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Datasheet for the decision of 29 September 2016

Case Number: T 1348/14 - 3.3.01

Application Number: 02709145.3

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Language of the proceedings: EN

Title of invention:
FORMULATION OF BORONIC ACID COMPOUNDS

Patent Proprietor:
The United States of America, represented by the Secretary, Department of Health and Human Services

Opponents:
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Headword:
Bortezomib formulation/UNITED STATES

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12, 13

Keyword:
Additional data, partially admitted
Inventive step (no), obvious alternative

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Case Number: T 1348/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 29 September 2016

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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted on 6 May 2014 revoking European patent No. 1355910 pursuant to Article 101(3)(b) EPC.

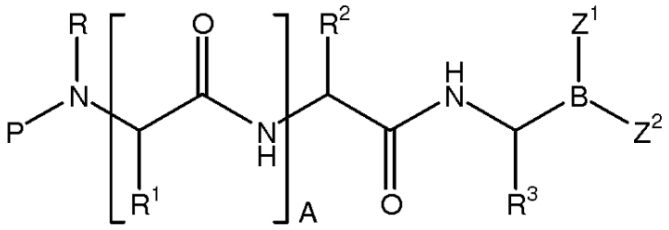
Composition of the Board:

Chairman	A. Lindner
Members:	L. Seymour
	M. Blasi

Summary of Facts and Submissions

I. European patent No. 1 355 910 is based on application No. 02 709 145.3, which was filed as international patent application published as WO 2002/59130.
Claim 1 as granted reads as follows:

"1. A compound of the formula (1):



(1)

wherein
P is hydrogen or an amino-group protecting moiety;
R is hydrogen or C_{1-12} alkyl;
A is 0, 1, or 2;
R^1, R^2, and R^3 are each independently hydrogen, C_{1-12} alkyl, C_{3-12} cycloalkyl, C_{6-14} aryl, or $-CH_2-R^5$;
R^5, in each instance, is C_{6-14} aryl, (C_{6-14})ar-(C_{1-12})alkyl, (C_{1-12})alk(C_{6-14})aryl, C_{3-12} cycloalkyl, heterocyclyl comprising 3 to 8 atoms, wherein one or more atoms is selected from N, O and S, heteroaryl comprising 5 to 14 atoms, wherein 1-4 atoms are selected from N, O and S, or $-W-R^6$, where W is a chalcogen and R^6 is C_{1-12} alkyl;
wherein the ring portion of any said aryl, aralkyl, alkyaryl, cycloalkyl, heterocyclyl, or heteroaryl in R^1, R^2, R^3, or R^5 can be optionally substituted; and
Z^1 and Z^2 together form a moiety derived from mannitol, wherein the atom attached to boron in each case is an oxygen atom, and
wherein the compound of formula (1) optionally is lyophilized."

II. The following documents are referred to herein:

(1) WO 96/13266

(7) Y Mori et al., Pigm. Cell Res. Sup., 1989, 2, 273 – 277

(8) WO 00/57887

(10) US-A-5 780 454

(18) A I Kim et al., J. Pharm. Sci., 1998, 87(8), 931 - 935

(19) S Wittaya-Areekul, S L Nail, J. Pharm. Sci., 1998, 87(4), 491 - 495

(27) Pharmazeutische Technologie, K H Bauer et al. (Eds.), Thieme Verlag, 1991, 126 - 129

(30) S Wu et al., J. Pharm. Sci., 2000, 89(6), 758 - 765

(31) M Pikal, "Freeze Drying" in Encyclopedia of Pharmaceutical Technology, Marcel Dekker, New York, 1994, Volume 6, 275 - 303

(35) R J Ferrier, "Carbohydrate Boronates" in Advances in Carbohydrate Chemistry and Biochemistry, 1978, Volume 35, 31 - 80

(36) "Parenteral Preparations", Chapter 84, in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co, 1990, 1565 - 1567

(39) R Voigt, Pharmazeutische Technologie, 9th Ed. Dt. Apotheker-Verl., Stuttgart, 2000, 23 - 24

(51) Test report entitled "Forced Degradation Study"

(52) Test report entitled "Reconstitution Study"

(53) Test report entitled "Reconstitution Studies Using Different Excipients"

(54) J Zhang et al., Anal. Biochem., 2004, 332, 253 - 260

(55) Test report entitled "Report on Reconstitution and Accelerated Stability Studies", dated 26 January 2015

(57) Third declaration of Dr Roel Fokkens, dated 7 July 2016

III. The appeal lies from the decision of the opposition division revoking the patent. The decision was based on a main request and auxiliary requests 1 to 6, all filed with letter dated 20 February 2014. The experimental evidence filed with the same letter was not admitted into the proceedings. The subject-matter of claim 11 of the main request was found to infringe Article 123(2) EPC, and that of the respective claims 1 of the auxiliary requests to lack an inventive step.

IV. The appellant (patentee) lodged an appeal against this decision. With the statement of grounds of appeal, auxiliary request 1 to 6 underlying the decision under appeal were submitted as main request and auxiliary requests 1 to 5, respectively, together with two

further auxiliary requests 6 and 7. In addition, documents (51) to (54) were filed.

V. Replies to the statement of grounds of appeal were received from respondents 3, 4, 5 and 7 (opponents 3, 4, 5 and 7), whereby respondent 3 additionally filed a test report as document (55).

VI. With letter dated 24 February 2016, respondent 3 requested accelerated processing of the appeal.

VII. Summons to oral proceedings were issued by the board on 7 March 2016.

VIII. Document (57) was submitted by respondent 6 (opponent 6) with letter dated 7 July 2016.

IX. With letter of 20 July 2016, the appellant withdrew all its claim requests, except for auxiliary requests 2 and 5, which were refiled as main request and auxiliary request, respectively.

Claim 1 of the main request differs from claim 1 as granted in the deletion of "optionally" (cf. above point I, last line of claim), and in the insertion of the following limitation at the end of the claim:

"and wherein said compound is a mannitol ester of *N*-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid".

Claim 1 of the auxiliary request differs from that of the main request in the further restriction defining that "said compound is D-mannitol *N*-(2-pyrazine)-carbonyl-L-phenylalanine-L-leucine boronate".

X. Oral proceedings were held before the board on 29 September 2016.

During the course of the oral proceedings, the appellant clarified that it no longer requested admittance of document (51) into the proceedings, and that it no longer wished to pursue its previous submissions based on an improved stability of the compound claimed.

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

On the question of admission of its claim requests, the appellant maintained that these formed part of both the opposition and appeal proceedings. Moreover, it had been clearly set out in the statement of grounds of appeal why, contrary to the view of the opposition division, the claimed subject-matter satisfied the requirements of inventive step.

With respect to documents (52) and (53), the appellant noted that this additional experimental evidence had initially been filed in the proceedings before the opposition division, as part of the written submissions under Rule 116 EPC, in direct response to the preliminary opinion of the opposition division issued with their summons to attend oral proceedings, as a *bona fide* attempt to address an issue of particular significance identified therein. The data had thus been filed in a timely manner, allowing the opponents adequate time to examine whether counter-experiments would be necessary and whether an adjournment would be required for this purpose. No such request had been received prior to oral proceedings before the opposition division. Therefore, the admission of the

appellant's additional evidence would not have necessitated an adjournment thereof. Moreover, the experiments in question were *prima facie* relevant, since they were legitimately designed to demonstrate that the enhanced reconstitution rate of the previously tested lyophilised formulations was due to the presence of the mannitol ester of bortezomib, rather than excess mannitol. It followed that the opposition division had erred in the exercise of its discretion, and its decision not to admit said additional evidence should therefore be overruled. In any case, documents (52) and (53) should be taken into account in the appeal proceedings.

Document (54) had previously been filed during opposition proceedings with the appellant's letter of 20 February 2014, and should be taken into account as being possibly required in the context of discussions with respect to document (53).

In contrast, document (55) should not be taken into account in the appeal proceedings pursuant to Article 12(4) RPBA, since it concerned matters that had been highlighted by the opposition division in its preliminary opinion accompanying the summons to attend oral proceedings. The corresponding data could therefore have been filed during the first instance proceedings, in response thereto, or, at the latest, in reaction to the filing of the patentee's data with letter of 20 February 2014. There could be no sound reason why respondent 3 had waited until its reply to the statement of grounds of appeal to file this document.

Document (57) had been filed by respondent 6 yet later, namely, after oral proceedings had been arranged by the

board. Until this time, respondent 6 had played no part in the appeal proceedings, and had therefore failed to make its case at the appropriate time as foreseen by Article 12(2) RPBA. In filing document (57), respondent 6 was seeking, at a very late stage, to reintroduce objections that had been raised in the first instance proceedings, but had hitherto played no role at appeal. Accordingly, document (57), and any related objections and requests, should not be admitted pursuant to Articles 12(4) and 13(1) RPBA.

On the issue of inventive step of the main request, the appellant started from document (30) as the closest prior art. The problem to be solved lay in the provision of bortezomib in a formulation having an improved rate of dissolution, rendering it readily available at the time of use in the clinic. The solution proposed in claim 1 related to the claimed lyophilised mannitol ester.

In order to demonstrate that this subject-matter successfully solved the problem posed, the appellant firstly relied upon the experimental studies laid out in Example 3, paragraphs [0072] and [0073], as well as Example 5, paragraph [0081], of the patent in suit. Therein, compositions comprising a lyophilised mannitol ester of bortezomib had been shown to exhibit enhanced reconstitution properties compared to the solid bortezomib drug substance.

The further evidence on file clearly supported the conclusion that the improved dissolution properties of the tested formulations had their origin in the lyophilised mannitol ester of bortezomib, rather than in the excess mannitol excipient.

In particular, the data in paragraph 105 of the appellant's letter of 18 February 2013, and in document (53), provided a comparison between lyophilisation of bortezomib in the presence of mannitol, and a number of further excipients, including other polyols such as trehalose and dextran, or glycine, which, like mannitol, was known to be a crystallising excipient, as confirmed in documents (18) and (19), respectively. Notwithstanding these similarities, it could be seen that significantly better reconstitution rates had been achieved with mannitol. Particularly given the magnitude of the difference observed, the only credible explanation was that ester formation between mannitol and bortezomib was at the origin of the unusually high rates of reconstitution achieved. In this context, the appellant further pointed to document (39) as teaching that excipients having a large number of hydroxyl groups facilitated dissolution of lyophilised products because they were able to form hydrogen bonds. Trehalose had eight hydroxyl groups, compared with mannitol's six. Therefore, if the presence of excess mannitol were the cause of the enhanced reconstitution rates, then the trehalose-based formulations would have been expected to reconstitute at least as rapidly.

Furthermore, in the experiments presented in document (52), the properties of the bortezomib drug substance had been compared to those of a mixed powder additionally containing a large excess of mannitol. Neither of the samples had been found to reconstitute in normal saline after 20 minutes. The fact that the presence of a large excess of mannitol had not resulted in any improvement confirmed that the same must be true in the case of the previously tested lyophilised formulations. Even if mannitol and bortezomib were not

as intimately mixed as in a lyophilised formulation, the mixed powder could nevertheless be considered to be a suitable and valid model for investigating the influence of excess mannitol.

Document (55) filed by respondent 3 could not support a contrary position, since the data was inconclusive. For example, sample 023P/A, containing excess mannitol in the lyophilisate, had been observed to dissolve more rapidly than sample 023P/B, comprising equimolar amounts of mannitol and bortezomib. However, the difference could equally be explained by the fact that the excess mannitol in sample 023P/A was driving the formation of the ester. It could not therefore be concluded that the properties of mannitol as an excipient were responsible for the more rapid reconstitution, as argued by the respondents.

The appellant therefore submitted that the opposition division had been wrong to reformulate the problem to be solved in a less ambitious manner.

Moreover, even if the problem were to be defined in a less ambitious manner, as lying in the provision of an alternative bortezomib compound or formulation for pharmaceutical use, the claimed invention would not be an obvious solution to the problem posed.

The appellant firstly submitted that the skilled person was a pharmaceutical scientist working in the field of formulation technology, and not a medicinal or organic chemist who was an expert in the chemistry of boronic acids. Hence, the suggestion in the decision under appeal that the skilled person would have consulted a document such as document (35), which was directed towards the use of boronic acids as reagents in

preparative carbohydrate chemistry, and combined its teaching with that in document (30) was impermissibly based on hindsight knowledge of the invention.

Moreover, the skilled person would have been aware of the fact that the inhibitory activity of boronic acid-based proteasome inhibitors relied on the covalent bonding of a hydroxyl group in the active site of the 20S proteasome to the boron atom of the boronic acid. He would therefore not have contemplated modifying this moiety for fear of loss of activity. Therefore, the skilled person would not have considered esters as described in document (1) as candidates for the development of a medicinal product. It was evident from the disclosure of document (1) as a whole that it was the boronic acids that were intended as the therapeutic agents, as could be derived from the fact that this was the form used in all the animal model studies. The esters taught in document (1) were designed as intermediates. It was not unusual to routinely test such intermediates in cell tests, as had been done in Table II.

Even were the skilled person to have contemplated such derivatives, there was no disclosure in the prior art as to how these should be synthesised. The specific process disclosed in Example 12 of document (1) involved precipitation from organic solvents. Moreover, it was known from document (30) that bortezomib was highly unstable under alkaline conditions. Accordingly, the skilled person would not have considered employing any process involving the use of a strong base, such as that disclosed in document (7) or (8). The skilled person would have been further dissuaded by the fact that the *p*-boronophenylalanine species disclosed therein was structurally very different from

bortezomib, not only in the absence of a peptide linkage, which was susceptible to hydrolysis, but also in the presence of a stabilising phenyl ring directly bound to the boron atom. Similarly, the skilled person would also not have contemplated employing the high-temperature process suggested in document (35), involving direct condensation in boiling benzene, with azeotropic removal of water.

The claimed invention was therefore not obvious, from the disclosure of document (30) taken alone, or in combination with any of the other cited documents.

This analysis applied equally to claim 1 of the auxiliary request.

XII. The respondents' arguments, insofar as they are relevant to the present decision, may be summarised as follows:

The appellant's main request and auxiliary request should not be admitted into the proceedings. These requests were identical to auxiliary requests 3 and 6 underlying the decision under appeal. However, in the statement of grounds of appeal, no discussion had been provided as to why the opposition division's findings in this regard were incorrect or why the requirements of the EPC were met. Hence, the requests had not been substantiated in the statement of grounds of appeal and were therefore to be considered as late requests.

The respondents further submitted that the opposition division had exercised its discretion correctly in not admitting the appellant's experimental evidence dated 20 February 2014, in view of its late filing and because it was *prima facie* irrelevant. In particular,

the comparative studies in question had not been properly constructed, in such a manner as to allow any conclusion to be drawn on the decisive question of whether the alleged effect was attributable to the presence of the mannitol ester as claimed, or rather to an excess of mannitol in the lyophilisate. Therefore, the board should not overrule the opposition division's decision by admitting this material, which had been resubmitted at appeal as documents (52) and (53).

Document (54) should also not be taken into account since it was post-published and could not be relied upon as evidence of common general knowledge.

Respondent 3 argued that document (55) should be taken into account in the proceedings, since it had been filed in reply to the statement of grounds of appeal, and to the continued assertions therein by the appellant with respect to the burden of proof of providing a proper comparison with the closest prior art. Moreover, the data filed did not relate to a fresh case, but merely supported previous submissions. There had been no necessity to file this document during opposition proceedings, since a strong and convincing case could be made based on the documents on file.

Respondent 6 argued that the board should admit document (57) in application of Article 13(1) RPBA. Even though respondent 6 had not filed a reply to the statement of grounds of appeal, it was still a party as of right, and should be given the opportunity to present arguments on any issue within the proceedings. Document (57) was not complex, since it did not contain any new evidence, but merely provided a step-by-step analysis of issues addressed in the decision under appeal. The timing of its filing was therefore

sufficient in order to allow the appellant to properly prepare its case in advance of oral proceedings before the board.

In their assessment of inventive step, the respondents agreed that document (30) could be regarded as being a suitable choice as closest prior art. However, the respondents contested that the comparative tests relied on by the appellant convincingly demonstrated that any improved effect had its origin in the formation of a mannitol ester of bortezomib as claimed.

The respondents firstly criticised that the experiments in Examples 3 and 5 of the patent in suit, at best, merely showed that lyophilised preparations containing bortezomib embedded in a lyophilised matrix of excess mannitol were advantageous regarding reconstitution time. However, this feature was not reflected in the claims. Mannitol was well-known in the art as being a lyophilisation excipient of choice for achieving beneficial performance, also with respect to dissolution of the lyophilised product, as confirmed in documents such as (27) and (39). In particular, as could be derived from document (18), mannitol was known to have the important advantage, when proper freeze-drying conditions were observed, of generating crystalline material, and thus providing a physically stable, pharmaceutically elegant product. Therefore, in view of the considerable expected beneficial influence of the excess mannitol in its capacity as excipient, no conclusion could be drawn from said experimental data regarding the contribution of mannitol ester formation, if any.

Similarly, in the studies in paragraph 105 of the letter of 18 February 2013, and in document (53),

reconstitution studies were presented using different excipients. At best, it could be concluded therefrom that mannitol was a good excipient with regard to speed of dissolution. However, in view of the fact that the excipients used for comparison were known to differ from mannitol in several respects, no sound conclusions could be drawn as to any possible role of mannitol ester formation in the effects observed. For example, trehalose was known to be a non-crystallising excipient, as disclosed in document (18), and glycine was less hydrophilic than mannitol and did not bear hydroxyl groups which would be expected to promote dissolution, as discussed in document (39).

Document (52) also could not help in this respect. Therein, a physical mixture (dry blend) of bortezomib and mannitol had been compared with a dry powder of bortezomib. The former differed in two aspects from the claimed compositions, namely, in the lack of a mannitol ester, and of a lyophilisation step. Hence, these experiments did not allow any conclusion regarding the extent to which each of these factors might be responsible for the results obtained.

Finally, it had been demonstrated in document (55) that lyophilised samples containing equimolar amounts of bortezomib and mannitol, such as sample 023P/B, did not exhibit the alleged advantageous reconstitution times, whereas the corresponding sample 023P/A containing excess mannitol in the lyophilisate dissolved immediately.

In view of the fact that the more ambitious problem defined by the appellant had not been solved for the entire breadth claimed, the problem to be solved was therefore to be defined in a less ambitious manner,

such as in the provision of an alternative bortezomib compound.

The skilled person charged with this task was made up of a team, including a pharmaceutical chemist having a good knowledge of organic chemistry. In the closest prior art document (30), reference 4 corresponding to document (10) was cited in relation to the synthesis and activity of bortezomib. Document (10), and its family document (1), suggested pharmaceutically acceptable boronate esters as equivalents to bortezomib, and dihydroxy compounds were disclosed as being preferred for the formation of said esters. Mannitol would be considered as a suitable polyol for this purpose, since it was well known in the art that it could be used to make a boronate esters, as illustrated in documents such as (7) and (8). The skilled person would thus have arrived at the mannitol ester of bortezomib without the exercise of inventive skill.

It would also have been obvious to provide such an ester as its lyophilisate, as this was a routine method widely used to stabilise compounds that were unstable in aqueous solution, as confirmed by documents (31), (36) and (39). Document (8) also taught such a step, as did document (1).

Contrary to the assertions of the appellant, no negative impact on activity would have been expected to result from ester formation, since it belonged to the common general knowledge, as reflected in document (35), that such esters readily underwent hydrolysis to yield the parent compound. Moreover, the data in Table II of document (1) demonstrated that ester formation did not affect activity.

Finally, the appellant's argument that the skilled person would not have known how to make the claimed compound was not persuasive, since several synthetic methods for obtaining boronate esters were available in the prior art, such as documents (1), (8) and (35), and the skilled person having a good knowledge of organic chemistry would have modified these according to requirement. In contrast to the appellant's allegations, the methods according to document (8) would be suitable for this purpose, since the final mixtures produced therein were at physiological pH. A basic reagent had only been used for solubilisation in an intermediate step, under conditions that were much milder than in document (30).

The respondents therefore concluded that the subject-matter of claim 1 of the main request did not fulfill the requirement of inventive step, and that the same considerations applied to the auxiliary request.

XIII. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the main request or the auxiliary request, both filed with letter of 20 July 2016.

Respondents 3 to 7 requested the dismissal of the appeal.

XIV. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. *Consideration of appellant's main request and auxiliary request*

Respondents 3, 4, 5 and 7 objected to the admission of the appellant's main request and auxiliary request into the proceedings.

These requests already formed part of the opposition proceedings, filed as auxiliary requests 3 and 6 with letter dated 20 February 2014, and were considered in the decision under appeal (cf. Facts and Submissions, point 18; grounds for the decision, points 9 and 11). They were subsequently submitted as auxiliary requests 2 and 5 with the statement of grounds of appeal, pursuant to Article 12(1)(a) RPBA (cf. above points IV and IX). Therein, a detailed chain of reasoning was presented in support of an inventive step in relation to the subject-matter claim 1 of the then main request (see points 17 to 72). Since the latter is identical to claim 1 of the present main request, and since the restriction to the D-mannitol ester had no bearing on the appellant's reasoning, it was clear that the same considerations applied by analogy with respect to the present requests. Therefore, contrary to the assertions of respondents 3, 4, 5 and 7, the appellant did provide a sufficient substantiation for the present requests in its statement of grounds of appeal, in accordance with Article 12(2) RPBA.

Accordingly, pursuant to Article 12(4) RPBA, the board saw no reason to exclude said requests from the appeal proceedings.

3. *Consideration of documents (52) to (55), (57)*

3.1 *Documents (52) and (53)*

Documents (52) and (53), submitted with the statement of grounds of appeal, contain comparative data which was initially filed on 20 February 2014, that is, one month before oral proceedings before the opposition division. In view of the fact that the opposition division's decision not to admit this data has been challenged by the appellant, the question that arises is whether the opposition division exercised its discretion taking into account the correct principles, in a reasonable manner under the circumstances of the case, and thus whether, when applying the established principles for reviewing discretionary first-instance decisions by the boards, there was a need to overturn the decision of the opposition division.

In the decision under appeal (see grounds for the decision, point 8.4), the opposition division considered said experimental data to be late filed, since the issue of the potential influence of the large excess of mannitol employed in the experiments disclosed in the patent in suit had already been raised by opponent 6 in paragraph [50] of its notice of opposition of 9 December 2011, and the preliminary opinion issued on 6 September 2013, in preparation for oral proceedings before the opposition division, had merely repeated this objection. However, it is apparent from the history of the file that this issue was only touched upon in a single sentence in only one of the

seven notices of opposition filed. Therefore, at this stage in the proceedings, it could not have been identified as being a decisive point, and was therefore only briefly addressed in the patentee's reply of 18 February 2013 "for the sake of completeness" (see paragraphs 99 and 100). This situation changed with the preliminary opinion of the opposition division, since said issue was highlighted as a point that "may in particular be addressed", along with the issue of "the significance of the comparison ... with other freeze-dried (PVP and trehalose) complexes". The board therefore concludes that the filing of the data on 20 February 2014 can be seen as a legitimate and *bona fide* response to this development in the proceedings, and that, in reaching its decision, the opposition division failed to give adequate consideration to these circumstances.

Additionally, the opposition division considered that the period of one month between filing and oral proceedings was insufficient for the opponents to carry out counter-experiments, and that admittance would therefore have entailed an adjournment of oral proceedings. However, neither the decision under appeal nor the minutes of the oral proceedings contain anything that would allow the conclusion that the opponents had expressed a wish to file counter-experiments at this stage of the proceedings, as opposed to arguing their case based on the documents already on file, nor is there any record that an adjournment of oral proceedings was requested.

In view of the above considerations, the board decided to overrule the decision of the opposition division in this respect and to take documents (52) to (53) into

account in the proceedings, in accordance with Articles 12(1), (2) and (4) RPBA.

3.2 *Document (54)*

During the course of the oral proceedings of 29 September 2016, the board decided to admit document (54), as being possibly linked to the appellant's submissions on document (53). However, in the event, the appellant did not rely on this document.

3.3 *Document (55)*

Document (55) was submitted by respondent 3, in its reply to the statement of grounds of appeal, pursuant to Article 12(1)(b) RPBA, and relates to a report on reconstitution and accelerated stability studies, in particular for samples obtained by lyophilisation of bortezomib in with equimolar amounts of mannitol.

In accordance with Article 12(4) RPBA, the board shall take take into account everything presented by the parties under Article 12(1) RPBA, to the extent it relates to the case under appeal and meets the requirements in Article 12(2) RPBA; however, it is within the discretionary power of the board to hold inadmissible evidence which could have been presented in the first-instance proceedings. In other words, the fact that evidence could have been filed in the first-instance proceedings is not in itself sufficient to automatically lead to non-admission; rather, this is a matter that is at the discretion of the board, having regard to the overall circumstances at hand, including the history of the file in the previous instance.

In the present case, as set out above in point 3.1, the issue of whether lyophilisation experiments employing an excess of mannitol could be viewed as representative for the full breadth claimed was highlighted in the opposition division's preliminary opinion issued on 6 September 2013. The appellant submitted that the respondents could and should have responded with their own experimental evidence during opposition proceedings had they wished to do so. However, the board considers that the response they chose, namely, to argue their case based on the documents on file, as casting doubt on the credibility of the evidence adduced by the patentee, was perfectly legitimate, and there was no requirement for them to base their case on counter-evidence. In the event, the opponents were successful before the opposition division, as can be seen from the outcome of the opposition proceedings (cf. above point III).

In its statement of grounds of appeal, the appellant presented its case as to why the opposition division had been wrong to arrive at its conclusion with respect to inventive step, and *inter alia* maintained that the opposition division should have dismissed the opponents' case as only being based on allegations, not substantiated by reference to convincing counter-evidence (see paragraph 51). The board therefore considers that document (55) is to be seen as having been submitted in direct reaction to this aspect raised in the statement of grounds of appeal. Moreover, it concerns one of the essential points addressed in the decision under appeal. Since its filing constitutes a normal and justified development in the appeal proceedings, the board sees no reason to make use of its discretionary power under Article 12(4) RPBA to hold document (55) inadmissible. Consequently, the

board decided to take this document into account in the appeal proceedings.

3.4 *Document (57) and related objections*

Document (57) was filed by respondent 6 after summons had been issued to attend oral proceedings before the board (cf. above points VII and VIII). This declaration concerns objections first raised under Article 100(b) EPC by respondent 6 during opposition proceedings, based on a challenge as to the structural identity of the ester obtained in Example 1 of the patent in suit.

The board notes that these objections were discussed in the decision under appeal, and it was decided in favour of the appellant on this point (see grounds for the decision, points 5.2 and 5.3). At appeal, respondent 6 did not file a reply to the statement of grounds of appeal. There is no obligation under Article 12(1)(b) RPBA for a non-appealing party to submit a reply. As party as of right under Article 107 EPC, respondent 6 was thus not prohibited from subsequently filing submissions during the appeal proceedings. However, in the absence of submissions under Article 12(1)(b) RPBA, the filing of document (57) and reintroduction of related objections by respondent 6 represents an amendment to its case, the admission of which is at the discretion of the board, in accordance with Article 13(1) RPBA.

As set out above, document (57) and related objections were submitted very late in the appeal proceedings. In none of the remaining submissions of the other parties pursuant to Article 12(1),(2) RPBA was said issue raised. Prior to the submission by respondent 6, the board and the appellant had every reason to believe

that said objections were not being pursued by the respondents, and were thus taken by surprise by this development. Respondent 6 did not provide any justification for the timing of its submissions, but argued that document (57) was not complex, since it did not contain any new evidence. This argument cannot hold, since document (57) does not stand alone, but is linked to a complex series of further declarations and experimental data cited therein. The submission of this material at such a late stage is not considered to constitute a legitimate use of the appeal proceedings.

Consequently, the board decided against the admission of document (57) and related objections.

4. *Main request, claim 1 - inventive step (Articles 52(1) and 56 EPC)*

4.1 Claim 1 of the main request is directed to a compound of the formula (1), wherein said compound is a mannitol ester of "*N*-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid", also known as "bortezomib", and is lyophilised (cf. above points I and IX).

4.2 The board considers, in agreement with the parties, that document (30) can be viewed as representing the closest state of the art.

Document (30) is specifically concerned with bortezomib, which is disclosed, with reference to document (10), as being a potent inhibitor of 20S proteasome, with potential therapeutic application as an anticancer agent. It is further described that, during efforts to produce formulations for parenteral administration, this drug had been found to be quite unstable when stored in certain aqueous solvent

mixtures, and that a study was therefore undertaken in order to investigate its degradation pathways under various conditions (see "Introduction" on pages 758 and 759). Based on these studies, it was concluded that the degradation of bortezomib under acidic and basic pH conditions involved initial loss of the boronic acid group via oxidation, followed by hydrolysis ultimately yielding degradant **D**, but that degradation was more rapid at basic pH (see, in particular, page 763, right-hand column, last paragraph and page 764, left-hand column, first paragraph, as well as corresponding Scheme 1 and Figure 4).

4.3 The appellant defined the problem to be solved in the light of document (30) as lying in the provision of bortezomib in a formulation having an improved rate of dissolution, rendering it readily available at the time of use in the clinic.

4.4 The solution as defined in claim 1 relates to the formulation of bortezomib as its lyophilised mannitol ester.

4.5 As the next step, in accordance with the problem-solution approach, it must be established whether it has been rendered plausible that the problem defined under point 4.3 has been successfully solved over the whole breadth claimed.

4.5.1 In this context, it is noted that there was disagreement between the appellant and the respondents with respect to the manner in which claim 1 was to be construed, in particular with respect to the extent to which, by virtue of the feature "wherein the compound of formula (1) is lyophilized", it allowed for the presence for further components, in addition to a

mannitol ester of bortezomib. However, the decisive point for the purpose of the present decision is that claim 1 does not require the presence of an excess of mannitol or any other additional component (cf. also patent in suit, claim 24).

4.5.2 In its submissions, the appellant firstly relied on the data provided in the patent in suit, in Example 3, paragraphs [0072] and [0073], and in Example 5, paragraph [0081]. Therein, it is demonstrated that a lyophilised formulation of bortezomib with D-mannitol prepared as described in Example 1 reconstitutes rapidly, in various aqueous solvents, including "0.9% w/v saline", whereas bortezomib was not soluble in the latter.

In Example 1 of the patent in suit, the lyophilised sample was obtained from a mixture comprising bortezomib and D-mannitol, which was "added as an excipient" in a ten-fold excess by weight, approximately corresponding to a twenty-fold molar excess. However, as set out above point 4.5.1, no feature requiring an excess of mannitol is reflected in claim 1. Moreover, excipients such as mannitol were well known in the art to promote the formation of physically stable cakes with good dissolution properties in aqueous media (see e.g. document (18), page 931, left-hand column, Introduction, lines 1 to 8; document (27), page 127, right-hand column, second and third complete paragraphs; document (39), page 24, right-hand column, last two paragraphs). The board therefore concludes that the comparative experiments described in Examples 3 and 5 of the patent in suit are not suitably designed to convincingly demonstrate that the observed improved dissolution rates have their

origin in the distinguishing feature of the invention as defined in above point 4.4.

4.5.3 The appellant further referred to the data in paragraph 105 of its letter of 18 February 2013, and in document (53). Therein, a comparison is provided between lyophilisation of bortezomib in the presence of various excipients, namely, mannitol, poly(vinyl pyrrolidone), trehalose, dextran and glycine. In each case, mannitol performed significantly better in terms of dissolution rate. The appellant argued that this difference could be seen as an indication that a distinctive phenomenon was involved in the case of mannitol, namely, ester formation with bortezomib. In this context, the appellant emphasised the similarities between the excipients used, such as the fact that both mannitol and glycine were crystallising solutes (see document (18), page 931, left-hand column, Introduction, lines 2 to 6; document (19), page 491, left-hand column, Abstract, lines 7, 8), and that mannitol and trehalose bore similar numbers of hydroxyl groups, which, in accordance with the teaching of document (39), promoted solubility. However, the board notes that, in each case, relevant differences can also be found between said excipients, such as the lack of hydroxyl groups in glycine, or the fact that trehalose is a non-crystallising solute (see document (18), page 933, right-hand column, lines 7 to 9). Therefore, in view of the numerous factors potentially at play, the inferences of the appellant based on these results are not considered to be sound. Hence, it is concluded that said data does not render it plausible that the results observed with the mannitol lyophilisate can be ascribed to the formation of an ester with bortezomib.

4.5.4 The same is true for the results presented in document (52). It is disclosed therein that a sample of bortezomib as a dry powder, and second sample as a dry powder mixture with excess D-mannitol exhibited equally poor reconstitution properties. However, documents (27) and (39) teach that one of the mechanisms by which lyophilisation can facilitate dissolution of the product obtained is through formation of a porous structure with a high internal surface area (see sections cited above in point 4.5.2). It is therefore again not possible to attribute the lack of effect in the mixed powder to the absence of ester formation, rather than the lack of a porous excipient matrix.

4.5.5 Finally, document (55) *inter alia* reports the results of dissolution of various bortezomib samples (see Sections 1 and 2). In particular, the sample produced in accordance with Example 1 of the patent in suit was found to dissolve immediately in 0.9% w/v saline, whereas bortezomib alone was found not to be soluble (Table 2, sample 023P/A vs. samples 024P/B, 021P/A-C), thus confirming the results obtained in the patent in suit. In addition, the process according to Example 1 of the patent in suit was repeated employing equimolar amounts of bortezomib and mannitol, to produce sample 023P/B, which only dissolved "after 25 minutes and 1 minute of sonication". In view of this result, it can be concluded that sample 023P/B, which, as set out in above point 4.5.1, is encompassed within the terms of claim 1, does not solve the problem as formulated above in point 4.3.

The appellant submitted that the difference in dissolution rates between samples 023P/A and 023P/B, could equally be explained by the fact that the excess mannitol in the former was driving the formation of the

ester, rather than by the properties of mannitol as an excipient. However, regardless of the underlying mechanism responsible for these observations, the fact remains that, without the presence of an excess of mannitol, rapid dissolution is not observed.

4.5.6 Thus, in view of the experimental results analysed above in points 4.5.2 to 4.5.5, the board does not consider it to be plausible that the problem as defined by the appellant has been successfully solved within the whole scope of claim 1.

4.6 The problem to be solved must therefore be reformulated in a less ambitious manner, as lying in the provision of an alternative formulation of bortezomib.

Having regard to the data provided in paragraph [0074] of the patent in suit, the board is satisfied that this problem has been solved.

4.7 It remains to be investigated whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

As summarised above in point 4.2, document (30), in its introduction, highlights the potential of bortezomib as a drug, with reference to document (10), and reports problems that had been encountered in formulating it as an aqueous solution, owing to degradation by oxidation and hydrolysis.

In seeking an alternative bortezomib formulation, the skilled person would, as a first step, have sought guidance from document (10), as the patent document originally disclosing bortezomib. In the following, reference is made to its family member, document (1),

since this was the document predominantly used by the parties in their submissions.

In document (1), bortezomib is specifically listed amongst the preferred proteasome inhibitors, "as well as pharmaceutically acceptable salts and boronate esters thereof" (see page 25, lines 3 to 5 and 8; and claims 23, 24, 57, 65 and 78). In view of this teaching, the skilled person would consider pharmaceutically acceptable boronate esters of bortezomib as constituting suitable derivatives for the formulation of bortezomib. With respect to the esters envisaged, document (1) further discloses cyclic boronate esters with "a moiety derived from dihydroxy compound having at least two hydroxy groups separated by at least two connecting atoms in a chain or ring, said chain or ring comprising carbon atoms, and optionally, a hetereoatom or heteroatoms which can be N, S, or O" (see, e.g., page 7, lines 27 to 30). This structural moiety is echoed in the corresponding alcohols listed on page 16, lines 16 to 21.

Based on this teaching from document (1), the skilled person would readily identify suitable hydroxy compounds to include mannitol, as a polyol exhibiting the above-mentioned structural features, and widely known to react with boric acid, and to be suitable for use in a pharmaceutical context for complexation with the boronic acid drug *p*-boronophenylalanine (*p*-PBA) (see document (7), page 273, right-hand column, first paragraph; page 275, Table 2; and document (8), page 2, lines 15 to 18; page 20, lines 20 to 23; page 14, Table 3; page 26, Example 7). It would therefore have been an obvious measure for the skilled person to derivatise bortezomib with mannitol in an analogous manner as a solution to the problem posed.

With respect to the further claimed feature specifying that the resulting ester is lyophilised, it is noted that lyophilisation is a standard method routinely used in the pharmaceutical industry for processing pharmaceutical products, and in particular to stabilise compounds susceptible to hydrolysis and oxidation (see e.g. document (31), page 275, second paragraph, first sentence; document (36), page 1565, first two paragraphs of section "Freeze-Drying"; document (39), page 23, left-hand column, last paragraph). This method is also employed in documents (1) and (8) (see e.g. document (1), page 53, line 19; document (8), page 5, lines 11 to 14). Therefore, particularly in view of the known susceptibility of bortezomib to degradation in solution (see document (30), as summarised above in point 4.2), and the expected sensitivity of its ester to hydrolysis (see document (35), pages 50 to 52, section "b. Hydrolysis of Boronates", in particular, page 51, bottom), the further feature of claim 1 specifying lyophilisation of the ester is considered to fall within the customary practice that would be contemplated by the skilled person.

It is therefore concluded that the skilled person would not require any inventive skill in order to arrive at the subject-matter claimed.

4.8 The appellant's further arguments in favour of inventive step do not hold for the following reasons:

4.8.1 Concerning the identity of the skilled person, it is plain from the patent in suit that it is addressed towards developing boronic acid drugs, and in particular bortezomib (see e.g. paragraph [0005], and examples). The board cannot agree that the skilled

person charged with this task would be limited to a formulation technologist, but rather consists of a team also including a medicinal chemist with a knowledge of the chemistry of boronic acids. Indeed, without such expertise, the skilled person would not be in a position to formulate this class of compound, as is evident from the patent in suit (e.g. paragraph [0004]), and also from document (30) (e.g. page 759, left-hand column, last complete paragraph; page 763, right-hand column, last paragraph).

4.8.2 Moreover, the skilled person would not have expected that esterification of the boronic acid group would result in loss of activity. As set out above in point 4.7, document (1) not only teaches the use of esters as intermediates, but also as suitable alternatives to acids in the pharmaceutical context. This teaching is consistent with the skilled person's knowledge regarding the tendency of boronate esters to equilibrate with their corresponding acids in solution (see e.g. document (7), page 275, right-hand column, reaction depicted and Table 2; document (8), page 14, Table 3; document (35), page 51, top). It can further be seen from the first two entries of Table II of document (1) that comparable 20S proteasome inhibition was observed for the boronic acid tested and its corresponding ester (page 80, see also title of table). The appellant criticised that these values related to *in vitro* data, but it is noted that the same type of test was also used in the patent in suit to demonstrate inhibitory activity (see paragraph [0074]).

4.8.3 Finally, it cannot be accepted that the skilled person would not have known how to synthesise the present compound:

With respect to the step of ester formation, processes involving direct condensation of the acid and alcohol are disclosed in the prior art (see document (1), page 16, lines 17, 18 and page 66, Example 12; document (8), page 5, lines 1 to 10; document (35), pages 37 to 39, section II.1). Moreover, as set out above in point 4.7, the further step of lyophilisation is also well known in the art. In particular, document (8) discloses this step in combination with the condensation step (see page 5, lines 1 to 14, and Example 7).

The appellant argued in this context that the methods cited above would be unsuitable for the synthesis of the present peptidyl boronic ester, owing to differences in structure and the specific reaction conditions employed. However, document (1) relates to the same class of compound, and the above-cited section of document (35) discloses methods of general applicability to cyclic boronates (see formula **12**). Similarly, the skilled person would have no reason to assume that the method of document (8) could not be adapted for the synthesis of further boronate esters, apart from *p*-PBA. Indeed, in document (7) the expected complexation behaviour of *p*-PBA is generally attributed to the presence of the boronic acid group (see page 273, right-hand column, first paragraph).

Concerning the reaction conditions suggested in these documents, it is noted that, in accordance with the description of the patent in suit (cf. paragraph [0059]), the use of organic solvents in ester formation is not excluded. Moreover, in document (35), condensation in boiling benzene is only disclosed by way of example. Finally, with respect to document (8), the appellant argued that the skilled person would have

been dissuaded from applying alkaline conditions to the present synthesis, since, as highlighted in document (30), this would have been expected to result in degradation. However, document (30) is concerned with the storage stability of bortezomib formulations (see "Introduction" on pages 758 and 759), and the relevant studies were conducted at 70°C and a pH of 12.0 (see e.g. page 761, Figure 4). In contrast, according to the process of document (8), basic conditions were employed in an intermediate solubilisation step, at a pH of between 8 and 10 with gentle heating (see e.g. page 5, lines 27, 28, and Examples 1 and 7), and the mixture finally produced was at physiological pH (page 5, lines 6 to 8). The skilled person would therefore have no cause for concern in applying these milder conditions in the synthesis of a bortezomib ester.

Consequently, the board can see no reason to doubt that the skilled person would be in a position to adapt the known processes of the prior art to the synthesis of the present compound.

4.9 In view of the above considerations, the board concludes that the subject-matter of claim 1 of the main request lacks an inventive step.

5. Auxiliary request, inventive step (Articles 52(1), 56 EPC)

In claim 1 of the auxiliary request, the defined compound claimed was further restricted to the D-mannitol ester. The appellant did not submit any additional arguments in favour of an inventive step for this request. Indeed, in view of the fact that the enantiomer of mannitol employed did not play any role in the analysis set out above in point 4, the reasoning

and conclusions apply *mutatis mutandis* to the subject-matter of the auxiliary request.

Hence, the auxiliary request is also rejected for lack of inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated