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**Datasheet for the decision
of 30 June 2020**

Case Number: T 1335/17 - 3.3.01

Application Number: 07824118.9

Publication Number: 2073802

IPC: A61K31/403

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMBINATIONS

Applicant:
Astex Therapeutics Limited

Headword:
Onalespib combinations/ASTEX

Relevant legal provisions:
EPC Art. 123(2), 54, 111(1)
RPBA 2020 Art. 11, 13(1)

Keyword:
Main request - admitted (yes) - added subject-matter (no) -
novelty (yes) - remittal (yes)



Beschwerdekammern

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Case Number: T 1335/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 30 June 2020

Appellant: Astex Therapeutics Limited
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Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on
19 December 2016 refusing European patent
application No. 07824118.9 pursuant to
Article 97(2) EPC.**

Composition of the Board:

Chairwoman R. Hauss
Members: J. Molina de Alba
M. Blasi

Summary of Facts and Submissions

- I. The appeal by the applicant (appellant) lies from the examining division's decision to refuse European patent application No. 07 824 118.9, announced on 24 November 2016 and posted on 19 December 2016.

The decision was based on the claims of a main request and two auxiliary requests.

- II. In the decision under appeal, the examining division considered that the subject-matter of claim 1 of each of the requests on file resulted from undisclosed selections within the combinations covered by claim 1 as filed. Therefore, all claim requests contravened Article 123(2) EPC.

By way of *obiter dictum*, the examining division gave its opinion that the combinations in claim 1 of each of the requests on file lacked novelty over the disclosure of document D1 (WO 2006/109085). Furthermore, in view of the lack of experimental evidence showing the therapeutic effect of the claimed combinations, they were neither inventive nor sufficiently disclosed.

- III. With the statement of grounds of appeal, the appellant filed six sets of claims as its main request and auxiliary requests 1 to 5.

- IV. The board scheduled oral proceedings in line with the appellant's request and gave its preliminary opinion in a communication dated 13 May 2020.

V. On 3 June 2020, the appellant filed a set of claims to replace the main request on file. The new main request contains eight claims. Independent claims 1, 5, 6, 7 and 8 read as follows:

"1. A combination comprising one or more ancillary compound(s) and a compound which is (2,4-dihydroxy-5-isopropyl-phenyl)-[5-(4-methyl-piperazin-1-ylmethyl)-1,3-dihydro-isoindol-2-yl]-methanone or a salt, solvate or tautomer thereof wherein the one or more ancillary compound(s) is selected from:

- I. tamoxifen, toremifene, raloxifene, medroxyprogesterone, megestrol/megestrel, aminoglutethimide, letrozole, anastrozole, exemestane, goserelin, leuprolide, abarelix, fluoxymestrone, diethylstilbestrol, ketoconazole, fulvestrant, flutamide, bicalutimide, nilutamide, cyproterone and buserelin;*
- II. interferon α -2b, interferon α -2a, aldesleukin, picibanil, romurtide, sizofiran, virulizin and thymosin alpha 1;*
- III. tretinoin, alitretinoin and bexarotene;*
- IV. rituximab, tositumomab, gemtuzumab ozogamicin, alemtuzumab, and bevacizumab;*
- V. irinotecan and topotecan;*
- VI. 5-fluorouracil, capecitabine, gemcitabine, cytarabine, fludarabine, raltitrexed, pemetrexed and methotrexate;*
- VII. vindesine, vinvesir, vinblastine, vincristine and vinorelbine;*
- VIII. paclitaxel and docetaxel;*
- IX. ixabepilone, patupilone, BMS-310705, KOS-862, ZK-EPO, BMS-247550 and desoxyeopthilone;*
- X. cisplatin, carboplatin, oxaliplatin, chloro(diethylenediamino)-platinum (II) chloride,*

*dichloro(ethylenediamino)-platinum (II),
spiroplatin, iproplatin, diamino(2-
ethylmalonato)platinum (II), (1,2-
diaminocyclohexane)malonatoplatinum (II), (4-
carboxyphthalo)-(1,2-diaminocyclohexane)platinum
(II), (1,2-diaminocyclohexane)-(isocitrato)platinum
(II), (1,2-diaminocyclohexane)-cis-
(pyruvato)platinum (II), onnaplatin, and
tetraplatin;*

*XI. daunorubicin, doxorubicin, idarubicin,
epirubicin, etoposide and teniposide;*

*XII. cyclophosphamide, ifosfamide/ifosphamide,
chlorambucil, carmustine, lomustine, mitomycin,
busulfan, estramustine, mechlorethamine, melphalan,
bischloroethylnitrosurea,
cyclohexylchloroethylnitrosurea,
methylcyclohexylchloroethylnitrosurea, nimustine,
procarbazine, dacarbazine, temozolimide and
thiotepa;*

*XIII. seliciclib, alvocidib, 7-hydroxy-
staurosporine, JNJ-7706621, BMS-387032, PHA533533,
PD332991, ZK-304709, and AZD-5438;*

XIV. celecoxib, etoricoxib and lumiracoxib;

*XV. trichostatin A, suberoylanilide hydroxamic
acid, JNJ-16241199, LAQ-824, MGCD-0103, and
PXD-101;*

XVI. lenalidomide and thalidomide;

*XVII. temozolomide, decitabine, 5-azacitidine,
pseudoisocytidine and 5-fluoro-2'-deoxycytidine;*

XVIII. bortezimib and bleomycin;

*XIX. AZD1152, MK0457, PHA-739358, MLN-8054, and
MP-235;*

*XX. herbimycin, geldanamycin, 17-AAG, 17-DMAG,
CNF-2024, and IPI-504;*

*XXI. bendamustine, INO-1001, BSI-201, AG-014699,
and ONO-2231;*

XXII. *atrasentan*; and
XXIII. *trastuzumab, cetuximab, panitumumab, tipifarnib, gefitinib, erlotinib, bevacizumab, sunitinib, imatinib mesylate, sorafenib, dasatinib, lapatinib, nilotinib, vandetanib, vatalinib and CHIR-258.*"

"5. A combination as defined in claim 1 for use:

i. in medicine;
ii. in treating a disease or condition comprising or arising from abnormal cell growth in a mammal;
or
iii. in the treatment of a proliferative disorder selected from a carcinoma of the bladder, breast, colon, kidney, epidermis, liver, lung, oesophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, gastrointestinal system, or skin; a hematopoietic tumour of lymphoid lineage; a hematopoietic tumour of myeloid lineage; thyroid follicular cancer; a tumour of mesenchymal origin; a tumour of the central or peripheral nervous system; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratoacanthoma; thyroid follicular cancer; or Kaposi's sarcoma."

"6. The use of a combination according to claim 1 for the manufacture of a medicament for the treatment of a disease which is

i. a disease or condition comprising or arising from abnormal cell growth in a mammal or
ii. a proliferative disorder selected from a carcinoma of the bladder, breast, colon, kidney, epidermis, liver, lung, oesophagus, gall bladder,

ovary, pancreas, stomach, cervix, thyroid, prostate, gastrointestinal system, or skin; a hematopoietic tumour of lymphoid lineage; a hematopoietic tumour of myeloid lineage; thyroid follicular cancer; a tumour of mesenchymal origin; a tumour of the central or peripheral nervous system; melanoma; seminoma; teratocarcinoma; osteosarcoma; xeroderma pigmentosum; keratoacanthoma; thyroid follicular cancer; or Kaposi's sarcoma."

"7. A compound which is (2,4-dihydroxy-5-isopropyl-phenyl)-[5-(4-methyl-piperazin-1-ylmethyl)-1,3-dihydro-isoindol-2-yl]-methanone as defined in claim 1 for use in the treatment of a disease state or condition comprising or arising from abnormal cell growth in a mammal, wherein the mammal is undergoing treatment with one or more ancillary compounds as defined in any claim 1."

"8. A pharmaceutical composition comprising a combination according to any one of claims 1 to 3 and a pharmaceutically acceptable carrier."

Dependent claims 2 and 3 differ from claim 1 by limiting the list of ancillary compounds to a selection of 17 and 7 compounds, respectively.

Dependent claim 4 differs from claims 1 to 3 by specifying that onalespib and the ancillary compound are physically associated or non-physically associated.

VI. By a communication dated 10 June 2020, the board cancelled the oral proceedings to continue the proceedings in writing.

VII. The appellant's arguments, where relevant to the present decision, may be summarised as follows.

The claims of the main request were based on the following passages of the application as filed.

- The combination of ancillary compounds with onalespib was disclosed in claims 1 and 100.
- The specific ancillary compounds now in claim 1 were disclosed on pages 100 to 152.
- The uses recited in claims 5 and 6 were disclosed in claims 44 and 49 and in the passage going from page 71, line 34 to page 72, line 18.
- Claims 7 and 8 were based on claims 61 and 71 as filed.

Regarding the novelty of the combinations defined in claim 1 over the content of document D1, the generic classes topoisomerase I inhibitors, antimetabolites and tubulin targeting agents disclosed on page 74 of D1 did not anticipate the specific compounds recited in claim 1.

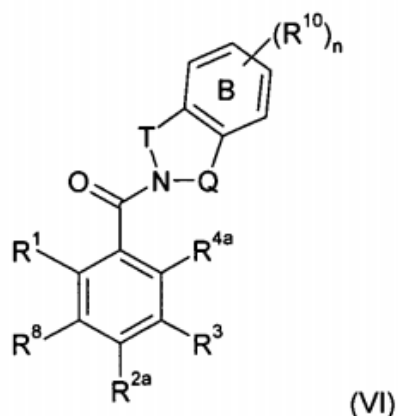
VIII. The appellant requested that:

- the decision of the examining division be set aside;
- the board decide that the claims of the main request filed with the letter dated 3 June 2020 met the requirements of Article 123(2) EPC and that the subject-matter it claimed was novel over the disclosure of document D1; and

- the case be remitted to the examining division for further prosecution.

Reasons for the Decision

1. The appeal is admissible. It complies with the requirements pursuant to Articles 106 to 108 and Rule 99(2) EPC.
2. The claims of the sole request ("main request") filed with the letter dated 3 June 2020 resolve the issues of added subject-matter raised by the board during the appeal proceedings and do not give rise to new objections. Therefore, the main request is admitted into the appeal proceedings pursuant to Article 13(1) RPBA 2020 (see also Article 24(1) and 25(1) RPBA 2020).
3. Amendments (Article 123(2) EPC)
 - 3.1 Claim 1
 - 3.1.1 Claim 1 of the application as filed defines a combination comprising one or more ancillary compounds and a compound of formula (VI):



(VI)

or a salt, solvate, tautomer or N-oxide of it.

3.1.2 Claim 1 of the main request contains restrictions in comparison to claim 1 as filed in three respects.

- The one or more ancillary compounds have been specified to be selected from a list of compounds divided into 23 groups.
- The compound of formula (VI) has been restricted to onalespib.
- N-oxide has been deleted as an option.

3.1.3 As pointed out by the appellant, claim 100 as filed claims a combination according to any of the preceding claims where the compound of formula (I) defined in any of claims 1 to 38 is onalespib. In this context, the board notes that:

- formula (VI) is an embodiment of the broader formula (I); and
- onalespib is the only specific embodiment of formulae (I) and (VI) singled out in the claims of the application as filed (claim 108 is even

more specific than claim 100 as it relates to onalespib L-lactate).

This preference for onalespib is confirmed by a general reading of the description as filed. Outside of the section dedicated to the examples, onalespib is the only compound of formula (I) disclosed in isolation, i.e. not within a list (see page 56, lines 20 to 23). It is also the only compound for which the chemical structure is drawn and to which a number is assigned (compound (1)). Immediately after the passage disclosing onalespib in isolation, in the ten following pages, the description discloses aspects of the invention which relate exclusively to onalespib, such as its addition salts, crystalline forms, preparations and pharmaceutical uses. Furthermore, in the section dedicated to the examples, onalespib is the only compound of formula (I) on which a crystal study was carried out (example 84) and the only compound proposed for the assessment of its effect in combination with ancillary compounds (example 89).

Accordingly, the board concludes that onalespib was clearly and unambiguously disclosed as the most preferred compound of formulae (I) and (VI) in the application as filed.

- 3.1.4 Since onalespib is individualised in the application as filed (in particular, in claim 100) and is also generally disclosed as the most preferred compound of formula (VI), it can be combined with any of the ancillary agents mentioned in claim 1 of the main request, which are disclosed and supported on pages 100 to 152 of the application as filed.

3.1.5 According to the established case law of the boards, the deletion of alternatives from lists of equally useful elements is generally considered admissible. Thus, the deletion of N-oxide from the options: "compound, salt, solvate, tautomer or N-oxide" in claim 1 as filed does not give rise to added subject-matter.

3.2 Claims 5 and 6

The use of the combinations of claim 1 in medicine or for treating a disease or condition comprising or arising from abnormal cell growth in a mammal is disclosed in claims 44 and 49 as filed, respectively (also see the general disclosures on page 12, lines 23 to 25, and page 10, lines 13 to 21, in association with page 23, lines 26 to 32).

Their use in the treatment of the specific proliferative disorders recited in claims 5 and 6 is disclosed in the passage of the description going from page 71, line 34, to page 72, line 18.

3.3 Claims 7 and 8

Claims 7 and 8 are based on claims 61 and 71 as filed, respectively (also see the general disclosures on page 14, lines 22 to 25, and page 12, lines 5 to 8, in association with page 23, lines 26 to 32).

3.4 Dependent claims

3.4.1 Claims 2 and 3 result from narrowing the selection of the ancillary compounds in claim 1. Specific passages in the description which disclose each of the ancillary

compounds selected in claims 2 and 3 are indicated in parenthesis:

Paclitaxel (page 118, line 6), cisplatin (page 122, line 7), dacarbazine (page 128, line 39), erlotinib (page 156, line 14), imatinib mesylate (page 156, line 24), sunitinib (page 156, line 30), nilotinib (page 156, line 37), trastuzumab (page 156, line 8), bortezomib (page 140, line 21), gemcitabine (page 114, line 10), cytarabine (page 114, line 10), decitabine (page 137, line 22), docetaxel (page 118, line 6), 5-fluorouracil (page 114, line 10), lapatinib (page 156, line 36), letrozole (page 102, line 21) and tamoxifen (page 99, line 9).

3.4.2 Claim 4 specifies that onalespib and the ancillary compound are physically associated or non-physically associated. These two options are supported by claims 39 and 41 as filed and, in fact, they do not result in any change of overall scope.

3.5 For these reasons, the claims of the main request meet the requirements of Article 123(2) EPC.

4. Novelty (Article 54 EPC) over document D1

4.1 According to its *obiter dictum*, the examining division took the view that document D1 (which is is an intermediate international patent application published on 19 October 2006) formed part of the state of the art according to Article 54(3) EPC and that its disclosure anticipated the subject-matter of claim 1 of the main request considered in the impugned decision.

The examining division argued that onalespib was one of the particularly preferred compounds of formula (I) in

D1 (see page 44, lines 5 to 6) and that D1 stated on page 74, lines 4 to 6 that the compounds of formula (I) could be administered together with topoisomerase I inhibitors, antimetabolites and tubulin targeting agents, i.e. classes to which several of the ancillary compounds of claim 1 belong.

4.2 Claim 1 of the current main request is essentially identical to claim 1 of the former main request before the examining division (with the exception that the latter contained an additional group of ancillary compounds). Thus, the examining division's objection also applies to the subject-matter of claim 1 at hand.

4.3 However, the board concurs with the appellant that the generic classes listed on page 74 of D1 do not anticipate specific compounds belonging to them.

The board was unable to identify any other passage in D1 which could be considered to disclose a combination of onalespib with one of the ancillary compounds recited in claim 1.

4.4 As a consequence, the subject-matter of claim 1 is novel relative to the disclosure of document D1 (Article 54 EPC).

4.5 Claims 2 to 8 also require the combination of onalespib with at least one of the ancillary compounds of claim 1 (claims 1 to 6 and 8), or their combined use in a therapeutic treatment (claim 7). Their subject-matter is therefore equally novel relative to the disclosure of D1.

5. Remittal (Article 111(1) EPC)
 - 5.1 The decision under appeal restricted itself to an assessment of added subject-matter under Article 123(2) EPC. Nevertheless, it contained comments on the issues of novelty in relation to document D1, inventive step and sufficiency of disclosure.
 - 5.2 The appellant requested that the case be remitted to the examining division if the board considered that the subject-matter of the main request fulfilled the requirements of Article 123(2) EPC and was novel with regard to document D1.
 - 5.3 The issues of added subject-matter and novelty with regard to D1 have been overcome in the set of claims of the main request before the board (see points 2 to 4 above) and the appeal is allowable. Accordingly, the board has discretion, pursuant to Article 111(1), second sentence, EPC, over whether to exercise any power within the competence of the examining division or to remit the case for further prosecution. Pursuant to Article 11 RPBA 2020, the board shall, however, not remit a case to the department whose decision was appealed for further prosecution, unless special reasons present themselves for doing so.

In this context, the board notes that the objection regarding lack of inventive step in the decision's *obiter dictum* was not properly substantiated. A main deficiency of the objection was that it failed to mention which piece of prior art was considered to represent the closest prior art.

The reasoning with regard to sufficiency of disclosure was kept on a very general level and did not appear to take account of the differences between the independent claims.

Thus, considering that the deficiencies of the objections of lack of inventive step and sufficiency of disclosure in the *obiter dictum* do not allow a proper review by the board, that a review of the decision under appeal is the primary object of the appeal proceedings, and that the appellant requested the remittal of the case to the examining division, special reasons present themselves for remitting the case to the examining division for further prosecution.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the examining division for further prosecution.

The Registrar:

The Chairwoman:



M. Schalow

R. Hauss

Decision electronically authenticated