AMPK activator O304

Type 2 Diabetes
Microvascular and Cardiorenal complications

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AMP activated protein kinase (AMPK)
- Key sensor and regulator of energy balance
- Activated by caloric restriction and/or exercise

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

**Exercise**
- By rewiring gene expression AMPK imposes long-term beneficial effects on whole body glucose and lipid metabolism
O304 & Preliminary 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**
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
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
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
Phase IIa TELLUS
Proof-of-concept; Safety and Efficacy

Study of O304 in 60 Type 2 Diabetes Patients on Metformin

- 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
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