential to substantially alter prognosis



Challenges of traditional licensing approach

Systemic amyloidosis:

- A clearly defined condition, BUT clinical manifestations and natural history show great diversity:
  - AL, AA, ATTR
  - Differing patterns organ involvement
  - Varying stages of disease at presentation
- Several approaches for clinical development:
  - underlying condition VS organ involvement
- The obligate co-administration of both developmental medicines further complicates the traditional development

Adaptive licensing proposed approach

- Initially studying a subgroup of patients with AL amyloidosis
  - AL represents ~80% of systemic amyloidosis patients (prev 1-5/10000)
- Possible to select initial patient population by clinical stage
- Propose adaptive licensing based on a robust clinically meaningful surrogate in this restricted population
  - commitment to follow up to investigate how surrogate translates into long term survival
- Defined nature of target population would allow for a focussed initial indication
  - treatment in specialist centres would facilitate this approach
- This population would provide solid evidence to guide further development

Adaptive licensing proposed approach

- Single Phase II and III trial using validated surrogate markers
- Named Patient Registry – follow-up for safety and to survival/PFS clinical endpoint
- Retreatment data
- New patient registry
- Access limited to specialist treatment centres and specific diagnostic criteria
- Commence Phase III in other subpopulations as results dictate

The EMA pilot experience

- Pilot Project launched in March 2014
- Our programme selected as a pilot
- Meetings of the Adaptive Licensing Discussion Group (ALDG)
- The discussions cannot be considered a formal advice: there is no in-depth discussion of scientific aspects, which is within the remit of a formal SA/PA procedure. It is a high-level early dialogue led by the SAWP chair and assigned coordinators to review the plausibility of the development plan and guide to the next –more formal - regulatory steps
- An HTA/SA parallel advice, shaped by this initial discussion
- Stakeholders to be involved in the procedure should be identified by the Applicant.

Challenges of Adaptive Licensing

- Managing off-label use
- Communicating benefits and risks to prescribers and patients
- Withdrawing indications or products
- Ensuring a predictable and attractive NPV
- Securing market access at a price that reflects the potential value
- Investment post-launch
- Length of product life
- Not always adapted for rare diseases

Personal views on Adaptive Licensing

- Real potential to streamline drug development and access for patients.
- Enables early alignment of perspectives :Regulators, Patient Experts, Clinicians, HTA, Sponsor
- Leads to early access and knowledge acquisition
- May result in more sustainable development: lower costs; earlier revenue generation

However...

- Misunderstanding on level of guidance companies may receive
- Advice is not binding
- Concept not universally accepted
- HTA and pricing still disconnected
- Any lessons to learn from FDA Breakthrough designation approach?

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Thank you for your attention!