An evidence-based risk-mitigation approach to study design in APOE4(-) mild to moderate AD

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ABSTRACT

- **Background:** AC-SD-03 is a proprietary formulation of tricaprilin, a ketogenic therapy for Alzheimer's disease (AD). Building on the known mechanism of action of ketones which act as an alternative source of fuel to brain cells which cannot metabolize glucose efficiently, on the data from Cerecin's studies, and on data from ketogenic diets, Cerecin optimized the PK and safety profile for AC-SD-03. PK-PD modelling was undertaken to understand the doses required to optimize clinical effect. In addition, a food effect and an ascending dose study were conducted in healthy older subjects. These activities were conducted in preparation for a Phase 3 AD study to start shortly, the ALTER-AD trial (NCT04187547).
- **Objective:** To use an evidence-based risk mitigation strategy to design a phase 3 study to increase probability of success.
- **Method:** The ALTER-AD trial has been designed to study the efficacy and safety of AC-SD-03 in APOE4(-) subjects with mild to moderate AD.
- **Result:** ALTER-AD design is a randomized placebo-controlled add-on to standard of care study of AC-SD-03 vs placebo, in APOE4(-) patients with mild to moderate AD. Key elements of the study design and how they have been informed by incremental accumulation of knowledge over 20+ years of development with a goal of mitigating risk will be presented.
- **Conclusion:** This Phase 3 study of AC-SD-03 in APOE4(-) patients with mild to moderate AD has been designed to mitigate risk and ensure success and builds on a firm understanding of the disease in an important subset of patients of AD.

BACKGROUND

Administration of ketogenic therapies is an evidenced-based approach to addressing the fundamental bio-energetic deficit in Alzheimer's disease

- 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 in mild to moderate AD [1,2]
- Other groups have shown efficacy with MCT compounds and ketogenic diets [3,4,5]
- However all MCT products are not the same; a MCT formulation used in the NOURISH AD study was not bioavailable. Therefore the study failed to adequately test the hypothesis [6]
- Moreover, many other AD compounds have failed to show benefit in Phase 3 trials despite promising results in Phase 2
- Cerecin therefore decided to take a very systematic approach to preparing for and designing its phase 3 study of CER-0001 (tricaprilin) in AD to minimize risk and maximize probability of success

OBJECTIVE

Evidence-based drug development and risk mitigation

To use an evidence-based risk mitigation strategy to prepare for and to design a phase 3 study to increase probability of success.

Issues to address

STEP 01 — **Proof of concept:**
Cerecin studies
Other MCT studies
Ketogenic diet studies

STEP 02 — **Compound related:**
A bioavailable formulation
Analytical methods
Understanding the ADME of the compound
Understanding the dose response and how to administer it

STEP 03 — **Study design related:**
Understanding the population to study
Determining the goals of the study
Understanding the outcome measures
Statistical design

STEP 1: CONFIRM SUPPORT FOR PROOF OF CONCEPT

Proof of concept of the effect of tricaprilin on cognition in APOE4 (-) AD patients has been shown by earlier Cerecin studies and is supported by independent research

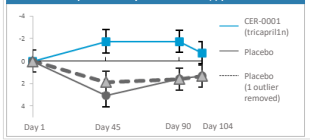
Phase 2b Study: Multi-center, Double-blind Placebo-controlled Study in Subjects with Mild-to-moderate Alzheimer's Disease showed a statistically ***significant and clinically meaningful*** effect on ADAS-Cog in APOE4(-) subjects

Design: n= 152,
90 Day intervention, Primary endpoint ADAS-Cog[2]

± AChEI (> 75 %) | AC-1202: 20g tricaprilin QD, orally N = 152 | Placebo

Double – blind (3 months) | 2 weeks washout

Pre-Specified Analysis in 55 APOe4 (-) patients



- Difference between active and placebo of 3.4 pts in ADAS-Cog seen at 90 days in APOE4 (-) patients

Time point	Score Difference	P-value
Day 45	4.8	0.0005
Day 90	3.4	0.015
Day 104 Washout	2.1	0.154

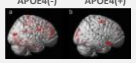
STEP 1: CONFIRM SUPPORT FOR PROOF OF CONCEPT

Tricaprilin Induced Changes in Regional Cerebral Blood Flow in APOE4 Non-carriers During a 45 days Course in Patients with Mild to Moderate Alzheimer's Disease[7]

Study: Investigator Initiated Trial at the David Geffen School of Medicine at the University of California Los Angeles

Design:
- Double-blinded, placebo-controlled, randomized clinical trial
- Sixteen subjects with mild-to-moderate AD (NINCDS-ADRDA criteria)
- Fourteen subjects received Axona ® (containing the active ingredient tricaprilin), 2 subjects were given placebo
- Subjects received 4 ^{15}O-water PET scans over the course of the study to assess rCBF: On day 1 and after 45 days of treatment

Results:
- Subjects lacking an ε4 allele had significantly elevated rCBF in the left superior lateral temporal cortex after 45 days (p=0.04)
- The anterior cerebellum, left inferior temporal cortex, and hypothalamus were also found to be regions of long-term increase in rCBF in these subjects
- Patients who possessed the ε4 allele did not display these changes in rCBF



Acute effects (Scan 1 vs. Scan 2) on treatment-naïve APOE4-negative (a) and APOE4- positive (b) groups (p < 0.01).

Long-term effects (Scan 1 vs. Scan 3) of 45 days of daily Axona on pre-dose rCBF in APOE4-negative (a) and APOE4-positive (b) groups (p < 0.01).

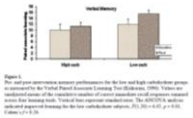
Conclusion: Daily ingestion of Axona® over 45 days was associated with increased blood flow in specific brain regions in patients lacking an apolipoprotein ε4 allele

Studies of ketogenic diets support utility of ketosis in AD

Krikorian et al. (2012) demonstrated improved memory performance that correlated with urine ketone levels

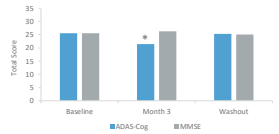
Randomly assigned 23 older adults with Mild Cognitive Impairment to either a high carbohydrate or very low carbohydrate diet for six weeks

For the low carbohydrate subjects:
- Verbal memory performance improved (p = 0.01)
- Weight reduced (p < 0.0001)
- Waist circumference reduce (p < 0.0001)
- Fasting glucose reduced (p =0.009)
- Fasting insulin (p = 0.005)
- Ketone levels were positively correlated with improved memory performance (p = 0.04)



Single-arm, pilot study in 15 subjects (10 completers) 3-month, MCT supplemented ketogenic diet followed by a 1-month washout[5]

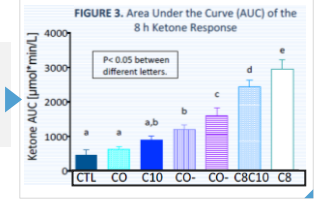
For the completed subjects:
- The mean of the ADAS-Cog (11) subscale score improved by 4.1 points during the diet (P = .02) and reverted to baseline after the washout
- Achieved ketosis (self-reported urine ketone assessments)



* p <0.02, Baseline vs KD by linear mixed model

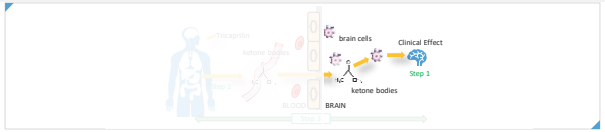
Vandenberghe et al 2017[8] demonstrated that tricaprilin is more ketogenic than other MCTs:
- Tricaprilin (C8) was more ketogenic than C8/C10 blends for both Cmax and AUC
- Capric triglycerides (C10) are weakly ketogenic
- Coconut oil (CO) is weakly ketogenic

FIGURE 3. Area Under the Curve (AUC) of the 8 h Ketone Response



STEP 1: CONFIRM SUPPORT FOR PROOF OF CONCEPT

Conclusion:
- Proof of concept for the effect of tricaprilin on cognition has been established
- Supported by data from ketogenic diets
- C8 (tricaprilin) is more ketogenic than other MCTs



STEP 2: UNDERSTANDING THE DRUG

Developing a bioavailable formulation of CER-0001 and understanding its performance characteristics to de-risk the Phase 3 study

- Formulation AC-1202 used in the phase 2B study showed excellent bioavailability which formed the basis of the positive results seen in the target population.
- Formulation AC-1204 used in the NOURISH-AD study was poorly bioavailable and this is suspected to be the reason for the failure to adequately test the trial hypothesis.
- Whilst safe (tricaprilin in GRAS), tolerability of tricaprilin, like other MCTs can be an issue. So the goal was to develop formulations that were bioavailable and well tolerated.
- In order to understand the bioavailability of various formulations and the ADME of the compound, bioanalytical methods were required.
- There were gaps in our knowledge regarding the compound:
  - How to administer tricaprilin to maximise bioavailability and minimise adverse events
  - Dose response
  - How high a dose would be tolerated in an older population.

- Working with Lonza (Bend, OR), several prototype formulations were developed. These were assessed in a rat PK model and the most promising formulations were taken to clinic.
- Bioanalytical (LCMS) methods were developed at Agilex, Australia and enzymatic and LCMS methods were compared in study AC-18-016.
- A food effect study was conducted, Study AC-18-016, to understand how to optimise bioavailability and tolerability. This study concluded that optimum administration was 30' after completing a meal (See CTAD Poster 17).
- Dose response was established via an in silico study. In this study, data from Cerecin's studies and data from S. Cunnane's lab at U of Sherbrooke were used to develop a PK/PD model.
- The PK/PD model suggested doses of 60g per day CER-001 were ideal. The safety and tolerability and PK of doses of up to 30g BID were tested in a healthy older population in Study AC-20-021 (See CTAD Poster 18).
- PK and tolerability were confirmed in study AC-19-017 (See CTAD Poster 18).

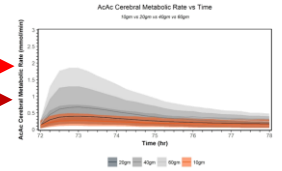
STEP 2: UNDERSTANDING THE DRUG

Multiple lines of evidence support a dose response

Based on a PK/PD model; the higher the dose, the greater the energy gap filled

Estimate fill 50% gap

Estimate fill 25% gap



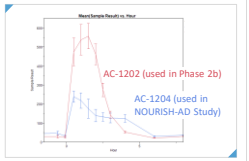
Conclusion: Dose is important to generate ketones in blood, to generate ketones in the brain, and to improve cognition

STEP 2: UNDERSTANDING THE DRUG

A PK Study confirmed that formulation impacts bioavailability and that AC-1204 (used in the NOURISH AD) study generated less than half the plasma level of ketones as AC-1202 (used in the Phase 2b study)

When NOURISH AD failed to meet its primary endpoint a bioavailability issue was suspected

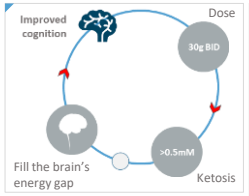
A pharmacokinetic study was conducted to examine the difference in PK profiles between:
AC-1202 (used in Phase 2b)
AC-1204 (used in NOURISH-AD Study)



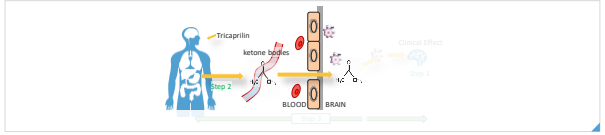
Conclusion: Formulation is important to generate ketones in blood, to generate ketones in the brain, and to improve cognition

STEP 2: UNDERSTANDING THE DRUG

By developing an understanding the new formulation of CER-0001 (AC-SD-03), we have a formulation that is de-risked.



The AC-SD-03 formulation is de-risked because it is:
- Safe (tricaprilin is GRAS).
- As bioavailable as the AC-1202 formulation on a gram per gram basis.
- We have confirmation from our studies and others that as the dose of tricaprilin is increased, so does the plasma ketone concentration. And as the plasma ketone concentration is increased, so is the uptake of ketones by the brain.
- Doses of up to 30g BID were well tolerated in an older population,



STEP 3: DESIGNING THE STUDY TO MEET SPECIFIC GOALS

The study was designed to meet the goal of showing a definitive improvement in cognition in a specific population, taking into account learnings from the last 10 years of drug development at Cerecin

Goal of the study was to show an effect on cognition essentially replicating the *statistically significant and clinically meaningful* effects seen in the phase 2 b study.

→ The goal is symptomatic improvement of cognition.
- Whilst there is evidence to support a disease modifying effect of tricaprilin, in AD, the goal of this study was to replicate the phase 2b study and show, once again, an effect on cognition.

The target population in which positive results had been seen previously was subjects with mild to moderate AD who are APOE4 (-).

→ 3 studies in mild to moderate population, showed the effects were predominantly seen in those who were APOE 4-
- Whilst there might be an effect in earlier stages of the disease, the goal of first demonstrating a symptomatic benefit dictated that the population to study would be one in which symptoms were well established

The APOE4 – population drove the predominant location of study sites in APAC.

The outcome measures were chosen based on what was likely to be:
- Of clinical meaningfulness
- Likely to have room for improvement in the selected population
- Likely to respond to the intervention
- Validated, in target population/language
- Widely accepted by regulators, scientists
- Practical and feasible in terms of patient burden.

→ The selected primary outcome measure: ADAS-Cog 11
- Secondary outcome measures:
  - For ADLs; The DAD had the most use/data in a Chinese population; the Amsterdam iADL may well replace this in the future as it is more widely developed and validated
  - CGIC as a general outcome
  - CFT and COWAT to fill some of the gaps of the ADAS-Cog.

The statistical design was important to mitigate risk given the high stakes in AD clinical research allowed for an interim analysis.

→ The statistical design was modelled off empirical data from a leading AD statistical consultancy.

STEP 3: DESIGNING THE STUDY TO MEET SPECIFIC GOALS

The resulting study design is efficient, meets the goals of the study, and is feasible to implement

The ALTER-AD Trial
Phase 3, double-blind, randomized, placebo-controlled trial in APOE4 (-) subjects with mild-to-moderately severe probable Alzheimer's Disease

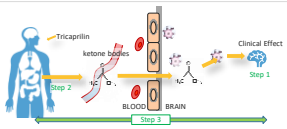
Design: n = 300
26 weeks intervention
Primary endpoint ADAS-Cog
Age: 50-85
MMSE: 14-26

Primary Objective	To assess the effect on cognition of daily administration of up to 60 g/day tricaprilin versus placebo on ADAS-Cog at 26 weeks
Secondary Objectives	• Safety and tolerability • Activities of daily living, clinical global impression of change, resource utilization, PK measures • Efficacy by dose and post-dose total ketone level

CONCLUSIONS

An evidence-based approach has been used to prepare for a risk-mitigated Phase 3 study of an agent addressing the bioenergetic deficit in AD

- This phase 3 study of AC-SD-03 in APOE4(-) patients with mild to moderate AD has been designed to mitigate risk and ensure success and builds on a firm understanding of the disease in an important subset of patients of AD
- This approach addresses:
  - Ensuring Proof of Concept before moving to phase 3
  - Understanding the compound, the dose response, the biology
  - Best practices in study design



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