Design of the first in human ArthemiR™ study of a novel drug, ATX-01, for the treatment of DM1

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OBJECTIVES

ATX-01 is a novel anti-microRNA in clinical development for the treatment of Myotonic Dystrophy. The objective of the current project was to design an efficient and feasible study to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical efficacy of ascending single and multiple doses of ATX-01 in participants with adult-onset Myotonic Dystrophy Type 1 (DM1).

METHODS

The Arthex drug development team proposed an initial design based on non-clinical data, regulatory guidance, and latest knowledge of DM1 clinical trial design.

The design was reviewed and modified based on feedback from patient groups, key opinion leaders in DM1, clinical study site staff, technical specialists, FDA, EMA, MHRA and Spanish National Regulatory feedback, and external drug development experts.

Learnings from other trials which preceded and are ongoing were incorporated.

RESULTS

The ArthemiR Trial Design was created and the study protocol was approved in at least 6 countries including the USA, Canada, UK, Spain, France and Italy.

The design ensures that risks to participants are minimized, whilst optimizing the design efficiency, to allow maximal knowledge building on the potential for ATX-01 to become a therapeutic in the DM space.

This was balanced with feasibility of conducting the study from various stakeholder viewpoints.

the ArthemiR™ trial

Methods: Input to Protocol Design (non-clinical data)

Mechanism of Action:

ATX-01 (X82108) is an antisense oligonucleotide designed to sterically block microRNA 23b (miR23b).

This leads to dual effects:

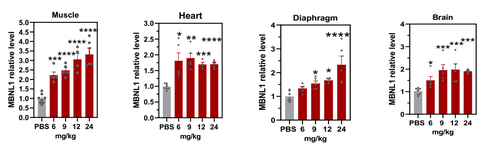
1. Increase in total MBNL
2. Destabilisation of DMPK foci and release of MBNL

The net increase in free cytoplasmic MBNL leads to splicing rescue and improvement in functional outcomes.

For further details on MoA please approach an Arthex representative or contact us at info@arthexbiotech.com

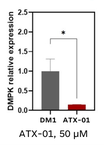
1. Increase in MBNL

MBNL is Elevated in Tissues Affected by DM1 (HSA^{LR} mice):



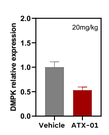
2. Decrease in DMPK

In vitro (human DM1 myotubes)



ATX-01, 50 µM

In vivo (NHP)



Primary Pharmacodynamics

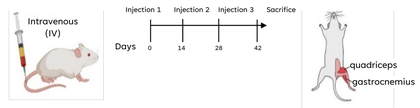
ATX-01 (X82108) was tested in the HSA^{LR} mouse model of adult onset DM1. ATX-01 rescues functional and molecular disease phenotypes:

Time-response experiment in DM1 mice (HSA^{LR})**

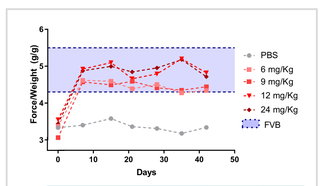
3 IV injections in HSA^{LR} mice (1 injection every 14 days). Sacrifice at day 42

Measurement of grip strength (days 0, 14, 28, and 42)

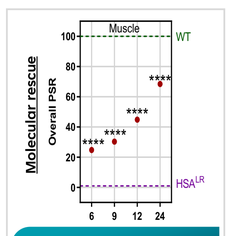
Measurement of molecular parameters in Gastrocnemius



Upregulation of MBNL1 using ATX-01 maintains muscle force and splicing rescue



Sustained normal strength



Dose dependent splicing rescue (PSR)

* FVB= Wild type healthy mice
**Mankodi et al. Science. 2000.

Non-clinical Safety Programme:

miR23b is a highly conserved microRNA across many species (including mice, rat, minipig, rabbits, NHP) allowing for the same sequence to be used in non-clinical and clinical studies.

Non-clinical and toxicology studies required for a FIH study were performed. Short-term toxicity studies were performed in rats, minipigs and non-human primates and led to the opening of an IND in the US, as well as clinical trial authorisations in Canada, EU, and the UK.

Effects seen across a range of CTG repeat lengths:

→ HSA^{LR} model (~ 250 repeats)

→ DMSXL model (~ 1000 to 1800 repeats)

Molecular and Functional Effects seen in Brain:

Inhibition of miR-23b in the Brain Corrects Neurological Defects in Adult DMSXL Model

→ *For further details on CNS effects, please approach an Arthex representative, or contact us at info@arthexbiotech.com*

Methods: External Input to Protocol Design

Industry Precedence

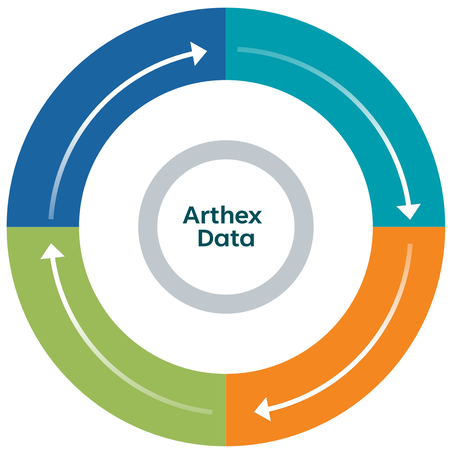
→ Publicly available information (e.g. from clinicaltrials.gov) on endpoints, participant selection criteria, overall study design

KOL/Expert Feedback

→ Selection of muscle testing assessments

→ Inclusion & Exclusion Criteria to ensure selection of the appropriate participants

→ Endpoints for target engagement & early efficacy



Patient Input

→ Patient lived experience

→ Visit timing and burden

→ Willingness to undergo invasive procedures such as muscle biopsies

Regulatory Feedback

→ Starting dose, dose increments, maximal dose

→ Safety biomarker testing

→ Exploratory efficacy endpoints

Design of the ArthemiR FIH Study

PRIMARY OBJECTIVES

Safety and tolerability of single and multiple ascending doses of ATX-01 in DM1 — **DESIGN** →

- Single-ascending dose (4 dose levels)
  - Follow-up 12 weeks
- Multiple-ascending dose (3 dose levels)
  - 3 doses, once every 2 weeks
  - Follow-up 12 weeks after 3rd dose

Endpoints: adverse events, clinical laboratory safety assessments (blood, urine), ECGs, Holter

SECONDARY OBJECTIVES

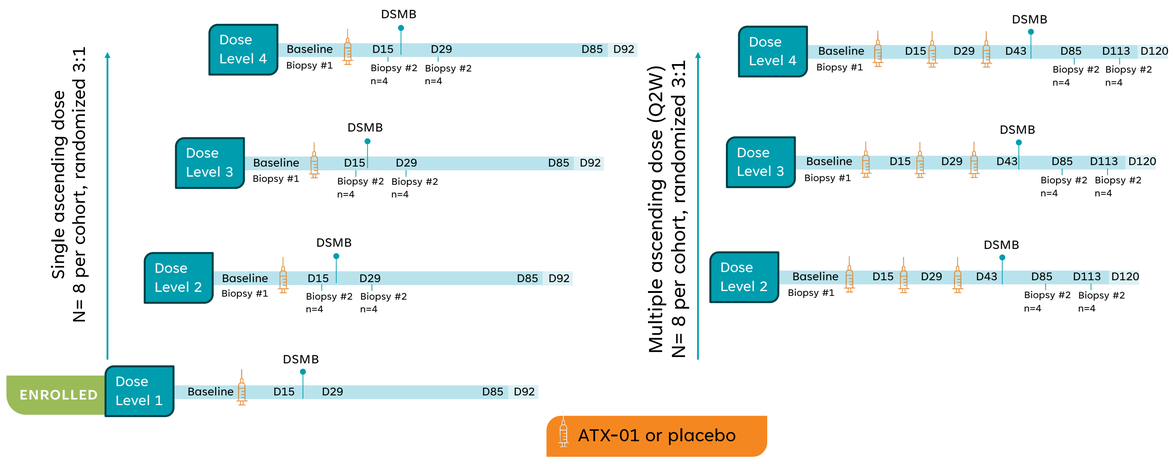
Target engagement at the muscle level via biomarkers — **DESIGN** →
- MBNL levels
- Splicing index

Preliminary efficacy — **DESIGN** →
- Myotonia (vHOT)

EXPLORATORY OBJECTIVES

Clinical endpoints — **DESIGN** →
- Quantitative myometry
- Other muscle function tests
- ClinROs and PROs on QoL, extra-muscular symptoms

ArthemiR Study Overview



Key Inclusion-Exclusion Criteria for the ArthemiR Trial

The goal is to ensure the safest population possible for FIH dosing, whilst selecting for a population where it may be possible to see an effect (targeted severity level of disease)

Inclusion Criteria

- Male or Female; Age 18-64
- Diagnosis of DM1 supported by >150 CTG repeats in the expanded region of the DMPK gene
- Able to walk
- Myotonia > 3 secs (delayed relaxation after contracting a muscle)
- Signed Informed Consent

Exclusion Criteria

- Congenital (from age <1 month) myotonic dystrophy
- Unable or unwilling to undergo muscle biopsies
- Taking anti-myotonia medication
- Moderate-advanced cardiac disease
- Other health conditions that might put participation at risk

ArthemiR™ Trial Key Outcome Measures

Safety and Tolerability

- Collection of adverse events
- Labs (blood and urine)
- ECGs, Holter

Pharmacokinetics

Pharmacodynamics (muscle biopsy)

- MBNL protein levels
- Splicing

Clinical Efficacy:

Muscle & Function Testing
- Myotonia (vHOT)
- Quantitative Myometry
- Other muscle/function tests

Clinician- and Patient-Reported Outcomes
- DM1 Activ^{C}
- Impact of symptoms on ADL
- Other ClinROs and PROs assessing extramuscular function

CONCLUSIONS & PRACTICAL IMPLICATIONS

Best practices in study design include considerations of patient safety, data integrity and feasibility. It is critical to obtain and evaluate inputs from different sources before deciding on a final study design. These best practices provide a framework for future trials targeting rare diseases like DM1. Future phases will explore long-term efficacy and broader applications of ATX-01 in related conditions.

Plan de Recuperación, Transformación y Resiliencia

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