Tricaprilin Shows Similar PK, Safety and Tolerability in Caucasians and Chinese

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ABSTRACT

- **Background:** Cerecin is developing ketogenic therapies for Alzheimer's disease (AD) based on earlier studies showing 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 which will be conducted in Asia and in the West. The pharmacokinetics of tricaprilin have been well-characterized by a series of clinical pharmacology studies.
- **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 understand differences between the two populations and any ethnic sensitivities.
- **Method:** In this analysis, data from several studies were included, including Cerecin's studies AC-18-016, AC-19-017 Part 1 and AC-19-017 Part 2. Study AC-18-016 was a food effect study of the AC-SD-01 formulation of tricaprilin, conducted in healthy young males (NCT03551769). 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). Both of these studies included Caucasian and Asian (Chinese) subjects and several analyses were conducted to compare the effects in Caucasians vs Chinese. To explore whether ethnicity affects total ketone body exposure after tricaprilin administration, the pharmacokinetic parameters AUC0-t and Cmax from the AC-19-017 study were examined and grouped by an individual's ethnicity (Chinese or Caucasian).
- **Result:** Differences between ethnicities in each study were minor and were less apparent when corrected for weight. When data from the 2 parts of study AC-19-017 were combined, the mean Cmax for total ketones in Chinese participants was 965 µM and 1000 µ M for Caucasian participants (p=0.78) and the mean total ketone AUC0-t for Chinese participants was 3011 h* µM; whereas, for Caucasian participants, the AUC0-t was 2953 h*µM. (p=0.89). No differences were seen in AE profile between Asian and Caucasian subjects.
- **Conclusion:** Exposure to total ketones, the active species after tricaprilin administration was no different for healthy ethnic Chinese participants compared to healthy Caucasians. There does not appear to be any ethnic difference in absorption or metabolism of tricaprilin to produce ketone bodies, or in their safety and tolerability profile.

BACKGROUND

CER-0001 (tricaprilin) is a ketogenic drug that has shown clinical efficacy in APOE4(-) subjects with mild to moderate Alzheimer's disease (AD).

- CER-0001 is a ketogenic therapy for Alzheimer's disease (AD) which has been shown to produce ketone bodies and improve cognition in subjects with mild to moderate AD.[1,2]
- Three studies have highlighted different effects of tricaprilin based on APOE4 status with greatest effects seen in the APOE4 (-) population.[1,2,3]
- Anywhere from 55-80% of patients with AD in Asia are APOE4(-)[4]
- AC-SD-03 is the latest formulation of CER-0001 to be developed for use in a Phase 3 study in mild to moderate AD which will be conducted in Asia and in the West. (See CTAD 2020 Posters 18 and 19)
- The pharmacokinetics of tricaprilin have been well-characterized by a series of clinical pharmacology studies. (See table 1 and CTAD 2020 Posters 17 and 18).
- It is important to consider ethnic sensitivity given the intended usage of tricaprilin in all populations

Table 1. Cerecin's Clinical Pharmacology Studies of Tricaprilin

Protocol no.	AC-16-011_BE	AC-16-012_BE	AC-16-013_BE	AC-17-014_BE
Clinicaltrials.gov	NCT02747602	NCT02833012	NCT02959710	NCT03063645
Crossover design	3-way	4-way	3-way	3-way
No. of subjects	16	20	16	16
Formulations	Oil, AC-1204	Oil, AC-1202, AC-1204, Axona	AC-1202, AC-1204	AC-1202, AC-SD-01
Site location	Celerion (Tempe AZ, USA)	Celerion (Tempe AZ, USA)	Celerion (Tempe AZ, USA)	Celerion (Lincoln NE, USA)
Date of study start	April 2016	July 2016	November 2016	March 2017

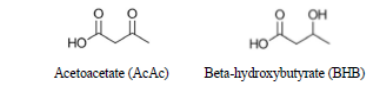
Protocol no.	AC-18-016_FE	AC-19-017, Part 1	AC-19-017, Part 2	AC-20-021
Clincaltrials.gov	NCT03551769	NCT03971123	NCT03971123	NCT04268953
Crossover design	2-part, up to 4-way	3-way	2-way	Dose titration
No. of subjects	10 Asian 10 Caucasian	6 Chinese 6 Caucasian	12 Chinese 8 Caucasian	12 Non-Chinese (Elderly)
Formulations	AC-SD-01	AC-SD-03, AC-SD-03P, AC-LMP-01	AC-SD-03, AC-1202	AC-SD-03
Site location	Nucleus Network (Melbourne, Australia)	Nucleus Network (Melbourne, Australia)	Nucleus Network (Melbourne, Australia)	Celerion (Tempe AZ USA)
Date of study start	August 2018	August 2019	March 2020	February 2020

BACKGROUND

CER-0001 (tricaprilin) is a ketogenic drug that has shown clinical efficacy in APOE4(-) subjects with mild to moderate Alzheimer's disease (AD).

- Tricaprilin is predominantly hydrolyzed in the small intestine to octanoic acid and glycerol. Octanoic acid is absorbed in the gastrointestinal tract and transported to the liver by portal circulation where it is oxidized to form the primary ketone bodies namely acetoacetate (AcAc) and beta-hydroxybutyrate (BHB) (Figures 1 and 2).[5]
- Ketone bodies can readily enter the brain and serve as an alternative energy substrate for the brain including under conditions of glucose deprivation as seen in Alzheimer's disease.
- Therefore, total ketone bodies (AcAC and BHB) represent the most relevant pharmacokinetic marker for tricaprilin.

Figure 1. Structure of primary ketone bodies produced from tricaprilin



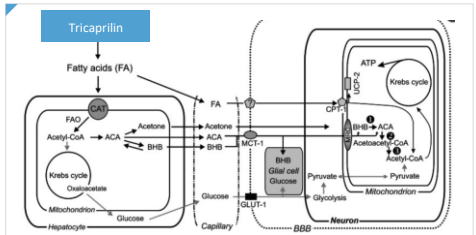


Figure 2. Pathways involved in tricaprilin ADME

OBJECTIVES

To better understand the effect of ethnicity on tricaprilin metabolism, safety, tolerability, PK, and clinical effect

- 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.

METHODS

Three studies included Caucasians and Asians. Data from these 3 studies were analysed by ethnic group

- In this analysis, data from several Cerecin studies were included:
  - Study AC-18-016 (See CTAD 2020 poster 17)
  - Study, AC-19-017 Part 1 (See CTAD 2020 poster 18)
  - Study AC-19-017 Part 2 (See CTAD 2020 poster 18)
- All of these studies included Caucasian and Asian (Chinese) subjects and several analyses were conducted to compare the effects in Caucasians vs Chinese.
- Ethnic Chinese participants were defined as all four grandparents being Chinese.
- The level of ketone bodies was quantitated using a validated LC-MS/MS bioanalytical assay.

RESULTS: SAFETY AND TOLERABILITY

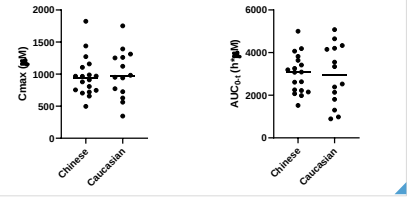
There were no differences in the safety and tolerability profile between Caucasians and Asians

- No differences were seen in the safety or tolerability profile between Chinese and Caucasians in any of the three studies.
- In all studies, mild-moderate, self-limited GI adverse events were seen (bloating, nausea, abdominal discomfort).

RESULTS: PK

There were no differences in the PK profile between Caucasians and Asians (Chinese)

Figure 3. Scatter plots of C_{max} and AUC_{0-t} for total ketone bodies after a single administration of 50g AC-SD-03 (20g tricaprilin) to healthy Chinese (n-18) or Caucasian (n=14)



Differences between ethnicities in each study were minor and were less apparent when corrected for weight.

When data from the 2 parts of study AC-19-017 were combined, the mean Cmax for total ketones in Chinese participants was 965 µM and 1000 µM for Caucasian participants (p=0.78) and the mean total ketone AUC0-t for Chinese participants was 3011 h*µM; whereas, for Caucasian participants, the AUC0-t was 2953 h*µM (p=0.89). (Figure 3)

RESULTS: LITERATURE REVIEW

There were no differences in the PK profile between Caucasians and Asians

- There are no known differences in the processes involved in the absorption, metabolism, distribution and elimination of medium chain triglycerides (MCTs) between Caucasians and Chinese, or in terms of the oxidation of medium chain fatty acids to ketone bodies.

CONCLUSIONS AND DISCUSSION

Similar safety, tolerability and PK were seen in Caucasians and ethnic Chinese

- Exposure to total ketones, the active species after tricaprilin administration, was no different for healthy ethnic Chinese participants compared to healthy Caucasians.
- There does not appear to be any ethnic difference in absorption or metabolism of tricaprilin to produce ketone bodies, or in their safety and tolerability profile.
- This is to be expected given the fundamental role ketone metabolism plays in providing an alternative fuel substrate for the brain, a process that would be essential to the survival of the human species. As such it is not surprising that it is unaffected by ethnic differences.
- Differences in clinical efficacy, in particular cognition, will be assessed in future trials as Cerecin conducts more studies of tricaprilin in an APOE4 negative population in Asia.

REFERENCES

1. *Reger, M. A., S. T. Henderson, et al. (2004). "Effects of beta-hydroxybutyrate on cognition in memory-impaired adults. " Neurobiol Aging 25(3): 311-4.*
2. *Henderson, S. T., J. L. Vogel, et al. (2009). "Study of the ketogenic agent AC-1202 in mild-to-moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial." Nutr Metab (Lond) 6(1): 31.*
3. *Torosyan N, Sethanandha C, Grill JD, et al. (2018). "Changes in regional cerebral blood flow associated with a 45 days course of the ketogenic agent, caprylidene, in patients with mild-to-moderate Alzheimer's disease: Results of a randomized, double-blinded, pilot study." Exp Gerontol 111: 118–121.*
4. *Crean et al. (2011). "Apolipoprotein E epsilon4 prevalence in Alzheimer's disease patients varies across global populations: a systematic literature review and meta-analysis." Dement Geriatr Disord 31(1): 20-30.*
5. *Owen, O. E. et al. (1967). Brain metabolism during fasting. J Clin Invest 46, 1589-1595.*

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