ASP3819
NON-CONFIDENTIAL SUMMARY

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ASP3819 SUMMARY

Items	Note
Product name	ASP3819
Mechanism of Action	Triple inhibition of ActRIIA, ActRIIB and Fn14
Modality	Engineered antibody (VHH armed IgG)
Target Indication at Astellas	Sporadic inclusion body myositis
Latest development phase	Preclinical stage

MECHANISM OF ACTION

- ✓ The myostatin/activin-ActRII pathway is involved in catabolic reactions in protein homeostasis in the skeletal muscle. Therefore, its inhibition tilts the protein homeostatic balance toward an anabolic state.
- ✓ TWEAK-Fn14 pathway is activated in various pathological condition and induces muscle atrophy via multiple downstream signals and its inhibition prevents the muscle atrophy.
- ✓ Simultaneous inhibition of myostatin/activin-ActRII and TWEAK-Fn14 pathways is expected to induce stronger anti-atrophy effect than single pathway inhibition when these two pathways are involved in muscle atrophy.

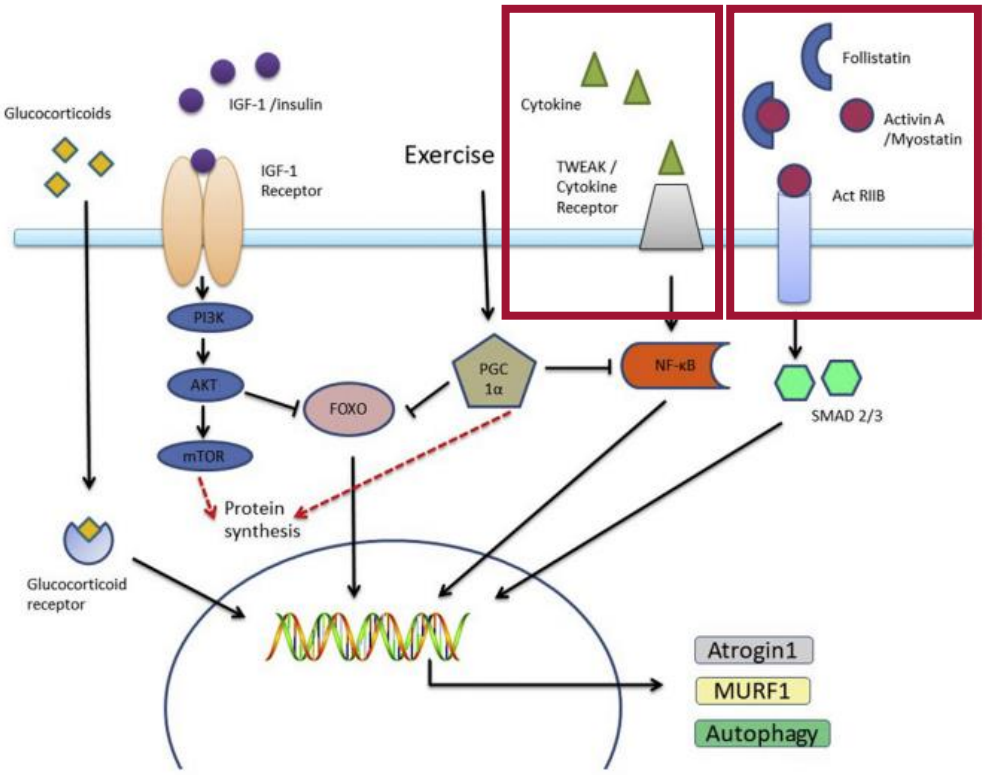

Fig. 1. Main intracellular pathways in muscle wasting.

Clinical Nutrition 2021;40:27-37 (modified)

ActR: Activin receptor
TWEAK: tumour necrosis factor (TNF)-like weak inducer of apoptosis
Fn14: Fibroblast growth factor-inducible 14

PRECLINICAL SUMMARY

Pharmacology

- ✓ ASP3819 showed the comparable ActRIIA and ActRIIB inhibitory effect to the reference antibody, Bimagrumab (anti-ActRIIA and B antibody, Novartis).
- ✓ ASP3819 showed strong Fn14 inhibitory effect without agonistic effect.
- ✓ Mouse surrogate antibody of ASP3819 showed stronger atrophy inhibition and grip strength amelioration than mouse surrogate antibody of Bimagrumab in steroid-induced myopathy model mice.

ADME

- ✓ In exploratory PK study in cynomolgus monkeys, ASP3819 exhibited a dose-dependent increase in exposure over the dose range of 3 to 30 mg/kg. All animals examined were positive for anti-ASP3819 antibodies on day 7 or later.
- ✓ Analytical method for GLP TOX study and clinical trials are yet to be validated.

Toxicity

- ✓ No GLP TOX study has been conducted yet.
- ✓ No concern has been observed in 2-times dosing non-GLP TOX study using rats and cynomolgus monkeys.
- ✓ In preliminary tissue cross reactivity study, membrane binding with ASP3819 was observed in various epithelial cell types, consistent with ActRIIA, ActRIIB and Fn14 expression.
- ✓ ASP3819 showed immunomodulatory effect in KLH prescreen assay.

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INTELLECTUAL PROPERTY

Patent covering ASP3819

- WO2022153997 (filed on 21.07.2022)