

Internal distribution code:

- (A) [-] Publication in OJ
- (B) [-] To Chairmen and Members
- (C) [-] To Chairmen
- (D) [X] No distribution

**Datasheet for the decision
of 23 June 2022**

Case Number: T 2785/17 - 3.3.02

Application Number: 09767050.9

Publication Number: 2318419

IPC: C07F5/02, C07F5/04, C07F5/06,
A61K38/05, A61P35/00,
A61P29/00, C07K5/06, C07K5/078

Language of the proceedings: EN

Title of invention:

BORONATE ESTER COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS
THEREOF

Patent Proprietor:

Millennium Pharmaceuticals, Inc.

Opponents:

Generics (U.K.) Limited
Actavis Group PTC ehf
Teva Pharmaceutical Industries Ltd

Headword:

Relevant legal provisions:

EPC Art. 56, 83, 123(2)
RPBA 2020 Art. 13(2)

Keyword:

Amendments

Inventive step

Sufficiency of disclosure

Amendment after summons

Decisions cited:

Catchword:



Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2785/17 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 23 June 2022

Appellant: Generics (U.K.) Limited
(Opponent 1) Station Close
Potters Bar
Hertfordshire EN6 1TL (GB)

Representative: FRKelly
27 Clyde Road
Dublin D04 F838 (IE)

Respondent: Millennium Pharmaceuticals, Inc.
(Patent Proprietor) 40 Landsdowne Street
Cambridge, MA 02139 (US)

Representative: Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA (GB)

Party as of right: Actavis Group PTC ehf
(Opponent 2) Reykjavíkurvegi 76-78
220 Hafnarfjörður (IS)

Party as of right: Teva Pharmaceutical Industries Ltd
(Opponent 3) 124 Dvora HaNevi'a St.
6944020 Tel Aviv (IL)

Representative: Hamm&Wittkopp Patentanwälte PartmbB
Jungfernstieg 38
20354 Hamburg (DE)

Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
16 October 2017 concerning maintenance of the
European Patent No. 2318419 in amended form.**

Composition of the Board:

Chairman	M. O. Müller
Members:	S. Bertrand
	P. de Heij

Summary of Facts and Submissions

I. The appeal by opponent 1 lies from the interlocutory decision of the opposition division that European patent No. 2 318 419 in amended form according to the main request comprising the set of claims filed on 26 October 2016 met the requirements of the EPC.

II. The following documents are used in the present decision:

D4	WO 96/13266 A1
D5	WO 03/105860 A1
D6	WO 2009/020448 A1
D7	WO 2004/064755 A2
D14	USSN 61/132,244
D15	USSN 61/211,499
D16	US 2002/0188100 A1
D17	US 2005/0282742 A1
D18	WO 02/059130 A1

III. In the impugned decision, the opposition division's conclusions included the following:

- The claims of the main request did not extend beyond the content of the application as filed.
- The invention defined in the claims of the main request was sufficiently disclosed within the meaning of Article 83 EPC.
- The subject-matter of the claims of the main request involved an inventive step in view of D16 as the closest prior art.

- IV. In its statement setting out the grounds of appeal, opponent 1 ("appellant") contested the reasoning of the opposition division.
- V. In its reply to the grounds of appeal, the patent proprietor ("respondent") submitted auxiliary requests 1 to 18.
- VI. The parties were summoned to attend oral proceedings on 23 June 2022 before the board.
- VII. In subsequent letters, opponents 2 and 3, parties to the appeal proceedings as of right within the meaning of Article 107, second sentence, EPC, and the appellant announced that they would not attend oral proceedings.
- VIII. In two further letters, the respondent provided further submissions on the allowability of the claims according to the main request.
- IX. Oral proceedings before the board took place on 23 June 2022 by videoconference in the absence of the appellant and opponents 2 and 3.
- X. The parties' final relevant requests were as follows.
 - The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.
 - The respondent requested that:
 - the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main request, filed during the oral proceedings of 23 June 2022

- auxiliary request 1, submitted as the main request on 26 October 2016, and auxiliary requests 2-19, filed as auxiliary requests 1-18 with the reply to the statement of grounds of appeal, be admitted into the proceedings and that the patent be maintained in amended form on the basis of one of the sets of claims of these auxiliary requests

XI. The appellant's case relevant to the present decision may be summarised as follows.

Main request

- Added subject-matter: claims 1 and 3 to 6 of the main request did not comply with Article 123(2) EPC.
- Novelty: the subject-matter of the claims of the main request was not novel.
- Inventive step:
 - The claims of the main request were not entitled to claim priority from D14. D6 could thus be invoked against inventive step of the subject-matter of claim 1 of the main request.
 - The subject-matter of the claims of the main request did not involve an inventive step in view of D6 or D16 as the closest prior art.
- Sufficiency of disclosure: the invention defined in claim 1 of the main request was not sufficiently disclosed.

XII. The respondent's case relevant to the present decision may be summarised as follows.

Main request

- Added subject-matter:
 - Claim 1 of the main request was based on claims 1, 2, 3 and 14 as filed and paragraph [0141] of the description as filed. In view of examples 1, 1a, 2 to 14, 18, 19, 28 to 45, 50 and 52, the backbone of the formula as described in paragraph [0141] was clearly the most preferred and could therefore be combined with the citrate boronic ester substituent provided by claim 14 as filed and, in any case, the single selection of this backbone was allowable.
 - There was no discrepancy between claim 14 and claim 2 as filed. Even if claim 2 as filed did not refer to any Z^1 or Z^2 rest, the skilled person would understand from the whole application as filed that the Z^1 and Z^2 rests were bound to the boron atom in the compound of formula (II) of claim 2 as filed.
 - Claim 3 was based on claim 16 as filed in an analogous manner as for claim 1.
 - Claims 4, 5 and 6 contained no new subject-matter based on their dependencies on any of claims 1 to 5.
- Novelty: the appellant had not substantiated its novelty objection. The attack of lack of novelty should not be part of the appeal proceedings.

- Inventive step:
 - D6 was prior art under Article 54(3) EPC only. Therefore, it was not comprised in the state of the art pursuant to Article 56 EPC. However, the subject-matter of the claims of the main request involved an inventive step in view of both D6 and D16 as the closest prior art.
 - As regards D16:
 - The compounds of formula (II) according to claim 1 of the main request differed from the boronic ester compounds of D16 in the citric acid rest and the ixazomib backbone, in particular the R^D group being 2,5 dichlorophenyl.
 - At the filing date of the patent, it was plausible that the claimed compounds were proteasome inhibitors. Therefore, the objective technical problem was at least the provision of alternative proteasome inhibitors.
 - There was no teaching available in D16 suggesting to replace the mannitol rest of the boronic ester prodrug disclosed in D16.
 - The alternative was not obvious, and the claimed subject-matter involved an inventive step.
- Sufficiency of disclosure:
 - The technical effect relating to the pharmaceutical activity of the claimed compounds was not incorporated in claim 1 of the main

request, and thus whether the claimed compounds achieved this effect was not to be examined under Article 83 EPC but rather under Article 56 EPC

- The invention defined in claim 1 of the main request was sufficiently disclosed.

Reasons for the Decision

Main request - Claims 1-6 filed on 23 June 2022 during the oral proceedings

Admittance of the main request

1. During the oral proceedings, the patent proprietor submitted a claim set according to the main request.

The claims of the main request are identical to the claims of the previous main request filed on 26 October 2016, except that claim 6 was deleted and claim 7 renumbered with its dependency adapted accordingly. This amendment represents an amendment of the appellant's appeal case made after issue of the summons.

2. In line with Article 13(2) RPBA 2020, which applies to the case at hand in accordance with the transitional provisions set out in Article 25(1) RPBA 2020, any such amendment must, as a rule, not be taken into account unless there are exceptional circumstances justified with cogent reasons by the party concerned.
3. During the oral proceedings, the board observed that claim 6 of the previous main request was not based on the application as filed since claim 14 as filed, by dependency on claim 3 as filed and reference to the

formula of claim 2 as filed, only encompassed one citric acid rest as the moiety formed by Z¹ and Z² together, while claim 6 of the previous main request could encompass more than one citric acid rest, e.g. a cyclic citric acid oligomer or polymer. The board had announced in its communication under Article 15(1) RPBA 2020 that whether claim 6 of the previous main request was based on the application as filed would be discussed during the oral proceedings and claims 2, 3 and 14 as filed were discussed in this communication. The reasoning set out above on these claims of the application as filed was made by the board for the first time during the oral proceedings.

The provision of this reasoning at the oral proceedings therefore represents, within the meaning of Article 13(2) RPBA 2020, exceptional circumstances justifying the late filing of the main request during oral proceedings.

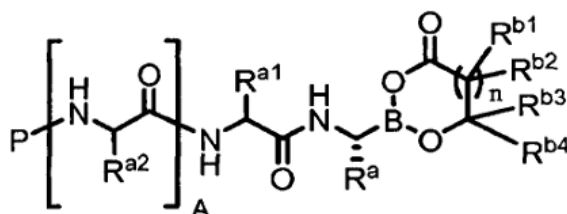
For this reason, the board decided to admit the main request filed during oral proceedings into the appeal proceedings.

Added subject-matter

4. Claim 1

4.1 Claim 1 of the main request reads as follows:

"1. A compound of formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:
A is 0;

R^a is isobutyl;

R^{a1} is hydrogen;

P is R^c-C(O)-;

R^c is -R^D;

-R^D is 2,5-dichlorophenyl;

each of R^{b1} and R^{b2} independently is hydrogen, -CO₂H, -OH or a substituted or unsubstituted aliphatic, aryl, heteroaryl or heterocyclyl group;

each of R^{b3} and R^{b4} independently is hydrogen, -CO₂H, or a substituted or unsubstituted aliphatic, aryl, heteroaryl or heterocyclyl group;

or R^{b2} and R^{b4} are each independently hydrogen, and R^{b1} and R^{b3}, taken together with the carbon atoms to which they are attached, form an unsubstituted or substituted fused 4- to 8-membered non-aromatic ring having 0-3 ring heteroatoms selected from the group consisting of O, N, and S, wherein said ring may be optionally fused to an unsubstituted or substituted 4- to 8-membered non-aromatic ring, or 5- to 6-membered aromatic ring having 0-3 ring heteroatoms selected from the group consisting of O, N, and S;

or R^{b2} and R^{b4} are absent, and R^{b1} and R^{b3}, taken together with the carbon atoms to which they are attached, form an unsubstituted or substituted fused 5- to 6-membered aromatic ring having 0-3 ring heteroatoms selected from the group consisting of O, N, and S, wherein said ring may be optionally fused to an unsubstituted or substituted 4- to 8-membered non-

aromatic ring, or 5- to 6-membered aromatic ring having 0-3 ring heteroatoms selected from the group consisting of O, N, and S; and

n is 0 or 1,

wherein each of R^{b3} and R^{b4} independently is hydrogen, C_{1-6} aliphatic, or $-(CH_2)_p-CO_2H$; and *p* is 0, 1 or 2, and

wherein $-OC(O)(CR^{b1}R^{b2})_nCR^{b3}R^{4b}O-$ is a moiety derived from citric acid." (Emphasis added by the board; underlined text representing additions compared to claim 2 as filed.)

The features "*wherein each of R^{b3} and R^{b4} independently is hydrogen, C_{1-6} aliphatic, or $-(CH_2)_p-CO_2H$; and *p* is 0, 1 or 2"*

 are disclosed in claim 3 as filed. Claim 3 as filed is only dependent on claim 2 as filed.

The feature "*wherein $-OC(O)(CR^{b1}R^{b2})_nCR^{b3}R^{4b}O-$ is a moiety derived from citric acid"* is based on claim 14 as filed reading "The compound of claim 3, wherein Z^1 and Z^2 together form a moiety derived from citric acid". Claim 14 as filed is only dependent on claim 3 as filed.

The features "*A is 0; R^a is isobutyl; R^{a1} is hydrogen; P is $R^C-C(O)-$; R^C is $-R^D$; $-R^D$ is 2,5-dichlorophenyl"* are disclosed in paragraph [0141] of the application as filed ("*In other certain embodiments, A is 0; R^a is isobutyl; R^{a1} is hydrogen; P is $R^C-C(O)-$; R^C is $-R^D$; $-R^D$ is 2,5-dichlorophenyl*").

4.2 The appellant submitted that there was no basis in the application as filed for the combination of claims 2 and 14 with paragraph [0141]. Paragraph [0141] provided just one of many possible combinations of the variables and was not identified as preferred.

The board does not agree. As set out above, there is disclosure in the application as filed to combine the features of claims 2 and 14 as filed since claim 14 is only dependent on claim 3 as filed, which itself is only dependent on claim 2 as filed. Thus, claim 14 as filed encompasses the features of claims 2 and 3 as filed.

In addition, as submitted by the respondent, there is a clear pointer to combine the features of claim 14 as filed with the features disclosed in paragraph [0141] of the application as filed, namely examples 1, 1a, 18, 19, 28 to 45, 50 and 52 of the application as filed, which all refer to compounds in which A, R^a, R^{al}, P, R^c and -R^D are as disclosed in paragraph [0141] of the application as filed while at the same time comprising units of citrate boronic esters according to claim 14 as filed. But even if the selection of the variables in paragraph [0141] were not preferred, this would mean that a single selection from the disclosed combinations of variables had been made. Such a single selection does not constitute added matter.

- 4.3 Furthermore, the appellant submitted that there was an inconsistency between claim 14 as filed, referring to rests Z¹ and Z², and claim 2 as filed, referring to a cyclic rest encompassing the boron atom and not to Z¹ and Z².

The board does not agree. It is true that claim 2 as filed does not refer to any Z¹ or Z² rest, while claim 14 as filed does. However, the skilled person reading claim 14 as filed would understand from the whole application as filed that the Z¹ and Z² rests mentioned are bound to the boron atom in the compound of formula (II) of claim 2 as filed. Hence, even though the two claims use different terminology for the boron unit,

there is no inconsistency between the two claims as argued by the appellant. This conclusion was set out in the communication under Article 15(1) RPBA 2020 and not disputed by the appellant.

5. Claim 2 of the main request is based on claim 15 of the application as filed. Hence claims 1-3 meet the requirements of Article 123(2) EPC.

6. The appellant also objected that claim 3 of the main request could not be based on the combination of claim 16 as filed and paragraph [0141] of the application as filed for the same reason that the variables disclosed in paragraph [0141] were not preferred.

6.1 Claim 3 of the main request refers to compounds of formulae (III), (IIIa), (IV) and (IVa). Claim 3 of the main request is dependent on claim 1 and therefore encompasses the features of claim 1.

The formulae (III), (IIIa), (IV) and (IVa) are disclosed in claim 16 as filed. As set out above, claim 1 of the main request finds a basis in claim 14 as filed in conjunction with claims 3 and 2 and paragraph [0141] of the application as filed.

Claim 16 as filed is only dependent on claim 14 as filed. Therefore, it discloses the combination of the features now in claim 3 of the main request with those of claim 1 of the main request.

7. The appellant also submitted that claims 4 and 5 of the main request, due to their dependency on claim 1 of the main request, and claim 6 of the main request, due to the reference to the compounds of claims 1 to 5 of the main request, did not have any basis in the application as filed.

7.1 Since the board concluded that claim 1 of the main request meets the requirements of Article 123(2) EPC, the appellant's submission on claims 4 and 5 is moot. Hence claims 4 and 5 meet the requirements of Article 123(2) EPC as well. Since, thus, claims 1-5 are based on the application as filed, the appellant's submission regarding claim 6 is moot such that also this claim meets the requirements of Article 123(2).

8. In view of the above, the board concludes that claims 1 to 6 of the main request meet the requirements of Article 123(2) EPC.

Novelty

9. The appellant, in the summary of its grounds of appeal (last page of the statement of grounds of appeal), submitted that the claims of the main request were not novel. In the communication under Article 15(1) RPBA 2020, it was concluded that no substantiation was provided by the appellant for its novelty objection. This conclusion was not disputed by the appellant.

10. Therefore, the board decided that the attack of lack of novelty was not part of the appeal proceedings in accordance with Article 12(3) RPBA 2020.

Inventive step

11. The patent states that the compounds of claim 1 of the main request are useful as proteasome inhibitors (paragraph [0002] of the patent). Proteasomes are protein complexes which degrade intracellular proteins by proteolysis, a chemical reaction that breaks peptide bonds (paragraph [0004] of the patent).

12. The appellant argued that it was not plausible that the claimed compounds showed activity as proteasome

inhibitors and objected to inventive step of the subject-matter of the claims of the main request in view of D6 or D16 as the closest prior art. The objective technical problem solved by the patent was at best the provision of an alternative proteasome inhibitor. The claimed solution was obvious in view of D16 alone or, starting from D6 as closest prior art, in light of D16-D18, D4, D5 and D7.

12.1 Admittance of the appellant's submissions regarding priority and inventive step based on D6 as the closest prior art; priority

D6 is a document having a filing date before the priority dates of the patent and being published after the priority dates and before the filing date of the patent. D14 and D15 are the priority documents of the patent.

The appellant submitted that the claims of the main request were not entitled to claim priority from D14. D6 could thus be invoked against inventive step of the subject-matter of claim 1 of the main request.

The respondent requested not to admit the appellant's submission regarding priority and inventive step based on D6 as the closest prior art.

However, there was no need to decide on the respondent's request not to admit the appellant's submission. This is because the board, in taking D6 and the appellant's inventive-step objection based on this document as the closest prior art into account, concluded (see below), in the respondent's favour, that the claimed subject-matter of the main request involved an inventive step.

13. D16 as the closest prior art

13.1 D16 (claim 1) discloses boronate ester peptide prodrugs which can be readily converted to boronic acid peptides useful for treating cancer. D16 is directed to proteasome inhibitors. The boronate esters of D16 are compounds of formula (1) as disclosed in claim 1 of D16. The compounds comprise a moiety derived from a sugar (see the definition of Z^1 and Z^2 in claim 1 of D16). In the compounds of formula (1), P is a hydrogen atom or an amino-group protecting moiety such as (2-pyrazine)carbonyl or (2-pyrazine)sulfonyl (paragraph [0082] of D16).

13.2 Distinguishing features

The distinguishing feature of claim 1 of the main request over D16 is at least the presence, in the boronate ester prodrugs, of a citric acid rest rather than a sugar group.

13.3 Objective technical problem

There is no comparative data on file comparing the compounds of D16 and the compounds according to claim 1 of the main request. Therefore, as set out in the board's communication under Article 15(1) RPBA 2020, the objective technical problem can be considered the provision of an alternative proteasome inhibitor. This was in fact the point of view taken by the appellant.

It follows from the application as filed and common general knowledge that this problem is indeed solved. The boronic ester compounds of claim 1 of the main request are prodrugs, i.e. after dissolution in an aqueous medium, the boronic ester compounds are hydrolysed in the boronic acid form, which is the active ingredient (paragraph [0223] of the patent and

paragraph [0006] of D16). Furthermore, as reasoned by the opposition division, the patent in suit indicates that the compounds of claim 1 of the main request are potent proteasome inhibitors (paragraph [0112]) and explains how the compounds are to be tested (at least example 20).

For the sake of completeness, it is noted that the appellant also argued that not all compounds covered by claim 1 are proteasome inhibitors. However, as stated in the board's communication under Article 15(1) RPBA 2020, this is in contradiction with the appellant's own formulation of the technical problem being the provision of alternative proteasome inhibitors. Furthermore, for the reasons given above, which were also contained in the board's communication under Article 15(1) RPBA 2020 and not disputed by the appellant after issue of this communication, the compounds covered by claim 1 can be assumed to be proteasome inhibitors.

13.4 Obviousness

The appellant relied on D16 and submitted that the solution proposed by claim 1 of the main request was obvious. The appellant submitted that it would have been obvious to a skilled person to modify the compounds disclosed in D16 to arrive at the compounds according to claim 1 of the main request, the reason being that D16 taught the skilled person that, to stabilise the drugs, they had to prepare a prodrug which hydrolyses rapidly to form the active compound (boronic acid).

The board does not agree. There is no teaching in D16 suggesting to replace the mannitol rest of the boronic ester prodrug disclosed in D16 with a citric acid rest.

Therefore, the claimed subject-matter is a non-obvious alternative.

Hence, the subject-matter of claim 1 and by the same token of claims 2 to 6 of the main request involves an inventive step in view of D16 as the closest prior art.

14. D6 as the closest prior art

14.1 Disclosure of D6

D6 discloses boronic acid and boronic ester compounds useful as proteasome inhibitors (claim 1 and abstract of D6). The boronic acid and boronic ester compounds of claim 1 of D6 are represented by formula (I). In this formula (I), Z^1 and Z^2 can together form a moiety derived from a boronic acid complexing agent, such as a mannitol rest (claim 3 of D6).

14.2 Distinguishing features

The compounds of formula (II) according to claim 1 of the main request differ from the boronic ester compounds of D6 in the citric acid rest. D6 does not disclose such a rest. As set out above, the moiety formed by Z^1 and Z^2 in formula (I) of D6 is preferably a mannitol rest.

14.3 Objective technical problem

Since the distinguishing feature of claim 1 of the main request over D6 is the same as the distinguishing feature of claim 1 of the main request over D16, the same objective technical problem is to be formulated, namely the provision of an alternative proteasome inhibitor.

14.4 Obviousness

The appellant relied on D16-D18, D4, D5 and D7 for attacking the obviousness of the solution proposed by claim 1 of the main request.

With regard to D16 as a secondary document, the inventive step in view of D6 as the closest prior art is to be acknowledged for the same reasons as those given for D16 as the closest prior art (13.4, *supra*).

Secondary documents D4, D5, D7, D17 and D18 disclose boronic ester and acid compounds and their use in pharmaceutical compositions. However, no passages in these documents were identified by the appellant in its statement of grounds of appeal, and none were found by the board, to show any teaching suggesting to replace the mannitol rest of the boronic ester prodrug disclosed in D6 with a citric acid rest. Hence, the claimed subject-matter is a non-obvious alternative.

Furthermore, the board notes that the appellant's argument that the claimed compound was a mere selection out of D6 is not correct. There is, as set out in the board's communication under Article 15(1) RPBA 2020, no generic disclosure in D6 embracing the compounds according to claim 1 of the main request. This was not disputed by the appellant after issue of this communication. Since there is no generic disclosure in D6, the subject-matter of claim 1 of the main request is not a selection out of the disclosure of D6.

In view of the above, the subject-matter of claim 1 and by the same token of claims 2 to 6 of the main request involves an inventive step in view of D6 as the closest prior art.

Sufficiency of disclosure

15. The appellant objected to sufficiency of disclosure of the compounds of claim 1 of the main request. It argued that the subject-matter of the claim was not disclosed in a sufficiently clear and complete manner to be carried out by a person skilled in the art across the whole scope of the claim. The appellant essentially submitted that there was no limitation on the number or type of substituents allowed in claim 1 of the main request and that the compounds encompassed by the claim would not necessarily have any physical or chemical properties in common, i.e. the properties to be used as boronic ester prodrugs to treat cancer. The respondent had not satisfied its burden of providing evidence of how to identify the working embodiments covered by claim 1 of the main request.
- 15.1 The board does not agree. As submitted by the respondent, the technical effect relating to the pharmaceutical activity is not incorporated in the claims of the main request, and thus whether the claimed compounds achieve this effect should not be examined under Article 83 EPC but rather Article 56 EPC. This conclusion was given in the communication pursuant to Article 15(1) RPBA 2020. The appellant did not dispute this conclusion.
- 15.2 Consequently, the board concludes that the invention underlying the subject-matter of claim 1 of the main request is sufficiently disclosed within the meaning of Article 83 EPC.
16. None of the appellant's objections against the claims of the main request is convincing.
17. In view of the above, the board concludes that the main request is allowable.

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 on the basis of claims 1 to 6 of the main request, filed during the oral proceedings of 23 June 2022, and a description possibly to be adapted thereto.

The Registrar:

The Chairman:



N. Maslin

M. O. Müller

Decision electronically authenticated