



Federal Institute
for Drugs
and Medical Devices

Current challenges in clinical development and regulatory decision-making - **regulator's perspective in the EMRN** -

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Disclaimer

- As a member of a NCA and government employee, I have **no Conflicts of Interest** to declare.
- **All information** presented here **is publicly available**.
- The content of this talk is my own and does not necessarily reflect the official views of the Federal Institute of Drugs and Medical Devices (BfArM) or the European Medicines Agency (EMA).

DMD- current challenges in regulatory decision-making

- DMD is a **rare, life-threatening and orphan disease**:
 - for marketing authorisation applications, usually a single placebo-controlled pivotal study is provided
 - consequently, the totality of evidence has a significant weight in the benefit/risk assessment of new drugs in DMD
 - the primary endpoint should be supported by adequate secondary endpoints (consistency across the different endpoints)
- DMD is a **heterogeneous disease** with respect to baseline characteristics, disease severity, disease progression and time to disease milestones. Therefore,
 - the study population should be rather homogeneous; efficacy endpoints should be chosen to cover the studied patient population; study duration needs to be sufficiently long to obtain robust effects
 - extrapolation to a broader patient population needs to be scientifically justified

Treatments for DMD in the EU



- Despite long standing experience with pivotal studies in DMD, demonstration of efficacy remains challenging (e.g. contextualization of statistical results and clinical relevance).
- Of note, even small functional effects might be important for patients and caregivers.

Clinical programmes in DMD

- **Translarna:**

- 1 pivotal, randomized, double-blind, placebo-controlled Phase IIb study (48 weeks)
- First SOB: 1 Phase III, randomized, double-blind, placebo-controlled study (48 weeks)
- Second SOB: 1 Phase III, randomized, double-blind, placebo-controlled study (72 weeks)
- Ataluren- treated DMD subjects in registry study “STRIDE” vs. external-controls from CINRG-DNHS

https://www.ema.europa.eu/en/documents/variation-report/translarna-h-c-2720-r-0071-epar-assessment-report-non-renewal_en.pdf

- **Vamorolone:**

- 1 pivotal, randomized, double-blind, placebo- and active-controlled Phase IIb study (24 weeks); db extension till week 48
- FOR-DMD study (Guglieri et al., 2022): comparison of three corticoid regimens in ambulatory DMD patients; used as external long-term control versus vamorolone
- Untreated (steroid-naïve) subjects from the CINRG-DNHS as external control for open-label Phase II studies

https://www.ema.europa.eu/en/documents/assessment-report/agamree-epar-public-assessment-report_en.pdf

- **Duvyzat:**

- 1 pivotal, randomized, double-blind, placebo-controlled Phase III study (18 months)
- Long-term efficacy: Duvyzat- treated subjects in the clinical studies vs. Natural History Studies ImagingDMD and CINRG

https://www.ema.europa.eu/en/documents/assessment-report/duvyzat-epar-public-assessment-report_en.pdf

Current knowledge gaps in DMD trials and what might be addressed in registries/ by Real-World Data

- Uncertainties of favourable/ unfavourable effects in controlled **(single)** pivotal trials
- Long-term efficacy regarding effects on disease milestones; long-term treatment strategies
- Long-term safety (missing information in the RMP; e.g. regarding physical growth and pubertal development)
- Better understanding of natural history and treatment landscape to inform planning and interpretation of prospective trials and support prioritization of effect measures
- For Duvyzat, two specific obligations (SOB) were imposed, that still need to be solved:
 - SOB#1: A randomized, placebo-controlled trial in ambulant patients
 - SOB#2: PAES to evaluate the long-term effectiveness and safety of givinostat in a “real-world” setting. A matched concurrent untreated cohort – in addition to the Published Natural History Results (McDonald CM, 2018) - should be foreseen in the study protocol.

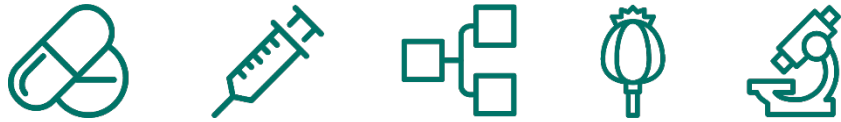
https://www.ema.europa.eu/en/documents/assessment-report/duvyzat-epar-public-assessment-report_en.pdf

Current knowledge gaps in DMD trials and what might be addressed in registries/ by Real-World Data

How can RWD collection be better standardised and better aligned to outcome measurements in clinical trials?

How can gaps within RWD be avoided that may undermine its supportive role for efficacy evaluation in clinical trials?

Thank you very much for your attention!



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