European Food Safety Authority

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to Symbiosal® and lowering of blood pressure and reduced risk of hypertension pursuant to Article 14 of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Han-Asiabiotech GmbH, submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Germany, 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 Symbiosal® and lowering of blood pressure and reduced risk of hypertension. The Panel considers that the food, Symbiosal®, which is the subject of the health claim, and the food, table salt, which Symbiosal® should replace, are sufficiently characterised. Lowering of blood pressure is a beneficial physiological effect for people who want to lower their blood pressure. Increased blood pressure is a risk factor for hypertension. In weighing the evidence, the Panel took into account that one human study with methodological limitations showed a decrease in blood pressure when Symbiosal® was consumed instead of table salt for eight weeks in the context of a salt-restricted diet, but that no other human studies in which these results have been replicated were provided, that the animal studies did not support the results of the human study and that no evidence was provided for a mechanism by which the food could exert the claimed effect. The Panel concludes that a cause and effect relationship has not been established between the consumption of Symbiosal® instead of table salt and lowering of blood pressure.

KEY WORDS

Symbiosal®, chitosan, sodium chloride, blood pressure, hypertension, health claims

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[1] On request from the Competent Authority of Germany following an application by Han-Asiabiotech GmbH, Question No EFSA-Q-2014-00366, adopted on 11 June 2015.

[2] Panel members: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Sean (J.J.) Strain, Inge Tetens, Hendrik Van Loveren, Hans Verhagen and Peter Willatts for the preparatory work on this scientific opinion.

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SUMMARY

Following an application from Han-Asiabiotech GmbH, submitted for authorisation of a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of Germany, 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 Symbiosal® and lowering of blood pressure and reduced risk of hypertension.

The scope of the application was proposed to fall under a health claim referring to disease risk reduction. The application included a request for the protection of proprietary data.

The food that is the subject of the health claim is Symbiosal®, which, according to the applicant, should replace table salt (i.e. sodium chloride, NaCl) in order to obtain the claimed effect. NaCl is a well characterised salt. Symbiosal® is produced by mixing sea salt (97 %) with chitosan (3 %), following a patented manufacturing process. Chitosan is a linear cationic polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine and *N*-acetyl-D-glucosamine. The Panel considers that the food, Symbiosal®, which is the subject of the health claim, and the food, table salt (i.e. NaCl), which Symbiosal® should replace, are sufficiently characterised.

The claimed effect proposed by the applicant is "lowers the rising of blood pressure when used as a replacement of traditional table salt. The rising of blood pressure is a risk factor for hypertension". The target population proposed by the applicant is "healthy mild hypertensive subjects, and people who want/need to lower the rising of their blood pressure". The Panel considers that lowering of blood pressure is a beneficial physiological effect for people who want to lower their blood pressure. Increased blood pressure is a risk factor for hypertension.

The applicant provided one human intervention study which assessed the effect of Symbiosal® on blood pressure when replacing table salt in the context of a salt-restricted diet. In this randomised, double-blind, cross-over study, 40 individuals with stage 1 hypertension received 3 g/day Symbiosal® or 3 g/day table salt (both as added salt in the diet). The two cross-over periods lasted eight weeks each and were separated by a washout of two weeks. Results of a paired t-test on the intention-to-treat population indicated that the reductions of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were higher when Symbiosal® was consumed instead of table salt (SBP: −8.7 ± 10.8 mmHg vs. −3.2 ± 8.5 mmHg, p = 0.0156; DBP: −7.2 ± 8.0 mmHg vs. −3.7 ± 7.4 mmHg, p = 0.0285). Similar results were obtained in a "per protocol" analysis. Highly significant period effects were observed for SBP and DBP, i.e. most of the reductions in blood pressure were observed during the first cross-over period. The Panel notes that significant period effects were observed for SBP and DBP. The Panel also notes that blood pressure did not return to baseline after the washout period. The Panel notes the limitations of the paired t-test for the analysis of cross-over designs when there are carry over and/or period effects. The Panel considers that this study with methodological limitations showed a decrease in SBP and DBP when 3 g Symbiosal® per day was consumed instead of table salt as added salt for eight weeks accompanied by a salt-restricted diet.

The Panel considers that the animal studies did not support the human study and that no evidence was provided for a mechanism by which Symbiosal® could lower blood pressure when consumed instead of table salt.

In weighing the evidence, the Panel took into account that one human study with methodological limitations showed a decrease in blood pressure when Symbiosal® was consumed instead of table salt for eight weeks in the context of a salt-restricted diet, but that no other human studies in which these results have been replicated were provided, that the animal studies did not support the results of the human study and that no evidence was provided for a mechanism by which the food could exert the claimed effect.

The Panel concludes that a cause and effect relationship has not been established between the consumption of Symbiosal® instead of table salt and lowering of blood pressure.

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BACKGROUND

Regulation (EC) No 1924/2006[4] 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, Articles 14 to 17 of this Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to Article 15 of this Regulation, an application for authorisation 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).

STEPS TAKEN BY EFSA

- The application was received on 20/05/2014.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction. The application included a request for the protection of proprietary data.
- On 28/07/2014, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- On 28/08/2014, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 03/09/2014.
- On 16/10/2014, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application and the scientific evaluation was suspended on 30/10/2014, in compliance with Article 16(1) of Regulation (EC) No 1924/2006.
- On 22/12/2014, EFSA received the applicant's reply and the scientific evaluation was restarted, in compliance with Article 16(1) of Regulation (EC) No 1924/2006.
- On 06/02/2015, the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application and the scientific evaluation was suspended on 19/02/2015, in compliance with Article 16(1) of Regulation (EC) No 1924/2006.
- On 15/04/2015, EFSA received the applicant's reply and the scientific evaluation was restarted, in compliance with Article 16(1) of Regulation (EC) No 1924/2006.
- During its meeting on 11/06/2015, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to Symbiosal® and lowering of blood pressure.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16 of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an

[4] 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.

opinion on the scientific substantiation of a health claim related to: Symbiosal® and lowering of blood pressure and reduced risk of hypertension.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of Symbiosal®, a positive assessment of its safety, nor a decision on whether Symbiosal® 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 17 of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address

Han-Asiabiotech GmbH, Industriestrasse 1, D-77731 Willstätt, Germany.

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

Food/constituent as stated by the applicant

According to the applicant, the food that is the subject of the health claim is Symbiosal®, which is a food supplement containing sea salt (97 %) plus chitosan (3 %).

Health relationship as claimed by the applicant

According to the applicant, consumption of Symbiosal® instead of standard table salt lowers blood pressure, thereby lowering the risk of hypertension. The applicant indicated "rising of blood pressure" as the risk factor and "high blood pressure (hypertension)" as the disease.

With regards to the mechanism by which the food would exert the claimed effect, the applicant indicated that the mechanism is not clearly known but that some findings suggest that chitosan may inhibit the increase of angiotensin-converting enzyme induced by an acute salt intake. The applicant also claimed that this inhibition might be mediated by blocking or counteracting the hypertensive effect of the chloride ions in sodium chloride (NaCl).

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "Symbiosal has been shown to lower the rising of blood pressure when used as a replacement of traditional table salt. The rising of blood pressure is a risk factor for high blood pressure (hypertension)".

Specific conditions of use as proposed by the applicant

The applicant proposes to replace standard table salt in the diet by Symbiosal®, up to a maximum total added salt intake of 3 g per day. This salt replacement (and restriction to the maximum of 3 g per day) should be accompanied by other lifestyle improvements, such as eating less fat and sugar and increasing physical exercise.

The target population proposed by the applicant are "mild hypertensive" subjects, and "people who want/need to lower the rising of their blood pressure".

Children, pregnant women and lactating women should not consume Symbiosal®.

ASSESSMENT

1. Characterisation of the food/constituent

The food that is the subject of the health claim is Symbiosal®, which, according to the applicant, should replace table salt (i.e. NaCl) in order to obtain the claimed effect (i.e. lowering of blood pressure).

NaCl is a well characterised salt constituted by sodium and chloride in a 1:1 molar ratio.

It is well established that high sodium intakes, mainly as NaCl (table salt), increase blood pressure, and that reducing dietary NaCl intakes helps to maintain a normal blood pressure (EFSA NDA Panel, 2011).

Symbiosal® is produced by mixing sea salt (97 %) with chitosan (3 %), following a patented manufacturing process (United States patent no 7.335.766 B2, Korean patent no 0520007). Chitosan is a linear cationic polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine and *N*-acetyl-D-glucosamine produced by partial deacetylation of chitin, which is a component of the exoskeleton of crustaceans and the cell walls of fungi.

An overview of the manufacturing process of Symbiosal® and information regarding its stability were provided.

Following a request for clarification of the active constituent in Symbiosal®, the applicant indicated that "Symbiosal® is not only a combination of NaCl with chitosan but a specific product where the combination of these substances follows a patented process". The applicant also claimed "that the hypertensive power of the salt contained in Symbiosal® has been reduced by the effect of the combination with chitosan according to a specific patented process".

The Panel considers that the food, Symbiosal®, which is the subject of the health claim, and the food, table salt (i.e. NaCl), which Symbiosal® should replace, are sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is "lowers the rising of blood pressure when used as a replacement of traditional table salt. The rising of blood pressure is a risk factor for hypertension". The target population proposed by the applicant is "healthy mild hypertensive subjects, and people who want/need to lower the rising of their blood pressure".

Blood pressure is the pressure (force per unit area) exerted by circulating blood on the walls of blood vessels. Hypertension, defined by convention as blood pressure above 140 mmHg (systolic) and/or 90 mmHg (diastolic), may compromise normal arterial and cardiac function.

The Panel considers that lowering of blood pressure is a beneficial physiological effect for people who want to lower their blood pressure. Increased blood pressure is a risk factor for hypertension.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in PubMed, Cochrane Library, Science Direct, Scirus, Springerlink and Wiley Interscience using the search terms "Symbiosal®", "salt", "NaCl", "chitosan", "blood pressure", "hypertension", "systolic" and "supplementation". Publications in English, French and Spanish were accepted. In addition, reference lists of retrieved articles were searched manually to identify relevant studies. Trials were included if they were "well designed" (i.e. randomised and blinded, with an adequate number of subjects). Studies in subjects on blood pressure lowering medication were excluded.

3.1. Studies investigating the effect of the food on blood pressure

3.1.1. Human studies

The applicant provided one human intervention study (Allaert, 2013a, b, unpublished, study report, claimed as proprietary by the applicant), which assessed the effect of the food (i.e. Symbiosal®) on blood pressure when replacing table salt in the context of a salt-restricted diet.

In this randomised, double-blind, controlled, multi-centre, cross-over study, 40 individuals (mean age 58.6 ± 12 years; mean body mass index 26.4 ± 4.9 kg/m^2; 24 women) with "mild hypertension" (mean ± standard deviation systolic blood pressure (SBP) 149.4 ± 4.7 mmHg) received 3 g/day Symbiosal® or 3 g/day table salt (both as added salt in the diet). The two cross-over periods lasted eight weeks each and were separated by a washout of two weeks. In order to be included in the study, participants had to have stage 1 hypertension (SBP 140-159 mmHg, or diastolic blood pressure (DBP) 90-99 mmHg) without receiving any antihypertensive treatment.

Power calculations indicated that considering a standard deviation of 15 mmHg, 15 study subjects per group would yield a power of 90 % (for $\alpha = 0.05$) to detect a difference in SBP of 10 mmHg between Symbiosal® and table salt (Allaert, 2013b, unpublished). In order to anticipate losses, 20 participants per group were recruited. Recruitment took place at 13 medical centres (practitioners), with one to four patients recruited per centre.

The study participants were instructed not to eat liquorice, to follow lifestyle advice about physical exercise and nutrition (e.g. to eat less fat and less sugar) and to restrict their added salt intake to a maximum of 3 g/day. There was no run-in period prior to the intervention. Participants were asked to use the dispensed saltcellars, which contained either Symbiosal® or table salt. In order to test consumption, the saltcellars were weighed at the end of each cross-over period. Salt consumption was comparable between the groups (first cross-over period, NaCl: 3.0 ± 1.5 g/day, Symbiosal®: 2.9 ± 1.6 g/day; second cross-over period, NaCl: 3.3 ± 2.4 g/day, Symbiosal®: 3.0 ± 1.7 g/day). The background diet (apart from alcohol consumption) of the study participants was not assessed. Twenty-four-hour urinary sodium analyses/ionograms were provided. There were no significant differences between the periods. Two subjects dropped out of the study (one subject withdrew for personal reasons and one subject dropped out because of an adverse event).

Blood pressure was measured at week 0 (i.e. baseline), week 8 (i.e. end of the first cross-over period), week 10 and week 18 (i.e. end of the second cross-over period) by a medical practitioner. Following a request for specifications of the protocol applied, the applicant indicated that blood pressure was measured (using a homologate electronic measuring device) with study participants in a sitting position, after a 10-minute rest, and at three different time points separated by 3-minute intervals. The average of the three measurements was used.

Treatment effects were investigated using two-way analysis of variance (ANOVA). Carry-over analysis was performed to determine whether any carry-over correction was necessary. Where no significant carry-over effect was found, the model was simplified by removing this effect. When the ANOVA indicated an overall treatment effect (i.e. $p < 0.05$), comparisons between the means of the two interventions (i.e. Symbiosal® or NaCl) were performed using a two-sided paired t-test. The statistical analysis was applied on the intention-to-treat population (ITT, n = 40, i.e. all randomised participants, with the last observation carried forward for missing data) and on the "per protocol" population (n = 37, i.e. all randomised participants minus two dropouts, minus one participant who lacked the washout period). Results of the paired t-test on the ITT population indicated that the reductions of SBP and DBP were higher when Symbiosal® was consumed instead of table salt (SBP: −8.7 ± 10.8 mmHg vs. −3.2 ± 8.5 mmHg, $p = 0.0156$; DBP: −7.2 ± 8.0 mmHg vs. −3.7 ± 7.4 mmHg, $p = 0.0285$). Similar results were obtained for the "per protocol" analysis. Highly significant period effects were observed for SBP ($p = 0.0006$) and DBP ($p < 0.0001$), i.e. most of the reductions in blood

pressure were observed during the first cross-over period. Variability between centres was not taken into account in the analysis.

The Panel notes that significant period effects were observed for SBP and DBP. The Panel also notes that blood pressure did not return to baseline after the washout period (SBP: 137.1 ± 9.4 mmHg (week 10) vs. 149.2 ± 4.9 mmHg (week 0, baseline) in the Symbiosal®-first group; 144.0 ± 10.7 mmHg (week 10) vs. 149.7 ± 4.6 mmHg (week 0, baseline) in the NaCl-first group). The Panel notes the limitations of the paired t-test for the analysis of cross-over designs when there are carry-over and/or period effects.

The Panel considers that this study with methodological limitations showed a decrease in SBP and DBP when 3 g Symbiosal® per day was consumed instead of table salt as added salt for eight weeks accompanied by a salt-restricted diet.

3.1.2. Animal studies

The applicant provided four publications (Kim et al., 2004; Kim et al., 2005; Park et al., 2009; Kim et al., 2010) which reported on five animal studies.

One animal study (Kim et al., 2004) was provided in Korean only, which did not allow a scientific evaluation by the Panel. Therefore, no conclusions can be drawn from this study.

The remaining four animal studies (Kim et al., 2005; Park et al., 2009; Kim et al., 2010 (reporting on two animal studies)) were reported to have been performed with various chitosan-containing salts.

Upon request for clarification, the applicant claimed that, even though it is not mentioned in the publications, the chitosan salt used in the studies by Kim et al. (2005), Park et al. (2009) and Kim et al. (2010) was Symbiosal®, produced according to the patented manufacturing process, and that the owner of the patent, Biotech in Mokpo, Korea, co-authored the papers.

In one animal study (Kim et al., 2005), spontaneously hypertensive rats (SHRs) were fed for eight weeks a diet containing chitosan salt (3 %) (claimed by the applicant to have been Symbiosal®), a diet containing commercial salt (3 %) or a control diet (seven rats per group). At the end of the study period, no significant differences in blood pressure between the groups were reported.

In the animal study by Park et al. (2009), SHRs were administered for two months (i) NaCl plus 3 % chitosan (claimed by the applicant to have been Symbiosal®), (ii) NaCl plus potassium chloride (KCl), (iii) NaCl, (iv) chitosan or (v) untreated control diet (five animals per group). The concentration of sodium given was 44 mM (1 g of sodium) per day. There were no statistically significant differences in blood pressure between the animals receiving the three salts at the end of the study.

One publication (Kim et al., 2010) reported on two animal studies and one *in vitro* study. One animal study was carried out in normotensive Sprague-Dawley rats and did not find any effects of chitosan salt (3 %) on blood pressure compared with table salt. The second study was performed in SHRs fed for five weeks (i) control diet (0 % salt), (ii) control diet plus captopril, (iii) a diet with 3 % chitosan salt (claimed to be Symbiosal®) or (iv) a diet with 3 % commercial salt (six rats per group). After five weeks, the rats in the chitosan salt group had a significantly lower SBP ($p < 0.001$, two-way ANOVA) than rats on the diet with commercial salt.

The Panel notes that four animal studies, i.e. three studies in SHRs and one study in normotensive rats, have been provided. Only one study (Kim et al., 2010), which used SHRs, showed a decrease in blood pressure when Symbiosal® was consumed instead of table salt.

The Panel considers that the animal studies do not support the results of the human study.

3.2. Studies on the mechanism by which the food could exert the claimed effect

The applicant indicated that the mechanism by which the food might exert the claimed effect is not clearly known but that some findings suggest that chitosan may inhibit the increase of angiotensin-converting enzyme (ACE) induced by an acute salt intake. The applicant also claimed that this "inhibition might be mediated by blocking or counteracting the hypertensive effect of the chloride ions in NaCl".

The applicant provided three animal studies (Kim et al., 2004, 2005; Park et al., 2009) in support of a mechanism by which Symbiosal® or other chitosan-containing salts could exert the claimed effect.

One animal study (Kim et al., 2004) was provided in Korean only, which did not allow a scientific evaluation by the Panel. Therefore, no conclusions can be drawn from this study.

In one animal study (Kim et al., 2005), SHRs were fed with "chitosan-salt (3 %)" (claimed by the applicant to have been Symbiosal®) diet, "commercial-salt (3 %)" diet or a control diet for eight weeks. ACE inhibition activity was measured in plasma according to the method by Chushman and Cheung (1971). The results of this assay were reported as descriptive statistics only. The Panel considers that no conclusions can be drawn from this study.

In the animal study by Park et al. (2009), SHRs were fed for two months (i) NaCl plus 3 % chitosan (claimed by the applicant to have been Symbiosal®), (ii) NaCl plus KCl, (iii) NaCl, (iv) chitosan or (v) an untreated control diet. At the end of the study, ACE-I and ACE-II concentrations were measured in serum (using rat angiotensin I and II enzyme immunoassay kits). There were no statistically significant differences in ACE I or ACE II serum concentrations between the groups.

The Panel considers that no evidence was provided for a mechanism by which Symbiosal® could lower blood pressure when consumed instead of table salt.

3.3. Weighing the evidence

In weighing the evidence, the Panel took into account that one human study with methodological limitations showed a decrease in blood pressure when Symbiosal® was consumed instead of table salt for eight weeks in the context of a salt-restricted diet, but that no other human studies in which these results have been replicated were provided, that the animal studies did not support the results of the human study and that no evidence was provided for a mechanism by which the food could exert the claimed effect.

The Panel concludes that a cause and effect relationship has not been established between the consumption of Symbiosal® instead of table salt and lowering of blood pressure.

CONCLUSIONS

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

- The food, Symbiosal®, which is the subject of the health claim, and the food, table salt (i.e. NaCl), which Symbiosal® should replace, are sufficiently characterised.

- The claimed effect proposed by the applicant is "lowers the rising of blood pressure when used as a replacement of traditional table salt. The rising of blood pressure is a risk factor for hypertension". The target population proposed by the applicant is "healthy mild hypertensive subjects, and people who want/need to lower the rising of their blood pressure". Lowering of blood pressure is a beneficial physiological effect for people who want to lower their blood pressure. Lowering of blood pressure reduces the risk of hypertension.

- A cause and effect relationship has not been established between the consumption of Symbiosal® instead of table salt and lowering of blood pressure.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on Symbiosal® and lowering of blood pressure and reduced risk of hypertension pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0415_DE). Month 2014. Submitted by Han-Asiabiotech GmbH.

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ABBREVIATIONS

ACE	angiotensin-converting enzyme
ANOVA	analysis of variance
DBP	diastolic blood pressure
ITT	intention-to-treat population
SBP	systolic blood pressure
SHR	spontaneously hypertensive rat