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

Description, Pages

1-27 as originally filed

Claims, Numbers

1-8 received on 22-12-2011 with letter of 22-12-2011

Drawings, Sheets

1/3-3/3 as originally filed

1 Article 123(2) EPC

The amendments submitted by the Applicant with letter dated 22.12.2011 are not permissible under Article 123(2) EPC, since the amendments add subject-matter that extends beyond the contents of the application as filed.

Present independent claims 1 and 5 are now directed to therapeutic compositions, "wherein said composition has a combination index (CI) of less than 1 for synergistic inhibition of PGE2 production". This definition also applies to independent claims 3 and 7, which are directed to compound combinations different from those of claims 1 and 5, as well to dependent claims 2, 4, 6 and 8.

According to the Applicant, support for this feature could be found in the specification. He referred to various passages, precisely to page 1 (lines 25-26), page 2 (lines 16-18), examples 2-3 and page 19 (lines 20-29) (Applicant's letter dated 22.12.2012, item I, 1).

Already the reference to 5 different passages indicates that the Applicant appears to have difficulties to indicate a basis in the sense of Article 123(2) EPC. In addition, the Applicant's interpretation that the cited passages would establish "a connection between COX-2 and prostaglandin E2 production and showing that the latter can be used for measuring selective inhibition of COX-2" (Applicant's letter dated 22.12.2012, item I, 1) appears to be highly speculative. Such an interpretation of a possible teaching of the application as originally filed, even if it were correct, could definitively not be followed for accepting an amendment in the sense of Article 123(2) EPC.

Moreover, the first 2 passages merely discuss a possible role of COX-2 inhibition. They do not allow the conclusion from COX-2 inhibition to PGE2 production or even its inhibition. Likewise, said passages do not mention the selective inhibition of COX-2.

With regard to the further passages, the Applicant appears to select one feature of a specific test system used in examples 1-3 of present application, i.e. PGE2 production in a RAW 264.7 cell model, in order to redefine the scope of the claims. In contrast, the application as originally filed refers to synergistic effects with regard to selective COX-2 inhibition. Both definitions are not to be considered as identical. Consequently, present amendments would represent a generalisation of a specific teaching only to be found in a particular context.

Therefore, said amendment of "a combination index (CI) of less than 1 for synergistic inhibition of PGE2 production" has not been taken into account for the further examination for present claims 1-10.

Further examination is done based on the wording of previous claims 1 and 8 worded as "wherein said composition, when administered to the animal, has a synergistic effect on specific inhibition of inducible COX-2 activity and having minimal effect on COX-1 activity".

For present claims 1-4, previously defined ratio of 1:10 to 10:1 has also be taken into account for present examination.

2 Articles 83 and 84 EPC

2.1 Previously, it was stated that previous claims 1-10 did not meet the requirements of Article 84 EPC in that the matter for which protection is sought is not clearly defined. The subject-matter of previous independent claims 1 and 8 were defined in terms of the result to be achieved, i.e. the synergistic effect on specific inhibition of inducible COX-2 activity and minimal effect on COX-1 activity. In the light of item 1, this applies accordingly to present independent claims 1, 3, 5 and 7.

Due to the wording of the claims, it is not clear whether present claims 1-4 might represent product claims or so-called "first or second medical use" claims. For present examination, said claims 1-4 have been interpreted as product claims.

2.2 Claims 1, 3, 5 and 7 have been drafted as separate independent claims. Under Article 84 in combination with Rule 43(2) EPC an application may contain more than one independent claim in a particular category only if the subject-matter claimed falls within one or more of the exceptional situations set out in paragraphs (a), (b) or (c) of Rule 43(2) EPC.

In this context the following is to be noted : in the present case, claims 3 and 7 refer to compositions comprising compounds which are merely described in generic terms. The application does not disclose any specific compound falling under the scope of said claims. Like original claim 6 the only reference in the description uses generic terms which refer to a multitude of different possible compounds (present application, page 8, lines 2-6).

This deficiency implies a lack of disclosure for said claims 3 and 7. In order to carry out the invention, the skilled person would first have to synthesize randomly numerous alternative conjugates. Then he would have to establish a suitable model for selective COX-2 inhibition and finally test the prepared compound combinations randomly in the model in order to see whether they would show a synergistic effect with regard to selective COX-2 inhibition. The same would apply with regard to a model for the assessment of synergistic inhibition of PGE2 production of present claim 1, as far as admissible (see also item 1 above). These efforts represent an undue burden to the person skilled in the art. Therefore, present claims 3 and 7 do not comply with the requirements of Article 83 EPC.

The Applicant is requested to delete said claims 3 and 7.

2.3 Previous objection with regard to the terms "curcuminoid species", "a diterpene lactone species" and "a triterpene species" have been overcome by incorporation of lists of specific compounds. The same applies to the term "derivative" which has been deleted.

2.4 Previously it was noted that the term "inflammation" is not considered to represent a well defined disease. Rather than referring to a specific disease the term relates to pharmacological mechanisms underlying certain diseases such as arthritis (European search opinion, item 4.8). Said interpretation is confirmed by the document cited by the Applicant which starts by "inflammation is part of the complex biological response of vascular tissues ...". Said document refers to a multitude of diseases wherein an inflammation might play a role. In other words, the term "inflammation" as such is well known, as far as relating to pharmacological mechanisms. However, said term does not represent a well defined disease. Thus, previous clarity objection still applies.

Therefore, the Applicant is requested again to delete said term.

2.5 If the Applicant is able to provide a basis in the sense of Article 123(2) EPC for the introduction of the term "wherein said composition has a combination index (CI) of less than 1 for synergistic inhibition of PGE2 production" in claims 1 and 8 the following issue will arise :

In order to carry out the invention, the skilled person would first have to establish a model for determining a synergistic inhibition of PGE2 production. Apart from the specific, exemplified model disclosed in present application, no guidance is given which criteria might be relevant for selecting a model for determining said PGE2 inhibition. Then the skilled person has to randomly screen compound combinations comprised in the lists of claims 1 and 5 in order to see whether the combination of the tested compounds would indeed result in a synergistic effect in the applied test system. The random screening of compounds in a test (which is not defined and which has to be established before) is considered to represent an undue burden to the person skilled in the art. Therefore, above cited definition, even if it were admissible under Article 123(2) EPC, would introduce a lack of disclosure in the sense of Article 83 EPC.

According to the Applicant the skilled person could carry out the invention guided by the examples without undue burden (Applicant's letter dated 22.12.2011, item II, 1). This reasoning can only be followed if the Applicant restricts the scope of the claims accordingly to the subject-matter of the examples. Apparently, the Applicant's reasoning does not take into account that the disclosure has to be sufficient to carry out the invention as claimed over the whole of the claimed scope.

3 Article 54 EPC

3.1 As stated previously (European search opinion, item 5.1) a composition can only be validly claimed as an invention once and cannot be validly claimed subsequently again under the guise of a specified pharmacological mechanism, for instance selective inhibition of COX-2. This also applies to a composition for use in the treatment of a specified disease which cannot be validly claimed subsequently again for the treatment of the same disease under the guise of said newly specified mechanism. In fact, the discovery of such a new way of action is not an invention, as the technical effect obtained remains the same (preventing or curing the same disease or alleviating its symptoms). The technical effect being identical, the use is not changed by the discovery of the mechanism. Only if such a discovery would lead to a better

technical effect, which may be put into a practical effect (e.g. another galenic composition which delivers the medicament more selectively at the required site or receptor), or to a new technical effect (e.g. the possibility to treat diseases hitherto not known to be cured by that medicament), a potential invention is made. The specification of a mechanism consequently does not limit or change the character of neither a composition claim nor a use limited product claim.

This reasoning applies mutatis mutandis to the amended definition by "a combination index (CI) of less than 1 for synergistic inhibition of PGE2 production", as far as this definition would be admissible under Article 123(2) EPC and disclosed in the sense of Article 83 EPC.

In other words, these features of selective inhibition of COX-2 or of inhibition of PGE2 production are features which are implicit to specific therapeutic combinations. The Applicant is reminded that incorporation of an implicit feature into a claim does not render its subject-matter novel over the disclosure of the prior art.

Consequently, the Applicant's reasoning that the synergistic inhibition of PGE2 production would render presently claimed subject-matter novel of previously cited prior art (Applicant's letter dated 22.12.2011, item II, 3) cannot be followed.

3.2 As also stated by the Applicant (Applicant's letter dated 22.12.2011, item II, 2) D5 discloses compositions comprising curcuma longa and tephrosia purpurea, i.e. compositions comprising curcumin and ursolic acid. As stated earlier, said composition is disclosed for use in the treatment of psoriasis (European search opinion, item 5.9).

Therefore and in the light of items 1, 2.4, 2.5 and 3.1, the subject-matter of present claims 1-5 and 7-8 is considered not to be novel over D5.

3.3 Previously, D7 was cited against novelty of previous set of claims (European search opinion, item 5.10). The composition of D7 comprises further ingredients, e.g. Cyperus rotundus (D7, abstract). According to present application Cyperus rotundus comprises inter alia oleanolic acid (present application, page 9, line 29)..

Therefore and in the light of items 1, 2.4, 2.5 and 3.1, the subject-matter of present claims 1-5 and 7-8 is considered not to be novel over D7.

3.4 Likewise, previously cited documents D8 and D9 are still novelty-destroying for present claims 1-5 and 7-8 (European search opinion, item 5.11).

3.5 Previously, D10 was cited against novelty of previous set of claims (European search opinion, item 5.12). The composition of D10 also comprises herbal extracts from Loranthus parasiticus, Crataegus pinnatifida and Zizyphus jujuba (D10, table 1). According to present description said plants all comprise oleanic acid. The last two extracts, i.e. from Crataegus pinnatifida and Zizyphus jujuba, further comprise ursolic acid (present application, page 9, line 11 - The composition is for the treatment of hepatic disorders including autoimmune liver disease (D10, page 2, lines 10-11). Autoimmune liver disease may be regarded as an inflammatory disease.

Therefore and in the light of items 1, 2.4, 2.5 and 3.1, the subject-matter of present claims 1-5 and 7-8 is considered not to be novel over D10.

3.6 Previously, D12 was cited against novelty of previous set of claims (European search opinion, item 5.14).

In the light of items 1, 2.4, 2.5 and 3.1, the subject-matter of present claims 1-5 and 7-8 is considered not to be novel over D12.

3.7 The subject-matter of present set of claims is directed to compositions comprising a list of 3 curcuminoids and as a second agent a triterpene selected from a list. The second component is to be found in an uncountable number of plants. Present description already states that "ursolic acid and oleanic acid are found in wide variety of botanicals" (present application, page 9, lines 7-8). The description then discloses some examples for ursolic acid and oleanic acid only. The list presently disclosed covers already a whole page of botanical sources for these two acids only (present application, page 9, line 11 - page 10, line 8).

Consequently, the documents cited in the search report merely represent some examples which are novelty-destroying for previous set of claims. Even for the slightly more restricted scope of present set of claims, a complete search of all compositions comprising the claimed ingredients would be impossible. It is to be noted that curcuma longa roots as such are already novelty-destroying for previous independent claim 1.

In view of the wording of a "composition comprising" almost any traditional botanical composition comprising curcuma would be novelty-destroying for present set of claims. In the absence of any definition in the application with regard to a composition consisting of the listed ingredients, it is not apparent how the Applicant could render presently claimed subject-matter novel.

4 Article 56 EPC

4.1 Should the Applicant intend to argue that previously mentioned ratio of 1:10 to 10:1 would render the subject-matter novel over the prior art, the following applies as discussed previously (European search opinion, items 6.1 and 6.4) :

The Applicant apparently extrapolates from the specific 1:4 and 1:2 ratios of the 3 tested combinations to the significantly broader range of 1:10 to 10:1 without even providing pharmacological data for different ratios as support for the 3 specific combinations. Consequently, the claimed range appears to be merely arbitrary.

With regard to present set of claims, the application merely discloses a synergistic effect for the combination of curcumin with either ursolic acid or oleanolic acid when combined in ratio of 1:2. In addition, said effect apparently only relates to compositions consisting of these two therapeutic components. Potential effects of further active ingredients comprised in the claimed compositions have apparently not been taken into account.

4.2 The objection of an arbitrary selection of a certain range also applies to the dosage form of present claim 6. The application does not disclose any data relating to the ranges of said dependent claim 6. Furthermore, it is to be noted that the ranges of 0.001 - 30.0 mg/kg body weight per day for the first component and 0.5 - 20.0 mg/kg body weight per day for the second component are extremely broad.

4.3 As discussed earlier the observed synergistic effects are to be considered as the discovery of mechanisms underlying the treatment of certain diseases with combinations as claimed (European search opinion, item 6.5). This feature does not confer novelty to the subject-matter of present claims as discussed above (see item 3.1). Such a discovery can only be taken into account for inventive step of a claim which is novel and only as far as directly relevant for the claimed subject-matter. Previously, it was also observed that the application merely describes theoretically how the efficacy of the claimed combinations in the treatment of the claimed diseases could be assessed (present application, examples 4-10).

4.4 While present examples discuss synergistic effects of curcumin with a second compound, i.e. andrographolide, ursolic acid or oleanoic acid, when combined together in a specific ratio, present set of claims is directed to compositions comprising inter alia a curcuminoid and a triterpene of present claim 1 (see items 3.7 and 4.1). The important role of numerous further ingredients which may be comprised in the claimed compositions has not been taken into account at all.

5 Final Remarks

5.1 It is not apparent how the Applicant may amend the claims in order to obtain protection for subject-matter not already covered by the scope of parent application EP 02 748 188.6.

5.2 Should the Applicant intend to submit a new set of claims, his attention is drawn to the following :

5.2.1 In view of the extreme broad scope of the application as originally filed introduction of further novelty-destroying documents is to be expected.

5.2.2 Therapeutic combinations comprising for instance curcumin and a triterpene in initially claimed ratio range being known from the prior art, a non-unity objection may be raised in the further procedure.

5.2.3 The Applicant requested oral proceedings under Article 116 EPC. He is informed that said oral proceedings are to be expected as the next step.