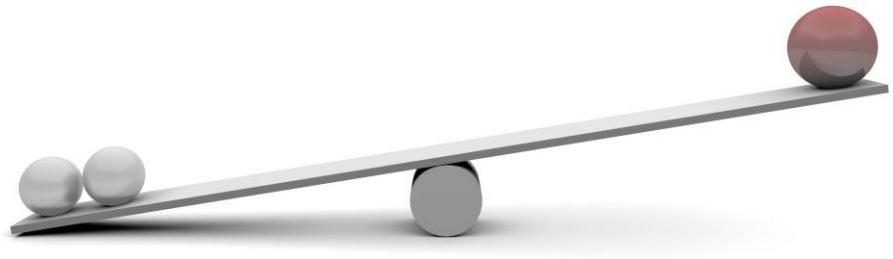
AMPK activator O304



Type 2 Diabetes
Microvascular and Cardiorenal complications

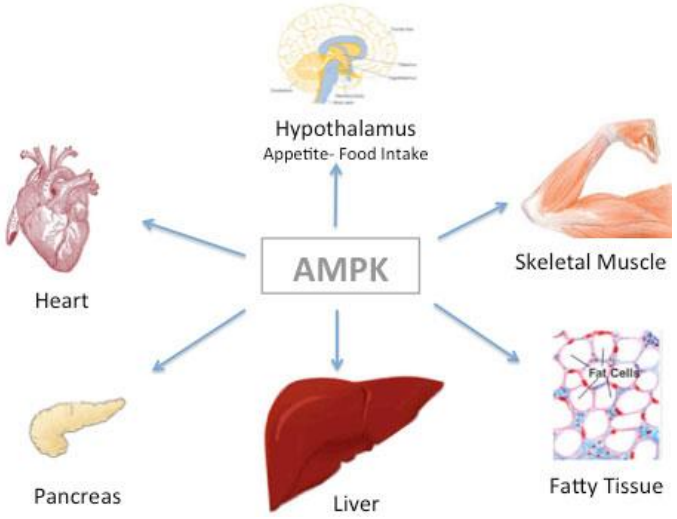
Betagenon

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

AMP activated protein kinase (AMPK)

- Key sensor and regulator of energy balance
- Activated by caloric restriction and/or exercise

Diet



Exercise

Short-term; AMPK phosphorylates over 60 different target proteins which quickly mediates uptake, storage and oxidation of various substrates in metabolically active tissues and organs

Long-term; By rewiring gene expression AMPK imposes long-term beneficial effects on whole body glucose and lipid metabolism

O304 & Prelinical results

O304 mimics the beneficial effects of caloric restriction/exercise on glucose hemostasis

Glucose disposal:

O304: - Increases insulin-independent glucose uptake in myotubes
- Increases glucose uptake in skeletal muscle
- Reduces insulin resistance
- Acts potently in combination with SGLT-2 inhibitors

β-cell function:

O304: - Suppresses the formation of IAPP amyloid in β-cells both in vivo and ex vivo
- Attenuates ER stress/preserves ER function in metabolically stressed islets
- O304 increases Arginine-induced insulin secretion i.e. promotes β-cell rest as; (Arginine stimulation provides an estimate of functional β-cell reserve)
- Suppresses amyloid formation, Reduces β-cell stress and & Promotes β-cell rest

O304 - Unique effects on glucose homeostasis

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O304 mimics the beneficial cardiorenal effects of caloric restriction/exercise

Cardiovascular and microvascular function:

O304: - Activates AMPK, increases stroke volume and reduces glycogen in heart
- Reduces blood pressure
- Improves peripheral microvascular perfusion
- Improves endurance

Renal function:

O304: - Activates AMPK and increases the expression of PGC1α in DIO mice, which show renoprotective effects.

Obesity and fatty liver:

O304: - Increases energy expenditure and reduces obesity and fatty liver
- Prevents adipose tissue inflammation
- The effect on glucose homeostasis is independent of but enhanced by reduction in obesity

Preclinical IND-Safety

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

- O304 was well tolerated
- No severe toxicity was observed up to 700 mpk/day in rat and 540 mpk/day in dog

- **NOAEL in rat was set at the middle dose 300 mpk/day**

  Increased minimal atresia of the tertiary follicles or mild reduction of the numbers of follicles/corpora lutea in the ovary were observed in 4 of 10 females at the high dose 700 mpk/day.

- **NOAEL in dog was set at the middle dose 180 mpk/day**

  At the high dose 540 mg/kg/day slight elevations of urea (less than 2-fold) and LDH (approx. 1.5-fold) were observed in both male and female dogs, which were normalized at the completion of the 14-day recovery period. These variations were regarded as transitory functional changes and were not associated with macroscopic or microscopic findings. There was no effect of treatment noted during urinalysis.

∇ **Long-term toxicology studies in rat and dog**

6 month tox study in rat: NOAEL 600 mpk, the highest dose tested

9 month tox study in dog: → Dosing completed, results pending

O304 & Clinical Studies

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Phase I Studies

SAFETY and Exploratory Efficacy Studies

(Dose range 100-2400 mg/day O304 as suspension)

- Young healthy subjects: **SAD 1-5 and MAD 1-3**

  SAD 1-5: 100-300-600-1200-2400mg/day
  MAD 1-3: (100-1200-2400mg) 5Doses in 17 days

- Type 2 diabetics in combination with Metformin: **MAD4**

  (2400mg) 5Doses in 17 days

- Middle aged obese subjects: **MAD5**

  (800mg/day) for 17 days

No safety issues were identified and O304 was well tolerated in the dose range 100-2400 mg/day

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Phase IIa TELLUS

Proof-of-concept; Safety and Efficacy

Study of O304 in 60 Type 2 Diabetes Patients on Metformin

∇ Inclusion criteria: - HbA1c at screen + MRI examination
- Not FPG at Day 1

∇ O304 at (1000 mg/day as suspension) daily for 28 days

No safety issues were identified and O304 was well tolerated in type 2 diabetics on metformin at 1000 mg/day

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Summary

Clinical Efficacy of O304

O304: ∇ **Reduces FPG and HOMA-IR**

∇ **Increases peripheral microvascular perfusion, assessed by MRI**

∇ **Reduces blood pressure**

∇ **Exerts a rapid, stable and reversible reduction in eGFR**

A combination of beneficial effects not observed
with any currently used T2D drug

Indications: - **O304 suited to mitigate T2D, diabetic kidney disease and peripheral arterial disease**

- Heart failure and Ischemic heart disease?//

Global patent covering O304 and divisional patent for T2D in the US Expires 2030

POTTER CLARKSON
Birmingham

Betagenon