efgartigimod Prevents Necrosis And Allows For Muscle Fiber Regeneration In A Humanized Mouse Model Of Immune-Mediated Necrotizing Myopathy

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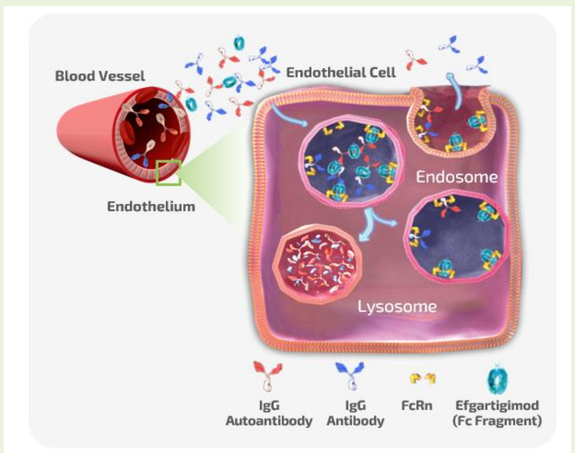
BACKGROUND

Immune-Mediated Necrotizing Myopathy (IMNM)

- IMNM is a severe form of myositis characterized by muscle weakness and elevated creatine kinase levels in serum
- Most IMNM patients have immunoglobulin G (IgG) autoantibodies directed against signal recognition particle (SRP) or hydroxy-3-methylglutaryl-CoA reductase (HMGCR)[1]
- Anti-HMGCR and anti-SRP IgGs are pathogenic and induce disease after adoptive transfer to mice by two separate mechanisms:
  1. myolysis following complement activation[2]; and
  2. impairment of muscle fiber regeneration[3]

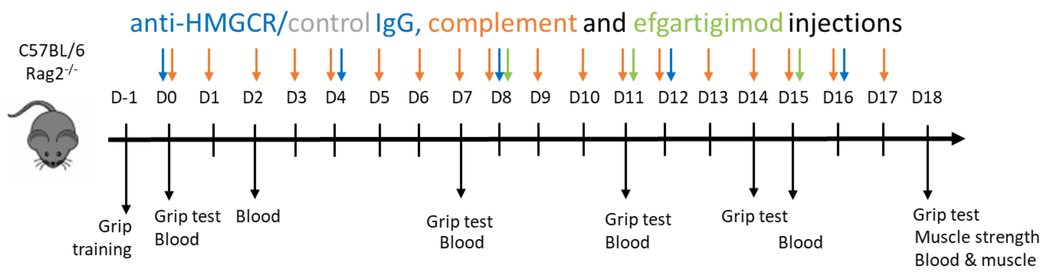
EFGARTIGIMOD: AN FcRn INHIBITOR[4-6]



FcRn, neonatal Fc receptor; IgG, immunoglobulin G.
Image adapted from Kang TH, Jung ST. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med.* 2019;51:1–9 and distributed under the terms of the Creative Commons CC-BY license (https://creativecommons.org/licenses/by/4.0/).

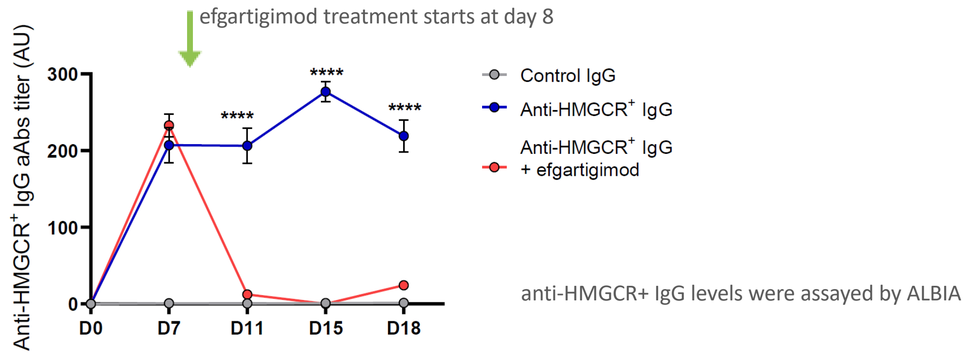
- The neonatal Fc receptor (FcRn) recycles IgG, extending its half-life and serum concentration[4]
- **efgartigimod is a human IgG1 Fc fragment, a natural ligand of FcRn,** engineered for increased affinity for FcRn[5]
- efgartigimod was designed to outcompete endogenous IgG, preventing recycling and **promoting lysosomal degradation of IgG**, without impacting its production[5-6]:
  - Targeted reduction of all IgG subtypes
  - No impact on IgM or IgA
  - No reduction in albumin levels
  - No increase in cholesterol
- efgartigimod is approved for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive in the US, as an add-on to standard therapy in adult patients with gMG who are AChR antibody positive in the EU, and for adult patients with gMG regardless of antibody status in Japan.

IMNM MODEL: PASSIVE TRANSFER OF PATHOGENIC IgGs



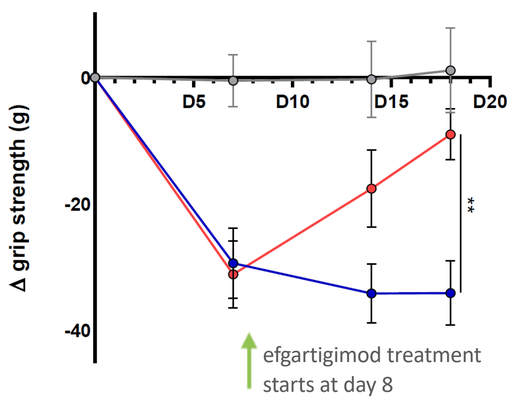
- 2 mg of IgG purified from a healthy volunteer or an anti-HMGCR+ IMNM patient were injected to Rag2$^{-/-}$ mice
- Mice were supplemented with fresh complement-active IgG-depleted human serum
- Treatment with efgartigimod started on day 8. This is after onset of disease, as assessed on day 7

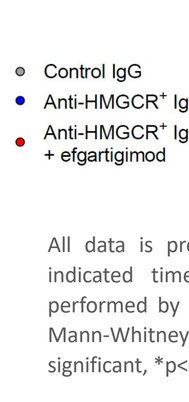
EFGARTIGIMOD REDUCES PATHOGENIC ANTI-HMGCR IgGs



anti-HMGCR+ IgG levels were assayed by ALBIA

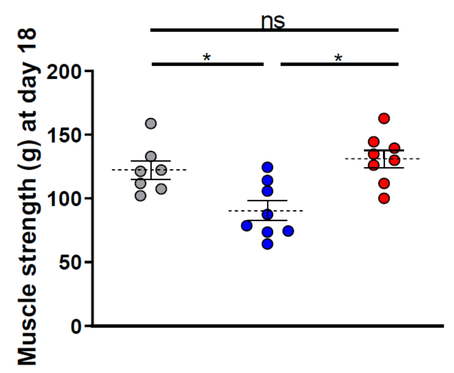
EFGARTIGIMOD RESTORES GRIP STRENGTH





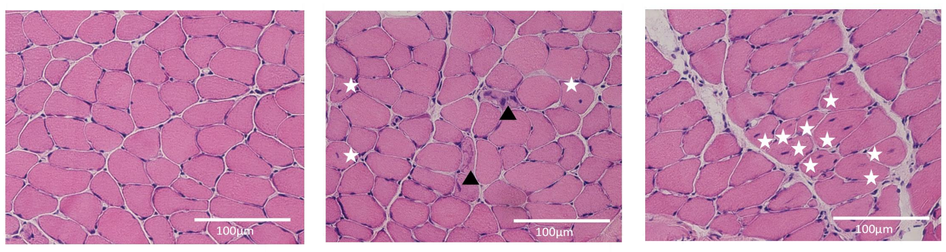
All data is presented as mean ± SEM for the indicated time points; statistical analysis was performed by two-way ANOVA (grip strength) or Mann-Whitney two-tailed test (others) ns: non-significant, *p<0.05, **p<0.01, ****p<0.0001

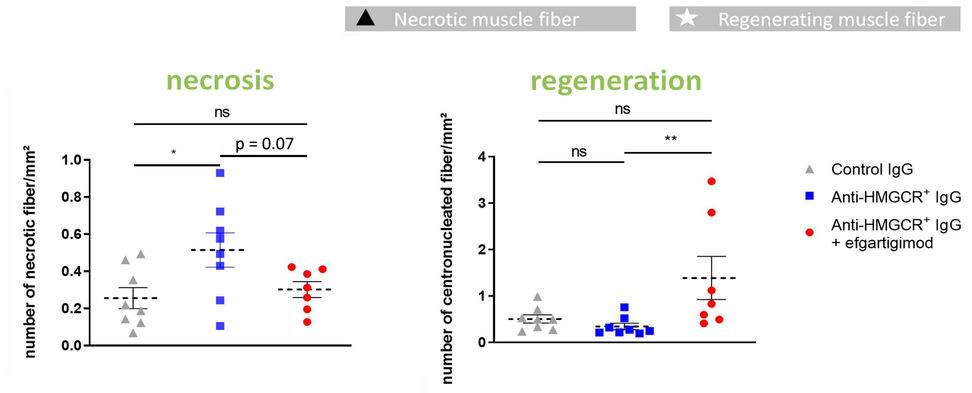
EFGARTIGIMOD RESTORES MUSCLE STRENGTH



Muscle strength: muscle contraction force was measured by in situ muscle contraction upon sciatic nerve electrostimulation on anesthetized mice.

EFGARTIGIMOD ALLOWS REGENERATION OF MUSCLE FIBER



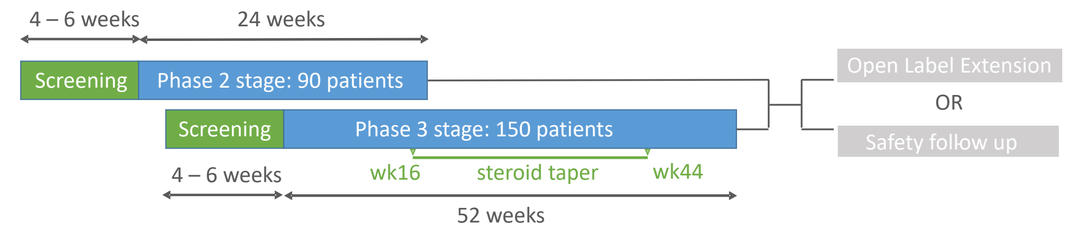


H&E staining showing necrotic and regenerating muscle fibers. Cells with central nuclei are markers of muscle fiber regeneration. Quantification of necrotic and regenerating muscle fibers.

EFGARTIGIMOD PH20 SC RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED TRIAL IN IIM

NCT05523167

Standard of care + weekly 1000 mg efgartigimod PH20 (hyaluronidase) subcutaneously or placebo (1:1, double blinded)
visit frequency: every 4 weeks



Diagnosis IIM
2017 ACR/EULAR criteria
Adjudication committee

Muscle weakness
MMT8 score of < 142/150

Active disease
Enzymes, ECG, MRI, rash, CDASI

Stratification
- **Subtype**
  - Dermatomyositis
  - Polymyositis (incl. Anti-Synthetase Syndrome)
  - IMNM
- **MDGA**
  - severe (MDGA ≥5)
  - non-severe (MDGA <5)

Total Improvement Score (TIS)
- MMT8
- Extramuscular
- Enzymes
- MDGA
- PGA
- HAQ-DI

Phase 2: data unblinded for analysis after ph2 LPLV and used for confirming the design of the Phase 3 stage prior to FPLV in the Phase 3

CONCLUSIONS

- efgartigimod results in an early reduction of pathogenic anti-HMGCR IgG antibodies in a humanized mouse model of IMNM[7]
- efgartigimod prevents further necrosis and allows muscle fiber regeneration, resulting in regain of muscle performance in a humanized mouse model of IMNM[7]
- These preclinical research results support investigating the therapeutic efficacy of efgartigimod through a clinical trial in patients with IIM (idiopathic inflammatory myopathies)

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OBe[3]: Research grants: Sanofi and AFM