Preliminary Results from a Phase 1-2 Gene Therapy Study of ATA-100, AAV9 Vector Encoding FKRP, in Patients with Limb Girdle Muscular Dystrophy R9

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PRAGUE WMS2024

The 29th Annual Congress of the World Muscle Society

8th - 12th October 2024, Prague, Czechia

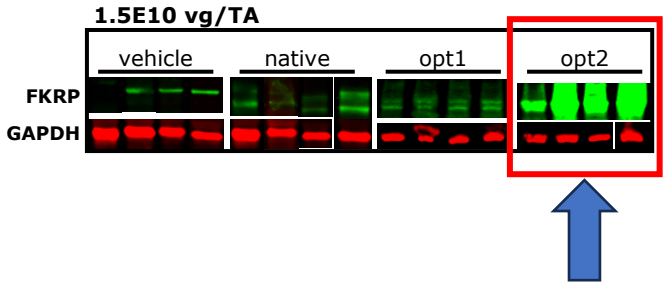
Disclosure

I have the following conflict/s of interest to declare:

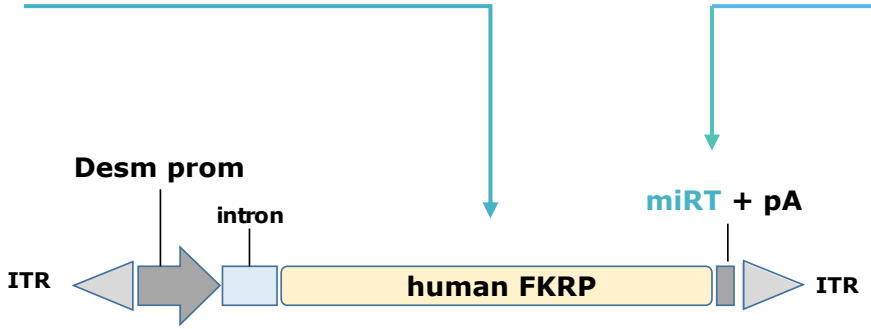
- Full-time employee at Atamyo Therapeutics

ATA-100 Construct

Codon optimization



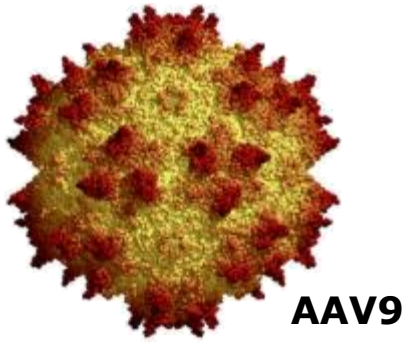
5x higher transgene expression with codon optimization



Production process

Developed at Genethon USP / DSP teams

Clinical batches produced at YposKesi



Heart toxicity when the transgene is overexpressed in cardiomyocytes

Insertion of **miR-208a target sequence** to modulate transgene expression in cardiac cells and prevent cardiac toxicity

ATA-100 fully Reverses Histological Muscle Damage and Restores Functions in LGMD-R9 Preclinical Models at Unprecedented Low Doses

FKRP mutation

Abnormal α-DG glycosylation

Muscles contraction-induced damages

Muscular Dystrophy

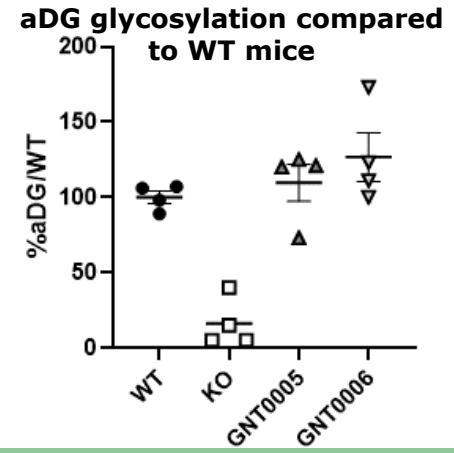
Full histological and force restoration observed at 9E12vg/Kg single dose

Single iv injection in FKRPdel KO mice
$4.5^{e}12$ to $1.8^{e}13$ vg/Kg

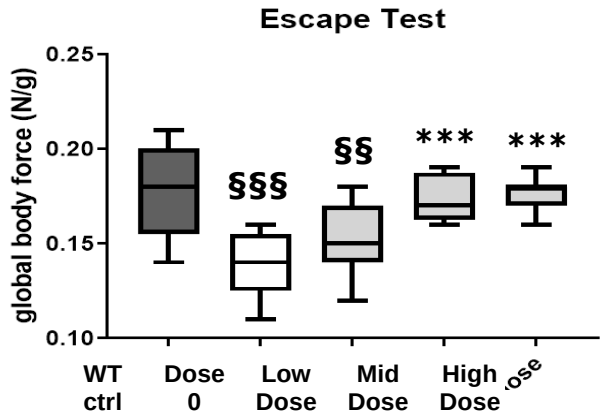
Read-out Time = 3 months post injection

	Psoas
HSA-FKRPdel KO mice	
HSA-FKRPdel mice + ATA-100[1]	Mid Dose 9.0E12 vg/Kg
Wild-Type mice Control	

Restoration of muscle cells histology with full recovery at mid/high dose



Full restoration of aDG glycosylation at 9E12 vg/Kg

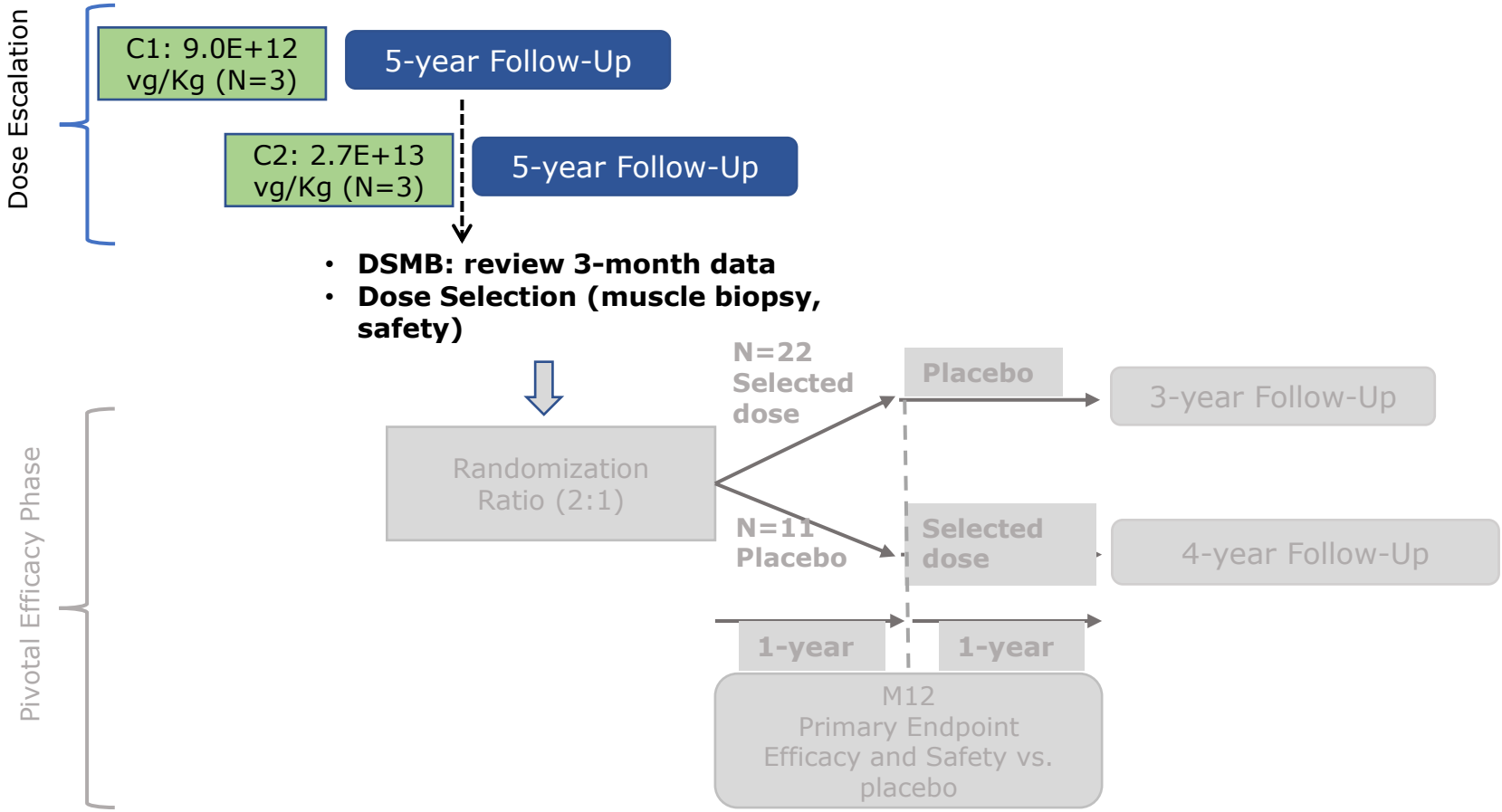


Full rescue of force after AAV9-FKRP gene transfer at mid-dose (9e12 vg/Kg)

§ : vs WT
***** : vs HSA-FKRPdel

Note: GNT005 corresponds to ATA-100/GNT0006 without the miRNA heart detargeting sequence

On-going Phase 1b ATA-001-FKRP Study



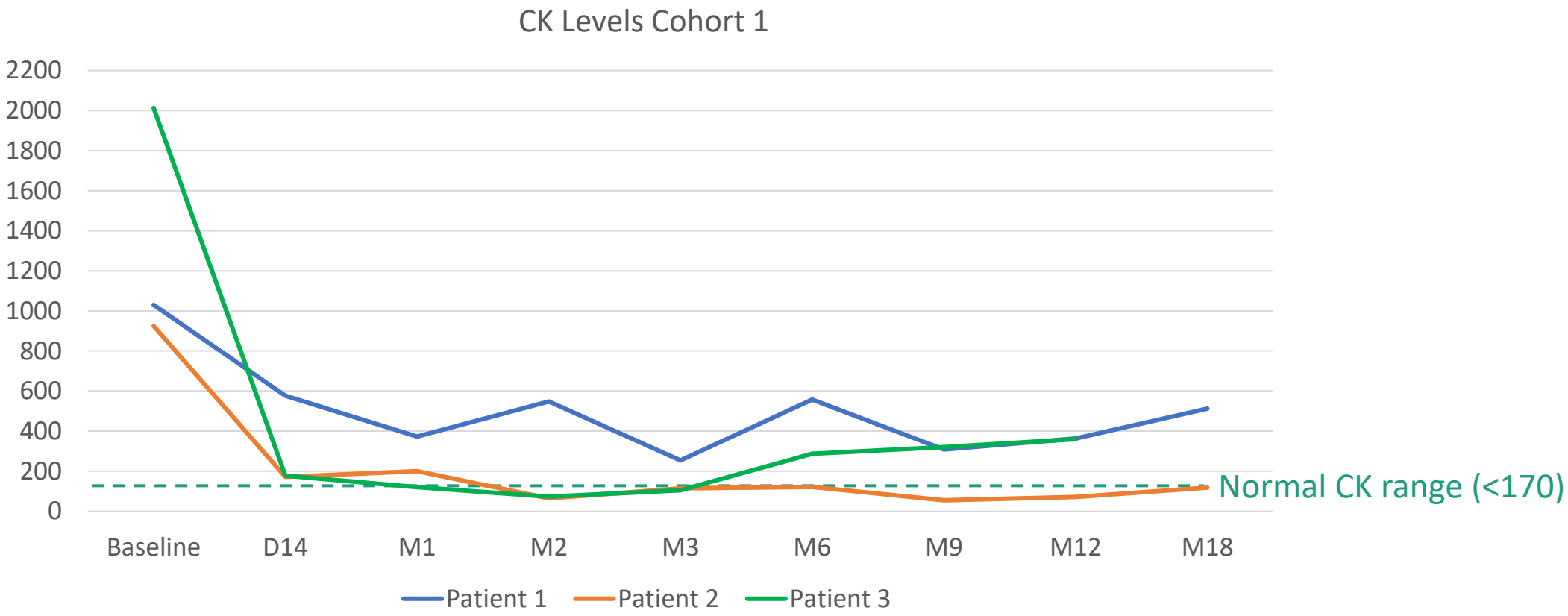
Homogeneous treated population

- 40% < FVC < 80%
- 10MWT within 30 sec max and able to rise from chair

Key endpoints

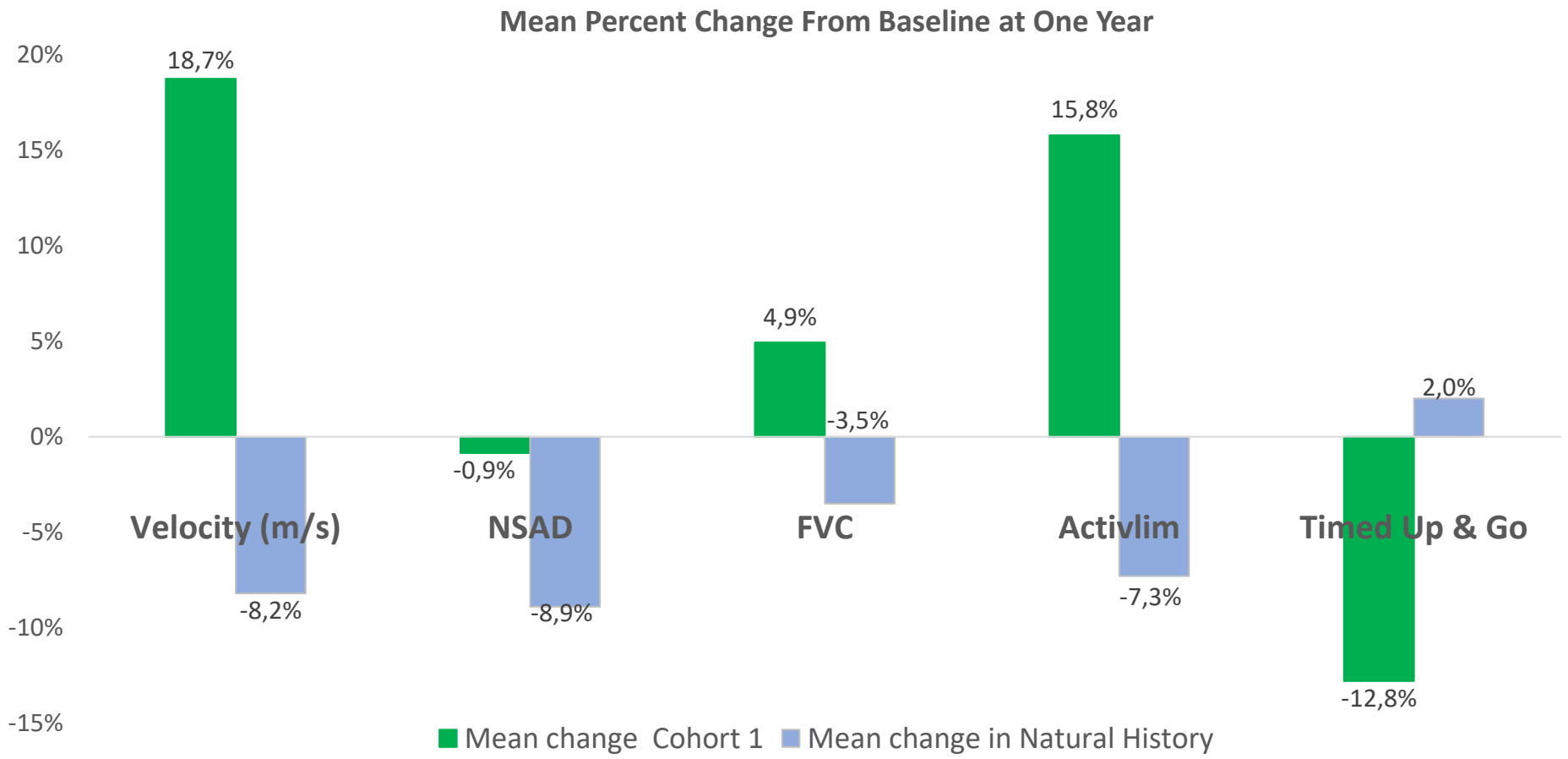
- Primary Endpoint: Safety and Tolerability
- Key secondary endpoints:
  - Transgene expression on 3-month muscle biopsy
  - NSAD, 10MWT, TUG, % fat repartition (muscle MRI), QoL questionnaires
- Biomarkers

All 3 Treated Patients Show Marked and Significant Decline in Creatine Kinase (CK)



- **Mean 86% CK decrease at 3 months, -73% at 6 months** following tapering of immunosuppressants
- Immunosuppressant regimen: 1mg/Kg/day prednisolone for 4 weeks, then decrease 10mg every other weeks up to discontinuation

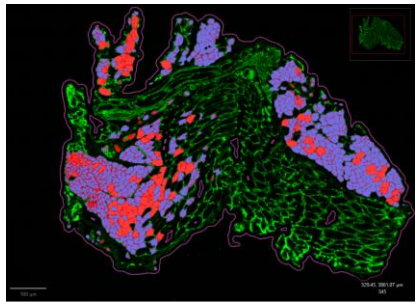
Global Functional Improvement in First Cohort Patients as Compared to Natural Evolution

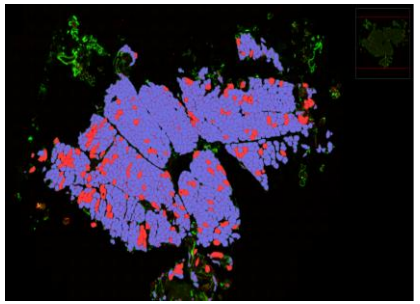


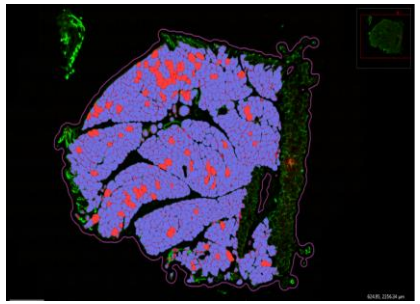
Patient 1: 29 years old, 51 kg, NSAD score at baseline 50; FVC at baseline 74%
Patient 2: 42 years old, 82 kg, NSAD score at baseline 51; FVC at baseline 73%
Patient 3: 42 years old, 54 kg, NSAD score at baseline 15; FVC at baseline 76%

ATA-100 Biodistribution in First 9E+12 vg/Kg Cohort in Line with Biodistribution Associated with Efficacy in Preclinical Models

	Patient 1 Biopsy 1Y (1)	Patient 2 Biopsy 3M	Patient 3 Biopsy 3M	***Preclinical observations***
Vector Copy Number *(FKRP copies / diploid genome)*	**0.254**	**0.557**	**0.560**	Significative improvement in force and histology with ≥ **0.21** copies, full restoration with ≥ **0.94**
% of FKRP positive fibers (2)	**10-15%(2)**	**9-11%(2)**	**7-9 %(2)**	Significative improvement in force and histology with ≥ **9%** positive fibers, full restoration with **≥17%** positive fibers



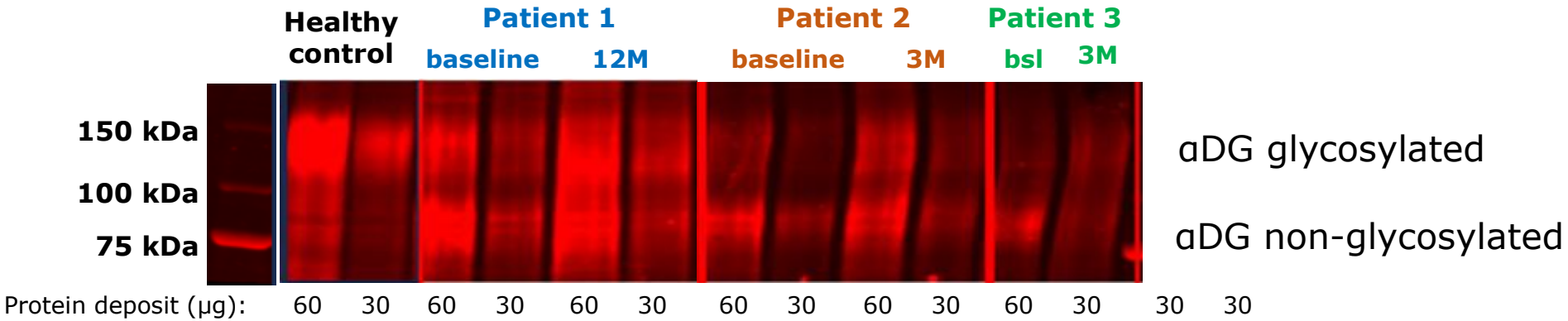




(1) Patient Dk-01-01 3-month biopsy suffered freezing issues

(2) Quantification of positive muscle fibers by In Situ Hybridization - % vary according to positive threshold and quantification method used (raw spots, spots/µm2, spots in cluster)

Improvement of αDG Glycosylation Observed in Patients' Biopsies in first 9E12 vg/Kg Cohort



		DK-01-01	DK-01-03	FR-01-04
α-DG glycosylation *(as % of healthy control)*	Baseline	40%	35%	25%
	3-month	70%	54%	80%
	Change from baseline	+75%	+53%	+220%

- **1st cohort patients display a baseline αDG glycosylation impairment (25% - 40% of healthy subject)**
- **αDG glycosylation improvement with ATA-100 is significant with a mean 30 percent points absolute increase in "low dose" phase 1b cohort – *potential endpoint for conditional approval***

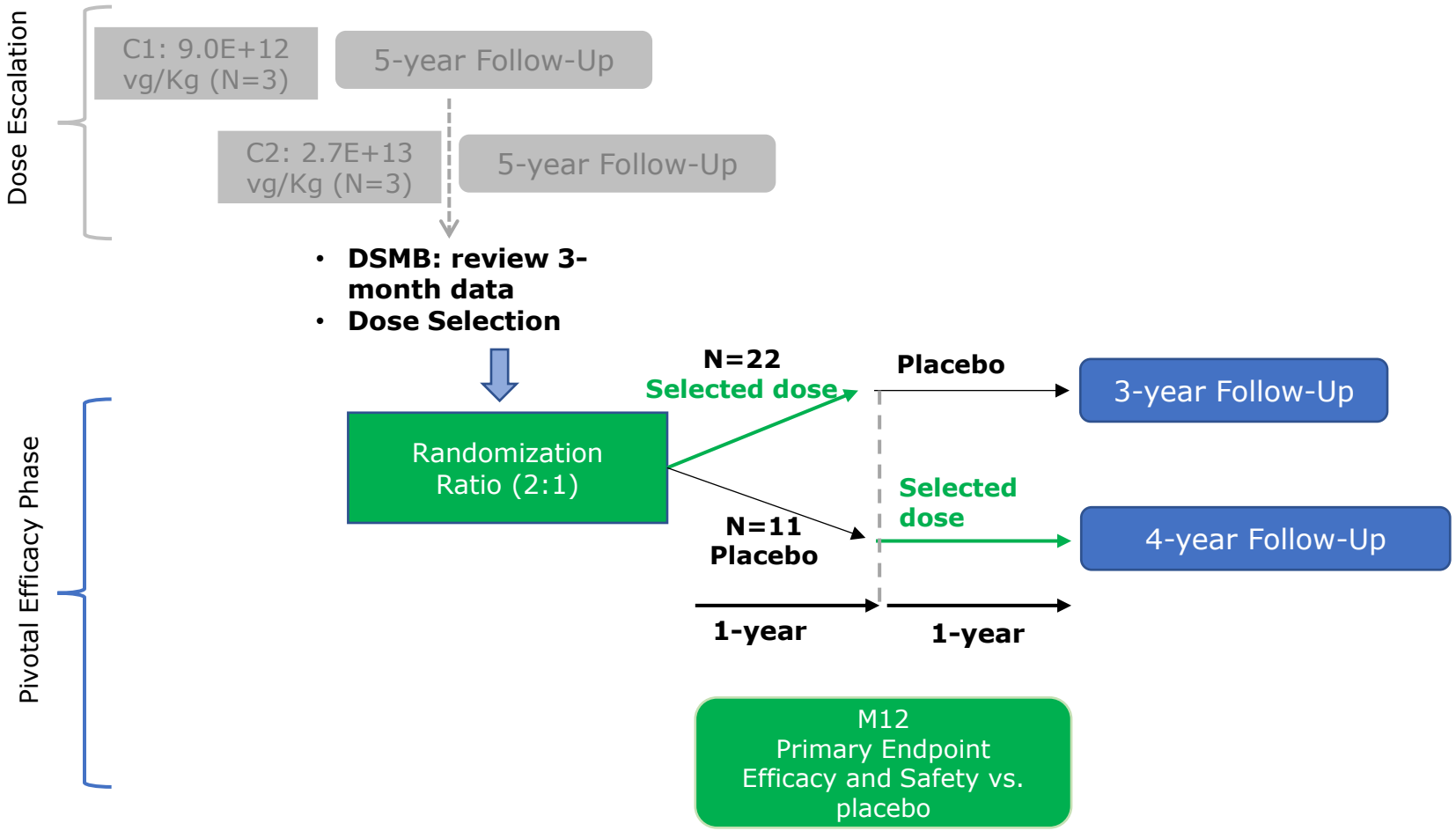
Confirmed Satisfactory Safety Profile

- **Satisfactory long-term safety in first three patients (24-, 18- and 12-month follow-up, respectively)**
  - No SAE observed in patients
  - Most frequent AEs related to corticosteroid treatment (nausea, vomiting, palpitations)
  - Mild to moderate and asymptomatic transaminase increases (up to 5x ULN or baseline)
    - End of corticosteroid tapering period
    - Well-controlled with IS treatment
  - Cardiac biomarkers are encouraging, including a marked decrease in pro-BNP for patient 2, which was 3x upper limit of normal at baseline due to history of cardiomyopathy

Based on one-month safety data of first cohort, DSMB considered the study could continue as planned per protocol, with the dosing of the 2nd cohort (2.7E13 vg/Kg dose)

- **Second cohort fully enrolled (6-, 3-, 1-month follow-up, respectively)**
  - No SAE observed in patients
  - Similar safety profile as cohort 1, except trend to earlier transaminase increase

Next Steps: Pivotal phase of ATA-001-FKRP Study



Homogeneous treated population

- 40% <FVC <80% and NSAD <40

Key endpoints

- Primary Endpoint: Combined FVC and NSAD change at Year 1 (O'Brien approach)
- Key secondary endpoints: 10MWT, TUG, % fat repartition (muscle MRI), QoL questionnaires
- Biomarkers

Thank You

Clinical Sites

Pr. John Vissing and site personnel (Copenhagen)

Dr Tanya Stojkovic and site personnel (Paris)

Pr. Volker Straub and site personnel (Newcastle)

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