The examination is being carried out on the **following application documents**

Description, Pages

1-66	filed in electronic form on	04-10-2011

Claims, Numbers

1-13	filed in electronic form on	07-08-2012

Clarity (Art.84 EPC)

The claims were limited to a 10:1 ratio between the pomegranate and the grape seed extracts. It is however not clear how this ratio is to be intended (weight ratio, volume ratio, molar ratio of active agents). For this reason, the claimed matter is not clear and does not allow the skilled person to determine unambiguously the scope of the claimed matter. It is also remarked that an extract could, depending on the amount of solvent and extraction conditions used, be very concentrated or very diluted. Accordingly, the simple reference to an unspecified "ratio" of the two extracts leaves a great variability in the nature of the combinations which are defined in the claims.

The mention to specific amounts in weight of the claimed extracts, as defined in claims 4-7 is also unclear, because no reference is made as to whether the extracts are in form of solutions, containing the extracted compounds, or in dried form.

For these reasons the claims are unclear (Art.84 EPC).

Allowability of the amendments (Art.76 EPC and Art.123(2) EPC)

The present application is a divisional application. Consequently its subject matter must meet the requirements of both Art.76 and Art.123(2) EPC.

Clam 1 is now directed to a combination of an extract of pomegranate and an extract of grape seeds in a 10:1 ratio. This ratio between the two extracts was not disclosed as such in the application. As basis for the amendment, the applicant referred to some specific compositions used for the experiments reported in table 12, paragraph [0148] and in tables 12-22 of the parent and of the present application as filed. However, the compositions described in these paragraphs, which describe experiments conducted with certain extract combinations are not fit for generalisation to any possible composition containing the claimed 10:1 ratio. The compositions described in these tables contain specific amounts of extracts. Furthermore, such extracts must have been obtained using particular extraction methods. Since the nature of an extract is

inevitably associated to the specific methodology and to the conditions used for the extraction, *e.g.* the type of solvent, extraction technique used, and the part of the plant extracted, the teaching of the specific experiments reported in the tables cannot be generalised to the generally defined ratio which is now characterising the claims.

This ratio claimed assumes a crucial importance in the present case, since according to the applicant it is this ratio which imparts the technical effect which confers inventiveness to the claimed invention. Since neither the application as filed, nor the parent application provide a clear and unambiguously disclosure of the extract ratio which is now defined in claim 1, (whatever this ratio is intended to be (weight, volume, molar), the introduction of this feature introduces subject matter in the sense of Art.76 and Art.123(2) EPC.

Similar arguments apply to claim 3, because the passages referred to as basis do not refer to the specific ratio 10:1 of pomegranate and grape seeds (paragraphs 0019 and 85) or refer to specific amounts of a particular extract of green tea or ipilavone (table 12 in paragraph 148). Claims 4-13 which depend from claim 1 and specify in weight specific amounts of the different extracts (whatever their nature might be), or the presence of additional ingredients, add further elements of selection which introduce additional subject matter.

In the proceedings concerning the prosecution of the parent application the applicant expressed the opinion that the skilled person would have assumed the claimed compositions to be "standardized extracts". As in that case, the examining division may not follow this argument: although some extracts can be reproduced and "standardised extracts" might exist, and be commercially available, there is nothing in the application, let alone in paragraph [0047], indicating that such extracts have been used for the aforementioned experiments, and that the claimed matter is limited to their use. Furthermore, standards may change over time and/or be different, depending *e.g.* on which pharmacopoeia is considered. It also is noted that the same document D33 filed by the applicant on May 9, 2012 indicates that the amount of active agents contained in a plant extracts (licorice in that case) can vary considerably: for example, the amount of triterpene saponins varies from 3 to 15%. Even in the "adjusted extract" of the German Pharmacopoeia (DAB) and in the "dry extract" of the German Drug Codex (DAC) there are variations in these components (4 to 6 % and 5 to 7% respectively). Remarkably, according to this same source there are also two types of licorice extracts, namely an "adjusted form" and a "dry form". For these reasons, the examining division is of the opinion that neither paragraphs [0121 - 0128], nor the other parts of the application as filed, taken alone or in combination, provide a clear and unambiguous disclosure of the composition or of the dietary complement having the weight ratio which is defined in the claims. Accordingly, the main request does not meet the requirements of Art.76 EPC and Art.123(2) EPC.

Inventive step (Art.56 EPC)

The examining division is still of the opinion that the application lacks inventive step, for the reasons already presented in the ESOP, which are reiterated here below.

The present application relates to the provision of medicines for the treatment of bone diseases, and in particular, for inhibiting, decreasing or preventing bone resorption. Although not explicitly mentioned in the claims, osteoporosis appears to be a preferred disease to be treated according to the invention (see paragraph [0004]). The applicant reports the discovery that various combinations of plant derived extracts can be used to treat improve bone metabolism. These extracts contain flavonoids or other related derivatives. In the applicant's opinion, this effect is mediated by a mechanism of action involving an increase in the expression of BMP-2 or the modulation of RANK-L. In view of the results, in order to treat the aforementioned conditions, the applicant proposes combinations of pomegranate and grape seed extracts, optionally in combinations with other ingredients, such as ipriflavone, green tee, Siberian Ginseng, Sophora Japonica, Licorice extracts, quercetine.

The use of these plant extracts to treat bone diseases (e.g. osteoporosis) is well known. It is also known that flavonoid compounds, (e.g. quercetin) stimulate osteoblast activity, promote bone growth and can be used for the treatment of osteoporosis:

Pomegranate

D22 teaches that pomegranate prevents reduction in bone weight and **D23** discloses the use of compositions comprising pomegranate to treat osteoporosis. Documents **D27**-**D29** indicate that the use of compositions comprising pomegranade and other herbal extracts was part of the traditional knowledge.

Grape fruit and seed extracts

D24 discloses the use of compositions comprising grape fruit extracts to increase skeletal density and **D25** and **D26** teach that grape seeds extracts have beneficial effect on bone formation, that they improve bone strength, and that they can be used to treat bone debility caused by a low level of calcium.

Green tea

Documents **D33** and **D34** teach that green tea and its active components enhance osteogenesis and strengthen bones.

Ipriflavone

D18 teaches that Siberian Ginseng and ipriflavone protect against Glucocorticoid induced osteoporosis.

Documents relating to the use of quercetin

D2 (see corresponding translation EP1847265) discloses the use of flavonoids, including quercetin to stimulate osteoblast activity, promote bone growth and to treat osteoporosis. The involvement of BMP-2 in the bone forming activity is also disclosed. See in particular paragraphs [0001, 0002, 0003, 0010, 0016, 0022], claims 1, 8, 9; "quercetin" in paragraph [0009]; claims 4, 16, 17, 18 and figure 3: activity of quercetin on fibroblast proliferation).

D3 (see e.g. column 2, lines 8-14, 29-61, claims) discloses the use of quercetin to treat bone diseases (e.g. osteoporosis).

D4 (see page 1, lines 5-20, page 8, lines 10-16, page 10, lines 30-37, examples 1-4, tables and claims) discloses the proliferative activity of quercetin on osteoblasts, its inhibitory activity on osteoclasts and its uses to treat osteoporosis.

D6 (see abstract) discloses the effects of quercetin on osteoclast differentiation and its use to inhibit bone resorption and to treat osteoporosis.

D30 (see paragraph [0005] and claims 1, 4) discloses compositions comprising quercetin, for strengthening and increasing bone mass.

Documents relating to the use of liquorice extract

D7 (see page 6, line 1-6, 10-12; claims 1, 5) and **D8** (abstract) disclose the use of licorice extract for the treatment and prevention of osteoporosis.

D31 and **D32** (see abstracts) discloses compositions comprising liquorice extract for the treatment of osteoporosis, which promote osteoblast growth, cell differentiation and osteoclast calcification and promote bone formation.

D35 (see abstract) discloses compositions comprising liquorice root for promoting bone growth.

Documents relating to the use of Sophora

D13 discloses the use of extracts from the sophora fruit to treat osteoporosis.

D15 discloses the use of extracts of Sophora (including Sophora Japonica) to treat diseases related to decrease of estrogen levels, including osteoporosis.

D16 and **D17** disclose the use of extracts of sophora japonica to treat menopause syndrome. Osteoporosis is mentioned among the conditions to be cured.

D19 (available on-line on 27-10-2005) teaches that Genistein from Sophora Japonica has beneficial anti - osteoporosis effects.

Documents relating to the use of ginseng

D18 teaches that Siberian Ginseng and ipriflavone protect against Glucocorticoid induced osteoporosis.

Documents relating to the use of pomegranate extracts

D22 teaches that pomegranate prevents reduction in bone weight and **D23** discloses the use of compositions comprising pomegranate to treat osteoporosis.

Documents **D27-D29** further reveal that compositions compositions comprising extracts of pomegranate were used since long time according to traditional knowledge, for use in the treatment of conditions characterised by reduction of bone tissue and rickets.

Document relating to the use of Ginko Biloba

D5 (see page 4, lines 19-23, paragraph [0020], claims 1,2, examples 1, 2) discloses the therapeutic activity of Ginkgo Biloba (comprising quercetin), to treat osteoporosis.

Documents relating to the use of grape fruits extracts

D24 discloses the use of compositions comprising grape fruit extracts to increase skeletal density and **D25** and **D26** teach that grape seeds extracts have beneficial effect on bone formation and promote bone formation.

Documents relating to the Involvment of BMP-2 and RANK-L

The involvement of the bone morphogenetic protein 2 (BMP-2) and of RANK-L in bone metabolism and the modulation of the expression or the activity of these proteins induced by flavonoids is also well known:

D9 shows that Soybean isoflavone (a flavonoid close to quercetin) increases the expression of BPM - 2, and increases bone mineral density in ovariectomized rats, preventing osteoporosis. **D10** shows that Celosia cristata L flavonoid increases the expression of BMP - 2 in diabetic rats.

D11 shows that the Genistein (a flavonoid very similar to quercetin) stimulates the BMP - 2 promoter and its use is suggested, together with other estrogens, to treat osteoporosis. This paper teaches that the effect on BMP-2 is shared by different estrogens and phytoestrogens, like Genistein.

D12 discusses the effects of quercetin on osteoclastic differentiation and the involvement of RANK-L.

The problem and its solution

Considering the teaching of the prior art, the problem underlying the subject matter can be seen as the provision of a further medicament to treat a bone disease involving bone resorption, (osteoporosis for example). In the absence of a clear evidence that the claimed invention produces a new unexpected technical effect, the idea to prepare the claimed combinations would have been obvious. In fact, a skilled person confronted with such problem would have been prompted to combine compounds or compositions known from the prior art to be effective for improving bone metabolism

and preventing bone resorption. In this way, just performing routine steps, the skilled person would have arrived to the claimed invention without recurring to an inventive activity.

The examining division may not follow the applicant's opinion that the prior art would not have prompted the skilled person to prepare the claimed combinations. It is common practice, in the art to which the invention pertains, to combine two or more active ingredients known be effective on a certain condition, in order to increase therapeutic effect and minimise side effects. Furthermore, as indicated e.g. in document D12 RANK-L was known to be implicated in bone metabolism. Accordingly, the finding that the therapeutic effects of certain compositions of the prior art are mediated by RANK-L is not surprising, and does not confer inventiveness to the claimed solution. It is also observed that uncovering the mechanism of action underlying the known therapeutic activity of a composition of the prior art, does not render such known use new or inventive, irrespectively of whether such composition is used alone or, as in the present case, in combination with others.

Since on the basis of the application as filed no further surprising effects can be observed when using combinations having the claimed 10:1 ratio of the the relevant extracts, the subject matter claimed may not be considered to involve an inventive step. In as far the applicant will argue that unexpected effects are produced by the claimed combinations, adequate evidence will have to be provided to prove that this effect is obtained using any of the claimed combinations and any ratio between the compounds used.