COMMITTEE PAPER FOR DISCUSSION **ACNFP/117/04**

ADVISORY COMMITTEE FOR NOVEL FOODS AND PROCESSES

BETA-HYDROXYBUTYRATE ESTER

ISSUE

Following the Secretariat's letter of 10 July **(Annex B attached)** the applicant has written to the Committee with an outline of a 28 day human study. The Committee is asked whether undertaking this study would meet the Committee's needs in demonstrating the safety of D-β-hydroxybutyrate ester.

Background

1. The Committee reviewed an application for D-β-hydroxybutyrate ester at its meetings in September and November 2013 and in February and April 2014.The Committee confirmed that it had considered all the data and arguments provided by the applicant and that its major concerns had not been addressed:
    a. The available data was not sufficient to conclude on the safety of the novel ingredient under the intended conditions of use, namely as a source of energy for elite athletes.
    b. Authorisation as a novel food means that products containing the novel ingredient can be freely marketed and it is not clear how consumption of such products would be restricted to that group.
2. The Secretariat wrote to the applicant with 3 possible options as to how to proceed with their application. One of the options was to undertake additional studies to address the uncertainties highlighted by the Committee.
3. The applicant has responded to the letter by requesting the Committee's advice on a human study it proposes to carry out. The outline of the human study is attached in the **Annex A** for the Committee's consideration.

COMMITTEE ACTION REQUIRED

4. The Committee is asked whether the study meets the Committee's needs in demonstrating the safety of D-β-hydroxybutyrate ester.
5. If not the Committee is asked to indicate what further advice it can provide to the applicant

Secretariat
November 2014

Annexes attached:

Annex A	**Outline of the 28 day human study**
Annex B	**Letter of 10 July 2014 from the ACNFP to the applicant**

ACNFP 117/04 ANNEX B

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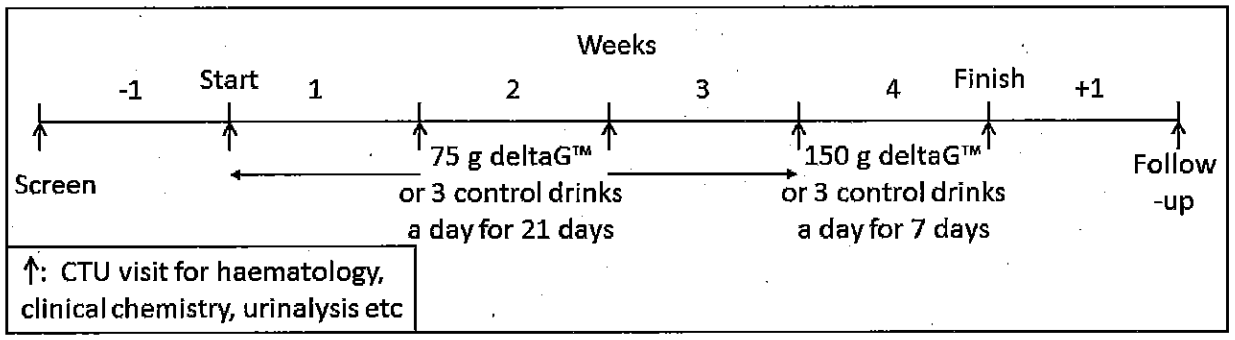
The safety and tolerability of deltaG™ drinks consumed thrice-daily for 28-days:

A placebo-controlled study in healthy humans

In an attempt to address the concerns of the ACNFP Committee regarding the safety of deltaG™, as outlined in the FSA letter of 10th July 2014, TdeltaS Ltd is submitting an outline of a human study to evaluate the safety and tolerability of deltaG™ drinks given thrice-daily for 28-days. This study will be conducted in 40 generally healthy male and female volunteers aged 18 years or older and within the normal BMI range of 18.5 to 29.9 kg/m^2. The study will be crossover in design with two 4-week arms (*i.e.* deltaG™ or control), separated by a 1-week washout period. Subjects will be randomly allocated, such that half the volunteers will consume control drinks first and deltaG™ drinks second, and the other half of the volunteers will consume deltaG™ drinks first and control drinks second.

The maximum intake of deltaG™ in humans is 2.1 g/kg body weight/day for 5 days.[1] During the first 21 days of the study, the volunteers will consume, daily, 3 x 25 g (75 g/day = 368 kcal) of deltaG™ or control drinks (see figure below). Each of the three drinks will be consumed prior to breakfast, lunch and dinner. During days 22 to 28 of the deltaG™ intervention, the intake of deltaG™ will be increased to 3 x 50 g per day (150 g/day = 735 kcal), resulting in a total daily intake of deltaG™ that is twice the maximum level currently recommended to be consumed on a daily basis within the novel food application. The control group will receive an isocaloric and isovolumetric beverage comprised of water, dextrose and bitter flavouring (quassine in Bitterness Booster, Symrise Pty Ltd) to ensure similarities in the taste and appearance of the deltaG™ and placebo drinks. The bitter flavouring is used widely as a flavour ingredient in foods and has no metabolic effects. Over 250 athletes have been unable to distinguish between control and deltaG™ drinks (*unpublished data*). Due to the very bitter taste of the deltaG and placebo drinks, all subjects will be asked to subsequently rinse their mouth with water.

Overview of deltaG™ study



Pre-study screening will include medical history, physical examination, body weight and height, vital signs (blood pressure, pulse rate, and temperature), 12 lead ECG plus blood and urine tests. Clinical chemistry and haematology laboratory tests, vital signs, and clinical adverse events will form the main body of the safety and tolerability data. Female volunteers will be tested to ensure that they are not pregnant.

Haematology: White blood cell count (WBC), red blood cell count (RBC), haemoglobin concentration, haematocrit, mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelet count.

Clinical chemistry: Albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, amylase, CO_2/bicarbonate, calcium, chloride, cholesterol, creatinine, creatine kinase, HDL cholesterol, LDL cholesterol, free fatty acids, gamma-glutamyltransferase, glucose, insulin, iron, lactate dehydrogenase, magnesium, phosphate, potassium, protein, sodium, total bilirubin, triglycerides and uric acid. The plasma ketones, β-hydroxybutyrate and acetoacetate, will also be measured.

Urinalysis: Specific gravity, pH, ketones, protein, glucose, occult blood, urobilinogen, bilirubin and microscopic evaluation.

The daily volumes for the first 21 days would be the same as recommended in the novel food submission whereas the daily volumes for the final 7 days would be twice the maximum recommended daily volume. Such a dosing regime will provide a chronic daily exposure that is unlikely to be achieved through recommended use as an energy source. Volunteers will make 7 visits at weekly intervals to the University of Oxford Clinical Trials Unit (CTU) for determination of the safety parameters (listed above), including haematology, clinical chemistry and urinalysis. Fasting blood samples will also be collected on the morning of days 1, 7, 14, 21, and 28 for ketone levels. While in the CTU and one hour after their first drink, volunteers will have their β-hydroxybutyrate and glucose levels measured in a drop of blood, obtained using a finger prick, in a handheld meter (Abbott). Adverse events will be recorded by an Independent Monitor and food intake diaries and a GI symptom record will be kept by all participants for later analysis by a dietician and statistician, respectively.

At the end of each intervention, all subjects will undergo a full post-study screen, including physical examination, body weight and height, vital signs (blood pressure, pulse rate and temperature) 12 lead ECG and blood and urine tests. One week following the last visit of the second intervention, all subjects will be asked to return to the CTU for determination of the safety parameters (listed above), including haematology, clinical chemistry and urinalysis. Tolerance will be determined through the assessment of the safety parameters and adverse events correlated with the circulating plasma β-hydroxybutyrate concentrations. The measured safety parameters will be evaluated for trends related to continual exposure.

Reference:

1. Clarke K, Tchabanenko K, Pawlosky R, Carter E, Todd King M, Musa-Veloso K, Ho M, Roberts A, Robertson J, Vanitallie TB, Veech RL. *Regul. Toxicol. Pharmacol.* 2012; 63: 401-408

ACNFP 117/04
ANNEX B

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10 July 2014

D-beta-HYDROXYBUTYRATE ESTER

Dear Professor Clarke,

Thank you for your letter of 21 March in which you sought further advice from ACNFP Members on how you might answer the Committee's remaining concerns about this novel ingredient. I am sorry it has taken so long to respond.

I should point out that the conclusions reported from the Committee's discussions are agreed by the whole Committee and they are not the views of individual members.

The Committee discussed your request at its meeting on 16 April and stated that its concerns are two-fold:

(a) The available data are not sufficient to conclude on the safety of the novel ingredient under the intended conditions of use, namely as a source of additional energy for elite athletes.

(b) Authorisation as a novel food means that products containing the novel ingredient can be freely marketed and it is not clear how consumption of such products would be restricted to that group.

The detailed rationale for these concerns was set out in my letter of 18 March. The Committee endorsed this as an accurate summary of the position and confirmed that the arguments set out in your reply into consideration. You highlighted an apparent contradiction between accepting the fact that humans can tolerate chronic ketosis, and expressing concern about the consumption of the ketone ester at levels that result in similar levels of circulating ketones. The Committee pointed out however that the purpose of their evaluation is to assess the safety of the novel when

consumed in large doses by already well-fed individuals. This is a key difference between references to ketone metabolism as a "normal" process when people experience periods of starvation and the situation which would pertain if this product was used by athletes or others. Of necessity, "elite" athletes will be already very well nourished and the aim of this product is to supply "extra energy" on top of an excellent supply of energy via the normal route of glucose and fatty acids from the diet.

In order for the Committee to complete its evaluation of safety under the intended conditions of use among elite athletes, it would need further evidence of safety, for example a longer animal feeding study and/or further clinical studies as described in the letter of 21 March.

For the second point, you have explained that the ketone ester would provide no benefit for people outside the target group. However, the Committee does not agree that people only consume foods and supplements that have a clear and proven benefit for them. The sort of information that would help here would be: a precise definition of the target group of "elite athletes"; expected frequency of use; labelling information and instructions for use that will accompany products containing the novel ingredient; post market monitoring of usage patterns and sales channels; monitoring of adverse reactions; accurate online information for the intended users of the product.

The Committee also discussed your request for a face-to-face meeting with Committee members but did not think that this was consistent with the Committee's collegiate approach and with its commitment to maximum openness.

I am sorry that this letter has been delayed due to competing priorities here in FSA and I hope that the information above will help you decide on how you wish to proceed with this application. Dr Lawrie's letter of 18 March set out the three possible options:

- To undertake additional studies to address the uncertainties set out above;
- For the ACNFP to complete its evaluation on the basis of the existing data.
  This would mean the FSA advising the European Commission and other Member States that further assessment is required. As set out in Article 7 of the novel food regulation (Regulation (EC) No 258/97), the application would then be referred to the European Food Safety Authority for its advice prior to a decision being taken at EU level;
  or
- To withdraw the application.

Finally, I should inform you that, as part of a recent restructure in the Food Safety Policy area of the FSA, work on novel foods will now fall under a new unit dealing with novel foods, GM food and food allergies. This new team will be headed by Dr Stephen Johnson, who fully takes up this post from 14 July 2014.

Yours sincerely,

Alison Asquith
Administrative Secretary to ACNFP
cc Professor Peter Gregory (ACNFP Chair)
Dr Stephen Johnson
Dr Ashley Roberts (Intertek)