Innovative Operational Approaches in a Global Phase 1/2 Trial in Myotonic Dystrophy Type 1 (DM1): Learnings from the ArthemiR™ Study

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BACKGROUND:

ArthemiR is a first-in-human, multinational, Phase 1/2 study of ATX-01, an antisense oligonucleotide targeting miR-23b for Myotonic Dystrophy Type 1. The trial involves complex biomarker-driven assessments, including serial muscle biopsies and multi-system evaluations, across multiple countries, requiring innovative operational strategies.

OBJECTIVES

To review operational strategies, adaptations, and lessons learned in ArthemiR to inform future rare disease and oligonucleotide trials.

METHODS

The study utilized ascending single and multiple dose cohorts with rigorous safety and biomarker monitoring. Key strategies included phased site activation leveraging specialist DM1 networks, iterative protocol refinements based on feedback, separate specialist biometrics CRO engagement, real-time site support, and ongoing stakeholder engagement through Arthex-led site visits and meetings with clinical sites, patient advocacy groups, and experts to ensure alignment of trial design with participant needs and site readiness.

LESSONS

Early collaboration with specialized networks and flexible protocol design are critical for rare disease trials. Specialized vendor engagement enhances data quality and operational resilience.

RESULTS

- Accelerated site activation and recruitment via experienced DM1 sites
- Agile protocol adjustments improved feasibility without compromising integrity
- Strong quality oversight and risk management ensured consistent complex endpoint collection
- Separating biometrics from operational CRO enhanced data quality and accountability
- Patient-centric logistics addressed sample handling, equipment needs, and language support
- Collaborative communication enabled proactive problem-solving and timely deliverables

the ArthemiR™ trial

Background: the ArthemiR™ Study

The ArthemiR study is a first-in-human, multinational, Phase 1/2 study of ATX-01, an antisense oligonucleotide targeting miR-23b, for Myotonic Dystrophy Type 1.

Mechanism of Action of ATX-01:

ATX-01 increases levels of free/available MBNL via two mechanisms:

1. Blocking the microRNA miR-23b, a repressor of MBNL expression
2. Release of MBNL from toxic DMPK RNA foci

Objectives of the ArthemiR trial:

The primary objective of this first-in-human study is to assess the safety of ATX-01. Several secondary and exploratory objectives are included to assess pharmacokinetics, pharmacodynamics, and preliminary efficacy data. These endpoints are included to gain as much knowledge as possible to further inform development of ATX-01.

Objective of this poster:

The objective of this poster is to review operational strategies, adaptations, and lessons learned in ArthemiR to inform future rare disease and oligonucleotide trials.

→ Please see poster #1176 for further details on the ArthemiR study design.

Challenges

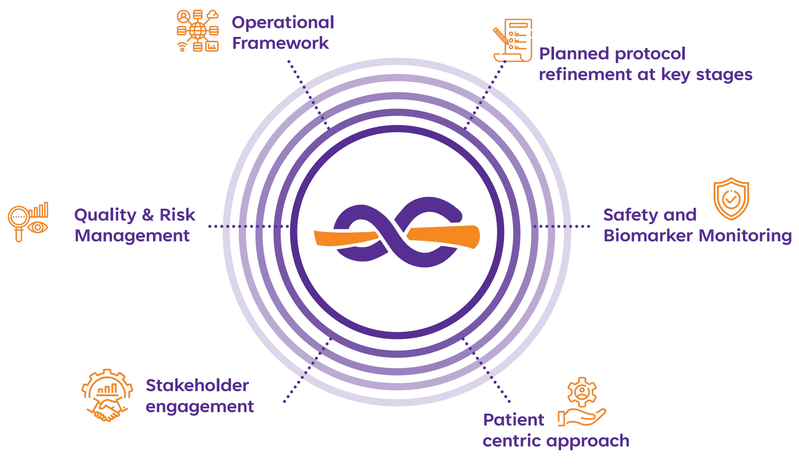
Rare Disease Trial Challenges:

- Limited global patient population (~1 in 8,000) requiring multinational approach
- Complex multisystem DM1 manifestations necessitating specialized clinical expertise and multiple endpoint assessments
- Novel antisense oligonucleotide mechanism requiring innovative biomarker strategies

Drivers of Operational Complexity:

- First-in-human safety profile (cohort management, sentinel dosing, safety review meetings) requiring adaptive trial design capabilities
- Serial muscle biopsies and complex evaluations demanding specialized site infrastructure including muscle testing assessments requiring specialised equipment and highly trained physiotherapists
- Multinational regulatory coordination across diverse healthcare systems and languages
- Burden of assessments for participants

Key Factors to Operationalise Success



Results

Protocol Considerations

- Iterative protocol adjustments to improve feasibility without compromising participant safety and data quality
  - Planned amendments after reaching certain safety milestones
  - Early feedback from sites collected and incorporated into amendments to assist
- Flexibility where possible, in visit scheduling and splitting of visits to facilitate site and participant scheduling
- Early cross-country regulatory dialogue to pre-empt common multinational barriers

Site Considerations

- Evidenced-based site selection criteria focusing on DM1 expertise and research infrastructure
- Phased and accelerated site activation and recruitment via established DM clinical research network
- Collaborative communication enabled proactive problem-solving and timely deliverables
  - Frequent sponsor-site contacts beyond standard monitoring visits
  - Sponsor-led visits for direct stakeholder involvement, feedback, problem-solving

Quality & Risk Management

- Strong quality oversight and risk-based management approach tailored to complex endpoints for consistent collection
- Separating biometrics from operational CRO enhanced data quality and accountability
  - Specialist biometrics team offering depth of biometrics experience enabling high quality deliverables ahead of time
  - Fully programmed DSMB outputs

Patient-Centricity

- Patient-centric logistics addressed sample handling, equipment needs, and language support
  - Patient input sought in study-related documents
  - Facilitation of site visit scheduling given the level and frequency of visits
  - Multilingual support and cultural considerations for multinational execution
  - Close contact with patient advocacy groups for input and advice

Lessons & Conclusion

- Early collaboration with specialized networks and flexible protocol design are critical for rare disease trials.
- Specialized vendor engagement enhances data quality and operational resilience.

Key Success Factors:

- Early collaboration with specialized DM1 networks reduced site activation time
- Flexible protocol design enabled real-time adaptations without compromising safety or data quality
- Dedicated biometrics expertise improved data quality and reduced timeline risks

Best Practice for Future Studies:

- Implement phased activation approach for all rare disease multinational studies
- Consider separating biometrics from operational CRO functions for complex endpoint studies
- Establish patient advocacy partnerships early in protocol development phase and maintain during study execution
- Develop a flexible regulatory strategy accommodating iterative protocol refinements

CONCLUSION

ArthemiR study demonstrates how innovative, patient-centric approaches facilitate global rare disease trials, offering a practical blueprint for future complex studies.

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