

# Development of tricaprilin, a ketogenic drug for Alzheimer's disease

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### **ABSTRACT**

Background: Cerebral glucose hypometabolism in posterior cingulate, parietal, temporal, and prefrontal cortex is an early feature of Alzheimer's disease (AD). Cells in these regions which exhibit a defect in glucose metabolism have been shown to preserve the ability to metabolise ketones. We report on an approach to induce ketosis and treat AD with a new drug formulation of an 8-carbon chain triglyceride, tricaprilin.

Method: Multiple formulations of tricaprilin were developed and tested in vitro. in vivo and in human studies to assess pharmacokinetics, safety and tolerability. The clinical studies were conducted in healthy human Caucasian and Asian volunteers and in a variety of food

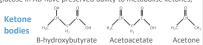
Result: Two new formulations, AC-SD-01 and AC-SD-03 showed desirable PK characteristics, leading to generation of ketones and excellent safety and tolerability, when administered in doses of 20g after a meal, in both Caucasians and Asians.

Conclusion: Formulation AC-SD-03 will be moved forward in drug development with an ascending dose study in healthy elderly subjects and a Phase 3 study in mild to moderate AD.

#### **BACKGROUND**

# Ketones can provide energy deprived cells in AD brains with

- The brain is highly metabolic so any deficiency in its metabolism results in a severe energetic stress and ultimately in cell death
- Normally, the brain relies almost exclusively on glucose as an energy substrate.1
- The brain accounts for only 2% of body weight but.
- Utilizes 25% of total body glucose (~120g /day)
- Receives 15% of cardiac output and uses 20% of total body oxygen
- ....so the body has a highly conserved physiological mechanism to utilize an alternative energy substrate in times of low glucose availability: ketone bodies
- Cerebral glucose hypometabolism is characteristic in AD, is progressive and correlates with cognitive decline.2
- Represents a serious problem for the brain which relies on glucose
- Regional declines in CMRglc occur early in AD.3
- Hypometabolism is most notable in the posterior cingulate, parietal, temporal, and prefrontal cortices - Regional low CMRglc can be detected decades before clinical signs of dementia
- Ketone bodies are the brain's natural back up fuel
- Ketone bodies are normally produced under conditions of low glucose availability, such as ketogenic diets
- Can provide up to 60 percent of one's brain energy needs4
- Cells which do not metabolise glucose in AD have preserved ability to metabolise ketones, the brains favoured fuel.5



Study KET-002-01

#### Cerecin has developed tricaprilin, a pure C8 medium chain triglyceride (MCT), to safely induce ketosis. Efficacy has been shown in two Phase 2 studies.

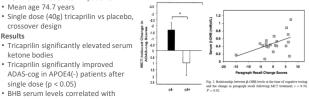
Rapid improvement is likely due to switch in neuronal metabolism to utilize the available

- 20 mild to moderate AD patients
- · Single dose (40g) tricaprilin vs placebo, crossover design

ketone bodies.6

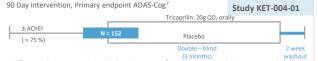
- ketone bodies · Tricaprilin significantly improved
- ADAS-cog in APOE4(-) patients after single dose (p < 0.05)
- · BHB serum levels correlated with improved memory (p < 0.05)

APOE4 non carriers ADAS-Cog scores improve in 90 minutes

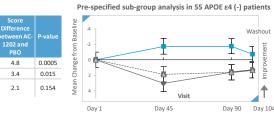


# BACKGROUND

Cerecin has developed tricaprilin, a pure C8 medium chain triglyceride (MCT). to safely induce ketosis. Efficacy has been shown in two Phase 2 studies.



- Difference between active and placebo group of 3.4 points in ADAS-Cog seen at 90 days
- 2 pts or more is generally deemed to be clinically meaningful
- Persistence of effect after washout could indicate potential disease modification



#### METHOD

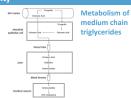
Day 90

Day 104

Washout

Multiple formulations of tricaprilin were developed in order to optimize the balance between ketogenesis and tolerability

Analytical methods were also developed and validated to measure tricaprilin, octanoic acid (OA), the compound that is absorbed from the gut, betahvdroxybutyrate (BHB) and acetoacetate (AcAc)



- Tricaprilin (AC-1202) - Placebo -- Placebo (1 outlier removed

# **METHODS and RESULTS**

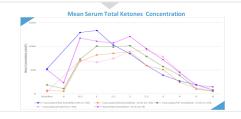
A food effect study confirmed the optimal manner in which to administer tricaprilin: 30' after completion of a meal

#### Study Design:

- · 2 sequential cohorts of 10 subjects
- Single dose administrations of 20g TC
- Cohort 1: Caucasians, 4 way
- crossover for condition
- Cohort 2: Asians, 2-way crossover for condition

#### Study Outcomes:

- Well tolerated, as a single dose, without titration in when given 30 mins after the end of meal;
- · Good PK when administered after a standard or high fat meal
- · No significant difference in PK or tolerability between Asians and Caucasians



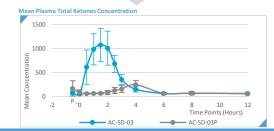
#### METHODS and RESULTS

Studies AC-19-017 Part 1 and Part 2 confirmed the safety, tolerability and PK of the latest formulation of tricaprilin, AC-SD-03

12 healthy young male volunteers in part 1 and 20 in part 2, ages 18-50 Part 1: 6 Caucasians, 6 Chinese; Part 2: 8 Caucasians, 12 Chinese, 3 way cross over and 2 way crossover Each formulation of tricaprilin contained 20g tricaprilin

#### Study Outcomes:

- · All formulations were well tolerated · Good Cmax from AC-1202 and AC-SD-03 in Caucasians and Chinese
- Mean baseline-adjusted total ketones Cmax greater than 500µM for each cohort separately and overall
- · AC-SD-03 (latest formulation) profile is similar to the AC-1202 profile
- · Placebo (AC-SD-03P) is non/minimally-ketogenic
- · No significant differences between Caucasians and Chinese

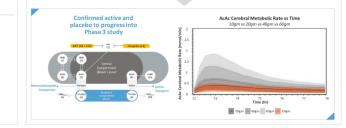


PK- PD modeling and simulation established that doses of 60g per day of tricaprilin would yield improved efficacy

Background: Dose finding is a necessary step in drug development prior to Phase 3 to ensure that adequate doses of the test agent are administered in confirmatory studies. As part of the risk mitigation strategy to prepare for a Phase 3 study, Cerecin set out to determine what doses would be expected to produce maximal results, based on optimal filling of the 'metabolic gap' which has been identified in AD patients brains on dual tracer (FDG-Acetoacetate) PET imaging. This metabolic gap represents the gap between energy consumption in healthy young brain cells vs AD brain cells. "Filling the gap" is correlated with improved cognition.5

Study Design: Using advanced analytics and working with a pharmacology modeler and statisticians, a PK-PD model was developed to fit available data which included cerebral metabolic rate data from ingestion of MCTs. Following development of the model, simulations were run to determine doses required to fill 25-50% of the metabolic gap

Study Outcomes: To 'Fill the Gap', more than 20g caprylic triglyceride is required. Our goal is to fill 25-50% of the metabolic gap to ensure a clinical effect. 60g per day of tricaprilin is the



## **METHODS and RESULTS**

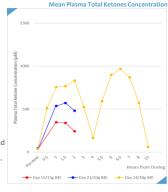
Study AC-20-021 demonstrated that one could safely titrate AC-SD-03 up to 30g tricaprilin BID in healthy elderly subjects

Phase 1, open-label trial to assess the safety, tolerability, and pharmacokinetics of the AC-SD-03 formulation of Tricaprilin in healthy older volunteers



## Study Outcomes:

- The AC-SD-03 formulation was well tolerated and all subjects were able to titrate to the full dose of 30g tricaprilin
- · The most common AEs were gastrointestinal in nature, were mild. resolved, and occurred mainly at the highest dose
- · PK was consistent with prior studies and demonstrated ketone levels in the targeted therapeutic range (above 300-500 μM)



## **RESULTS**

The AC-SD-03 formulation of tricaprilin and its method of administration are optimised for safety, tolerability and PK in Asians and Non-Asians AC-SD-03 is a novel proprietary formulation of tricaprilin which has been optimised for

- safety, tolerability, PK and PD. It is bioavailable, produces ketone levels in the targeted therapeutic range, is well tolerated
- and is appropriate for use in pivotal studies.
- · Titration and dosing regimens as well as how to administer have been thoroughly evaluated in preparation for Phase 3.

### CONCLUSION

Tricaprilin, formulated as AC-SD-03 will be assessed in a double blind, placebo controlled, MCRT, trial in mild to moderate AD, The ALTER-AD TRIAL

 Formulation AC-SD-03 will be moved forward in drug development. A Phase 3 study in mild to moderate AD will start soon and will test doses of up to 30g tricaprilin BID in APOE4 (-) subjects with mild to moderate AD



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