Clinical trials primarily fail due to safety

Need a step-wise approach to de-risk trials (go/no-go decision points for safety/efficacy at all stages)

The only *truly failed* trial is a trial that we learn nothing from, & thus fail to improve patient health & design of the next clinical trial

*Take Home:* Essential to extract lessons learned from each clinical trial so that the massive efforts of the entire community are not wasted
Duchenne DYS Upregulation Programs

• **PTC Therapeutics**
  - EMA conditional marketing authorization (subject to Ph 3 data) Ph 3 with Genzyme (DB, P-C), failed 1° endpoint (6MWT)
  - FDA Refuse-to-File letter

• **BioMarin**
  - Ph 3, Prosensa/GSK, (DB, P-C) failed 1° endpoint (6MWT) plus safety
  - FDA Complete Response Letter
  - EMA informal feedback on intent to issue a negative opinion

• **Sarepta Therapeutics**
  - Ph 2b (DB, PC) 1° endpoint: % DYS+ fibers; sponsor & FDA differ on outcome
  - NDA filing based on *post hoc* analysis of open-label study (6MWT; major data for NDA was from non-PC studies)
  - Apr 2016 FDA AdComm negative recommendation; FDA decision pending
Understand Tractability

• **Lesson**: Can’t wait for complete mechanistic understanding, but unresolved, key gaps in disease basic science can be disruptive

• Do you understand the loss- or gain-of-function & downstream cellular mechanisms to move forward?
  • Differential stability/functionality of skipped DYS
  • Genetic modifiers (SPP1, LTBP4)
  • Other functions of DYS

• A failure to understand the biology can negatively impact both candidate therapeutic rationale & clinical trial design
Rationale for Trials: Preclinical Efficacy

• **Lesson**: Understand & take what the preclinical models give you, but don’t ignore or magnify their lessons

• DMD models affirmed the linkage between DYS levels/distribution & functional benefit
  • Studies in mdx established both dose-response and PK/PD relationship

• Problem: the mouse ‘doesn’t have the disease’ (see Dubowitz, V) & increases in DYS didn’t translate

• Decision: understand mouse endpoint value; substantive level of effect >> simple statistical significance
FDA on DYS Quantification*

- ‘Sample heterogeneity (intra & inter-patient/muscle); lack of high & consistent sample quality; lack of a reference standard’ (e.g., purified DYS protein’)

- ‘Need to test functionality of new [skipped, read-through] DYS’

- ‘Inability to distinguish between revertant & drug-induced DYS’

- ‘Need for robust assay reproducibility in a linear range & at very low levels of quantification’

- ‘Co-expression of genes with potentially redundant functions (e.g., utrophin)’

- **Lesson**: Biomarkers essential in getting early signal of efficacy (see BIO); FDA biomarker qualification programs need to be pursued

*BioMarin Ad Com; similar in Sarepta Ad Com*
Level of Effect

• **Lesson**: Limited level of effect is problematic for development programs

• Restoring DYS targeted by the 3 programs; preclinical & BMD data directly link DYS levels to functional outcomes—with low DYS, linkage not seen in trials

• Effect limited by adequacy of dosing/delivery—dose levels in trials < preclinical efficacious dose; dose-limiting toxicity & costs hindered full exploration of dosing; better exposure via improved backbone chemistries needed

• Acknowledge sampling errors with small biopsies from one of many muscles

• DYS levels in trials (FDA: ‘trace’ by WB) were variable & far below need established by mdx studies & BMD patient analyses

• By IHC, DYS distribution in trials limited to ‘pockets’ of fibers; Low DYS levels/distribution make open label studies & post hoc re-analysis of functional data difficult for FDA to accept
Clinical Operational Readiness

- **Lesson**: Ensure sufficient trial readiness (understanding of the patient population, tool availability/validity, & capacity to conduct clinical trials) in order to facilitate design & decision making

- Do you have sufficient understanding of the patient population?
  - Limited natural history (progression patterns & heterogeneity) negatively impacts trials
  - Failure to share/consolidate (CPI model) silo’ed data, slowed progress

- Is system in place to manage samples/evaluate biomarkers, control for bias, & account for the sensitivity/specificity of analytic tools?
  - Handling of biopsy material
  - Assay reagents/methodology; including independent/blinded analyses
  - Value of qualified biomarkers

- Is GMP manufacturing capacity sufficient for an adequate trial size (adequately powered)?
Clinical Trials 1

- **Lesson**: Doing things in a hurry can delay, rather than accelerate, a definitive regulatory outcome (e.g., DMD vs. SMA)

- FDA legally requires ‘adequate and well-controlled trials’

- In trial design, attention to sample size & control/comparator populations is critical

- Problem of un-blinding by social media

- Limitations of post hoc analysis

- Notable differences between FDA and EMA (particularly conditional approval with rapid pull back with EMA)
FDA on Natural History Controls*

- FDA ICH E10 Guidance; design limitations:
  - ‘Inability to control bias is the major & well-recognized limitation, & is sufficient in many cases to make the design unsuitable’
  - ‘It is always difficult, & in many cases impossible, to establish comparability of the treatment & control groups’
  - ‘It is well documented that untreated historical-control groups tend to have worse outcomes than an apparently similarly chosen control group in a randomized study’
  - ‘An external control group is often identified retrospectively, leading to potential bias in its selection’

- **Lesson**: Every therapeutic candidate needs a comparator; the key question is which comparator; understand nat hist limitations

*BioMarin Ad Com; similar in Sarepta Ad Com
Clinical Trials 2

• **Lesson**: Registration endpoint, study group choices & implementation strategy need to be objective & clear

• Plan to evaluate outcome that is clinically meaning to patient

• 6MWT endpoint difficult—poor reliability, non-linear progression & susceptible to motivation; need for other endpoints (other timed function or respiratory?); loss of ambulation call to exclude = ‘subjective’

• Standardized protocols essential (site to site variability problematic)

• Potential biases in endpoint measure protocols need to be recognized

• FDA wasn’t as ‘directive’ on endpoints as assumed
‘I would prefer seeing randomisation very, very early" in the drug testing process, Woodcock remarked, adding "even if there's a small, tiny effect, it may be meaningful to that patient population. If they can show there is definitely a small effect in a terrible disease, we will approve that drug.’
FDA Feedback

• **Lesson**: Essential to work with FDA & EMA to facilitate the controlled studies needed for clear answers; Regulators legally constrained on public comments—sponsor’s communication must be transparent & clear

• FDA consistently advised for P-C trials & for pre-defined analytic strategies in DMD; strategy of accelerated approval with limited data/analyses not pre-defined can delay drug approvals

• FDA has stated ‘flexibility’ granted them in FDASIA is for indications with unmet need; understand that flexibility is in *interpretation of science*, not in *circumventing need for scientific evidence* (regulatory bar has not gone down)
Final Thoughts

• Were DYS-targeted drug candidates sufficiently de-risked at each stage of development? Assays & data independently validated? Candidate & dose fully optimized? Need to mitigate well-known reasons for many clinical failures!

• For DM:
  • Develop adequate preclinical rationale
  • Optimize endpoint selection & trial design
  • Biomarkers/PD markers, existence & technology, are essential
  • Attend to level of effect (go/no-go)
  • Mitigate therapeutic misconception
  • Appreciate the impact pushing poor rationale, trial design, & weak data may have upon progress in the disease