Design, baseline characteristics, and 6-12 months follow-up from a LGMDR9 natural history study

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INTRODUCTION

- FKRP-related LGMDR9 is an autosomal recessive limb-girdle muscular dystrophy, a class of genetic muscle diseases characterized by progressive weakness predominantly in proximal limb muscles.
- LGMDR9 is highly variable in presentation, as patients can either present a severe weakness with rapid deterioration and loss of ambulation in their teens or a later onset with milder disease evolution. The average age at diagnosis is 30 years.
- Patients with LGMDR9 are prone to respiratory involvement and dilated cardiomyopathy.
- Some ambulant patients may require non-invasive ventilation (NIV) with the earliest sign of involvement being diaphragmatic and a drop in their forced vital capacity (FVC).
- To reinforce published data on the natural history of LGMDR9 and expand the geographic outreach, Genethon launched a natural history study (NHS) in three European countries (NCT03842878), which will function as a non-concurrent control group for the gene therapy trial (NCT05224505) sponsored by Atamyo.
- Atamyo coordinated discussions with experts ensuring that the selection of parameters measured in the NHS and the gene therapy trial are robust and clinically meaningful.

METHODS

- Fifty-two ambulant patients have been enrolled in this NHS study from Denmark, France, and the UK.
- Nearly half of patients were assessed at baseline, 6 months and 1 year (n=33) and 6 patients have completed the study.
- The study is planned to follow all patients for up to 2 years.
- The change from baseline in muscular function is measured using the NSAD, 10-meter walk test, timed up and go (TUG).
- The change from baseline in respiratory function is measured by the Forced Vital Capacity (FVC). Cardiac and muscle MRI are performed yearly (see poster 330).
- Mean age at enrolment was 37.6 years (range, 16 to 75). Mean age at diagnosis was 29.8 years (range, 4 to 69).

RESULTS

- Majority of patients were homozygous for the common mutation L276I (46/52).
- Baseline data showed a mean sitting forced vital capacity (FVC) of 74.2% (range, 24 to 103%) with mean 10-meter walk/run test of 10.70 sec (range, 2.2 to 30 sec) and a mean NSAD score at 30.5 (range, 3 to 54).
- Among the population enrolled in the NHS, 34 patients met the future gene therapy trial inclusion criteria of sitting FVC between 40-80% at baseline and 10MWT performed in less than 13 sec.
- This subgroup was slightly older (mean age 39.6 years) with mean sitting FVC of 65% and mean NSAD score of 25.2 at baseline.
- This subgroup with moderate phenotype may serve as non-concurrent comparative group for the up-coming gene therapy trial.

Genetic and Demographic Data

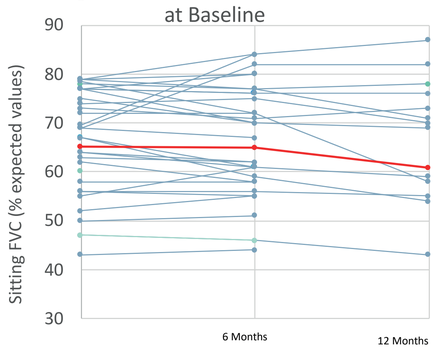
	FVC < 80%	FVC ≥ 80%	Total
n	34	18	52
Male	12	4	16
Female	22	14	36
Mean Height (cm)	170	169.1	169.7
Mean Weight (Kg)	69	72.9	70.4
Mean age at Diag	28.6	26.1	27.8
Mean time since Diag	11.4	8.2	10.3
% homozy L276I	85%	90%	88%

Sitting FVC Data (% of Expected Values)

Aggregated data

Sitting FVC (%)	FVC < 80% at baseline	FVC ≥ 80% at baseline	Total
Bsl (mean)	65.06	91.33	74.16
6M (mean)	64.91	88.38	72.73
12M (mean)	60.84	87.08	71.17
Chg from bsl	-3.28	-3.45	-3.34
% chg at 12M	-5.08%	-3.89%	-4.61

Percent decrease from baseline at 12M in FVC is higher in the subgroup of patients with FVC < 80% at baseline



Muscular Function Data

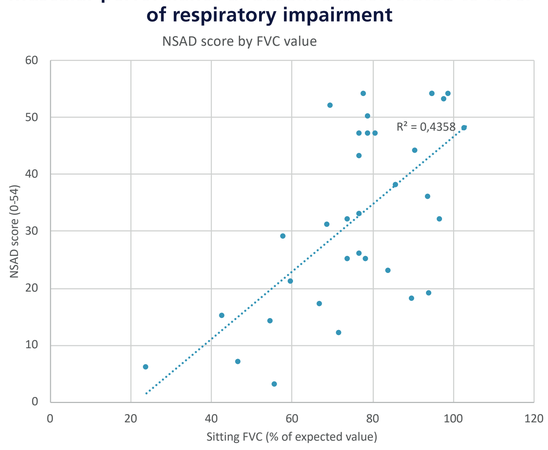
NSAD	FVC < 80%	FVC ≥ 80%	Total
Baseline (n=52)	25.2	40.4	30.5
6M (n=49)	24.7	41.1	30.3
12M (n=33)	24	42.2	31.1
% chg at 12M	-13.4%	0.6%	-7.9%

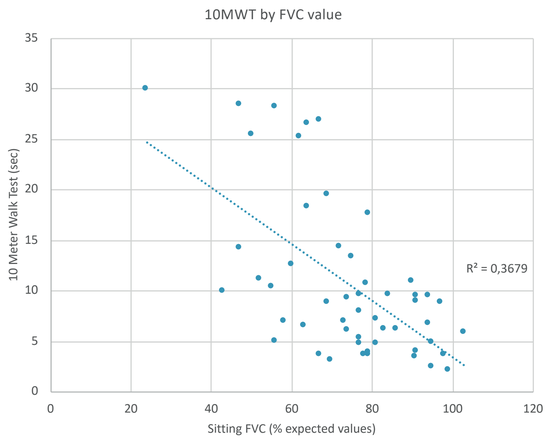
Subgroup with FVC < 80% at baseline performed more poorly than overall population in muscular function tests (with lower NSAD score and greater time to complete the 10MWT
Progression of disease is more pronounced in the subgroup with FVC < 80% at baseline, as evidenced by greater percent change from baseline in NSAD score and 10MWT over one year follow-up

10MWT	FVC < 80%	FVC ≥ 80%	Total
avg time bsl	12.95	6.46	10.7
avg time 6M	20.08	6.02	15.3
avg time 12M	17.34	6.12	12.31
% chg at 12M	26.1%	-4.9%	12.2%

Correlation between FVC and Muscular Performance

Muscular performance at baseline is correlated to level of respiratory impairment





DISCUSSION

- GNT-015-FKRP is a prospective natural history study in patients with LGMD R9/2i.
- 52 patients were enrolled in DK, UK, and FR with 6-monthly assessment of respiratory and muscular functions. As of 31/07/2022, 33 patients have completed the 12M visit.
- Screening patients based on FVC at baseline allows selection of population with moderate to severe phenotype with more rapid progression compared to overall population.

CONCLUSION

- Atamyo/Genethon NHS in LGMD R9 constitutes a large prospective cohort assessed every 6 months with validated muscular, respiratory, and cardiac endpoints over 2 years.
- One-year data demonstrated a high correlation between respiratory involvement and muscular performance.
- Progression of disease is more pronounced in the subgroup with respiratory impairment.
- The 2-year data from the NHS may serve as non-concurrent comparative group for the up-coming gene therapy trial with GNT-0006 (AAV9-FKRP).