

ETUDE DE CAS: ALLÉGATIONS DE SANTÉ DANS LE DOMAINE DE LA SANTÉ OSSEUSE

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Introduction

- ▣ Poor bone health is a major public health problem, at least in Western countries.
- ▣ Up to 60% of the variance in bone mass is determined by genetic factors.
- ▣ Environmental factors account for the remainder, including nutritional intake.

PLAN OF THIS TALK

- ▣ History of opinion made by EFSA in the field of bone health
- ▣ The problem of surrogate markers in bone health
- ▣ EFSA Guidances
- ▣ The GREES point of view
- ▣ Few words on cartilage health

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Femarelle[®] and bone mineral density

Scientific substantiation of a health claim related to “Femarelle[®]” and “induces bone formation and increases bone mineral density reducing the risk for osteoporosis and other bone disorders” pursuant to Article 14 of the Regulation (EC) No 1924/2006¹

Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies

(Question No EFSA-Q-2008-078)

Adopted on 04 August 2008 by written procedure

PANEL MEMBERS

Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Karin Hulshof, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Andreu Palou, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.

- ▣ The Panel concludes that a cause and effect relationship has not been established between the consumption of Femarelle® and increased BMD, increased bone formation, or decreased risk of osteoporosis or other bone disorders in post-menopausal women.

- ▣ The intervention study compared the effect of two intake levels (644 mg/day or 344 mg/day) of DT56a soy derivative on BMD in postmenopausal women.
- ▣ A significant difference between the two treatment groups for the change in BMD over the 12 month intervention period was observed for the lumbar spine (BMD increased in the group receiving 644 mg/day) but not for the femoral neck.

SCIENTIFIC OPINION

Scientific Opinion in relation to the authorisation procedure for health claims on calcium and vitamin D and the reduction of the risk of osteoporotic fractures by reducing bone loss pursuant to Article 14 of Regulation (EC) No 1924/2006¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2, 3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver a scientific opinion in relation to the authorisation procedure for health claims on calcium and vitamin D and the reduction of the risk of osteoporotic fractures by reducing bone loss pursuant to Article 14 of Regulation (EC) No 1924/2006. A cause and effect relationship was established between the intake of calcium, either alone or in combination with vitamin D, and reducing the loss of BMD, which may contribute to a reduction in the risk of bone fracture. This relationship implies that the critical nutrient in relation to the claimed effect is calcium. The Panel proposes that at least 1200 mg of calcium from all sources or at least 1200 mg of calcium and 800 I.U. of vitamin D from all sources to be consumed daily should be considered for the purpose of setting conditions of use for a risk reduction claim on the loss of BMD, which may contribute to a reduction in the risk of bone fracture. The target population is women 50 years and older. Tolerable Upper Intake Levels (UL) have been established for calcium and vitamin D in adults.

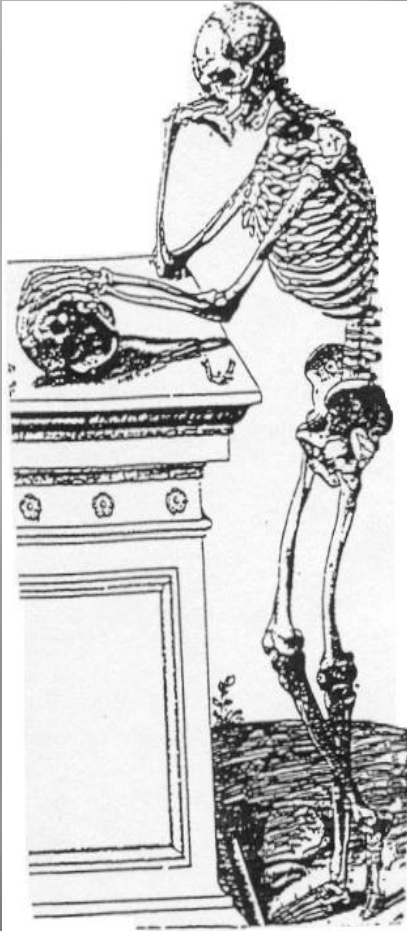
- ▣ A cause and effect relationship was established between the intake of calcium, either alone or in combination with vitamin D, and reducing the loss of BMD, which may contribute to a reduction in the risk of bone fracture.
- ▣ Based on large RCTs and meta-analyses with BMD and fracture as endpoint

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Definition

- ▣ A surrogate endpoint is "a biomarker intended to substitute for a clinical endpoint".
- ▣ Surrogate markers are used when the number of events is very small, thus making it impractical to conduct a clinical trial to gather a statistically significant number of endpoints.

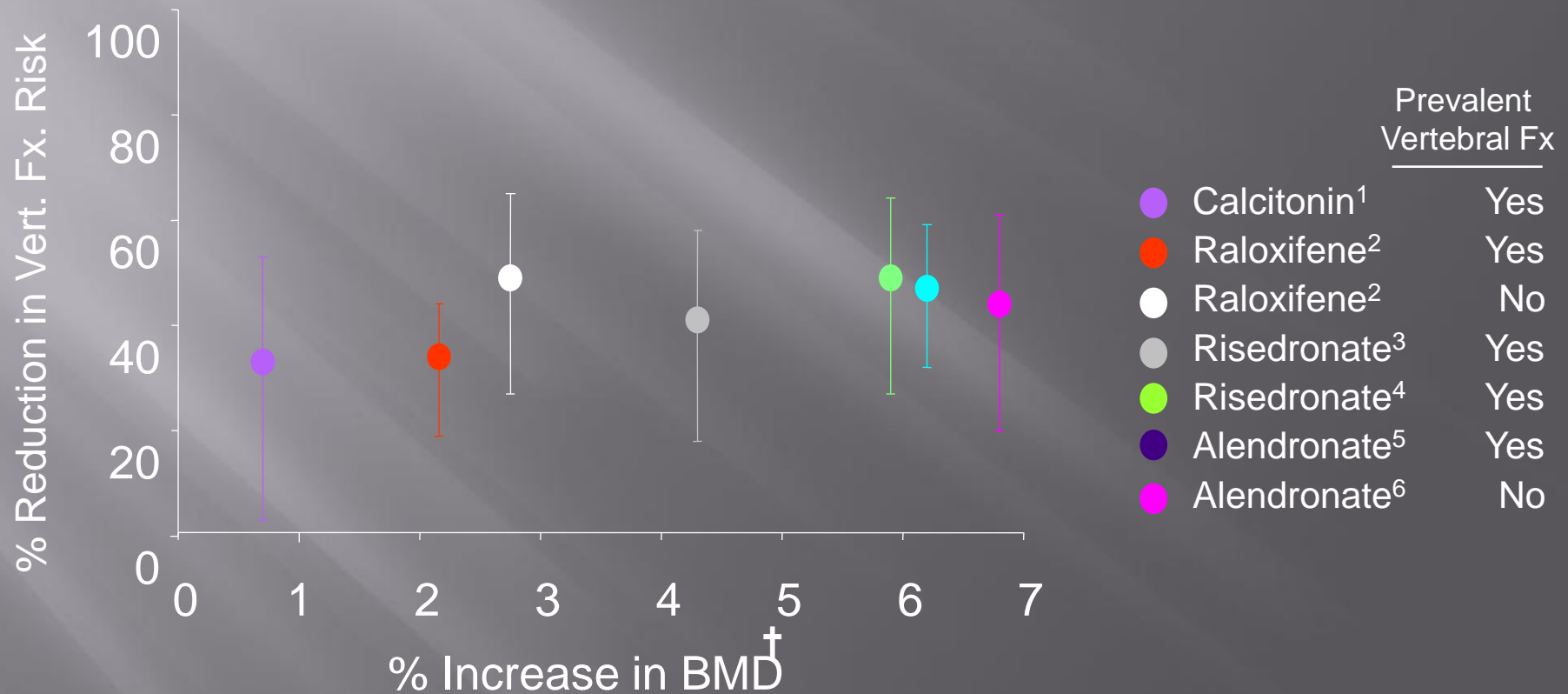
Relation of BMD to Fracture Risk



How important is change in BMD with treatment?

- ▣ Treatments for osteoporosis increase BMD & reduce risk
- ▣ Is the reduction in fracture risk with treatment due to the increase in BMD?

Relationship between the Risk of Vertebral Fracture and Increases in BMD*



*Not head-to-head comparison; [†]vs placebo. Error bars represent 95% confidence intervals.

¹Chesnut CH, et al. *Am J Med.* 2000;109:267-276; ²Ettinger B, et al. *JAMA.* 1999;282:637-645; & data on file, Eli Lilly and Company; ³Harris ST, et al. *JAMA.* 1999;282:1344-1352; ⁴Reginster J-Y, et al. *Osteoporosis Int.* 2000;11:83-91; ⁵Black DM, et al. *Lancet.* 1996;348:1535-1541; ⁶Cummings SR, et al. *JAMA.* 1998;280:2077-2082.

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DRAFT SCIENTIFIC OPINION

Guidance on the scientific requirements for health claims related to bone, joints, and oral health¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2, 3}

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Dietetic Products, Nutrition and Allergies (NDA) to draft guidance on scientific requirements for health claims related to bone, joints, and oral health. This draft guidance has been drawn from scientific opinions of the NDA Panel on such health claims. Thus, this guidance document represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims in these areas. It is not intended that the document will include an exhaustive list of beneficial effects and studies/outcome measures which are acceptable. Rather, it presents examples drawn from evaluations already carried out to illustrate the approach of the Panel, as well as some examples which are currently under consideration within ongoing evaluations. This draft guidance document was endorsed by the NDA Panel on 25 March 2011, and is released for public consultation from 26 April 2011 to 31 August 2011.

- ▣ This draft guidance document was endorsed by the NDA Panel on 15 25 March 2011, and is released for public consultation from 26 April 2011 to 31 August 2011.

3. Bone and joints

3.1. Claims related to maintenance of bone and to the reduction in the risk of osteoporotic fractures

Contribution to the maintenance of normal bone throughout the lifespan is considered to be a beneficial physiological effect. Evidence for the scientific substantiation of these claims can be obtained from human studies by assessing the relationship between the food/constituent and measures of bone mass and bone mineral density (BMD) using appropriate methods of measurement (e.g. dual-emission X-ray absorptiometry (DXA)) and study duration (e.g. at least one year). Biochemical markers of bone turnover (e.g. of bone formation and bone resorption) can be used as evidence for a mechanism by which the food/constituent could exert the claimed effect. An increase in bone formation and/or a decrease in bone resorption are considered beneficial physiological effects when they lead to an increase (or reduced loss) in bone mass/density.

A decrease in BMD is associated with an increased risk of osteoporotic fractures. However, modification of BMD is only beneficial when the change has a positive impact on fracture incidence. Increasing BMD, or limiting the reduction of BMD in older adults including post-menopausal women has been shown to reduce the risk of osteoporotic fractures following certain dietary interventions (e.g. calcium supplementation) but not others (e.g. fluoride supplementation), probably because BMD (g/cm^2) does not provide any information on the micro-architecture of bone. Therefore, for reduction of disease risk claims in older adults, measures of both BMD and fracture incidence should be

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Objective

- ▣ To define the relevant biomarker for bone health
- ▣ To provide recommendations for the design and the methodology of clinical studies which need to be fulfilled to assert claims related to bone health.

Methods

- ▣ Two 1-day meetings organized by the Group for the Respect of Ethics and Excellence in Science (GREES)
- ▣ Literature search up to August 2010 using keywords including health claims, nutrition, bone, osteoporosis, clinical study methodology, surrogate endpoint.

Results

- ▣ The GREES panel considers that :
 - clinical data in humans are indispensable, and that health claims cannot be accepted solely on the basis of animal data;
 - different levels of health claims should be considered based both on the endpoint used and on the information provided by animal studies.

Results

- ▣ Pre-clinical models
- ▣ Acceptable health claims in human bone health
- ▣ Design of clinical studies

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Pre-clinical models

- ▣ The assessment of bone strength is considered to be the most relevant in the field of bone health claims.
- ▣ The assessment of bone health would benefit from the measurement of bone strength *in vivo*.
- ▣ No validated non-invasive tools capable of measuring bone strength *in vivo* are available to date.
- ▣ Biomechanical tests of resistance to fracture provide an objective measure of overall bone strength.

Pre-clinical models

▣ Objectives:

- To assess a direct effect of the food product on bone strength
- To better understand the mechanism of action of the food product
- To validate surrogate variables used in human animal data to see if these variables reflect bone strength

Results

- ▣ Pre-clinical models
- ▣ Acceptable health claims in human bone health
- ▣ Design of clinical studies

Acceptable health claims

- ▣ The GREES panel considers that
 - six different health claims could be accepted for an effect of food products on bone health.
 - different wording to reflect the level of evidence of the effect could be used depending on the effect that is (always), may (demonstrated only under certain circumstances) or might be (logically expected benefit from physiology but yet not demonstrated) beneficial for bone health.

1. Improvement of calcium bioavailability

- ▣ Defined as the proportion of calcium in foods which is absorbed and utilised for normal metabolic functions.
- ▣ Could have an article 13 claim:
 - “X increases calcium absorption”
 - “X increases calcium bioavailability”.

2. Maintenance of bone metabolism

- ▣ Through an effect on osteoclast regulatory proteins
- ▣ Markers of osteoclastogenesis include RANKL and OPG
- ▣ Markers of osteoclast number include TRAcP and Cat K
- ▣ Would not fulfil a claim related to article 14.
- ▣ Might have the label under the article 13: “X contributes to the maintenance of bone metabolism”.

3. Maintenance or changes in bone turnover marker

- ▣ Reference markers of bone formation (s-PINP) and resorption (s-CTX)
- ▣ Might have the claim:
 - “X maintains normal bone remodelling that could contribute to the normal structure and function of bones”
 - “X increases markers of bone formation that could contribute to the normal structure and function of bones”
 - “X decreases markers of bone resorption that could contribute to the normal structure and function of bones”.

3. Maintenance or changes in bone turnover marker

- ▣ BTMs are only indicators of fracture risk,
- ▣ Change in BTM induced by a product is not necessarily associated with a change in fracture risk or bone strength.
- ▣ Animal models are useful to assess if changes in BTMs due to the intake of the food product are associated with an increase in bone strength.

3. Maintenance or changes in bone turnover marker

- ▣ Effect on BTMs together with
 - animal studies that showed improved bone strength or
 - a relationship between changes in BTMs induced by the food product and bone strength
- ▣ Could have the claim:
 - “X contributes to the maintenance of normal bone remodelling (or increases bone formation or decreases bone resorption) that is associated with bone strength
 - “X contributes to the maintenance of normal bone remodelling (or increases bone formation or decreases bone resorption) that increases bone strength”
 - “X increases bone strength”

4. Maintenance or improvement in bone structure

- ▣ Methods include *in vitro* μ CT, *in vitro* μ MRI, *in vivo* pQCT, and *in vivo* high-resolution MRI
- ▣ Assessment of bone structure is not sufficiently validated to be a reliable surrogate of bone strength.
- ▣ Animal models are needed to assess the relationship between changes in bone microarchitecture induced by the food product and any increase in bone strength.

4. Maintenance or improvement in bone structure

- ▣ Effect on microarchitecture together with
 - animal studies that showed improved bone strength or
 - a relationship between changes in microarchitecture induced by the food product and bone strength
- ▣ Could have the claim:
 - “X improves bone microarchitecture that increases bone strength”
 - “X increases bone strength”

5. Maintenance or increase in bone mineral density

- ▣ BMD is only a surrogate marker for bone strength or fracture risk,
- ▣ Changes in BMD with a food product are not clearly associated with changes in bone strength or fracture risk
- ▣ Increase in BMD may not be associated with an increased bone strength or decreased fracture risk

5. Maintenance or increase in bone mineral density

- ▣ A food product with a positive effect on BMD could have the claim:
 - “X increases BMD. A low BMD is associated with an increased risk of fracture”
 - “X maintains BMD. A low BMD is associated with an increased risk of fracture”.

5. Maintenance or increase in bone mineral density

- ▣ Effect on BMD, together with
 - animal studies showing an improvement in bone strength or
 - a relationship between BMD changes induced by the food product and bone strength
- ▣ Could have the claim:
 - “X increases (or maintains) BMD that could reduce the risk of fracture”
 - “X increases (or maintains) BMD that increases bone strength”
 - “X increases bone strength”.

6. Reduction of the risk of fracture

- ▣ According to the regulation it cannot be claimed as such without mentioning the effect on a risk factor.
- ▣ A reduction in the fracture risk is obviously supportive for a claim on the reduction of an identified risk factor.

Results

- ▣ Pre-clinical models
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- ▣ Design of clinical studies

1. Population

- ▣ Representative of the population targeted for the food product.
- ▣ The tested population must be equivalent to the user population with respect of ethnicity, age, physiological status (such as menopause for example), life habits (such as exercise) and diet.
- ▣ No densitometric criteria are required for inclusion.

2. Design

- ▣ The ideal design would be a multicentre RCT.
- ▣ The control could be a placebo, another active product or nothing, depending on the tested food.
- ▣ When possible, subjects and/or investigators should be blinded of the intervention.
- ▣ When RCT is not possible (in practice or from an ethical point of view):
 - Well-designed prospective cohort studies
 - Case-control studies
 - Observational studies
 - Cross-over studies
 - All acceptable if accompanied by other data (e.g. animal data, effect on multiple surrogate endpoints).

3. Duration of study

- ▣ Should be predetermined
- ▣ Should depend on the outcome

4. Statistical analysis

- ▣ Intention-to-treat analysis
- ▣ Beta risk equal to or less than 20%.
- ▣ Sample size of the study must be calculated prior to the start of the study.
- ▣ Possible confounding variables should be managed using appropriate statistical analysis.
- ▣ Within group (end vs baseline) and between groups comparisons should be made.

5. Diet habit & lifestyle

- ▣ Critical effect modifiers must be controlled
- ▣ Intakes of other nutrients or foods, on which the tested nutrient is dependent, must be optimized.
- ▣ Any supplementation with other food products known to have an effect on bone (e.g. calcium and/or vitamin D) should be consistent within all patient groups.

6. Observance

- ▣ Should be monitored during the study

7. Safety

- ▣ All adverse experiences should be fully documented with separate analysis of adverse events, dropouts and patients who died while being on the study.

Conclusion

- ▣ The level of health claim may differ according to
 - the surrogate end-point used
 - additional animal studies provided to support the claim.
- ▣ The ideal study design is a RCT but, in some particular cases, prospective cohort, case-control or observational studies can be acceptable.
- ▣ General principles of the consensus reached are in line with the principles adopted in the EFSA's published opinions.
- ▣ This consensus is subject to future modifications when new validated surrogate markers will be available.

Assessment of health claims in the field of bone: a view of the Group for the Respect of Ethics and Excellence in Science (GREES)

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Abstract

Summary Health claims for food products in Europe are permitted if the nutrient has been shown to have a beneficial nutritional or physiological effect. This paper defines health claims related to bone health and provides guidelines for the design and the methodology of clinical studies to support claims.

Introduction Regulation (EC) no. 1924/2006 on nutrition and health claims targeting food products was introduced in Europe stating that health claims shall only be permitted if the substance in respect of which the claim is made has been shown to have a beneficial nutritional or physiological effect. The objective of this paper is to define health claims related to bone health and to provide guidelines for the design and the methodology of clinical studies which need to be adopted to assert such health claims.

Methods Literature review followed by a consensus discussion during two 1-day meetings organized by the Group for the Respect of Ethics and Excellence in Science (GREES).

Results The GREES identified six acceptable health claims related to bone health based on the potential of food products to show an effect on either the bioavailability of calcium or osteoclast regulatory proteins or bone turnover markers or bone mineral density or bone structure or fracture incidence. The GREES considers that well-designed human randomized controlled trial on a relevant outcome is the best design to assess health claims. The substantiation of health claim could also be supported by animal studies showing either an improvement in bone strength with the food product or showing the relationship between changes induced by the food product on a surrogate marker and changes in bone strength.

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to glucosamine alone or in combination with chondroitin sulphate and maintenance of joints (ID 1561, 1562, 1563, 1564, 1565) and reduction of inflammation (ID 1869) pursuant to Article 13(1) of Regulation (EC) No 1924/2006¹

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

European Food Safety Authority (EFSA), Parma, Italy

On the basis of the data available, the Panel concludes that a cause and effect relationship has not been established between the consumption of glucosamine, either as glucosamine hydrochloride or as glucosamine sulphate, either alone or in combination with chondroitin sulphate and maintenance of normal joints in the general population.

3.2. Claims related to maintenance of joints and to the reduction in the risk of osteoarthritis

Contribution to the maintenance of normal joints is considered to be a beneficial physiological effect.

Possible outcomes related to joint structure and function include, for example, joint space width, mobility, stiffness and (dis)comfort (e.g. pain).

Studies performed in non-diseased (including high risk) population subgroups in which the incidence of disease (e.g. osteoarthritis or (osteo)arthritis) is the outcome measure could be used for substantiation of health claims on maintenance of normal joints.

Patients with osteoarthritis or (osteo)arthritis of different origin (rheumatoid arthritis, psoriatic arthritis, arthritis of infectious origin) are not representative of the general population with regard to the status of joint tissues, and therefore studies on subjects with osteoarthritis or (osteo)arthritis of different origin relating to the treatment of symptoms of these diseases (e.g. erosion of articular cartilage, and reduced mobility of joints) cannot be used for the scientific substantiation of health claims on the maintenance of normal joints in the general population.

Osteoarthritis is a disease characterised by the erosion of articular cartilage. Cartilage degeneration may proceed to clinical osteoarthritis. Slowing cartilage degeneration in individuals without osteoarthritis may reduce the risk of development of the disease, and thus studies measuring the rate of cartilage degeneration (e.g. changes in joint space width) in individuals without osteoarthritis could be used for the scientific substantiation of disease risk reduction claims.

- ▣ General vs specific population
- ▣ Validated tools in the general population
- ▣ Effect on structure (X-ray)
- ▣ Surrogate markers

GENERAL CONCLUSION

- ▣ No definitive answer.
- ▣ No definitive guidelines.
- ▣ Improvement in surrogate is necessary.
- ▣ Collaborations are very important.

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