Administering tricaprilin after a meal optimises bioavailability and minimises adverse events

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ABSTRACT

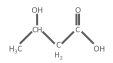
- **Background:** Cerebral glucose hypometabolism in posterior cingulate, parietal, temporal, and prefrontal cortex is an early feature of Alzheimer's disease. These regions exhibit declines in glucose metabolism but have been shown to preserve the ability to metabolize ketones. Therefore, Cerecin is developing tricaprilin as treatment for Alzheimer's. Multiple formulations of tricaprilin, an 8-carbon chain triglyceride ketogenic therapy, were developed and tested in vitro, in vivo and in human studies to assess pharmacokinetics, safety and tolerability.
- **Objective:** To understand how food ingestion affects PK, safety and tolerability of a new formulation of tricaprilin in healthy young men of Caucasian and Chinese descent.
- **Method:** This food effect clinical study (Study AC-18-016) was conducted in healthy human Caucasian and Asian volunteers and in a variety of food conditions to better understand the influence of food ingestion on PK and on tolerability. It employed a 2-part, 4-way and 2-way cross-over design (NCT03551769).
- **Result:** This novel formulation of tricaprilin 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 Chinese.
- **Conclusion:** In future clinical studies, tricaprilin will be administered 30' after completion of a meal to optimize bioavailability and minimize any GI adverse events.

BACKGROUND

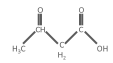
Ketones can provide energy-deprived brain cells in AD brains with an alternative fuel

- 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)
  - ….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]
- Regional declines in CMRglc occur early in AD, decades before clinical signs of dementia.[3]
- Ketone bodies are the brain's natural back up fuel, normally produced under conditions of low glucose availability, such as ketogenic diets or fasting and an provide up to 60 percent of one's brain energy needs[4]
- Cells which do not metabolize glucose in AD have preserved ability to metabolize ketones, the brains favored fuel.[5]

Ketone bodies



β-hydroxybutyrate



Acetoacetate

Acetone

Cerecin has developed CER-0001 (tricaprilin) a pure C8 medium chain triglyceride (MCT), to safely induce ketosis. Efficacy has been shown in two Phase 2 studies

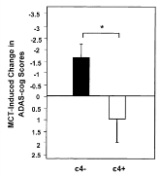
Study KET-002-01 [6]

Design

- 20 mild to moderate AD patients
- Mean age 74.7 years
- Single dose (40g) tricaprilin vs placebo, crossover design

Results

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



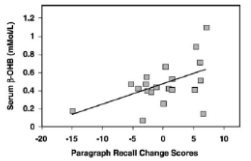


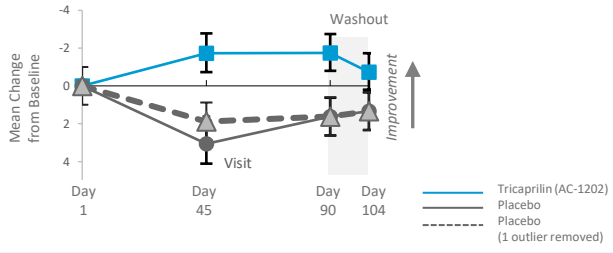
Fig. 2. Relationship between β-OHB levels at the time of cognitive testing and the change in paragraph recall following MCT treatment; $r = 0.50$, $P = 0.02$.

Study KET-004-02 [7]

90 day intervention, primary endpoint ADAS-Cog

Pre-specified sub-group analysis in 55 APOE ε4 (-) patients

Time point	ADAS-Cog Score Difference between AC-1202 and PBO	P-value
Day 45	4.8	0.0005
Day 90	3.4	0.015



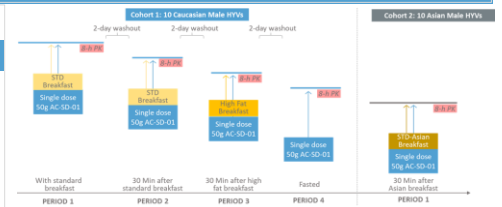
STUDY OBJECTIVE

Study AC-18-016_FE was designed to understand how to administer tricaprilin relative to food ingestion

STUDY METHODS

Study AC-18-016_FE was designed as a 2 Cohort study with 4 periods in Cohort 1 and 2 periods in Cohort 2

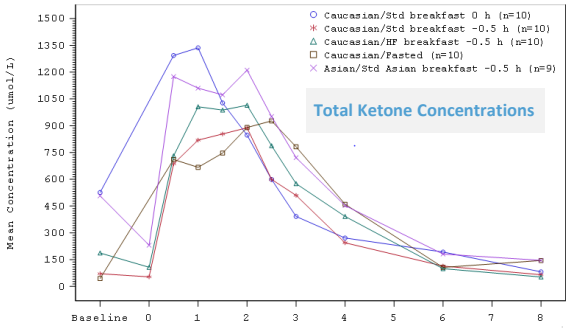
- 2 sequential cohorts of 10 subjects each
- Single dose administrations of 20g tricaprilin dose administered as AC-SD-01 50g
- Cohort 1: Caucasians, 4-way crossover for condition
- Cohort 2: Asians, 2-way crossover for condition
- Analyses done using 2 methods: enzymatic and LCMS
- Conducted in Melbourne, Australia at Nucleus Network; IQVIA as CRO



STUDY RESULTS

Optimal time to administer tricaprilin is 30 mins after completion of a meal, to optimize PK and tolerability

- Optimal PK (Cmax and AUC) when administered with food
- Reasonable PK when administered 30 mins after a meal, especially a high fat meal
- Worst PK when administered on an empty stomach
- With a 20g dose of tricaprilin, ketone levels above 500µM are obtained
- Some confounding due to differences in baseline levels



Enzymatic vs LCMS methods:
Total ketones and BHB look comparable between methods (90% CI within the 80-125 interval), acetoacetate exposure parameters were around 1.22 to 1.30-fold higher for LCMS

Ketones (total and BHB):

- Best PK (Cmax and AUC) when administered with food
- Reasonable PK when administered 30' after a meal, especially a high fat meal
- Worst PK when administered on an empty stomach
- With a 20g dose of tricaprilin, ketone levels above 500µM are obtained
- Some confounding due to differences in baseline levels

Asians vs Caucasians:
Difficult to make comparisons; probably similar; up to 20% greater exposure for same dose in Asians

CONCLUSIONS

This food effect study indicates that the best time to administer AC-SD formulations of tricaprilin is 30 mins after completion of a meal

Safety – Tolerability

- Safe
- No new unexpected events
- Conditions 2 and 3 well tolerated as a single dose, without titration in healthy young men: administration 30 mins after the end of a standard or a high fat meal
- Not well tolerated when administered with a meal (10 mins after the start of a meal) or on an empty stomach (worst tolerated)

Pharmacokinetics

- Best PK when administered *with* food
- Good PK when administered *after* a standard or high fat meal
- Plasma ketone levels in 500-1000 µM range readily obtained after a single dose in healthy young men under the fed conditions. Note higher baseline ketones than in earlier studies.
- Probably similar PK in Asians and Caucasians; up to 20% difference between Caucasians and Asians when adjusted for weight but could be explained by baseline differences; to be confirmed in population PK in later studies

Overall

Best balance of PK and tolerability: administer 30 minutes after the end of a meal

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