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Case Number: T 0855/20 - 3.3.01

Application Number: 13764904.2

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Language of the proceedings: EN

Title of invention:
COMPOSITIONS AND METHODS TO IMPROVE THE THERAPEUTIC BENEFIT OF INDIRUBIN AND ANALOGS THEREOF, INCLUDING MEISOINDIGO

Applicant:
Brown, Dennis

Relevant legal provisions:
EPC Art. 84

Keyword:
Claims - clarity (no)

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Case Number: T 0855/20 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 20 July 2021

Appellant: (Applicant)	Brown, Dennis 3475 Edison Way Suite R Menlo Park, 94025 (US)
Representative:	Körfer, Thomas Mitscherlich PartmbB Patent- und Rechtsanwälte Sonnenstrasse 33 80331 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 5 November 2019 refusing European patent application No. 13764904.2 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. The decision under appeal is the examining division's decision refusing European patent application No. 13 764 904.2, announced on 16 September 2019 and posted on 5 November 2019.

II. The decision was based on the sets of claims of an amended main request and 11 auxiliary requests, all filed on 16 August 2019.

III. Independent claim 1 of the **main request** reads as follows:

"1. A non-therapeutic method for preparation of a medicament to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy,

wherein the suboptimally administered drug therapy is a drug therapy with meisoindigo or a pharmaceutically acceptable salt of meisoindigo as a therapeutically active compound as defined below;

where Phase I toxicity previously precluded further human clinical evaluation;

where Phase II trials were previously limited with <25% response rates or no significant tumor responses were identified;

where the outcome of Phase III clinical trials was either medically or statistically not significant to warrant regulatory submission or approval by government agencies for commercialization, or where clinical response rates as a monotherapy were less than 25%;

or where side effects had previously been severe enough to limit wide utility;

the non-therapeutic method comprising the steps of:

(a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the suboptimally administered drug therapy in the treatment of a cancer selected from the group consisting of acute myelogenous leukemia and colorectal cancer; and

(b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the suboptimally administered drug therapy,

wherein the suboptimally administered drug therapy comprises administration of a therapeutically active agent selected from the group consisting of:
i) meisoindigo; and (ii) a pharmaceutically acceptable salt of meisoindigo,

wherein the pharmaceutically acceptable salt of meisoindigo is selected from the group consisting of:

(i) a salt with a positively-charged ion selected from the group consisting of sodium, potassium, aluminum, lithium, calcium, magnesium, zinc, ammonium, caffeine, arginine, diethylamine, N-ethylpiperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl-morpholine, piperazine, piperidine, triethylamine, trimethylamine, ethanolamine, diethanolamine, N-methyl-glucamine, and tris(hydroxymethyl)aminomethane; and

(ii) a salt with a negatively-charged ion selected from the group consisting of chloride, bromide, iodide, carbonate, nitrate, sulfate, bisulfate, phosphate, monohydrogen phosphate, dihydrogen phosphate, metaphosphate, pyrophosphate, formate, acetate, adipate, butyrate, propionate, succinate, glycolate, gluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilate, mesylate, 4'-hydroxybenzoate, phenylacetate, mandelate, embonate

(pamoate), methanesulfonate, ethanesulfonate, ethanedisulfonate, benzenesulfonate, pantothenate, 2-hydroxyethanesulfonate, p-toluenesulfonate, sulfanilate, cyclohexylaminosulfonate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfonate, glucoheptanoate, glycerophosphonate, heptanoate, hexanoate, 2-hydroxyethanesulfonate, nicotinate, isonicotinate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfurate, 2-phenylpropionate, picrate, pivalate, thiocyanate, mesylate, undecanoate, stearate, algenate, β-hydroxybutyrate, salicylate, galactarate, galacturonate, caprylate, isobutyrate, malonate, suberate, sebacate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, phenylacetate, isethionate, lactobionate, p-aminobenzoate, sulfamate, diethylacetate, pimelate, aminosulfonate, acrylate, γ-hydroxybutyrate, and methoxybenzoate; and

wherein the factor or parameter is selected from the group consisting of:

(I) dose modification, wherein the dose modification is a modification suitable to improve the efficacy and/or reduce the side effects of the suboptimally administered drug therapy selected from the group consisting of:

(i) continuous i.v. infusion for hours to days;

(ii) doses greater than 5 mg/m^2/day;

(iii) progressive escalation of dosing from 1 mg/m^2/day based on patient tolerance

(iv) administration of single and multiple doses escalating from 5 mg/m^2/day via bolus;

(v) oral dosages of below 30 mg/m^2 ;

(vi) oral dosages of above 130 mg/m^2 ;

(vii) chronic low dose administration of from about 10 mg/day to about 25 mg/day;

(viii) intermittent administration of from about 50 mg to about 150 mg twice weekly or three times weekly;

(ix) administration of from about 50 mg/day to about 150 mg/day for 10-14 days per month; and

(x) chronic daily dosing at a dose of equal to or greater than 100 mg/day;

(II) patient/disease phenotype, wherein the analysis of patient or disease phenotype suitable to improve the efficacy and/or reduce the side effects of the suboptimally administered drug therapy is carried out by a method selected from the group consisting of:

(i) use of a diagnostic tool, a diagnostic technique, or a diagnostic assay to confirm a patient's particular phenotype;

(ii) use of a method for measurement of a marker selected from the group consisting of histone deacetylase, ornithine decarboxylase, VEGF, a protein that is a gene product of a prostate specific gene, a protein that is a gene product of jun, and a protein kinase;

(iii) surrogate compound dosing; and

(iv) low dose pre-testing for enzymatic status; and

(III) patient/disease genotype, wherein the analysis of patient or disease genotype suitable to improve the efficacy and/or reduce the side effects of the suboptimally administered drug therapy is carried out by a method selected from the group consisting of:

(i) use of a gene chip;

(ii) use of gene expression analysis;

(iii) use of single nucleotide polymorphism (SNP) analysis; and

(iv) measurement of the level of a metabolite or a metabolic enzyme."

IV. Claim 1 of **auxiliary requests 1, 2 and 4** is identical to claim 1 of the main request.

V. Claim 1 of **auxiliary requests 3 and 5** is identical to claim 1 of the main request except that, after the final item mentioned under option (III):

"(iv) measurement of the level of a metabolite or a metabolic enzyme",

these claims add yet a further option (IV) for the selection of the factor or parameter to be modified:

"(...); and (IV) use of a prodrug system, wherein the prodrug system is selected from (...)",

further defined by a list of sub-items (i) to (xi).

VI. Claim 1 in each of **auxiliary requests 6 to 11** corresponds to claim 1 of the main request, except for the following modifications.

(a) Auxiliary requests 6 to 11 each contain certain deviations in wording in comparison with claim 1 of the main request (differences underlined by the board):

- *"where Phase I toxicity previously precluded"* becomes *"where Phase I toxicity precluded"*;
- *"where Phase II trials were previously limited"* becomes *"where Phase II trials where limited"*;
- *"where clinical response rates as a monotherapy were less than 25%"* becomes *"where clinical response rates as a monotherapy are less than 25%"*;
- *"where side effects had previously been severe enough"* becomes *"where side effects are severe enough"*;

- under item (b) of claim 1, *"wherein the suboptimally administered drug therapy comprises"* becomes *"wherein the suboptimally administered drug therapy comprised"*.

(b) In claim 1 of each of auxiliary requests 6 to 11, four sub-items are added to the list relating to dose modification according to item (I) (differences in comparison with claim 1 of the main request underlined by the board):

"(i) continuous i.v. infusion for hours to days;
(ii) biweekly administration;
(iii) doses greater than 5 mg/m^2 /day;
(iv) progressive escalation of dosing from 1 mg/m^2/ day based on patient tolerance;
(v) use of caffeine to modulate metabolism;
(vi) use of isoniazid to modulate metabolism;
(vii) selected and intermittent boosting of dosage administration;
(viii) administration of single and multiple doses escalating from 5 mg/m^2 /day via bolus;
(ix) oral dosages of below 30 mg/m^2 ;
(x) oral dosages of above 130 mg/m^2 ;
(xi) chronic low dose administration of from about 10 mg/day to about 25 mg/day;
(xii) intermittent administration of from about 50 mg to about 150 mg twice weekly or three times weekly;
(xiii) administration of from about 50 mg/day to about 150 mg/day for 10-14 days per month; and
(xiv) chronic daily dosing at a dose of equal to or greater than 100 mg/day;"

(c) In addition to this, claim 1 of **auxiliary request 9** includes option (IV) as defined in claim 1 of auxiliary request 3 (see point V. above).

(d) Claim 1 of **auxiliary request 10** is identical to claim 1 of auxiliary request 6, and claim 1 of **auxiliary request 11** is identical to claim 1 of auxiliary request 9, except that under item (a), the indication *"in the treatment of a cancer selected from the group consisting of acute myelogenous leukemia and colorectal cancer"* becomes *"in the treatment of colorectal cancer"*.

VII. In the decision under appeal, the examining division ruled that the subject-matter of claim 1 of the main request fell under the exception to patentability under Article 53(c) EPC and also lacked clarity under Article 84 EPC, and that the same objections also applied to auxiliary requests 1 to 11.

VIII. The applicant (appellant) filed an appeal against this decision. With the statement setting out the grounds of appeal, the appellant submitted further sets of claims as auxiliary requests 12 to 23.

IX. Except for minor editorial changes, claim 1 of **auxiliary requests 12, 13, 14, 16, 18, 19, 20 and 22** is identical to claim 1 of the main request (see point III. above), and claim 1 of **auxiliary requests 15, 17, 21 and 23** is identical to claim 1 of auxiliary request 3 (see point V. above).

X. In preparation for oral proceedings, the board issued a communication according to Article 15(1) RPBA advising the appellant of its preliminary opinion.

XI. Oral proceedings before the board were held on 20 July 2021.

The appellant was heard on the issue of lack of clarity under Article 84 EPC raised in point 5.2 of the board's communication, namely the objection that claim 1 was directed to a method for the "preparation of a medicament" but failed to define a step by which a medicament was prepared. The board pointed out that while features (I) to (III) of claim 1 defined factors or parameters of drug therapy to be identified and modified, this did not necessarily involve making modifications to a medicament and its preparation (as argued by the appellant). *Inter alia*, it was also discussed whether the claimed "preparation of a medicament" could be understood to encompass mere instructions on how to improve a drug therapy.

XII. The appellant's arguments may be summarised as follows.

Claim 1 of the main request was not directed to a further medical use but simply defined a method for the preparation of a medicament. The medicament so prepared must be suitable for improving the efficacy and/or reducing the side effects of a suboptimally administered drug therapy with the active agent meisoindigo or one of its pharmaceutically acceptable salts in the treatment of a specified cancer.

The application as filed expressly mentioned in paragraph [0392] of the description that the method claims of the invention provided specific method steps.

Claim 1 itself stated that the claimed method for preparation of a medicament comprised the steps of (a) identifying a relevant factor or parameter and (b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the

suboptimally administered drug therapy. The result of this modification step was the end product, i.e. the medicament to be prepared.

Items (II) and (III) of claim 1 also involved specific method steps, as further illustrated in paragraphs [0124] to [0127] of the description.

As to the board's objection that modifying factors or parameters according to items (II) and (III) did not actually translate into steps of a method for preparing a medicament, the following considerations should be taken into account.

While it was not disputed that items (I) to (III) were presented in claim 1 as alternative choices for the factor/parameter to be modified, the selection of a phenotype or genotype according to items (II) and (III) could well necessitate adapting a medicament to the metabolic situation of a patient group, in particular by dose modification according to item (I). Thus, items (I), (II) and (III) were interrelated and could not be regarded in isolation.

Medicaments could obtain regulatory approval only together with their specific dosage instructions. Modifying the factors or parameters according to items (I), (II) or (III) of claim 1 always involved changes to the medicament. These changes could include physical changes to the dosage form or, at least, changes to the dosage instructions, thus resulting in the end product prepared by the claimed method. The dosage instructions derived from items (I), (II) and (III) should, therefore, be taken into account as technical features in the context of method claim 1.

The same arguments applied to the auxiliary requests.

XIII. The appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division for further prosecution if the board arrived at the conclusion that the requirements of Articles 53(c) and 84 EPC were met for any of the following requests:

- the main request or auxiliary requests 1 to 11, all filed on 16 August 2019
- auxiliary requests 12 to 23, all filed with the statement setting out the grounds of appeal

or, in the alternative, that the decision under appeal be set aside and that a patent be granted on the basis of:

- the claims of the main request filed on 16 August 2019, original pages 1 to 171 of the description and pages 1/5 to 5/5 of the drawings

or on the basis of:

- the claims of one of auxiliary requests 1 to 11, all filed on 16 August 2019, or
- the claims of one of auxiliary requests 12 to 23, all filed with the statement setting out the grounds of appeal.

Reasons for the Decision

1. Main request - clarity (Article 84 EPC)

1.1 To facilitate understanding of the following analysis, claim 1 of the main request can be reduced to its basic structure as follows:

"1. A (...) method for preparation of a medicament to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy (...) comprising the steps of:

(a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the suboptimally administered drug therapy (...) and

(b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the suboptimally administered drug therapy(...)

wherein the factor or parameter is selected from the group consisting of:

(I) dose modification (...);

(II) patient/disease phenotype (...);

(III) patient/disease genotype (...)."

1.2 This exercise reveals that although purporting to claim a method for the preparation of a medicament, claim 1 does not actually define any step by which a medicament is prepared. Rather, the steps mentioned relate to (a) identifying a factor or parameter of drug therapy and (b) modifying the drug therapy with respect to that factor or parameter. Such a modification does not necessarily affect the preparation of the medicament that is to be used in the therapy (as set out in more

detail below). The definition of claim 1 therefore lacks clarity.

1.3 The passage in paragraph [0392] of the application as filed (cited by the appellant) reads as follows:

> *"The method claims of the present invention provide specific method steps that are more than general applications of the laws of nature (...). In some contexts, these claims are directed to new ways of using an existing drug."*

This passage does not state that the "specific method steps" are steps of a method for preparing a medicament. In fact, the set of claims as originally filed did not include a claim to a method for preparing a medicament. Thus, the cited passage is not relevant to the issue under point 1.2.

1.4 According to claim 1, the factor or parameter of drug therapy to be modified must be selected from three alternatives, namely options (I) to (III).

1.5 Reading options (II) and (III) together with features (a) and (b), the claim appears, at first sight, to require modifying the phenotype or genotype of a patient or disease, which seems quite ambitious from a technical viewpoint. In all likelihood, the actually intended meaning was that a patient or patient group is to be selected according to the phenotype or genotype of the patient(s) or the disease.

In either case, the alternatives according to options (II) and (III) do not involve or imply any particular mandatory method step in the preparation of a medicament.

The sub-items listed under (II) and (III) (numbered (i) to (iv) in each case) relate to methods for analysing

phenotype or genotype. The passage in the description cited by the appellant (paragraphs [0124] to [0127]) essentially reproduces these features, none of which defines a method step for preparing a medicament.

1.6 The appellant argued that the selection of a phenotype or genotype according to items (II) and (III) may necessitate adapting the medicament to the metabolic situation of a patient group, e.g. by dose modification according to option (I).

1.7 This argument already fails because nothing suggests that dose modification would be inevitable in the context of options (II) and (III).

1.8 Moreover, neither the general concept of dose modification nor option (I) as more specifically defined in claim 1 would necessarily involve method steps for preparing a medicament.

1.8.1 When reading option (I) in light of features (a) and (b), claim 1 appears to require that the parameter "dose modification" be modified. It is to be assumed that this is actually intended to mean that the dose or dosage regime in an existing "suboptimal" drug therapy is to be modified.

1.8.2 The options for accomplishing this, listed as sub-items (i) to (x), are all dosage instructions. These instructions, and dosage modification in general, do not necessarily require a change to existing dosage forms which would be reflected in a manufacturing step. For instance, if a dosage form of a specific formulation strength already exists, a dosage regimen requiring higher or escalating doses, or one requiring intermittent or chronic dosing, can be implemented without a need for manufacturing a different product.

1.9 The appellant also argued that the dosage instructions should be taken into account as technical features.

1.10 However, dosage instructions as such define a therapy, and changes to dosage instructions define a change of therapy: they are not steps in a method for preparing a medicament. Claim 1 does not define a mandatory step of printing the dosage instructions, either, and if it did, the actual information content of the text to be printed would in any case not affect the mere process of preparing the dosage form and medicament.

1.11 In conclusion, the appellant's arguments fail to overcome the objection regarding lack of clarity according to point 1.2 above.

1.12 For these reasons, claim 1 of the main request does not meet the requirements of Article 84 EPC.

2. Auxiliary requests 1 to 11

2.1 The differences in claim 1 of each of auxiliary requests 1 to 11 in comparison with claim 1 of the main request have been listed above (see points IV. to VI.).

2.2 The addition of further alternatives to the claim (namely, option (IV) in auxiliary requests 3, 5, 9 and 11 and sub-items (ii), (iv), (vi) and (vii) in auxiliary requests 6 to 11) cannot change the assessment regarding clarity set out in section 1.

2.3 Limiting the targeted cancer to colorectal cancer (auxiliary requests 10 and 11) does not affect these conclusions, either.

2.4 The minor editorial changes in auxiliary requests 6 to 11 (see point VI.(a) above) appear to have occurred

erroneously. They have no impact on the assessment of clarity set out in section 1.

2.5 Hence, claim 1 of each of auxiliary requests 1 to 11 does not meet the requirements of Article 84 EPC for the same reasons as claim 1 of the main request.

3. Auxiliary requests 12 to 23

3.1 In all of auxiliary requests 12 to 23, claim 1 corresponds to either claim 1 of the main request or claim 1 of auxiliary request 3, with minor editorial changes which do not change the meaning (see point IX. above).

3.2 For the reasons presented in sections 1 and 2 above, these claims, and therefore also claim 1 in each of auxiliary requests 12 to 23, do not meet the requirement of clarity under Article 84 EPC.

3.3 In view of this outcome, a discussion of the admittance of auxiliary requests 12 to 23 under Article 12(4) and 12(6) RPBA is not required.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated