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Datasheet for the decision of 12 March 2020

Case Number: T 1011/17 - 3.3.01

Application Number: 12160638.8

Publication Number: 2478905

IPC: A61K31/4709, A61K31/496, A61P35/02

Language of the proceedings: EN

Title of invention:
Treatment of imatinib resistant leukemia using 4-amino-quinoline-3-carbonitriles

Patent Proprietor:
Wyeth LLC

Opponent:
Generics (UK) Ltd (trading as Mylan)

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

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Case Number: T 1011/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 12 March 2020

Appellant: (Opponent)	Generics (UK) Ltd (trading as Mylan) Albany Gate Darkes Lane Potters Bar EN6 1AG Hertfordshire (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Wyeth LLC 235 East 42nd Street New York, NY 10017-5755 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 21 February 2017 rejecting the opposition filed against European patent No. 2478905 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	P. de Heij

Summary of Facts and Submissions

I. European patent No. 2 478 905 was granted with a set of twelve claims. The independent claims read as follows:

> *1. The compound 4-[(2,4-Dichloro-5-methoxy-phenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile, or a pharmaceutically acceptable salt thereof, for use in the treatment of a BcrAbl positive leukemia, wherein the leukemia is resistant to treatment with imatinib, and wherein the leukemia has a resistance-associated nucleic acid mutation in the bcrabl gene that is 949T>C.*
>
> *7. The use of the compound 4-[(2,4-Dichloro-5-methoxy-phenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a BcrAbl positive leukemia, wherein the leukemia is resistant to treatment with imatinib, and wherein the leukemia has a resistance-associated nucleic acid mutation in the bcrabl gene that is 949T>C.*

The compound mentioned in these claims is also known as **SKI-606** or **bosutinib** (see paragraph [0009] of the patent in suit).

II. The patent was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

III. In the proceedings before the opposition division, the patent proprietor contended that the opposition was inadmissible, and if deemed admissible, it should be rejected as unallowable.

IV. The documents cited in the opposition and appeal proceedings include the following:

D3: Biochimica et Biophysica Acta 1754, 3-13 (2005)

D4: Oncogene 22, 7389-7395 (2003)

D5: Cancer Cell 2, 117-125 (2002)

D8: Cancer Res 66(23), 11314-11322 (2006)

D23: Cancer Res 66(11), 5790-5797 (2006)

V. The decision under appeal is the decision of the opposition division rejecting the opposition, announced on 4 November 2016 and posted on 21 February 2017.

VI. According to the decision under appeal:

(a) the opposition was admissible,

(b) the grounds for opposition under Articles 100(b) and (c) EPC did not prejudice the maintenance of the opposed patent,

(c) the claimed subject-matter was novel (Articles 100(a), 52(1) and 54 EPC),

(d) the claimed subject-matter furthermore involved an inventive step (Articles 100(a), 52(1) and 56 EPC). Starting from the technical teaching of document D8 as the closest prior art, the technical problem to be solved was the identification of a further subgroup of chronic myeloid leukemia patients resistant to therapy with imatinib who would benefit from treatment with bosutinib. In view of the experimental data provided in examples 1 and 24 of the patent in suit, it was credible that the

technical problem was solved by the patient sub-population defined in claim 1. However, D8 would not have pointed the person skilled in the art towards patients carrying the 949T>C/F317L mutation but rather towards other mutants.

VII. The opponent (appellant) filed an appeal against that decision. In the statement setting out the grounds of appeal, the appellant pursued only the issue of inventive step.

VIII. Oral proceedings before the board were held on 12 March 2020.

IX. The appellant's arguments may be summarised as follows:

The appellant agreed with the assessment of the opposition division as to the closest prior art, the distinguishing feature and the objective technical problem to be solved.

Bosutinib had been developed specifically to treat imatinib-resistant *BcrAbl*-positive leukemia. Document D8 related to a systematic investigation into the activity of bosutinib against particular models of imatinib resistance, including point mutations of the *bcrabl* gene. As reported in D8, the only point mutation tested that could not be treated by bosutinib was the T315I mutation, which was, however, known to be uniquely difficult to treat. Thus, D8 provided a general expectation that bosutinib would be active in standard situations in which chronic myeloid leukemia (CML) was resistant to imatinib. 949T>C/F317L was merely a further known imatinib-resistant mutant (as disclosed in document D3) against which bosutinib would have been tested, starting with simple routine screening. This would have been an obvious way for the skilled person to broaden the investigation of D8.

While numerous point mutations associated with imatinib resistance were known, selecting one from a number of equally obvious prevalent alternatives did not require inventive skill. On the basis of the available information, the 949T>C/F317L mutation would not have been believed to be particularly difficult to treat, and without a reason for taking a sceptical attitude, the person skilled in the art would have had a reasonable expectation of success. Even without an expectation of any sort, the person skilled in the art would have conducted routine testing since there existed no technical prejudice with regard to the 949T>C/F317L mutation. Thus, the 949T>C/F317L mutation would have been identified as being susceptible to treatment with bosutinib.

X. The respondent's (patent proprietor's) arguments may be summarised as follows:

The selection of the 949T>C/F317L mutation from the large number of known point mutations conveying resistance to imatinib treatment could only have been made with hindsight of the invention claimed in the patent in suit. At the relevant date, the person skilled in the art would have had no reason to expect success for the specific patient population defined in claims 1 and 7. Rather, there were good reasons to doubt that a successful outcome might be achieved. Moreover, it was known that in cases where genetic mutations were concerned, pre-clinical models were flawed and neither *in vitro* nor *in vivo* models were reliably predictive of actual clinical efficacy. Under these circumstances, the person skilled in the art would not have had sufficient incentive for initiating the clinical studies required to establish the efficacy of bosutinib specifically in the case of a sub-population of patients carrying the 949T>C/F317L

mutation. The testing of humans in a clinical setting could not be considered to be on the same level as routine testing or screening. Accordingly, the person skilled in the art would not have been in a "try-and-see" situation but would have required a reasonable expectation of success to proceed and move to a clinical setting.

XI. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked.

XII. The respondent (patent proprietor) requested that the appeal be dismissed and that the patent be maintained as granted.

Reasons for the Decision

1. Admissibility of the appeal

The appeal complies with Articles 106 to 108 EPC and Rule 99 EPC and is therefore admissible.

2. Inventive step

Patent in suit

2.1 The patent in suit explains in its "Background" section (see paragraphs [0002] and [0003]) that imatinib (or "STI-571") was being used in the treatment of chronic myeloid leukemia (also called chronic myelogenous leukemia). The drug blocks the activity of the tyrosine kinase protein *BcrAbl*, an abnormal protein driving the overproduction of abnormal white blood cells characteristic of leukemia. The aberrantly activated tyrosine kinase *BcrAbl* is causally associated with

chronic myeloid leukemia (CML) and acute lymphocytic leukemia (ALL).

2.2 It was known that many patients eventually developed resistance to imatinib treatment due to mutations in the cancer cells, in particular point mutations in the *bcrabl* gene (see paragraphs [0002] and [0004]).

2.3 The patent in suit seeks to provide a treatment for imatinib-resistant *BcrAbl*-positive leukemia by providing a suitable alternative to imatinib (see paragraphs [0004], [0012] and [0014]).

2.4 This is achieved, according to the patent in suit (see paragraph [0001] and independent claims 1 and 7), by using bosutinib or a salt of it to treat patients suffering from *BcrAbl*-positive leukemia having the 949T>C resistance-associated mutation in the *bcrabl* gene. According to example 1 of the patent in suit (see paragraph [0046]), the amino acid change which corresponds to the nucleic acid mutation 949T>C is F317L (a phenylalanine [F] at amino acid position 317 mutated to leucine [L]).

Starting point in the prior art

2.5 It is common ground that prior-art document D8 represents a suitable starting point for the assessment of inventive step. The board has no reason to use a different starting point.

2.6 Document D8 relates to a study investigating the *in vitro* and *in vivo* activity of SKI-606 (bosutinib) against imatinib-resistant *BcrAbl*-positive neoplastic cells (see D8: title). In particular, four clinically relevant mutants of *BcrAbl* were selected to be assayed with bosutinib, namely T315I, Y253F, E255K and D276G (D8: paragraph bridging pages 11320 and 11321).

The document discloses *in vitro* results showing that bosutinib retained activity in three of the four point mutants tested, the exception being T315I, an imatinib-resistant mutation known to be particularly difficult to treat (see D8: abstract and page 11317, table 1). D8 also reports that the activity against Y253F, E255K and D276G was confirmed *in vivo* in mouse models (see D8: page 11318, Figure 4; page 11321, column 1, lines 13 to 30).

2.7 D8 does not discuss the 949T>C resistance-associated mutation in the *bcrabl* gene (corresponding to F317L). However, the amino acid F317 is marked as a residue of interest in the schematic diagram of interactions of docked bosutinib with the intermediate conformation of the *Abl* protein in Figure 6D of D8.

Objective technical problem and solution

2.8 The parties agreed that:

- the technical feature distinguishing the claimed subject-matter from the disclosure of document D8 was the treatment of the patient sub-population carrying the 949T>C/F317L mutation,

- the objective technical problem to be solved was the identification of a further patient subgroup within the imatinib-resistant *BcrAbl*-positive leukemia patient population that would benefit from treatment with bosutinib.

2.9 The appellant did not dispute that the subject-matter defined in claims 1 and 7 solved this technical problem.

Obviousness of the solution

2.10 Thus, the only issue to be determined is the obviousness of the claimed solution.

2.11 Seeing that the focus of document D8 is on screening for the activity of bosutinib against several CML models of resistance to imatinib, and faced with the technical problem defined above (see point 2.8), the person skilled in the art would have consulted further documents relating to the treatment of imatinib-resistant leukemia with second-generation *BcrAbl* tyrosine kinase inhibitors, such as the review article D3.

2.12 D3 mentions the problem of imatinib resistance and refers to recent progress made in the development of second-generation drugs designed to combat imatinib-resistant mutant forms of *BcrAbl* (see D3: abstract). The drugs mentioned in D3 include nilotinib, dasatinib and bosutinib (see page 9, 2.2.3 (SKI-606), where it is also mentioned that bosutinib had been reported to have shown activity against Y253H, E255V, E255K and F359V mutant *BcrAbl*).

Table 1 on page 6 of D3 presents a comparison of imatinib, nilotinib and dasatinib for their effects on autophosphorylation and proliferation in cells expressing native *BcrAbl* and "some of the most prevalent imatinib-resistant mutant forms of the enzymes identified in patients", which include F317L *BcrAbl*.

2.13 Thus, it was known that the F317L mutation belonged to a group of prevalent imatinib-resistant mutations. The activity of other second-generation *BcrAbl* tyrosine kinase inhibitors had already been screened against this group of mutations, including against the F317L mutation.

2.14 While it was not in dispute among the parties that numerous imatinib-resistant mutations were known from the prior art (D3: page 3, column 2, last full sentence

mentions "over 35 [...] mutant forms"), the board agrees with the appellant that the person skilled in the art seeking to solve the technical problem would have taken a "try-and-see" approach for the routine screening for the activity of bosutinib against further prevalent *BcrAbl* mutations.

2.15 The board is not convinced that the person skilled in the art would have made predictions about the activity of bosutinib against the F317L mutation which would have resulted in an expectation of failure preventing this mutation from even being taken into consideration for preliminary screening.

The skilled person would not have formed an expectation that the F317L mutation was going to be as difficult to treat as the notorious T315I mutation (known to be uniquely difficult) as the F317L mutation differed from the T315I mutation in that it was known to be susceptible to treatment with nilotinib and dasatinib (see D3: table 1) and to confer only moderate resistance to imatinib (see D5: page 121, column 1, first full paragraph).

While, in a study comparing the activity of dasatinib against 15 imatinib-resistant *BcrAbl* mutants, the F317L mutant was found to be less sensitive to the drug than other mutants, this was attributed in the prior art to structural moieties of dasatinib, namely pyrimidine and thiazole rings, which are not present in bosutinib (see D23: page 5795, column 1, lines 1 to 23 and D3: page 4, Figure 1). Hence, it would not have appeared meaningful or conclusive to extrapolate the properties of dasatinib to bosutinib.

Therefore, the person skilled in the art would have had no reason to adopt a particularly sceptical attitude. There existed no technical prejudice or conclusive

theory which would have dissuaded the person skilled in the art from testing bosutinib against the F317L mutation using *in vitro* screening and appropriate animal models.

2.16 The outcome of such tests was, however, uncertain.

2.17 As pointed out moreover by the respondent, especially in cases where genetic mutations are concerned, neither *in vitro* nor *in vivo* laboratory models, albeit informative as a first approach, are reliably predictive of actual clinical efficacy since their relevance to mechanisms of resistance in the leukemic cells of patients being treated is unknown (see document D4, page 7390, column 2, second paragraph). It was not contested by the appellant that clinical relevance is difficult to predict in this field.

2.18 As a consequence, there is no straightforward road which would automatically have led the person skilled in the art from the combined teaching of documents D8 and D3 to the subject-matter of claims 1 and 7.

2.19 Present claims 1 and 7 are, in fact, not concerned with a *BcrAbl* mutant that passed certain routine screening tests but with a (further) *BcrAbl* mutant susceptible to the therapeutic use of bosutinib in the treatment of *BcrAbl*-positive leukemia.

2.20 In view of the considerations set out in point 2.17 above, more extensive studies would have been required to confirm the efficacy of bosutinib in human leukemia patients with imatinib-resistant cancer cells carrying the F317L mutation. In this context, the person skilled in the art would no longer have been in a "try-and-see" situation but would have required a reasonable expectation of success as an incentive for moving to

further much more extensive and larger studies in a clinical setting.

2.21 At the priority date of the patent in suit, it may have been obvious to include the F317L mutation in routine screening tests with bosutinib, but the outcome of such tests was as yet unknown. Based on the information on file, it cannot be confirmed that the outcome of such tests would have provided an incentive for the skilled person to proceed with more extensive clinical testing specifically in the case of the F317L mutation.

2.22 Nor is the information provided originally in document D8 sufficient to give rise to a positive expectation of success.

According to D8, bosutinib was found to be active against three of the four point mutations tested. The three "treatable" mutations (Y253F, E255K and D276G) are said to be representative of two different mechanisms by which mutations can cause resistance to imatinib (D8: paragraph bridging pages 11320 and 11321). There is no teaching in D8 which would have enabled the person skilled in the art to identify an evident similarity or analogy between the F317L mutation and any of Y253F, E255K and D276G. Thus, the data presented in D8 cannot be extrapolated to conclusively predict the efficacy of bosutinib with regard to the F317L mutation. In any case, the tests reported in D8 (see point 2.6 above) did not go beyond *in vitro* screening and *in vivo* animal models and their results, or the statement in D8 that bosutinib was generally found (in such models) to be more active than imatinib, are not necessarily indicative of clinical efficacy.

This assessment is not changed by the fact that document D3 mentions certain further mutants

believed to be affected by bosutinib (D3: page 9, 2.2.3; see point 2.12 above).

According to Figure 6D of D8, the F317 residue of the *Abl* protein was believed to engage in a van der Waals interaction with bosutinib, while the T315I mutation, known to be the most difficult mutant to tackle, was thought to be in a critical position in the binding pocket of the protein and to be involved in direct electrostatic interaction, by hydrogen bonding, with both imatinib and bosutinib. This difference could not, however, have amounted to providing an expectation of clinical success for bosutinib in the case of the F317L mutation.

2.23 For these reasons, the subject-matter of independent claims 1 and 7 and the dependent claims involves an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated