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Datasheet for the decision of 28 January 2019

Case Number: T 0237/15 - 3.3.01

Application Number: 03711372.7

Publication Number: 1487426

IPC: A61K31/13, A61K31/44, A61P35/00

Language of the proceedings: EN

Title of invention:
METHODS OF INDUCING TERMINAL DIFFERENTIATION

Patent Proprietor:
Sloan-kettering Institute For Cancer Research

Opponent:
Generics [UK] Limited

Headword:
SAHA/Sloan

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no) - all requests

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Case Number: T 0237/15 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 28 January 2019

Appellant: (Patent Proprietor)	Sloan-kettering Institute For Cancer Research 1275 York Avenue New York, NY 10065 (US)
Representative:	Uexküll & Stolberg Partnerschaft von Patent- und Rechtsanwälten mbB Beselerstraße 4 22607 Hamburg (DE)
Respondent: (Opponent)	Generics [UK] Limited (trading as Mylan) Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 December 2014 revoking European patent No. 1487426 pursuant to Article 101(2) and Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	M. Pregetter
	P. de Heij

Summary of Facts and Submissions

I. European patent No. 1 487 426 is based on European patent application No. 03711372.7, filed as an international application published as WO2003/075839.

II. The following documents, cited during the opposition and appeal proceedings, are referred to in this decision:

(2) Marks et al., Nature Rev. Cancer, Dec. 2001, 194-202

(11) Kelly et al., Proceedings of ASCO, 2001, 20(87a), entry 344

(12) Schellens et al., Eur. J. Pharm. Sci., 2000, 12, 103-110

(30) Expert declaration of Dr Punam Sandhu, 14 April 2015, 11 pages

(31) Li et al., J. Pharm. Biomed. Anal., 2000, 22, 33-44

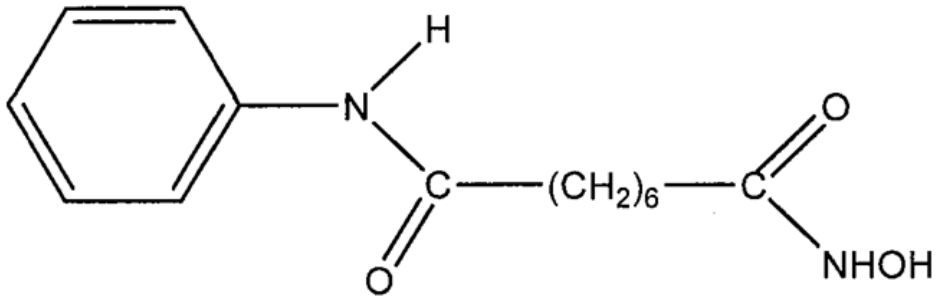
(32) Burton et al., J. Pharmacol. Exp. Ther, 2002, 303(3), 889-895

(33) Kantharaj et al., Drug Development - A Case Study Based Insight into Modern Strategies (Ed. C.Rundfeldt), Chapter 5, 2011, pages 101-120

(34) Shin et al., Drug Metab. Dispos, 2014, 42, 974-982

III. Independent claim 1 of the patent in suit as granted reads as follows:

"1. A single dose of up to 400 mg of suberoylanilide hydroxamic acid (SAHA) represented by the following structure:



or a pharmaceutically acceptable salt or hydrate thereof, characterised in that the dose is for oral administration for use in the treatment of a cancer in a patient."

Furthermore, nine auxiliary requests are on file. Claim 1 of each auxiliary request can be summarised as follows:

Claim 1 of auxiliary request 1 corresponds to claim 1 as granted, with the term "or a pharmaceutically acceptable salt or hydrate thereof" having been deleted.

Claim 1 of auxiliary request 2 corresponds to claim 1 of auxiliary request 1, with the patient being characterised as "human".

Claim 1 of auxiliary request 3 corresponds to claim 1 of auxiliary request 1, with the single dose being limited by the term "daily".

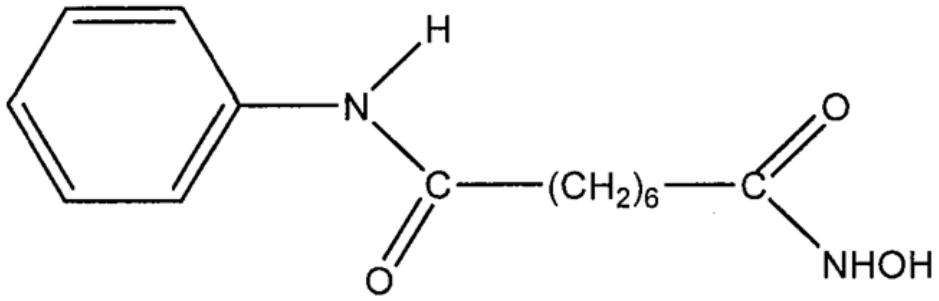
Claim 1 of auxiliary request 4 corresponds to claim 1

of auxiliary request 3.

Claim 1 of auxiliary request 5 corresponds to claim 1 of auxiliary request 3, with the single dose being defined to be within 50 to 400 mg.

Claim 1 of auxiliary request 6 corresponds to claim 1 of auxiliary request 5, with the patient being characterised as "human".

Claim 1 of auxiliary request 7 reads as follows:
"1. A single daily dose of up to 400 mg of suberoylanilide hydroxamic acid (SAHA) represented by the following structure:



characterised in that the dose is for oral administration for use in the treatment of a cancer in a human patient, wherein the single dose is 200 or 400 mg."

Claim 1 of auxiliary request 8 corresponds to claim 1 of auxiliary request 7, limited to 400 mg.

Claim 1 of auxiliary request 9 corresponds to claim 1 of auxiliary request 8, with the term "daily" having been deleted.

IV. Oral proceedings were held on 28 January 2019 in the absence of the respondent, as announced by letter dated 27 December 2018.

V. The appellant's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

When starting from document (2) as the closest prior art, the complete disclosure of this document had to be considered and not only isolated parts thereof. After discussing mechanistic aspects of histone deacetylases (HDACs) and cancer, document (2) listed 15 HDAC inhibitors (Table 3). SAHA was only one of these. When reporting on animal studies, document (2), again, mentioned several HDAC inhibitors and various modes of administration. Of the HDAC inhibitors specifically mentioned in document (2), only two proved ultimately to be suitable for therapy. Of the two specific HDAC inhibitors disclosed for oral administration in animal studies, only one, i.e. SAHA, made it to further clinical trials.

In human patients SAHA was administered only intravenously. In the absence of any information on the type of study, the merely general statement of oral administration could not lead to any conclusions. In fact, document (2) concluded that there were a number of challenges to be overcome in the development of HDAC inhibitors as cancer drugs (page 200, last two paragraphs).

In sum, document (2) taught that numerous HDAC inhibitors were tested as new cancer drugs. One of many compounds reviewed was SAHA, which had been administered intravenously to humans in clinical trials and administered orally to rats.

The technical problem thus resided in providing an improved medical use for SAHA. The problem was solved by providing a single dose of up to 400 mg of SAHA for oral administration for use in the treatment of a cancer patient. The provision in oral form represented a significant improvement over intravenous administration.

The claimed solution was not obvious. This was explained in Dr Sandhu's declaration (30). Scientific literature, in the form of document (12) and further corroborated by documents (31), (32), (33) and (34), confirmed that the complexity of absorption of anticancer drugs by the human body made it impossible to predict the outcome of the administration of this type of drugs to human patients by a new route. On page 104, left-hand column, second paragraph, it was explained that oral pharmacokinetics of anti-cancer drugs were not predictable due to certain mechanisms involving drug-transporters and metabolism. In the following paragraph, it was reported that rodent and other preclinical models did not enable accurate extrapolation about oral pharmacokinetics to the clinic. From document (12) it could thus be deduced that there was a real problem in predicting oral bioavailability of anti-cancer drugs. In view of the findings of document (12), a person of ordinary skill had no reasonable expectation of success when administering SAHA orally for the first time to human patients.

In summary, it was to be stressed that in the particular field under consideration, there was no predictability and consequently no reasonable expectation of success.

The line of argument given above applied to all claim requests. The auxiliary requests were further distinguished from the teaching of document (2) by defining the solution in a more limited manner. There was no expectation of success for these solutions.

The subject-matter of claim 1 of all requests on file thus involved an inventive step.

VI. The respondent's arguments, presented in writing and summarised only insofar as they are relevant to the present decision, are as follows:

Document (2), representing the closest prior art, clearly and unambiguously disclosed on pages 199 and 200 that SAHA could suppress tumour growth when administered orally to rats or mice, that studies to define the optimal therapeutic dosage regimen were ongoing, and that studies with an oral formulation of SAHA were underway.

It was normal routine procedure to start with an animal model and to then transfer the knowledge obtained for the animal model to humans. Dosages were continuously optimised. In view of the limited data included in the opposed patent, the technical problem to be solved could be seen, if at all, in the provision of an alternative therapeutic use of SAHA by finding a suitable oral dose of SAHA for the treatment of human patients.

In view of document (2), the skilled person would have had a reasonable expectation of success to find a suitable dosage range when conducting dose escalation studies in human patients, as oral SAHA had already

been successfully trialled in rats and mice. Finding the optimum dosage was a matter of routine experimentation which did not require inventive skill. Single daily administration was typical and desirable with regard to patient compliance. Continuous schedules and daily administration were, moreover, typical modes of administration which the skilled person would take into account when performing routine dose escalation studies in order to find a suitable administration scheme.

The data presented in document (30) was post-published. Document (12) related only to anti-cancer drugs in general.

No inventive step could be acknowledged for any of the requests on file.

VII. The appellant requested:
-that the decision under appeal be set aside and that the patent be maintained as granted or, alternatively, that the patent be maintained on the basis of one of the sets of claims of auxiliary requests 1 to 9, submitted with the grounds of appeal;
-that auxiliary requests 1 to 9 and documents (29) to (34) be admitted into the appeal proceedings;
-that documents (36) to (38), submitted by the respondent, not be admitted into the appeal proceedings.

The respondent (the minutes of the oral proceedings erroneously mention 'the appellant') requested in writing:
-that the appeal be dismissed;
-that auxiliary requests 1 to 9 and documents (29) to (34) not be admitted into the appeal proceedings;

-that, in case documents (29) to (34) were to be admitted into the appeal proceedings, documents (36) to (38) be admitted as well;
-that the case not be remitted to the opposition division for discussion of remaining grounds for opposition.

Reasons for the Decision

1. The appeal is admissible.

2. As announced in its letter dated 27 December 2018, the respondent did not attend the oral proceedings.

In accordance with Rule 115(2) EPC and Article 15(3) RPBA, the oral proceedings were held without the respondent. By deciding not to attend the oral proceedings, the respondent has chosen not to make any further submissions during such proceedings. The respondent has been treated as relying on its written case.

3. *Admission*

3.1 *Auxiliary requests 1 to 9*

In accordance with Article 12(4) RPBA, auxiliary requests 1 to 9, all filed with the statement setting out the grounds of appeal, have been admitted into the appeal proceedings. Taking into consideration the arguments brought forward by the appellant under point 3 of page 3 of the letter dated 17 February 2016, which were not rebutted by the respondent, the board has considered these requests as an appropriate

reaction to the reasoning of the impugned decision.

3.2 *Documents*

The board has considered the filing of document (30) to be an appropriate reaction to the impugned decision and has thus admitted document (30) in accordance with Article 12(4) RPBA.

The further documents filed in the appeal proceedings are not relevant to the present decision. No decision on their admission has been taken.

4. *Inventive step*

The patent in suit relates to the use of histone deacetylase (HDAC) inhibitors, especially suberoylanilide hydroxamic acid (SAHA), for inducing terminal differentiation of neoplastic cells and thereby aiding in the treatment of tumours in patients. The invention aims to provide suitable dosages and dosing schedules of these compounds and develop formulations, preferably oral formulations, which give rise to steady, therapeutically effective blood levels of the active compounds over an extended period of time (e.g. paragraphs [0001] and [0017]).

4.1 *Main request*

Claim 1 of the main requests defines the administration of a single dose of up to 400 mg of SAHA by oral administration in the treatment of cancer in a patient.

4.2 The impugned decision relies on document (2) as the closest prior art. The use of document (2) as the closest prior art has not been contested by the

appellant.

Document (2) is a review article discussing HDAC inhibitors in the context of cancer therapy (abstract). Mechanistic considerations involving HDAC are discussed on the first pages of document (2). Table 3 shows 15 HDAC inhibitors of a great variety of molecular structures (short-chain fatty acids, hydroxamic acids, cyclic tetrapeptides, benzamides). A description of animal studies follows. In this chapter of document (2), it is stated that SAHA and MS-275 (a benzamide-type HDAC inhibitor) suppress tumour growth when administered orally to rats or mice that have solid tumours (page 199, right-hand column, paragraph 3). Document (2) then turns to "HDAC inhibitors as new cancer drugs" (heading preceding second paragraph on page 200, left-hand column). SAHA and pyroxamide are said to have recently entered clinical trials (page 200, left-hand column, last paragraph). Tumour regression and symptomatic improvement were observed at doses of SAHA that have no clinical toxicity (page 200, right-hand column, first paragraph). The passage goes on to state that "Studies to define the optimal therapeutic regimen are ongoing. Studies with an oral formulation of SAHA are also underway." Finally, the last two paragraphs of document (2) point to the challenge of finding the optimal dose, timing of administration and duration of therapy by HDAC inhibitors, and state that further research is needed to elucidate certain mechanistic aspects (page 200, right-hand column, last two paragraphs).

While the clinical trials with SAHA rely on intravenous administration of the drug (see reference 91 of document (2), which is on file as document (11)), the

animal studies described in the passage on page 199, right-hand column, third paragraph, disclose successful treatment of rats or mice by oral administration of SAHA. In view of the effects achieved in these animal tests, i.e. the suppression of tumour growth in rats or mice, there remain no doubts that SAHA is bioavailable when given orally.

These animal studies are thus the most promising starting point in the assessment of inventive step. Since document (2) discloses specific studies involving SAHA, other parts of document (2) which relate to other HDAC inhibitors or discuss more general aspects are not relevant for the present decision.

4.3 The difference between the subject-matter of claim 1 of the main request is thus the dosage regimen, in particular the dose, and, potentially, the type of patient.

It is irrelevant for the present decision whether the term "patient" refers exclusively to humans or whether it also includes animals. Consequently, the present decision assumes, in line with the appellant's assertion, that a "patient" is necessarily human. However, no decision on this issue is taken.

4.4 The appellant has formulated the technical problem as the provision of improved treatment with SAHA. This problem is based on treatment providing oral administration of SAHA. However, in view of the starting point, i.e. the oral administration of SAHA to rats or mice, chosen by the opposition division and the respondent and, adopted by the board, formulating of the technical problem in this way is not justified. The passage on page 199, right-hand column, paragraph 3,

already discloses oral administration. Issues and effects linked to oral administration, such as bioavailability and blood levels over a certain period of time, already form part of this starting point. An improvement which is due to the oral mode of administration can thus not form part of the technical problem.

Consequently, the technical problem is the provision of a treatment regimen for human patients based on oral administration of SAHA.

4.5 The problem has been solved. Reference is made to the data in the patent in suit.

4.6 It remains to assess whether the solution proposed in claim 1 of the main request is obvious.

4.6.1 The step from pre-clinical animal studies to clinical studies involving human patients is an unavoidable step when developing a new medicament. In the present case, the skilled person, aware of the complete disclosure of document (2), would take this step with a reasonable expectation of success. This expectation of success is based on the teaching of page 200, right-hand column, first paragraph, which discloses that SAHA was successfully used in the treatment of solid tumours in human patients (administered intravenously). Consequently, a skilled person, in the knowledge that SAHA is bioavailable when given orally in animal studies and having been given the information that SAHA achieves effective treatment in humans when introduced directly into the blood stream, would expect an effective treatment also for oral administration in human patients.

The determination of the optimum dosage regimen required to achieve the therapeutic effect in the (human) patient is a matter of routine experimentation for the skilled person. Such routine tests do not require inventive skill and can consequently not establish an inventive step.

4.6.2 *Further arguments presented by the appellant concerning the absence of a "reasonable expectation of success":*

The appellant argued that a skilled person had no reasonable expectation of success. These arguments are based in particular on document (12) and the expert declaration (30).

Document (12) describes problems relating to oral formulations of anti-cancer drugs in form of poor and highly variable oral bioavailability of many anti-cancer drugs (abstract, introduction). Two mechanisms underlie the variable oral pharmacokinetics: firstly the high affinity for drug-transporters, e.g. P-glycoprotein, and secondly the high extraction of the drug by extensive metabolism in the gut wall and/or liver, during "first-pass" (page 104, left-hand column, second paragraph). Document (12) reports that, despite the widespread use of models such as rodents, there are no optimal preclinical in vitro or in vivo models available that enable accurate extrapolation of preclinical data about oral pharmacokinetics to the clinic (page 104, left-hand column, third paragraph). It is stated that a more rational approach based on preclinical concepts and results is urgently needed. Thus, document (12) explains why there can be no certainty of success when transferring animal test results to clinical situations. However, in the context of the assessment of inventive step by the

problem-solution approach, no certainty of success is required.

The expert declaration by Dr Sandhu, provided as document (30), discusses aspects of the bioavailability of SAHA when administered orally. Under point 1, the exceptional and unexpected high oral bioavailability of SAHA compared with other cancer drugs is mentioned. In line with document (12), document (30) mentions factors influencing oral bioavailability (point 2). In point 3, it is stated that results of preclinical studies on animal species and in vitro represent indicators which help to decide whether further pursuit in the clinic is justified. It is then explained, that, since oral bioavailability of SAHA in rats, dogs and monkeys was low (data shown in Table 1), and since it was furthermore known that SAHA had a low solubility across the physiological pH range (data shown in Table 3) and was classified as a low permeability compound, the skilled person could not have predicted that SAHA would have high oral bioavailability in humans and be a viable oral drug in the treatment of cancer (point 3). However, the assessment of inventive step is to be based on the skilled person's knowledge at the effective date. Knowledge not available on or before this date (like the knowledge based on the disclosure in post-published document (30) and documents (32), (33) and (34)) cannot be taken into account for the assessment of inventive step. It is thus irrelevant for the assessment of inventive step that the data presented in document (30) points to low oral bioavailability of SAHA in certain animal models. The same applies to solubility across the physiological pH range and permeability. Document (31) cannot have influenced the skilled person's expectations of success as it concerns a different agent, depsipeptide, and,

contrary to depsipeptide, SAHA had already been shown to be bioavailable when given orally to rats or mice. In this context it is noted that the admission of documents (31) to (34) has not been discussed. This fact is however irrelevant, since the contents of these documents do not influence the outcome of the proceedings.

It is also noted that developments taking place after the effective date, such as which of the actives mentioned in a document (here the further HDAC inhibitors mentioned in document (2)) were further developed, could not have influenced the skilled person.

4.7 The board therefore concludes that the subject-matter of claim 1 of the main request does not involve an inventive step.

5. *Auxiliary requests 1 to 9*

The subject-matter of the auxiliary requests differs from the subject-matter of the main request on account of features relating to the form of SAHA, i.e. free compound versus pharmaceutically acceptable salt, and on account of various features related to the dosage regimen. The dosage regimen is further defined by features relating to the frequency of administration (single daily dose) and to limitations in the doses (introduction of a lower limit of the dose or limitation to a specific dose).

The arguments presented by the appellant in the discussion of inventive step of the main request all relate to use of the compound SAHA as such. The reasoning provided in point 4 above for the main

requests thus applies directly to the auxiliary requests, which all define the use of SAHA.

The further restrictions concerning the dosage regimen lead to the definition of a more restricted solution to the problem discussed for the main request. It has been found for the main request that the determination of the optimum dosage regimen was well within the skills of a person skilled in the art. This finding also applies directly to more limited dosage regimens. Continuous administration of single daily doses is one of the options the skilled person would consider when performing routine dose escalation studies.

Consequently, the more limited dosage regimens of auxiliary requests 1 to 9 are obvious for the same reasons as given for the main request. The subject-matter of claim 1 of each of auxiliary requests 1 to 9 does not involve an inventive step.

6. Having arrived at a negative conclusion on inventive step for all requests on file, it is not necessary to discuss other grounds for opposition.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated