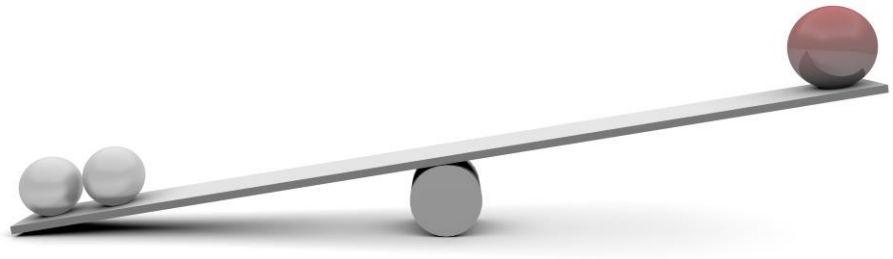
AMPK activator O304



Aimed for Energy Imbalance Disorders

This project has received funding from the European Union´s Horizon 2020 research and innovation programme under grant agreement No 754268

Betagenon

AMP-activated protein kinase (AMPK)

- ***Sensor and Regulator of Energy Balance***

- ***Activated by reduced energy charge***

  * ***Caloric restriction and/or***
  * ***Physical activity***

Activated AMPK;

* Increases glucose and lipid metabolism in multiple organs/tissues
* Improves cardiac function and peripheral blood flow to supply nutrients
* Acts in the hypothalamus to stimulate food intake

⇒ ***Restores energy charge***

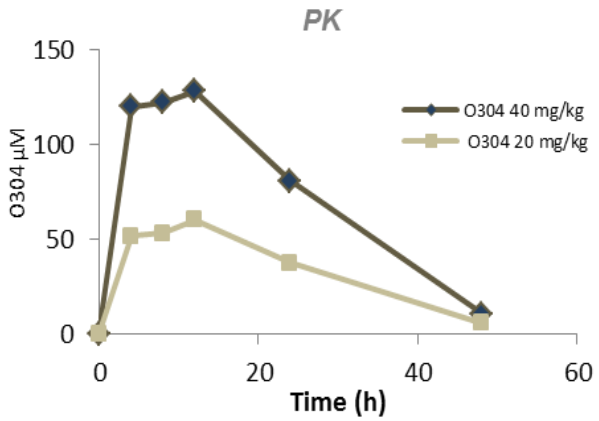
⇒ ***Selective activation of AMPK outside the brain is a promising approach to prevent/cure obesity, T2D and CVD***

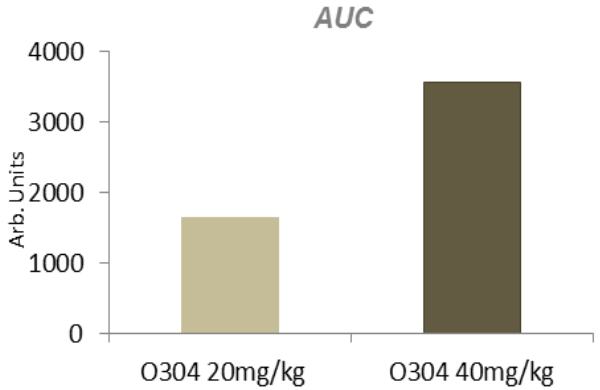
Preclinical studies with AMPK activator O304

O304 activates AMPK by suppressing the dephosphorylation of p-T172 AMPKα without inhibiting PP2C

O304 is orally available

Single dose in rat



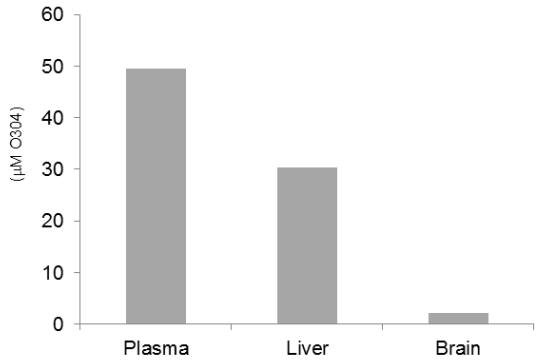


Long t 1/2

O304 does not cross the blood-brain barrier

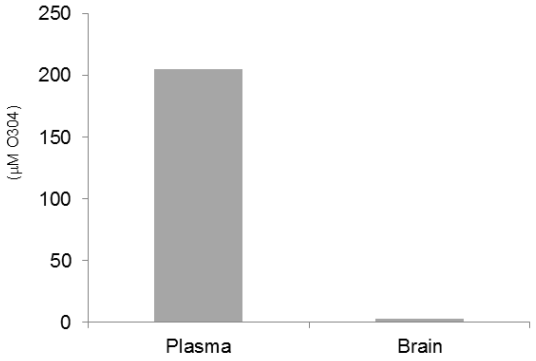
Distribution of O304 in rat

O304 at 40mg/kg/Day for 3 weeks



OnTarget Chemistry
Part of the Recipharm Group

O304 at 200mg/kg/Day for 7 Days



O304 protects against diet-induced hyperglycemia, glucose uptake and insulin resistance

O304 protects against diet-induced obesity and fatty liver

AMPK and Cardiovascular function

Cardiac function

- *Loss of AMPK in cardiomyocytes causes systolic and diastolic dysfunction*
- *AMPK increases $Ca2^{+}$ sensitivity of force development*

Vascular function

- *AMPK activation enhances endothelial cell survival and vasodilation and reduces smooth muscle cell proliferation*

O304 improves Cardiovascular function and increases Endurance

IND-enabling 28-day tox studies of O304 in rat and dog

O304 was well tolerated at all dose levels investigated.

No severe toxicity was observed in 4-week studies up to 700 and 540 mg/kg/day in rats and dogs, and the NOAEL was established at 300 and 180 mg/kg/day, respectively.

Hypoglycemia was not observed at any dose

O304 in the Clinic

Aimed for:

Type 2 Diabetes and Cardiovascular Disease

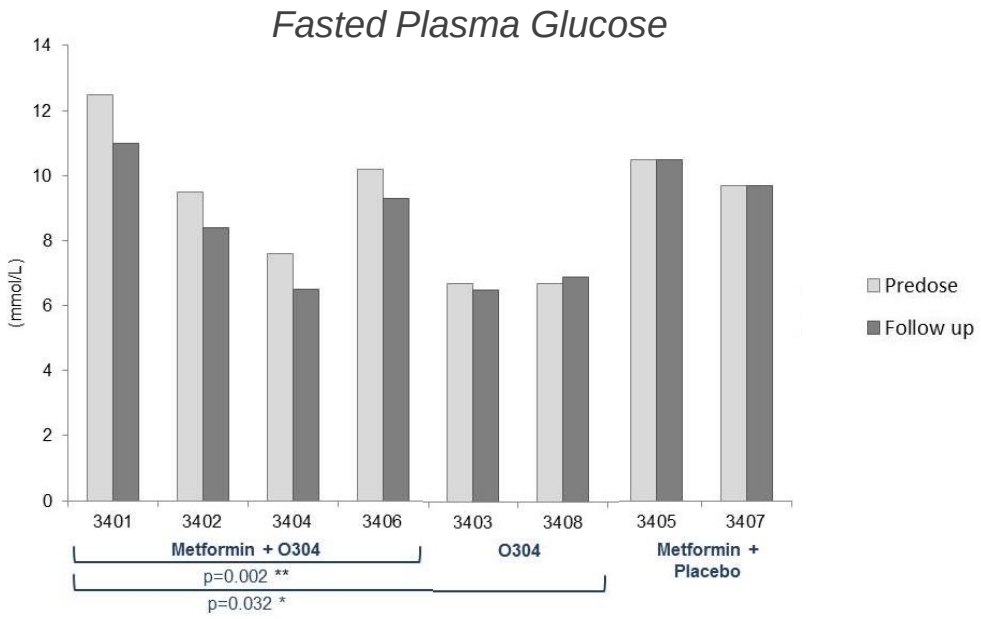
Phase I

O304 is safe and very well tolerated

In young healthy subjects, in middle aged obese subjects, and in type 2 diabetics in combination with Metformin
(Dose range 100-2400 mg/day)

Phase I MAD4 Study (17 days)

O304 reduces significantly fasting plasma glucose in type 2 Diabetics treated with Metformin

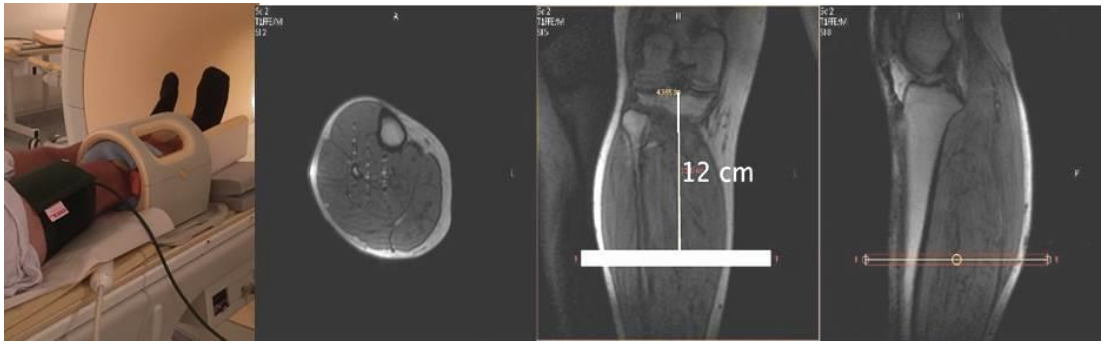


CLINICAL TRIAL CONSULTANTS AB
TRANSLATING SCIENCE INTO TREATMENT

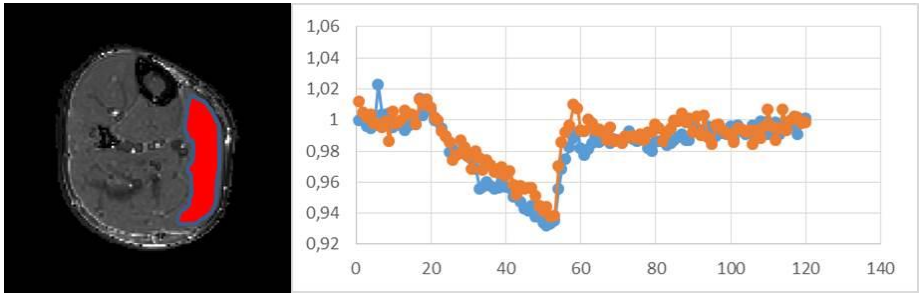
Betagenon

Phase I MAD5 study in middle-aged obese subjects

Setup for monitoring reactive hyperemia in calf muscle by (Microvascular perfusion)



Relative T2* curves for the same patient at baseline (blue) and follow-up (orange)



M. Gastrocnemius

Betagenon

ANTAROS MEDICAL

Linear fit (blue line) of the change in T2 during the hyperemic flow following release of the cuff*

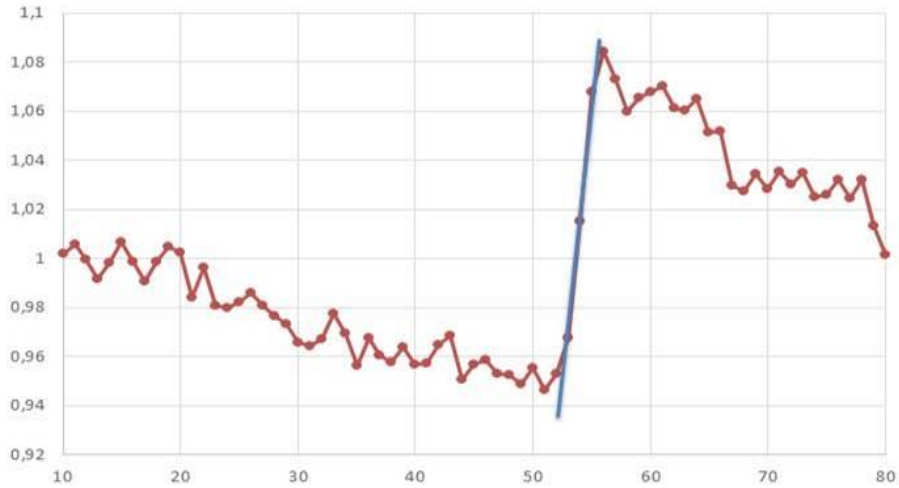


Figure shows the linear fit (blue line) of the change in T2 during the hyperemic flow following release of the cuff around the thigh.*

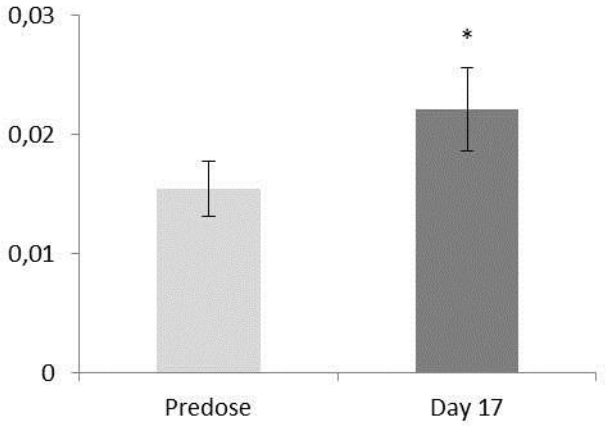
Betagenon

ANTAROS MEDICAL

Compared to baseline, O304 significantly increases the rate of hyperemic perfusion in M. Gastrocnemius

All 8 subjects recived O304

Subject	Slope BL	Slope FU	diff (post-pre)	change from baseline (%)
S1-134	0,0189	0,0269	0,008	29,7
S1-135	0,01	0,0127	0,0027	21,3
S1-136	0,0178	0,0171	-0,0007	-4,1
S1-137	0,0244	0,0332	0,0088	26,5
S1-140	0,0217	0,0393	0,0176	44,8
S1-141	0,0049	0,0161	0,0112	69,6
S1-144	0,0147	0,0178	0,0031	17,4
S1-145	0,0109	0,0136	0,0027	19,9
Average	0,015413	0,022088	0,006675	**28,1**
	p-value (change from baseline)			**0,015**



Relevant for Peripheral arterial disease and Diabetic vascular disease

Betagenon

ANTAROS MEDICAL

Phase IIa in Type 2 Diabetics initiated

STUDY TITLE

Effect on fasting plasma glucose (FPG) of once daily oral administration during 28 days of O304 suspension (1000 mg/day) in subjects with Type 2 Diabetes (T2D)

(**TELLUS**)

A single-centre, randomised, parallel-group, double-blinded, placebo controlled phase IIa study in 66 Type 2 Diabetics on Metformin

Patent covering O304 granted in the US, EU, Japan, China and multiple additional countries