15 de noviembre de 2022

ATX-01: a first-in-class disease-modifying therapy for Myotonic Dystrophy type 1 (DM1)

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Disclaimer

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ARTHEX´s mission

We develop treatments for unmet medical needs modifying gene expression by controlling miRNA levels

Advantages of our strategy targeting miRNAs

Target specificity

miRNA target binding based on sequence complementarity. Potential off-target binding is easy to predict, investigate and mitigate

Pathway modulation

miRNAs are fine-tuned regulators of gene expression by inhibiting the synthesis of proteins* involved in key pathological pathways

FUNDING

ARTHEx has raised €6.9M in equity funds and >€4.5M in grants

*Bartel. Cell. 2004. doi: 10.1016/s0092-8674(04)00045-5

Meet our Dedicated Team

A team of fully dedicated experts with strong expertise in neuromuscular diseases, CMC, tox, and clinical development

Beatriz LLamusí
CEO/CSO and Co-founder

CEO since inception. 15+ years investigating pathogenesis and therapies for neuromuscular diseases

Judith Walker
CMO

Neurologist. 5+ years as a CMO. 20+ years in regulatory and clinical operations and strategy

Pedro Fernandez
Director of Operations

Responsible for operations since inception. 5+ years in IP and project management

Jordi Petit
CFO

Interim CFO since inception
15+ years of experience in financial management of Biotechs

Sheila Soriano
Head of CMC

Analytical chemist with 3+ experience in project management

Nuria Barquero
Head of Preclinical Toxicology

European Registered Toxicologist
5+ years in Preclinical Development

Estefania Cerro
Research Director

9+ years investigating therapies for DM1

Judy Carmody
Head of Quality

Interim Head of Quality .25+ years of specific expertise driving vision in quality and CMC operations

Main international KOLs involved in our project

Arthex is working with the main international KOLs active in the field of RNA synthesis, RNA therapeutics, and clinical management, to support our development

Ramón Eritja

Research professor at IQAC. Leader of Nucleic Acids Chemistry group and CIBER-BBN. Academic world expert in nucleic acids chemistry and synthesis.

Eric Marcusson

Current CSO Providence Therapeutics
Ex Regulus Senior Director Drug Discoery
Ex IONIS Director Antisense Drug Discovery
>20 years in preclinical RNA therapeutics

Muthiah Manoharan

Senior Vice President, Drug Innovation Alnylam: first chemist hired at Alnylam. Pioneer of the RNA therapeutics and GalNac technology
>20 years in oligonucleotide chemistry

Ruben Artero

Professor of Genetics in the University of Valencia.
Co-founder and pioneer in research of MBNL function and regulation. Expert in DM MoA.

Guillaume Bassez

Neurologist responsible for the DM1 registry of patients in France
Senior Physician and Neuroscientist, Assistant Professor at the National Neuromuscular Reference Center, Pitie Salpetriere University Hospital, France.

Nicholas Johnson

Neurologist. coordinator of the Myotonic Dystrophy Clinical Research Network (DMCRN) in USA.
Vice Chair of Research at Virginia Commonwealth University

Our work is focused on impacting the lives of DM patients across the globe

Patient Advocacy Groups

6

Rational design of microRNA inhibitors
Enhanced AntimiR delivery (EntRy™) platform

Arthex is developing antiense oligonucleotides that inhibit microRNAs (AntimiR* technology) with a high level of specificity.
The combination of antimiR specificity and conjugate-mediated enhancement of potency and delivery, allows highly effective target engagement in selected tissues, and reduced toxicity.

AntimiR oligo

- Sequence selected for high specificity
- Combination of optimal chemical modifications to increase durability and affinity
- Protection against immune system activation
- In vitro and in vivo safety and efficacy assessment

Hydrophobic conjugate

- Lipophilic profile-based selection
- Proprietary intellectual property
- Increased target engagement in target tissues
- Decrease accumulation in kidney
- In vitro and in vivo safety and efficacy assessment

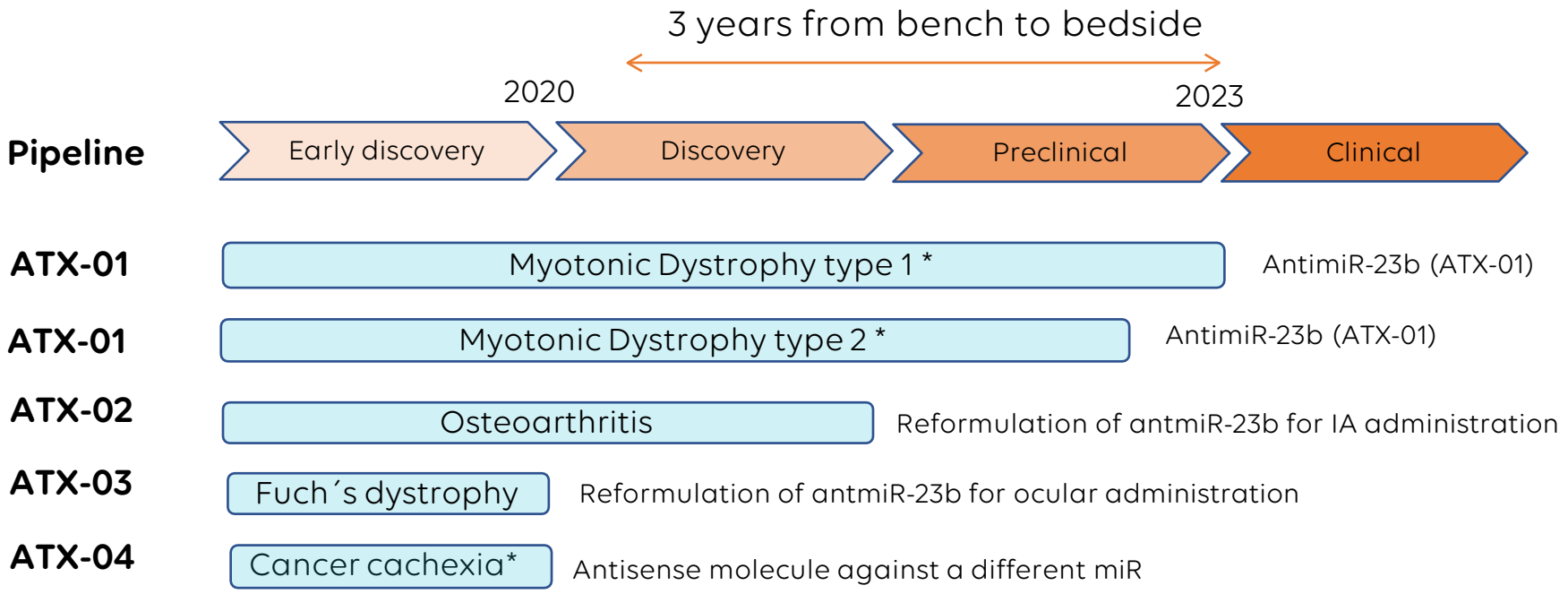
Lead antimiR

- Higher concentration and potency in target tissues
- Higher durability of effects
- No complement activation
- No hemolytic potencial
- Safe for kidney and liver

*Rupaimoole R, et al. Nat Rev Drug Discov. 2017. doi: 10.1038/nrd.2016.246.

AntimiR oligonucleotides to treat unmet medical needs

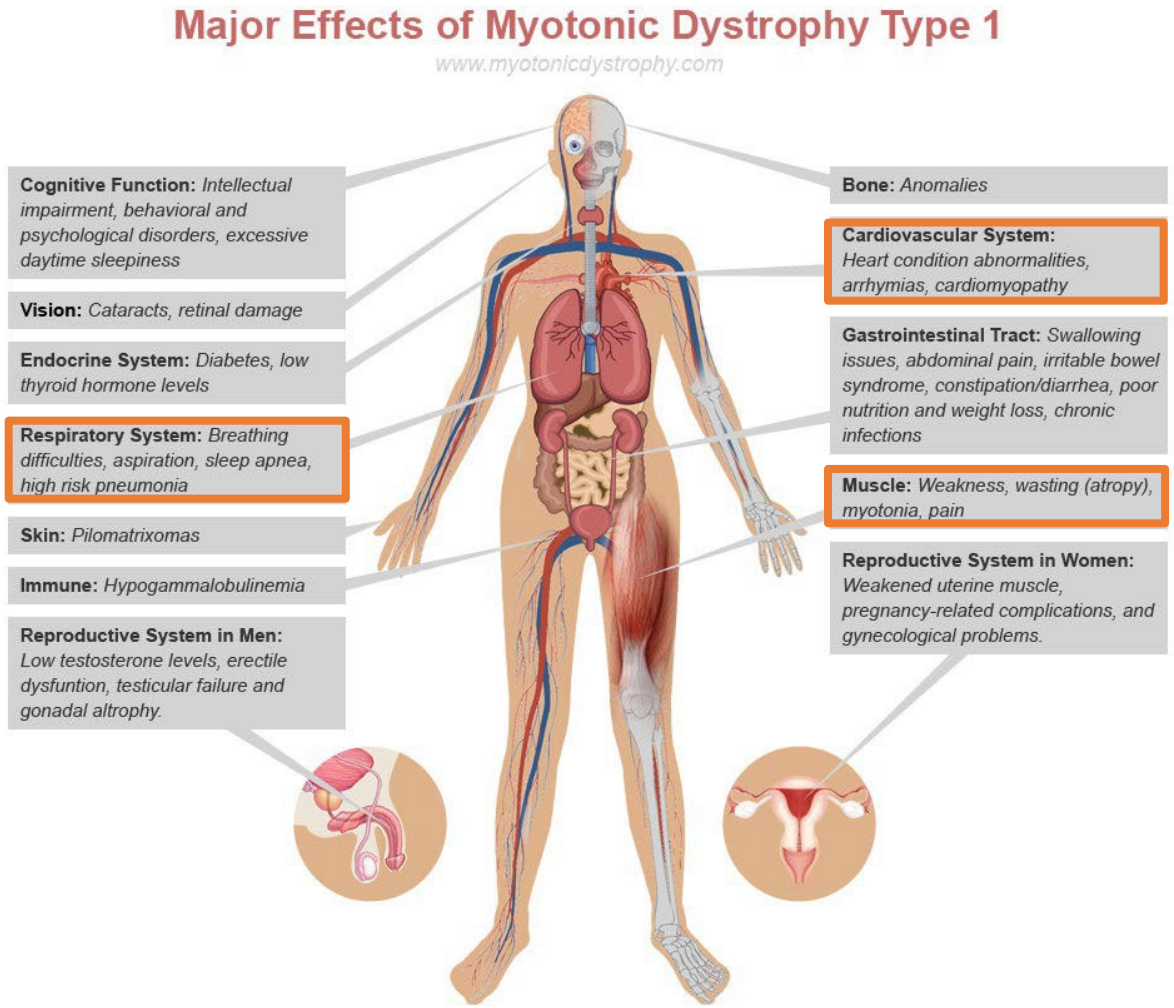
Developing antimiR-based treatments for unmet medical needs.



*Orphan drug designation applicable

Myotonic Dystrophy (DM1), remains an unmet need

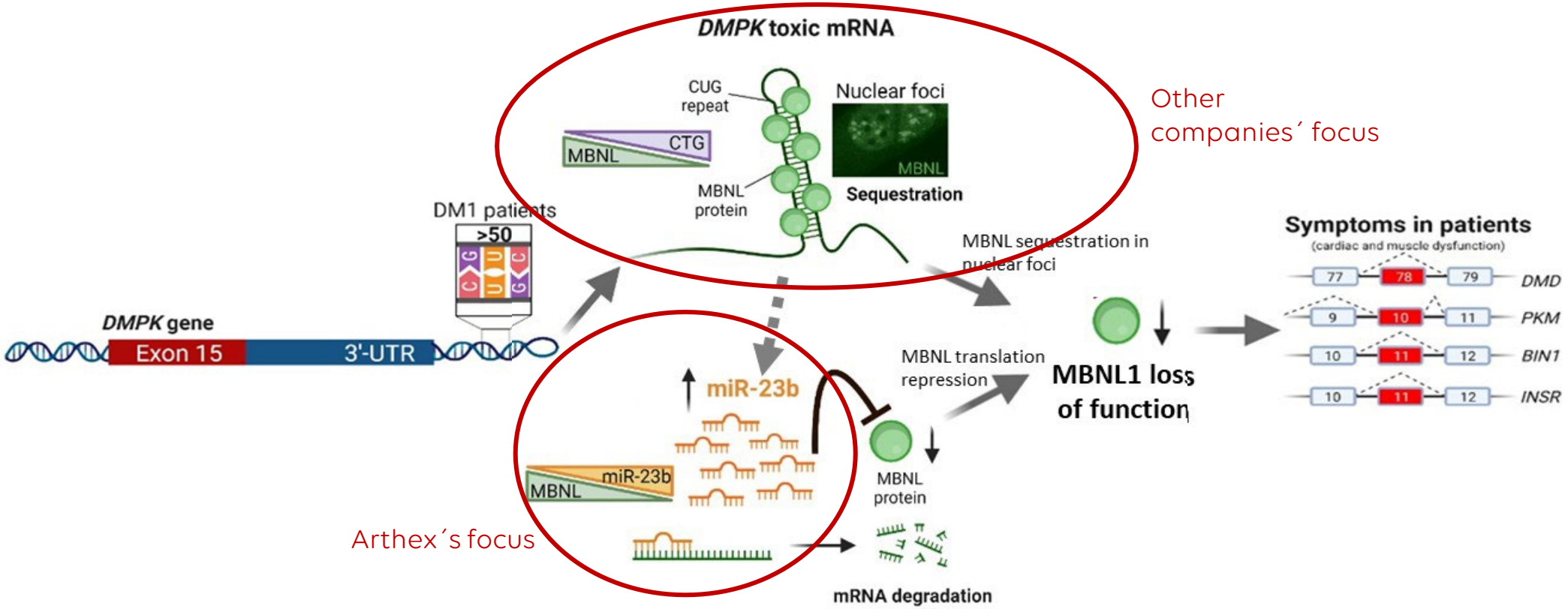
- Monogenic autosomal dominant progressive disease that primarily affects muscle
- Rare, highly disabling disease.
- Shortened life expectancy (45-60 years).
- Orphan disease.
  Global Prevalence= 1/3000-8000*
- Estimated patient numbers based on diagnosis:
  - 40 000 in US and 70 000 in EU.
  - Underdiagnosed disease so true prevalence likely higher
- Adult and pediatric.



*Ashizawa et al.,. Neurol Clin Pract. 2018 . doi: 10.1212/CPJ.0000000000000531..

Myotonic dystrophy type 1 (DM1) is a complex disease with a well-described molecular origin of symptoms

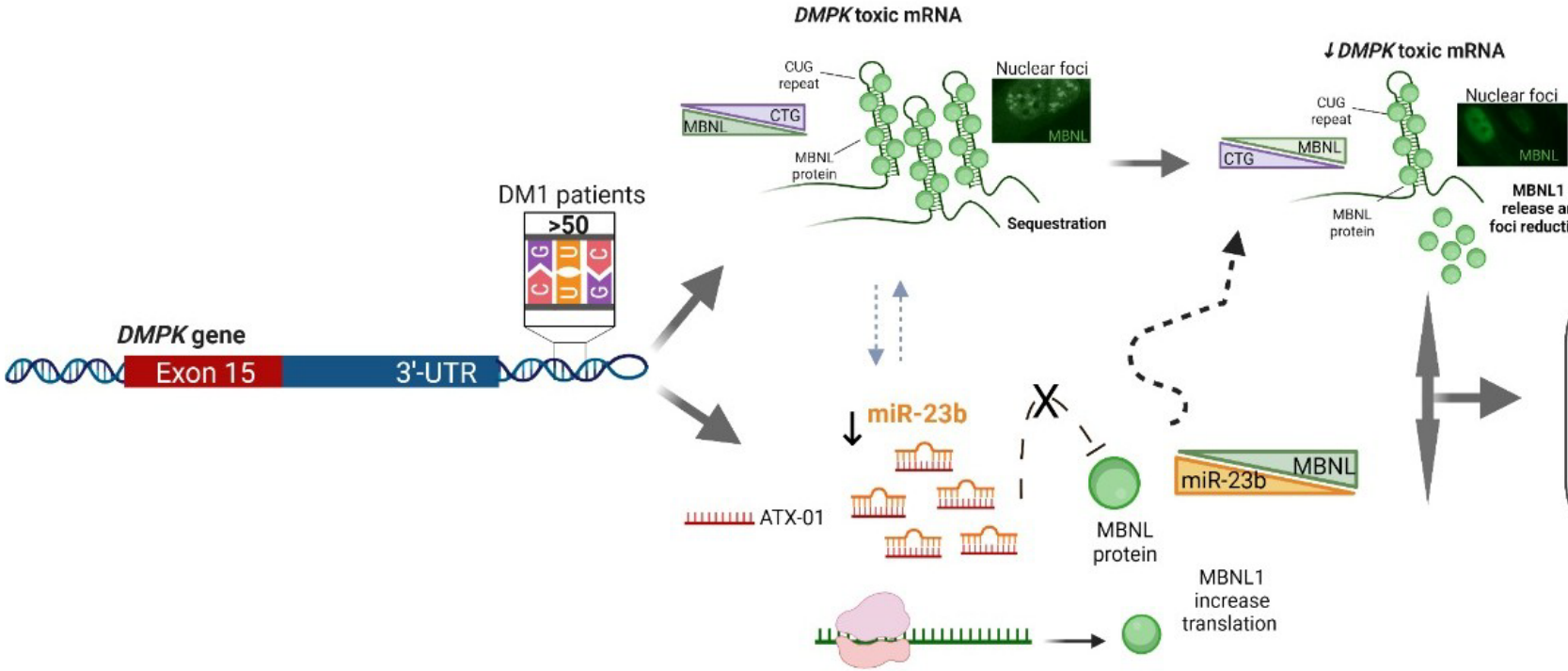
Genetic origin: abnormal DNA expansion (CTG repeats) in a non-coding region of DMPK gene.
Symptoms origin: MBNL loss of function, which produces mis-splicing of MBNL-regulated transcripts.

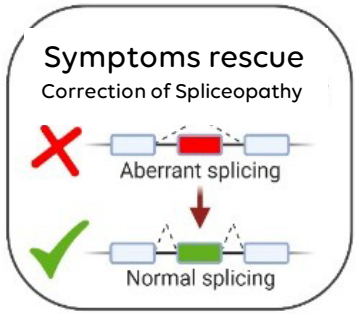


ATX-01 is a first in class therapy directly addressing the phenotypical cause of the disease

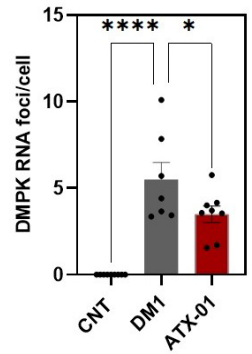
ATX-01 is a 16nt length antisense oligonucleotide linked to a hydrophobic conjugate. ATX-01 inhibits miR23-b, whereas the conjugate allows the delivery of the oligonucleotide to the most relevant tissues affected in DM1, namely, muscle, heart and nervous system.
"Dual target therapeutic approach": Inhibition of miR-23b reduces the expression of the toxic DMPK foci at the origin of the disease, and upregulates MBNL proteins, rescuing disease phenotypes in *in vitro* and *in vivo* models of disease.

Active MBNL1 increases by two mechanisms*

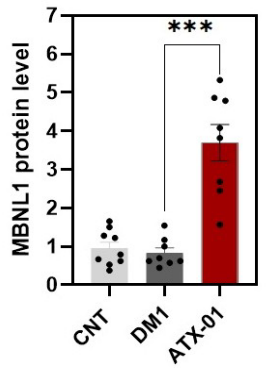




1. Reduction of toxic DMPK foci



2. Increase MBNL1 protein levels



* Studies performed in human DM1 and control primary myoblasts treated with ATX-01 50nM.

Robust POC of maintainance of effects with repeat dosing in a murine adult onset model of DM1

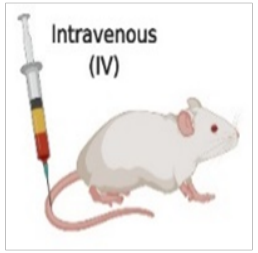
Sustained rescue of phenotypes in HSA^{LR} DM1 mouse model treated with once-monthly dose

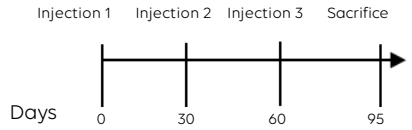
Time-response experiment in DM1 mice (HSA^{LR})

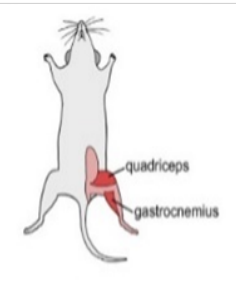
3 IV injections in HSA^{LR} mice (1 injection every 30 days). Sacrifice at day 95

Measurement of grip strength (days 0, 14, 30, 60 and 95)

Measurement of molecular parameters in Gastrocnemius

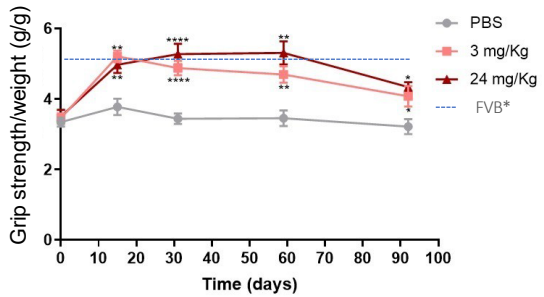






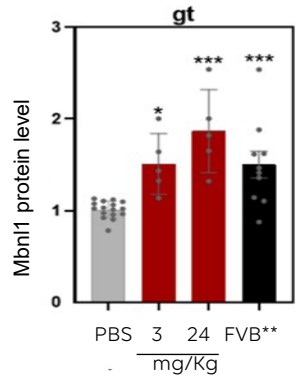
Upregulation of MBNL1 using ATX01 maintains muscle force and splicing rescue

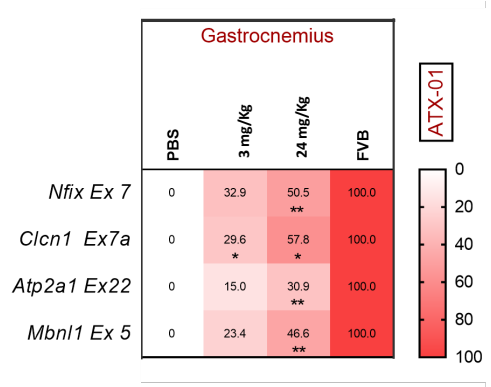
Functional rescue



Sustained normal strength

Target Engagement



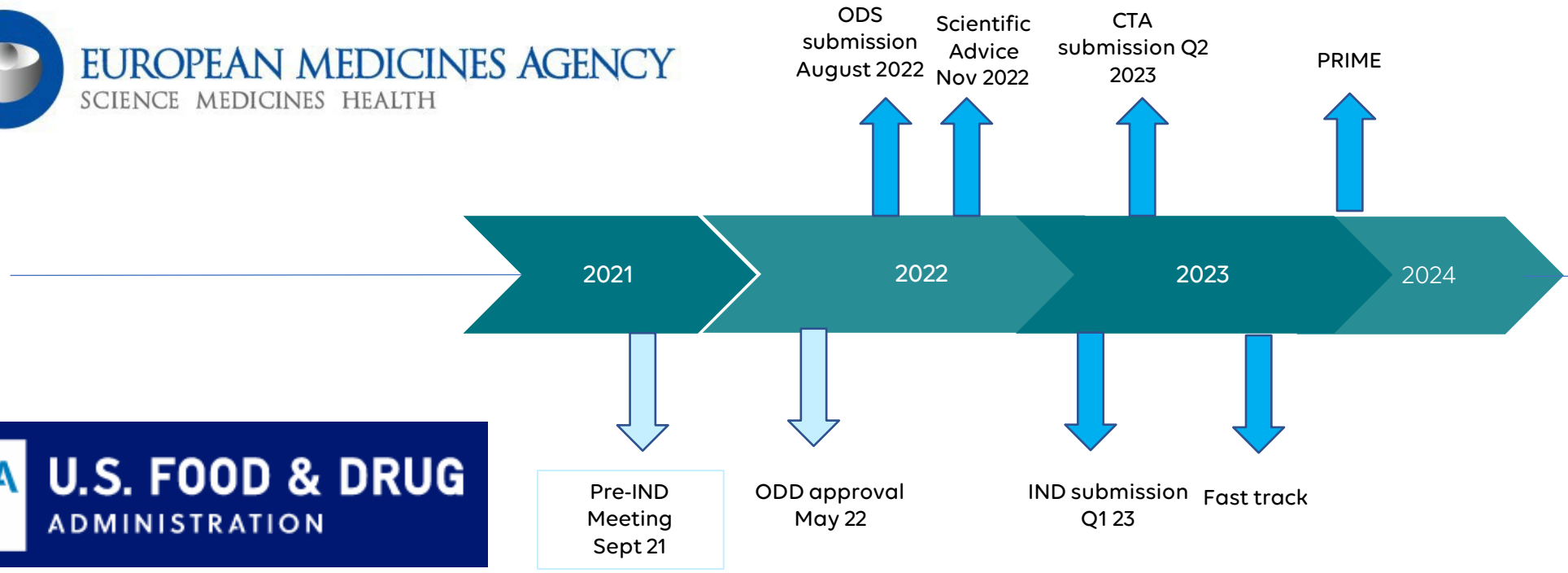


Elevation of MBNL1 and splicing rescue at day 95 after initiation of treatment

* FVB= Wild type healthy mice

The regulatory strategy considers US and EU and takes advantage of schemes available for innovative products in rare indications

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



FDA U.S. FOOD & DRUG ADMINISTRATION

Pre-IND Key Outcomes:

- Complete regulatory package in rats and minipigs
- NHP only needed for immunotox
- PHI/II study on patients
- Chronic tox studies should be submitted before OLE

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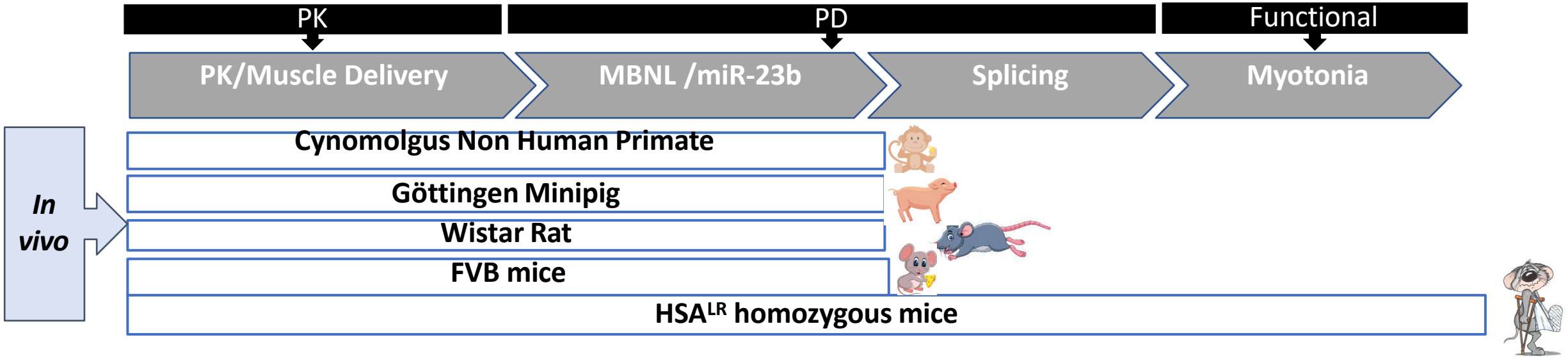
Data from in vitro and in vivo models demonstrate that ATX-01 is efficiently delivered to muscle and drives disease modification

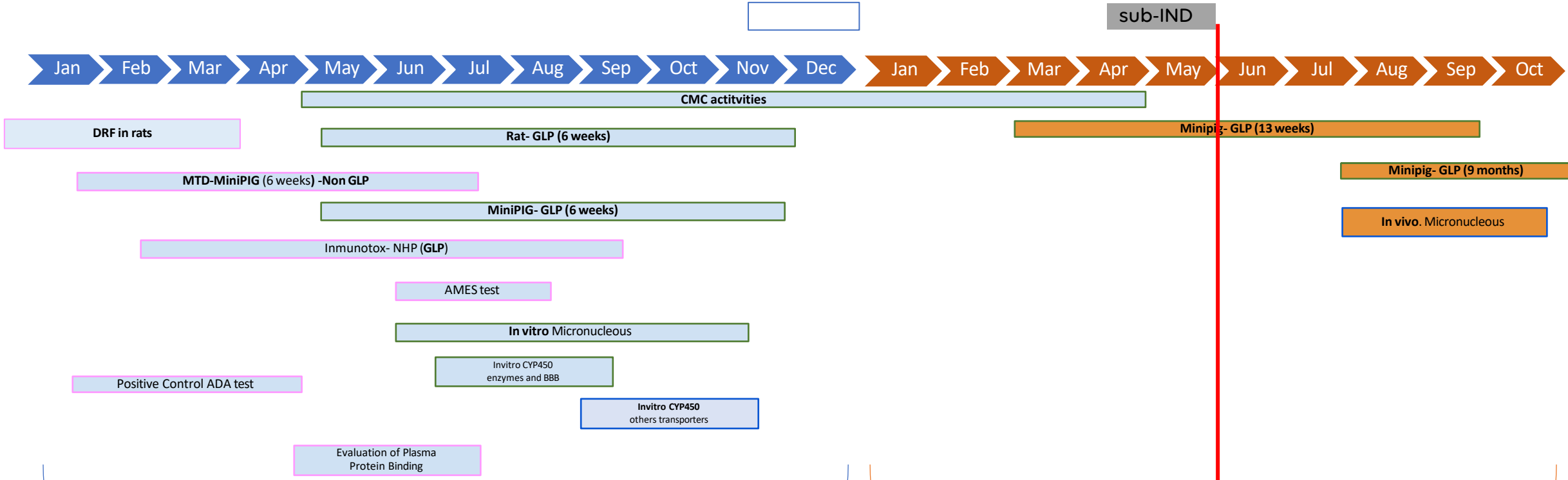


In vitro

- Rat 2 rat embryo fibroblasts
- Porcine fetal testis fibroblast ST cells
- Primary myoblast lines from DM1 patients
- Immortalized human DM1 cell line

CMC and Preclinical developmental plans are on track for IND submission in Dec 2022

Regulatory roadmap validated in a pre-IND meeting with FDA in September 2021



Studies that will support the PhI/IIa Proposed to the FDA

GLP design: IV biweekly injections. Total of 3 administrations. Recovery period of 8 weeks.

Finished studies, report available under request

Chronic GLP tox studies that will support long-term treatment in subsequent trials (In parallel to PhI/IIa)

The Clinical Development Plan is streamlined, adaptive and global (EU + US)

2021 | 2022 | 2023-24 | 2025-26 | 2027 | 2028 | 2029

Phase I/IIa

Phase II/III (Registrational Study)

ATX-1

Exit opportunities after complete results of SAD

FIH Clinical Trial

- 2-part study: SAD, MAD
- Optional open label extension (OLE) study
- In ambulatory DM1 adults
- Objectives:
  - Primary: Safety and tolerability
  - Secondary: Pharmacodynamics (target engagement and POC)
  - Tertiary: Clinical efficacy (muscle-related)
  - Exploratory: extra-muscular (cornea, brain, heart)

Confirmatory Clinical Trial

- Double blind randomised controlled study
- Ambulatory DM1 adults
- Primary Objective: Clinical efficacy

Pre-IND meeting FDA-completed (sept 2021)

End of Phase 2 meeting FDA, Fast Track and Breakthorugh applications

NDA and MAA submissions

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Arthex holds method protection for ATX-01 (and other compounds) in DM1, and is pursuing composition of matter protection for ATX-01 and its ENTRY™ delivery platform

Patent WO2018050930 / PCT/EP2017/073685

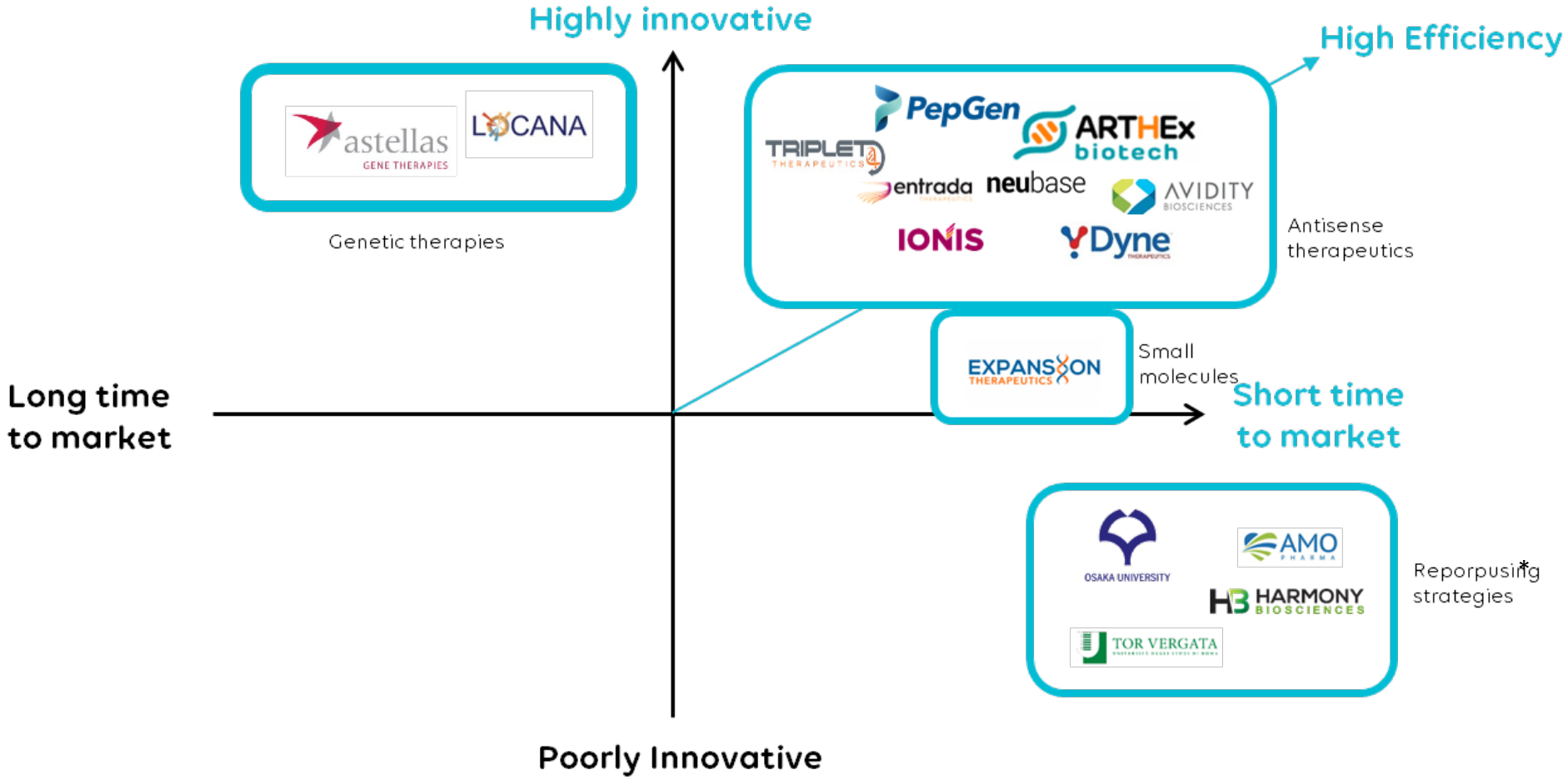
- Method protection: therapeutic use of specific sequences of antimiR-23b and antimiR-218 against myotonic dystrophy (including ATX-01)
- Granted in US, JP and AU
  - provisional applications filed in US and AU to expand the protection to the product
- In process in EPO, HK, CA and IL.
- Freedom to operate with the chemical modifications used
- Protection provided until 2036

Patent 2: filed in May 2022

- Type of protection
  - Composition of matter of ATX-01 and ENTRY™ technology platform
- Protection provided until 2042

We occupy a very strong position in the market

Arthex' innovative dual-effect approach and the tissue delivery strategy, enable low therapeutic doses of ATX-01. ATX-01 has shown target engagement in all the main tissues affected in DM1, including heart and brain, which are not reached by other ASO-based therapies.



*Repurposing molecules are inespecific treatments mainly focussed on cognitive dysfunction

Main risks are

- ATX-01 is a first-in-class treatment
- Two direct competitors (Dyne and Avidity) are already in clinical pase
- Other antisense oligonucleotides against DM1 have underwent serious events in clinical phase (recently, Avidity's Marina Study of AOC-1001)
- Current inflation & deflation is against our needs of funding situation: a delay in closing current series A will significantly harm the Project
- We have never tested the chronic toxicology

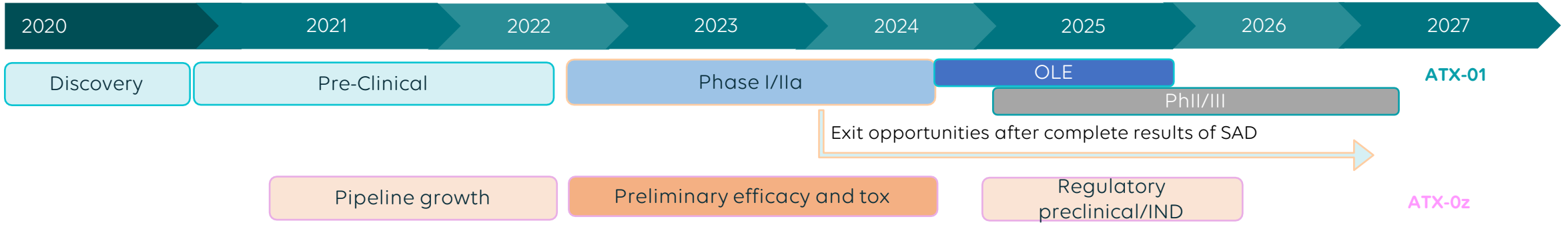
Our competitive advantage

ENTRY platform (fatty acid)

Team up with pharma partners

Current toxicology is clean in 4 species

Series A will support completion of the Phase I/II study and the chronic tox to support the registrational trial



Private funders : €7 M raised

Public funders :€1.5 M raised

€ 8.5 M raised

Milestones:
- Lead selection ATX-01
- IND readiness ATX-01

- PoC data with antimiRs in 2 new indications

Series A € 23-25M

Milestones:
- PhI/IIa (SAD+MAD)
- Chronic preclinics needed for long-term studies

- Preliminary efficacy and toxicology data in models of new indications

+OLE (€ 12M)*

Provided safety and data from molecular biomarkers or patient´s benefit is confirmed:
- OLE of up to 1 year of duration
- With all patients included in the PhI/IIa

+PhII/III (€ 40M)**

PhII/III with at least 100 new patients treated at the selected dose 1 year

*The size of the round A will depend on whether the OLE is included or not
**OLE and PhII/III study could be initiated in parallel

ARTHEx biotech

Join us to improve the lives of patients with unmet medical needs

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