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NWT-02, a fixed combination of lutein, zeaxanthin and docosahexaenoic acid in egg yolk and reduction of the loss of vision: evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006

EFSA Panel on Dietetic Products, Nutrition and Allergies (EFSA NDA Panel), Dominique Turck, Jean-Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Kristina Pentieva, Yolanda Sanz, Anders Sjödin, Martin Stern, Daniel Tomé, Henk Van Loveren, Marco Vinceti, Peter Willatts, Ambroise Martin, Sean (J.J.) Strain and Alfonso Siani

Abstract

Following an application from Newtricious R&D B.V., submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of the Netherlands, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to NWT-02 and a reduction of the loss of vision. The food proposed by the applicant as the subject of the health claim is NWT-02. NWT-02 is standardised by its content in lutein (≥ 1.10 mg), zeaxanthin (≥ 0.20 mg) and docosahexaenoic acid (DHA) (≥ 170 mg). The Panel considers that the food/constituent that is the subject of the health claim, NWT-02, a fixed combination of lutein, zeaxanthin and docosahexaenoic acid in egg yolk, is sufficiently characterised. The claimed effect proposed by the applicant is 'reduces loss of vision'. The target population proposed by the applicant is 'healthy adults over 50 years of age'. The Panel considers that a reduction of the loss of vision is a beneficial physiological effect. The applicant provided two human intervention studies for the scientific substantiation of the claim. The Panel considers that the only study from which conclusions can be drawn for the scientific substantiation of the claim did not show an effect of NWT-02 on vision. The Panel concludes that a cause and effect relationship has not been established between the consumption of NWT-02, a fixed combination of lutein, zeaxanthin and docosahexaenoic acid in egg yolk, and a reduction of the loss of vision.

Keywords: NWT-02, vision, vision acuity, health claim

Requestor: Competent Authority of the Netherlands following an application by Newtricious R&D B.V

Question number: EFSA-Q-2017-00539

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Summary

Following an application from Newtricious R&D B.V., submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of the Netherlands, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to NWT-02, a fixed combination of lutein, zeaxanthin and docosahexaenoic acid (DHA) in egg yolk and a reduction of the loss of vision.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.

The general approach of the NDA Panel for the evaluation of health claims applications is outlined in the EFSA general guidance for stakeholders on health claim applications and the guidance on the scientific requirements for health claims related to functions of the nervous system, including psychological functions.

The food proposed by the applicant as the subject of the health claim is NWT-02. NWT-02 is standardised by its content in lutein (≥ 1.10 mg), zeaxanthin (≥ 0.20 mg) and DHA (≥ 170 mg), the food constituents which are claimed by the applicant as being responsible for the claimed effect. The Panel considers that the food/constituent that is the subject of the health claim, NWT-02, a fixed combination of lutein, zeaxanthin and DHA in egg yolk, is sufficiently characterised.

The claimed effect proposed by the applicant is 'reduces loss of vision'. The target population proposed by the applicant is 'healthy adults over 50 years of age'. The Panel considers that a reduction of the loss of vision is a beneficial physiological effect.

The applicant provided two human intervention studies for the scientific substantiation of the claim. The Panel considers that the only study from which conclusions can be drawn for the scientific substantiation of the claim did not show an effect of NWT-02 on vision.

The applicant also provided a meta-analysis including the results of the two human studies provided and three additional studies on NWT-02 which did not assess any outcomes related to vision. The Panel considers that no conclusions can be drawn from these studies or the meta-analysis for the scientific substantiation of the claim.

In the absence of evidence for an effect of NWT-02 on vision, the studies provided by the applicant on the proposed mechanisms by which the food/constituent could exert the claimed effect, or studies on different combinations of lutein, zeaxanthin and omega-3 fatty acids not complying with the characterisation of NWT-02, were not considered by the Panel for the scientific substantiation of the claim.

In weighing the evidence, the Panel considers that the only study from which conclusions can be drawn for the scientific substantiation of the claim did not show an effect of NWT-02 on vision.

On the basis of data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of NWT-02, a fixed combination of lutein, zeaxanthin and DHA in egg yolk and a reduction of the loss of vision.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1924/2006[1] harmonises the provisions that relate to nutrition and health claims and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

1.2. Interpretation of the Terms of Reference

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to NWT-02 and a reduction of the loss of vision.

The present opinion does not constitute and cannot be construed as, an authorisation for the marketing of NWT-02, a positive assessment of its safety nor a decision on whether NWT-02 is or is not classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

2. Data and methodologies

2.1. Data

Information provided by the applicant

Food/constituent as stated by the applicant

According to the applicant, the food for which the health claim is made is NWT-02: egg yolk (fresh/liquid or powder) containing docosahexaenoic acid (DHA), lutein and zeaxanthin. The food is based on food constituent NWT-02 plus buttermilk, flavouring and sugar – for use in readily absorbable dietary supplement formats (sachets) as well as in beverages.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect relates to: 'reduces loss of vision. Visual function as measured by Best Corrected Visual Acuity (BCVA). BCVA is measured in subjects that range from having signs of ageing in the eye to intermediate signs of age-related macular degeneration (AMD), the most common cause of vision loss of people aged over 50. It is associated with a gradual loss of central vision, which is needed for detailed work when focusing is important (such as reading and driving)'.

Mechanism by which the food/constituent could exert the claimed effect as proposed by the applicant

According to the applicant, NWT-02 contains several bioactive components (DHA, lutein and zeaxanthin), which have separately already been proven to have a role in visual function. DHA is an

[1] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

omega-3 fatty acid that is a primary structural component of the retina. Biophysical and biochemical properties of DHA affect photoreceptor membrane function by altering permeability, fluidity, thickness and lipid-phase properties. DHA functions in neurogenesis, neurotransmission, protection against oxidative stress and inflammation. It is concentrated in the rod cells of retinal photoreceptors, where it facilitates conformational change and the subsequent signal transduction cascade triggered by a light signal, which shows the importance of DHA in visual function. Lutein and zeaxanthin are both xanthophylls, members of a group of natural carotenoid pigments produced by plants. Humans are unable to synthesise lutein and zeaxanthin. Within the structure of the eye, the natural yellow colour of the macula lutea ('the yellow spot') consists mainly of the carotenoids lutein, zeaxanthin and meso-zeaxanthin. Macular carotenoids (as measured through macular pigment optical density (MPOD)) protect eye function through different mechanisms, amongst which are protection against (mainly shortwave, blue) light and as antioxidant. Alternatively, lutein affects immune responses and inflammation. Mechanisms to explain the anti-inflammatory effect of lutein include reactive oxygen species (ROS) scavenging during the inflammatory process and inhibition of nuclear factor-kappa B (NF-κB) activation.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: 'Consumption of NWT-02 reduces loss of vision'.

Specific conditions of use as proposed by the applicant

According to the applicant, the target population for the intended health claim is healthy adults over 50 years of age. This population is a prime target for products aiming at counteracting the reduced loss of visual function because these adult individuals can commonly display levels of established biomarkers that indicate increased risk for deterioration in vision. The studied product contains egg yolk. Therefore, individuals allergic to egg should avoid consuming any foods to which the product has been added. The finished product used in the human intervention studies was a combination of NWT-02, buttermilk and flavouring. Individuals that are lactose intolerant and/or allergic to cacao or dairy or who have specific flavouring-related problems should avoid using the product as well.

Approximately 15 g of NWT-02 food ingredient containing DHA (≥ 170 mg), lutein (≥ 1.10 mg) and zeaxanthin (≥ 0.20 mg) should be consumed once daily in either a dietary supplement or in a beverage format. For beverages, a volume between 50 and 500 mL can be consumed daily to deliver the target level. The desired effect on visual acuity was demonstrated after chronic consumption over a minimum 6–12 month period.

Data provided by the applicant

Health claim application on consumption of NWT-02 and a reduction of the loss of vision pursuant to Article 13.5 of Regulation 1924/2006, presented in a common and structured format as outlined in the Scientific and technical guidance for the preparation and presentation of applications for authorisation of health claims.[2]

As outlined in the General guidance for stakeholders on health claim applications,[3] it is the responsibility of the applicant to provide the totality of the available evidence.

This health claim application includes a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006.

Data claimed to be proprietary and confidential by the applicant include: manufacturing process, stability information, detailed information on unpublished I-TEAM (2017) study, unpublished meta-analyses and pooled analysis (specified in details in Confidentiality Decision).

[2] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle HJ, Naska A, Neuhäuser-Berthold M, Nowicka G, Pentieva K, Sanz Y, Sjödin A, Stern M, Tomé D, Van Loveren H, Vinceti M, Willatts P, Martin A, Strain JJ, Heng L, Valtuena Martınez S and Siani A, 2017. Scientific and technical guidance for the preparation and presentation of a health claim application (Revision 2). EFSA Journal 2017;15(1):4680, 31 pp. https://doi.org/10.2903/j.efsa.2017.4680.

[3] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2016. General scientific guidance for stakeholders on health claim applications. EFSA Journal 2016;14(1):4367, 38 pp. https://doi.org/10.2903/j.efsa.2016.4367

2.2. Methodologies

The general approach of the Dietetic Products, Nutrition and Allergies (NDA) Panel for the evaluation of health claim applications is outlined in the EFSA general guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016).

The scientific requirements for health claims related to functions of the nervous system, including psychological functions are outlined in a specific EFSA guidance (EFSA NDA Panel, 2012).

3. Assessment

3.1. Characterisation of the food/constituent

The food proposed by the applicant as the subject of the health claim is NWT-02. NWT-02 is standardised by its content in lutein (≥ 1.10 mg), zeaxanthin (≥ 0.20 mg) and DHA (≥ 170 mg), the food constituents which are claimed by the applicant as being responsible for the claimed effect.

NWT-02 is available as beverage and as powder. The beverage and powder formulations are derived from fresh egg yolks. Comparable bioavailability for lutein has been reported for both formulations of NWT-02 (Bunger et al., 2014). NWT-02 is intended for use in readily absorbable dietary supplement formats as well as in foods and beverages.

The details of the manufacturing process were provided and claimed as confidential by the applicant. Information related to stability and batch-to-batch variability was provided.

The Panel considers that the food/constituent that is the subject of the health claim, NWT-02, a fixed combination of lutein, zeaxanthin and docosahexaenoic acid in egg yolk, is sufficiently characterised.

3.2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is 'reduces loss of vision'. The target population proposed by the applicant is 'healthy adults over 50 years of age'.

Vision is a defined function of the eye and nervous system. An increase, maintenance or reduced loss of vision is a beneficial physiological effect for the general population, including, for example, visual display terminal workers. Claims may focus on vision under specific light conditions, for example, improvement of visual adaptation to the dark. The scientific evidence for the substantiation of health claims related to vision can be obtained from human intervention studies showing an effect on visual function by using standard tests of visual acuity and contrast sensitivity (e.g. measures of contrast acuity thresholds and distance and near visual acuity tests). Evidence for an effect on the incidence of clinically diagnosed eye-related diseases associated with the impairment of vision (e.g. age-related macular degeneration and cataract) by using valid clinical diagnostic tools could also be used for the scientific substantiation of claims on the maintenance of vision (EFSA NDA Panel, 2012).

With respect to the study population, subjects with vision deficits without clinically diagnosed diseases which may be responsible for the deficit could be an appropriate study group for claims on the maintenance of vision as long as the methods and inclusion/exclusion criteria used to characterise the study group are clearly identified in the study design. The rationale for extrapolation of the results obtained in patients with a clinically diagnosed impairment of vision (e.g. cataract, age-related macular degeneration, diabetic retinopathy, inherited retinal degeneration and retinal vascular occlusive disease) to the target population for the claim (e.g. subjects without the vision impairment) should be provided and will be considered on a case-by-case basis (e.g. evidence that the mechanism by which the food constituent may exert the claimed effect in patients with the disease is also relevant for subjects without the disease) (EFSA NDA Panel, 2012).

The Panel considers that a reduction of the loss of vision is a beneficial physiological effect.

3.3. Scientific substantiation of the claimed effect

The applicant performed a literature search in the PubMed and Cochrane databases using the term 'visual acuity' together with the individual food constituents in NWT-02 ('lutein' or 'zeaxanthin' or 'docosahexaenoic acid' or 'DHA'). Excluded were studies in infants, young people, pregnant women and post-surgery individuals; studies in which subjects received cotreatment (e.g. vitamin A); studies focusing on end points other than visual acuity (speed of neuronal processing, photo-stress, recovery and diagnostics); studies using a specific food containing either lutein, zeaxanthin or DHA (wolfberry,

yellow carrots) but not their combination; studies focusing on disease incidence (such as AMD incidence); studies looking at specific ocular diseases (choroideremia, glaucoma, cataracts).

The applicant provided two human intervention studies for the scientific substantiation of the claim. The first study investigated the effect of NWT-02 on a wide range of variables, including visual function as a secondary outcome. The results of the study are reported in two publications (Van der Made et al., 2014, 2016), of which only one reports on outcomes related to visual function (Van der Made et al., 2016). Upon a request from EFSA, the applicant also provided the clinical study report (NWT-02_CRS Piv1_Final, 2015 – unpublished), which contains information about all variables assessed in the study. The second study was specifically designed to investigate the effect of NWT-02 on visual function, which was the primary outcome of the study (I-TEAM, 2017 – unpublished study report).

Both studies included subjects with early or intermediate AMD. The applicant was requested by EFSA to justify how the results obtained in these subjects could be extrapolated to the target population for the claim (healthy adults over 50 years of age). In reply, the applicant noted that, even if subjects with either early or intermediate stages of AMD were included in the studies, an exclusion criterion for both studies was vision impairment, defined as visual acuity ≤ 0.5. The Panel considers that the results of studies conducted in subjects with early or intermediate stages of AMD but without vision impairment (vision acuity > 0.5) can be extrapolated to the target population for the claim (i.e. healthy adults over 50 years of age).

The first study (NWT-02_CRS Piv1_Final, 2015 – unpublished; Van der Made et al., 2016) was a randomised, double-blind, placebo-controlled, two-arm parallel intervention which assessed the effects of NWT-02 given as a beverage (80 mL of fresh drink per day containing 1.5 egg yolk and buttermilk and, on average 1.38 $\pm$ 0.16 mg of lutein, 0.21 $\pm$ 0.02 mg of zeaxanthin and 160 $\pm$ 10 mg of DHA) for 1 year as compared to a control beverage (a buttermilk drink without egg yolk matched for colour and taste to the test beverage given in the same amounts) in a group of subjects 50 years of age and older.

Inclusion criteria were drusen (small yellow deposits in the macula) and/or retinal pigment epithelium alterations in at least one eye in fundus photographs and visual acuity > 0.5. Individuals with ocular media opacities, diagnosis of diabetes or cardiovascular diseases, history of allergy to eggs and individuals using dietary supplements containing lutein or zeaxanthin or lipid-lowering medications were excluded from the study.

Subjects were allocated to the test or placebo beverages according to a pre-established, computer-generated randomisation scheme. Allocation was concealed in sequentially numbered, sealed envelopes and stored by the study coordinator.

A total of 101 subjects were randomised (52 in the test group and 49 in the control group, mean age 62 $\pm$ 7 and 63 $\pm$ 8 years, respectively, and gender ratio (m/f) 17/34 and 15/34, respectively).

The primary objectives of the study were to assess the effects of NWT-02 on changes in MPOD, changes in amount of early macular degeneration signs on fundus photographs (drusen or retinal pigment epithelium changes in fundus photography) and changes in plasma lutein and zeaxanthin concentrations. Changes in MPOD were the primary outcome of the study, and this variable was used for power calculations. Secondary outcomes were: morphological changes of the retina; changes in BCVA, contrast sensitivity (six different spatial frequencies tested) dark adaptation, field of vision, vascular function (by means of flow-mediated vasodilation – FMD) and lipid metabolism (serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, serum triglycerides, ApoA1, ApoB concentrations).

BCVA was measured with an internally illuminated Early Treatment Diabetic Retinopathy Study – ETDRS logMAR chart at 4 m. Contrast sensitivity was evaluated by computer testing with the use of vertical stripes at different greyscale tones on six spatial frequencies (at 0.5, 2, 4.0, 8.0, 12.0 and 16.0°). Rod rate dark adaptation was measured with the use of a seven-parameter model using the Nelder–Mead method. Peripheral visual field was evaluated by perimetry.

All outcomes were measured three times (at baseline, and after 6 and 12 months).

Sample size ($n = 48$ subjects) was calculated assuming that MPOD will improve by 12%, with a MPOD measuring error of 17%, $\alpha = 5\%$, power of 90% and a 10% dropout rate. A similar sample size was calculated to power the study on BCVA, assuming a difference between groups at 12 months of 0.10 lines after adjusting for baseline values, with an expected standard deviation (SD) for each group of 0.10, with 90% power and $\alpha = 0.05$. The authors argue, however, that for one of the secondary outcome parameters in this study which was FMD, 50 subjects per group should be included to detect

a difference in FMD of at least 1%, assuming a SD of 1.7%, a dropout rate of 10%, a power of 80% and a significance level of 5%.

The Pearson Chi-square test (for categorical variables) and the unpaired Student's *t*-test (for continuous variables) were used to assess baseline differences between groups. Linear Mixed Models' analyses with subject ID as grouping factor and diet and time and their interaction term as covariate were performed to evaluate differences in MPOD and visual acuity.

Twelve participants dropped out (six subjects in each group) and the reasons for dropping out were reported. Finally, 89 participants finished the study (46 in the test group and 43 in the control group).

The applicant claims that the statistical analyses were performed for the 'intention to treat (ITT)' and 'per protocol (PP)' populations, defined as subjects with at least one measurement for a given outcome variable after baseline (either at 6 or at 12 months) and subjects with measurements at both 6 and 12 months for a given outcome variable, respectively. The Panel notes that the number of subjects considered with respect to each outcome variable for the 'ITT' and 'PP' analysis differed (ranging from 38 to 46 subjects per group depending on the outcome variable and the analysis performed) that subjects with missing data for a given outcome (one or two data points, depending on the analysis) were just removed from the analyses and that compliance with the protocol was not considered to define the PP population. The Panel considers that the statistical analyses were conducted in two different populations of completers rather than on true ITT or PP populations.

At baseline, no statistically significant differences were found between the two groups for age, plasma lutein and zeaxanthin concentrations, MPOD and BCVA.

No significant differences between groups were found in relation to rod rate dark adaptation or contrast sensitivity in either analysis. A significant decrease of 0.0052 ± 0.0017 LogMAR units per month (i.e. half a line increase on ETDRS chart over 1 year) was observed in the lutein group as compared to the control group ($p < 0.01$ as reported in the publication; $p < 0.001$ as reported in the study report). The Panel notes that BCVA was a secondary outcome of the study and that the statistical analysis was not corrected for multiple testing. Following a request for clarification by EFSA, the applicant provided a reanalysis of the data only for some variables (plasma lutein and zeaxanthin concentrations, MOPD and BCVA) following a gate-keeping procedure consisting of three steps: 1) significance in plasma levels of both lutein and zeaxanthin; 2) significance in BCVA outcome; 3) significance in MPOD functionality. In the first step, the significance level was split into two ($p < 0.025$) to account for two variables (plasma lutein and zeaxanthin concentrations). For the next step (significance of the BCVA outcome), the significance parameter was kept at $p < 0.05$ with the argument that only one variable was being assessed. The Panel notes, however, that about 20 different outcome variables were assessed in this study, that the gatekeeping adjustment for multiplicity of outcomes was planned and performed a posteriori and that the correction of the statistical analysis conducted by the applicant is not appropriate for the study design.

The Panel notes that this study has important methodological limitations (statistical analyses on completers only; the outcome variables related to vision were secondary outcomes among many others; no adequate correction for multiplicity of outcomes) and considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

The second human intervention study submitted was a four-centre, parallel, double-blind, randomized, placebo-controlled study (I-TEAM, unpublished study report, 2017) which assessed the effect of NWT-02 on parameters of visual function.

An inclusion criterion was early or intermediate AMD (Age-Related Eye Disease Study (AREDS) categories 2 or 3). Other inclusion criteria were age at least 50 years; body mass index (BMI) between 18 and 35 kg/m^2; vision > 20/40 for Snellen visual acuity; lutein intake including supplements < 2 mg/day; DHA intake including supplements < 150 mg/day; normal haematologic parameters and normal values for plasma albumin and parameters of liver and kidney function. Subjects were excluded if they were taking supplements of carotenoids, fish oil or n-3 fatty acids 1 month prior to the start of the study.

The primary outcome was visual acuity measured as BCVA. Secondary outcomes were contrast sensitivity (by Pelli-Robson chart), MPOD (by heterochromatic flicker photometry), serum zeaxanthin concentration and basic laboratory blood tests.

Power calculation was based on a 90% power to detect a true difference of 0.10 lines on a BCVA chart, with a between-group SD of 0.15 lines and a dropout rate of 20%. A sample size of 115 subjects was estimated.

Based on this calculation, the study was designed to include 120 participants. Subjects were recruited at four sites: Boston (US), Manchester (UK), Bonn (Germany) and Nijmegen (Netherlands).

The randomisation list was generated centrally by the clinical research organisation selected by the study sponsor. Subjects were allocated to consume either NWT-02 or placebo daily for 1 year, in a ratio of 1:1. A subject was given the next number in sequence to maintain double blinding at the sites.

The NWT-02 beverage was supplied as a dry powder (in sachet format) and was prepared, at the time of consumption, by the addition of water. The placebo was also a powder formulation supplied in sachets and had similar energy content and organoleptic properties. The subjects were requested to dissolve the content of one (test or placebo) sachet in 60 mL water and to consume the beverage shortly after preparation.

Three visits were scheduled: at baseline (randomisation), at 6 months and at 12 months. Subjects were contacted by phone every 2 months to record any adverse events.

A total of 120 subjects were randomised (n = 59 to the NWT-02 group and n = 61 to the placebo group; mean age 72 years, 52% women). Early and intermediate stage AMD was diagnosed in 26% and 67% of participants, respectively. There were 21 dropouts (9 in the NWT-02 and 12 in the placebo group). The reasons for dropouts were reported.

To evaluate differences in outcomes between the NWT-02 group and placebo, the General Estimating Equation (GEE) was used, applying repeated measurements in a stepwise approach. In the GEE model, various factors were taken into account: baseline value, age, gender, BMI, diastolic blood pressure, centre, time, treatment and interaction between time and treatment. Fit of the model was addressed via Wald Chi-square test. Outlier analysis was conducted using Grubbs test (two-sided).

The primary statistical analysis was the ITT analysis including all randomised subjects and all centres. No information was provided on the methods used to account for missing data. The results were also presented for the ITT population except the identified outliers.

One centre used a different scoring system for BCVA compared to the other centres. The results obtained in this centre were modified to make them comparable to the other centres.

No significant treatment per time interaction was found on BCVA in the main analysis (ITT analysis considering all centres). Inclusion of centre as a factor did not affect the outcome of the statistical analysis. No significant treatment per time interaction was found in relation to changes in contrast sensitivity.

The applicant also reported the results of a post hoc analysis considering only the two centres with the highest recruitment (77% of all subjects). The Panel notes that this subgroup analysis was not preplanned and considers that no conclusions can be drawn from this analysis for the scientific substantiation of the claim.

The Panel considers that this study did not show an effect of NWT-02 on vision.

Three additional studies submitted by the applicant on NWT-02 did not assess any outcomes related to vision (Bunger et al., 2014; Kelly et al., 2014; Severins et al., 2015). The applicant also provided a meta-analysis including the results of the two studies described above (Van der Made et al., 2016; I-TEAM, 2017). The Panel considers that no conclusions can be drawn from these studies or the meta-analysis for the scientific substantiation of the claim.

In the absence of evidence for an effect of NWT-02 on vision, the studies provided by the applicant on the proposed mechanisms by which the food/constituent could exert the claimed effect, or studies on different combinations of lutein, zeaxanthin and omega-3 fatty acids not complying with the characterisation of NWT-02, were not considered by the Panel for the scientific substantiation of the claim.

Weighing of the evidence

In weighing the evidence, the Panel considers that the only study from which conclusions can be drawn for the scientific substantiation of the claim (I-TEAM, 2017) did not show an effect of NWT-02 on vision.

The Panel concludes that a cause and effect relationship has not been established between the consumption of NWT-02, a fixed combination of lutein, zeaxanthin and docosahexaenoic acid in egg yolk and a reduction of the loss of vision.

4. Conclusions

On the basis of the data presented, the Panel concludes that:

- The food/constituent, NWT-02, a fixed combination of lutein, zeaxanthin and docosahexaenoic acid in egg yolk, is sufficiently characterised.

- The claimed effect proposed by the applicant is 'reduces loss of vision'. The target population proposed by the applicant is 'healthy adults over 50 years of age'. Reduction of the loss of vision is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of NWT-02, a fixed combination of lutein, zeaxanthin and DHA in egg yolk and a reduction of the loss of vision.

Steps taken by EFSA

Health claim application on 'NWT-02' and 'reduction of the loss of vision' pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0459_NL). Submitted by Newtricious R&D B.V., Onderwijsboulevard 225, 5223 DE 's-Hertogenbosch, the Netherlands. The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.

1) This application was received by EFSA on 29/6/2017. On 2/8/2017, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
2) On 11/8/2017, EFSA received the missing information as submitted by the applicant.
3) The scientific evaluation procedure started on 13/9/2017.
4) On 15/9/2017, the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application. The scientific evaluation was suspended on 22/9/2017 and was restarted on 4/10/2017, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
5) On 3/10/2017, EFSA received the applicant's reply (which was made available to EFSA in electronic format on 3/10/2017).
6) On 13/12/2017, the NDA Panel, having evaluated the data submitted, adopted by written procedure an opinion on the scientific substantiation of a health claim related to NWT-02 and a reduction of the loss of vision.

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Abbreviations

AMD	Age-related Macular Degeneration
AREDS	The Age-Related Eye Disease Study
BCVA	Best-Corrected Visual Acuity
BMI	Body Mass Index
DHA	docosahexaenoic acid
ETDRS	Early Treatment Diabetic Retinopathy Study
FMD	flow-mediated vasodilatation
GEE	General Estimating Equation
HDL	High-density lipoprotein
ITT	Intention to treat
LDL	Low-density lipoprotein
MPOD	macular pigment optical density
NDA	EFSA Panel on Dietetic Products, Nutrition and Allergies
PP	Per protocol
ROS	Reactive Oxygen Species