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Datasheet for the decision of 10 January 2025

Case Number:	T 0542/23 - 3.3.07
Application Number:	18162971.8
Publication Number:	3400943
IPC:	A61K31/517, A61K45/06, A61K31/337, A61K31/7068, A61K39/395, A61P35/04, A61P35/00
Language of the proceedings:	EN

Title of invention:

COMPOUNDS FOR USE IN THE TREATMENT OF BRAIN METASTASES IN A PATIENT WITH ERBB2+ BREAST CANCER

Patent Proprietor:

Array Biopharma, Inc.

Opponents:

Teva Pharmaceutical Industries Ltd
Sandoz AG

Headword:

Treatment of brain metastases/ARRAY

Relevant legal provisions:

EPC Art. 54(2), 56

Keyword:
Inventive step - state of the art - standard of proof - obvious solution

Decisions cited:
T 0421/14, T 1210/05, T 0843/15, T 0545/08

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Case Number: T 0542/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 10 January 2025

Appellant: (Opponent 1)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
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Appellant: (Opponent 2)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Patent Proprietor)	Array Biopharma, Inc. 3200 Walnut Street Boulder, CO 80301 (US)
Representative:	Forresters IP LLP Skygarden Erika-Mann-Straße 11 80636 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 7 February 2023 rejecting the opposition filed against European patent No. 3400943 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	L. Basterreix

Summary of Facts and Submissions

I. European patent 3 400 943 ("the patent") was granted on the basis of thirteen claims.

Claim 1 of the patent as granted defines:

"An amorphous solid dispersion comprising amorphous N4-(4-([1,2,4]Triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-N6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine or amorphous (2-((4-((4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)amino)quinazolin-6-yl)amino)-4-methyl-4,5-dihydrooxazol-4-yl)methanol and a dispersion polymer, for use in treating brain metastases in a patient with ErbB2+ breast cancer."

The patent refers to the first compound as "ARRY-380" and to the second compound as its metabolite "AR00440993".

II. Two oppositions were filed against the grant of European patent 3 400 943 on the grounds that its subject-matter lacked inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as originally filed.

Opponent 1 and opponent 2 filed appeals against the decision of the opposition division to reject the opposition.

The opposition division cited *inter alia* the following documents:

D3: Cancer Research (April 2012), Volume 72, Issue 8, Supplement, Abstract 852
D4: Expert Opin. Druq Deliv. (2011), 8(9), 1121-1140
D9: Poster: "Amorphous dispersion development of ARRY-380, an ErbB2 selective inhibitor", Lindemann et al.
D9a: web.archive.org/web/20150827010938/http://arraybiopharma.com/publications/?ccm_paging_p_b971=7 (Printout Wayback-Machine, 27 August 2015)
D11: Drug Development and Industrial Pharmacy, Review Article, early online 1-13, 24 October 2014, DOI: 10.3109/03639045.2014.971027
D13: Journal of Pharmarmaceutical Sciences (2010), 99(2), 578-597
D14: Journal of Drug Delivery Science and Technology (2015), 30, 342-351

The opposition division arrived at the following conclusions:

(a) Claim 1 as granted did not include subject-matter extending beyond the content of the original application.

(b) The patent sufficiently disclosed the claimed invention.

(c) The priority was not valid for the claimed subject-matter. Document D3 therefore represented prior art.

(d) Document D9, which related to a poster presentation, did not represent prior art, because

it could not be established that the content of the poster of document D9 had become available to the public before the filing date for the patent.

(e) The difference between the claimed subject-matter and the closest prior art represented by document D3 concerned the defined form of an amorphous solid dispersion for the compound to be used. The objective technical problem was the provision of an improved formulation having increased dissolution and decreased pH variability of the bioavailability.

The prior art did not suggest the defined amorphous solid dispersion as solution to this problem. Document D4 actually presented a disincentive by teaching improved stability of crystalline solid dispersions over amorphous solid dispersions.

III. In its communication under Article 15(1) RPBA the Board expressed *inter alia* the preliminary opinion that the subject-matter of the patent as granted would not involve an inventive step starting from document D3 as closest prior art, if document D9 was found to represent complementary prior art. The Board questioned whether document D9a demonstrated that the content of document D9 formed part of the prior art.

IV. The arguments of the opponents relevant to the present decision are summarized as follows:

Document D9a, which represented a printout from an internet archive site, provided convincing evidence that document D9 represented prior art by indicating the publication of a poster with the same title and the same first author at a

conference held before the filing date of the patent and by providing a link which lead to the same poster as document D9. In this context it was relevant that document D9 as well as document D9a originated from the patent proprietor. In line with the considerations in T 421/14 the standard of proof to be applied in this context was the balance of probabilities.

Document D3 represented a suitable starting point in prior art describing ARRY-380 as active agent for the same indication as defined in claim 1 as granted.

The difference of the claimed subject-matter with the teaching of document D3 concerned the provision of this active agent in the form of an amorphous solid dispersion.

The experimental results reported in the patent did not demonstrate any improvement for ARRY-380 in the defined amorphous form with respect to the closest prior art, because the experiments involved a comparison of an amorphous solid dispersion of amorphous ARRY-380 with a crystalline form of the hemi-ethanolate of ARRY-380 rather than ARRY-380 as the free base described in document D3.

If the problem to be solved in view of document D3 was nevertheless to be formulated as the provision of an improved formulation having increased dissolution and decreased pH variability of the bioavailability, the claimed subject-matter did still not involve an inventive step in view of document D9, because this document already described the improved dissolution and decreased pH

variability of the bioavailability to result from the formulation of ARRY-380 in an amorphous solid dispersion.

V. The arguments of the patent proprietor relevant to the present decision are summarized as follows:

Document D9 related to a poster presentation without any indication of a publication date. In line with the considerations in T 1210/05 and T 843/15 a strict standard of proof applied for any finding that document D9 represented prior art, namely the standard of proof beyond reasonable doubt ("up to the hilt"). However, even on the balance of probabilities the opponents had not convincingly shown with document D9a, that the content of document D9 had been presented to the public before the filing date of the patent. Document D9a itself was published only after this filing date and any link in document D9a to document D9 could therefore not represent prior art. It was furthermore not at all evident from the reference in document D9a to a presentation under the same title and by the same first author as the poster of document D9 at a conference in 2012 that indeed the content of document D9 was presented at this conference. In particular, document D9a did not provide the required evidence as to the actual content of the presentation at the conference or even whether the presentation actually took place at the conference in 2012. This could only be established on the basis of witness testimony.

The difference of the claimed subject-matter with the closest prior art represented by document D3 concerned the provision of the active agent in the

form of an amorphous solid dispersion. The improved dissolution and pH variability of the bioavailability of amorphous solid dispersions of ARRY-380 in comparison to the crystalline suspension of the hemi-ethanolate of ARRY-380 reported in the patent demonstrated the effect of the distinguishing feature.

Document D4 explained that amorphous solid dispersions are commonly known to be unstable because they are prone to crystallisation. Document D11 confirmed the difficulties commonly associated with the preparation of amorphous solid dispersions. In this context document D13 indicated that micronisation was the most common method for increasing solubility. It was also common knowledge, as indicated by document D14, that a generic approach to drug solubility is not possible, because each drug presents specific challenges and because the modification of the solubility can have an unpredictable and adverse effect on the *in vitro* or *in vivo* behaviour. Faced with the identified objective technical problem the skilled person would therefore only with hindsight combine the teaching of document D3 with the teaching of document D9. Accordingly, the skilled person would on the basis of the prior art not arrive at the claimed solution in an obvious manner.

VI. The appellant-opponents requested that the decision under appeal be set aside and the patent be revoked in its entirety.

VII. The respondent-patent proprietor requested that the appeal be dismissed and the patent be maintained as granted.

Reasons for the Decision

1. Priority

The finding in the decision under appeal that the priority was not validly claimed for the subject-matter of the patent as granted has not been contested in the appeal proceedings. The relevant date for the determination of the prior art is therefore the filing date of 25 March 2013.

2. Public availability of document D9

2.1 Document D9 relates to a poster presentation with the title "Amorphous Dispersion Development of ARRY-380, an ErbB2 Selective Inhibitor" and mentions C. Lindemann from Array Biopharma Inc. as its first author. The name "ARRAY Biopharma" is also mentioned in the title section of the document. Document D9 does not itself indicate that this poster had been presented to the public before the filing date of the patent.

Document D9a presents a print-out of the Wayback Machine capture of 27 August 2015: "http://web.archive.org/web/20150827010938/http://arraybiopharma.com/publications/?ccm_paging_p_b971=7", which presents under the heading "Publications" a link ("-> Open PDF File") associated with the following reference:

"ARRY-380 / Breast Cancer
10/17/2012
American Association of Pharmaceutical Scientists, Annual Meeting and Exposition.
Amorphous Dispersion Development of ARRY-380, an ErbB2 Selective Inhibitor.
C. Lindemann, et al.
-> Open PDF File"

The opponents have argued that the link presented in document D9a (with the heading "Open PDF file") lead directly to document D9. This has not been contested by the patent proprietor. As a matter of fact, document D9 itself is marked by a reference to "http://web.archive.org/web/20150827010938/http://arraybiopharma.com/publications/?ccm_paging_p_b971=7" (see bottom line of D9).

The opponents have further argued that document D9 as well as document D9a originate from the patent proprietor, which has not also been contested by the patent proprietor.

2.2 Document D9a does not merely refer to a presentation for a conference on 17 October 2012 under the same title and from the same first author as document D9, but actually indicates by the presented link to document D9 that this presentation indeed concerned the poster of document D9. Moreover, by listing this presentation under the heading "Publications" with the date of 17 October 2012 document D9a further indicates that the poster of document D9 was indeed presented to the public at the Annual Meeting and Exposition of the American Association of Pharmaceutical Scientists on 17 October 2012.

2.3 The patent proprietor argued that document D9a does not provide the required evidence as to the actual content of the presentation at the conference or even whether the presentation took actually place at the conference in 2012. In its view the standard of proof beyond reasonable doubt applied in this regard and what was actually presented at the conference could in its view only be proven on the basis of witness testimony.

2.4 According to the established jurisprudence the proceedings before the EPO are conducted in accordance with the principle of the free evaluation of evidence. In accordance with this principle, the deciding instance takes its decision on the basis of all the evidence available in the proceeding in the light of its conviction arrived at freely on the evaluation whether an alleged fact has occurred or not (see Case law of the Boards of Appeal of the EPO, 2022, 10th edition, III.G.4.1 and III.G.4.3).

Absolute conviction in the sense of certainty is and cannot not be required. The jurisprudence refers to the "balance of probabilities" as the standard of proof to be generally applied, including in cases where the publication date of a poster is at stake, but recognizes that depending on the circumstances of the case, in particular if the evidence in support of a fact falls within one party's sphere of influence, a stricter standard of proof beyond reasonable doubt, also referred to as "up to the hilt", may apply (see Case law of the Boards of Appeal of the EPO, *supra*, III.G.4.3, III.G.4.3.3; see in particular T 421/14, reasons 7.5-7.6, T 1210/05, reasons 2.4.2, and T 843/15, reasons 2.3.1). However, as explained in the developing jurisprudence, also in case the determination is made on the basis of the balance of

probabilities the facts on which any finding of public availability is based must be established with sufficient degree of certainty in order to convince the deciding instance in view of all the relevant evidence that they have indeed occurred (see T 545/08, reasons 11). In this context the Board concurs with the considerations in T 768/20 (see reasons 2.1.2, with reference to Case law of the Boards of Appeal of the EPO, III.G.4.3.1) that the mentioned standards are both only fulfilled if the deciding body is persuaded that the alleged fact is true.

2.5 The proprietor's argument, that only witness testimony could provide convincing evidence of what was actually presented at the conference in 2012 mentioned in document D9a, is not persuasive in view of the above mentioned principle of the free evaluation of evidence.

As explained in section 2.2 above, document D9a identifies the poster of document D9 as the content of the presentation to the public which it indicates to have taken place at a conference in 2012. Document D9a represents according to the Board convincing evidence of this publication date of the content of document D9, considering that document D9a as well as document D9 to which it refers originate from the sphere of influence of the patent proprietor, especially since the proprietor has not argued that the content of document D9a represented in section 2.1 above is incorrect, let alone presented any evidence in support of such argument. Accordingly, the Board finds no reason to doubt the publication of the content of document D9 in 2012 as indicated in document D9a.

2.6 The Board therefore considers that document D9a provides convincing evidence that the content of

document D9 had been made available to the public before the filing date of the patent and thus forms part of the prior art under Article 54(2) EPC.

3. Inventive step

3.1 Differences with the closest prior art

Document D3 indicates the compound ARRY-380 to be useful in the treatment of the same condition as defined in claim 1 of the patent as granted. It was not in dispute that document D3 represents a suitable starting point in the prior art and that the subject-matter of claim 1 as granted differs from the teaching in document D3 in that the defined compound is provided in the form of an amorphous solid dispersion.

3.2 Formulation of the objective technical problem

3.2.1 The opponents do not contest the finding in the decision under appeal that the patent demonstrates an enhanced dissolution and reduced pH variability of bioavailability for the claimed amorphous solid dispersions of ARRY-380 in examples 6-15 in comparison to the crystalline suspension of the hemi-ethanolate of ARRY-380 of reference example 21. The opponents dispute instead the relevance of this comparison, because in their view the hemi-ethanolate used for the comparison does not represent the form of ARRY-380 described in document D3.

The Board observes, however, that document D3 does not identify the used form of ARRY-380 nor exclude that the used form was a solvate, whereas at the same time no evidence has been provided that the ethanol in the hemi-ethanolate of reference example 21 actually

affects the dissolution properties. The Board therefore agrees with the decision under appeal that the comparative results reported in the patent may be regarded to demonstrate the effect of enhanced dissolution and reduced pH variability of bioavailability associated with the distinguishing feature of the subject-matter of claim 1 with respect to the prior art.

Accordingly, the Board considers, in line with the finding in the decision under appeal, that the objective technical problem starting from document D3 may be defined as the provision of an improved formulation with enhanced dissolution as well as decreased pH variability of bioavailability.

3.3 Assessment of the solution

3.3.1 In view of the identified objective technical problem the skilled person would consult prior art addressing the further development of formulations comprising ARRY-380, in particular prior art describing formulations with advantageous characteristics such as enhanced dissolution and decreased pH variability of its bioavailability.

Document D9 (see D9, under "In vitro dissolution testing of amorphous dispersions" and "In vivo pharmacokinetics of ARRY-380 in canines") discloses the same data regarding the characteristics of ARRY-380 in the form of an amorphous solid dispersion in comparison to ARRY-380 in the form of a crystalline suspension in terms of its dissolution and the pH variability of its bioavailability as provided in the patent (see the *in vitro* data in examples 6-15 as compared to example 21 and the *in vivo* data in Table 6 of example 22).

Document D9 explicitly concludes that these data suggest that the use of ARRY-380 in the form of an amorphous dispersion allows for improved exposure and variability in oncology patients over a wide range of gastric pH (see D9, under "Conclusions").

Faced with the identified objective technical problem starting from document D3 the skilled person would therefore take account of document D9 and would in view of the explicit conclusion in document D9 arrive in an obvious manner at the subject-matter of claim 1 as a solution to this problem.

3.3.2 The patent proprietor's argument that the skilled person would not have combined the teaching of documents D3 and D9 without hindsight having regard to the common general knowledge reflected in documents D4, D11, D13 and D14 is not considered convincing.

As explained in section 3.3.1 above, the skilled person who intends to provide a solution to the identified technical problem would consider and apply the teaching in document D9, because this document addresses the same technical problem.

The fact that amorphous solid dispersions are prone to crystallisation during storage, as indicated in document D4 (see page 1123, left column) and document D11 (see page 9, left column) would not deter the skilled person from applying the teaching of document D9 by providing ARRY-380 as an amorphous solid dispersion for use in the treatment indicated in document D3 taking account of the mentioned explicit conclusion in document D9. In this context the Board observes that document D9 (see under "Stability screen of amorphous dispersions") presents the same results

from testing the stability of amorphous dispersions as the patent (see example 20, Table 5) and reports in the same manner as the patent (see example 20, paragraph [0132]) that XRPD analysis over the course of the study did not show evidence of crystallisation for the tested solid dispersions.

The complicated nature of the method of preparing amorphous solid dispersions and the difficulty to scale up the manufacturing process referred to in document D11 (see page 9, left column) would also not prevent the skilled person from arriving at the claimed subject-matter in an obvious manner, because document D9 describes a suitable method for preparing ARRY-380 in the form of amorphous solid dispersions (see D9, under "Methods") which essentially corresponds to the method of preparation described in the patent (see examples 5-15).

The reference in document D13 (see page 589, left column) to micronization as the most frequently used method for improving the solubility of an active substance cannot be considered to teach away the solution to the objective technical problem suggested in document D9, because document D13 does not address the specific problem of the pH variability of the bioavailability of ARRY-380.

Document D14 (see page 349, left column) concludes that the development of a generic approach to solve drug solubility issues is not possible due to the different specific challenges presented by different drugs and possible unpredictable effects of the modification of the solubility of a drug on its in vitro and in vivo behaviour. This conclusion only supports the application of the teaching of document D9 to solve the

identified problem starting from document D3, because document D9 specifically concerns the development of an improved formulation of the same compound used in document D3, namely ARRY-380, and presents favourable experimental results concerning the *in vitro* and *in vivo* behaviour of this compound when formulated as an amorphous solid dispersion.

3.4 Accordingly, the Board concludes that the subject-matter of claim 1 of the patent as granted does not involve an inventive step.

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:

A. Vottner A. Usuelli

Decision electronically authenticated