Internal distribution code:

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

Datasheet for the decision of 4 August 2020

Case Number: T 0967/16 - 3.3.08

Application Number: 07797432.7

Publication Number: 2016198

IPC: C12Q1/68

Language of the proceedings: EN

Title of invention:
METHOD FOR PREDICTING A RISK OF ADVERSE DRUG REACTIONS BY DETERMINATION OF HLA-B 1502

Patent Proprietor:
Academia Sinica
Pharmigene Inc.

Opponent:
ZBM Patents ApS

Headword:
Oxcarbazepine Stevens-Johnson Syndrome/ACADEMIA SINICA PHARMIGENE

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 13(1), 13(2)

Keyword:
Main request (claims as granted) - inventive step (no);
Auxiliary requests 1 to 7 - withdrawn;
Auxiliary request 8 - admission in appeal (no);

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

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 0967/16 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 4 August 2020

Appellant: (Opponent)	ZBM Patents ApS Box 33 Fruebjergvej 3 2100 Copenhagen Ø (DK)
Representative:	Dr Kalhammer, Georg Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstraße 2 80538 München (DE)
Respondent: (Patent Proprietor 1)	Academia Sinica 128, Sec. 2, Acedemia Sinica Road Nan-Kang Taipei 115 Taiwan (CN)
Respondent: (Patent Proprietor 2)	Pharmigene Inc. 4F, No. 17, Ln. 171, Sec. 2, Jiuzong Road Neihu Dist. Taipei City 11494 (TW)
Representative:	Dr Exner, Torsten Michalski Hüttermann & Partner Patentanwälte mbB Speditionstraße 21 40221 Düsseldorf (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 1 March 2016 rejecting the opposition filed against European patent No. 2016198 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	P. Julià
	D. Rogers

Summary of Facts and Submissions

I. European patent no. 2 016 198 is based on the European patent application no. 07 797 432.7, published under the PCT as International patent application WO 2007/134235 (hereinafter "the patent application"). The patent was granted with 9 claims.

II. An opposition was filed on the grounds set forth in Articles 100(a), (b) and (c) EPC. The opposition division considered that none of these grounds of opposition prejudiced the maintenance of the patent as granted and, accordingly, rejected the opposition.

III. The opponent (appellant) lodged an appeal and, in the statement setting out its grounds of appeal, maintained the objections raised at first instance under Article 100(a) in conjunction with Article 56 EPC, and Article 100(b) EPC.

IV. The patent proprietors (respondents) replied thereto and filed auxiliary requests 1 to 7.

V. Both parties requested oral proceedings as an auxiliary measure.

VI. The parties were summoned to oral proceedings and, in a communication pursuant to Article 17 of the Rules of Procedure of the Boards of Appeal (RPBA 2020), were informed of the board's provisional opinion on the issues of the case. In particular, the board stated that the main request (claims as granted) and auxiliary requests 1 to 7 did not fulfil the requirements of Article 56 EPC.

VII. The respondents replied thereto and, in later submissions, filed auxiliary request 8.

VIII. Oral proceedings were held on 4 August 2020. During these proceedings, the respondents withdrew auxiliary requests 1 to 7.

IX. The following documents are cited in this decision:

(3): U.K. Misra *et al.*, Postgrad. Med. J. 2003, Vol. 79, pages 703 and 704;

(4): US 2005/0100926 (publication date: 12 May 2005);

(10): Y-C. Chen et al., J. European. Acad. Dermatol. Venerol. 2008, pages 1 and 2;

(17): "Current Medical Diagnosis & Treatment", 45th edition 2006, ed. L.M. Tierney *et al.*, pages 792-793, 984, 1077 and 1078;

(19): S.C. Schachter, Exp. Opin. Invest. Drugs 1999, Vol. 8(7), pages 1103 to 1112.

X. Claim 1 of the main request (claims as granted) reads as follows:

"1. A method of assessing a risk of a human patient for developing an adverse drug reaction in response to a drug, comprising:
detecting the presence of HLA-B*1502 in a sample obtained from the patient, and
correlating the presence of HLA-B*1502 in the sample with an increased risk for an adverse drug reaction in the patient in response to the drug, wherein the adverse drug reaction is Stevens-Johnson syndrome or

toxic epidermal necrolysis and the drug is oxcarbazepine or licarbazepine."

XI. Claim 1 of auxiliary request 8 reads as claim 1 of the main request, except for the additional feature at the end of the claim:

"1. ... [as claim 1 of the main request] ..., and wherein the presence of HLA-B*1502 in the sample indicates a probability of the patient to develop Stevens-Johnson syndrome or toxic epidermal necrolysis that is at least 10-fold as high as said probability of the general population."

XII. The appellant's submissions, insofar as relevant to the present decision, may be summarised as follows:

Main request
Article 100(a) EPC (Article 56 EPC)

Under the heading "Summary of the invention", the closest prior art document (4) disclosed that the HLA-B*1502 allele was associated with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN; Lyell's syndrome) induced by a variety of drugs. The correlation with HLA-B*1502 was most significant for carbamazepine (CBZ)-induced SJS/TEN, since all patients tested had a HLA-B*1502 allele. The last sentence of paragraph [0087] stated that HLA-B*1502 was used to predict the risk of SJS/TEN, particularly CBZ-induced SJS/TEN. Paragraph [0088] further stated that other aromatic anticonvulsants, including phenytoin and phenobarbital, caused similar adverse drug reactions (ADRs) as CBZ and therefore, HLA-B*1502 could be employed to assess the risk for ADRs to these aromatic anticonvulsants, including metabolites and derivatives

of CBZ, phenytoin and phenobarbital. Thus, the method disclosed in document (4) differed from that of claim 1 only in that the latter concerned the aromatic anticonvulsants oxcarbazepine (OXC) or licarbazepine (LIC).

Starting from document (4), the objective technical problem was the provision of a method of assessing a risk of a human patient having a HLA-B*1502 allele for developing SJS/TEN in response to a drug alternative to those disclosed in document (4). The solution proposed by the claimed subject-matter, namely OXC or LIC, was obvious from document (4) alone, or in combination with any of documents (3) or (19).

According to paragraph [0088] of document (4), aromatic anticonvulsants with a broad range of structures could cause SJS/TEN and the HLA-B*1502 allele could be used for assessing the risk of developing SJS/TEN associated with them. Example 1 of document (4), which was identical to Example 3 of the opposed patent, showed a correlation of 47% for the aromatic anticonvulsant phenytoin with a structure very different from that of CBZ. Thus, it was obvious to a skilled person that for aromatic anticonvulsants structurally closer to CBZ, such as OXC and LIC, this correlation was also present and could also be used for assessing the risk of SJS/TEN associated with these anticonvulsants in HLA-B*1502 carriers.

The similarity of the structures of CBZ and OXC and cross-reactivities between these aromatic anticonvulsants were known in the art, for instance from documents (3) or (19). Example 7 of the opposed patent merely contained technical information, namely the presence of CBZ and OXC cross-reactivity in

relation to some ADRs, that was analogous to the information provided in documents (3) and (19). Starting from document (4), a skilled person would have turned to any of these documents and, knowing that OXC and LIC were aromatic anticonvulsants structurally close to CBZ and having cross-reactivities with CBZ, would have considered OXC and LIC to be obvious alternatives to the aromatic anticonvulsants cited in document (4) for use in the method of assessing a risk of developing SJS/TEN.

As regards the expectation of success, the skilled person was taught in paragraph [0088] of document (4) that this method of assessing a risk was expected to be successful for a large range of aromatic anticonvulsants with structures and cross-reactivities less similar to CBZ than those of OXC or LIC. Therefore, the skilled person had a reasonable expectation of success also for OXC and LIC. The fact that OXC and LIC had a metabolic pathway different from CBZ could not have lowered this expectation because, at the priority date, it was not known which metabolic intermediate caused, and was associated with, the development of SJS/TEN.

Admission of auxiliary request 8 into the proceedings

The respondents had provided no reasons to explain why this late filed auxiliary request could not have been filed at earlier stages of the proceedings. The amendment introduced into this request was a feature taken from the description which raised new issues requiring time for study and allowing the appellant to prepare and submit appropriate arguments such as, for instance, whether there was a basis in the patent application linking the new feature to the specific

HLA-B*1502 allele (Article 123(2) EPC), an assessment of whether the disclosure of Example 7 of the opposed patent was enough to render the new feature and the claimed method plausible (Article 83 EPC). New prior art was also possibly required for addressing the new feature introduced into this request (Article 56 EPC).

XIII. The respondents' submissions, insofar as relevant to the present decision, may be summarised as follows:

Main request
Article 100(a) EPC (Article 56 EPC)

The closest prior art document (4) neither mentioned nor suggested any of the aromatic anticonvulsants OXC or LIC. Therefore, none of them was obvious from this document alone. The first sentence in paragraph [0088] of document (4), namely that other drugs used as anticonvulsants caused similar side effects, suggested that the mode of action, rather than structural similarities, were the basis for the side effects overlap. However, there was no reference to any particular side effect in this paragraph, let alone skin complications or SJS/TEN development and, as could be seen from the prior art, such as from Table 24-3 of document (17), the side effects' overlap was rather limited. Thus, the statement made in this paragraph of document (4) would have been understood by a skilled person as being purely speculative, and the subsequent conclusion based on this speculation with regard to metabolites and derivatives left the scope of the term derivative open. Moreover, none of the drugs speculated about in this paragraph was substituted only at the 10-position, but not at the 11-position, as it was the case for OXC and LIC. There were striking structural and steric differences between CBZ and OXC or LIC

arising from, *inter alia*, the presence (in energetically stable CBZ) or absence (in OXC, LIC) of a double bond between the two benzene moieties. Furthermore, CBZ was known to have physiological properties different from those of OXC and LIC. Thus, no conclusion could be drawn from paragraph [0088] of document (4) that could have provided an incentive to a skilled person for linking OXC or LIC side effects with HLA-B*1502 in any way.

According to the established case law, a suggestion or pointer in the art was first required for assessing whether there was a reasonable expectation of success (see "Case Law of the Boards of Appeal of the EPO", 9th edition 2019, I.D.7.1, 200). There was no suggestion in document (4) as regards OXC or LIC and such a suggestion could not be derived from the common general knowledge of a skilled person as defined in the case law (see "Case Law", *supra*, I.D.8.1, 203). Document (17), a textbook representing the common general knowledge of a skilled person, reported that when CBZ-induced ADRs were diagnosed in a patient, OXC was chosen as a safer alternative because OXC had fewer side effects and a different metabolic pathway than CBZ (page 1078 of document (17)). Indeed, similar effects between CBZ and OXC or LIC were not to be expected. On the contrary, differences between these anticonvulsants in terms of side effects were acknowledged in the art; OXC had fewer side effects and was better tolerated than CBZ (see also document (10)). In view thereof, a skilled person would not have expected CBZ to be physiologically equivalent to OXC or LIC and thus, there was no reason for a skilled person, when starting from document (4), to consider OXZ or LIC.

Document (3) referred to a patient who developed CBZ-induced mild skin rashes and OXC-induced oral mucosa ulceration. Mild skin rashes were clinically, pathologically and immunologically distinct from SJS/TEN, and the incidences of rashes and SJS/TEN were also very different. The pathogenesis of SJS/TEN was unknown, and since it was extremely unlikely that different side effects had the same physiological basis, the cross reactivity between CBZ and OXC known for mild skin rashes could not be ascribed to certain alleged similarities between these anticonvulsants. Thus, the skilled person was aware that any conclusions drawn from document (3) as regards CBZ and OXC in the context of mild skin rashes did not indicate or suggest a potential effect of these anticonvulsants with respect to SJS/TEN. In light of the general common knowledge of a skilled person, document (3) provided no motivation for considering CBZ and OXC to be interchangeable, the less so in a method of predicting side effects because there was no suggestion in document (3) with regard to such a method for any of these two anticonvulsants. It was only following the disclosures found in the opposed patent that it became apparent that the structural, steric and metabolic differences between CBZ and OXC or LIC in the context of HLA-B*1502 and ADRs did not play a decisive role.

Likewise, document (19) stated that CBZ and OXC had very different metabolic pathways. A skilled person would have considered to switch from a CBZ to an OXC treatment because OXC was a safer anticonvulsant with fewer and different side effects from those associated with CBZ. Document (19) referred also to the appearance of a rash in patients treated with OXC but not to the occurence of SJS/TEN, that were known to be associated with CBZ. In view of the important differences between

the structures of CBZ and OXC or LIC as well as their different metabolism and associated side effects, the skilled person would not have considered OXC or LIC to be obvious alternatives to CBZ in the method of assessing a risk for developing SJS/TEN disclosed in document (4).

The method of claim 1 was obvious neither from the closest prior art document (4) alone nor from a combination of document (4) with either document (3) or (19). Even if, for the sake of the argument, a skilled person would have considered OXC or LIC as alternatives to CBZ, in view of the important structural, steric, metabolic, physiological, and pathological (associated side effects) differences between these aromatic anticonvulsants the skilled person did not have a reasonable expectation of success.

Admission of auxiliary request 8 into the proceedings

Auxiliary request 8 was an attempt to overcome the objection raised under Article 56 EPC against the main request (Rule 80 EPC). The feature introduced into claim 1 of this request had a basis in the paragraph bridging pages 5 and 6 of the patent application; this generic disclosure could be combined with the specific SJS/TEN as required in claim 1. The introduction of this new feature did not raise, *prima facie*, any new issues under any other article of the EPC. The filing of this request was the last chance for the respondents to save their patent.

XIV. The appellant (opponent) requested to set aside the decision under appeal, not to admit auxiliary request 8 into the proceedings, and to revoke the patent.

XV. The respondents (patent proprietors) requested, as their main request, to dismiss the appeal or, in the alternative, to admit auxiliary request 8 into the proceedings, to set aside the decision under appeal and to maintain the patent upon the basis of auxiliary request 8.

Reasons for the Decision

Main request (claims as granted)
Article 100(a) EPC (Article 56 EPC)

The closest prior art

1. It is common ground between the parties that document (4), a US patent application filed by four inventors, two of them being also inventors of the opposed patent, represents the closest prior art. This document discloses "a method of predicting the risk of a patient for developing adverse drug reactions, particularly SJS or TEN", based on the finding that "HLA-B*1502 is associated with SJS/TEN that is induced by a variety of drugs". In particular, "[t]he correlation with HLA-B*1502 is most significant for carbamazepine-induced SJS/TEN, wherein all the patients tested have the HLA-B*1502 allele" (cf. paragraphs [0031] and [0039] of document (4)).

2. These statements are based on the results described in Example 1 of document (4) which correspond essentially to those reported in Example 3 of the opposed patent. This example describes a study carried out "[i]n the cohort of 238 individuals with ADRs", wherein "112 cases were diagnosed to have SJS/TEN, and 126 individuals had milder cutaneous adverse drug reactions ... to various medications. Among the

112 SJS/TEN patients, 42 individuals were exposed to carbamazepine (tegretol), 17 had allopurinol, and 53 were on various medications other than carbamazepine or allopurinol" (cf. paragraph [0128] of document (4)). According to paragraph [0129], "[t]he patients were subject to HLA typing as described in Materials and Methods. As shown in Table 1, a DNA variant allele in the HLA-B locus (HLA-B*1502) was associated in patients with drug-induced SJS/TEN, particularly in patients receiving carbamazepine (tegretol)". Indeed, "HLA-B*1502 was detected in 42 of 42 (**100%**) SJS/TEN patients who received carbamazepine. The allele was also found in 17 of 53 (**32%**) SJS/TEN-patients who received other drugs ... Particularly, eight of 17 patients (**47.05%**) who developed SJS/TEN after taking phenytoin also carry the HLA-B*1502 allele" (emphasis by the board) (cf. paragraph [0131] of document (4)).

3. These results are then immediately compared with those reporting the presence of the HLA-B*1502 allele in a carbamazepine-tolerant group (4.1%, 3/73), a phenytoin-tolerant group (0%, 0/32), patients who had milder adverse drug reactions other than SJS (6.3%, 9/142), and the general population (5.3%, 5/94). As further stated in paragraph [0130] of document (4), "[b]y using the tolerant group as control, the odds ratio, sensitivity, specificity, positive predictive value, and negative predictive value for B*1502 associated carbamazepine-induced SJS/TEN, were 1712, 100%, 95.89%, 96.0%, and 100%, respectively". Therefore, it is concluded that "[w]ith such a high predictive value and sensitivity, typing of this HLA-B allele can be used in identifying high-risk patients for drug-induced SJS/TEN, particularly tegretol-induced SJS/TEN" (cf. paragraph [0131] of document (4)).

4. In the board's view, this disclosure informs the skilled person of a correlation between the development of SJS/TEN induced by several aromatic anticonvulsants and the presence of the HLA-B*1502 allele. Whilst for CBZ-induced SJS/TEN the predictive value of this correlation is 100%, i.e. all patients developing SJS/TEN have the HLA-B*1502 allele and patients not (or hardly, 4.1%) developing SJS/TEN do not have the HLA-B*1502 allele, this correlation has a different value for other aromatic anticonvulsants. In particular, for phenytoin, 47.05% of the patients developing SJS/TEN as ADR have the HLA-B*1502 allele and patients not developing SJS/TEN (0%) when treated with phenytoin do not have this allele. Thus, the skilled person is taught that the predictive value of the correlation between HLA-B*1502 and the development of SJS/TEN is different for, and depends on, the specific aromatic anticonvulsant upon which the patient is treated. It can be as high as 100% (CBZ) or as low as 47% (phenytoin), or even lower (32%) (for the reported "other drugs").

5. It is with this information and teaching in mind that a skilled person reads the last sentence in paragraph [0087] of document (4), which states that "HLA-B*1502 is used to predict the risk for SJS/TEN, particularly carbamazepine-induced SJS/TEN", and the disclosure of paragraph [0088] stating that "[o]ther aromatic anticonvulsants, including phenytoin ... and phenobarbital, cause similar adverse drug reactions as carbamazepine. Therefore, HLA-B*1502 can be employed to assess the risk for adverse drug reactions to these other aromatic anticonvulsants as well. The aromatic anticonvulsants for which HLA-B*1502 can be used as a risk factor also include metabolites and **derivatives** of carbamazepine, phenytoin or phenobarbital" (emphasis by

the board). Immediately thereafter, a list of several specific metabolites and derivatives is disclosed, including among others, "carbamazepine-10, 11 epoxide, carbamazepine-10, 11-diol, carbamazepine 2,3-diol, dihydro carbamazepine, carbamazepine catechol and carbamazepine o-quinone" (cf. paragraph [0088] of document (4)).

6. The board does not agree with the respondents that this disclosure is only speculative and considers that, in light of the information and teaching referred to above, a skilled person would have understood that the value of the correlation disclosed in document (4) would be different for each one of these specific metabolites and derivatives, including the metabolites and derivatives of CBZ. As disclosed in document (4) and stated by the board above, these values could be as high as 100% or as low as 47%, or even lower.

The objective technical problem and the proposed solution

7. Starting from document (4), the objective technical problem is the provision of a method of assessing a risk of a human patient carrying a HLA-B*1502 allele for developing SJS/TEN induced by, or associated with, an aromatic anticonvulsant other than those disclosed in document (4). The board does not consider this formulation to require or be based upon hindsight. The inclusion of the HLA-B*1502 allele in this definition is justified because it is indeed the correlation of this allele and the anticonvulsant-induced SJS/TEN which constitutes the core of the disclosure of document (4) and thus, the starting point for the formulation of the technical problem (cf. "Case Law", *supra*, I.D.4.3.1, 190).

8. The claimed subject-matter, wherein the alternative aromatic anticonvulsants are oxcarbazepine (OXC) or licarbazepine (LIC), solves this problem.

Obviousness and expectation of success

9. In the board's view, this solution was obvious to a skilled person. Even though there are important structural and steric differences between CBZ and OXC or LIC, the structures of OXC and LIC are much closer to that of CBZ than the structures of other aromatic anticonvulsants cited in document (4), such as phenytoin or phenobarbital. Moreover, there is prior art on file showing that OXC is a known alternative, if not the first choice, for replacing a CBZ treatment in patients developing CBZ-associated ADRs, in particular SJS/TEN, because OXC is known to be much safer, with fewer and different side effects, than CBZ. However, the presence of OXC-induced SJS/TEN was also known in the art, even though it was much less frequent than the CBZ-induced SJS/TEN (cf. documents (3), (17) and (19)). In view thereof, the board considers that no inventive skill was required to select OXC or LIC as alternative aromatic anticonvulsants in order to solve the above mentioned technical problem.

10. The key question to be answered in the present case is whether there was a reasonable expectation of success (cf. "Case Law", *supra*, I.D.7, 200). According to the established case law, the expectation of success depends on the complexity of the technical problem to be solved. Whilst for very ambitious problems important difficulties might be expected *a priori*, less ambitious problems might normally be associated with a higher expectation of success (cf. "Case Law", *supra*, I.D.7.1,

200; *inter alia*, T 688/14 of 24 July 2019, point 25.2 of the Reasons).

11. In the present case, there is no requirement in the method of claim 1 as regards the predictive value of the correlation between the HLA-B*1502 allele and the adverse drug reaction SJS/TEN developed in response to, or associated with, the OXC or LIC treatment. In other words, the expectations of a skilled person for the value of this correlation could be as high as 100% but also, and more importantly, as low as 47% or even lower than those reported in document (4) for other aromatic anticonvulsants less, or not at all, related to CBZ. In this sense, the formulated technical problem is not very ambitious and thus, the skilled person has a high expectation of success.

12. The reasons put forward by the respondents to support a lowering of the skilled person's expectations of success are not convincing.

12.1 As regards the structural and steric differences between CBZ and OXC or LIC, the disclosure and teachings of document (4), as stated repeatedly above, are not limited to the specific CBZ but considered applicable to aromatic anticonvulsants in general. The structures of both, OXC and LIC, are closer to the structure of CBZ than the structures of other aromatic anticonvulsants cited in document (4). These differences would not have lowered the skilled person's expectations nor led away from OXC or LIC.

12.2 Nor could these expectations be lowered by the differences in the metabolic pathways of CBZ and OXC as reported in document (19). There is no reason for a skilled person to expect that all aromatic

anticonvulsants cited in document (4) share the same metabolic pathway. In view of their different structures and properties, the expectation of a skilled person would rather be the opposite. Moreover, there is neither a reference in document (4) to the actual product(s) or metabolic intermediate(s) responsible for the development of SJS/TEN nor a disclosure of any physiological and/or pathological mechanism(s) explaining such a development. Nor are such a mechanism(s) and metabolic intermediate(s) derivable from any of the documents on file. Indeed, the disclosure and teachings of document (4) do not rely thereupon but merely identify the presence of a correlation which, for some aromatic anticonvulsants, is very high and, for others, is much lower. Thus, in the board's view, differences in their metabolic pathways would not have lowered the skilled person's expectations or led away from OXC or LIC

12.3 In fact, these differences in the structure and properties of the aromatic anticonvulsants cited in document (4) may lie behind the various adverse drug reactions and side effects associated with them as well as with the large variance in the frequency and intensity of their adverse reactions and side effects. However, the correlation disclosed in document (4) concerns only SJS/TEN as adverse drug reaction. Even though at a much lower frequency than CBZ, the development of SJS/TEN as ADR associated with, or induced by, OXC and LIC was known and reported in the art. For patients with OXC or LIC-associated SJS/TEN, the skilled person could reasonably expect, in line with the disclosure and teachings of document (4), a correlation between the development of said OXC or LIC-associated SJS/TEN and the specific HLA-B*1502 allele. All the more so, because the value of this correlation

could also be reasonably expected to lie within the broad range of values reported in document (4) for CBZ and other aromatic anticonvulsants, i.e. as high as 100% or as low as 47% or even lower.

13. Therefore, the requirements of Article 56 EPC are not fulfilled by the main request.

Admission of auxiliary request 8 into the appeal proceedings

14. Auxiliary request 8 was filed by the respondents after notification of the summons to oral proceedings had been issued by the board. Article 13(2) RPBA 2020 states that any amendment to a party's appeal case made after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances which have been justified with cogent reasons by the party concerned. Article 13(1) RPBA 2020 states that any amendment to a party's appeal case after it has filed its grounds of appeal or reply is subject to the party's justification for its amendment and may be admitted only at the board's discretion. The board shall exercise its discretion in view of, *inter alia*, the state of the proceedings, the suitability of the amendment to resolve the issues which were admissibly raised by the other parties in appeal, whether the amendment is detrimental to procedural economy, and whether the amendment, *prima facie*, overcomes the issues raised by the other parties in appeal and does not give rise to new objections.

15. Although the board informed the parties of its provisional opinion by a communication issued on 16 April 2020, the respondents in their submission of 10 July 2020 informed the board that they had neither

received this communication by mail nor been made aware by a register alert of the issuance of the board's opinion. In a submission dated 20 July 2020, the respondents provided substantive arguments in reply to the board's provisional opinion. Auxiliary request 8 was not filed with this submission but only with respondents' submissions dated 2 August 2020, i.e. two days before the scheduled oral proceedings.

16. The amendment introduced into claim 1 of auxiliary request 8 is a feature taken from the description of the patent application. This feature was neither present in any of the dependent claims of the main request nor in any of auxiliary requests 1 to 7 filed with the respondents' reply to the statement of grounds of appeal (later withdrawn at the oral proceedings before the board). According to the respondents, the introduction of this feature is a fair attempt to overcome the objection raised under Article 56 EPC against the main request. The board notes that this objection was already raised, together with objections under Articles 123(2) and 83 EPC (Articles 100(c) and 100(b) EPC, respectively), in the Notice of opposition, i.e. at the very beginning of the opposition proceedings. No reasons have been provided by the respondents why auxiliary request 8 could not have been filed at earlier stages of the proceedings, in particular as early as in the reply to the statement of grounds of appeal or with the respondents' submissions filed on 20 July 2020, i.e. two weeks before the scheduled oral proceedings, instead of (hardly) two days before these proceedings.

17. Whilst the respondents argued that the feature introduced into claim 1 of auxiliary request 8 raises no new issues, the appellant argued quite the opposite.

In particular, the appellant referred to an issue under Article 123(2) EPC because the new feature was taken from a generic disclosure in the description of the patent application mentioning neither the HLA-B*1502 allele nor the specific adverse drug reaction SJS/TEN. The appellant referred also to an ambiguity arising from the introduction of a reference population ("the general population") into claim 1 of auxiliary request 8 (Article 84 EPC). Moreover, auxiliary request 8 required the appellant to carry out a new search for prior art related to the new feature.

18. As regards the argument that auxiliary request 8 is the "last chance" for the respondents to save their patent, the board refers to the case law which clearly states that there is no established "last chance" doctrine or any absolute right for a patent proprietor to such a "last chance" request. Submissions of the parties late filed in appeal proceedings, regardless of whether they are requests, facts, objections or evidence, are always subject to Articles 12 and 13 RPBA 2020 and their admissibility, including that of late filed requests, is always a matter of the board's discretion (cf. "Case Law", *supra*, V.A.4.12.7, 1252; *inter alia*, T 837/07 of 6 October 2010, point 16 of the Reasons, T 1624/16 of 10 July 2019, point 3.3 of the Reasons).

19. Under these circumstances, the board, in the exercise of its discretion (Article 13 RPBA 2020), does not admit auxiliary request 8 into the proceedings.

Conclusion

20. In the absence of a request fulfilling the requirements of the EPC, the patent has to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

I. Aperribay B. Stolz

Decision electronically authenticated