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Datasheet for the decision of 19 October 2022

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PHARMACEUTICAL FORMULATION 514

Patent Proprietor:
Kudos Pharmaceuticals Limited

Opponent:
Teva Pharmaceutical Industries Ltd.

Headword:
Olaparib solid dispersion/KUDOS

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - non-obvious solution

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Case Number: T 0814/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 19 October 2022

Appellant: (Opponent)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
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Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 17 January 2019 concerning maintenance of the European Patent No. 2346495 in amended form**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Molina de Alba
	R. Romandini

Summary of Facts and Submissions

I. This appeal is directed against the opposition division's interlocutory decision finding that the patent as amended in the form of auxiliary request 1 filed with the letter dated 6 October 2017 met the requirements of the EPC.

II. Claim 1 of the request held allowable by the opposition division was identical to claim 1 as granted. It read as follows:

"*1. A pharmaceutical formulation comprising an active agent in solid dispersion with a matrix polymer, wherein the active agent is 4-[3-(4-cyclopropanecarbonyl-piperazine-1-carbonyl)-4-fluoro-benzyl]-2H-phthalazin-1-one or a salt or solvate thereof, and the matrix polymer exhibits low hygroscopicity and high softening temperature.*"

The active agent cited in claim 1 is also known by its common name olaparib.

III. The patent had been opposed on the grounds of added subject-matter and lack of inventive step.

IV. The prior art documents cited in the decision under appeal included the following:

D2: C. Leuner et at., Eur. J. Pharm. Biopharm., 2000(50), 47-60
D3: US 4,801,460
D5: WO 2008/047082

V. In the decision under appeal, the opposition division considered that claims 18 and 19 of the main request added subject-matter. However, the claims of auxiliary request 1 met the requirements of Article 123(2) EPC and their subject-matter was inventive starting from document D5 as the closest prior art.

VI. 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.

VII. With its reply to the statement of grounds of appeal, the patent proprietor (respondent) requested that the appeal be dismissed (main request). In addition, it filed three sets of claims as auxiliary requests.

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

IX. Oral proceedings were held before the board on 19 October 2022. At the end of the oral proceedings, the board announced its decision.

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

Document D5 was the closest prior art, in particular the olaparib immediate release tablet implicitly disclosed on page 18, lines 31 and 32. The formulation in claim 1 differed from that closest prior art in that it was a solid dispersion with a matrix polymer that exhibits low hygroscopicity and high softening temperature. This difference had the effect of increasing the bioavailability of olaparib; it was not credible that every matrix polymer according to claim 1 would provide a stable solid dispersion of olaparib,

let alone at any drug loading. The experimental data in the patent demonstrated that solid dispersions with high drug loadings tended to be less stable and could result in olaparib crystallisation.

Table 12 showed a reduction in the dissolution rate of the kleptose-based formulation at the higher drug loading (1:2 vs 1:3) after three months at 40°C/75% RH. Table 6 showed that solid dispersions having a drug loading of 25 wt.% were stable, but drug loadings of 50 wt.% led to crystallisation after 1 week at 30°C/60% RH (copovidone) or they were not measured (kleptose). In the case of Eudragit L100-55, crystallisation occurred at both 25 wt.% and 50 wt.% drug loading.

Therefore, the difficulty of formulating olaparib for administration to a patient had not been overcome by the subject-matter of claim 1; the objective technical problem was merely the provision of an olaparib formulation with improved bioavailability.

The solution proposed in claim 1 was obvious. It was implicit in D5 that olaparib was sparingly soluble in water. Therefore, in view of the common general knowledge presented in D2 that solid dispersions enhance the bioavailability of sparingly soluble drugs, the skilled person would have formulated olaparib as a solid dispersion.

Even if stability were acknowledged as a technical effect, the solution proposed in claim 1 remained obvious because the conventional matrix polymers listed in D2 included some according to claim 1, namely copovidone, HMPC, HPC, HPMCP and Eudragit L. As it was known that the matrix polymer had an influence on the

stability of solid dispersions, the skilled person would have found the better suited polymers by routine experimentation.

D3 also rendered the claimed subject-matter obvious because it disclosed copovidone as a suitable matrix polymer for the solid dispersion of sparingly soluble active compounds.

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

D5 was a suitable springboard for the assessment of inventive step; it was concerned with the preparation of a crystalline form of olaparib but was unspecific with regard to its formulation. The subject-matter of claim 1 differed in that olaparib was formulated as a solid dispersion with matrix polymers having low hygroscopicity and high softening temperature. This had the technical effect that olaparib was in a bioavailable and stable form, even at the drug loading required for administering the therapeutic dose. Therefore, the objective technical problem was providing an olaparib formulation suitable as a pharmaceutical dosage form for administration to patients. The appellant's argument that the solid dispersions of claim 1 do not solve the problem posed was flawed. The appellant was right that there was a tendency towards instability when increasing drug loading. Indeed, that was the teaching in paragraph [0015] of the patent. Nevertheless, the claimed formulations were stable and suitable for administration to patients; the exceptions in the patent cited by the appellant did not prove the contrary.

In Table 6, crystallisation in the Eudragit L100-55 dispersion could be avoided by preparing the formulation with acetone/MeOH rather than DCM/MeOH. In the case of copovidone at 50 wt.% drug loading, crystallisation was already present right after preparation but it was not investigated why crystallisation occurred and whether it progressed over time. In any case, a certain degree of crystallisation did not necessarily render the formulation unstable or unsuitable for administration to patients.

The invention did not require a specific value for stability, drug loading or bioavailability but an adequate balance between these three interrelated properties. Formulations that do not make technical sense, e.g. because of the instability caused by an excessively high drug loading, would not be encompassed by claim 1. The claimed subject-matter solved the objective technical problem for drug loading ranges considered reasonable by the skilled person. The presence of some crystallisation at high drug loadings did not render the formulation unsuitable; crystalline forms could be less bioavailable to some extent because they dissolved more slowly than amorphous forms, but they were neither toxic nor unsuitable for administration to patients. Furthermore, stability was relative, it did not need to be assured at high temperatures or for long periods of time.

The solution proposed in claim 1, was not obvious. D5 suggested several conventional formulations for olaparib but never referred to solid dispersions, which were not conventional but complex and sophisticated; the obvious option was rather the formulation as an immediate release tablet. In fact, it was after finding that an immediate release tablet did not provide

sufficient bioavailability, that the required daily dose of olaparib could be quite high, and that a lipid formulation did not admit sufficient drug loading, that the patent inventors decided to formulate olaparib as a solid dispersion. There was no motivation for such a formulation without that previous knowledge. Therefore, the combination of D5 with D2 or D3 was based on hindsight. Furthermore, it was unexpected that matrix polymers known from D2 and D3 to be suitable for solid dispersions, such as polyethylene glycol, poloxamers and PVP, did not provide sufficiently stable formulations with olaparib. The limitation in claim 1 to matrix polymers having low hygroscopicity and high softening temperature was a purposive selection that provided stable solid dispersions at the drug loadings required for the administration of olaparib.

XII. The parties' final 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 appeal be dismissed (main request), implying that the patent be maintained in the version held allowable by the opposition division. Alternatively, the respondent requested that the patent be maintained in amended form on the basis of one of the sets of claims filed with the reply to the statement of grounds of appeal as auxiliary requests 1 to 3.

Reasons for the Decision

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

2. Inventive step (Article 56 EPC) - main request

The main request is the request held allowable by the opposition division. Its claim 1 is identical to claim 1 as granted (see point II above).

2.1 The patent (paragraphs [0002], [0004], [0007], [0008], [0010], [0011], [0012] and [0021]) is directed to the formulation of olaparib in solid dispersion with a matrix polymer that has low hygroscopicity and high softening temperature. Based on the solubility and permeability of olaparib, the patent inventors expected that olaparib could be administered to patients in the form of an immediate release tablet. However, the administration of this formulation to dogs revealed that the bioavailability of the active compound was lower than expected (Example 6, Table 28, first entry). Although this problem was initially solved by formulating olaparib in a lipidic formulation, this formulation did not admit drug loadings beyond 10% (Example 6, Table 28, second to fourth entries). As the therapeutic dose of olaparib was found to be quite high (up to 400 mg), the lipidic formulation was unsuitable for administration in an acceptable number and size of dosing units. According to the patent, the formulation set out in claim 1 solves this problem because it increases the bioavailability of olaparib and remains stable at the high drug loading required for administration to patients. Stability in the sense of the patent is the ability of olaparib to remain in

amorphous form, i.e. not to crystallise (paragraph [0018], last sentence).

2.2 The parties agreed that document D5 is the closest prior art. The board has no reason to take another stance.

D5 is concerned with the preparation and characterisation of olaparib in its crystalline form A (page 3, lines 5 to 9; page 4, lines 20 to 22; claim 1). This teaching is discussed in detail on pages 1 to 15 and is illustrated by the examples on pages 21 to 31. In addition, D5 makes generic remarks on the therapeutic use of olaparib as a PARP inhibitor (page 16, line 4 to page 17, line 10), possible modes of administration (page 17, lines 13 to 26), possible formulations (page 17, line 28 to page 19, line 28), and possible dosages (page 20, lines 3 to 24). However, D5 does not disclose any actual formulation or dosage form; the text extending from page 18, line 27 to page 19, line 9, merely proposes conventional formulations that may be used for the administration of olaparib. This is apparent from the absence of specific embodiments and the constant use of the wording "may be". Therefore, with respect to formulations, the only teaching that the skilled person could derive from D5 is that olaparib in crystalline form A can be formulated in any conventional form, e.g. as a tablet.

The appellant submitted that the passage on page 18, lines 31 and 32 of D5 would implicitly disclose an immediate release tablet because this is the basic and more conventional form of tablets. Therefore, this would be the closest prior art.

The board disagrees. The passage follows a paragraph proposing different formulations for oral administration, namely capsules, cachets, tablets, powders, granules, suspensions or pastes. After that, the passage cited by the appellant states:

"*A tablet may be made by conventional means, e.g. compressing or molding, optionally with one or more accessory ingredient.*"

This passage in combination with its preceding paragraph merely tells the reader that tablets are one among various possible formulations for oral administration and that they can be prepared by conventional methods. Nothing in this disclosure implies the formulation of immediate release tablets in particular; the conventional means of compressing and molding could be applied to any type of tablet. Therefore, in the board's view, the closest prior art is the crystalline form A of olaparib.

2.3 The parties agreed that the formulation of claim 1 differs from the disclosure in D5 in that olaparib is formulated in solid dispersion with a matrix polymer having low hygroscopicity and high softening temperature.

2.4 They discussed two technical effects associated with this difference: a higher bioavailability and a higher stability of olaparib, especially at the high drug loadings required for administration to patients.

2.4.1 The appellant did not contest that the formulation of claim 1 enhanced the bioavailability of olaparib with regard to the closest prior art. In fact, the appellant cited D2 to demonstrate that it was common general

knowledge that the bioavailability of sparingly soluble active compounds, as was the case with olaparib, could be improved by formulating the active compound as a solid suspension (statement of grounds of appeal, point 4.2.3, last paragraph, and point 4.3.1). This is also confirmed by Table 28 of the patent, which shows that the bioavailability of olaparib in some of the formulations generally disclosed in D5 (page 27 to 30), namely tablets, capsules and suspensions, is considerably lower than that reached by solid dispersions according to claim 1 having kleptose, AQOAT, HPMC-606, HP55S or copovidone as the matrix polymer.

2.4.2 The matter of dispute between the parties was whether the formulation of claim 1 stabilises olaparib at any weight ratio of olaparib:matrix polymer, especially at high drug loadings. On this point, the appellant referred to the stability results shown in Tables 6 and 12 of the patent.

The hygroscopicity and softening properties of the polymers tested in Tables 6 and 12 are disclosed in Table 4 of the patent. In their discussion of Tables 6 and 12, the parties considered that polymers such as HPMC-606, HPMC-phtalate, Eudragit L100-55, Kleptose HP, HPC and copovidone were according to claim 1, whereas polymers such as PEG6000, Poloxamer F68, Poloxamer F127, PVP K25, PVP K30, Eudragit E100 and PVP were not according to claim 1. The discussion focused in particular on Eudragit L100-55 and copovidone as polymers according to claim 1, and PVP as not being according to claim 1.

Table 6 presents the stability results of olaparib solid dispersions with different polymer matrices after

one week and/or one month at 30°C and 60%RH. The results show that the solid dispersions according to claim 1 generally do not experience crystallisation at drug loadings of 25 wt.%, 33 wt.% or 50 wt.%. This is the case in particular of dispersions containing HPMC-606, HPMC Phtalate, Kleptose HP, HPC or Kleptose/ HPMC-606 as the matrix polymer. Issues of crystallisation were encountered in two instances when polymers according to claim 1 were used. The first instance was when the dispersion was prepared with Eudragit L100-55 using DMC/MeOH as the solvent system (page 14, lines 19-20). Nevertheless, the same formulation was stable when the solvent system was acetone/MeOH (page 14, lines 21 and 22). In the second instance, when copovidone was loaded at 50 wt.% (page 14, line 55) crystallisation occurred at the outset of the test. No crystallisation occurred with the same polymer at a drug loading of 25%. In the board's view, on the basis of the information and evidence available and the analysis made of Table 6, it can be concluded that solid suspensions according to claim 1 are generally stable for administration to patients. Regarding the matrix polymers not according to claim 1, PVP did not exhibit crystallisation and the test with Eudragit E100 at 50 wt.% drug loading had the same problems as those with Eudragit L100-55 and copovidone. Dispersions with PEG6000, Poloxamer F68 and Poloxamer F127 showed crystallisation even at the lower drug loading of 25 wt.%.

In the same line, Table 12 shows that olaparib solid dispersions with kleptose or HPMCP at a drug loading of 25 wt.% (olaparib:polymer ratio 1:3) did not experience crystallisation or a substantial drop in the dissolution rate of olaparib, even after 3 months at 40°C and 75%RH. In contrast, a PVP formulation with

25 wt.% drug loading was stable up to one month, but after three months it experienced a significant drop in the dissolution rate from the initial 92% to 66%, and showed some crystallisation. At drug loadings of 33 wt.% (olaparib:polymer weight ratio 1:2), the HPMCP-based formulation remained highly stable after three months while the kleptose-based formulation was stable for one month; after three months, it showed some drop in the dissolution rate, from 81% to 66%, but did not exhibit crystallisation. The drop in the dissolution rate was even more important for the PVP-based formulation, which fell from the initial 81% to 55% after three months. From these data, the board concludes that even under harsher conditions than those tested in Table 6, the dispersions according to claim 1 remain stable for at least three months while PVP starts to show some signs of instability. Amorphous olaparib was unstable under any of the tested conditions.

2.4.3 Therefore, the experimental data in the patent demonstrate that the solid dispersions of claim 1 are suitable for administering a therapeutic dose of olaparib to patients; they generally exhibit sufficient stability and bioavailability even at drug loadings as high as 50 wt.%. Solid suspensions with matrix polymers not according to claim 1 were unsuitable or did not perform so well.

2.5 Consequently, the board agrees with the respondent that the objective technical problem is the provision of an olaparib formulation suitable as a pharmaceutical dosage form for administration to patients.

The appellant contested that this problem is solved across the whole breadth of claim 1 because the claim

is drafted too broadly. The appellant made the criticism that claim 1 does not define any amounts or weight ratios of olaparib and the matrix polymer, so the claim would encompass formulations with high drug loadings that would not exhibit the required stability and bioavailability for administration to patients.

The board disagrees. The appellant is right that the higher the drug loading, the more likely crystallisation is to occur. This was not disputed and is acknowledged in the patent (paragraph [0015]). However, as argued by the respondent, the presence of some amounts of crystalline olaparib does not necessarily render the solid dispersions unsuitable for administration to patients; the patent teaches in paragraph [0060] that the active agent may be dispersed as individual molecules or as discrete domains of crystalline or amorphous drug. Crystallisation would reduce bioavailability to some extent because crystalline forms are more difficult to dissolve than amorphous forms or individual molecules. But some degree of crystallisation does not make the formulation necessarily unsuitable for administration to patients. Furthermore, the skilled person cannot be expected to work within unreasonable ranges of drug loadings that would result in a massively oversaturated product that would no longer qualify as a solid dispersion. Therefore, the board considers that the formulations proposed in claim 1 are a suitable solution to the objective technical problem.

2.6 On the issue of obviousness, the appellant cited documents D2 and D3 as prior art to be combined with D5. The board agrees with the respondent that this combination of documents could only be made with hindsight.

The appellant correctly argued that D5 implicitly discloses that olaparib has a low solubility in water. This can be derived from the molecular structure of olaparib and the fact that olaparib was recrystallised from water, water/methanol and water/ethanol (page 23, lines 24 to 27, and page 26, lines 4 to 13 and lines 20 to 29). However, this implicit disclosure is only qualitative; a low solubility in water cannot be equated with an insufficient bioavailability for administration in a conventional dosage form. In fact, the inventors of D5 suggested formulating olaparib in a conventional form, even though they knew that it had a low solubility in water. The patent disclosed for the first time that olaparib was not sufficiently bioavailable when administered in a conventional form such as an immediate release tablet. This was also the case for the finding that the therapeutic dose of olaparib was high, and therefore required formulations having high drug loadings which could raise stability issues.

Gathering the knowledge presented in the patent for the first time requires a considerable amount of research and could in no way be derived from D5. The fact that this research belongs to the common methodology for developing drugs does not render its results obvious. The essential point is that, on the filing date of the patent, the skilled person did not know that olaparib was particularly difficult to formulate because it required high drug loadings and presented bioavailability and stability issues.

Therefore, the skilled person would have formulated olaparib in any of the conventional formulations suggested on pages 18 and 19 of D5, rather than as a

solid dispersion. They had no motivation to turn to D2 or D3, which are concerned with the issue of improving the bioavailability of sparingly soluble drugs (D2: abstract; D3: column 1, lines 19 to 22). Firstly, they were not aware of any bioavailability issues in relation to olaparib and believed that conventional formulations were suitable for administration to patients. Secondly, even if they wished to improve the bioavailability of olaparib and decided to formulate it as a solid dispersion, they would have observed stability issues for which D2 or D3 do not provide any guidance. D2 (page 58, last paragraph) even recognises that there is still a need for better prediction of whether a particular drug/carrier combination will lead to a true solution or a partly crystalline dispersion, and whether the dispersion will remain physically stable. The patent shows that the selection of matrix polymers of claim 1 is particularly suited to addressing this issue for the specific case of olaparib. In contrast, matrix polymers disclosed in D2 but not according to claim 1 (polyethylene glycol and poloxamers) were not a suitable solution, and PVP, disclosed in both D2 and D3, did not perform as well as the polymers according to claim 1.

Therefore, the skilled person would not have arrived at the solid dispersion of claim 1 without the knowledge made available in the patent. This is also the case for the subject-matter of the other independent claims of the main request, namely claims 21 and 24, which are directed to a therapeutic use and a preparation method of the solid dispersion of claim 1.

2.7 Therefore, the board concludes that the subject-matter of the main request involves an inventive step, as required by Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated