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Datasheet for the decision of 17 August 2021

Case Number: T 0072/18 - 3.3.01

Application Number: 06789025.1

Publication Number: 1912640

IPC: A61K31/4045, A61K31/4965, A61K31/165, A61P35/00

Language of the proceedings: EN

Title of invention:
USE OF THE HDAC INHIBITOR PANOBINOSTAT FOR THE TREATMENT OF MYELOMA

Patent Proprietor:
Secura Bio, Inc.

Opponent:
Generics [UK] Limited

Relevant legal provisions:
EPC Art. 100(b), 100(a), 56

Keyword:
Grounds for opposition - insufficiency of disclosure (no)
Inventive step - (yes)

Decisions cited:
G 0003/14, T 0967/97

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Case Number: T 0072/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 17 August 2021

Appellant: (Opponent)	Generics [UK] Limited Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Secura Bio, Inc. 1887 Whitney Mesa Drive 1050 Henderson, NV 89014 (US)
Representative:	Cooley (UK) LLP Dashwood 69 Old Broad Street London EC2M 1QS (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 19 October 2017 rejecting the opposition filed against European patent No. 1912640 pursuant to Article 101(2) EPC.**

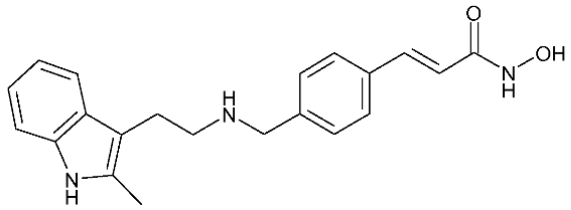
Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	M. Blasi

Summary of Facts and Submissions

I. European patent No. 1 912 640 (patent in suit) was granted with a set of eight claims. The independent claims read as follows:

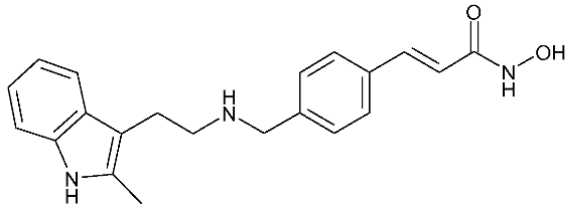
"**1.** The use of an HDAC inhibitor for the preparation of a medicament for the treatment of myeloma, wherein the HDAC inhibitor is *N*-hydroxy-3=[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide having the formula (III)



(III)

or a pharmaceutically acceptable salt thereof, and wherein the myeloma is resistant to conventional chemotherapy.

3. An HDAC inhibitor which is *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide having the formula (III)

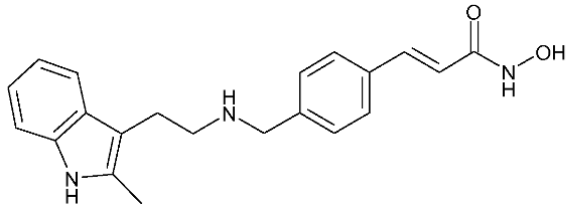


(III)

or a pharmaceutically acceptable salt thereof, for use in the treatment of myeloma, wherein the myeloma is resistant to conventional chemotherapy.

5. A combination for use in the treatment of myeloma comprising an HDAC inhibitor and a compound effecting apoptosis of myeloma cells, in which the active

ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier, wherein the HDAC inhibitor is *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl] phenyl]-2*E*-2-propenamide having the formula (III)



(III)

and wherein the compound effecting apoptosis of myeloma cells is bortezomib.

8. A pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against myeloma, of a combination according to Claim 5 and at least one pharmaceutically acceptable carrier, for use in the treatment of myeloma."

The remaining claims are dependent claims.

II. The HDAC (i.e. histone deacetylase) inhibitor of formula (III) is also called panobinostat.

III. The patent was opposed under Article 100(a) and (b) EPC on the grounds that the claimed subject-matter did not involve an inventive step and was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

IV. The documents cited in the opposition and appeal proceedings included the following:

D1: Blood 102(7), 2615-2622 (2003)

D2: Clinical Cancer Research 10, 3839-3852 (2004)

D4: PNAS 101(2), 540-545 (2004)

D9: Cancer Research 66(11), 5781-5789 (1 June 2006)

D10: WO 02/22577 A2

D12: Mol Pharmacol 68(4), 917-932 (online 14 June 2005)

D13: BLOOD 101(10), 4055-4062 (2003)

V. The decision under appeal (announced on 2 October 2017 and posted on 19 October 2017) is the opposition division's decision rejecting the opposition, in accordance with the patent proprietor's main request.

VI. According to the decision under appeal:

(a) The claimed subject-matter met the requirement of sufficiency of disclosure (Article 100(b) EPC), as the suitability of panobinostat for the treatment of myeloma resistant to conventional chemotherapy was rendered credible by the examples described in the opposed patent (paragraphs [0025] to [0036]), and the suitability of bortezomib for the treatment of myeloma had been known from the prior art.

(b) Document D10, which disclosed HDAC inhibitors including panobinostat but did not mention the treatment of myeloma, was considered less suitable as a starting point for the assessment of inventive step than documents D1 and D2.

D1 related to the treatment of drug-resistant multiple myeloma with the HDAC inhibitor NVP-LAQ824 and was the closest prior art for claims 1 to 4.

D2, which related to a combination therapy for myeloma using bortezomib and an HDAC inhibitor, was the closest prior art for claims 5 to 8.

Taking the post-published evidence regarding efficacy in document D9 into account, the

subject-matter of all the claims involved an inventive step.

VII. The opponent (appellant) filed an appeal against this decision.

VIII. Oral proceedings before the board, scheduled in view of corresponding requests by the parties, were held on 17 August 2021.

IX. The appellant's arguments may be summarised as follows:

Sufficiency of disclosure

The insufficiency objection concerned claims 1 and 3 of the patent in suit. Both related to panobinostat for treating myeloma that was "resistant to conventional chemotherapy". The plain meaning of this feature was that the myeloma to be treated must be resistant to all conventional chemotherapy (as opposed to the respondent's position that resistance to at least one conventional agent was required).

The appellant was not contesting the credibility of the experimental results reported in the patent regarding the efficacy of panobinostat against four myeloma cell lines that were resistant to bortezomib, doxorubicin, mitoxantrone or melphalan, respectively. However, these results could not simply be extrapolated to other drug-resistant myelomas. Whatever the interpretation of the feature "resistant to conventional chemotherapy", the data reported for specific cell lines did not render it credible that panobinostat was active against other variants of myeloma that had developed resistance to chemotherapy.

Numerous treatments were available or bound to become available over time. A myeloma could become resistant to a particular treatment for many different reasons.

Even if panobinostat were suitable for treating some of these myelomas, the skilled person received no guidance in the application as filed and in the patent in suit to identify further myelomas that could be treated with panobinostat.

Some treatments (known or newly discovered) were based on HDAC inhibition and might well prove more effective than panobinostat. It was also to be expected that some myelomas would develop resistance to panobinostat itself.

Inventive step

Inventive step must be assessed from every legitimate starting point, and this included document D10, which could not simply be dismissed without further analysis. In fact, D10 was the basic patent for panobinostat and was cited in the application as filed. D10 related to the same general technical field and purpose as the patent in suit as it disclosed the suitability of HDAC inhibitors, including panobinostat, for treating proliferative disorders.

Starting from the teaching of document D10, the objective technical problem was to provide a further use of panobinostat. This problem was realistic since finding new uses for a known drug was a standard problem in pharmaceutical development. The objective technical problem was solved by the subject-matter of claims 1, 3 and 5 of the patent as granted, which related to the treatment of myeloma.

In order to solve the objective technical problem, the person skilled in the art would have turned to other documents relating to the same substance class (i.e. hydroxamic-acid-derived HDAC inhibitors).

The use of panobinostat for treating a myeloma that was resistant to conventional chemotherapy (claims 1 and 3) was suggested by the teaching of D10 combined with the teaching of documents D12, D1 and D13 relating to uses of structurally similar drugs of the same substance class, in particular NVP-LAQ824.

The use of panobinostat in combination with bortezomib for treating a myeloma (claim 5) was suggested by the teaching of D10 combined with the teaching of D2 and D4, which disclosed combinations of bortezomib and HDAC inhibitors for the treatment of myeloma.

X. The patent proprietor's (respondent's) arguments may be summarised as follows:

Sufficiency of disclosure

Since a granted patent enjoyed a presumption of validity, the burden of proof was on the appellant to substantiate its alleged doubt regarding sufficiency of disclosure. The appellant had not shown by argument or evidence that any specific treatment according to claims 1 and 3 did not work.

According to the patent in suit (paragraphs [0025] and [0036]), four different cell lines had been tested, each resistant to a different chemotherapy agent that had been conventional in the treatment of myeloma at the priority date. Thus the examples were representative of the claimed scope and sufficed to demonstrate the suitability of panobinostat for the therapeutic purpose claimed.

The requirement of sufficiency of disclosure had to be satisfied at the effective date of the application/patent: future developments (as invoked by the appellant) naturally could not play a role in this. It would not be particularly difficult for the person

skilled in the art to establish which chemotherapies were conventional at the priority date as these were mentioned in the patent in suit and in the prior art.

Inventive step

Document D10 was not a feasible starting point for the assessment of inventive step since it did not concern the same purpose or effect as the claimed inventions. The closest prior art for a second-medical-use claim, as a rule, could only be a disclosure relating to the same therapeutic use. Documents D1 and D2 were more appropriate choices as they related to the treatment of myeloma. Within the framework of the problem-and-solution approach, several approaches to assessing inventive step would only be warranted if there were equally valid starting points.

If an approach starting from D10 were nevertheless to be considered, the entire group of hydroxamate HDAC inhibitors of formula (I) rather than only panobinostat must be chosen as the specific starting point in D10 to avoid hindsight. In that case, the objective technical problem must be defined as the provision of further medical uses of the compounds identified in D10.

As to obviousness, the person skilled in the art would not have had any incentive to select panobinostat, which was one of 265 compounds disclosed in D10. They would instead have tried to find new uses for those compounds tested in the examples of D10, none of which was panobinostat (compounds CMD1 to CMD5: see page 74, last paragraph).

Furthermore, the secondary documents relied on by the appellant related to individual agents different from panobinostat. The therapeutic benefit of panobinostat for treating myeloma could not simply have been derived

from what was known about the efficacies of other, structurally different, members of the class of HDAC inhibitors.

XI. The parties' requests, as far as relevant to this decision, were as follows.

(a) The appellant requested that the decision under appeal be set aside and the patent be revoked.

(b) The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. Admissibility of the appeal

The appeal complies with Articles 106 to 108 EPC and Rule 99 EPC; it is admissible.

2. Sufficiency of disclosure (Article 100(b) EPC)

Claim analysis

2.1 While the patent in suit does not provide an explicit definition of the expression "resistant to conventional chemotherapy", it is apparent from the general context that the use of panobinostat according to claims 1 and 3 is conceived as a second-line therapy in myeloma that has shown resistance to established, or first-line, chemotherapy.

2.2 The expression "conventional" is used in the same way in the prior art, to designate therapies and agents that were standard at the respective time of writing (see, for instance, D1: abstract, second sentence; D2: abstract, first sentence; D4: page 540, right-hand

column, lines 12 to 17). It is presented as a benefit of HDAC inhibitors that they may overcome drug resistance (see D13: abstract), i.e. resistance to established, or conventional, chemotherapy.

2.3 Thus the skilled person will understand that the criterion "resistant to conventional chemotherapy" is met when the myeloma is resistant to at least one conventional drug (or first-line therapy), as there would then be occasion for attempting treatment with a different drug, e.g. a second-line drug like panobinostat.

2.4 In contrast, the appellant's interpretation (i.e. that the myeloma to be treated must be resistant to all conventional chemotherapy options) is not self-evident. While it may reflect one possible meaning, there is no technical reason for reading this specific limitation into the claim. Moreover, nothing in the description supports the appellant's restrictive reading.
The examples use cell lines resistant to just one drug, and there is no suggestion at any point that multiple resistance of the myeloma is intended to be a pre-requisite of the treatment envisaged.

2.5 The person skilled in the art would also infer that, in the context of the patent in suit, the term "conventional chemotherapy" can only relate to treatments which were conventional at the time of writing, but not to treatments that might be developed and established at a later time.

Sufficiency assessment

2.6 Sufficiency of disclosure of the claimed subject-matter must be satisfied at the effective date of the patent, on the basis of the information provided in the patent

application as filed and the common general knowledge then available to the person skilled in the art.

2.7 In the context of drug resistance required in claims 1 and 3 as granted, four drugs are identified in the examples of the patent in suit and the application as filed, namely bortezomib, doxorubicin, mitoxantrone and melphalan.

Both documents report in identical passages that:

(i) myeloma cell lines each resistant to a different one of bortezomib, doxorubicin, mitoxantrone or melphalan were provided (patent in suit: paragraph [0025]; application: page 18, last paragraph);

(ii) according to experimental evidence, panobinostat inhibits myeloma cell growth in such cell lines, described as "resistant to conventional therapies" (patent in suit: paragraph [0036]; application: page 22, second paragraph).

While no detailed quantitative data are provided, the experimental methods are described (patent: paragraphs [0026] to [0035]; application: page 19, first paragraph to page 22, first paragraph) and the overall result is indicated (see item (ii) above).

2.8 The appellant did not contest the credibility of these findings with respect to the exemplified cell lines. Its concern was rather that the scope of claims 1 and 3 was not commensurate and the claimed invention could not be carried out across the entire scope claimed since

- the experimental results could not be extrapolated;

- other treatments might prove more effective than panobinostat and some myelomas would develop resistance to panobinostat itself;
- no guidance was provided for selecting further variants of myeloma treatable with panobinostat from among numerous current and future options.

Moreover, it might not even be possible to establish which treatments were "conventional" at the effective date.

2.9 These arguments cannot succeed, for the following reasons:

2.9.1 Any issue raised in relation to new and potentially more effective treatments becoming available over time is irrelevant, as future treatments are not "conventional chemotherapy" within the meaning of the claims (see point 2.5 above).

2.9.2 The application as filed reports favourable experimental results (uncontested by the appellant) for four examples of cells resistant to drugs which were regarded as conventional chemotherapy in myeloma (see points 2.7 and 2.8 above). In the absence of specific counter-evidence, this is considered as adequately representative of the scope claimed.

2.9.3 In particular, the appellant did not show

- that there was a multitude of further conventional chemotherapy options for treating myeloma;
- that there are non-working embodiments (i.e. myelomas resistant to conventional chemotherapy and to panobinostat).

2.9.4 Nor did the appellant substantiate its argument that it would be difficult for the person skilled in the art

to establish which treatments were conventional at the effective date.

Indeed, this is an issue concerning the requirement of clarity (Article 84 EPC) rather than that of sufficiency of disclosure. Since it does not arise from an amendment to the granted claims, it cannot be dealt with in opposition appeal proceedings (see Decision of the Enlarged Board of Appeal, G 3/14, OJ EPO 2015, A102, Order).

In any case, however, it is common in the field of oncology for there to be only a limited number of approved "conventional" chemotherapy options. These are typically well documented. The skilled person working in the technical field would be well aware of conventional treatments. There is no reason why they should not be able to determine which treatments were established practice at a given time.

2.10 For these reasons, on the basis of the evidence on file, the ground of opposition under Article 100(b) EPC does not prejudice maintenance of the patent as granted.

3. Inventive step (Articles 100(a), 52(1) and 56 EPC)

Patent in suit

3.1 The patent in suit seeks to provide treatment options for myeloma involving an HDAC inhibitor (see paragraphs [0001] to [0004] of the patent in suit). The patent describes hydroxamate-type HDAC inhibitors of general formula (I) (paragraphs [0004] and [0005]).

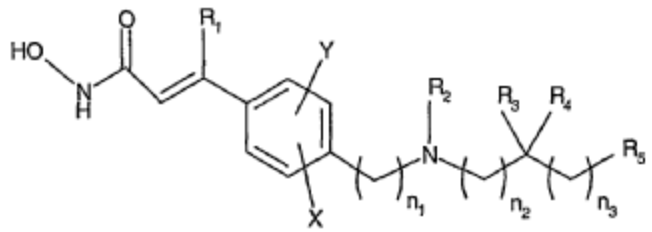
3.2 The claims as granted (see point I above) relate to further medical uses involving the HDAC inhibitor panobinostat conforming to formula (III)

- for the treatment of myeloma resistant to conventional chemotherapy (claims 1 to 4),
- or, in combination with bortezomib, for the treatment of myeloma (claims 5 to 8).

Starting point in the prior art

3.3 The appellant did not contest the opposition division's finding that the claimed subject-matter involved an inventive step starting from the technical teaching of documents D1 and D2. It argued instead, as it had also done in the proceedings before the opposition division, that inventive step should alternatively be assessed starting from the technical teaching of document D10.

3.4 D10 (see claim 1) relates to hydroxamate HDAC inhibitors of formula (I). This is the same general formula (I) as shown in the patent in suit:



(I)

D10 lists the structures of 265 specific compounds conforming to formula (I), including panobinostat (see page 63, compound 200). In addition, panobinostat is highlighted as one of three "important" embodiments, and its synthesis is disclosed (see D10: page 17, fourth paragraph; claim 38; page 28, Example P3).

D10 teaches that compounds of formula (I), owing to their activity as deacetylase inhibitors, are expected to be useful as pharmaceuticals for the treatment of proliferative diseases, mainly tumour diseases/cancers, or other hyperproliferative conditions (D10: page 1, first paragraph; page 3, line 31 to page 4, line 10;

page 25, line 18 to page 26, line 12). In the examples, D10 reports some initial pre-clinical data obtained with five compounds.

3.5 The respondent took the view that the appellant's inventive-step approach should not be considered, since D10 was "not feasible" as a starting point, or in any case less promising than D1 and D2. In support of its view, the respondent referred to various decisions of the Boards of Appeal.

3.6 As the appellant's objection regarding lack of inventive step was based on an approach starting from document D10, the board took this approach into account. In this context, the following considerations are relevant:

3.6.1 If there were several possible approaches, starting from different prior-art disclosures, which might have led the skilled person to the claimed subject-matter, the rationale of the problem-and-solution approach developed in the Boards' case law requires that all these approaches be assessed before an inventive step can be acknowledged (see T 967/97, Reasons 3.2; Case Law of the Boards of Appeal of the European Patent Office, 9th edition 2019 ["Case Law"], I.D.3.1).

3.6.2 This principle follows from Article 56 EPC, which requires the existence of an inventive step having regard to the (entire) state of the art (subject to the exclusion under Article 56, second sentence, EPC).

3.6.3 A promising starting point for the assessment of inventive step is typically a prior-art disclosure that relates to the same or a similar purpose or objective as the claimed invention and has the most relevant technical features in common. Further criteria are the similarity of the technical problem to be solved, and

the disclosure's association with the same, or a closely related, technical field as the patent in suit (Case Law, I.D.3.1-3.4).

3.6.4 The board does not share the respondent's view that the content of D10 is remote from the claimed inventions:

- D10 discloses HDAC inhibitors, including panobinostat itself (page 17, fourth paragraph; page 28, Example P3; page 63, compound 200; claim 38).
- It also teaches that these compounds may be useful in the treatment of proliferative diseases (see claims 37 and 38; page 1, first paragraph; paragraph bridging pages 3 and 4; page 25, line 18 to page 26, line 12). While the stated medical indication is more broadly defined than the treatment of myeloma, it still relates to the same field of medicine and general treatment purpose. Thus the situation in this case differs from the situation addressed in T 2571/12 mentioned by the parties, which involved an issue of entirely unrelated medical indications (Reasons 4.2: lung disease vs. neuropsychiatric disorders).

In view of the similarities in technical features and purpose, D10 qualifies as a potentially promising starting point for the assessment of inventive step

3.6.5 Both the respondent and the opposition division (in the decision under appeal) reasoned, nevertheless, that there was no need to consider D10 because it was not an equally valid, or "equally likely", starting point in comparison with documents D1 and D2. The reason given for this was the fact that D10 did not specifically address the treatment of myeloma.

3.6.6 The board sees no merit in this argument for the following reasons:

(a) While D1 and D2 relate to the treatment of myeloma, they do not disclose panobinostat. D10, on the other hand, discloses panobinostat, but does not specifically mention myeloma as one of the targeted proliferative diseases.

As already pointed out (see point 3.6.4 above), the treatment of myeloma is not entirely unrelated to the indication "treatment of proliferative diseases". It is also a common situation in pharmaceutical development that further uses for known compounds are sought and explored.

Thus, inventive-step approaches starting from either category of document, with correspondingly different objective technical problems to be solved, may be considered viable approaches and as such are equally valid starting points.

(b) Indeed, it would be difficult to conclude, by preliminary evaluation only, that an assessment starting from document D10 and carried out on the basis of a different objective technical problem must be less likely to lead the skilled person to the claimed subject-matter than alternative approaches starting from documents D1 and D2.

The outcome would evidently also depend on the further steps of the problem-and-solution approach, in particular the consideration of the further state of the art in the form of supplementary documents, in light of the respective objective technical problems.

(c) The case law relied on by the respondent does not support its position on this issue either.

In a case relating to a further medical use, it is certainly possible that a prior-art disclosure relating to the same medical use as the claimed invention may be considered the most appropriate starting point in the prior art, and other disclosures not relating to this same use may be dismissed *a priori* as less promising. However, such a rating will depend on the specific circumstances of the individual case and will have to be supported by pertinent reasoning.

The board is unable to identify in T 986/02 (Reasons 5-6), T 734/12 (Reasons 33-36) and T 2181/08 (Reasons 20) cited by the respondent any generally applicable statement contradicting the established case law or this board's reasoning set out above in points 3.6.1 to 3.6.6(b). The cited passages merely recapitulate general considerations recurrent in the case law and/or explain what was deemed to be the most appropriate way forward in each individual case.

Thus, the argument that document D10, as a matter of principle, is a less realistic or less promising choice for a starting point than D1 or D2 owing to its broader definition of the intended medical use cannot succeed.

3.7 Hence, the opposition division was wrong to refuse considering the problem-and-solution approach starting from D10 in substance.

3.8 Another disputed issue was the question of which particular disclosure in D10 was the most appropriate starting point. In this context, the respondent contended that the correct starting point in D10 was

not panobinostat but the general group of HDAC inhibitors of formula (I) (see point 3.4 above).

3.9 The board does not reach the same conclusion, for the following reasons:

3.9.1 As mentioned above (see point 3.6.2), Article 56 EPC requires the existence of an inventive step having regard to the (entire) state of the art (subject to the exclusion under Article 56, second sentence, EPC).

3.9.2 Within the context of the problem-and-solution approach, it is therefore both permissible and appropriate to select, within a piece of prior art used as the starting point (in this case, document D10), the embodiment closest to the subject-matter of the claim to be assessed (in this case, panobinostat). Panobinostat is simply the "most promising springboard" among the various disclosures in D10. While certainly based on knowledge of the claimed subject-matter, this pre-selection of a disclosure in a document does not introduce inappropriate hindsight any more than the pre-selection of a closest-prior-art document does. It merely streamlines the process by avoiding the need to haphazardly try out all possible options in D10 (one of them being panobinostat anyway).

3.9.3 Panobinostat is not just encompassed by the Markush formula (I) of D10. It is also disclosed as an individualised embodiment (compound 200, prepared according to Example P3, one of three individually listed options in claim 38). Selecting panobinostat as the starting point would thus be the appropriate choice even if this embodiment were not, moreover, characterised in D10 as one of three "important" (i.e. preferred) compounds of formula (I) (see point 3.4 above and D10: page 17, fourth paragraph).

3.9.4 In contrast, the approach suggested by the respondent would involve taking a step back and starting the analysis from the entire group of HDAC inhibitors of formula (I). An additional step of selecting panobinostat would then be required. Since panobinostat was already selected in the context of D10 as a distinct embodiment, the respondent's approach, in these circumstances, is artificial and inappropriate.

Objective technical problem and solution

3.10 The subject-matter of claims 1 and 3 differs from the disclosure of document D10 regarding panobinostat in the use of panobinostat for treating a myeloma that is resistant to conventional chemotherapy.

3.11 The subject-matter of claims 5 and 8 differs from the disclosure of document D10 regarding panobinostat in the use of panobinostat in combination with bortezomib for treating a myeloma.

3.12 The objective technical problem solved by claims 1, 3, 5 and 8 is to provide a specific medical use of panobinostat.

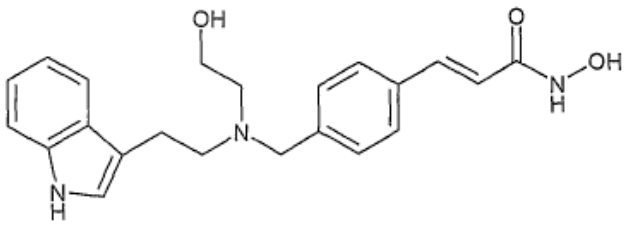
Obviousness of the solution

3.13 Document D10 discloses that panobinostat, as one of compounds 1 to 265, has histone-deacetylase-inhibiting activity (D10: page 73, sentence following the table). Five other HDAC inhibitor compounds of formula (I) were tested *in vitro* and in murine models for their activity against lung carcinoma and colon tumour cell growth, with favourable results (D10: examples). The document does not provide experimental data regarding the efficacy and safety of panobinostat in any particular therapeutic indication.

3.14 At this very early stage of drug development, the person skilled in the art seeking to solve the objective technical problem would have required more information about panobinostat, its properties and potential uses.

3.15 The supplementary documents relied on by the appellant (i.e. D1, D12, D13, D2 and D4) do not provide this information as they all relate to other HDAC inhibitors only.

3.16 *N*-hydroxy-3-[4-[[2-hydroxyethyl-[2-(1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, also called NVP-LAQ824, is one of the preferred compounds of general formula (I) mentioned in D10 (see D10: page 17, paragraph 4; claim 38; compound CMD2 of the examples, see page 74, last paragraph).



Since NVP-LAQ824 is structurally similar to panobinostat, the appellant argued that the prior art's teaching, in documents D1 and D12, about its activity against myeloma would have provided an incentive for the person skilled in the art to investigate the benefit of panobinostat in myeloma. Documents D13, D2, D4 and D12 supported this teaching as they related to the activity of further HDAC inhibitors against myeloma. D2 and D4 also disclosed combinations with bortezomib.

3.17 However, consulting documents about other compounds would not have been a particularly straightforward and expedient way of getting a clearer picture of

panobinostat. In any case, if taken into consideration at all, the supplementary documents would not have given rise to an expectation of success regarding any specific medical use of panobinostat, for the following reasons:

3.17.1 With regard to panobinostat itself, it was only known that the compound was a hydroxamic-acid-derived HDAC inhibitor. Neither D10 nor the supplementary documents provide any data or other teaching for this compound in relation to any specific therapeutic indication.

3.17.2 Document D12, published shortly before the patent's priority date, is a review article on HDAC inhibitors, which had come to be explored as a new class of potential anticancer agents (see D12: paragraph bridging the columns on page 919). All HDAC inhibitors in development were believed to comparably inhibit mammalian class I and II HDACs, which had been described as having an association with cancers (D12: paragraph bridging the columns on page 918).

D12 provides an overview of findings for different chemical classes of HDAC inhibitors, in relation to various therapeutic indications (but does not mention panobinostat).

In this context, D12 reports that specific hydroxamic-acid-derived HDAC inhibitors - NVP-LAQ824 and SAHA (suberoylanilide hydroxamic acid) - had shown activity against myelomas, among other therapeutic indications (D12: page 920, right-hand column, lines 49 to 52; page 921, left-hand column, lines 14 to 17 citing D1).

Nevertheless, the skilled person would not have obtained any direct incentive from this document to investigate any particular therapeutic indication in connection with panobinostat.

3.17.3 As far as NVP-LAQ824 is concerned, only initial pre-clinical results, in relation to lung and colon cancer and myeloma, were known for this compound from D10 (examples relating to lung and colon cancer), D1 and D12 (citing D1). Document D1 focuses on myeloma and is based on preclinical *in vitro* and mouse model studies (see D1: title and abstract; page 2616, left-hand column, lines 18 to 24). It had not been shown in clinical trials that NVP-LAQ824 provided satisfactory efficacy and safety for any of these indications.

3.17.4 In any case, no meaningful and conclusive extrapolation to panobinostat would have been possible on the basis of data relating to NVP-LAQ824. A shared general mechanism (in this case HDAC inhibition) and structural similarity of two compounds do not guarantee that their activities and clinical benefit will be comparable. It is common general knowledge that drugs have to undergo individual development and clinical testing. More extensive studies with panobinostat itself would have been required to confirm its potential benefit in myeloma.

3.17.5 The other supplementary documents (D2, D4 and D13) report pre-clinical results in relation to myeloma for SAHA (also covered in D12, see point 3.17.2 above) and sodium butyrate. Sodium butyrate, as a short-chain fatty acid, belongs to a different chemical class. SAHA, while a hydroxamic acid derivative, does not fall within the general formula (I) of HDAC inhibitors considered in the patent in suit (see paragraph [0005]). For this reason, the skilled person would not have consulted documents D13, D2 or D4 in order to obtain more information about possible uses of panobinostat. Their teaching, in any case, is more remote from the claimed subject-matter than that of D1.

3.17.6 Arriving at the claimed subject-matter would have required a multiple-step drug development programme, with a number of crucial decision points based on newly-acquired data.

One of these decision points would have been to select myeloma as an indication to be investigated as a possible use for panobinostat. While the skilled person could have made this selection and started pre-clinical testing of panobinostat in myeloma, the state of the art did not provide any particular motivation for doing so, as it related to different compounds.

Still less would it have put the skilled person on a pre-determined path that would have led to the claimed subject-matter without further crucial decision points.

Rather, the skilled person would have had to carry out their own research programme to obtain further data which might eventually have provided them with a reasonable expectation of success as an incentive for moving to the stage of clinical studies.

3.18 In conclusion, the information provided in the prior art would not have been sufficient to give rise to an expectation of success for investigating the use of panobinostat in myeloma in a multiple-tier drug development programme. The information leading to the claimed subject-matter would have had to be acquired by the skilled person's own research first.

3.19 These reasons are sufficient to render the subject-matter of all the independent claims inventive. This also applies to the dependent claims, as the appellant did not provide further arguments on that account.

3.20 As a consequence, the ground of opposition under Article 100(a) regarding lack of inventive step does not prejudice maintenance of the patent as granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated