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Datasheet for the decision of 10 April 2019

Case Number: T 0235/13 - 3.3.01

Application Number: 05728903.5

Publication Number: 1743653

IPC: A61K45/00, A61K38/00, A61K38/22, A61P19/00, A61P43/00, C12Q1/02, G01N33/15, G01N33/50, C07K14/47, C12N15/00, C12N15/09

Language of the proceedings: EN

Title of invention:
COMPOSITION FOR INCREASING BODY HEIGHT

Applicant:
Nakao, Kazuwa

Headword:
Composition for treating short stature disorders/NAKAO

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

This datasheet is not part of the Decision.
It can be changed at any time and without notice.

Decisions cited:
T 1422/12, T 0440/91

Catchword:

This datasheet is not part of the Decision.
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Case Number: T 0235/13 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 10 April 2019

Appellant: (Applicant)	Nakao, Kazuwa 4-1-2, Kitakutsukake-cho, Ohe Nishikyo-ku Kyoto-shi, Kyoto 610-1101 (JP)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 26 July 2012 refusing European patent application No. 05728903.5 pursuant to Article 97(2) EPC**

Composition of the Board:

Chairman	A. Lindner
Members:	T. Sommerfeld
	P. de Heij

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division, in which European patent application 05728903.5, based on an international application published as WO2005/094890, was refused under Article 97(2) EPC.

In the decision under appeal, the examining division decided that the main request and auxiliary request 1 lacked novelty and that auxiliary request 2 lacked inventive step.

II. The applicant (hereinafter, the appellant) lodged an appeal against the decision of the examining division, requesting that the decision be set aside and that a patent be granted according to the sole claim request (referred to as the main request) filed with the statement of the grounds of appeal.

III. The board sent a communication pursuant to Rule 100(2) EPC and Article 17(1) RPBA. In said communication the board expressed a negative opinion regarding Articles 84, 123(2), 54(2) and 56 EPC.

IV. The appellant filed a reply dated 18 June 2018, together with a new main request and an auxiliary request.

Claim 1 of the **main request** reads as follows:

"1. A composition for use in a method of treatment of a patient with short stature but having no achondroplasia and wherein said short stature is selected from the group consisting of:
(1) short stature caused by endocrine abnormalities,

(2) short stature caused by non-endocrine abnormalities, and
(3) secondary short stature caused by chemotherapy or radiation therapy,
wherein the composition comprises type C natriuretic peptide (CNP) as an active ingredient and is administered by injection, wherein the CNP is CNP-53 from mammals, including human, or birds."

Claim 1 of the **auxiliary request** differs from claim 1 of the main request in that the therapeutic indications have been amended as follows:

"1. ...
(1) short stature caused by ~~endocrine abnormalities~~ growth hormone hyposecretion, short stature caused by hypothyreosis or short stature caused by adrenocortical hyperfunction,
(2) ~~short stature caused by non endocrine abnormalities~~ familial short stature, fetal hypoplastic short stature or short stature caused by chromosome abnormalities, and
(3) secondary short stature caused by chemotherapy or radiation therapy,
..."

V. Oral proceedings took place on 10 April 2019 as scheduled. At the end of oral proceedings, the chairman announced the board's decision.

VI. The documents cited in the examination and appeal proceedings include the following:

D1 US 2003/0068313
D3 Chusho H. et al. 2001, PNAS 98(7), 4016-4021
D5 Komatsu Y. et al. 2002, J. Bone Miner. Metab. 20,

331-336

D7 WO 02/074234

D12 Hunt P.J. et al. 1994, J. Clin. Endocrinol. and Metab. 78(6),1428-1435

VII. The appellant's arguments, in so far as relevant to the present decision, may be summarised as follows:

Although the application only presented data for CNP-22 transgenic mice, it nevertheless discussed CNP-22 and CNP-53 at the same level of disclosure (page 9, fourth paragraph). This was also derivable from the prior art document D12 (first page, left-hand column, lines 9 to 12). Hence, the results obtained with the CNP-22 transgenic mice could be extrapolated to CNP-53, and post-published evidence confirmed the results in the application and also showed that CNP-53's bioavailability was much higher, with CNP-53 therefore being particularly suited for systemic administration.

Document D7 could be considered the closest prior art. It disclosed compositions for treating skeletal dysplasias, especially achondroplasia. It did not mention CNP-53 at all and only used CNP 1-22, or CNP 5-22 (actually 6-22) and variants thereof (Figure 3 and bottom of page 8). Apart from Example 1, an ex vivo experiment with bones from the achondroplasia mouse model, there were no more data in D7 regarding therapeutic effect, the other examples being related to attempts to overcome the problem of CNP's short half-life in circulation.

The claimed subject-matter differed from D7 on account of the use of the CNP-53 peptide and the specific short stature conditions. The effect linked to the use of CNP-53 was an increased therapeutic efficacy due to the

improved bioavailability, and this effect should be taken into account, following decisions T 1422/12 and T 440/91. Since CNP was known in the prior art to act locally and to have a short half-life in circulation (D7, page 3, first paragraph, and page 20; D3, page 4019, right-hand column, line 4 from bottom; D5, page 334, left-hand column, second paragraph, and Figure 5; D12, abstract, right-hand column, first sentence), the skilled person would understand that the CNP-53 could be administered by injection only because of its improved bioavailability.

The technical problem was thus to be formulated as the provision of an improved therapy for specific short stature conditions, other than achondroplasia, in particular with respect to increased efficacy due to higher bioavailability.

The claimed solution was not rendered obvious by D7, which in fact taught away from the claimed solution, as it suggested other ways to overcome the problem, in particular different administration routes like implantation of a depot or administration by an Alzet pump. D1 would not be taken into account because it was specifically about the treatment of achondroplasia (Title; page 1), it relied on the known local mode of action, therefore using a cartilage-specific promoter (CMP) to produce the CNP-transgenic mice (Example 1), and it was not clear which CNP was in fact used in the examples. There would be thus no incentive to take CNP-53 and to administer it by injection in order to solve the technical problem, and there would be no reasonable expectation of success because there was no evidence of the suitability of systemic administration.

If the improved bioavailability of CNP-53 were to be disregarded in the formulation of the technical problem, the problem would have to be formulated as the provision of an alternative compound for use in the treatment of short stature conditions other than achondroplasia.

Again the solution would not be obvious, for the same reasons as discussed above. D12 taught that CNP-22 and CNP-53 had the same biological activities but provided no information as to bioavailability. It was the application that overcame the general prejudice regarding bioavailability by showing in the experiment with CNP-22 that systemic administration had an effect on bone growth. The same arguments applied also to the auxiliary request.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims of the main request or, alternatively, on the basis of the set of claims of the auxiliary request, both of which were filed with the letter dated 18 June 2018.

Reasons for the Decision

1. The appeal is admissible.

2. Main request - Inventive step

2.1 The present application is directed to compositions "for increasing the body height of an individual, comprising a guanyl cyclase B (GC-B) activator as an

active ingredient", wherein said compositions "can be used for treatment of a patient with short stature free from FGFR3 abnormality" (paragraph [0001] of the application as published). According to paragraph [0042] of the application as published, FGFR3 abnormality "refers to achondrogenesis or achondroplasia, which is caused by growth inhibition of cartilage bones resulting from mutations in the fibroblast growth factor receptor 3 (.FGFR3) gene, or achondrogenesis or achondroplasia caused by function control failure of FGFR3 or overexpression of FGFR3 gene resulting from mutations in the FGFR3 gene". As to the composition to be used, it comprises a GC-B activator as an active ingredient, which is preferably a CNP (C-type natriuretic peptide) or a derivative thereof, and more preferably CNP-22 or CNP-53 from mammals, including human, or birds (paragraphs [0014], [0020] and [0021] of the application as published).

2.2 Any document directed to the same purpose as the present application, namely treatment of short stature disorders which are not related to a FGFR3 abnormality i.e. achondroplasia, could be a suitable starting point for the discussion of inventive step. Document D7, which is directed to the treatment of skeletal dysplasias (e.g. Title; page 5, first paragraph), i.e. pathological situations of reduced bone growth, is one such document. The fact that achondroplasia is not excluded in D7 does not render this document less suitable as the starting point for the discussion of inventive step, because D7 concerns all skeletal dysplasia disorders in general.

2.3 The difference from present claim 1 is that D7, which teaches using CNP peptides in general and CNP-22 in particular, does not disclose CNP-53, let alone as a

therapeutic agent for skeletal dysplasia disorders, nor does it mention the specific groups of diseases listed in claim 1. The application does not teach that there is any particular effect or advantage associated with using CNP-53 instead of CNP-22 in the treatment of the claimed disorders. Hence, the technical problem is formulated as the provision of an alternative therapy for the treatment of pathological situations of short stature, other than achondroplasia. The solution is the subject-matter as claimed, namely the use of CNP-53 peptides, and, in view of the teachings of the application and of the prior art (D7, D12), the board is satisfied that the solution plausibly solves the technical problem.

2.4 The appellant argued that the technical problem should be formulated as the provision of an improved therapy for the specific short stature conditions, since CNP-53 had the unexpected property of improved bioavailability (because of the increased half-life) compared with CNP-22. Although this property had been shown only a posteriori, it should nevertheless be taken into account, in line with decisions T 1422/12 and T 440/91.

2.5 The board notes that the alleged unexpected property of improved bioavailability of CNP-53 in comparison with CNP-22 was not disclosed at all, or even hinted at, in the application as filed, which, as a matter of fact, teaches both CNP-22 and CNP-53 as equally suitable therapeutic agents and only presents data for CNP-22 transgenic mice. The same teaching, i.e. that CNP-22 and CNP-53 are biologically equivalent, can also be derived from the prior art, e.g. D12 (see also below). The now alleged advantage of CNP-53's longer half-life in comparison with CNP-22, with the associated higher bioavailability in circulation, was only acknowledged

later and therefore cannot be taken into consideration in the formulation of the technical problem. Thus, although post-published evidence may be used to confirm the teaching of the application as filed, it cannot be taken into account as evidence for a further, previously undisclosed, effect, such as a hitherto unknown specific advantage for which there was no suggestion at all in the application as filed.

2.6 In this respect, the present situation differs from the case underlying decisions T 1422/12 and T 440/91, and therefore the conclusions reached in these decisions are not applicable to the present case. According to said decisions, "any effects may be taken into account, so long as they concern the same field of use and do not change the character of the invention" (T 1422/12, point 2.3.2, referring to T 440/91, points 4.1 and 4.2). In T 1422/12, the board decided that the technical problem could be formulated to include a further technical effect, namely increased stability, despite this not being disclosed in the application in relation to the invention. However, the background section of the patent application underlying T 1422/12 related to improving the performance characteristics of pharmaceutical products, and thus the formulation of the technical problem as disclosed above did fall "within the framework of the invention as disclosed in the application in suit" (T 1422/12, point 2.3.3). This is not the case for the present application, which fails to indicate, in either the disclosure of the invention or the discussion of the prior art, any improvement to a therapy, let alone improved bioavailability of the therapeutic compound. Hence, this further effect does change the character of the invention and for this very reason cannot be taken into account.

2.7 It next has to be examined whether the claimed solution involves an inventive step.

2.8 As mentioned above, D7 is not restricted to achondroplasia but rather relates to treatment of skeletal dysplasia disorders in general, of which achondroplasia happens to be the most common form and one of known aetiology (D1, paragraph [0004]; D3, abstract, lines 13 to 14) for which animal models are available (D7, Example 1, first paragraph on page 16). This explains why most prior art documents, such as those on file, relate to achondroplasia. However neither the prior art nor the application teaches that the therapeutic approach for achondroplasia cannot be extrapolated to other forms of short stature disorders. Hence, the skilled person would consider the conclusions of D7, based on the experiments carried out with an achondroplasia mouse model, to be relevant also for other forms of short stature disorders. Moreover, the role of natriuretic peptides and in particular CNP in endochondral ossification was known in the prior art, as reviewed in D7 (page 4, lines 13 to 27). Endochondral ossification in the cartilaginous growth plate determines longitudinal bone growth (D7, page 1, lines 11 to 15) and is the physiological process that is affected in short stature disorders. In view of the fact that D7 suggests using CNP in general (e.g. claim 2), the skilled person would a priori consider any CNP mature form to be equally suitable for the purpose of treating pathological situations of short stature.

2.9 It was known from the prior art that there were two mature forms of CNP, namely "the 22-amino acid form (CNP-22) and the N-terminal-extended form (CNP-53), each with similar biological activities" (D12, page

1428, left-hand column, lines 9 to 12). Therefore, the skilled person would consider that, since the two CNP mature peptides were biologically equivalent, the results obtained with CNP-22 in D7 could be expected with CNP-53 as well. Accordingly, the claimed solution is considered obvious from D7 in combination with common general knowledge, such as represented by D12.

2.10 The appellant argued that, independently of the technical problem being formulated as an improvement or an alternative, the solution as claimed could still not be considered obvious, since there was no hint or suggestion in the prior art pointing to the surprising property of higher CNP-53 bioavailability. Moreover, the skilled person would expect CNPs to act only locally, and would therefore not consider systemic administration of the composition to be suitable for the therapy of the claimed diseases.

2.11 As set out under point 2.6, the alleged technical effect of improved bioavailability cannot be taken into account for the assessment of inventive step. In any event, this effect is not relevant when the objective technical problem to be solved is the provision of a mere alternative.

2.12 The board furthermore disagrees that the skilled person would be deterred from systemic administration of CNP-53 in view of the fact that CNPs were known to act locally and to have a short half-life in circulation. First, systemic administration (or, more specifically, administration by injection, as in the claim) is also disclosed in the closest prior art D7, as admitted by the appellant. Despite acknowledging the problem of CNP's short half-life in circulation, D7 does disclose systemic administration of CNP by injection, by using

an Alzet pump (e.g. Example 3). Moreover, D7 envisages systems for overcoming this problem, including e.g. the concomitant administration of inhibitors of the neutral endopeptidase (NEP), which was considered to be responsible for the CNP short half-life in circulation (Example 5). It should be noted that the claimed subject-matter does not exclude the administration of further compounds apart from CNP-53. Second, the issues of short half-life in the circulation and local action are not specific to the CNP-53 form but rather to CNP in general, as acknowledged in the prior art (D7 supra; D5, page 334, left-hand column, second paragraph, as regards local action). Thus any prejudice as to systemic administration would be valid for all forms of CNP: said alleged prejudice had however already been overcome by D7 for CNP-22 and there were no reasons to believe that the same solutions would not be available for CNP-53 too.

2.13 Claim 1 of the main request is thus considered to lack inventive step. The main request is not allowable for lack of compliance with Article 56 EPC.

3. Auxiliary request - Inventive step

3.1 Claim 1 of this request differs from claim 1 of the main request in that the disorders to be treated have been further defined (for the exact wording, see section IV). However, this amendment is not deemed to contribute to inventive step, nor has the appellant argued so.

3.2 The auxiliary request is thus also not allowable for lack of compliance with Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated