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Datasheet for the decision of 4 July 2022

Case Number: T 1214/18 - 3.3.02

Application Number: 07836007.0

Publication Number: 2049506

IPC: C07D277/28, C07D417/14, A61K31/427, A61P31/12

Language of the proceedings: EN

Title of invention:
MODULATORS OF PHARMACOKINETIC PROPERTIES OF THERAPEUTICS

Patent Proprietor:
Gilead Sciences, Inc.

Opponents:
Teva Pharmaceutical Industries Ltd
Trösch, Dominique
Georg Kalhammer/Stephan Teipel

Relevant legal provisions:
EPC Art. 123(2), 56

Keyword:
Amendments
Inventive step

Decisions cited:
T 0948/02

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Case Number: T 1214/18 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 4 July 2022

Appellant 1: (Opponent 1)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
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Appellant 2: (Opponent 2)	Trösch, Dominique Xaver-Weismor-Strasse 16 81829 München (DE)
Representative:	Trösch, Dominique c/o HGF Europe LLP Neumarkter Straße 18 81673 München (DE)
Respondent: (Patent Proprietor)	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Party as of right: (Opponent 3)	Georg Kalhammer and Stephan Teipel c/o Lederer & Keller Unsöldstrasse 2 80538 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 21 March 2018 concerning maintenance of the European Patent No. 2049506 in amended form.**

Composition of the Board:

Chairman M. O. Müller
Members: A. Lenzen
M. Blasi

Summary of Facts and Submissions

I. This decision concerns the appeals filed by opponents 1 and 2 (appellants 1 and 2) against the opposition division's interlocutory decision (decision under appeal), according to which European patent No. 2 049 506 (patent) in amended form meets the requirements of the EPC.

II. The following documents, filed before the opposition division, are relevant to the present decision:

D2 Yano, J. K. et al., J. Biol. Chem. 2004, 279(37), pages 38091 to 38094

D3 Becker, S. L., Expert Opin. Investig. Drugs 2003, 12(3), pages 401 to 412

D4 Kempf, D. J. et al., Proc. Natl. Acad. Sci. USA 1995, 92, pages 2484 to 2488

D5 Kempf, D. J. et al., Antimicrob. Agents Chemother. 1997, 41(3), pages 654 to 660

D6 Xu, L. et al., ACS Med. Chem. Lett. 2010, 1, pages 209 to 213

D8 Babine, R. E. et al., Chem. Rev. 1997, 97, pages 1359 to 1472

D9 Wermuth, C. G., The Practice of Medicinal Chemistry, 2nd edition, 2003, pages 617 to 630

D12 Expert declaration of Prof. Dr. Thierry Langer

D14 Kumar, G. N. et al., JPET 1996, 277(1), pages 423 to 431

D22 EMA Assessment report Tybost

D23 Marzolini, C. et al., J. Antimicrob. Chemother. 2016, 71, pages 1755 to 1758

D25 Technical annex (2 pages)

D26 Ekroos, M. et al., PNAS 2006, 103(37), pages 13682 to 13687

D27 Declaration of Professor Nico P. E. Vermeulen
D28 Sevrioukova, I. F. et al., PNAS 2010, 107(43), pages 18422 to 18427
D30 Guengerich, F. P., PNAS 2006, 103(37), pages 13565 to 13566

III. With their statements of grounds of appeal, the appellants filed the following documents

D31 Remington, The Science and Practice of Pharmacy, 20th edition, 2000, pages 401 and 402
D32 WO 2005/039551 A2

with respect to issues which are accepted below in favour of the appellants. These documents are therefore not relevant to the present decision.

IV. With its reply to the statements of grounds of appeal, the patent proprietor (respondent) filed the set of claims of auxiliary request 1.

V. By letter dated 27 July 2021, the joint opponents 3 stated that they would not be attending the oral proceedings.

VI. In preparation for the oral proceedings, scheduled at the parties' request, the board issued a communication pursuant to Article 15(1) RPBA 2020.

VII. By letter dated 23 June 2022, appellant 2 stated that he would not be attending the oral proceedings.

VIII. Oral proceedings before the board were held on 4 July 2022 in the presence of appellant 1 and the respondent. In accordance with Article 15(3) RPBA 2020 and Rule 115(2) EPC, the board decided to continue the

proceedings in the absence of appellant 2 and joint opponents 3, who had been duly summoned but chose not to attend. The respondent made auxiliary request 1 filed with the reply to the statements of grounds of appeal its main request. At the end of the oral proceedings, the chair announced the order of the present decision.

IX. Summaries of the appellants' objections are contained in the reasons for this decision.

The joint opponents 3 did not file any submissions on substantive issues.

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

- It was crucial for the requirements of Article 123(2) EPC whether or not the claimed subject-matter was directly and unambiguously disclosed in the application as filed. However, whether the claimed subject-matter conferred an "unwarranted" advantage, as alleged by appellant 2, was irrelevant. The set of claims of the main request met the requirements of Article 123(2) EPC.

- In its communication pursuant to Article 15(1) RPBA 2020, the board had correctly found that D14 did not disclose deshydroxyritonavir. Therefore the inventive-step objection based on D14 and starting from deshydroxyritonavir could not succeed.

  At any event, the correct closest prior art was not D14 but D3. The pharmacoenhancer ritonavir disclosed in D3 was the most suitable starting point for assessing inventive step. The objective

technical problem was to provide a compound (i) which lacked HIV-1 protease inhibitory activity, (ii) which was a potent inhibitor of CYP3A and exhibited increased selectivity towards enzymes of this subfamily relative to enzymes of other CYP subfamilies, and (iii) which retained oral bioavailability. Starting from ritonavir, the skilled person would not have arrived at the compound of the claims, i.e. cobicistat. More specifically, D9 suggested grafting the solubilising moiety onto parent drugs in order to increase their solubility. The skilled person would not have inferred from this that the morpholinoethyl group should be bonded to a simple carbon atom or even replace an entire group of the parent drug, as was the case with cobicistat. The skilled person, even if considering this structural modification, would not have made it with the reasonable expectation of essentially maintaining the extent of CYP3A inhibition and increasing the selectivity towards CYP3A compared with other CYP isoforms. As pointed out by the board at the oral proceedings, D5 (table 1, ritonavir vs. A-81272) showed that the left part of ritonavir was very important for CYP3A inhibition. Furthermore, appellant 1's contention that steric bulk alone was the determining factor for selectivity towards CYP3A over other CYP isoforms, was contradicted by the respondent's data in D25. Lastly, crystal structures of deshydroxyritonavir or ritonavir with CYP3A4 were not known before the priority date of the patent. Therefore the skilled person could not have successfully used computer-aided modelling methods. The invention claimed in the main request therefore involved an inventive step.

XI. The parties' final requests were as follows:

Appellants 1 and 2 requested that the decision under appeal be set aside and the patent be revoked in its entirety.

The respondent requested that the patent be maintained in amended form based on the set of claims of the main request, filed as auxiliary request 1 with the reply to the statements of grounds of appeal.

Opponent 3 did not file any request.

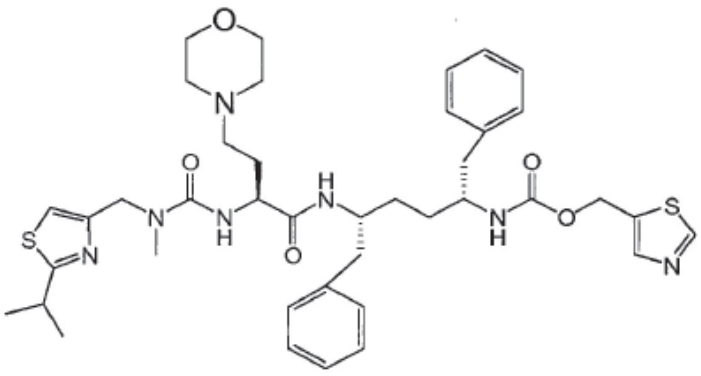
Reasons for the Decision

Main request

1. The set of claims of the main request consists of the following two independent claims:

Claim 1

"*A compound of the formula*



or a pharmaceutically acceptable salt thereof."

—

Claim 2

"*A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.*"

The compound whose structure is shown in claim 1 is example S of the application as filed. In agreement with the parties, this compound is referred to as cobicistat in this decision.

Thus claim 1 is directed essentially to cobicistat and claim 2 to a pharmaceutical composition comprising it.

2. Amendments (Article 123(2) EPC)

2.1 Claim 1 of the main request is based on claim 26 of the application as filed.

Claim 2 of the main request is based e.g. on the combination of claims 1 and 51 as filed. Claim 51 as filed discloses a pharmaceutical composition comprising a compound of claim 1 as filed, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient. Claim 1 as filed, to which claim 51 as filed refers, discloses a compound of a broadly defined formula I. In the example section of the application as filed, example S, i.e. cobicistat, is mentioned as one of several compounds in accordance with this formula I. Thus, with regard to the combination of claims 1 and 51 as filed, the subject-matter of claim 2 of the main request is the result of a single selection of cobicistat from the application as filed. Such a single selection does not generate new subject-matter.

2.2 According to appellant 2, formula I in claim 1 as filed comprised an uncountable number of compounds. By contrast, with respect to this formula I, claims 1 and 2 of the main request were limited to the single specific compound cobicistat. This put the respondent in the unforeseeable position of arguing that cobicistat had a technical effect over the other compounds disclosed in the application as filed which were in accordance with formula I. However, it was not disclosed that this technical effect was better with cobicistat than with other compounds. This gave the respondent an unwarranted advantage.

This is not convincing. For claimed subject-matter to meet the requirements of Article 123(2) EPC, it is crucial whether or not it is directly and unambiguously disclosed in the application as filed ("gold standard"). This is the case, see above. Only if subject-matter which is not directly and unambiguously disclosed were to be considered allowable could this lead to an unwarranted advantage for the respondent. Nothing other was decided in decision T 948/02 (point 2.4.1 of the Reasons), on which appellant 2 relied in support of its argument.

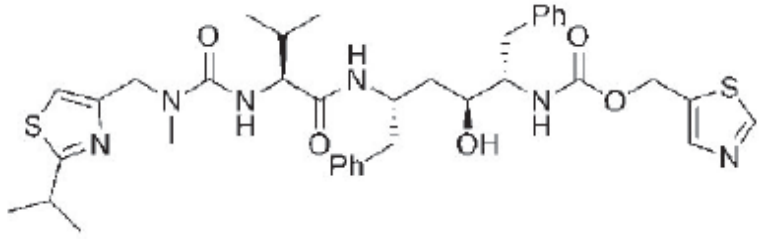
2.3 Thus claims 1 and 2 of the main request meet the requirements of Article 123(2) EPC.

3. Inventive step (Article 56 EPC)

D14 as the closest prior art

3.1 Appellant 2 was of the opinion that D14 could be considered as the closest prior art.

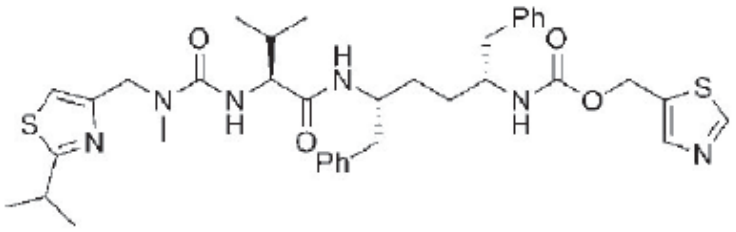
3.2 D14 discloses that ritonavir, i.e. the compound with the following structure,



,

undergoes cytochrome P450 (CYP)-mediated biotransformation in human liver microsomes to three major metabolites M1, M2 and M11 (for their structures, see figure 1). The authors of D14 speculate that the formation of M1 proceeds via hydroxylation at the methylene group between the 5-thiazolyl group (on the right in the above structure) and the carbamoyl group (page 430, left-hand column, lines 28 to 41). M2 differs from ritonavir only in that the methine hydrogen atom of the *iso*-propyl group on the 4-thiazolyl group (on the left in the above structure) is replaced by a hydroxy group. M11 is stated to be the product of an N-dealkylation (page 427, right-hand column, last paragraph).

3.3 According to appellant 2, it was common general knowledge that the hydroxylation reactions leading to M2 or occurring in the course of the formation of M1 proceeded via a free-radical mechanism. On this basis, the skilled person would have recognised that ritonavir itself was also the product of a CYP-mediated hydroxylation. Therefore not only ritonavir but also its precursor with regard to a CYP-mediated hydroxylation, namely deshydroxyritonavir, was directly and unambiguously disclosed in D14. Deshydroxyritonavir is a compound with the following structure:



According to appellant 2, deshydroxyritonavir only differed from cobicistat in that the morpholinoethyl group of the latter was replaced with an *iso*-propyl group. Deshydroxyritonavir was therefore a suitable starting point for assessing inventive step.

3.4 This is not convincing. D14 explicitly deals only with the CYP-mediated metabolism of ritonavir. The formation of ritonavir itself, on the other hand, is not the subject of D14 at all. At least against this background, deshydroxyritonavir cannot therefore be regarded as directly and unambiguously disclosed in D14 even if, as argued by appellant 2, ritonavir was the product of a CYP-mediated hydroxylation of deshydroxyritonavir. This notwithstanding, in the present case it is even highly questionable, to say the least, whether ritonavir is the inevitable product of a CYP-mediated hydroxylation of deshydroxyritonavir:

- CYP is a class of enzymes. Enzymes are well known to be very substrate-specific. Hence it cannot simply be assumed that deshydroxyritonavir also undergoes a CYP-mediated hydroxylation, let alone a hydroxylation at a specific carbon atom to give ritonavir.
- It is not at all clear why the alleged CYP-mediated hydroxylation of deshydroxyritonavir should lead to ritonavir but not instead to metabolites corresponding to M1, M2 and/or M11.

The above-mentioned points, which had already been pointed out in the board's communication pursuant to Article 15(1) RPBA 2020, were not challenged by any of the appellants in the further course of the appeal proceedings.

Consequently, D14 does not directly and unambiguously disclose deshydroxyritonavir, i.e. appellant 2's starting point for assessing inventive step. The objection of lack of inventive step based on D14 cannot therefore succeed.

D3 as the closest prior art

3.5 Both appellants and the respondent agreed that D3 can be considered as the closest prior art for the claimed subject-matter and that, within D3, ritonavir is the most suitable starting point for assessing inventive step (for ritonavir's structure, see above).

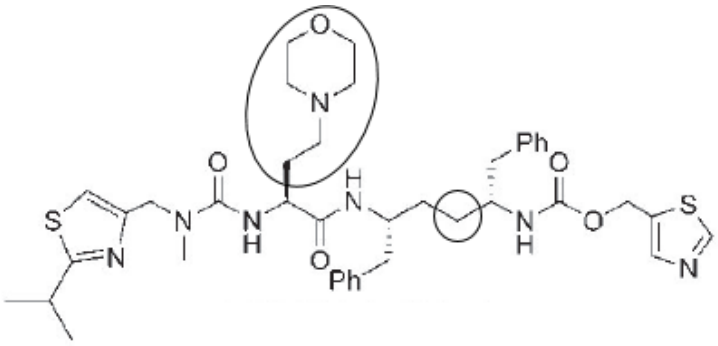
D3 (abstract; point 1) discloses the use of the HIV protease inhibitor ritonavir as a booster/ pharmacoenhancer. Co-administration of ritonavir with another HIV protease inhibitor can increase exposure to the latter due to the inhibitory effect of ritonavir on the CYP isoform 3A4 (CYP3A4), i.e. the enzyme that is largely responsible for the metabolism of said HIV protease inhibitors.

As is evident from the introductory paragraphs [0001] to [0003], the patent also relates to such boosters/ pharmacoenhancers. The role of ritonavir in D3 is assumed in the present case by cobicistat.

3.6 Cobicistat differs from ritonavir in that

- it does not contain a free hydroxy group
- it contains a morpholinoethyl group instead of an *iso*-propyl group.

These differences are pointed out in the following structure of cobicistat:



3.7 Effects linked to the distinguishing features

- In contrast to ritonavir, cobicistat has no HIV-1 protease inhibitory activity (D6: table 1; D22: point 2.3.7 on page 24 and paragraph "Antiviral activity" on page 43; patent: paragraph [0511]).

  This overcomes the following drawback of ritonavir: due to the HIV protease inhibitory effect of ritonavir, which is present but relatively low compared with other HIV protease inhibitors, resistance to ritonavir is more likely to develop if used at low levels and/or as the sole HIV protease inhibitor. As cobicistat has no HIV-1 protease inhibitory effect, such resistance to cobicistat cannot develop.

Contrary to appellant 2's allegation, this is not the only difference in terms of effect between cobicistat and ritonavir:

- Cobicistat has essentially the same strong inhibitory effect on enzymes of the CYP3A subfamily as ritonavir and a comparable or reduced inhibitory activity in relation to other CYP isoforms (D6: table 3; D22: point 2.3.7 on page 24; patent: paragraph [0511]; D23: abstract).

  This overcomes another drawback of ritonavir: as a potent inhibitor not only of CYP3A4 but also of other CYP isoforms such as CYP2D6, CYP2C8 and CYP2C9, ritonavir can adversely affect metabolism of other drugs metabolised by these isoforms which the patient takes in combination with ritonavir. Cobicistat's increased selectivity towards CYP3A means that the risk of such drug-drug interactions is reduced compared with ritonavir, and a significant number of co-medications that adversely interact with ritonavir are not affected by cobicistat.

- Cobicistat has better solubility than ritonavir in both neutral (pH 7.4) and acidic (pH 2.2) conditions (D6: page 212, left-hand column, penultimate paragraph).

  It follows that cobicistat has at least the same oral bioavailability as ritonavir.

3.8 In view of these effects, the objective technical problem is to provide a compound

(i) which lacks HIV-1 protease inhibitory activity,
(ii) which is a potent inhibitor of CYP3A and exhibits increased selectivity towards

enzymes of this subfamily relative to enzymes of other CYP subfamilies

(iii) which retains oral bioavailability.

This objective technical problem had already been set out in the board's communication pursuant to Article 15(1) RPBA 2020. In the further course of the appeal proceedings, none of the parties took a different view.

Obviousness - appellant 1's objection

3.9 As regards obviousness, appellant 1 essentially argued as follows:

The skilled person would - with a reasonable expectation of success - have made one of the two structural changes (1. replacement of the free hydroxy group of ritonavir with a hydrogen atom; 2. replacement of the *iso*-propyl group of ritonavir with a morpholinoethyl group) to solve some of the three partial problems (i) to (iii) of the objective technical problem to a certain extent and the further structural change to solve the still-outstanding partial problem(s) (this was referred to by the parties as the partial problems approach). Put differently, cobicistat was merely the result of a rational approach to drug design starting from ritonavir. An inventive step could therefore not be acknowledged. The considerations underlying this approach, in short, were the following:

(a) It was well-known that HIV-1 protease belonged to the family of aspartic proteases. Because their mode of action was well-established it was evident that the free hydroxy group of ritonavir was

crucial to its HIV-1 protease inhibitory activity. This was corroborated by the crystal structure of ritonavir bound to HIV-1 protease.

Therefore the skilled person would have recognised that deshydroxyritonavir, i.e. the derivative of ritonavir which was devoid of the free hydroxy group (for deshydroxyritonavir's structure, see above), had to have either no or a diminished HIV-1 protease inhibitory activity compared with ritonavir. The skilled person wanting to solve partial problem (i) above (provision of a compound which lacks HIV-1 protease inhibitory activity) would thus have removed the free hydroxy group of ritonavir.

(b) The binding of ritonavir to the central heme iron in the active site of CYP3A was through the N atom of the unsubstituted 5-thiazolyl group. The free hydroxy group to be removed from ritonavir was sufficiently far away from this group. Furthermore, the crystal structures of CYP3A4 alone and with ketoconazole or erythromycin showed that the active site of CYP3A4 was hydrophobic.

Thus, if anything, the replacement of the polar free hydroxy group of ritonavir with a hydrogen atom had to favour CYP3A binding. Consequently, the skilled person would not have feared that deshydroxyritonavir was a worse inhibitor of CYP3A than ritonavir (partial problem (ii) above).

(c) Since it was devoid of a polar free hydroxy group, the skilled person would have expected deshydroxyritonavir to have lower solubility/ bioavailability than ritonavir.

Thus the skilled person would have contemplated binding a solubilising moiety to deshydroxyritonavir in order to increase solubility/bioavailability again (partial problem (iii) above).

(d) With regard to the placement of the solubilising moiety, the skilled person would not have considered parts of the molecule which were important for the interaction with CYP3A. In the case of ritonavir, these were the unsubstituted 5-thiazolyl group and the hydrophobic core flanked by the two benzyl groups. Moreover, the skilled person would not have changed any polar parts of the molecule, as this would have entailed the risk of lower solubility/bioavailability.

Thus the skilled person would quickly have settled on the hydrophobic *iso*-propyl group of the valine building block as the prime candidate for the introduction of the solubilising moiety and would have replaced this hydrophobic group with the solubilising moiety.

(e) With regard to the type/structure of the solubilising moiety, the following had to be borne in mind:

- The solubilising moiety should not interfere with the hydrophobic binding mode in the active site of CYP3A4. Since CYP3A4 was present mainly in liver microsomes with a pH of 7.4, the solubilising moiety should be uncharged at this pH. Preferably, the solubilising moiety should be

charged at lower pH values to increase its solubility/bioavailability in the stomach.
- It was well-established before the priority date of the patent that CYP3A4 was the CYP isoform having the largest and structurally most flexible active site. Therefore larger solubilising moieties should shift the binding preferences towards the CYP isoform family capable of accommodating such large groups, i.e. towards CYP3A (partial problem (ii) above).
- The crystal structure of ritonavir bound to HIV-1 protease showed that the HIV-1 protease binding pocket was not able to accommodate a group which was larger than the *iso*-propyl group. Therefore a large solubilising moiety should eliminate any residual HIV-1 protease inhibitory activity (partial problem (i) above).

Thus, in view of the skilled person's common general knowledge, the choice of the morpholinoethyl group as the solubilising moiety would have been an obvious one to make. This group was positively charged at the pH values in the stomach but neutral at the pH values in the liver, increasing solubility/bioavailability at the site of absorption while not interfering with CYP3A inhibition at the site of action. The effect of a particular solubilising moiety such as the morpholinoethyl group on the interaction with HIV-1 protease or CYP3A could also be easily investigated by computer-aided (*in silico*) modelling methods. This allowed the skilled person to verify that the large morpholinoethyl group

- provided cobicistat with a higher selectivity towards CYP3A compared with other CYP isoforms

- did not change CYP3A inhibition of cobicistat compared with ritonavir
- eliminated any residual HIV-1 protease inhibitory activity.

3.10 This objection is not convincing for at least the following reasons:

3.10.1 The above line of reasoning is based, *inter alia*, on the contention that the skilled person would have chosen the morpholinoethyl group as the solubilising moiety and replaced the *iso*-propyl group of the valine building block with it when faced with the task of designing a new drug starting from ritonavir. As evidence that the use of the morpholinoethyl group as a solubilising moiety was part of the common general knowledge, appellant 1 referred to D9.

D9 is a book chapter which concerns the conversion of a water-insoluble drug into a water-soluble one by covalently attaching an appropriate solubilising moiety (page 617, first sentence). The solubilising moieties are subdivided into three different categories: acidic ionisable moieties, basic ionisable moieties and nonionisable moieties. D9 gives the morpholinoethyl group as an example of a basic ionisable moiety. According to the only relevant passage in D9 (table 36.2), the morpholinoethyl group is introduced into a parent drug by O-alkylation, thus requiring a free hydroxyl group for attachment. Other methods or examples showing a different way of introducing this group are not disclosed in D9. In view of this disclosure, the skilled person would not have inferred from D9 that - let alone how - a morpholinoethyl group should be attached directly to a carbon atom of a parent drug, which is the case with cobicistat.

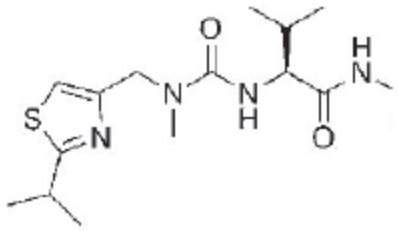
Appellant 1 pointed to the following passage in D9 (page 623, right-hand column, penultimate paragraph; emphases added)

> "*Solubilization* ***with basic side chains*** *involves two essential strategies:* ***either direct binding of the amine function on a carbon atom of the parent molecule,*** *or linking it to a function already present: alcoholic or phenolic hydroxyl, carboxylic acid, amine or amide.*"

and argued that D9 taught very clearly the direct attachment of the basic morpholinoethyl group to a carbon atom of a parent drug. However, the above passage cannot be understood as teaching that every basic ionisable moiety could be directly attached to every carbon atom of the parent drug, as this depends on the structures of both the solubilising moiety and the drug. This becomes clear e.g. from the paragraph which immediately follows the above passage and which states that in the case of simple tertiary amines grafting is possible by exchange reactions or by Mannich reactions (and Mannich reactions for instance require the presence of a carbonyl group on the parent drug). This argument cannot therefore change the above conclusion.

Apart from the above concerns, which had also been expressed by the opposition division (decision under appeal, point 9.2.2 on page 14) and which alone would be sufficient to acknowledge inventive step, the board also cannot agree with at least the following further points from appellant 1's line of reasoning:

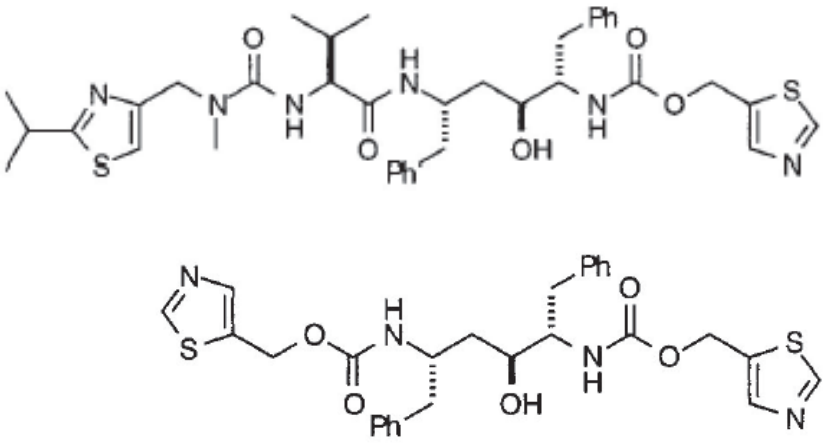
3.10.2 According to appellant 1, the skilled person would not have considered attaching the solubilising moiety to those parts of the molecule which were important for the inhibition of CYP3A. In the case of ritonavir, these were the unsubstituted 5-thiazolyl group and the hydrophobic core flanked by the two benzyl groups. Consequently, the skilled person would only have considered attaching a solubilising moiety to the left side of the molecule:



As changing polar groups of this side (i.e. the amide, urea and substituted 4-thiazolyl groups) entailed the risk of lower solubility/bioavailability, the skilled person would have replaced the hydrophobic *iso*-propyl group of the valine building block with the solubilising moiety, i.e. the morpholinoethyl group. At the oral proceedings before the board, appellant 1 further argued that there was no indication in the prior art that the above left side was important for the inhibition of CYP3A. Thus the skilled person would have had the reasonable expectation that this structural modification would not significantly diminish CYP3A inhibition.

This is not convincing for the reason alone that appellant 1's contention that the above left part was not important for the inhibition of CYP3A is untenable. For example, D5 (table 1) compares the inhibition of CYP3A by ritonavir (shown again below on top) with that

of, *inter alia*, the truncated analogue A-81272 (shown below underneath):



This truncated analogue differs from ritonavir only in that its left side is different. Nevertheless, contrary to appellant 1's contention suggesting no substantial inhibitory difference between ritonavir and this analogue, ritonavir (IC_{50} = 0.38 µM) proved to be an inhibitor at least about 6 times more potent than its analogue A-81272 (IC_{50} = 2.3 µM).

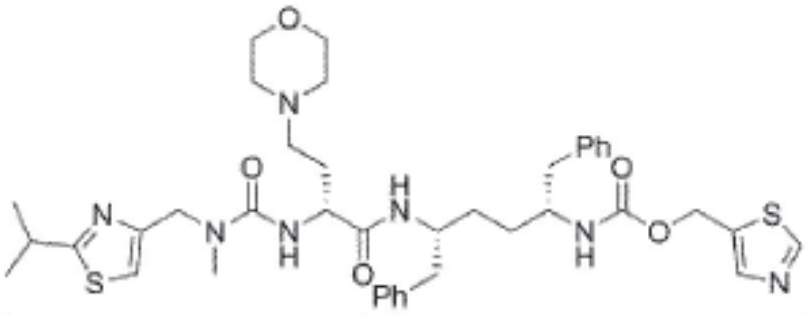
This shows that the above left side is very important for the inhibition of CYP3A and that a structural modification in this part of the molecule cannot, at least not with a reasonable expectation of success, be expected to have no detrimental effect on the extent of CYP3A inhibition.

When confronted with this comparison at the oral proceedings, appellant 1 explained that in the truncated analogue a polar group, namely the thiazolyl group, was brought closer to the hydrophobic active site of CYP3A. The result described above would therefore have been expected by the skilled person. However, this argument contradicts appellant 1's own contention that the left part was not important for the

inhibition of CYP3A. Furthermore, it also raises the question of why the skilled person - who allegedly would expect a negative influence of a polar group in spatial proximity to the active site - would have considered replacing the *iso*-propyl group, which is in spatial proximity to the active site too, with the morpholinoethyl group which, even in its unprotonated form, is more polar than the *iso*-propyl group.

3.10.3 Further according to appellant 1, it was well established before the priority date of the patent that CYP3A4 was the CYP isoform having the largest and structurally most flexible active site. On this basis, appellant 1 concluded that larger solubilising moieties such as the morpholinoethyl group should shift the binding preferences towards the CYP isoform family capable of accommodating such large groups, i.e. towards CYP3A.

Again, this is not convincing. D25 (table B) compares cobicistat to one of its epimers, namely the following compound B2:



Compound B2 differs from cobicistat only in that the absolute configuration of the stereogenic centre to which the morpholinoethyl group is attached is inverted (in the structures depicted in this decision, the morpholinoethyl group lies above the plane of the paper in cobicistat and underneath it in compound B2). The

size of the solubilising moiety is exactly the same in both cases. Following appellant 1's logic, compound B2 should have the same selectivity profile as cobicistat. However, this is not the case. While both compounds have the same inhibitory potency against CYP3A, cobicistat's inhibitory potency against other CYP isoforms is much less compared with that of its epimer. Thus, contrary to appellant 1's assertion, the size of the solubilising moiety is not predictive of selectivity towards CYP3A compared with other CYP isoforms.

In this context, appellant 1 submitted that the skilled person starting from ritonavir would have had no immediate reason also to change the stereochemistry of the backbone and would have preferred to keep the changes as simple as possible. However, this is beside the point, as the above comparison is not intended to show what the skilled person would or would not have done, but that there is no merit to appellant 1's theory regarding the impact of steric bulk on selectivity.

3.10.4 Appellant 1 also argued that crystal structures containing the target enzymes were known before the priority date of the patent. This data could be used in computer-aided (*in silico*) modelling methods. This allowed the skilled person to examine, *inter alia*, whether a molecule containing a particular solubilising moiety at a certain position solved the objective technical problem or not. Thus the skilled person would easily have verified that a derivative of deshydroxyritonavir in which the *iso*-propyl group was replaced with the morpholinoethyl group solved the objective technical problem.

This argument entails trying to modify deshydroxyritonavir with different solubilising moieties (possibly also at different positions of the molecule) and determining, via above-mentioned modelling methods, whether the envisaged molecule solves the objective technical problem. Whether this approach actually constitutes a research project and thus an undue burden, as argued by the respondent, does not have to be decided in the present case, as this argument fails for another reason, namely the fact that - at least with respect to the interaction with CYP3A - no modelling methods that allowed predictions with a reasonable degree of accuracy were available in the present case.

D8 is a review article that deals with molecular recognition between, among other things, various enzymes and their inhibitors. It explicitly points out the importance of elucidating crystal structures from which the interactions between an enzyme and its inhibitor can be seen (page 1361, left-hand column, penultimate paragraph and page 1382, right-hand column, last paragraph). On this basis, an attempt can be made to make predictions about the influence of structural changes in the inhibitor on its interaction with the enzyme.

Considering that the crystal structure of ritonavir bound to HIV-1 protease was already known before the priority date of the patent (D4: figure 2), it may be acknowledged in favour of appellant 1 that it was at least possible to attempt to make predictions about the interaction of ritonavir derivatives, such as deshydroxyritonavir or cobicistat, with HIV-1 protease. However, crystal structures of deshydroxyritonavir or ritonavir bound to a CYP isoform, let alone CYP3A4,

were not known before the priority date of the patent (D28 reports on the crystal structure of ritonavir bound to CYP3A4, but is not prior art). While the crystal structures of CYP3A4 alone (D2) and of CYP3A4 bound to the inhibitors ketoconazole and erythromycin had been published (D26), both D26 (page 13686, left-hand column, second paragraph) and D30 (page 13566, left-hand column, second paragraph), an article published in the same issue as D26 in which a different author comments on the results reported in D26, explicitly warns against applying the results of D26 to molecules other than ketoconazole and erythromycin. These cautionary statements in the literature essentially coincide with the view of the respondent's expert in D27, but not with that of appellant 1's expert in D12. The board therefore ultimately does not consider the latter to be convincing.

3.10.5 To summarise the above points:

Even assuming in favour of appellant 1 that the choice of the morpholinoethyl group as the solubilising moiety was obvious, the way in which this group was incorporated into cobicistat still cannot be considered obvious.

Further, the skilled person, even if considering replacing the *iso*-propyl group with a morpholinoethyl group, would not have done so with the reasonable expectation of not altering the extent of CYP3A inhibition and even increasing the selectivity towards CYP3A compared with other CYP isoforms. Computer-aided modelling methods would not have given a reasonable degree of accuracy in the present case and would have left the skilled person uncertain about the influence

of this structural modification on the extent of CYP3A inhibition and the inhibition of other CYP isoforms.

Obviousness - appellant 2's objection

3.11 According to appellant 2, the objective technical problem starting from ritonavir was "*to improve ritonavir as taught in D3, particularly by trying to obtain a drug that is not itself an inhibitor of HIV protease*" (statement of grounds of appeal, point 2.4 on page 7), thus taking into account only one of the three problems mentioned above under point 3.8. However, as set out above, the objective technical problem has to be formulated in more-ambitious terms. Whether an inventive step is to be acknowledged for this reason alone can be left open at this point, as appellant 2's line of argument regarding the obviousness of the solution is not convincing.

3.12 Appellant 2 set out that to solve the objective technical problem of obtaining a drug that was not itself an inhibitor of HIV protease the skilled person would have routinely modified the substituents on ritonavir, replacing the *iso*-propyl group of the valine building block with a morpholinoethyl group (note: this results in a compound containing both the morpholinoethyl group of cobicistat and the free hydroxy group of ritonavir - referred to as "compound A" hereinafter). Compound A had to have a lower HIV protease inhibitory activity than ritonavir due to steric hindrance. Further, D3 taught the undesired CYP-mediated metabolism of, *inter alia*, ritonavir. The skilled person would have recognised that the degradation of the drug actually desired, i.e. compound A, could be reduced if it was itself an immediate metabolic degradation product. In light of

the teaching conveyed by D14 that CYP-mediated metabolism causes hydroxylation, the skilled person would have provided a prodrug of compound A which was devoid of the free hydroxy group. This required prodrug was cobicistat. Therefore the skilled person would have arrived at cobicistat.

3.13 It follows that appellant 2's line of reasoning is based on the proposition that cobicistat is metabolised to compound A *in vivo*. However, there is no apparent reason why this transformation should occur, at least not with a reasonable expectation of success, as the above reasoning, where it was concluded that there is no apparent reason why the transformation of deshydroxyritonavir to ritonavir should occur, applies *mutatis mutandis*. For this reason alone, appellant 2's objection fails to convince.

Obviousness - conclusion

3.14 Consequently, the subject-matter of claim 1 and that of claim 2 (the same reasoning applying *mutatis mutandis*) involves an inventive step within the meaning of Article 56 EPC. The main request is therefore allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent in amended form with the following claims, and a description to be adapted thereto:

   Claims 1 and 2 of the main request, filed as auxiliary request 1 with the reply to the statements of grounds of appeal

The Registrar: The Chairman:

M. Schalow M. O. Müller

Decision electronically authenticated