EMA experience on joint scientific advice
EMA/HTA with ATMPs

EBE 7th Annual Regulatory Conference

“Advancing the delivery of ATMPs to patients”

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ATMPs – challenges in their lifecycle

Innovative therapeutic approaches
High complexity/cost

Specificities in development affect ATMP approvals and patient access

Relevance of disease guidance

- proof of concept
- small populations
- adaptive/optimal study designs
- sustained efficacy
- retreatment
- real world data
- disease registries

Need for early inter-disciplinary dialogue with all relevant stakeholders
ATMPs – Marketing authorisation

- 13 ATMPs granted MA
- 2 conditional marketing authorisations / 1 under exceptional circumstances
- Limited evidence package of medicines approved under CMA / exceptional circumstances - need for post-authorisation data collection and planning

- HTA bodies have rarely given unrestricted positive recommendations for CMA products
- Difficult to assess added value – mostly orphan products, lack of comparator treatments


- Even for full approvals, the clinical development package is not so comprehensive as for other medicines – most full approvals for ATMPs require post-marketing studies.
- More efficient collaboration between manufacturers, HTA bodies, and regulators can improve the suitability of evidence for making decisions that are sensitive to limited evidence.
Parallel EMA-HTA Scientific Advice Consultation

Started in 2010 / important tool for the convergence of the requirements of European regulators and HTA bodies.

✓ Initial evidence generation for MAA / reimbursement
✓ Post licensing evidence generation
✓ Broad advice / qualification procedure

% EMA-HTA Procedures / Product Type

Total number of parallel procedures 2013-2018(Oct) = 117

- 47% Bio(techno)logical
- 42% Chemical
- 11% Advanced Therapy
EMA-HTA parallel procedures for ATMPs: ~ 6% of total SA/PA procedures for ATMPs

EMA-HTA parallel procedures for chemicals/bio(techno)logicals: ~ 4%
Multi-stakeholder platform for advice
EMA and EUnetHTA equal partners
(new platform since July 2017)

Efficient evidence generation meeting the needs for each stakeholder

- Respect for roles and remits
- Centralised HTA involvement via EUnetHTA
- For all parallel advice/early dialogue procedures: streamlined logistics and greater HTA coordination
- HTA (Early Dialogue) working party - consolidated HTA advice
- Building on success of previous pilots; interactive focused meetings
- Since inception, all ATMP parallel requests have been consolidated procedures
Parallel EMA-HTA Scientific Advice Consultation

The impact of engagement across decision-makers in evidence generation planning
First analyses

**Topic 1: Level of alignment**

Level of agreement (position of HTA bodies vs. regulators; review of clinical trial features based on 31 scientific advice procedures):
- full agreement
- partial agreement
- disagreement

Tafuri et al., Br J Clin Pharmacol (2016), Volume 82, 965-973
Parallel EMA-HTA Scientific Advice Consultation

The impact of engagement across decision-makers in evidence generation planning
First analyses

**Topic 2: Uptake in development / comparator**

Tafuri et al., Br J Clin Pharmacol (2018), Volume 84, 1013-1019
Topics in parallel EMA-HTA consultation for ATMPs

% Area of advice

- Population
- Comparator
- Endpoints
- Other study design characteristics
- Therapeutic added value
- Economic evaluation
- Overall efficacy and safety data package
Examples (1)

Extension of indication/extrapolation
Do the CHMP and HTAs agree with the proposal to submit X month data provided that an extrapolation model successfully demonstrates that protein production at X months is a predictor of clinical outcome at Z months?

QoL/intra-patient comparison
Do the CHMP and HTAs agree a clinically meaningful benefit of x product would be a significant improvement in Health-Related Quality-of-Life, comparing patients treated with X product to the same patients on prior Y therapy?

Real-world Evidence Generation Plan
Do the CHMP and HTAs agree with the proposed approach to Real-world Evidence data collection?
Submission strategy / Conditional MA / exceptional circumstances

- Do the CHMP and HTAs agree that, based on the long-term survival data from X study, an application for a CMA or for an authorisation under exceptional circumstances may be appropriate?

- Would CHMP and HTAs accept the following submission strategy for registration and reimbursement of the proposed indication?
  - Safety and primary efficacy analysis with X month data
  - Safety and durability of effect assessment with Y month data before CHMP opinion
  - Longer-term follow-up, annual safety and efficacy update over a total of Z years as post-approval commitment
Do the CHMP and HTAs agree that:

a) robust and compelling data generated in a single-arm, non-randomized study can support registration and reimbursement in the target patient population?

b) the primary efficacy endpoint and secondary endpoints, including duration of response, are adequate to support establishment of the risk-benefit profile?

c) the proposed analyses of the primary and secondary endpoints are adequate to evaluate benefit/risk and the added value for HTA bodies?

d) the proposed Patient Reported Outcome (PRO) tools applied in the phase II study are adequate to establish a clinical benefit?
Conclusions

ATMP development is complex

• EMA encourages early scientific and regulatory discussions regarding pre- and post-marketing evidence generation

Scientific advice/Protocol assistance

• Key tool to optimise collection of robust data on the benefits and risks of ATMPs and to plan long-term data collection

Parallel EMA/HTA scientific advice

• Common platform to receive feedback from both stakeholders
• Promotes efficient evidence generation on key issues of development

Benefit for patients

• Well designed and appropriate clinical trials protect patients
Thank you for your attention

Further information

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