Novel formulation AC-SD-03 of tricaprilin leads to excellent PK and safety in doses up to 30g BID

Lilian Chow, MRDM; Lars Nelleman*, MD; Bruce H. Morimoto**, PhD; Judith Anne Walker*, MD*

ABSTRACT

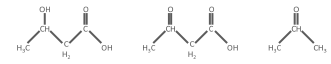
- **Background:** Cerecin is developing ketogenic therapies for Alzheimer's disease (AD). Ketones are an excellent source of fuel for cells in the posterior cingulate, parietal, temporal, and prefrontal cortex which have reduced ability to metabolize glucose whilst preserving the ability to metabolize ketones. Earlier studies have shown that ketone therapy can improve cognition in AD. AC-SD-03 is the latest formulation to be developed for use in a Phase 3 study in mild to moderate AD.
- **Objective:** To assess the pharmacokinetics, safety and tolerability of Cerecin's newest proprietary formulation of tricaprilin, AC-SD-03, in healthy young male Caucasian and Asian volunteers. To assess the ketogenic properties of a placebo to AC-SD-03 prior to moving to Phase 3 clinical studies. To assess the properties of a prototype slow-release formulation of tricaprilin. (Studies AC-19-017 Parts 1 and Parts 2). To ensure tolerability of the dose and titration regime to be used in a phase 3 study, in a healthy older population. (Study AC 20-021)
- **Method:** Study AC-19-017 was a 2-part study conducted in healthy young male volunteers and tested AC-SD-03 ; a prototype, slow release formulation of tricaprilin; an earlier formulation of tricaprilin; and a placebo to AC-SD-03. (NCT03971123). Study AC-20-021 was a multiple ascending dose study conducted in 12 healthy older (50 years +) subjects over 24 days, with doses of tricaprilin increasing from 5 g once a day to 30g twice a day. (NCT04268953)
- **Result:** AC-SD-03 showed expected bioavailability and excellent safety and tolerability, when administered in single doses of 20g after a meal, in both Caucasians and Asians. AC-SD-03 was well tolerated in a healthy older population when titrated to a dose of 30g of tricaprilin BID. At this dose, desirable PK characteristics, leading to generation of ketones and excellent safety and tolerability, were seen.
- **Conclusion:** Formulation AC-SD-03 has demonstrated excellent PK, safety and tolerability in young males and in an older healthy population, in doses of up to 30g BID, and will be moved forward into a Phase 3 study in mild to moderate AD.

BACKGROUND

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

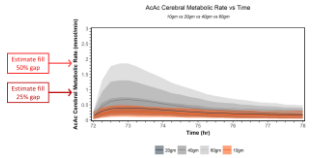
- The brain is highly metabolic so any deficiency in its metabolism results in a severe energetic stress and ultimately in cell death
- Normally, the brain relies almost exclusively on glucose as an energy substrate.[1]
- Cerebral glucose hypometabolism is characteristic in AD, is progressive and correlates with cognitive decline.[2]
- Regional declines in CMRglc can be detected 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]
- Cerecin has developed CER-0001 (tricaprilin) a pure C8 medium chain triglyceride (MCT), to safely induce ketosis.
- Efficacy has been shown in 2 Phase 2 studies.[6,7]
- Multiple formulations of tricaprilin were developed and tested in animal models prior to human PK studies
- Analytical methods were also developed and validated to measure tricaprilin, octanoic acid (OA), the compound that is absorbed from the gut, β-hydroxybutyrate (BHB) and acetoacetate (AcAc)

Ketone bodies



β-hydroxybutyrate Acetoacetate Acetone

A PK PD model was developed which suggested that doses of up to 60g per day were required to achieve optimal PK and brain uptake of ketones in AD



OBJECTIVES AND METHODS STUDY AC-19-017

Study AC-19-017 Part 1 and Part 2 was designed to determine the safety tolerability and PK of a single dose of tricaprilin in various formulations as well as placebo to tricaprilin.

- **Study Objectives:**
  1. Safety and tolerability of 4 tricaprilin formulations and 1 placebo formulation
  2. To compare ketone body, tricaprilin, and octanoic acid levels of the above formulations
- **Study Design:**
  PART 1: 12 healthy young (age 18-50) male volunteers (6 Caucasians, 6 Chinese)
  PART 2: 20 healthy young (age 18-50) male volunteers (8 Caucasians, 12 Chinese)
  Part 1 : 3-way crossover: tricaprilin as AC-SD-03, tricaprilin as AC-LMP-01 (a prototype novel formulation), AC-SD-03 placebo
  Part 2: 2-way crossover: tricaprilin as AC-SD-03, tricaprilin as AC-1202
- **Study Operations:**
  - Conducted at Nucleus Network, Australia; Syneos Health as CRO
  - Analyses done using bioanalytical methods at Agilex, Australia

OBJECTIVES AND METHODS STUDY AC-20-021

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 Objectives:

1. Safety and tolerability of a repeated-dose administration tricaprilin formulated as AC-SD-03 in doses increased from 5g per day to 30g BID of tricaprilin, in healthy older subjects
2. To compare ketone body, tricaprilin, and octanoic acid levels after repeat dosing up to 30g BID

Study Design:

- 12 subjects (healthy volunteers, ages 50 +)
- Multiple dose, Open label
- Two doses administered per day, titrating from 5g tricaprilin per day to 30g BID over 24 days
- Each test product administered 30 minutes after completing a meal. Dose 1 administered after a standard breakfast and dose2 after a standard lunch
- PK sampling was collected on pre-dose and post-dose of Day 15, 21 and 24

Study Operations:

- Conducted in Phoenix, Arizona , Celerion as CRO
- Analyses done using bioanalytical methods at Agilex, Thebarton, Australia

Up-titration Schedule:

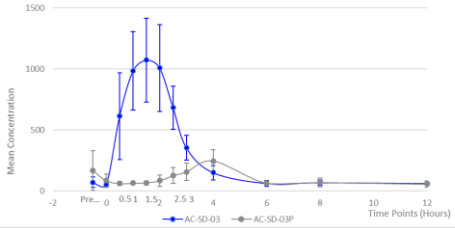
Days	Dose of tricaprilin
1-4	5g BID
5-9	10g BID
10-15	15g BID
16-21	20g BID
22-24	30g BID

PK RESULTS STUDY AC-19-017 PART 1

AC-SD-03 had the desired properties for an agent in AD

- Target ketone Cmax (greater than 500µM) reached from AC-SD-03 in Caucasians and Chinese
- Placebo (AC-SD-03P) is non/minimally-ketogenic
- No significant differences between Caucasians and Chinese (see CTAD 2020, Poster 20)

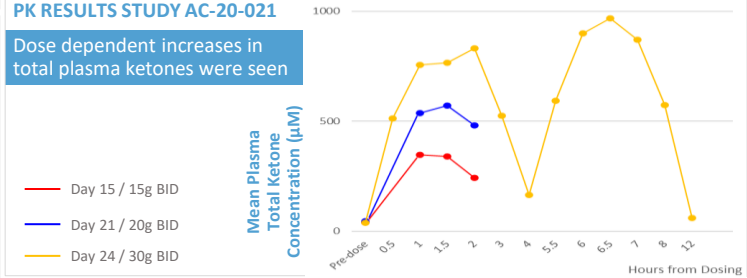
Mean Plasma Total Ketones Following the Administration of a single 20g dose of Tricaprilin or Placebo*



*Excluding outlier

PK RESULTS STUDY AC-20-021

Dose dependent increases in total plasma ketones were seen



SAFETY AND TOLERABILITY RESULTS STUDY AC-19-017

All formulations were well tolerated, with no safety concerns

Part 1	AC-SD-03	AC-SD-03P
Number of subjects dosed, N	12	12
Number of TEAEs, n	8	1
Number of subjects with TEAEs, N (%)	7 (58.3%)	1 (8.3%)
Gastrointestinal disorders Nausea	7 (58.3%) 5 (41.7%)	1 (8.3%) 0

Part 2	AC-SD-03	AC-1202
Number of subjects dosed, N	21	20
Number of TEAEs, n	13	15
Number of subjects with TEAEs, N (%)	11 (52.4%)	12 (60.0%)
Gastrointestinal disorders Abdominal distension Abdominal discomfort Nausea	11 (52.4%) 5 (23.8%) 3 (14.3%) 3 (14.3%)	12 (60.0%) 8 (40.0%) 4 (20.0%) 1 (5.0%)

- IMP was administered as a single-dose without titration
- Adverse events were mild and resolved spontaneously

SAFETY AND TOLERABILITY RESULTS STUDY AC-20-021

All subjects were able to titrate to the top dose with no safety concerns

- The AC-SD-03 formulation was well tolerated, and all subjects were able to titrate to the highest dose of 30g tricaprilin BID
- The most common AEs were gastrointestinal in nature, were mild, resolved and occurred mainly at the highest dose

CONCLUSIONS FROM STUDY AC-19-017

Safety, tolerability and PK of AC-SD-03 are appropriate to move forward into later stage development

- Good Cmax from AC-1202 and AC-SD-03 in Caucasians and Chinese
- No significant differences between Caucasians and Chinese (See CTAD 2020 poster P20 for further analyses)

CONCLUSIONS FROM STUDY AC-20-021

Study AC-20-021 demonstrated that one could safely titrate AC-SD-03 up to 30g tricaprilin BID in healthy elderly subjects and produce ketone levels in the desired range for therapeutic effect

- 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)

OVERALL CONCLUSIONS OF CERECIN'S PHASE 1 PROGRAMME FOR AC-SD-03

Tricaprilin, formulated as AC-SD-03, is a viable formulation with good tolerability and PK in doses up to 30g BID in healthy young and elderly subjects

- AC-SD-03 is a novel proprietary formulation of tricaprilin which has been optimized 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 future clinical trials
- Titration and dosing regimens as well as how to administer have been thoroughly evaluated in preparation for late phase studies
- Additional analyses show comparability of PK in Caucasians and Chinese (See CTAD P20)
- This formulation of tricaprilin will be moved forward in clinical development

**Cerecin Pte Ltd, 8 Shenton Way #08-02 AXA Tower, Singapore 068811; **Cerecin INC, 44 Cook Street, Suite 100-71 Denver, CO 80206, USA*

REFERENCES

1. Clarke, D. D. and L. Sokoloff (1994). New York, Raven Press: 645-680.
2. Mosconi, L., M., et al. (2007). Exp Gerontol 42(1-2): 129-38.
3. Reiman, E. M., et al. (2004). Proc Natl Acad Sci U S A 101(1): 284-9.
4. Owen, O. E. et al. (1967). J Clin Invest 46, 1589-1595.
5. Castellano, C.A et al. (2015) J Alzheimer's Dis. 43(4):1343-53.
6. Reger MA et al. (2004) Neurobiol of Aging; 25: 311–314.
7. Henderson ST et al. Nutr Metab (Lond) 2009; 6(1): 31

CTAD 04-07 November 2020, Poster #18