

# THE CLINICAL VALUE OF MUSCLE-TARGETED ORAL NUTRITIONAL SUPPLEMENTS CONTAINING ACTISYN™

## Evidence Overview

**ActiSyn™**: a unique combination of specific nutrients (100% whey protein, leucine, vitamin D) **designed to stimulate muscle protein synthesis (MPS)**<sup>1-4</sup>



### 100% WHEY PROTEIN

A high-quality protein: rich in essential amino acids and especially rich in leucine<sup>5</sup>

A "fast" protein: its fast digestion results in high and rapid bioavailability of amino acids for the muscle, which is associated with increased MPS<sup>5,6</sup>

### VITAMIN D

Vitamin D sensitizes the muscle anabolic response to leucine, thereby facilitating MPS<sup>7,8</sup>

### LEUCINE

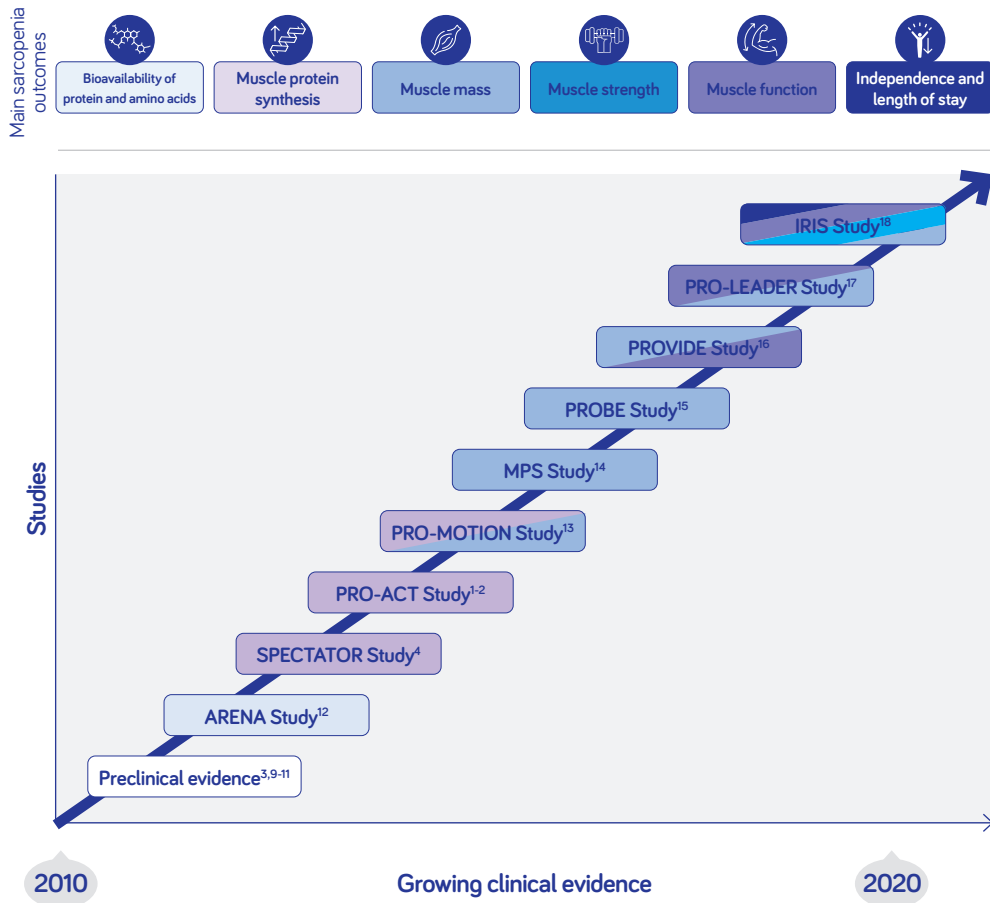
An essential amino acid that is a powerful activator of MPS<sup>9</sup>

Underpinned by preclinical evidence on the efficacy of whey protein, leucine and vitamin D on muscle growth<sup>5-8</sup> ActiSyn™ was conceptualized and trademarked\* by Danone Nutricia in 2012. ActiSyn™ has since been incorporated into Nutricia's range of Muscle-Targeted ONS (MT-ONS). Over the last decade, the clinical efficacy of MT-ONS with ActiSyn™ has been examined, creating an extensive evidence base.

\*ActiSyn™ is a registered trademark according to the European Union Intellectual Property Office (EUIPO).



# Evidence supporting and demonstrating efficacy of MT-ONS with ActiSyn™\*



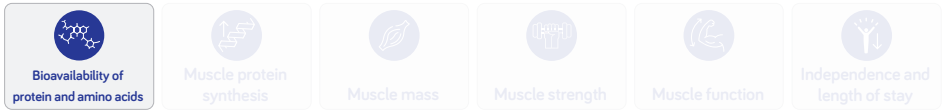
In this material, MT-ONS with ActiSyn™ (unless otherwise specified) is referring to a product currently known as FortiFit®. The branding of this product can differ per country. See the overview at the end of this document to view the full MT-ONS with ActiSyn™ range.

\*This document includes randomized controlled trials (RCTs) which investigate the concept of MT-ONS with ActiSyn™ on the mode of action of muscle building, as well as RCTs which investigate MT-ONS with ActiSyn™ in relevant patient populations in key clinical settings where MT-ONS is indicated (for example: patients with sarcopenia\*\*, (neuro)rehabilitation patients, and (diabetic) obese older adults.

\*\*Sarcopenia defined by EWGSOP(2) or at least two of the diagnostic criteria included in the EWGSOP(2)<sup>19</sup>



Scan here for narrative review by Dr. Emanuele Cereda to learn more on the evidence to date on ActiSyn™ and to learn why it should be considered as first-line nutritional support for sarcopenia



Relevant abbreviations:

EAA: essential amino acids, AA: amino acids

Community Setting

HEALTHY OLDER ADULTS

**ARENA Study<sup>12</sup>** (Luiking YC, et al. Clin Nutr 2016;35:48-58)

**Aim:** Assess the effects of protein source (leucine-enriched whey vs. casein) and energy density (150kcal/serving vs 320 kcal/serving) on bioavailability of AA for the muscle in various ONS\*

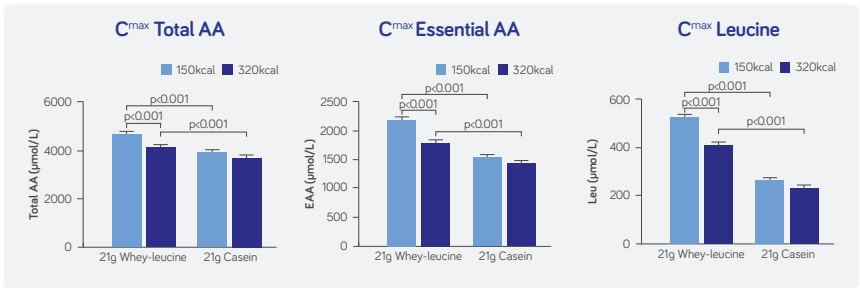
**Study design:** RCT; single blind, cross-over

**Study population:** Healthy older subjects with normal weight or slight overweight (mean BMI 26.0), mean age 67.4y (N=12)

**Primary outcome:** Maximum serum leucine concentration (Leu C<sup>max</sup>) [µmol/L]

**Results:**

- The leucine-enriched whey protein ONS led to significantly higher maximum serum leucine concentrations, as well as significantly higher peak EAA and total AA (secondary outcomes) compared to casein protein ONS across both energy densities
- The maximum concentrations of serum leucine, EAA and total AA were higher in the low-caloric vs. high-caloric ONS. The leucine-enriched whey protein ONS (W150 and W320) had greater bioavailability of AA than casein protein ONS (C150 and C320)



**Conclusions:**

The leucine-enriched, whey protein ONS had greater bioavailability of amino acids than the casein protein-based ONS at both energy densities (150kcal/serving and 320kcal/serving)

The lower energy density (150 kcal/serving) ONS had higher bioavailability of amino acids compared to the higher energy density (320 kcal/serving) ONS in this healthy older adult population

\*Study products: All products contained 20,7 g protein/serving (iso-nitrogenous) **A:** Whey/leucine, 150kcal/serving **B:** Casein, 150 kcal/serving **C:** Casein, 320 kcal/serving **D:** Whey/leucine, 320 kcal/serving



Bioavailability of protein and amino acids



Muscle protein synthesis



Muscle mass



Muscle strength



Muscle function



Independence and length of stay

Relevant abbreviations:

MPS: muscle protein synthesis

Community Setting

### SPECTATOR study<sup>4</sup> (Luiking YC, et al. Nutr. J. 2014;13:9)

**Aim:** Assess the effect of leucine-enriched whey protein ONS\* on MPS vs. isocaloric, milk-like isocaloric ONS\*\*

**Study design:** RCT; double-blind

**Study population:** Healthy older adults, mean age 69y (N=20)

**Primary outcomes:** MPS rate

#### Results:

- Supplementation with leucine-enriched whey protein ONS significantly increased MPS compared to milk-like isocaloric control



#### Conclusions:

Leucine-enriched whey protein ONS resulted in higher MPS than isocaloric, milk-like control ONS in healthy older subjects

\*Leucine-enriched whey protein ONS supplement: 20g whey protein, 3 g leucine, 150kcal. \*\*Milk-like control supplement: 6g protein/serving (20% whey, 80% casein), 150kcal

HEALTHY OLDER ADULTS

PATIENTS WITH SARCOPENIA

### PRO-ACT study<sup>1-2</sup> (Kramer IF, et al. J Clin Endocrinol Metab 2015;100:4124-32; Kramer IF, et al. Clin Nutr. 2017;36:1440-9)

**Aim:** Assess the effect of MT-ONS with ActiSyn™ compared to an isocaloric control and an iso-nitrogenous control on MPS in healthy older men following bolus intake; and to assess the effect of MT-ONS with ActiSyn™ on MPS in older male patients with sarcopenia compared to healthy older men

**Study design:** RCT, double blind study (healthy older adults) and single arm study (patients with sarcopenia)

**Study population:** Healthy older males, mean age 69y (N=45) and older male patients at risk or with sarcopenia, mean age 81y (N=15)

**Primary outcomes:** MPS rate

#### Results:

- MT-ONS with ActiSyn™ significantly increased MPS compared to baseline and compared to the isocaloric control, and the isonitrogenous control significantly increased MPS compared to baseline
- MT-ONS with ActiSyn™ significantly stimulated MPS in older male patients with sarcopenia, and to a similar extent as in healthy older adults



#### Conclusions:

MT-ONS with ActiSyn™ intake resulted in higher MPS than iso-caloric control in healthy older adults, and MT-ONS with ActiSyn™ intake similarly increased MPS in sarcopenic and healthy older adults



Bioavailability of protein and amino acids



Muscle protein synthesis



Muscle mass



Muscle strength



Muscle function



Independence and length of stay

Relevant abbreviations:  
MPS: muscle protein synthesis

### PRO-MOTION Study<sup>13</sup> (Chanet A, et al. J Nutr. 2017;147:2262-1)

**Aim:** Assess the acute and long-term effects of MT-ONS with ActiSyn™ supplementation (in addition to breakfast) compared to placebo\* on MPS and muscle mass, respectively

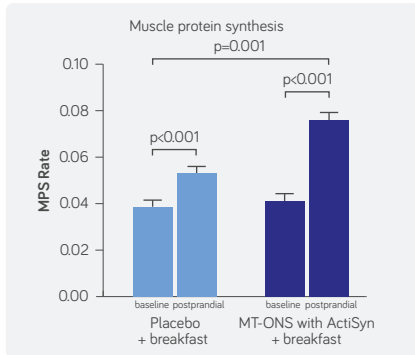
**Study design:** RCT; double-blind, acute and 6 week intervention

**Study population:** Healthy older males, mean age 70y (N=24)

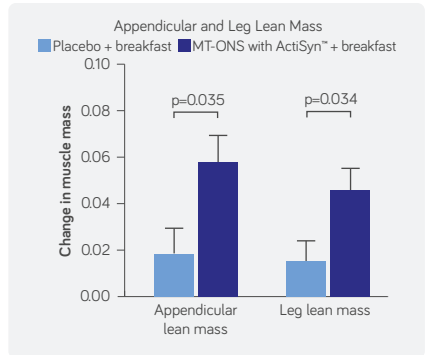
**Primary outcome:** MPS rate

#### Results:

- Acute effects: MT-ONS with ActiSyn™ supplementation (in addition to breakfast) led to significantly greater increase in MPS rate compared to supplementation with placebo (in addition to breakfast)
- Long-term effects: 6-week supplementation of MT-ONS with ActiSyn™ led to significant increases in appendicular lean mass and leg lean mass (secondary outcomes)



**Figure 1. Acute effect**  
MT-ONS with ActiSyn™ in addition to breakfast significantly stimulated MPS.  
\*non-caloric control



**Figure 2. Long term effect**  
6-week intake of MT-ONS with ActiSyn™ significantly increased appendicular lean mass. This is largely due to increased leg lean mass.



#### Conclusions:

MT-ONS with ActiSyn™ supplementation (in addition to breakfast) more effectively stimulated MPS compared to placebo (non-caloric control) and increased muscle mass after 6-week intervention in healthy older adults



Bioavailability of protein and amino acids



Muscle protein synthesis



Muscle mass



Muscle strength



Muscle function



Independence and length of stay

Relevant abbreviations: :

AMM: appendicular muscle mass

### MPS Study<sup>14</sup> (Verreijen AM, et al. Am J Clin Nutr. 2015;101:279-86)

**Aim:** Assess the effects of MT-ONS with ActiSyn™ in combination with resistance exercise training (as part of weight loss program) compared to isocaloric control (combined with resistance exercise training) on preservation of AMM

**Study design:** RCT; double-blind, parallel group, 13-week trial

**Study population:** Obese older adults, mean age 63y (N=80)

**Primary outcome:** AMM

#### Results:

- MT-ONS with ActiSyn™ led to significant improvement in AMM compared to control group receiving isocaloric control



#### Conclusions:

MT-ONS with ActiSyn™ supplementation in combination with resistance exercise training (as part of weight loss program) preserved skeletal muscle mass when compared to isocaloric control in obese older adults

### PROBE Study<sup>15</sup> (Memelink RG, et al. Nutrients. 2020;13:64)

**Aim:** Assess the effects of MT-ONS with ActiSyn™ vs isocaloric control as part of lifestyle intervention (dietary counseling and exercise program of resistance and high-intensity training) on muscle mass and glycemic control

**Study design:** RCT; double-blind, parallel group, 13-week trial

**Study population:** Obese, (pre-)diabetes type II older adults, mean age 66y (N=123)

**Primary outcome:** Leg muscle mass

#### Results:

- Increase in leg muscle mass (primary outcome) in intervention (receiving MT-ONS with ActiSyn™) vs control group was not statistically significant (P=0.060)
- Significant increase in AMM and total lean mass (secondary outcomes) in intervention group (receiving MT-ONS with ActiSyn™) vs control group
- Improvements in fasting plasma glucose between intervention and control group were not statistically significant (P=.936); other measures of glycemic control (fasting plasma insulin, HOMA-IR and Matsuda index) were significantly improved in intervention vs control group



#### Conclusions:

MT-ONS with ActiSyn™ supplementation as part of lifestyle intervention significantly increased muscle mass in obese older adults with (pre-)diabetes type II



Bioavailability of protein and amino acids



Muscle protein synthesis



Muscle mass



Muscle strength



Muscle function



Independence and length of stay

Relevant abbreviations:

SPPB: Short Physical Performance Battery, AMM: Appendicular muscle mass

### PROVIDE Study<sup>16</sup> (Bauer JM et al, J Am Med Dir Assoc. 2015; 16: 740-7)

**Aim:** Assess the efficacy of MT-ONS with ActiSyn™ supplementation vs iso-caloric control on muscle mass, strength and function

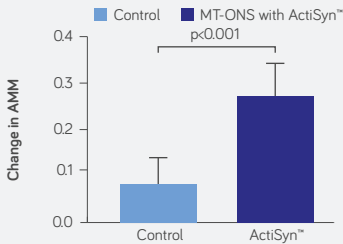
**Study design:** RCT; double blind, 13-week trial

**Study population:** Patients with sarcopenia, mean age 78y (N=380)

**Primary outcome(s):** Handgrip strength (measure of muscle strength), SPPB Performance score (measure of muscle function)

#### Results:

- Significant increase in handgrip strength and SPPB (primary outcome) in intervention group vs baseline but not vs control
- Significant improvement in muscle mass in intervention group (secondary outcome) vs baseline and control group (Figure 1)
- Significant improvement in chair-stand time (as part of SPPB test; individual test was secondary outcome) in intervention group vs baseline and control group (Figure 2)

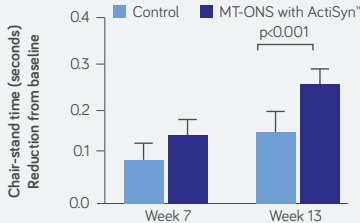


#### Baseline AMM (kg) Mean (SEM)

Control	17.5 (0.30)
MT-ONS with ActiSyn™	17.9 (0.31)

Predicted mean effect size [95% CI]  
0.17 kg [0.01 - 0.34]; p=0.044

Figure 1. Effect on muscle mass



#### Baseline chair-stand time (s) Mean (SEM)

Control	18.4 (0.45)
MT-ONS with ActiSyn™	18.6 (0.39)

Predicted mean effect size [95% CI]  
1.01 sec (0.19, 1.77); p=0.018

Figure 2. Effect on chair stand time test



#### Conclusions:

MT-ONS containing ActiSyn™ significantly improved handgrip and SPPB score (primary outcomes) vs baseline but not vs control group, and led to significant improvements in muscle mass and lower extremity muscle function (secondary outcomes) in older patients with sarcopenia



Bioavailability of protein and amino acids



Muscle protein synthesis



Muscle mass



Muscle strength



Muscle function



Independence and length of stay

Relevant abbreviations:

TUG test: Timed Up and Go Test, PD: Parkinson's Disease

### PRO-LEADER Study<sup>17</sup> (Barichella M, et al. Neurology. 2019;93:e1-e12)

**Aim:** Assess the effects of MT-ONS with ActiSyn™ supplementation (given with standard diet vs no supplementation with standard diet) combined with multidisciplinary intensive rehabilitation treatment (MIRT)\* on muscle mass and function

**Study design:** RCT; parallel group, assessor-blind, 4-week trial

**Study population:** Cognitively intact patients with PD or parkinsonism and undergoing a 30-day MIRT, mean age 67y (N=150)

**Primary outcome:** 6-minute walking test (6MWT) (measure of muscle function)

#### Results:

MT-ONS with ActiSyn™ in combination with MIRT compared to control led to significant improvements in:

- 6MWT
- Walking speed and TUG test (secondary outcomes)
- Preservation of muscle mass (secondary outcomes)



#### Conclusions:

Supplementation of MT-ONS with ActiSyn™ in combination with MIRT improved muscle function and preserves muscle mass in patients with PD or parkinsonism

\*MIRT entailed a multidisciplinary, aerobic, motor-cognitive, intensive, and goal-based rehabilitation treatment with previous proven efficacy in this patient population

### IRIS Study<sup>18</sup> (Rondanelli M, et al. J Cachexia Sarcopenia Muscle. 2020;11:1535-1547)

**Aim:** Assess the effects of MT-ONS with ActiSyn™ supplementation compared to isocaloric control in combination with physical rehabilitation program on muscle mass, strength and function as well as independence and length of stay in rehabilitation

**Study design:** RCT; parallel-group, double-blind, 4-8 week trial (individualized rehabilitation program)

**Study population:** Patients with sarcopenia admitted to in-patient rehabilitation program, mean age=81y (N=140)

**Primary outcome:** Gait speed (measure of muscle function)

#### Results:

MT-ONS with ActiSyn™ supplementation + physical rehabilitation led to significant improvements in:

- Gait speed
- Muscle mass, muscle strength and muscle function (secondary outcomes)
- Independence (secondary outcome) and to an average 10.5-day earlier discharge from rehabilitation



#### Conclusions:

MT-ONS with ActiSyn™ in combination with exercise intervention (compared to isocaloric control combined with exercise intervention) resulted in significant improvements in muscle mass, strength, function, as well as independence and reduced length of stay in rehabilitation in patients with sarcopenia



## SUMMARY OF THE CLINICAL VALUE OF MT-ONS CONTAINING ACTISYN™

### Muscle-Targeted ONS with ActiSyn™ results in:

Increase in muscle protein synthesis in healthy<sup>1,2,13</sup> older adults and in patients with sarcopenia<sup>2</sup>



Improvement in muscle mass in healthy older adults<sup>13</sup>



Improvement in muscle mass and function (secondary outcome measures) in patients with sarcopenic<sup>16</sup>



### Muscle-Targeted ONS with ActiSyn™ combined with physical exercise results in:

Improvement in muscle mass in obese older adults<sup>14</sup>, in type II diabetes older adults<sup>15</sup>, in patients with Parkinson's Disease<sup>17</sup> and patients with sarcopenia in rehabilitation<sup>18</sup>



Improvement in muscle strength in patients with sarcopenia in rehabilitation<sup>18</sup>



Improvement in muscle function in patients with parkinsonism or Parkinson's Disease<sup>17</sup> and in patients with sarcopenia in rehabilitation<sup>18</sup>



Improvement in independence and significant reduction in rehabilitation time and 10.5 days earlier discharge from rehabilitation in patients with sarcopenia undergoing rehabilitation<sup>18</sup>



Consumption of MT-ONS with ActiSyn™ is demonstrated as safe and tolerable over a 6-month period<sup>20</sup>

## Nutricia Range of Muscle-Targeted ONS (MT-ONS) containing ActiSyn™

		FortiFit®	Fortimel® Advanced
Per serving	Volume	150mL (40 g powder + 125mL water)	200mL
	Protein	21 g protein	
	ActiSyn™	100% whey protein 3 g leucine in total	
		800 IU/20 µg vitamin D	400 IU/10 µg vitamin D
	Energy	150 kcal/serving	300 kcal/serving
	Usage	Supplement	Suitable as a Sole Source of Nutrition

The branding of these products can differ per country.

## References

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