



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Advancing Gene-Targeted Therapies for Central Nervous System Disorders

EU-Regulatory considerations

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Presenter disclosure information and disclaimer

I have nothing related to this presentation to disclose

Disclaimer

The view expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflection the position of the European Medicines Agency or one of its Committees or Working Parties.

Outline:

How can EMA assist you as developers:

- Organization of EMA
- Scientific advice
- Regulatory procedures
- Early access mechanisms

What are the issues from a regulatory perspective:

- Quality,
- Non-clinical
- Clinical development

EMA organization

Network of Medicinal Agencies from 28 EU Member States
(+ IS & NO)

- Committee for Human Medicinal Product (CHMP)
- Committee Advanced Therapies (CAT)
- Committee for Orphan Medicinal Products (COMP)
- Paediatric Committee (PDCO)
- Pharmacovigilance Risk Assessment Committee (PRAC)

+ a number of working parties (BWP and SAWP, CNSWP most relevant)

EMA is responsible for assessment of Marketing Approval of new medicines.

Approval of clinical trials resides with the national agencies

Marketing authorisation procedures (until December 2018)

- 13 ATMPs authorised (6 GTMP, 3 CTMP, 4 TEP)
 - Chondroelect – TEP – Comm Dec 5/10/09 / MA withdrawn July 2016
 - **Glybera – GTMP – Comm Dec 25/10/12 / MA ended Oct 2017**
 - MACI – TEP, combined ATMP – Comm Dec 27/6/13 / MA not renewed (end MA 27/6/18)
 - Provenge – sCTMP - Comm Dec 6/9/13 / MA withdrawn May 2015
 - Holoclar – TEP – Comm Dec 17/2/15
 - Imlygic – GTMP – Comm Dec 16/12/15
 - Strimvelis – GTMP – Comm Dec 26/5/16
 - Zalmoxis – CTMP - Comm Dec 18/8/16
 - Spherox – TEP – Comm Dec 10/7/17
 - Alofisel – CTMP –Comm Dec. 23/3/18
 - Yescarta – GTMP – Comm Dec 23/8/18
 - Kymriah – GTMP – Comm Dec 23/8/18
 - **Luxturna – GTMP – Comm Dec 22/11/18**

CAT statistics 2009- Dec 2018

Three products (two GTs) currently under review.

6-8 additional products expected to file for MAA in 2019

General guidance for developers of GTMPs

- Revised Gene therapy Parental guideline – 2018
- Guideline of risk-based approach for ATMPs - 2014

Ongoing GLs

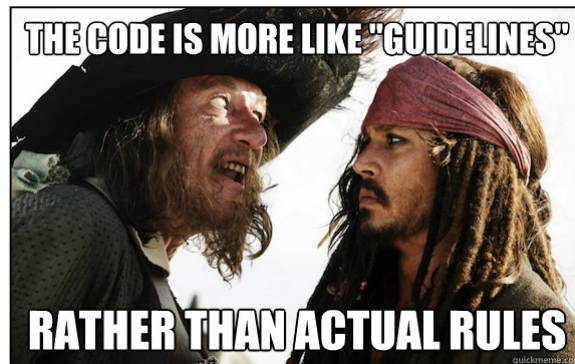
- Guideline on requirements for Investigational ATMPs (external consultation Q1 2019)
- Revision Guideline for genetically modified cells (updated due to progress related to CAR-T cells and gene editing techniques -external consultation July 2018)

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Hector Barbossa

Support to developers

Innovation task forces (ITF)

- Agency-wide coordination
- Briefing meetings: forum for early dialogue with drug developers

Micro-, small- and medium-sized enterprise (SME) office

- EMA's SME office to promote innovation and the development of new medicines
- dedicated personnel support: responds to practical or procedural follow-up of product development
- SME specific incentives

Early access mechanisms in EU

PRIME (Priority Medicines)

- To foster development of medicines with a high public health potential
 - Reinforced scientific and regulatory advice
 - Optimise development for robust data generation
 - Enable accelerated assessment
 - CMA or full MA

Eligibility to PRIME:

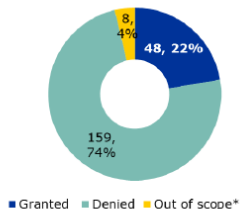
- justification of potential major public health benefit/unmet medical need (criteria similar to those for accelerated assessment)
- Data to demonstrate the potential to address the unmet medical need

⁸ What does PRIME offer:

- Early appointment of Rapporteur, tailored support, iterative SA at major development time points.



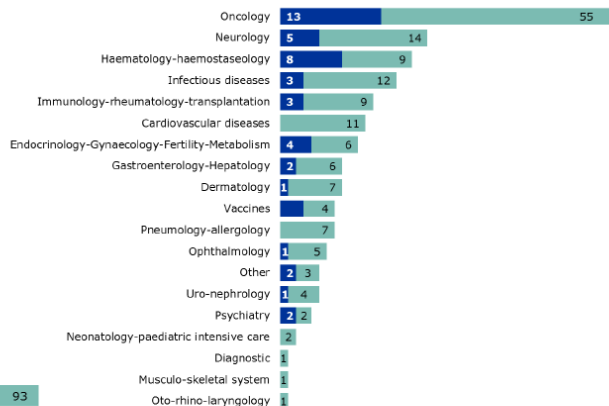
Cumulative overview of recommendations on PRIME eligibility requests adopted by 13 December 2018



By type of applicant



By therapeutic area



Out of the 48 PRIME granted, 20 were for ATMPs (42%):

- 18 are GTMPs, 2 CTMP

- 9 Oncology
- 5 Haematology
- 2 Immunology – rheumatology – Transplantation
- 1 Ophthalmology
- 2 Neurology
- 1 Other (X-linked myotubular myopathy)

Support to developers

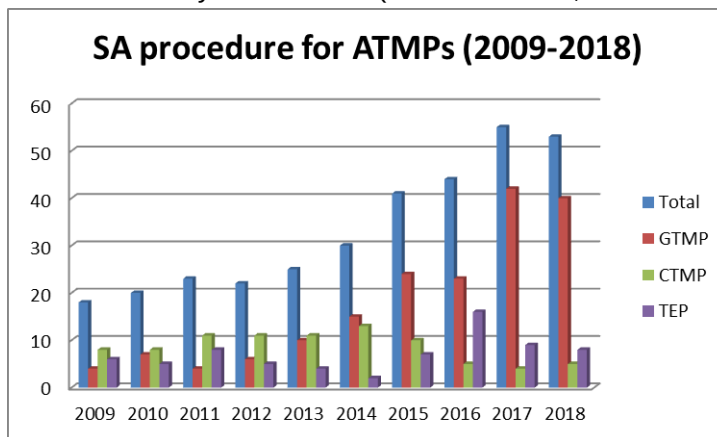
Scientific advice

➔ Incentive: early – late / increase regulatory certainty

- Open to all applicants
- To provide regulatory input on issues not covered by current guidelines, or where deviations from guidelines are planned.
- Scientific advice is given from the SAWP in collaboration with the CAT (+ other committees & working parties)
- Possibility for parallel EMA Scientific Advice procedure with FDA
- EMA/HTA parallel scientific advice

Scientific Advice for ATMPs (2009- end 2018)

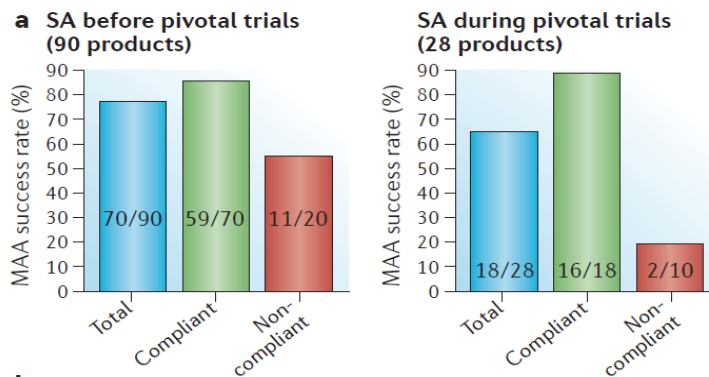
- 325 SA procedures started – CAT involved (routinely) in all SA for ATMPs
- Increase in SA's for ATMPs over period 2012 – 2017
- Majority of SA nowadays for GTMP (76% in 2017; 75% in 2018)



SA requests until end 2018

Impact of Scientific Advice

Impact of timing for SA on outcome



SA before pivotal trail; positive MAA for 78 %

SA during pivotal trial; positive MAA for 64 %

Mattias P. Hofer et al; Regulatory Watch. Nature Review Drug Discovery 17 April 2015

Recurring non-clinical issues in Scientific Advice procedures

- Data to support starting dose for FIH trial
- Rational for administration route IV, IT, ICS, IP etc (CNS, LSD etc)
- Supportive data from relevant large animal models (including juvenile)
- Vector construct (rational for choice of serotype, promoter/regulatory elements)
- Data from “relevant” non-clical studies performed with ”similar” vectors?
- Need for primate data (relevant for high dose IV administration).
- Integration/carcinogenicity/transmission studies

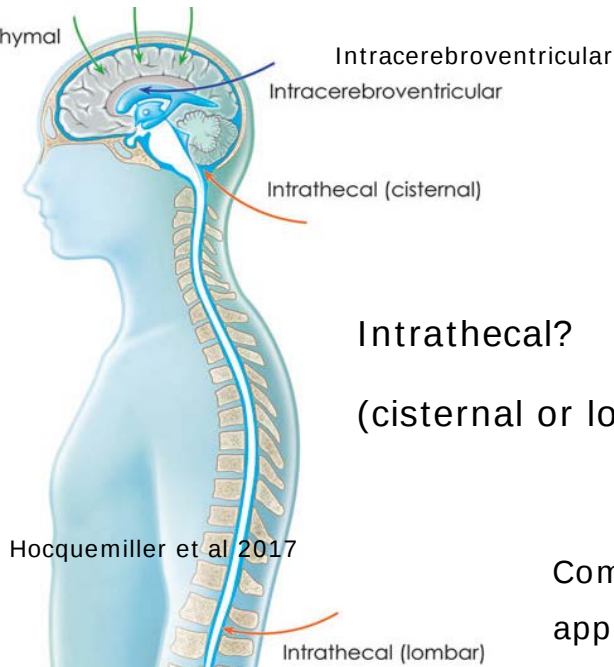
What is the optimal route for targeting the CNS?

Direct intraparenchymal injection

- Number of injection sites/
injection volume?
- Uniformity of transduction?
- Diffusion gradient?
- Axonal, dendritic AAV
transport?

Intrathecal delivery

- More uniform distribution?
- Enable foetal delivery?
- Large doses needed
- Preimmunity?
- Increased immunoresponses
- Retreatment?



Intrathecal?
(cisternal or lumbar)

Combination
approaches?

Recurring clinical issues in Scientific advice

- Starting dose /dose finding
- Administration route(s) and combinations (Should be informed by animal data)
- Use of immune dampening regimens
 - prophylactic or on demand?
 - Steroids only or combinations?
 - Duration?
- Primary and secondary endpoints?
 - Current treatment modalities don't always inform choice of endpoints e.g. FIVII and FIX; ABR, FC, or FAL?
 - Biomarkers, enzyme levels/ substrate reduction to support efficacy claims
- Immunogenicity
- Paediatric development

Recurring clinical issues in Scientific advice

Delivery to CNS (LSD, Neuromuscular disorders etc)

- Trial design (feasibility of RCT vs Single arm, novel trial design)?
- Historical controls - registry data, Prospective vs retrospective, use of propensity score matching etc.
- Patient selection criteria
- Endpoints (primary, secondary, exploratory)
- Biomarkers, enzyme levels/ substrate reduction to support efficacy claims or used as surrogate endpoints?
- Study duration?
- Success criteria
- Evidence level sufficient to support MA /CMA (feasibility of confirmatory trial)?
- Data requirement for HTA (cost/benefit)?

Knowns and Unknowns

“There are known knowns. These are things we know that we know.

There are known unknowns. That is to say, there are things that we now know we don't know.

But there are also unknown unknowns. These are things we do not know we don't know“



Donald Rumsfeld

Thank you for your attention!

Thanks to

Patrick Celis, CAT
Anna Travido, SAWP
Zahra Hanazi, PRIME
Falk Ehman, ITF

~ **500** clinical trials using ATMPs in EU (2009-2017)

~ **320** ATMP classifications

~ **310** scientific advice requests

21 MAAs reviewed



13 ATMPs approved



2 withdrawn
2 ended

Market

9
licensed
ATMPs



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AG

Early access mechanisms in EU

Conditional marketing authorisation

- MP for seriously debilitating/life-threatening diseases; for use in emergency situations; for orphan MP
- Criteria: B/R positive + unmet medical need + immediate availability outweighs risk due to missing data + comprehensive data can be provided

Accelerated assessment

- Medicinal products of major public health interest and in particular from the viewpoint of therapeutic innovation

Early access mechanisms in EU

- Adaptive pathways
 - Scientific concept of development and data generation
 - Iterative development with use of real-life data
 - Extension of indication after initial approval
 - Conditional MA (eg on basis of surrogate endpoint) → full MA
 - Engagement with other healthcare-decision makers
 - Patients, prescribers, HTA

→ Pilot project since March 2014