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Datasheet for the decision of 19 October 2021

Case Number: T 0980/19 - 3.3.02

Application Number: 10006835.2

Publication Number: 2251344

IPC: C07F5/02, C07F5/04, C07C7/00, C07K5/06, C07K5/08, C07K5/078, A61K38/00, A61K38/05, A61K31/69, A61P35/00, A61P29/00, C07K7/02

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:
HGF Limited
Pfizer Inc.
Accord Healthcare Ltd
LEK Pharmaceuticals d.d.
Synthon B.V.
Fresenius Kabi Deutschland GmbH
Pentafarma Sociedade Técnico-Medicinal S.A.
Generics (U.K.) Limited
Teva Pharmaceuticals Inc.

Headword:

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2), 76(1), 107, 112a(1)
RPBA Art. 12(4), 13(1), 13(3)
EPC R. 80, 106
RPBA 2020 Art. 12(1)(a), 25(3)

Keyword:
Allegation of public prior use and accompanying evidence - filed for the first time in appeal
Inventive step
Sufficiency of disclosure
Amendments
Request to continue proceeding in writing
Objection under Rule 106 EPC

Decisions cited:
R 0009/14, T 0152/03, T 0952/06, T 0007/07, T 0724/08, T 0406/09, T 0518/10, T 0691/12, T 1348/14, T 0239/16, T 1711/16

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 0980/19 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 19 October 2021

Appellant: (Patent Proprietor)	THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health, Office of Technology Transfer, Suite 325 6011 Executive Boulevard, Rockville, MD 20852 (US)
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Appellant: (Opponent 1)	HGF Limited 1 City Walk Leeds Yorkshire LS11 9DX (GB)
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Appellant: (Opponent 2)	Pfizer Inc. 235 East 42nd Street New York, NY 10017 (US)
Appellant: (Opponent 3)	Accord Healthcare Ltd Sage House 319 Pinner Road North Harrow Middlesex HA1 4HF (GB)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)

Appellant: (Opponent 4)	LEK Pharmaceuticals d.d. Verovskova 57 1526 Ljubljana (SI)
Representative:	Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstraße 2 80538 München (DE)
Appellant: (Opponent 5)	Synthon B.V. Microweg 22 6545 CM Nijmegen (NL)
Representative:	Prins, Hendrik Willem Arnold & Siedsma Bezuidenhoutseweg 57 2594 AC The Hague (NL)
Appellant: (Opponent 7)	Pentafarma Sociedade Técnico-Medicinal S.A. Rua da Tapada Grande, n. 2 2710-089 Abrunheira (PT)
Representative:	Kutzenberger Wolff & Partner Waidmarkt 11 50676 Köln (DE)
Appellant: (Opponent 8)	Generics (U.K.) Limited Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Appellant: (Opponent 9)	Teva Pharmaceuticals Inc. 5 Basel St. 49131 Petach Tikva (IL)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Party as of right: (Opponent 6)	Fresenius Kabi Deutschland GmbH Else-Krömer-Strasse 1 61352 Bad Homburg (DE)
Representative:	Fresenius Kabi Deutschland GmbH Patent Department Pharmaceuticals Division Borkenberg 14 61440 Oberursel (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 7 March 2019 concerning maintenance of the European Patent No. 2251344 in amended form.**

Composition of the Board:

Chairman M. O. Müller
Members: P. O'Sullivan
P. de Heij

Summary of Facts and Submissions

I. This decision concerns the appeals filed by the patent proprietor and opponents 1, 2, 3, 4, 5, 7, 8 and 9 against the decision of the opposition division, according to which European patent 2 251 344 in amended form met the requirements of the EPC.

II. The patent was opposed under Article 100(a) (novelty and inventive step), (b) and (c) EPC. In its decision, the opposition division held that the subject-matter of the sets of claims according to the (then) main request, auxiliary request 1 and auxiliary request 2 lacked inventive step. The set of claims of auxiliary request 3 was found to be allowable.

III. The following documents were among those cited by the parties in opposition proceedings:

D1: WO 96/13266 A1
D2: US 5,780,454
D5: Wu et al., J. Pharm. Sci., 2000, pages 758-765
D7: Pikal, M., Freeze Drying, Encyclopedia of Pharmaceutical Technology, 1994, Vol. 6, pages 275-303
D8: Remington's Pharmaceutical Sciences; Parenteral Preparations, Chapter 84, 18th Ed., 1990, pages 1565-1567
D10: Voigt, R., Pharmazeutische Technologie, 2000, pages 23-24
D11: Kim, A. I. et al., J. Pharma. Sci., 1998, pages 931-935
D13: WO 00/57887 A1
D14: Mori, Y., et al., Pigment Cell Research, 1989, pages 273-277

D16: Yoshino K. et al., Strahlenther Onkol., 1989, pages 127-129

D17: R. J. Ferrier, "Carbohydrate Boronates" in Advances in Carbohydrate Chemistry and Biochemistry, 1978, Volume 35, pages 31-80

D19: WO 02/059130 A1 (published parent application)

D23: Jennings, T.A., Lyophilization: Introduction and Basic Principles, 1999, pages 29-33

D26: Decision T 1348/14

D28: Extract from the minutes of the oral proceedings before the opposition division on the parent patent

D32: Cappola, "Freeze Drying", Protein Formulation and Delivery, 2000

D35: Experimental report: "Report on Reconstitution and Accelerated Stability Studies" dated 26 January 2015

D36: Experimental report: "Report on Stability Studies" dated 23 December 2016

D42: Declaration of Dr Roel Fokkens dated 23 December 2016

D43: Curriculum Vitae of Dr Fokkens

D44: Test Report supplied by Dr Fokkens

D45: Document entitled "Overview of Mass Spectrometry"

D46: Pramanik, B.N., et al., Applied Electrospray Mass Spectrometry, 2002

D53: Second declaration of Dr Roel Fokkens dated 11 December 2017

D62: NMR Experimental Report dated 16 October 2017

D62a: Addendum to D62 dated 11 October 2018

D63: NMR Experimental Report

D64: Third declaration of Dr Roel Fokkens dated 19 September 2018

IV. The following documents, renumbered by the board as indicated below, were filed during appeal proceedings.

By the opponents:

A1: The Story of Velcade™ - A Biotech Love Story
A2: Slide 16 of A1
A3: Slide entitled "PS-341 finished drug product (lyophilized)"
A4: J. Adams et al., Cancer Research, 59, 1999, pages 2615-2622
A5: United States Pharmacopoeia, "Mannitol"
A6: C. Aghajanian et al., Clinical Cancer Research, Vol. 8, 2002, pages 2505-2511
A7: Articles from clinicaltrials.gov entitled "PS-341 in treating patients with advanced solid tumors or lymphoma"
A8: Velcade - poster
A9: Search results from clinicaltrials.gov
A10: Further search results from clinicaltrials.gov
A11: Summary of product characteristics of Velcade™
A12: Kelly et al., J. Am. Chem. Soc., 1993, vol.115, 12637-12638
A13: A. B. Shenvi, Biochemistry, 1986, 25, pages 1286-1291
A14: Summary of Product characteristics for Velcade™, 20 February 2019
A15: Expert report of Tanya Mercier dated 4 July 2019
A16: Physicians' Desk Reference, 36th Edition, 1982, page 1638
A17: Chemical stability of Pharmaceuticals, A Handbook for Pharmacists, 2nd Edition, 1986, page 356
A18: American Hospital Formulary Service (AHFS), Drug Information, 1991, page 757
A19: Physicians' Desk Reference, 45th Edition, 1991,

pages 2373-2374
A20: Physicians' Desk Reference, 40th Edition, 1986, page 1670
A21: Physicians' Desk Reference, 45th Edition, 1991, pages 1585 and 1587
A22: Mosby's GenRx, Ninth Edition, 1999, page II-942
A23: Drug Facts and Comparisons, 1999, page 694
A24: The Cytotoxics Handbook, Second Edition, (British Library date stamp 23 April 1993), page 290
A25: Mosby's Complete Drug Reference (Physician's GenRx). Seventh Edition, 1997, pages II-780 and II-782
A26: Mosby's Complete Drug Reference (Physician's GenRx), Seventh Edition, 1997, page II-982
A27: Physicians' Desk Reference, 54th Edition, 2000. page 3006
A28: Physicians' Desk Reference, 33rd Edition, 1979, page 883
A29: Patient Information Leaflet for Prevacid®, May 2009
A30: US 5,536,735
A31: Elliott et. al., Am. J. Clin. Pathol., 2001, vol. 116, pages 637-646
A32: Modern Pharmaceutics; Chapter 22 - Biotechnology based Pharmaceuticals; S K Edmond Rouan, 1996, pages 843-867
A33: Cosmogen® product information
A34: Flolan® product information
A35: Hycamtin® product information
A36: Regitme® product information
A37: Nipent® product information
A38: Vecuronium bromide® product information
A39: WO 2013/178788 A2
A40: AJ Reddi, International Journal of Medical Sciences, 2013, vol. 10(6), pages 747-750

A41: Lucena et al., Eur J Hosp Pharm 2014:21 (Suppl 1), pages A1-224
A42: Experimental report by Mark Hooper Consulting
A43: Supplementary update on bortezomib freeze-dried sample study
A49: Pharmaceutics: The science of dosage form design, Ed. M E Aulton, 1988, pages 223-229
A50: Fourth declaration of Dr Fokkens.
A51: Identical to D38
A52: Printout from clinicaltrials.gov for the study with identifier: NCT00023712
A53: Declaration of Ms Pranoti Pathak, Bortezomib for injection formulation, 20 June 2019

By the patent proprietor:

A44: Declaration of Alice Choi dated 24 March 2020
A44a: Curriculum Vitae of Alice Choi
A44b: Informed consent form
A44c: PS-341 Pharmacy manual
A45: "Handling cytostatic drugs"
A46: Teicher and Anderson, Commentary
A47: Annex of approved lyophilized products
A47a: Mosby's GenRx, ninth edition, 1999
A47b: Mosby's GenRx, tenth edition, 2000
A47c: Physicians' Desk Reference, 55th Edition, 2001
A48: EMA Scientific discussion - Velcade

V. With a communication pursuant to Article 15(1) RPBA, the board set out its preliminary opinion. With regard to inventive step, the board set out the view, in agreement with all parties, that D5 was a suitable closest prior art disclosure for the assessment of inventive step. Furthermore, the board expressed the view that the closest prior art disclosure in D5 was represented by the formulation of bortezomib in 2%

EtOH/normal saline at pH 6.9, depicted in figure 5. This view lay in contrast to the opinion of the patent proprietor, also set out in the board's communication, according to which the closest prior art disclosure in D5 was represented by the solid bortezomib drug substance.

VI. Oral proceedings before the board were held by videoconference on 18 and 19 October 2021. During the proceedings, opponent 5 withdrew its previously formulated request not to hold oral proceedings by videoconference. Furthermore, opponent 9 requested that the board adjourn proceedings and continue the case in writing to allow for the assessment of inventive step to be addressed on the basis of a different closest prior art document to D5. After this request was rejected by the board, opponent 9 stated that its right to be heard had been infringed, and submitted a written objection under Rule 106 EPC (attached to the minutes of the oral proceedings).

VII. Requests relevant to the present decision

The patent proprietor requested:

- that the contested decision be set aside and that the patent be maintained as granted (main request);
- alternatively, that the patent be maintained on the basis of auxiliary requests 1 or 2, both filed with the statement of grounds of appeal, or auxiliary requests 3 to 8, filed with the reply to the statements of grounds (auxiliary request 3 being identical to auxiliary request 3 found allowable by the opposition division, thus implying dismissal of the opponents' appeals);

- that the objection of lack of novelty based on an alleged public prior use, filed by opponent 9 with the statement of grounds of appeal, together with the documents on which it was based, i.e. documents A1-A10, not be admitted into the proceedings;
- that documents A12, A15-A41 and A52 not be admitted into the proceedings;

All opponents requested that the contested decision be set aside and that the patent be revoked in its entirety.

Opponent 1 additionally requested:

- that documents D52 and D61 not be taken into account, since the effect allegedly proven by these documents was not plausible on the basis of the disclosure in the application as filed;
- that documents A1 to A10 (submitted by opponent 9), A31 to A38, A52 and A53 be admitted into the proceedings;
- that documents A44 to A48 not be admitted into the proceedings.

Opponent 2 additionally requested that documents A14 to A30 be admitted into the proceedings.

Opponent 3 additionally requested that documents A42 and A43 be admitted into the proceedings.

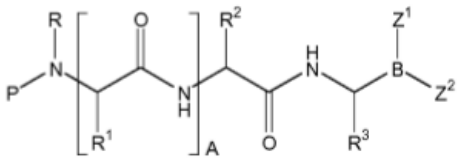
Opponent 5 additionally requested that documents A1 to A10, A12, A15, A31 to A38 and A52 be admitted into the proceedings.

Opponent 9 additionally requested:

- that auxiliary requests 1, 2 and 4 to 8 not be admitted into the proceedings;
- that the objections of lack of novelty and lack of inventive step based on a public prior use and documents A1 to A10 be admitted into the proceedings;
- that documents A12 and A13 be admitted into the proceedings;
- that documents A44 to A48 not be admitted into the proceedings in the event that documents A1 to A10 were not admitted;
- that, in case the patent was not revoked, the case be remitted to the opposition division to address novelty;
- that the proceedings be continued in writing in order to discuss inventive step starting from a different closest prior art than document D5.

VIII. The sole claim of the main request reads as follows:

"1. A lyophilized powder comprising mannitol and 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 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, alkaryl, 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) is lyophilized and wherein said compound is a mannitol ester of N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid."

The sole claim of auxiliary request 1 differs from that of the main request in that it concerns:

- "A lyophilized powder comprising *D-mannitol*", wherein
- "the compound of formula (1) is lyophilized and wherein said compound is ~~a~~ D-mannitol ester of *N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine* ~~*boronic acid*~~ *boronate*.

(deletions and additions compared to the claim of the main request).

IX. The arguments of the patent proprietor, insofar as relevant to the present decision, may be summarised as follows:

Admittance - allegation of public prior use and associated documents relevant to novelty and inventive step

- Documents A1 - A10 and A52 and the objections of lack of novelty and inventive step based thereon were not to be admitted into the proceedings. The documents should have been submitted and the objections raised in the opposition proceedings and there was no legitimate reason for the late filing. Furthermore, the conditions set out in T 691/12 for admittance of a novelty objection based on a public prior use had not been met.

Admittance - further documents relevant to inventive step

- Documents A12, A15 - A38, A40 and A41 submitted by the opponents were not be admitted into appeal proceedings.

- Documents A46, A47 (including annexes A47a, A47b, A47c and A47d) and A48 submitted by the patent proprietor were to be admitted into the proceedings.

Main request - patent as granted

Amendments - Article 100(c) EPC

- The grounds for opposition under Article 100(c) EPC did not prejudice maintenance of the patent as

granted. In particular, not only the specific term "D-mannitol", but also the general term "mannitol" was directly and unambiguously disclosed in the parent application as filed (D19), in combination with the further features of contested claim 1.

Auxiliary request 1

Amendments - Article 123(2) EPC

- The different aspects of the invention described in paragraphs [0054] to [0135] of D19 (the parent application) were related, such that the features presented in each of these aspects could be combined. Also in view of described preferred features, these paragraphs disclosed the features of the claimed subject-matter in combination. In addition, preferred features could be inferred from the examples. A basis for two-fold lyophilisation, contrary to what was argued by the opponents, was not required, since the claimed subject-matter could not be interpreted to comprise such a feature.

Inventive step - Article 56 EPC

- D5 was the closest prior art. The closest prior art embodiment in D5 was the solid bortezomib drug substance. The distinguishing features of claim 1 over D5 were that bortezomib was in the form of its mannitol ester, in the presence of free mannitol, and in the form of a lyophilised powder. The technical effects of the distinguishing features were improved long-term solid stability (hereinafter: "solid stability"), improved dissolution behaviour, and the provision of a

stable solution. The objective technical problem was the provision of a form of bortezomib which, as compared to the solid bortezomib drug substance, has an improved long term stability and an improved dissolution behaviour in normal saline or water for injection, whilst providing for a stable solution on dissolution and whilst allowing the free boronic acid or bortezomib to be readily liberated at the time of use in the clinic. The solution to this problem involved an inventive step in view of the prior art documents cited by the opponents.

Sufficiency of disclosure

- The invention defined in the claim of auxiliary request 1 was disclosed in a manner sufficiently clear and complete for it to be carried out by the person skilled in the art.

X. The arguments of the opponents, insofar as relevant to the present decision, may be summarised as follows. The specific opponent submitting the argument in question is identified only if deemed relevant to the decision, in particular in view of the fact that many arguments were submitted by more than one opponent:

Admittance - allegation of public prior use and associated documents relevant to novelty and inventive step

- Documents A1 - A10 and A52 and the objections of lack of novelty and inventive step based thereon were to be admitted into the proceedings. The novelty objection was *prima facie* relevant and in particular the criteria for admittance of a novelty objection based on a public prior use according to

decision T 691/12 had been fulfilled. A new search had been performed in response to the surprising decision of the opposition division to maintain the patent on the basis of auxiliary request 3. The information in A1 had been hidden in a slide and was difficult to retrieve. The documents had been filed at the earliest possible time and the patent proprietor had had sufficient time to consider them and the accompanying objections. The same objections were raised in pending proceedings for divisional application EP 3 078 667 A. Consequently, not considering the documents in the present proceedings would lead to undesirable diverging decisions and legal uncertainty.

Admittance - further documents relevant to inventive step

- Documents A12, A15 - A38, A40 and A41 submitted by the opponents were to be admitted into appeal proceedings.

- Documents A46, A47 (including annexes A47a, A47b, A47c and A47d) and A48 submitted by the patent proprietor were not to be admitted into the proceedings.

Main request - patent as granted

Amendments - Article 100(c) EPC

- The ground for opposition under Article 100(c) EPC prejudiced maintenance of the patent as granted. The claimed subject-matter resulted from a series of selections of features from within the disclosure in the parent application as filed

(D19), with different levels of preference. The four aspects of the invention described in D19 referred to separate and distinct embodiments which, for the purpose of determining the content of the parent application as filed to assess the presence of added-subject-matter, could not be combined. The combination of features in claim 1 was thus not directly and unambiguously disclosed in D19. Claim 1 was also to be interpreted to include a two-fold lyophilisation for which no basis existed in D19. Furthermore, D19 lacked any basis for the definition in contested claim 1 of the aryl group in R^1, R^2, R^3 and R^5.

Auxiliary request 1

Inventive step - Article 56 EPC

- D5 was the closest prior art. The closest prior art embodiment was either the solution disclosed in figure 5 comprising 2% EtOH in normal saline at pH 6.9, or the statement in D5 that bortezomib is intended for parenteral administration. The distinguishing features of claim 1 over D5 were that bortezomib is in the form of its mannitol ester, in the presence of free mannitol, and in the form of a lyophilised powder. The alleged technical effects of improved solid stability of the lyophilised powder, improved dissolution behaviour, and the provision of a stable solution had not been demonstrated, in particular across the entire scope of the claim. The objective technical problem (although formulated slightly differently amongst the opponents) was essentially the mere provision of an alternative formulation of bortezomib. Furthermore, even if the problem were formulated to

include the achievement of the effects mentioned above, the solution would be obvious to the skilled person, in particular in view of the common general knowledge concerning lyophilisation, the use of mannitol as a preferred bulking agent, and the known dissociation of boronic acid esters to provide boronic acids in aqueous solution. Therefore, the subject-matter of claim 1 lacked an inventive step.

Sufficiency of disclosure

- The invention defined in the claim of auxiliary request 1 was not disclosed in a manner sufficiently clear and complete for it to be carried out by the person skilled in the art.

Procedural issues

The request to continued the proceedings in writing (opponent 9)

- The proceedings should be continued in writing in order to discuss inventive step starting from a different closest prior art than document D5, such as D2. The reason was that the board in its communication pursuant to Article 15(1) RPBA preliminarily had formulated a different problem on which the opponent had relied in its preparations.

Objection under Rule 106 EPC

- The following written objection under Rule 106 EPC was submitted:

  "*We herewith raise a procedural objection under Rule 106 EPC due to a violation of our right to be heard according to Article 113 EPC because the Technical Board of Appeal rejected O9's request to continue the proceedings in writing in order to discuss inventive step based on a closest prior art different from D5.*"

Reasons for the Decision

1. All requests - Priority

It was submitted in writing that the subject-matter underlying the patent was not entitled to the claimed priority date. However, as noted by the board in the communication pursuant to Article 15(1) RPBA sent in preparation for oral proceedings, none of the opponents' submissions against the allowability of the main request or auxiliary request 1 (nor for that matter, any other request) relied on the invalidity of the priority. None of the opponents raised this issue during oral proceedings before the board. Consequently, the board concluded that validity of the claimed priority is not relevant to the present case, and consequently does not need to be assessed.

2. Admittance - allegation of public prior use and associated documents relevant to novelty and inventive step & admittance of further documents relevant to inventive step

2.1 Documents A1-A10 filed by opponent 9 with the statement of grounds of appeal and the novelty objection based thereon

2.1.1 With the statement of grounds of appeal, opponent 9 submitted for the first time that the subject-matter of the claim of auxiliary request 3 found allowable by the opposition division lacked novelty in view of the administration of Velcade® in clinical studies that had started before the priority and filing date of the contested patent. Claim 1 of said auxiliary request 3 comprised a limitation to a specific molar ratio of D-mannitol to the D-mannitol ester of bortezomib of between 10:1 and 100:1 (hereinafter: "the molar ratio"). Velcade® was the authorised and marketed medicinal product of bortezomib falling within the scope of claim 1. Specifically, the basis for the allegation, document A1, a Powerpoint presentation entitled "The Story of Velcade™ - A Biotech Love Story", disclosed on page 16 a photo of a vial and an indication of "4000 vials (February 1999)". According to opponent 9, A1 and associated evidence A2 - A10 demonstrated that these vials constituted a lyophilised powder according to claim 1 as maintained (comprising a 10-fold weight excess of mannitol (A1, slide 16; 2.5 mg PS-341 and 25 mg Mannitol USP), and that the relevant clinical trials had begun well before the priority or filing date of the contested patent. Since the finished drug product of A1 had been administered to many patients, a huge number of clinical staff had obtained and used said product. There was also no evidence of

any confidentiality agreement, and it was highly unlikely that all unused product was returned at the end of the clinical trials. Thus, the product was available to the public before the effective date of the patent, and the subject matter of the claim maintained by the opposition division lacked novelty.

Since the subject-matter of the respective claim 1 of present higher ranking requests (main request, auxiliary requests 1 and 2) was broader, the same applied thereto accordingly.

2.1.2 The patent proprietor requested that said objection of lack of novelty based on an alleged public prior use, together with the documents on which it was based, i.e. documents A1 - A10, not be admitted into the proceedings.

2.1.3 As the statement of grounds of appeal of opponent 9 was filed before the date of entry into force of RPBA 2020, Article 12(4) RPBA 2007 applies (Article 25 RPBA 2020). Under Article 12(4) RPBA 2007, the board has the power not to admit into the proceedings *inter alia* facts and evidence that could have been presented in opposition proceedings.

Therefore, an important question in relation to admittance is whether there are circumstances on the basis of which it may be concluded that the submission of A1-A10 and the corresponding allegations of fact based on these documents could not have been reasonably expected during opposition proceedings.

2.1.4 In a first observation, the board notes that opponent 9 did not argue that the evidence A1-A10 was not

available (i.e. retrievable) during opposition proceedings.

2.1.5 Opponent 9 argued that the relevant information in A1 was hidden in slide 16 thereof and therefore difficult to retrieve. The acceptance of auxiliary request 3 by the opposition division, comprising in claim 1 the molar ratio, was impossible for the opponent to foresee during opposition proceedings. Specifically, with the preliminary opinion sent with the summons to oral proceedings, the opposition division had stated that the subject-matter of such a claim would lack inventive step. During oral proceedings, the opposition division reversed this position on the basis of the restriction to the molar ratio. This surprising development represented sufficient justification for a new search directed to this more limited subject-matter. Consequently, the admittance of A1-A10 into appeal proceedings was justified.

2.1.6 The board disagrees with this view. Firstly, the alleged difficulty in retrieving A1 in a search applies equally to the retrieval of the same document in opposition proceedings, such that any such difficulty cannot serve as a justification for the submission of A1-A10 only with the statement of grounds of appeal. The board in this respect follows the view expressed, for example in decision T 724/08 (reasons, 3.4), that it is of no relevance whether certain disclosures were merely difficult to retrieve, since this cannot be to the detriment of procedural economy and the principle of fairness to the other party.

Irrespective of this, and as noted by the patent proprietor, the contested patent formed the basis for the authorisation of a viable medicinal product

comprising bortezomib, known as Velcade®, marketed around the world for the treatment of multiple myeloma. Since it was well known that bortezomib was in clinical trials before the patent was granted in 2016, all of the information was available before expiry of the period for filing an opposition under Article 99(1) EPC.

2.1.7 Furthermore, the subject-matter of auxiliary request 3 found allowable by the opposition division (and comprising the molar ratio feature) lies entirely within the scope of claim 1 as granted. There is therefore no reason why a search performed within the time period of Article 99(1) EPC could not have been directed towards, and led to the evidence now submitted. In addition, as stated by the patent proprietor, the request in question was first submitted as auxiliary request 5 with the patent proprietor's reply to the notices of opposition dated 17 August 2017. Hence if not within the time limit of Article 99(1) EPC, the opponent could at the very latest have submitted the new objection and related documents A1 to A10 in response to the proprietor's submission.

2.1.8 The opponent argued that the opposition division's finding that auxiliary request 3 was allowable could not have been foreseen on the basis of the allegedly surprising molar ratio feature. This request had been filed originally as auxiliary request 5 and had only later in opposition proceedings become auxiliary request 3 from a total of 8 auxiliary requests, the implication, as the board understands it, being that the opponent could not be expected to perform complete searches for relevant prior art for all possible amendments in each individual request. The board notes

however that the same molar ratio feature was present in claim 1 of auxiliary request 3 filed with the reply to the notices of opposition, while auxiliary requests 2 and 4 filed with the same letter comprised a similar feature differing only in that the claimed molar ratio was broader (5:1 to 100:1). Therefore, it would have been apparent at least from the amended claim requests submitted with the reply to the notices of opposition as a whole that the molar ratio feature in general was a central line of defence underlying the patent proprietor's position. Therefore, the board's conclusion above remains valid, namely that if not within the period specified in Article 99(1) EPC, A1 - A10 and the objections based thereon should have been filed at the latest in response to the patent proprietor's reply to the notices of opposition with which said requests were submitted.

This conclusion is not altered by the arguments of the opponent that the preliminary opinion of the opposition division, set out in the communication accompanying the summons to oral proceedings, may have been the opposite to that taken in the contested decision. Specifically, said preliminary opinion cannot serve to justify the submission of evidence in response thereto when said evidence should already have been submitted at an earlier stage of the opposition proceedings as set out above.

2.1.9 It was also argued that the novelty objection should be admitted into the proceedings since it was *prima facie* relevant. However, *prima facie* relevance does not entitle a party to file new documents and advance new facts only in appeal. The board in this respect agrees with the position taken in T 724/08, reasons 3.4, in which it was stated that the board is under no

obligation to admit a document merely because of its *prima facie* relevance. The board furthermore underlines that whether such documents and new facts are admitted into the proceedings is a matter for the discretion of the board, weighing all of the circumstances of the case.

2.1.10 It was also argued that the patent proprietor and the board had had enough time to consider the newly filed evidence in view of the fact that on the day of oral proceedings before the board, approximately 2.5 years had elapsed since its submission.

This period of time is however not decisive in determining whether said evidence should be admitted in the proceedings. In the case at hand, in view of the circumstances set out above, the board considered that the arguments in favour of admittance were not sufficient to outweigh the considerable negative effect on fairness and procedural economy.

2.1.11 None of the further arguments submitted by the opponents in this regard convinced the board that A1-A10 and the related objection should be admitted into the proceedings. Specifically,

- during oral proceedings the opponent relied on decision T 691/12 (originally cited by the patent proprietor), in which the deciding board stated (reasons, 2) that an allegation of public prior use can only be admitted if at least the following three criteria are fulfilled: a) there must be no evident abuse of procedure, b) the public prior use must be *prima facie* so relevant that it casts doubt on the validity of the patent, and c) the public prior use has been fully proven, requiring no

further investigations to establish its nature or context. The opponent argued that these criteria had been fulfilled in relation to the filing of A1-A10. In particular in relation to criterion c), in view of decision T 0007/07, the prior use had been made publically available. Furthermore, if there was a doubt with regard to whether criterion c) was fulfilled in the present case, it was the patent proprietor who, according to established case law, held the burden of proof in demonstrating that a confidentiality agreement existed. Specifically, all of the information regarding any obligation to confidentiality of medical personnel and participants to a clinical trial lay within the power of the patent proprietor.

The board is of the following view. Decision T 691/12 sets out the view of the deciding board that an allegation of public prior use submitted for the first time in appeal proceedings may be admitted into proceedings if at least three separate criteria a)-c) are met. The implication is therefore that if one of these criteria is not met (as was the case in T 691/12), the public prior use should not be admitted. This decision however does not state, and does not allow, the reverse conclusion that if all three criteria are met, an allegation of public prior use *must* be admitted, but rather that it *may* (T 691/12, reasons 2, "... *kann ...berücksichtigt werden...*"). As stated above, it is left to the discretion of the board to weigh all of the circumstances of the case.

- Opponent 9 argued that as expressed in e.g. T 406/09, an appellant who has lost the opposition proceedings should be given the opportunity to fill

the gaps in its arguments by presenting further evidence in the second instance.

However, in that decision, new documents were submitted to demonstrate that a feature on the basis of which novelty was acknowledged by the opposition division (the content of mannose and galactose) could not render the claimed subject matter novel over a specific document. In the present case in contrast, the new documents form the basis for an entirely new novelty objection introduced into appeal proceedings for the first time. The circumstances are therefore different, and the conclusions in T 406/09 cannot be applied to the present case.

- Attention was also drawn to the divisional application EP 3 078 667 A, for which, according to the opponent, the same objection had been raised during the opposition period. Therefore, not considering the objection in the present proceedings would lead to undesirable diverging decisions and a lack of legal certainly.

  However, appeal proceedings in the present case are separate from and unconnected to proceedings in relation to another application or patent, and there is no legal basis for citing circumstances in a separate pending procedure as a justification for admittance in the present procedure.

2.1.12 Consequently, pursuant to Article 12(4) RPBA 2007, the board decided not to admit documents A1-A10 and the novelty objection based thereon into the appeal proceedings.

2.2 Document A52 and associated objections based on novelty and inventive step - public prior use

2.2.1 This document was submitted by opponent 1 with the letter dated 7 September 2021. Since the first summons to oral proceedings was sent with the letter dated 25 November 2019, the admittance thereof, according to Article 25(3) RPBA 2020 relating to transitional provisions, is governed by the provisions of Article 13 RPBA 2007.

2.2.2 A52 is a printout from the web page clinicaltrials.gov describing a clinical trial involving bortezomib, and was submitted to support the allegation of public prior use first submitted by opponent 9 on the basis of documents A1-A10. Furthermore, with the letter dated 7 September 2021 (points 93 and 94), opponent 1 briefly set out an argument regarding obviousness over D5 "in view of the disclosed vials" employed in A52.

In the same way as for A1-A10 and the related novelty objection submitted by opponent 9, A52 and the related novelty and inventive step objections could and should have been filed before the opposition division. Therefore, had A052 and related objections been filed with the statement of grounds of appeal, they would not have been admitted under Article 12(4) RPBA 2007. This conclusion cannot change in view of the fact that they were filed even later and thus fall under Article 13(1) RPBA 2007.

For these reasons, the board decided not to admit A52 and the novelty and inventive step objections based thereon, also in combination with documents A1-A10, into the proceedings pursuant to Article 13(1) RPBA 2007.

2.3 The request of opponent 9, in case the patent was not revoked, that the case be remitted to the opposition division to address novelty

Submitted at the outset of oral proceedings, opponent 9 requested that if patent was not revoked, the case be remitted to the opposition division to examine novelty on the basis the public prior use in view of documents A1-A10 addressed above. This request however presupposes that the relevant evidence A1-A10 is admitted into the proceedings. Since as set out above, the board decided not to admit A1-A10, the request was moot and there was no need for it to be considered by the board. In fact, subsequent to submitting the request, at no point during the oral proceedings did opponent 9 reiterate or refer in any other way to this request.

2.4 Documents A44 (including A44a, A44b and A44c contained therein) and A45

Filed by the patent proprietor with the reply to the statements of grounds, the opponents requested that these documents not be admitted into the appeal proceedings. As the patent proprietor acknowledged, A44 and A45 were highly relevant only in the event that A1 - A10 were admitted into the proceedings. Since the latter were not admitted, the board also decided not to admit A44 or A45 into the proceedings pursuant to Article 12(4) RPBA 2007.

2.5 Admittance - further documents relevant to inventive step

2.5.1 Documents A12, A15 - A38, A40 and A41 were submitted by the opponents with their respective statements of grounds of appeal, in the framework of objections related to Article 56 EPC. The patent proprietor requested that said documents not be admitted into appeal proceedings.

Pursuant to Article 12(4) RPBA 2007, the board decided to admit A12, A15 - A38, A40 and A41 into the proceedings. Since the patent proprietor was not adversely affected by their admittance, it is not necessary for the board to provide its reasons in this regard.

2.5.2 Documents A46, A47 (including annexes A47a, A47b, A47c and A47d) and A48 were submitted by the patent proprietor with the reply to the opponents' statements of grounds of appeal. Opponents 1 and 9 requested that said documents not be admitted into the proceedings. The board decided to admit these documents into the proceedings. However, since none of these documents were relevant to the board's conclusions set out in the present decision, there is no need for the board to provide its reasons in this regard.

2.5.3 D52 and D61 were filed by the patent proprietor in opposition proceedings and comprise post-filed experimental data concerning the long-term solution stability of reconstituted bortezomib. Opponent 1 requested that they not be taken into account since the effect allegedly proven therein was not plausible on the basis of the disclosure in the application as

filed. Since these documents were not required for the board to reach its conclusion as set out below in relation to inventive step, there was no need for the board to decide on the request of opponent 1 that they not be admitted into proceedings.

2.6 Admittance - document A39

Document A39 was submitted by opponent 3 with the statement of grounds of appeal for the purpose of demonstrating that a two-fold lyophilisation (infra) was technically sensible in the context of contested claim 1. The patent proprietor requested that A39 not be admitted into the proceedings.

The board decided to admit A39 into the proceedings pursuant to Article 12(4) RPBA 2007. Since the patent proprietor was not negatively affected by the admittance of A39 (infra), there is no need for the board to provide its reasons in this regard.

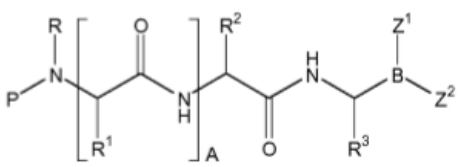
Main request

3. Amendments - Article 100(c)

3.1 Amendments

The sole claim of the main request reads as follows:

"1. A lyophilized powder comprising mannitol and a ~~A~~ compound of the formula (1):



(I)

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, alkaryl, 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 ~~sugar~~ mannitol, wherein the atom attached to boron in each case is an oxygen atom, and
wherein the compound of formula (1) is lyophilized and wherein said compound is a mannitol ester of N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid."
(underlining and strike-through denoting addition and deletion respectively compared to claim 1 of both the parent application as filed and the application as filed, D19 and D20 respectively.

N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid is hereinafter referred to as "bortezomib".

In simplified form, claim 1 refers to a lyophilised powder comprising

- free mannitol and
- a mannitol ester of bortezomib.

3.1.1 The opponents submitted that claim 1 of the main request did not fulfill the requirements of Article 76(1) EPC and Article 123(2) EPC. It was undisputed by the parties that any conclusion drawn with regard to compliance with Article 76(1) EPC in relation to the parent application as filed (D19) would apply equally with regard to compliance with Article 123(2) EPC in relation to the application as filed. Accordingly, in the following, only compliance with Article 76(1) EPC is assessed with regard to D19.

3.1.2 The opponents emphasised the four "aspects" of the invention disclosed in D19, namely

- a first aspect directed to compounds having formula (1) (paragraphs [0007]-[0015] and [0054] - [0086]);
- a second aspect directed to a composition comprising a compound of formula (2) in the form of a lyophilised powder (paragraphs [0016] - [0025] and [0087] - [0101]);
- a third aspect directed to a method of formulating a boronic acid compound (paragraphs [0026] - [0031] and [0102] - [0133]) and
- a fourth aspect directed to compositions prepared according to the methods of the invention (paragraphs [0032] and [0134] - [0137]).

It is of note that the composition of the second aspect is in the form of a lyophilised powder (paragraph [0099], first sentence).

3.1.3 The opponents in their arguments generally characterised these aspects as referring to separate and distinct embodiments which, for the purpose of determining the content of the parent application as filed, could not be combined. For example, it was argued that the specific D-mannitol ester of bortezomib was disclosed in paragraph [0078] of D19 only in connection with the first aspect. Since said ester was not disclosed in connection with the second aspect which concerned a lyophilised powder and was not linked to the first aspect, there was no disclosure of the D-mannitol ester of bortezomib in combination with a lyophilisation according to second aspect.

3.1.4 The board holds the view that a strict literal support is not what is required by Articles 123(2) or 76(1) EPC. Rather, the subject-matter of the claim in question should be directly and unambiguously derivable from the (parent) application as a whole, as understood by the skilled person.

In this regard the board agrees with the patent proprietor that the four aspects of the invention are interconnected and would be understood as such by the skilled person. Firstly, it is stated in the introductory part of the summary of the invention (D19, paragraph [0006]) that the invention concerns "*... the discovery that lyophilization of an aqueous mixture comprising a boronic acid compound and a compound having at least two hydroxyl groups produces a stable composition that readily releases the boronic acid compound*". Hence, the "second aspect" of lyophilisation applies to the disclosure of the parent application as filed in general rather than only in relation to this second aspect. Further explicit indications that the first and second aspect are interrelated are provided

throughout the description of the parent application as filed. More specifically but not exhaustively:

- in paragraph [0096] it is stated that the preferred values for variables in formula (2) in the second aspect, which concerns a lyophilised powder, are described above for the first aspect;
- in paragraph [0101] it is stated that the "*compounds and compositions according to the first and second aspects of the invention may be prepared by the methods described herein...*". Since the method described in the patent is that according to the third aspect (paragraphs [0102] - [0107]), and includes steps a) and b), step b) being the lyophilisation of the mixture, a link is clearly established between the first and second aspects of the invention, i.e. lyophilisation;
- in paragraph [0113] it is described that the preferred dihydroxy compounds according to the third aspect are those described for the second aspect. Since the method according to the third aspect is also intended to prepare the compounds according to the first aspect (paragraph [0101]), a further indirect link is established between the first and second aspects.

Contrary to the opponents' statement, D19 thus provides basis for the D-mannitol ester of bortezomib in combination with a lyophilisation.

3.1.5 The opponents further argued that contested claim 1 (supra) was worded such that in the first line it was directed to "[a] *lyophilized powder comprising mannitol and a compound of the formula (1) ...*", while in the last two lines thereof, it was stated that "*... the compound of formula (1) is lyophilized ...*". According

to the opponents, claim 1 worded as such amounted to a disclosure of a "two-fold lyophilization", namely that the composition required that the lyophilised powder of line 1 comprise a lyophilised compound of formula (1) according to the final two lines of the claim. Document A39 demonstrated that such a two-fold lyophilisation was technically reasonable. Specifically, A39 disclosed a process for producing a specific drug intended for reconstitution with water for injection, comprising the steps of providing the lyophilised drug substance, dissolving said lyophilised drug substance in mannitol containing water for injection to provide an aqueous mixture, and subsequently lyophilising the aqueous mixture to provide the drug product (A39, page 11, third paragraph). Furthermore, according to the contested decision, paragraph 39, the patent proprietor had conceded that "*[t]he only technically reasonable way of interpreting is that firstly the compound lyophilized and, thereafter, the composition comprising the boronic acid and the mannitol is lyophilized*". Since the scope of contested claim 1 at least included the technically reasonable possibility of a two-fold lyophilisation, and since D19 failed to provide basis for said two-fold lyophilisation, contested claim 1 added subject-matter.

3.1.6 The board does not share the opponents' view and agrees with the patent proprietor that claim 1 cannot be interpreted to include a two-fold lyophilisation as argued by the opponents. Claim 1 refers to a lyophilised powder comprising mannitol and a compound of the formula (1). In a lyophilised powder, each component, i.e. also the compound of formula (1) is necessarily lyophilised. Hence, the text in the penultimate line of contested claim 1 that "*the compound of formula (1) is lyophilized*" must be

understood as redundant to the subject-matter of the claim, rather than to mean that the compound of formula (1) must first be lyophilised and then the composition comprising it must be lyophilised again. It is to be noted that claim 1 is directed to a lyophilised powder *per se*, and thus describes the nature of the powder and not the process for its preparation. Hence the fact that lyophilisation is mentioned twice cannot imply that the claim requires two process steps, each requiring a separate lyophilisation. Furthermore, although A39 may indeed demonstrate that a two-fold lyophilisation is technically reasonable in that it had previously been performed in the preparation of a specific drug substance, A39 is a patent document which, according to established case law, is not part of the common general knowledge of the skilled person. In the interpretation of claim 1 therefore, the skilled person would not be influenced by the disclosure of A39. Even if two-fold lyophilisation were to be considered feasible by the skilled person, in view of what has been set out above, the skilled person would still not have any reason to assume that such two-fold lyophilisation is covered by the specific wording of claim 1.

3.1.7 Concerning the passage in the contested decision according to which the patent proprietor, during oral proceedings before the opposition division, allegedly endorsed the interpretation of claim 1 to include a two-fold lyophilisation, the board is of the following view. A position taken by a professional representative on a technical issue does not necessarily reflect the thinking of the skilled person. It is the latter which is decisive in relation to the interpretation of a claim.

3.1.8 It was furthermore argued by the opponents that in relation to the Markush definition of the compounds of formula (1) provided in claim 1, D19 lacked any basis for the definition of the aryl group in R^1, R^2, R^3 and R^5 as "C_6-C_{14} aryl" without the additional qualification in paragraph [0044] of D19 that said aryl moiety must comprise 1 to 3 aromatic rings. However, as noted by the patent proprietor, since claim 1 limits the nature of the compound of formula (1) to a mannitol ester of bortezomib, the Markush definition of said aryl groups is redundant, and the objection must therefore fail.

3.1.9 The opponents furthermore submitted that the subject-matter of contested claim 1 resulted from a series of selections from within the disclosure of D19, without any pointers to do so. In particular, the skilled person was required to select and combine:

(a) the specific boronic acid compound bortezomib in paragraph [0125] from the compounds listed *inter alia* in paragraphs [0125]-[0133];

(b) mannitol as the dihydroxy compound forming the ester with the boronic acid, chosen from paragraph [0098];

(c) the inclusion, in the form of a lyophilized powder of a "free dihydroxy compound" from paragraph [0099], and

(d) mannitol as the "free dihydroxy compound", despite mannitol (disclosed in paragraph [0098]) not being specifically mentioned in paragraph [0099].

3.1.10 The board is of the view that the selections referred to by the opponents are disclosed in D19 starting from the second aspect.

The second aspect of the invention (D19, paragraphs [0087] to [0101]) discloses a composition comprising a compound of formula (2) in a lyophilised powder.

The compound of formula (2) comprises a dihydroxy compound (Z^3 and Z^4 in formula (2)) which forms an ester with a boronic acid (see in particular paragraphs [0087] and [0097]). It is of note that the preferred values for the variables P, R, A, R^1, R^2, R^3, R^5 and R^6 are as described for the first aspect (paragraph [0096]).

With regard to the specific selections outlined above, the board notes the following.

(a) Selection of the specific boronic acid compound bortezomib

N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid, i.e. bortezomib as required by contested claim 1, is mentioned in the first aspect of the invention (paragraph [0078]) as a preferred boronic acid in a list including specific D-mannitol boronic acids (paragraphs [0078]-[0086]). Furthermore, by virtue of the fact that bortezomib is the only boronic acid featured in the examples (D19, paragraphs [0138] - [0150]), it represents the boronic acid of choice to the skilled person reading D19, i.e. the single most preferred boronic acid compound.

(b) Selection of mannitol as the dihydroxy compound forming the ester with the boronic acid

The dihydroxy compound (represented by Z^3 and Z^4 in formula (2) (relating to the second aspect; paragraph [0087] of the parent application as filed), in a particularly preferred embodiment, is mannitol, most preferably D-mannitol (paragraph [0098]). That D-mannitol is the dihydroxy compound of choice is confirmed by the exclusive use thereof in the examples, to the exclusion of any other dihydroxy compound, as well as claim 32 of D19, directed specifically to the lyophilised compound D-mannitol-*N*-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronate. Consequently, D19 provides basis for the combination in the context of the lyophilised powder of the second aspect of the invention of D-mannitol as the most preferred dihydroxy compound, with bortezomib as the most preferred boronic acid as addressed above.

(c) the inclusion, in the lyophilized powder of a "free dihydroxy compound"

In paragraph [0099] it is disclosed that it is preferred that the composition also comprises the free dihydroxy compound. The examples, all of which disclose the use of excess D-mannitol, and therefore the presence of free dihydroxy compound in the products, serve as an additional pointer towards the inclusion of free dihydroxy compound as a preferred embodiment.

(d) Selection of mannitol as the "free dihydroxy compound"

With regard to the choice of mannitol also as the "free dihydroxy compound" (c.f. line 1 of contested claim 1), the following applies. It is stated in paragraph [0099] of D19 that in some preferred embodiments, the

composition also comprised **the** free dihydroxy compound. It is apparent to the skilled reader that the definite article "the" refers to the specific dihydroxy compounds chosen from the previous paragraph, i.e. "mannitol, most preferably D-mannitol". The preference for D-mannitol is borne out by *inter alia* example 1, according to which D-mannitol is employed both as the dihydroxy compound forming the ester with the bortezomib, and as the free dihydroxy compound. Further indications that the dihydroxy compound is employed both to form the boronic ester and as the free dihydroxy compound are comprised within the description of the parent application as filed. For example, the method according to the third aspect, which can be employed to prepare the compositions of the second aspect (paragraph [0101] of the parent application as filed), comprises the singular "*a* compound having at least two hydroxy groups..." (paragraph [0106]). Additionally, in paragraph [0110] of the parent application as filed, reference is made to the w/w ratio of the dihydroxy compound (singular) to the boronic acid compound, again indicating that even if present in excess (i.e. also as the free dihydroxy compound referred to above), the dihydroxy compound remains the same. Since D-mannitol is the dihydroxy compound of choice in D19 as set out above, it follows that D19 also provides a pointer to the selection of D-mannitol as the "free dihydroxy compound" in contested claim 1 (line 1).

Consequently, in view of the above, the parent application as filed provides a basis for the combination of the most preferred specific boronic acid compound bortezomib with D-mannitol as the most preferred dihydroxy compound, forming the ester with the boronic acid, as well as the most preferred

lyophilized powder that includes D-mannitol as the "free dihydroxy compound". Contrary to the arguments of some of the opponents, this embodiment does not constitute a combination of features of different levels of preference.

3.1.11 However claim 1 is not limited to D-mannitol, but merely "mannitol". It was therefore a matter of dispute whether the parent application as filed provided a basis for "mannitol" in combination with the further features of claim 1.

The patent proprietor argued that although D-mannitol was recited as the most preferred dihydroxy compound in paragraph [0098] of the parent application as filed, paragraph [00098] also stated that "... the dihydroxy compound is a sugar, as described above...". This referred to paragraph [0064] of D19 in relation to the first aspect in which a definition of the term "sugar" was provided, and in which it was stated that "*...the sugar is a reduced sugar, more preferably mannitol or sorbitol...*". Since paragraph [0064] did not require D-mannitol as the preferred sugar, it led the skilled person to the realisation that also "mannitol" was preferred. Furthermore, it was stated in paragraph [0068] of the parent application as filed that although D-mannitol was preferred, the L-configuration may also be used, thus providing the skilled person with the teaching to use the latter. In view of the totality of the teaching of D19 therefore, the skilled person would be directed to the use of mannitol in general. D19 therefore provided a basis for this term in combination with the further features of contested claim 1.

The board does not share this view. As set out in detail above, the various aspects of the invention in

D19 are linked together. Therefore, the fact that a statement in relation to the first aspect (paragraph [0064]) omits a preference for D-mannitol does not detract from the fact that this preference is expressed elsewhere in D19, both in relation to the second aspect and the first aspect (paragraph [0068]) as set out above. Furthermore, the rationale underlying the board's view regarding the basis in D19 for the combination of features (a)-(d) as set out above was that within the disclosure of D19, there was a specific and unambiguous pointer towards the selection of preferred embodiments from potential alternatives, for example, the selection of D-mannitol and bortezomib. Since mannitol in D19 is taught to be a less preferred alternative to D-mannitol, by the same rationale it follows that there is no direct and unambiguous disclosure in D19 of the combination of less preferred "mannitol" with the further preferred features of contested claim 1. Contested claim 1 therefore does not fulfill the requirements of Articles 76(1) or 123(2) EPC.

3.2 It follows that the ground for opposition under Article 100(c) EPC prejudices maintenance of the patent as granted, and the main request is not allowable.

Auxiliary request 1

The sole claim 1 of the auxiliary request 1 differs from claim 1 of the main request in that it is specified that the lyophilised powder comprises "***D-****mannitol*", and the compound of formula 1 is recited as being "***D-****mannitol* ~~*ester of*~~ *N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine* ~~*boronic acid*~~ ***boronate***" (addition and deletion compared to claim 1 of the main request)

4. Admittance

4.1 Auxiliary request 1 was filed by the proprietor with its statement of grounds of appeal.

With the reply to the statement of grounds of appeal, opponent 9 requested that *inter alia* auxiliary request 1 not be admitted into proceedings on the basis of the requirement that the statement of grounds of appeal and the reply shall contain a party's complete case (Article 12(3) RPBA 2020). The proprietor's explanation with respect to auxiliary request 1 involved a mere identification of the amendments and the basis therefor, without explaining their merit in support of inventive step.

4.2 Present auxiliary request 1 is identical to auxiliary request 1 filed before the opposition division and found to lack inventive step in the contested decision. According to the minutes of oral proceedings, neither opponent 9 nor any other opponent requested during oral proceedings that said request not be admitted into the opposition proceedings.

4.3 Article 12(1)(a) RPBA 2020 stipulates that appeal proceedings shall be based on *inter alia* the decision under appeal. Since the contested decision is in part based on the subject-matter of auxiliary request 1, it follows that this request must also be part of the appeal proceedings.

4.4 It is also doubtful whether the board has any discretion at all to exclude requests which were admitted by the opposition division.
Article 12(4) RPBA 2007 refers to the power of the

board to hold inadmissible *inter alia* requests which could have been presented or were not admitted in the first instance proceedings, but is silent concerning requests which were both submitted and admitted.

4.5 Even if it were concluded that the board has the necessary discretion, this would be limited to assessing whether to overturn the decision of the opposition division to admit the requests in question. The board overrules the decision of the first instance department only if it either failed to exercise its discretion in accordance with the right principles, or exercised its discretion in an unreasonable way. However, in the present case there is no evidence that the opposition division did not exercise its discretion correctly, in particular in view of the fact that the admittance of the requests at that stage was not contested.

4.6 The opponents referred to decision decision T 1711/16 (reasons 10.3) to support their request not to admit auxiliary request 1. However, in the case underlying decision T 1711/16, the auxiliary requests in question, although filed for the first time one month before oral proceedings before the opposition division, were not addressed in the contested decision for the reason that the patent was maintained on the basis of a higher ranking request. As set out above, in the present case, the contested decision addressed the relevant request in its reasons and concluded that the requirements of Article 56 EPC were not met. Incidentally, it is self-explanatory why this request overcomes the objection which led to the finding that the claim of the main request added subject-matter, namely that the claim now requires D-mannitol and the corresponding D-mannitol ester. Consequently, no explicit explanation is

required, and the request is sufficiently substantiated. The requirement that the statement of grounds contain the party's complete case is therefore fulfilled in this regard.

4.7 The above opinion was expressed by the board in the communication pursuant to Article 15(1) RPBA, sent in preparation for oral proceedings. At oral proceedings before the board, opponent 9 merely referred to its written submissions.

In view of the foregoing, the board decided to reject the request not to admit auxiliary request 1 into the proceedings.

5. Compliance with Rule 80 EPC

5.1 Opponent 8 submitted that the amendment in the claim defining a mannitol "boronate" rather than a mannitol ester of boronic acid (c.f. claim 1 of the main request) was not occasioned by a ground for opposition and thus did not comply with Rule 80 EPC (statement grounds of appeal, paragraph 57). However, as noted by the proprietor (reply to the grounds of appeal, paragraphs 10-13), the amendment in question was submitted in response to, and thus can be considered to be occasioned by, an objection according to which the wording in the claim as granted did not meet the requirements of Article 76(1) or Article 123(2) EPC.

This opinion was expressed by the board in the communication pursuant to Article 15(1) RPBA, sent in preparation for oral proceedings. At oral proceedings before the board, opponent 8 merely referred to its written submissions.

5.2 It follows that the subject-matter of claim 1 of auxiliary request 1 fulfills the requirements of Rule 80 EPC.

6. Articles 76(1) and 123(2) EPC

Claim 1 of the main request was found to add subject-matter since it recited "mannitol" and the mannitol ester of bortezomib, and not the preferred D-mannitol according to D19, the parent application as filed. Since claim 1 of this request is limited to D-mannitol and the ester thereof with bortezomib, this objection no longer applies. A further objection advanced by some of the opponents concerned the basis for a specific molar ratio. However, similarly to claim 1 of the main request, this feature is not part of claim 1 of auxiliary request 1, and this objection therefore does not apply.

Since the opponents at oral proceedings merely referred the board to their arguments submitted in relation to the main request, the board concludes that the subject-matter of claim 1 of auxiliary request 1 complies with the requirements of Articles 76(1) and 123(2) EPC.

7. Inventive step - Article 100(a) & 56 EPC

During oral proceedings before the board, inventive step was addressed in the context of the main request. In relation to auxiliary request 1, the opponents merely referred the board to their arguments submitted in relation to the main request. Therefore, the same objections applied to auxiliary request 1 as for the main request. These objections are addressed in the following.

According to the patent, the invention relates to stable, pharmaceutically acceptable compositions prepared from boronic acid compounds (paragraph [0001]). According to paragraph [0006], such formulations would be conveniently prepared, would exhibit enhanced stability and longer shelf life as compared to the free boronic acid compound, and would readily liberate the bioactive boronic acid compound when administered.

As set out above, contested claim 1 of this request is directed to a lyophilised powder comprising free D-mannitol and a D-mannitol ester of bortezomib.

7.1 Closest prior art

All parties agree that D5 is a suitable closest prior art disclosure. The board sees no reason to deviate from this view.

7.1.1 D5 is a journal article entitled "Degradation pathways of a peptide boronic acid derivative, 2-Pyz-(CO)-Phe-Leu-$B(OH)_2$". The derivative recited in the title corresponds to bortezomib, the free boronic acid moiety of the mannitol ester recited in claim 1 at issue. The study underlying D5 arose from the observation that "*during an effort to formulate [bortezomib] for parenteral administration, the compound showed erratic stability behaviour and was quite unstable in certain solvents*" (D5, page 758, right hand column, final paragraph). The stability of bortezomib in several solvents was then investigated, and the isolation of degradants A, B, C and D is described (page 758, final line - page 759, first partial paragraph). The aim of D5 is then stated: "*to understand the degradation pathways and possible mechanisms under various*

conditions, [the degradants] were isolated and identified. Some observations on the effect of ascorbic acid and EDTA on the stability of [bortezomib] were also observed" (page 759, left hand column, first full paragraph).

7.1.2 Regarding the latter stability observations, the investigators of D5 first studied the degradation of bortezomib with exposure to hydrogen peroxide and under acidic and basic conditions (headings on page 760), demonstrating that degradation was complete (hydrogen peroxide, figure 2), or significant (acidic or basic conditions, figure 4; basic conditions led to more rapid degradation). Further investigations were carried out on the effect in solution of ascorbic acid and EDTA on the stability of bortezomib (page 762, under heading "Effects of Ascorbic acid and EDTA..."). The rationale behind these further investigations was that, as a result of mechanistic studies also described in D5, the investigators had determined that the major degradation pathway of bortezomib was oxidative in nature, and the product (bortezomib) appeared to be optimally stable under acidic conditions. Thus, ascorbic acid was added to the mixtures (page 764, right hand column, first paragraph). However, contrary to expectations, the presence of ascorbic acid actually accelerated degradation in a solution of bortezomib (in 2% EtOH and 98% normal saline at pH 2.8) at 25°C over a period of 14 days: 21.8% of the drug substance degraded in the presence of ascorbic acid, compared to 5.9% in the absence thereof (table 1; page 764, right hand column). It is then postulated in D5 that the apparent accelerated degradation of bortezomib in the presence of ascorbic acid was due to the production of hydrogen peroxide, the production of which from oxygen was accelerated when both ascorbic acid and transition

metals were present. Metal ions in the mixture could have come from the solvent or from tightly bound metal ions in the starting bortezomib, or may have leached from glass containers (page 764, right hand column, middle).

7.1.3 It was this theory that led the investigators of D5 to test a parenteral solution with EDTA, which was added to the mixture at pH 6.9 (2% EtOH in normal saline), with the intention of chelating the possible contaminant metal ions and to study whether its presence could reduce the oxidation caused by molecular oxygen. In the test however, it was found that the solution comprising EDTA unexpectedly degraded faster than the sample that did not contain EDTA over 8 months of storage (page 764, right hand column, bottom). The result of this test is depicted in figure 5.

In summary, D5 is concerned with investigating and elucidating degradation products produced during formulation efforts to prepare bortezomib for parenteral administration. The degradation products are identified and characterised, and mechanisms for their formation are proposed.

7.2 The closest prior art disclosure in D5

7.2.1 Some of the opponents argued that the closest prior art disclosure in D5 was represented by the solution comprising 2% EtOH in normal saline at pH 6.9, without the addition of EDTA (page 762, right hand column, under heading "Effects of ascorbic acid ..."; figure 5). Other opponents rather stated that the closest prior art was merely the statement in D5 that bortezomib is intended for parenteral administration (page 758, right hand column, second paragraph).

7.2.2 The proprietor on the other hand submitted that in view of the disclosure in D5 that bortezomib free acid was unstable when dissolved in various aqueous solvent mixtures used in parenteral formulations, the skilled person would consider the solid bortezomib drug substance disclosed in D5 (page 759, left hand column, "Experimental section", compound NSC-681239) as the closest embodiment (see paragraph 17 of the proprietor's grounds of appeal and in particular paragraphs 147-153 of the reply to the opponents' grounds of appeal).

7.2.3 The board is of the following view. D5 is not concerned with the development of suitable solutions for parenteral administration, but rather seeks to investigate degradation pathways, identify the causes of degradation, characterise said degradants and elucidate mechanisms explaining said pathways (D5, abstract). The solution comprising 2% EtOH in normal saline at pH 6.9 of figure 5, although displaying a certain stability compared to the same solution comprising EDTA according to the figure, is not intended in D5 to constitute a medicament for parenteral administration, but merely a medium in which the effect of EDTA could be assessed (D5, page 762, right hand column, "Effects of Ascorbic acid and EDTA ...", second paragraph). Therefore, in view of the purpose of D5 to investigate degradation pathways as addressed above, it is not reflective of a real-world scenario to conclude that the skilled person would consider this solution, or any of the other solutions disclosed in D5, as a reasonable starting point for the development of a medicament. Rather, the skilled person would see these solutions solely as fit for their intended purpose: to investigate and elucidate the

degradation pathways of bortezomib as addressed above, and not as solutions suitable for drug administration. This understanding would furthermore be reinforced by the teaching in D5 that "*during an effort to formulate [bortezomib] for parenteral administration, the compound showed erratic stability behavior and was quite unstable in certain solvents*" (D5, page 758, right hand column, second paragraph) - which at least implicitly indicates to the skilled person that attempts to formulate a suitable parenteral solution had failed.

7.2.4 In view of this, the board agrees with the patent proprietor that the starting point for the assessment of inventive step in D5 must be the solid bortezomib drug substance, with the exclusion of any of the disclosed solutions of bortezomib. On the other hand, the board does not share the patent proprietor's view that D5 would teach the skilled person that since the preparation of solutions for parenteral administration had failed, other forms of administration should be investigated with a view to providing a medicament (e.g. in tablet form). Rather, the board broadly agrees with the position set out by opponent 2 (letter dated 22 May 2020, points (26) to (28)) in stating that D5 is silent on recommending a definitive formulation, and that the only concrete statement in D5 is that bortezomib is for parenteral administration as set out above.

For these reasons, the board concluded that the starting point in D5 for the assessment of inventive step is the solid bortezomib drug substance disclosed in D5, to be formulated in a later stage for parenteral administration.

7.3 Distinguishing features

7.4 The solid bortezomib drug substance (hereinafter: solid drug substance") disclosed in D5 contains bortezomib alone in the free acid form, i.e. not in the form of an ester and not in admixture with free mannitol. Furthermore, the solid drug substance in D5 is not lyophilised.

7.5 Although expressed in different ways by the parties, the distinguishing features of contested claim 1 in relation to the solid drug substance of D5 were not a matter of dispute. These are:

- the mannitol ester of bortezomib,
- the presence of free mannitol;
- in the form of a lyophilised powder.

7.6 Effects of the distinguishing features

According to the patent proprietor, the technical effects of the distinguishing features were

(a) improved long-term stability (hereinafter: "solid stability")
(b) improved dissolution behaviour, and
(c) the provision of a stable solution

Each of these alleged effects will be addressed in turn in the following.

7.6.1 Effect (a): improved solid stability

The patent proprietor argued that *inter alia* the evidence in the patent (example 5, paragraphs [0082] and [0084]), A11 and D36 demonstrated an improved solid

stability for the lyophilised powder of contested claim 1 compared to the solid drug substance of D5.

Example 5 of the patent concerns the "stability of formulations" (hereinafter the board will instead employ the term "composition"). In paragraph [0082] it is stated that the solid drug substance was prepared according to US 5,780,454 (D2 in the present proceedings) as a white amorphous powder. It is non-lyophilised and contains bortezomib alone. It thus reflects the starting point within D5, as discussed above. When stored at 2-8°C, the product was not stable for longer than 3-6 months. In contrast, the lyophilised solid product according to claim 1 prepared in example 1 was stored at various temperatures up to 50°C. The solid stability was monitored for up to 18 months (by HPLC) and no loss of drug or presence of degradation products was detected (patent, paragraph [0084]). Therefore the data in the patent demonstrates the effect of improved solid stability over the non-lyophilised solid drug substance.

It was argued by the opponents that the data in paragraphs [0082] and [0084] of the patent could not be compared, as there was no indication that stability testing was done under the same conditions, in particular in terms of the atmosphere under which the samples were tested. In the view of the board however, even though not stated explicitly, it can be assumed, in the absence of any indication to the contrary, that the tests were carried out under the same conditions since solid stability was the purpose of example 5, and the skilled technician would know to use the same conditions in order to provide technically meaningful results.

Further evidence supporting solid stability can be found in document A11 (the summary of product characteristics for the commercial medicament Velcade®). As stated above, Velcade® is a marketed medicinal product composition, and is a lyophilised powder according to claim 1. In A11 it is stated that the lyophilised composition has a shelf life of at least three years (A11, page 30, section 6.3, "Unopened vial").

In D36, various samples were prepared and tested for solid stability (in terms of total degradation products (Area%) from HPLC) at different temperatures either under an atmosphere of nitrogen or air. Sample 1A comprised bortezomib as a dry powder only (i.e. the solid drug substance), while sample 5A comprised a solid lyophilised powder prepared from bortezomib and mannitol in 10-fold excess as described in example 1 of the patent (i.e. according to contested claim 1) (D36, "Sample preparation" and table 1). After 3 months at 50°C under air, sample 1A comprising bortezomib dry powder degraded by 8.96% versus baseline ("initial" reading). Corresponding sample 5A according to claim 1 on the other hand demonstrated 0.68% degradation (D36, table 2). An improvement in solid stability for a lyophilised powder according to claim 1 is therefore also demonstrated in D36 compared to the non-lyophilised solid drug substance alone. This conclusion was also recognised by the authors of D36 (page 4, final paragraph) in which it is stated that extensive degradation was seen for dry bortezomib under air at 50°C for 3 months, and generally that lyophilisation had some protective effect against high temperature storage conditions under air. There is also no reason to doubt that the effect demonstrated for sample 5A

could be achieved for other ratios of mannitol to bortezomib.

In relation to the data in D36 the opponents submitted several counter-arguments.

First, it was argued that the effect of improved solid stability versus the solid drug substance should be ignored since said drug was unformulated and therefore not in a form suitable for administration. This argument must fail however, since as set out above, the solid drug substance disclosed in D5 is the only suitable starting point in D5 for the assessment of inventive step.

It was also argued that although there was an improvement in solid stability at 50°C for 3 months, there was no such improvement at 40°C (D1, sample 1A versus 5A, column entitled "total 40°C, 3m"). Solid stability at 50°C was therefore not a decisive technical effect for formulating a successful medicament. The board notes however that accelerated solid stability testing is commonly carried out at higher temperatures (see for example D35, page 4, final paragraph) to allow conclusions to be drawn with regard to stability at time periods exceeding the length of the tests. The argument that the results at 50°C are not technically relevant can therefore only be seen as an unsubstantiated allegation.

It was also submitted that the results in table 2 of D36 were not demonstrated for samples under nitrogen. However, the stability and degradation studies discussed above were carried out in air, which comprises oxygen. Therefore, these studies reflect the instability of bortezomib to oxygen, which is more

relevant than instability under nitrogen, an inert gas. In any case, the stability under air cannot be ignored, even if no improvement under nitrogen was observed.

Additionally, it was argued that in D36, the relevant comparison was between samples 3A and 5A, since the former comprised lyophilised bortezomib in the absence of mannitol. However, as noted by the patent proprietor, for the purpose of determining the effect of the distinguishing features according to the problem-solution approach, it is a comparison with the closest prior art which is required, and the closest prior art is represented by sample 1A, i.e. the non-lyophilised solid drug substance alone.

Finally, it was argued that the solid stability results depicted in table 3 of D35 were in contradiction with those in D36. Specifically, sample 024P/B of D35, which comprised bortezomib only (i.e. the solid drug substance; see D35, table 1, page 3, final entry) was the most stable of all samples tested in accelerated testing, e.g. at 60°C for 14 days (D35, table 3, sample 024P/B, row at "60°C 14d"). However, in view of the fact that the timescale of the testing in D35 (14 days) is much shorter than that for which degradation was recorded in D36 (3 months), no contradictions can be drawn from a comparison of D35 and D36 with regard to solid stability, i.e. long term stability (see point 7.6 above). The opponents' arguments with regard the evidence in D35 therefore failed to convince the board.

In conclusion, the effect of improved solid stability has been demonstrated.

7.6.2 Effect(b): improved dissolution behaviour

The patent proprietor argued that based on the evidence provided in the patent as well as experimental report D35, the lyophilised powder according to claim 1, compared to the solid drug substance, displayed improved dissolution behaviour when reconstituted.

The board concluded that this effect has not been demonstrated across the scope of contested claim 1, and consequently, cannot be taken into account in the formulation of the objective technical problem. In view of the fact that inventive step was acknowledged (infra), there is no need for the board to provide its reasons in this regard.

7.6.3 Effect (c) the provision of a stable solution

The patent proprietor argued that the lyophilised powder of contested claim 1 provided for a stable solution. An improvement was not alleged - the provision of a stable solution was itself a valid effect, since it had been reported in D5 that bortezomib "*showed erratic stability behaviour and was quite unstable in certain solvents*" (D5, page 758, right hand column). Evidence for a stable solution was provided *inter alia* by the patent and D35.

In the patent, with regard to the reconstituted lyophilised product of example 1 (paragraph [0085]), it is stated that "*the solution showed no sign of degradation when stored at ambient temperatures (23 °C) for 43 hours. No special care was taken to protect the solution from light*".

In experimental report D35, the results presented included data on solution stability 43 hours after the initial reading for each sample tested, including the samples according to claim 1 (table 3, second entry for each respective sample ("43h rec.")). The authors of D35 concluded that the solution stability was good and similar for all samples (page 6, first full paragraph). Although it was also stated that the presence/absence of mannitol does not play any role in said stability, the fact remains that the data in D35 does not speak against the stability of the solutions reconstituted from a lyophilised powder according to contested claim 1.

The opponents argued in particular that solution stability could not be recognised in view of the fact that no comparative data with regard to the stability of the solutions disclosed in D5 had been submitted, in particular the solution disclosed in figure 5 (2% EtOH and 98% normal saline at pH 6.9; upper curve). This argument is however not convincing since, as set out above, the aqueous solutions of D5 do not represent a suitable starting point for the assessment of inventive step, and therefore no comparison is necessary. Furthermore, even if the stability of the solutions disclosed in figure 5 of D5 were to be compared with that of a solution prepared from the lyophilised powder of contested claim 1 as stated by the patent proprietor, the alleged effect is not one of improvement, but merely the provision of stable solutions. As set out above, proof has been provided by the patent proprietor that this problem is solved.

In view of the foregoing, and in particular in the absence of any evidence to the contrary, the effect of providing a stable solution has been demonstrated.

7.7 The objective technical problem

In view of these effects, the objective technical problem underlying the subject-matter of claim 1 vis à vis the disclosure in D5 identified by the board as the starting point in the assessment of inventive step (supra), is as follows:

The provision of a solid form of bortezomib having improved solid stability and which can be formulated into a stable solution.

7.8 Obviousness

7.8.1 The opponents submitted that the solution to this problem would have been obvious to the person skilled in the art. In particular in view of *inter alia* D8, it would have been obvious to lyophilise in order to achieve improved solid stability.

7.8.2 The board is of the following view. First, it is acknowledged that the process of lyophilisation is well known in the preparation of compositions for parenteral administration. According to D8, a book extract concerning freeze-drying (lyophilisation):

"*The particular advantages of* [lyophilisation] *are the biologicals and pharmaceuticals which are relatively unstable in aqueous solution can be processed and filled into dosage containers in the liquid state ...* [t]*hey can be ... stored in the dry state in which there are relatively few stability problems.*

Further advantages are that the products are often more soluble and/or more rapidly soluble, dispersions are

stabilized throughout their shelf life, and products subject to degradation by oxidation have enhanced stability because the process is carried out in a vacuum." (D8, page 1585, paragraph bridging left and right hand columns and right hand column, first full paragraph).

Similarly, D7, a chapter on freeze drying in the "Encyclopedia of pharmaceutical technology" teaches that:

"*In general, a product is freeze dried if the aqueous solution does not have enough stability for marketing, and if the product cannot be crystallised in bulk" (D7, page 275, second paragraph).*

During oral proceedings the opponents were asked to indicate which documents on file pointed to an increase in solid stability by lyophilisation, specifically compared to the solid drug substance, rather than compared to an aqueous solution. Some opponents pointed to D8.

However, as recited above, D8 teaches that lyophilisation is advantageous for pharmaceuticals which are relatively unstable in aqueous solutions, but provides no indication that it could lead to an improvement in solid stability relative to the non-lyophilised solid drug substance alone.

Consequently none of the prior art cited by the opponents points to an improved solid stability compared to the solid drug substance of D5 linked to lyophilisation.

7.8.3 With regard to the inclusion of D-mannitol in the lyophilised powder of claim 1, in particular in molar excess, in order to arrive at the claimed features of a D-mannitol ester of bortezomib and free D-mannitol, the opponents argued that if the skilled person were to have chosen to lyophilise, it would have been an obvious measure to add a bulking agent for bortezomib, more specifically to add D-mannitol, since it was common general knowledge that D-mannitol was the most commonly used bulking agent for lyophilisation. More specifically, the opponents referred to *inter alia* documents D10, D11, D23, D32, A15, A16-A30, and A32-38.

Firstly, as set out above, the skilled person was not prompted by the prior art to lyophilise in the first place in order to achieve improved solid stability compared to the solid drug substance, and would therefore not have contemplated a bulking agent.

Second, even if the skilled person were to have lyophilised, there was no pointer in the prior art to using D-mannitol as the bulking agent in combination with lyophilisation to solve the above-mentioned problem. Specifically, it can be acknowledged by the board on the basis of the above documents, as argued by the opponents, that mannitol is one of the most commonly used bulking agents (or excipients) in lyophilised pharmaceutical products intended for parenteral administration (see e.g. D11, page 931, left hand column, first sentence; D23, page 29, penultimate line; D32, page 182, table). Furthermore, as

demonstrated in expert declaration A15 (supported by A16-A29), many approved lyophilised products for reconstitution comprise mannitol as a bulking agent in excess (A15, table 1, "Mannitol: active molar ratio"). A32 also discloses a list of FDA approved biotechnology products, some of which were lyophilised, of which some ("Leukine", "Prokine" and "Protropin") comprised mannitol in the composition (A32, table 2). A33-A38 are further examples of approved lyophilised products comprising mannitol in excess.

However, as noted by the patent proprietor, and supported by *inter alia* D7, D8, D23, D32 and A32, mannitol was not the only bulking agent that could be employed, or that had previously been employed in lyophilised products approved before the priority date of the contested patent. Specifically, other bulking agents had been used in the state of the art and included *inter alia* glycine, sodium phosphate, potassium phosphate, citric acid, tartaric acid, gelatin, dextrose, dextran, lactose, maltose, glucose, sorbitol, sodium chloride, PVP and sucrose (see in particular D7, page 296, lines 2-3; D8, page 1566, right column, second full paragraph; D23, page 33, first paragraph, lines 4-5 and table 2.2; D32, table on page 182; and A32, table 2, "Humatrope" and "Intron A").

7.8.4 With regard to the formation of a D-mannitol ester of bortezomib, the opponents pointed to the reference to D1 in closest prior art D5 (reference 4), which would have provided the teaching to the skilled person to form an ester of bortezomib with a dihydroxy compound. In particular, D1 taught cyclic boronate esters with a moiety derived from dihydroxy compounds having at least two hydroxyl groups separated by at least two

connecting atoms in a chain or ring (D1, page 7, lines 27-30). Since D-mannitol fell within the definition of the dihydroxy compounds in D1, D1 taught the skilled person to consider it as a suitable choice for making a boronate ester. It was also argued that mannitol was already known to be suitable for forming esters with boronic acids from *inter alia* D13, D14 or D16.

The board notes however that, apart from the fact that the skilled person was not prompted by the prior art to lyophilise in the first place, none of these documents suggest to the skilled person that D-mannitol should be used as a bulking agent for the purpose of producing a lyophilised product. For example, D13, although disclosing complexes of a specific compound, p-boronophenylalanine, with polyols such as mannitol chosen from a list, has nothing to do with the properties or use of mannitol as a bulking agent (D13, page 5, lines 11-14 and page 7, lines 11-12). There is therefore no support for the opponents' arguments that the skilled person would have consulted those documents in order to provide such a product.

7.8.5 The opponents suggested that the skilled person would have employed D-mannitol as a bulking agent essentially since it was the best known bulking agent in the preparation of lyophilised products intended for parenteral administration. Furthermore, the interaction (i.e. reaction) of D-mannitol with bortezomib to form the mannitol ester would not have been of any concern to the skilled person in view of *inter alia* D17, a review article entitled "Carbohydrate boronates". More specifically, with regard to the reconstitution of the lyophilised powder of contested claim 1 in aqueous solution, D17 was common general knowledge and taught that carbohydrate boronates are readily susceptible to

hydrolysis on addition of water (D17, page 50 and 51). In view of the common general knowledge therefore, the skilled person would have expected hydrolysis of the D-mannitol ester of bortezomib upon reconstitution, to release the active bortezomib compound.

Therefore, in the preparation of the product of contested claim 1, the use of D-mannitol was in fact two-fold - it was not only used in excess as a bulking agent, but was also used to form a D-mannitol ester with bortezomib.

7.8.6 The board however agrees with the patent proprietor that the skilled person, if searching for a bulking agent/excipient, would not in the first place have selected such an agent if it were known to react with bortezomib to provide a composition of a drug in which the drug substance is modified, in particular since many other bulking agents were known and used in the art. Rather, the skilled person would recognise that the process of formulating a drug substance into a pharmaceutical composition is not meant to alter the chemical structure of said substance. Therefore, despite mannitol being a common bulking agent, the skilled person would have been dissuaded from employing D-mannitol as the bulking agent of choice.

7.8.7 Some opponents argued that even if the effect of improved solid stability were recognised (effect (a), above), said effect could only be characterised as a so-called "bonus effect", because the skilled person would have lyophilised bortezomib in the presence of D-mannitol to provide the known advantages associated with the lyophilised form, i.e. *inter alia the* avoidance of degradation during long term storage as a liquid.

However, as stated by the patent proprietor during oral proceedings, the assumption that a certain second effect is a bonus effect relative to a certain first effect obtained by the claimed subject matter presupposes that the skilled person trying to obtain the first effect is confronted with a one-way street situation in which the claimed feature, in the present case, lyophilisation in the presence of mannitol as a bulking agent, would be applied as the only possible course of action such that the second effect is automatically obtained. However, the board notes that at the effective filing date of the present patent, the state of the art, in particular closest prior art D5, did not comprise a composition of bortezomib intended for administration to a patient. Therefore, in order to arrive at a lyophilised powder according to claim 1, the skilled person would have been required to carry out the following combination of deductive steps:

- choose to lyophilise
- in the presence of a bulking agent
- said agent being D-mannitol
- in an amount sufficient to a) react with bortezomib to result in a D-mannitol ester thereof, and b) to be present in the lyophilised powder product in addition to the D-mannitol ester,
- while at the same time realising that the D-mannitol ester so prepared would release bortezomib on reconstitution in a manner such as to provide a solution suitable for parenteral administration.

The conclusion that the skilled person would have necessarily carried out the above steps in order to achieve (a stable solution of) bortezomib as a liquid, even if aware of the separate elements of the common general knowledge required to do so, in terms of lyophilisation, the use of a bulking agent, in particular in excess, and the dissociation of boronate esters in aqueous solutions to provide boronic acids, as set out above, can only result from an ex-post facto analysis of the invention and is therefore not convincing. No one-way street situation exists. For this reason, the board concluded that the subject-matter of claim 1 involves an inventive step pursuant to Article 56 EPC.

7.8.8 The relevance of decision T 1348/14 in relation to the parent patent

The opponents in their submissions drew parallels with decision T 1348/14 (D26 in the present proceedings) in respect of the parent patent. The facts of that case are however not directly relevant to the present case, for the following reasons.

In the parent case, the deciding board was faced with a claim directed to the lyophilised mannitol ester of bortezomib *per se*. The board considered the alleged improved rate of dissolution of the bortezomib formulation. Therefore, although the document considered the closest prior art by the deciding board was the same as in the present decision, the objective technical problem formulated by the board was different to that set out above, and the facts were different at least in that the issue of solid stability did not play a role. Furthermore, the conclusion in T 1348/14 was *inter alia* based on the conclusion that the claim in

question did not require an excess of mannitol (*inter alia* reasons, 4.5.5), which is different to the present situation in which a different claim and a different objective technical problem is under consideration, requiring the presence of D-mannitol in addition to the D-mannitol ester of bortezomib. The opponents' argument based on T 1348/14 must thus fail.

7.9 In conclusion, the subject-matter of the sole claim of auxiliary request 1 involves an inventive step pursuant to Article 56 EPC.

8. Sufficiency of disclosure

8.1 Introduction

As set out above, claim 1 of the main request refers to a lyophilised powder comprising the D-mannitol ester of bortezomib and free D-mannitol. This composition is formed according to the patent (see, e.g., paragraph [0010]) by lyophilising a mixture of bortezomib and free D-mannitol.

It is established jurisprudence of the boards of appeal that a successful objection of lack of sufficiency of disclosure presupposes that there are serious doubts, substantiated by verifiable facts. In order to establish insufficiency of disclosure, the burden of proof is upon the opponents to establish, on the balance of probabilities, that a skilled person reading the patent and using common general knowledge, would be unable to carry out the invention.

8.2 The opponents argued that the invention defined in contested claim 1 was not sufficiently disclosed based on the following objections:

(a) the ester prepared in example 1 was not the D-mannitol ester as specified in claim 1, i.e. a monomer, but a specific dimeric ester;

(b) the patent failed to enable the preparation of the cyclic D-mannitol-boronate ester specified in claim 1 in all possible ring sizes;

(c) the patent did not enable the skilled person to prepare a lyophilised powder from a low ratio of D-mannitol to bortezomib or from ratios higher than those exemplified;

(d) the patent was silent on the specific lyophilisation conditions required to prepare a certain degree of esterification in the lyophilised product;

(e) the patent was silent on how the molar ratio of free D-mannitol to D-mannitol ester in the lyophilisate was to be determined;

(f) the use of t-butanol was a requirement in the preparation of a lyophilised powder according to the examples, but was absent in the claim;

(g) boronate esters as claimed were unstable;

(h) the patent was silent concerning the production of a powder resulting from a two-fold lyophilisation.

Each of these objections will be addressed in turn in the following.

8.3 Objection (a): the ester prepared in example 1 was not the D-mannitol ester as specified in claim 1, i.e. a monomer, but a specific dimeric ester.

8.3.1 The opponents (in particular opponent 5) submitted that by following the preparation of the lyophilised powder as demonstrated in example 1 of the patent, a product was obtained which did not correspond to the product recited in claim 1, namely a D-mannitol ester of bortezomib, the reaction product of one molecule of D-mannitol and one molecule of bortezomib (hereinafter in the context of objection (a): "bortezomib mannitol ester"). Rather, according to the analyses of opponent 5, the compound obtained was a larger molecule such as that depicted in the following structure (D42, point 56, figure 3; hereinafter: the "larger molecule"):

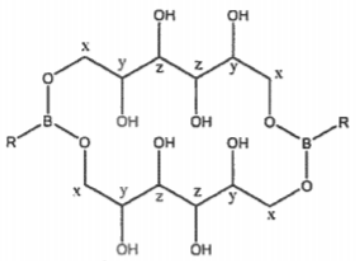


Figure 3

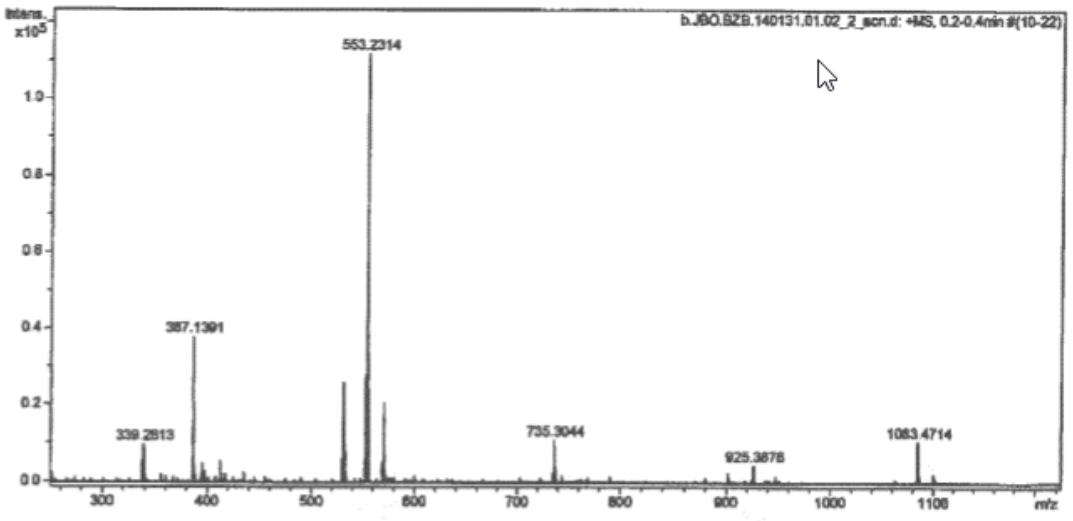
This structure is a reaction product of two molecules of bortezomib $RB(OH)_2$ and two molecules of D-mannitol (the corresponding structure drawn out in full is depicted in D42, figure 9 on page 15).

8.3.2 In the opposed patent, the product obtained in example 1 was analysed by Fast Atom Bombardment mass spectroscopic (FAB-MS) analysis. The resulting spectrum is reported in the patent to show a strong signal at m/z = 531 (paragraph [0074]. This molecular weight

corresponds to that of the claimed product, i.e. a bortezomib D-mannitol ester formed from one bortezomib and one D-mannitol molecule.

8.3.3 Opponent 5 argued that FAB-MS was not a technique suitable for determining the structure of a compound (D42, page 5, I.3, first bullet point), since it led to the fragmentation of the analysed molecules during the measurement. In the present case, therefore, the peak seen at 531 did not correspond to the product obtained in example 1 of the opposed patent, but to a fragment of this product. Rather, Electrospray Ionization Mass spectroscopy (ESI-MS) was the method of choice for the skilled person in the characterisation of organic molecules (D42, point 41; D45, page 7, final paragraph; D46, second page, final paragraph, first sentence). This method used softer conditions and thus did not lead to any fragmentation of molecules.

The ESI-MS spectrum produced by the opponent (figure 3 of D42) is reproduced below



Two peaks in this spectrum were discussed by the parties, namely the most intense peak at 553 and the peak at 1083.

The opponent considered the peak at 1083 to correspond to the sodium cationised product (i.e. ($M + Na^+$); corresponding to a MW of 1060 for M and 23 for sodium) obtained in example 1 of the contested patent, and the peak at 553 to correspond to a fragment of this product, formed during measurement. Contrary thereto, the proprietor considered the peak at 553 to correspond to the sodium cationised product (i.e. ($M + Na^+$)) obtained in example 1 of the contested patent and the peak at 1083 to result from an cluster ion formed from the non-covalent association of two bortezomib D-mannitol ester molecules (recited in contested claim 1) with a single sodium ion (i.e. ($2M + Na^+$); corresponding to two molecules of MW 530 and 23 for sodium). Hereinafter this cluster ion is referred to as a "cluster").

8.3.4 The board's analysis in the following is based upon the following assumptions, to the opponents' advantage:

- FAB-MS as referred to in the patent is not a suitable method for determining the structure of the product of example 1 of the patent; and
- ESI-MS as relied upon by the opponent is the most suitable technique for characterising the product of example 1 of the patent.

The remaining question is therefore whether it has been demonstrated by ESI-MS that the product of example 1 is a larger molecule resulting in a peak at 1083 different from that as defined in contested claim 1, as argued by the opponents, or whether the peak at 1083 represents a

cluster of two molecules according to claim 1, formed during measurement, as argued by the patent proprietor.

8.3.5 The board's position is as follows.

Opponent 5 referred to *inter alia* D45 to explain why ESI-MS was a superior technique to FAB-MS. On page 7 of D45 (final paragraph), the following is stated:

"*ESI-MS is a soft ionisation method and* ***fragmentation of chemical compounds is usually not observed*** *unless dissociation is induced during transport into the mass spectrometer. Moreover, relatively weak noncovalently bonded structures, such as multimers, remain intact.*" (emphasis added)

It is apparent from the opponent's ESI-MS spectrum (D42, figure 3) that the base peak, defined as the peak with the highest intensity, occurs at approximately 553.

The opponent's statement thus lies in apparent contradiction to the analysis of the opponent set out above whereby the product of example 1 was represented by the peak at 1083 in the spectrum in figure 3 of D42, and the most intense base peak at 553 represented a fragment formed during the measurement. If fragmentation of chemical compounds is not usually observed in ESI-MS, why did fragmentation occur to produce a **fragment** characterised by the **base peak** at 553 in the ESI-MS spectrum of D42, figure 3, while the alleged larger molecule at 1083 produced a peak of much weaker intensity? In particular since it can be assumed that the expert of the opponent desired to minimize fragmentation in order to identify a peak corresponding to the product, and not merely a fragment, the ESI-MS

was presumably run under conditions suitable for minimising said fragmentation (see D46, page 2, final paragraph, first sentence).

8.3.6 Further doubt is cast on the opponent's conclusions by D46, a book chapter entitled "*Characterization of Pharmaceutical and Natural Products by Electrospray Ionization Mass Spectrometry*", also submitted by opponent 5 as evidence of the suitability of ESI-MS to the present analysis. The teaching of D46 supports the conclusion set out above in D45. In the introduction of D46, the following is stated:

"*As a nearly general method of ionisation, ESI can be successfully applied to over 90% of organic compounds in pharmaceutical research, and that immediately makes it the method of choice for characterization of drug substances. Additionally, ESI is a soft ionisation technique that yield a simple,* ***easy-to-interpret mass spectrum in which the protonated [M + H]$^+$ or cationized ([M + Na]$^+$, [M + K]$^+$, etc.) molecules typically correspond to the base peak.***" (emphasis added; D46, page 2, first complete paragraph)

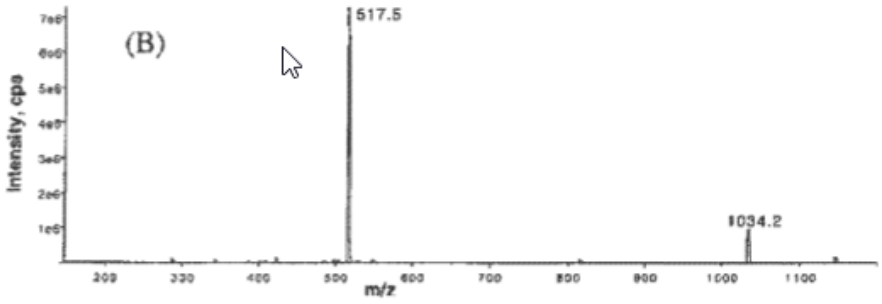
D46 therefore supports the teaching in D45 that fragmentation does not occur, and furthermore teaches that the base peak is typically the peak corresponding to the charged molecule analysed during the measurement, rather than being formed during it.

8.3.7 Furthermore, in a sub-chapter entitled "*Characterization of small molecules. A. Determination of molecular weight*" (D46, page 3), it is stated that the ESI process is quite suitable for providing molecular weight information (first paragraph, lines 2-3). Further in the text, an example of the ESI-MS

analysis of an organic reaction product is described (paragraph bridging page 3 and 4). The relevant passage reads as follows:

"*The corresponding mass spectrum is illustrated in Fig. 1B. The* ***base peak in the spectrum is the protonated molecule [M+H]$^+$ at m/z 517.5,*** *indicating a molecular mass of 516.5 daltons (Da). The spectrum also displays a* ***proton-bound dimer[2M+H]$^+$ of the reaction product at m/z 1034.2,*** *which further confirms the assignment of the molecular weight. The formation of this type of dimeric ions* [sic] *is quite common in ESI-MS; the formation depends on the nature of the compound as well as on the experimental conditions.* ***Proton-bound dimers can be easily distinguished from their covalent analogs*** *on the basis of the observed mass-to charge ratios.*" (emphasis added by the board)

Figure 1B of D46 is reproduced below:



According to this passage, the base peak in the spectrum at 517.5 corresponds to the molecule tested. While the identity of said organic product is not known, its molecular weight is very similar to the bortezomib D-mannitol ester recited in contested claim 1. Furthermore, the spectrum in figure 1B bears a striking resemblance to that of figure 3 and even more so figure 8 of D42, in particular since in view of the

argument of opponent 5 set out during oral proceedings that further peaks in figure 3 of D42 present in addition to those at 553 and 1083 were attributable to the presence in the sample of a large excess of D-mannitol.

8.3.8 D46 also discloses the ESI-MS of a further "pharmaceutical compound" in figure 4. In the text above figure 4, it is stated that:

"*Clearly, the spectrum shows the* ***protonated molecule*** ***$[M+H]^+$*** ***at m/z 503****, along with several other adduct ions, including $[M+Na]^+$ at m/z 525, [****$2M+H]^+$*** ***at m/z 1005, and*** ***$[2M+Na]^+$*** ***at m/z 1027****. The presence of these adduct ions may complicate the mass spectrum; however, they do provide additional information for the correct assignment of the molecular weight." (emphasis added)*

Figure 4 is reproduced below:

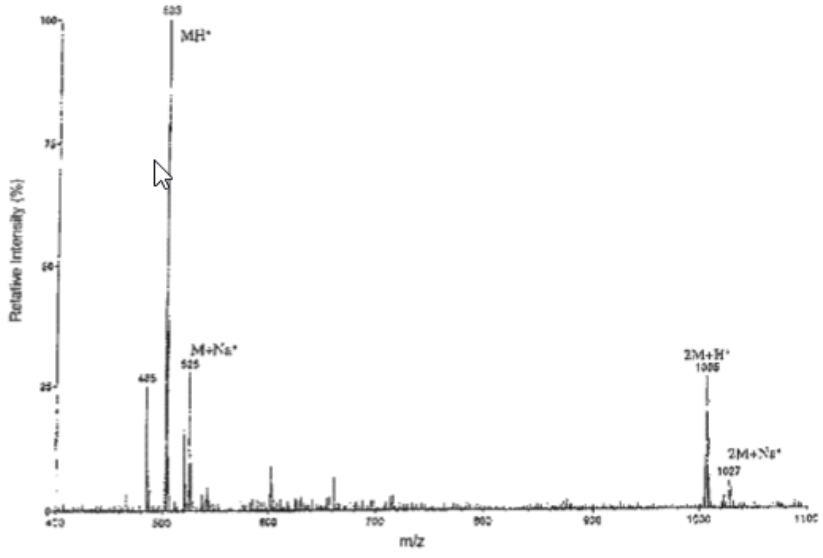


Figure 4 The mass spectrum of an ESI-produced pharmaceutical compound.

Similarly to figure 1B addressed above, the spectrum of figure 4 of D46 also bears a striking resemblance to that of figure 3 of D42. Also for this spectrum, and

consistent with the analysis in D46 of figure 1B as set out above, it is concluded in the above passage that the base peak at 503 corresponds to the molecule tested, while the peak at 1005 corresponds to a cluster ($[2M+H]^+$).

8.3.9 In summary, the information provided by the expert of opponent 5 in document D45, as well as in a book chapter concerning characterisation by ESI-MS (D46) teaches that:

- fragmentation does not normally occur in ESI-MS;
- the base peak typically corresponds to the molecule in question; and
- peaks attributable to a cluster formed during the measurement are common in ESI-MS spectra.

Hence, from the above it can be deduced that in the opponent's ES-MSI spectrum (D42, figure 3), the peak at 553 corresponds to the product as obtained in example 1 and the peak at 1083 results from a cluster, or to use the term employed in D46, "proton-bound dimers".

8.3.10 Opponent 5 argued that further experiments carried out by Dr Fokkens proved that the peak at 1083 in the ESI-MS spectrum of figure 3 of D42 corresponded to a larger molecule $[M+Na]^+$ obtained in example 1 of the patent, and not to a cluster of bortezomib D-mannitol ester molecules as recited in contested claim 1. More specifically ESI-MS analyses were carried out at different sample dilutions (see D53, points 20-21; D64, page 3, first and second paragraphs; A50, points 46 - 54). The opponent argued that if cluster formation would have occurred at higher concentrations, the extent of cluster formation would decrease at lower concentrations (i.e. higher dilutions; see expert declaration D64, page 3, first and second full

paragraphs; D42, page 11, point 53; opponent 5, statement of grounds of appeal, page 10, second paragraph). The opponent concluded from the results of the dilution experiments that irrespective of the dilution of the sample, the ESI-MS spectrum remained unchanged for the peaks at *inter alia* 1083, thus providing proof that the peak at 1083 did not represent a cluster formed during the measurement (D53, point 21).

The board notes firstly, as addressed during oral proceedings, that the specific data and results from the dilution program described by the opponent was not submitted, in particular with any of the four expert declarations D42, D53, D64 or A50. Furthermore, although it is stated in D53 that "***the method of choice*** *for avoiding any doubt on the formation of high molecular weight cluster ion ... in the mixture of product before entering the ion source of the mass spectrometer is to perform a dilution program*", as noted by the patent proprietor, there is no evidence on file to support this allegation. On the contrary, D46 describes adjustment of the "cone voltage" as a means to distinguish (non-covalent) proton-bound dimers from their covalent analogues, and makes no mention of a dilution program. Although opponent 5 in oral proceedings stated that the dilution program was chosen because the cone voltage could not be adjusted in the specific ESI-MS apparatus ("Q2 Brucker daltonic") used by the expert in D42, this does not answer the question of whether such a dilution program conclusively demonstrates the alleged result.

Consequently, in particular in view of the consistent evidence provided by D45 and D46 in relation to the interpretation of ESI-MS spectra as set out above, this

argument fails to convincingly demonstrate that the product of example 1 of the patent is a larger molecule as argued by the opponent.

8.3.11 The opponent additionally submitted that further experiments carried out in D42 proved that the peak at 1083 in the ESI-MS spectrum of figure 3 of D42 corresponded to the product obtained in example 1 of the patent. To confirm this characterisation, the sodium ion peak at 1083 was isolated and subjected to tandem MS/MS mass spectroscopy to demonstrate the fragmentation pattern (D42, paragraph bridging pages 12 and 13; figures 7 and 8). The large intensity peak shown in the spectrum of figure 7 at 553 as the only product formed during the MS/MS experiment indicated the fragmentation of the peak at 1083 in the mass spectrometer. Since the ratio between the peaks at 553 and 1083 was almost the same in figure 7 (and 8) and figure 3, the signal at 553 was a fragmentation product of the peak at 1083.

Although in the following only figure 7 is addressed (for the practical reason that a comparison of ratios as addressed below is easier), the same arguments apply to figure 8 of D42. Figure 7 is reproduced below:

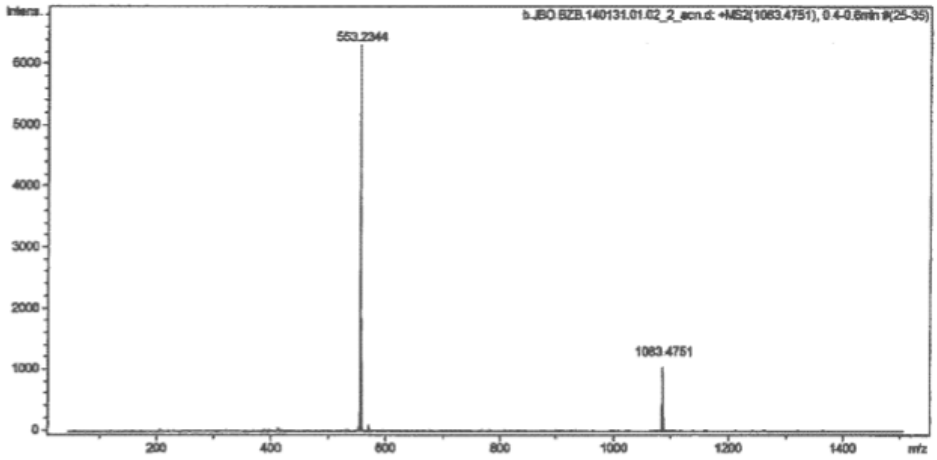


Figure 7: MS/MS of ion 1083 by Electrospray Ionisation mass spectrum of JBO.BZB.140131.01.

The opponent concluded from the spectrum of figures 7 that the large intensity of the ion at 553 as being the only product formed during the MS/MS experiment strongly indicated the fragmentation of the component with 1083 in the second part of the mass spectrometer (D42, page 12, paragraph bridging pages 12 and 13 and figure 7, page 13). The tandem MS/MS is addressed again in A50. Here, it is argued that since the intensity ratio between the peak at 553 and the peak at 1083 in figures 7 and 8 was "substantially the same" as the ratio for the same two peaks in the spectrum of D42, figure 3, the peak at 553 was a fragmentation product of the peak at 1083 and formed during the MS analysis, and was therefore not present ab initio in the product of example 1 of the patent.

The board does not agree with the opponents' arguments. It is indeed clearly apparent as stated by the opponent that a fragmentation took place in view of the fact that the 1083 peak separated in the first MS gives rise to a further peak at 553 in the second MS. However,

this fact in itself does not serve as proof that the 1083-peak corresponds to the $[M+Na]^+$ ion, i.e. the product of example 1 of the patent, as argued by opponent 5. Specifically, if the peak at 1083 were in fact to correspond to a cluster of 2 molecules of the product obtained in example 1 of the patent as argued by the patent proprietor, the fragmentation thereof in the second MS (due to weaker non-covalent interactions) would be more likely to occur than the fragmentation of the corresponding covalently bonded larger molecule postulated by the opponent, at least according to the teachings of D45 and D46 as addressed above. Furthermore, the opponents' argument that the peak at 1083 corresponded to the $[M+Na]^+$ ion because the ratio in intensity between figures 3 and 7 is "substantially the same" is also not convincing. As set out by the board during oral proceedings, the ratio in intensity as read from figure 3 and figure 7 is not substantially the same. A rough calculation from the y-axis of figure 3 provides a ratio of 1.1:0.1, or approximately 11:1 for the ratio of the peak at 553 to the peak at 1083, while the corresponding ratio in figure 7 is approximately 6200:1000 (read from the y-axis), corresponding to approximately 6:1. Consequently, even if it were to be assumed that similar ratios would be conclusive with regard to the opponent's argument, at least based on the available data submitted by the opponent, the respective ratios are not "substantially the same". Consequently, the opponent's argument must fail.

Finally, as argued by the patent proprietor during oral proceedings, the spectrum in figure 7 is not consistent with what would be expected if it indeed depicted fragmentation of an $[M+Na]^+$ ion to provide a fragment at 553, as alleged by the opponent. Specifically, since

fragmentation necessarily involves breaking bonds, one would expect more than a single fragmentation peak at 553, which, following the opponent's argument, would represent a clean split of the larger molecule $[M+Na]^+$ ion into a fragmentation ion representing a single D-mannitol moiety and a single bortezomib moiety. At the very least, one would expect further peaks representing, for example, ions comprising one D-mannitol moiety and two bortezomib moieties, two D-mannitol moieties and one bortezomib moiety, a D-mannitol moiety and a bortezomib moiety. No such peaks are however evident in the spectrum depicted in figure 7. On the contrary, if in fact the spectrum in figure 7 were to depict the fragmentation of a cluster of two molecules of bortezomib D-mannitol ester into its constituent bortezomib D-mannitol ester molecules according to claim 1, then the spectrum obtained in figure 7 would correspond exactly to what would be expected, namely a separation of the cluster into separate molecules. This conclusion would apply all the more so since in line with D45 and D46, if the peak at 1083 were to represent a larger molecule, fragmentation thereof would not be expected.

Consequently, also for this reason, the opponent's argument must fail.

8.4 Objection b): the patent failed to enable the preparation of the cyclic D-mannitol-boronate ester specified in claim 1 in all possible ring sizes.

The patent (paragraphs [0037] - [0043]) describes the structures of *inter alia* preferred D-mannitol boronate ester compounds falling within the scope of contested claim 1. In the structures depicted, the boron esters form 5- or 6-membered rings. It is stated that

structures with larger boronate ester ring sizes are also possible.

In particular opponent 3 (statement of grounds of appeal, pages 21-22) submitted that there was no disclosure in the patent of how to form boronate esters falling under contested claim 1 which differ from each other in the boronate ring size. The skilled person was therefore unable to prepare a boronate ester having a specific ring size, and the subject-matter of contested claim 1 was insufficiently disclosed.

The board notes that contested claim 1 is directed to a lyophilized powder comprising "*D-mannitol* [bortezomib] *boronate*". Since the claim is silent with regard to a required ring size, it follows that as long as a lyophilised powder comprising **any** D-mannitol bortezomib ester can be prepared, the requirements of sufficiency of disclosure are fulfilled. This situation is not comparable to that in which the patent does not enable the preparation of compounds falling with a claim defined by a Markush formula as was the situation in decision T 952/06, cited by the opponent to support its argument, because those compounds are explicitly covered by the claim by way of the generic Markush formulation.

8.5 Objection c): the patent did not enable the preparation of a lyophilised powder from a low ratio of D-mannitol to bortezomib, or from ratios higher than those exemplified.

Contested claim 1 requires the presence of D-mannitol and a D-mannitol ester of bortezomib, without a limitation as to the molar ratio thereof. The opponents argued that a statement in D28 (paragraph 1.11.3;

minutes of oral proceedings in the opposition proceedings for the parent patent, EP 1 355 910 B1) attributed to the patent proprietor, indicated that it was not possible to obtain the mannitol ester of bortezomib using any molar ratio. According to said statement, when trying to lyophilise a 1:1 ratio of bortezomib to mannitol, only a smear is obtained and it is necessary to add a bulking agent to make the invention work.

Although the patent proprietor contested the accuracy of this statement (reply to the statements of grounds of appeal, point 97), this issue, in the view of the board, is inconsequential. In the present case, the patent contains working examples which provide guidance about how to carry out the invention and in particular about which molar ratios to apply. On the basis of this guidance, the skilled person would have been able to select molar ratios that lead to the claimed product. It is to be noted that the burden of proof lies with the opponents, and the opponents have not provided any proof, let alone one that would have raised serious doubts that the skilled person taking into account the opposed patent would not be able to select molar ratios that lead to the claimed product. To the contrary, the opponents' evidence itself demonstrates the successful preparation of lyophilised powders at mannitol to bortezomib ratios, even above and below those disclosed in the examples of the patent (e.g. D35, samples 022P/B and 023P/B; A42, page 1, "Summary").

8.6 Objection d): the patent was silent on the specific lyophilisation conditions required to prepare a certain degree of esterification in the lyophilised product.

It was argued in particular by opponent 1 that the patent failed to disclose the specific conditions such as pH and temperature which affect the degree of boronate ester formation, in particular how to achieve complete esterification. Similar arguments were submitted by opponents 7 and 9.

Firstly, contested claim 1 does not require a specific degree of esterification, but merely requires the presence of D-mannitol and a D-mannitol bortezomib ester. Hence, the opponents argument that the skilled person is not able to select conditions such that a specific esterification degree is achieved is without substance. Since the claim does not require any specific degree of esterification, it cannot be argued that the skilled person cannot carry out the invention on the ground that he does not know how to achieve any particular esterification degree. Irrespective of this, in the same way as for the molar ratio, the examples of the patent (e.g. paragraphs [0072] and [0075]) provide guidance regarding the lyophilisation conditions which should be applied.

8.7 Objection e): the patent was silent on how the molar ratio of free D-mannitol to D-mannitol ester in the lyophilisate was to be determined.

According to opponent 9, the claims would lack sufficient disclosure since the patent did not disclose such a method. This objection was primarily directed against the subject-matter of auxiliary request 3. To the extent that it was also raised against auxiliary request 1, it is moot, since claim 1 does not require a specific ratio, but merely the presence of D-mannitol in addition to the D-mannitol bortezomib ester. Nevertheless, as noted by the patent proprietor, in

view of the analyses carried out by the opponents in D62, D63 and A42, the determination of the mannitol and mannitol-bortezomib ester ratio by NMR would appear to be part of the common general knowledge of the skilled person. Therefore, even if it were relevant to the issue of sufficiency, there is no evidence that the skilled person could not determine the molar ratio in the lyophilised product, if desired.

8.8 Objection f): the use of t-butanol was a requirement in the preparation of a lyophilised powder according to the examples, but was absent in the claim.

It was argued in particular by opponent 7 that since example 1 of the patent disclosed the use of t-butanol as organic solvent, and claim 1 did not refer to any such solvent, the subject-matter defined in claim 1 was insufficiently disclosed.

In this regard the board agrees with the patent proprietor. Claim 1 defines a product, and it is therefore unnecessary to define the method and reagents by which it is prepared. Furthermore, as set out above in relation to objection c), the examples of the patent demonstrate how to prepare the lyophilised powder of claim 1 and thus provide guidance how to obtain the claimed product.

8.9 Objection g): boronate esters as claimed were unstable.

Opponent 1 briefly submitted that since boronic esters were widely known to be unstable, and since the patent provided no teaching as to how to avoid this, claim 1 was insufficiently disclosed.

The board notes that extensive evidence on file demonstrates a certain stability with regard to the mannitol-boronate ester of claim 1. More specifically, said ester was sufficiently stable to undergo NMR analysis (D62, D63 and A42) and ESI-MS (see objection a), above). Furthermore, claim 1 does not require a specific stability. For at least these reasons, the objection must fail.

8.10 Objection h): the patent was silent concerning the production of a powder resulting from a two-fold lyophilisation

Opponent 7 also argued that since claim 1 included a two-fold lyophilisation and the patent was silent in this regard, sufficient disclosure was lacking.

It was established by the board in relation to Article 100(c) EPC (infra) that claim 1 is not to be interpreted such as to include a two-fold lyophilisation. This objection is consequently moot.

8.11 It follows from the foregoing that the opponents' arguments in relation to objections a) - h) fail to convince the board that the invention defined in contested claim 1 is insufficiently disclosed.

8.12 In view of the foregoing, the invention defined in the claim of auxiliary request 1 is disclosed in a manner sufficiently clear and complete for it to be carried out by the person skilled in the art.

9. Since no further objections were outstanding, the subject-matter of auxiliary request 1 is allowable.

Further procedural requests

10. The request to continue the proceedings in writing (opponent 9)

10.1 Before addressing this request, it is necessary to outline the aspects of the case history relevant thereto:

On 8 October 2020, the board issued a communication pursuant to Article 15(1) RPBA, in which the board *inter alia* addressed the question of which disclosure within the closest prior art document D5 would be considered by the skilled person as a suitable starting point for inventive step. The board observed the following:

"10.9. The proprietor on the other hand submitted that in view of the disclosure in D5 that bortezomib free acid was unstable when dissolved in various aqueous solvent mixtures used in parenteral formulations, the skilled person would consider the solid bortezomib drug substance disclosed in D5 (page 759, left hand column, "Materials and instruments") as the closest prior art (see paragraph 17 of the grounds of appeal and in particular paragraphs 147-153 of the reply to the grounds of appeal).

10.10. The board does not share the opinion of the proprietor [...]

10.11. [...] *In view of the stability data presented in figure 5 of D5 therefore, the board considers that the closest prior art disclosure in D5 is represented by the formulation of bortezomib in 2% EtOH/normal saline at pH 6.9, depicted in figure 5."*

At the beginning of the inventive step discussion on day 1 of the oral proceedings, the chair stated that, contrary to what the board had stated in the communication pursuant to Article 15(1) RPBA, the board was now of the preliminary opinion that the solution disclosed in figure 5 of document D5 was not necessarily the closest starting point for the assessment of inventive step. This could also be the solid bortezomib substance or the solid bortezomib substance to be prepared for parental administration (minutes, page 5, third paragraph).

The parties were subsequently heard in a first round on the starting point for the skilled person for the assessment of inventive step, the effects of the distinguishing features and the technical problem solved thereby (minutes, page 5, fourth paragraph).

In this context the patent proprietor argued an improvement as regards the long term solid stability of the bortezomib drug substance, and an improvement in dissolution behaviour, whilst providing for a stable solution (minutes, page 5, third and fourth paragraph).

After deliberation by the board, the chair expressed the view of the board that the starting point for the assessment of inventive step was the solid bortezomib substance disclosed in D5, to be formulated in a later stage for parenteral administration. The chair further stated that the effects of solution stability and improved solid stability had been credibly demonstrated and that the objective technical problem seemed to be the achievement of the two acknowledged effects (minutes, page 6, second paragraph).

The parties were subsequently invited to present their views on the issue of obviousness of the claimed subject-matter. Before giving the floor to the parties the chair noted that should any party wish to add anything with regard to the objective technical problem, it was free to do so (minutes, page 6, third paragraph).

After having confirmed that there were no further comments from the parties regarding inventive step of the main request, the chair at 21:00 hours announced adjournment of the oral proceedings until day 2 and stated that the board would deliberate on the issue of inventive step with regard to the main request (minutes, page 7, first paragraph).

After resumption of oral proceedings on day 2, and after a further break for deliberation, the chair announced the opinion of the board that the main request involved an inventive step (minutes, page 7, second paragraph).

Opponent 9 subsequently asked the board to indicate which objective technical problem the board had considered. Should it have been to provide certain effects with regard to the solid drug substance, proceedings should be continued in writing. After a brief deliberation, the chair stated that in line with what had been stated by the board already before as regards the objective technical problem, the board was of the opinion that the problem at least included the provision of a solid form of bortezomib having improved solid stability and which could be formulated into a stable solution (minutes, page 7, third paragraph).

Opponent 9 then made the request to be discussed in the present section of the decision, namely that the proceedings be continued in writing in order to discuss inventive step starting from a different closest prior art than document D5 (minutes, page 7, fourth paragraph).

10.2 Opponent 9 based its request on the ground that the board in its communication pursuant to Article 15(1) RPBA preliminarily had formulated a different problem on which the opponent had relied in its preparations. The opponent in particular argued that the board's statement regarding the problem on day 2 of the oral proceedings implied that the problem would be completely different to the problem discussed throughout the proceedings so far. Since the opponent had only become aware of the new formulation of the problem during oral proceedings, it did not have the opportunity to present an inventive step objection starting from a different closest prior art, such as D2 or D1.

10.3 The board decided to reject the opponent's request to continue the proceedings in writing, for the following reasons.

The problem defined by the chair during the oral proceedings and relied upon in the present decision is the provision of a solid form of bortezomib having improved solid stability, and which can be formulated into a stable solution (minutes, page 7, third paragraph and point 7.7 of the Reasons, supra). Contrary to opponent 9's assertion, this problem and its reference point, i.e. the solid bortezomib drug substance, was by no means put forward for the first time during the oral proceedings, but was part of e.g.

the proprietor's written reply to the statements of grounds of appeal (point 204):

"In light of the technical effects that are identified supra and demonstrated in the patent and in the additional documents on file, the objective technical problem, ***when starting from the closest prior art embodiment of document D5, i.e. from the solid bortezomib drug substance disclosed therein,*** *can be formulated in the following manner:*

To provide a form of bortezomib which, ***as compared to the solid bortezomib drug substance,*** *has an i****mproved long term stability*** *and an improved dissolution behaviour in normal saline or water for injection,* ***whilst providing for a stable solution on dissolution*** *and whilst allowing the free boronic acid of bortezomib to be readily liberated at the time of use in the clinic" (*emphasis added by the board*)*

Improved long term stability compared to the solid bortezomib drug substance is what is referred to in the present decision as improved "solid stability" (point 7.6 of the Reasons, above; see also page 5, third paragraph of the minutes) and corresponds to the first part of the objective technical problem defined by the chair during the oral proceedings and relied upon in the present decision. The provision of a stable solution on dissolution corresponds to the second part of the problem defined by the chair during the oral proceedings and relied upon in the present decision.

The fact that the proprietor saw more problems to be solved (in particular improved dissolution behaviour in normal saline or water for injection), which were in the end not accepted by the board is of no relevance.

What is decisive is that the problem relied on by the board, including the reference point of a solid bortezomib drug substance, was known to opponent 9 on the basis of the written file.

Consequently, had opponent 9, in view of the technical problem according to the patent proprietor as set out above, considered an alternative prior art document to be more relevant than the closest prior art disclosure D5, such prior art and accompanying objections and arguments should have been filed at the latest in response to the patent proprietor's reply to the statements of grounds of appeal. Indeed, opponent 9 filed a further submission dated 16 August 2021 subsequent to the patent proprietor's reply and entitled "*In response to the communication of the Board .. and the submissions of the patentee*", but chose not to address issues raised in the patent proprietor's reply in relation to inventive step.

In its subsequent communication the board did not agree with the proprietor's starting point within D5, i.e. the solid bortezomib drug substance. However, this cannot justify the dismissal of - and therefore lack of preparation in response to - arguments filed by another party in writing and preliminarily not accepted by the board. In particular in inter-partes proceedings, it is the parties' responsibility to reply to objections raised by the opposing party or parties as it sees fit.

Even if, for the sake of argument, the problem formulated by the board during the oral proceedings and relied upon in the present decision had not been put forward during the written appeal proceedings, opponent 9's request to continue the proceedings in writing to be able to present a new inventive step

attack on the basis of a different closest prior art document could not have been allowed. The board in particular fails to see why the formulation of the allegedly new objective technical problem would have made it necessary for opponent 9 to start from a different closest prior art. A change of the objective technical problem may result in a need to change the subsequent step of the problem and solution approach, i.e. the discussion of whether the skilled person, confronted with this problem, would have arrived at the claimed subject-matter in an obvious manner. The board fails to see however how a change in the problem makes it necessary to start from another closest prior art document. After all, the opponent was completely free, right from the beginning of the opposition proceedings, to start from any closest prior art document it saw fit.

Opponent 9 alleged that the problem defined by the chair on day 1 of the oral proceedings was different from that defined by the chair on day 2 of the oral proceedings. Even though this is of no relevance for the allowability of the opponent's request to continue the proceedings in writing, the board notes the following: the problem defined by the chair on day 1 of oral proceedings before the board was the achievement of solution stability and improved solid stability taking the solid bortezomib drug substance of D5 as the starting and thus reference point (minutes, page 6, second paragraph). The problem defined by the chair on day 2 included at least the provision of a solid form of bortezomib having improved solid stability and which can be formulated into a stable solution (minutes, page 7, third paragraph). The problem defined on day 1 is not, in terms of words, identical to the definition of the problem given on day 2. Despite this difference

in words, the board fails to see however, in terms of technical content, any difference between the two problems.

11. Objection under Rule 106 EPC

11.1 During oral proceedings and subsequent to the board's decision not to grant the request to continue the proceedings in writing as set out above, opponent 9 filed a written objection under Rule 106 EPC in which it made explicit reference to a fundamental violation of Article 113 EPC (see document attached to the minutes of oral proceedings). The objection reads as follows:

"*We herewith raise a procedural objection under Rule 106 EPC due to a violation of our right to be heard according to Article 113 EPC because the Technical Board of Appeal rejected O9's request to continue the proceedings in writing in order to discuss inventive step based on a closest prior art different from D5.*

11.2 The board does not agree that the right to be heard has been violated by not allowing opponent 9's request.

As set out in detail above, there were ample reasons for the board to arrive at the decision to not allow this request. Furthermore, as equally mentioned above, the technical problem formulated by the board during the oral proceedings had already been argued by the patent proprietor with the reply to the statements of grounds of appeal, and relative to the same starting point in the closest prior art document D5 as chosen by the board during oral proceedings, namely the solid bortezomib drug substance. The technical problem as

formulated during oral proceedings consequently does not result in any change in the framework of the discussion on inventive step compared to that proposed by the patent proprietor at the outset of appeal proceedings. The opponent therefore had adequate opportunity to respond to the patent proprietor's arguments in writing. The opponent however decided not to avail of this possibility.

11.3 Consequently, the objection of opponent 9 under Rule 106 EPC was dismissed.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent with the following claims and a description to be adapted thereto:

Claim 1 of auxiliary request 1, filed with the statement of grounds of appeal.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated