**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 November 2022

**Case Number:** T 0199/20 - 3.3.07

**Application Number:** 09751617.3

**Publication Number:** 2300013

**IPC:** A61K31/505, A61K31/513

**Language of the proceedings:** EN

**Title of invention:**
PHOSPHOROUS DERIVATIVES AS KINASE INHIBITORS

**Patent Proprietor:**
Takeda Pharmaceutical Company Limited

**Opponent:**
Generics (UK) Ltd

**Headword:**
ALK-inhibitors/TAKEDA

**Relevant legal provisions:**
EPC Art. 56

**Keyword:**
Inventive step (yes) - formulation of the objective technical problem

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 0199/20 - 3.3.07**

# D E C I S I O N
# of Technical Board of Appeal 3.3.07
# of 4 November 2022

| | |
|---|---|
| **Appellant:** (Opponent ) | Generics (UK) Ltd<br>Station Close<br>Potters Bar<br>Hertfordshire EN6 1TL (GB) |
| **Representative:** | Elkington and Fife LLP<br>Prospect House<br>8 Pembroke Road<br>Sevenoaks, Kent TN13 1XR (GB) |
| **Respondent:** (Patent Proprietor) | Takeda Pharmaceutical Company Limited<br>1-1, Doshomachi 4-chome<br>Chuo-ku<br>Osaka-shi, Osaka (JP) |
| **Representative:** | Carpmaels & Ransford LLP<br>One Southampton Row<br>London WC1B 5HA (GB) |
| **Decision under appeal:** | **Decision of the Opposition Division of the European Patent Office posted on 17 October 2019 rejecting the opposition filed against European patent No. 2300013 pursuant to Article 101(2) EPC** |

**Composition of the Board:**

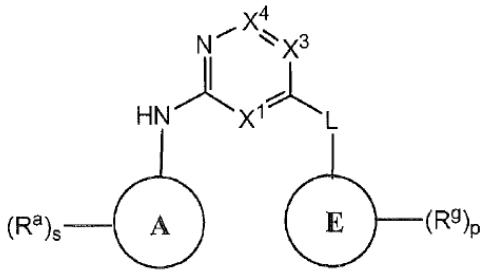
| | |
|---|---|
| **Chairman** | A. Usuelli |
| **Members:** | J. Molina de Alba |
| | L. Bühler |

## Summary of Facts and Submissions

I. The decision under appeal is the opposition division's decision rejecting the opposition filed against European patent No. 2 300 013.

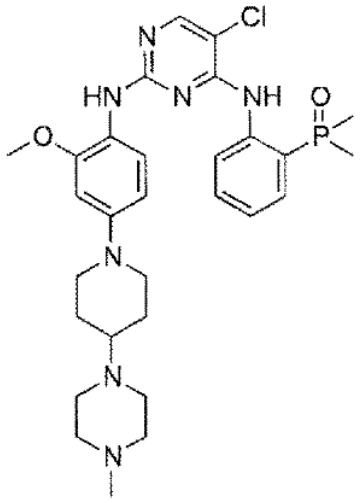
II. The patent had been granted with 24 claims.

Claim 1 as granted was directed to a compound of the following generic formula:




wherein $X^1$ is N; $X^3$ is $CR^d$; $X^4$ is $CR^e$; Ring A and Ring E are each phenyl rings; L is NH; s is 1, 2, or 3; and
p is 1, 2, or 3 (see the patent for the definition of $R^a$, $R^d$, $R^e$ and $R^g$).

Claim 14 as granted was limited to the following compound according to claim 1:



This compound is commonly known as brigatinib.

Claims 15 to 24 as granted were directed to different aspects of brigatinib, namely its pharmaceutically acceptable salts (claim 15), pharmaceutical compositions (claim 17), therapeutic uses (claims 16 and 19), methods of preparation (claims 20 to 22) and synthetic intermediates (claims 23 and 24).

III. The patent was opposed on the grounds of Article 100(a), for lack of inventive step, 100(b) and 100(c) EPC.

In the appealed decision, the opposition division concluded that the patent as granted did not add subject-matter. Furthermore, the claimed subject-matter was sufficiently disclosed and involved an inventive step starting from document D8 (WO 2004/080980 A1) as the closest prior art.

IV. The opponent (appellant) filed an appeal requesting that the opposition division's decision be set aside and that the patent be revoked in its entirety.

V. With its reply to the statement of grounds of appeal, the patent proprietor (respondent) requested that the appeal be dismissed. In addition, it maintained the sets of claims filed as auxiliary requests 1 to 7 with the letter dated 29 October 2018, and filed new sets of claims as auxiliary requests 8 to 11.

VI. The board scheduled oral proceedings, in line with the parties' requests, and gave its preliminary opinion.

VII. The parties made written submissions in response to the board's preliminary opinion.

VIII. Oral proceedings were held before the board on 4 November 2022. At the oral proceedings, the respondent made the claim set filed as auxiliary request 1 with the letter dated 29 October 2018 its main request.

This main request contains ten claims and its subject-matter is identical to that of claims 14 to 24 as granted. Claim 1 is directed to brigatinib or a pharmaceutically acceptable salt thereof.

At the end of the oral proceedings the board announced its decision.

IX. The appellant's arguments relevant to the present decision can be summarised as follows.

Document D8 was the closest prior art. The application as filed did not credibly show that brigatinib was an ALK inhibitor; the test results on page 235 neither included brigatinib nor demonstrated a structure-activity relationship allowing the conclusion that brigatinib was an ALK inhibitor. A structural

modification of the compounds shown to be active would disrupt biological activity.

Therefore, no technical effect could be acknowledged for brigatinib and the objective technical problem had to be defined as the provision of further compounds. Brigatinib was merely an arbitrary compound.

X. The respondent's arguments relevant to the present decision can be summarised as follows.

Starting from D8 as the closest prior art, the subject-matter of the main request differed in the structure of brigatinib. The technical effect provided by this difference was the inhibition of ALK. The effect had been credibly demonstrated by the structure-activity relationship derivable from the ALK inhibitors disclosed on page 235 of the application as filed.

Therefore, the objective technical problem was the provision of alternative kinase inhibitors, in particular ALK inhibitors, for the treatment of cancer. The appellant had not disputed that brigatinib was a non-obvious solution to this problem.

XI. The parties' final requests were the following:

- 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 patent be maintained in amended form on the basis of the claims of the main request, filed as auxiliary request 1 with the letter dated 29 October 2018.

Alternatively, the respondent requested that the patent be maintained either as granted or as amended according to the claims of one of auxiliary requests 2 to 7, filed with the letter dated 29 October 2018, and auxiliary requests 8 to 11, filed with the reply to the statement of grounds of appeal.

## Reasons for the Decision

1. The appeal is admissible. It meets the requirements of Articles 106 to 108 and Rule 99(2) EPC.

2. Claim 1 of the main request - inventive step

2.1 It was common ground between the parties that D8 is a suitable starting point for the assessment of inventive step.

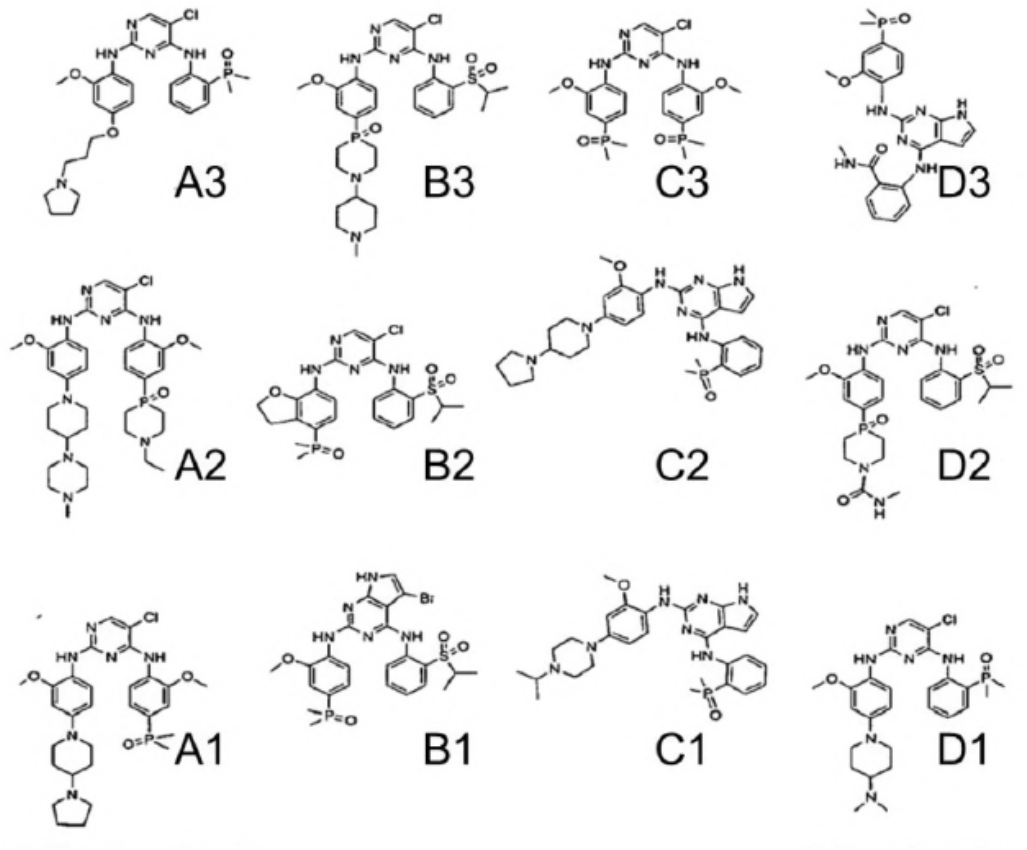
Like the patent, D8 (Formula I on page 1, in which A is most preferably C) is directed to compounds having a 2,4-di(phenylamino)-pyrimidine core structure and to their use for the treatment of cancer. The compounds of D8 (page 15, penultimate paragraph to page 17, second paragraph) are inhibitors of FAK, but some of them are also inhibitors of ZAP-70, IGR-IR and ALK (page 17, third paragraph to page 18, first paragraph). In the experimental part of D8, illustrative compounds were tested as FAK, ZAP-70 and IGR-IR inhibitors (see Examples 53 to 59 on pages 155 to 161 and the summary on pages 164 to 170). According to page 20, first paragraph, some compounds were also tested for ALK inhibition.

2.2 Brigatinib (the compound of claim 1) differs from the compounds in D8 in its specific structure, especially in that it bears a dimethylphosphoryl group on the phenyl ring of the substituent at position 4 of the pyrimidine ring. D8 does not contemplate the possibility of this phenyl ring bearing a phosphorous-based substituent (see the definition of substituents $R^0$ to $R^3$ on page 1 of D8).

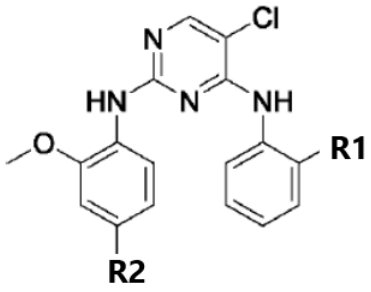
2.3 The technical effect produced by this difference was disputed by the parties. The appellant contested the respondent's position that the application as filed credibly shows that brigatinib is an ALK inhibitor.

The board agrees with the respondent for the following reasons.

On page 235, the application as filed reported the structure of 12 compounds found to have $IC_{50}$ values under 1 nM when tested for ALK inhibition. The compounds have been designated as A1 to D3 in the figure below.

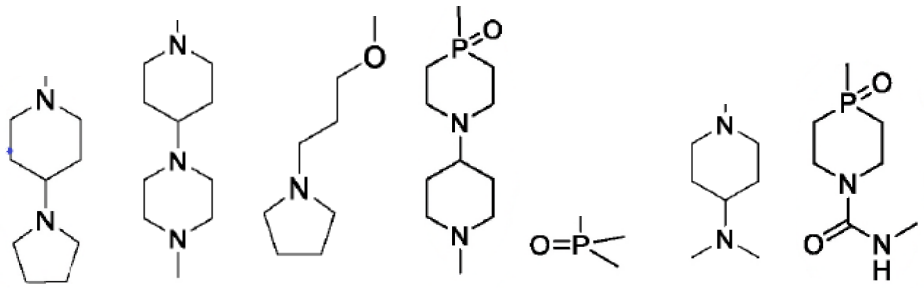



A comparison of pyrimidine-based compounds A1, A2, A3, B3, C3, D1 and D2 reveals that the following core structure is an important feature for inhibiting ALK:




This core structure appears to tolerate a certain variability of substituents R1 and R2 without losing its ALK inhibitory effect; R1 can be dimethylphosphoryl (D1 and A3), isopropylsulfonyl (B3 and D2) or methoxy with an additional phosphorous-based substituent at the p-position of the phenyl ring (A1, A2 and C3), while R2

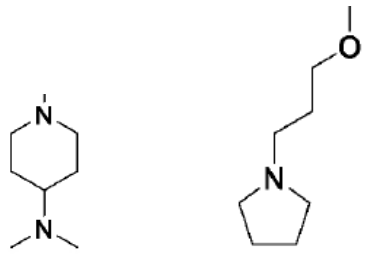
can be one of the following groups (in A1, A2, A3, B3, C3, D1 and D2, respectively):



This variability of substituents without loss of the ALK inhibitory effect is also confirmed in the analogous pyrrolopyrimidine-based compounds B1, C1, C2 and D3.

Brigatinib is structurally closely related to the pyrimidine-based compounds above; it has the same core structure, with R1 dimethylphosphoryl and R2 4-(4-methylpiperazin-1-yl)piperidin-1-yl (second substituent from the left, i.e. R2 of A2).

Therefore, although brigatinib was not tested in the application as filed, the structure-activity relationship derivable from the results presented on page 235 let the reader expect that it inhibits ALK to a similar extent to compounds A1, A2, A3, B3, C3, D1 and D2. This appears particularly likely when comparing the structure of compounds having the same R1 and looking at the variability of R2 without loss of activity. For instance, compounds D1 and A3 which, like brigatinib, have R1 dimethylphosphoryl, have a significantly different R2 without loss of activity, namely:



Therefore, the results presented on page 235 provide (indirect) evidence that R2 4-(4-methylpiperazin-1-yl) piperidin-1-yl, which did not impair activity in A2, will also be non-detrimental when R1 is dimethylphosphoryl, as in brigatinib.

The board therefore holds that, contrary to the appellant's view, the experimental results in the application as filed demonstrate a structure-activity relationship which allows the conclusion that brigatinib is an ALK inhibitor.

2.4 The problem can then be formulated as the provision of an alternative ALK inhibitor.

2.5 On the basis of the board's conclusion, the appellant accepted that the experimental results in the application as filed made it credible that brigatinib is an ALK inhibitor, and that brigatinib was not an obvious solution to the technical problem of providing an alternative ALK inhibitor starting from the disclosure of document D8. It did not, therefore, raise any argument in this respect.

The board agrees that brigatinib is a non-obvious solution to the skilled person seeking alternative ALK inhibitors, since there is no hint in D8 of the modifications required to arrive at brigatinib, let alone to provide a new ALK inhibitor.

3. During the oral proceedings before the board, the appellant confirmed that it had no inventive step objections against any of the independent claims of the main request other than claim 1.

4. Therefore, the board concluded that the subject-matter of the main request involves an inventive step and meets the requirement of Article 56 EPC. As no further objections were raised in appeal proceedings against the main request, it follows that the patent is to be maintained on the basis of the main request.

**Order**

**For these reasons it is decided that:**

- The decision under appeal is set aside.

- The case is remitted to the opposition division with the order to maintain the patent on the basis of claims 1 to 10 of the main request, filed as auxiliary request 1 with the letter dated 29 October 2018, and, if need be, a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated