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# Datasheet for the decision of 5 July 2022

**Case Number:** T 1442/19 - 3.3.02

**Application Number:** 12167589.6

**Publication Number:** 2487161

**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.
Cooke, Richard

**Relevant legal provisions:**
EPC Art. 76(1), 56
RPBA Art. 12(4)

**Keyword:**
Divisional application - added subject-matter
Inventive step
Late-filed request - submitted with the reply to the statements of grounds of appeal

**Decisions cited:**
T 2037/17, T 1214/18, T 2635/18, T 0735/19

**Catchword:**
Extension of subject-matter: selection from an indication of equally preferred items (e.g. formed by several independent claims) disclosed in the application as filed (see point 2.4.1 of the Reasons)

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**Case Number: T 1442/19 - 3.3.02**

# D E C I S I O N
# of Technical Board of Appeal 3.3.02
# of 5 July 2022

| | |
|---|---|
| **Appellant 1:**<br>(Opponent 1) | Teva Pharmaceutical Industries Ltd.<br>124 Dvora HaNevi'a St.<br>6944020 Tel Aviv (IL) |
| **Representative:** | Eder, Michael<br>df-mp Dörries Frank-Molnia & Pohlman<br>Patentanwälte Rechtsanwälte PartG mbB<br>Theatinerstrasse 16<br>80333 München (DE) |
| **Appellant 2:**<br>(Opponent 2) | Cooke, Richard<br>c/o Elkington and Fife LLP<br>Patents Department<br>3-4 Holborn Circus<br>London EC1N 2HA (GB) |
| **Representative:** | Elkington and Fife LLP<br>Prospect House<br>8 Pembroke Road<br>Sevenoaks, Kent TN13 1XR (GB) |
| **Respondent:**<br>(Patent Proprietor) | GILEAD SCIENCES, INC.<br>333 Lakeside Drive<br>Foster City,<br>California 94404 (US) |
| **Representative:** | Carpmaels & Ransford LLP<br>One Southampton Row<br>London WC1B 5HA (GB) |
| **Decision under appeal:** | **Interlocutory decision of the Opposition Division of the European Patent Office posted on 23 April 2019 concerning maintenance of the European Patent No. 2487161 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. 2 487 161 (patent) in amended form meets the requirements of the EPC.

The patent originates from European patent application No. 12 167 589.6, which is a divisional application of European patent application No. 08 743 531.9.

II. The following documents are relevant to the present decision:

P2 Priority application US 60/958,716 of the patent
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
D18 WO 2008/010921 A2
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
D26a Guengerich, F. P., PNAS 2006, 103(37), pages 13565 to 13566
D27 Declaration of Professor Nico P. E. Vermeulen
D28 Sevrioukova, I. F. et al., PNAS 2010, 107(43), pages 18422 to 18427

III. With the reply to the statements of grounds of appeal, the patent proprietor (respondent) filed, *inter alia*, the sets of claims of auxiliary requests 1 and 2.

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

V. On 5 July 2022, oral proceedings were held before the board in the presence of all the parties. The board decided to admit auxiliary request 2 into the proceedings. At the end of the oral proceedings, the chair announced the order of the present decision.

VI. The parties' final requests relevant to this decision were as follows:

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

  Appellant 2 also requested that auxiliary requests 1 and 2 not be admitted into the proceedings.

- The respondent requested that the appeals be dismissed, implying that the patent be maintained in amended form as held allowable in the decision under appeal (main request), or alternatively that the patent be maintained in amended form based on one of the sets of claims of auxiliary requests 1 or 2, each filed with the reply to the statements of grounds of appeal.

VII. The parties' appeal cases relevant to the present decision can be summarised as follows:

Appellants 1 and 2

- The subject-matter of claim 3 of the main request and auxiliary request 1 was the result of a double selection from the parent application as filed without there being any pointer to this effect. This view was supported by decisions T 1255/18 and T 3139/19. According to T 1255/18, the information conveyed to the skilled person was crucial to the question of whether a set of items constituted a list in patent law terms but not the form in which these were presented. According to T 3139/19, the limitation to only one item still required a selection even if the corresponding list comprised only two items. The main request and auxiliary request 1 therefore did not meet the requirements of Article 76(1) EPC.

- Summaries of the appellants' objections to auxiliary request 2 are contained in the reasons for this decision.

Respondent

- Summaries of the respondent's arguments relating to the main request and auxiliary request 1 are contained in the reasons for this decision.

- Based on the board's preliminary opinion in its communication pursuant to Article 15(1) RPBA 2020, auxiliary request 2 had to meet the requirements of Article 76(1) and Article 123(2) EPC. The priority claimed from P2 was also valid.

  The pharmacoenhancer ritonavir disclosed in D3 was the most suitable starting point for assessing inventive step. The objective technical problem was to provide a pharmaceutical composition comprising a pharmacoenhancer (i) which lacked HIV-1 protease inhibitory activity, (ii) which was a potent inhibitor of CYP3A and exhibited increased selectivity for 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 taking this structural modification into consideration, 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 subject-matter claimed in auxiliary request 2 therefore involved an inventive step.

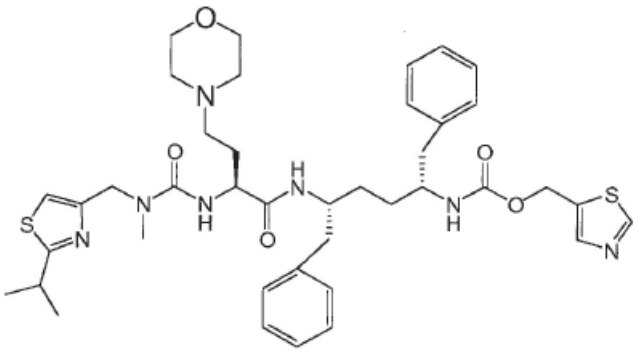
## Reasons for the Decision

Main request

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

Claim 1

"*A pharmaceutical composition comprising a compound of formula IIBb*



(IIBb)

*or a pharmaceutically acceptable salt, and/or solvate thereof, a pharmaceutically acceptable carrier or excipient and at least one additional therapeutic agent.*"

Claim 2

"*The pharmaceutical composition of claim 1, wherein the at least one additional therapeutic agent is metabolized by cytochrome P450 monooxygenase.*"

Claim 3

"*The pharmaceutical composition of any one of claims 1 to 2, wherein the at least one additional therapeutic agent is selected from the group consisting of HIV protease inhibiting compounds.*"

Claim 4

"*The pharmaceutical composition of claim 3, wherein: said HIV protease inhibiting compounds are selected from the group consisting of amprenavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147*

*(AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859.*"

The compound whose structure is shown in claim 1 is example S of the parent application as filed. In agreement with the parties, it is referred to as cobicistat hereinafter. Thus claim 1 relates to a pharmaceutical composition comprising, *inter alia*, cobicistat and at least one additional therapeutic agent. In claims 2 to 4, the additional therapeutic agent is defined further as metabolised by cytochrome P450 monooxygenase, as an HIV protease inhibiting compound, and as being selected from a group of specific compounds, respectively.

2. Amendments (Article 76(1) EPC)

2.1 In line with the parties, the board refers to the published version (WO 2008/103949 A1) for the disclosure of the parent application as filed.

2.2 Claim 3 of the main request relates to a pharmaceutical composition comprising, *inter alia*, an HIV protease inhibiting compound as the additional therapeutic agent and cobicistat.

The respondent acknowledged that the HIV protease inhibiting compound of claim 3 is the result of a selection from the parent application as filed. The only dispute between the parties concerned the question of whether or not cobicistat involves a further selection.

2.2.1 As regards cobicistat, the following parts of the parent application as filed are relevant (it should be recalled that example S is cobicistat):

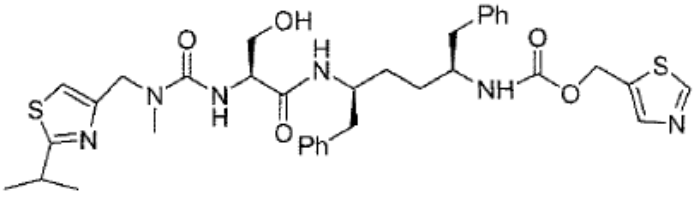
(a) page 217, line 1 to page 393, line 5, with syntheses of compounds according to the invention; four methods of synthesis for example S are disclosed on pages 251 to 259

(b) page 194, lines 21 ff.; this passage reads:

"*For example, such combinations can comprise Example P, S, or X, or a pharmaceutically acceptable salt, solvate, and/or ester thereof in combination with two or three additional therapeutic agents selected from the group consisting of [...]*"

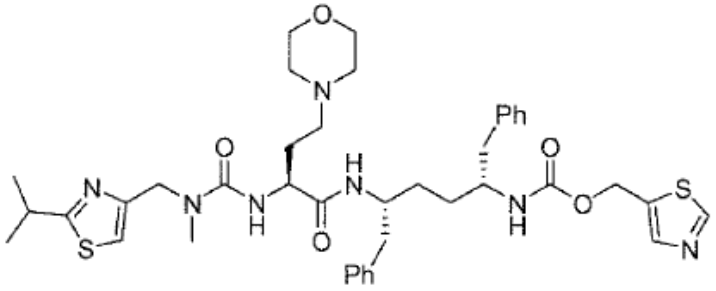
(c) claims 19 to 21; these claims read as follows:

"*19. A compound which is:*



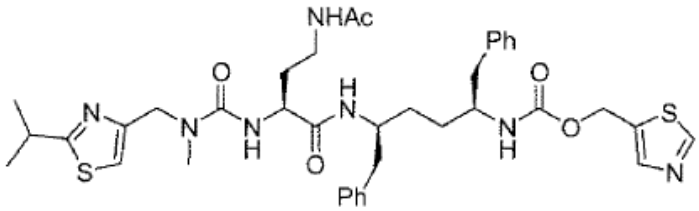

*or a pharmaceutically acceptable salt, ester, and/or solvate thereof.*

*20. A compound which is*



*or a pharmaceutically acceptable salt, ester, and/or solvate thereof.*

*21. A compound which is*



*or a pharmaceutically acceptable salt, ester, and/or solvate thereof.*"

Each of these claims is an independent claim. They relate to examples P (claim 19), S (claim 20) and X (claim 21).

(d) page 401, lines 3 to 7; this passage reads:

"*Experimental data based on representative Examples **P**, **S**, and **T** have a CYP450 3A4 inhibition activity in a range represented by an $IC_{50}$ from about 80-150 nM, a CYP450 2C9 inhibition activity in a range represented by an $IC_{50}$ from about 1000-10,000 nM, and a protease*

*inhibition activity in a range represented by HIV $EC_{50}$ greater than about 30,000 nM.*"

2.2.2 Part (a) does not present cobicistat as preferred to the other examples of the parent application as filed.

In parts (b) and (d), cobicistat is presented at the same level of preference as two other examples, namely examples P and X and examples P and T, respectively.

As regards part (c), claims 19 to 21 have essentially the same wording. They only differ from each other with respect to the compounds claimed, but do not in any way suggest that one of their compounds is preferred over the other two. Thus, similarly to part (b), part (c) also presents cobicistat at the same level of preference as examples P and X.

It follows that in each of the above cases cobicistat must be selected from an indication of equally preferred examples, i.e. an enumeration of items ("list"), to arrive at the subject-matter of claim 3.

2.3 Thus to arrive at the subject-matter of claim 3 both the HIV protease inhibiting compound and cobicistat have to be selected from lists of the parent application as filed. It is established case law that such a double selection results in subject-matter which extends beyond the content of the (parent) application as filed unless there is a pointer to the specific combination claimed. However, in the present case there is no such pointer.

2.4 The respondent took the view that the subject-matter of claim 3 of the main request was directly and

unambiguously disclosed in the parent application as filed for the following reasons:

2.4.1 According to the respondent, the parent application as filed disclosed (see e.g. part (a) above) and encompassed (see e.g. claim 1 as filed) a multitude of different compounds. Of these compounds, three, including cobicistat, were elevated above all the others in the parent application as filed. At least parts (b) to (d) of the parent application as filed, therefore, were not to be understood according to case law as lists from which cobicistat had to be selected. This was particularly true of claims 19 to 21. As they contained cobicistat in individualised form in claim 20, cobicistat was a standalone embodiment of the invention and did not require a selection. This view was confirmed by decisions T 735/19 and T 2635/18. At the very least, the fact that cobicistat was individualised in claim 20 had to be understood as a pointer to precisely this compound.

The board cannot agree with this argument. The concept of lists does not require a list necessarily to have a particular format, for example a table or with each item introduced with a number or bullet point, nor is it applicable only to such formats. Rather, the information conveyed to the skilled person is crucial. If the skilled person is confronted with an indication of equally preferred items, this indication of items forms an enumeration or "list". Although it may be more obvious for parts (a), (b) and (d) that their indication of compounds forms a list, it is also true of part (c), i.e. claims 19 to 21. This can be illustrated by the fact that, as far as the disclosure is concerned, there is no difference between part (c), mentioning examples P, S and X in individual claims,

and the hypothetical situation in which these examples are all contained in a single claim, the latter situation being more akin to what is usually referred to as a list.

Since claims 19 to 21 form a list, the mere fact that cobicistat is individualised in claim 20 cannot be understood as a pointer to this compound as argued by the respondent - a view that might possibly have been accepted if cobicistat had been the only compound mentioned in the claims.

That claims 19 to 21 form a list, of which limitation to only one constitutes a selection, is precisely what distinguishes the present case from those underlying decisions T 735/19 and T 2635/18, on which the respondent relied to support its argument that a claim was a standalone embodiment and that a limitation to its subject-matter did not constitute a selection.

In T 2635/18 (Reasons, point 3.1.1), it was indeed held that starting from the embodiment of a dependent claim of the application as filed did not constitute a selection. However, contrary to the present case, with regard to the dependent claim in question, there were no other dependent claims with regard to which a selection would have had to be made. A similar assessment was made in case T 735/19 (Reasons, point 1.2), albeit with regard to Article 54 EPC. The claim at issue was directed to a contact lens comprising, *inter alia*, a hydrogel comprising phosphorylcholine groups. Dependent claim 32 of the prior-art document relevant to novelty of the subject-matter of the claim at issue disclosed a contact lens comprising as a component a polymer of hydroxyethyl methacrylate and a phosphorylcholine derivative. The competent board held

that starting from the embodiment of claim 32 did not constitute a selection. This conclusion again is not in contradiction to that in the present case because in T 735/19 there were no other dependent claims in the relevant prior-art document relating to compounds which were preferred equally to that of dependent claim 32.

2.4.2 The respondent also argued that even if claims 19 to 21 were considered as a list, this list was very short. In this context, decision T 2037/17 was relevant. This decision found a double selection from two very short lists to be an allowable amendment.

The board cannot agree with this argument either. The fact that the lists in passages (b) to (d) and in particular in claims 19 to 21 comprise only three compounds and are thus to be regarded as very short, as submitted by the respondent, does not render a selection superfluous. Even if decision T 2037/17 (Reasons, point 1.3) were understood to mean that a double selection from two lists of only two items was allowable, as argued by the respondent, this has no bearing on the present case, where the lists including cobicistat and the HIV protease inhibiting compound comprise three and significantly more than two items, respectively.

2.4.3 It follows that claim 3 does not meet the requirements of Article 76(1) EPC. The main request is not allowable.

Auxiliary request 1

3. Claim 3 of auxiliary request 1 is identical to claim 3 of the main request. Thus auxiliary request 1 is not

allowable for the same reasons as set out above with regard to the main request.

Auxiliary request 2

4. The set of claims of auxiliary request 2 consists of two claims. They are identical to claims 1 and 2 of the main request (see above). In other words, the set of claims of auxiliary request 2 differs from that of the main request only in that claims 3 and 4 of the latter have been deleted.

5. Admittance (Article 12(4) RPBA 2007)

5.1 The set of claims of auxiliary request 2 was filed with the respondent's reply to the statements of grounds of appeal. Pursuant to Articles 24 and 25 RPBA 2020, the question of admittance was to be decided on the basis of Article 12(4) RPBA 2007.

Appellant 2 requested that auxiliary request 2 not be admitted into the proceedings. He argued that claims 3 and 4 of the main request corresponded to claims 10 and 11 as granted. Appellant 2 had raised objections under Article 76(1) EPC against claims 10 and 11 as granted in the notice of opposition and in the subsequent submissions. The set of claims of auxiliary request 2, which no longer contained these claims, should therefore already have been filed before the opposition division and not only on appeal. It was correct that the opposition division had given a positive preliminary opinion on Article 76(1) EPC, but this wrong assessment had been corrected by the board at the oral proceedings. The position of appellant 2 should not be worsened by the admittance of auxiliary request

2 merely because the opposition division was wrong on this point.

5.2 The board's position is as follows:

While it is true that appellant 2 had raised objections under Article 76(1) EPC against the now-deleted claims very early in the opposition proceedings, further objections to the other granted claims were also raised, not only under Article 76(1) EPC. In fact, two oppositions had been filed with a particular focus on granted claim 1 and relying on Article 100(a), (b) and (c) EPC as grounds for opposition, including several objections and submissions relating to the invalidity of a claimed priority. Against this background, the objections under Article 76(1) EPC against the now-deleted claims constituted a side aspect of the oppositions initially filed. In view of this specific situation, it could not have been expected of the respondent to have presented the set of claims of auxiliary request 2 already in response to the oppositions. Moreover, the opposition division issued a preliminary opinion in which it came to the conclusion that the requirements of Article 76(1) EPC were met. Therefore there is no reason apparent to the board in the present case why the claims of auxiliary request 2 should have been filed before the opposition division.

Furthermore, the claims of auxiliary request 2 were filed at the earliest possible stage on appeal, namely with the reply to the statements of grounds of appeal. The amendments made are straightforward as they merely involve the deletion of dependent claims from the main request and do not give rise to new issues.

Therefore the board, exercising its discretion under Article 12(4) RPBA 2007, decided to admit auxiliary request 2 into the proceedings.

6. Amendments (Article 76(1) EPC)

6.1 The parent application as filed (pages 2 to 4) summarises its invention as relating in particular to the following three aspects:

(i) specific compounds
(ii) pharmaceutical compositions comprising such compounds and a pharmaceutically acceptable carrier or excipient
(iii) pharmaceutical compositions comprising such compounds together with at least one additional therapeutic agent and a pharmaceutically acceptable carrier or excipient (see e.g. paragraph bridging pages 3 and 4, or page 190, last paragraph).

The parties agreed that cobicistat is an example of the compounds mentioned in (i) to (iii) above.

Thus, starting from aspect (iii), it just needs cobicistat to be selected as the compound to arrive at the subject-matter of claim 1 of auxiliary request 2. It is established case law that such a single selection does not generate subject-matter which extends beyond the content of the (parent) application as filed.

6.2 While the appellants agreed with the structure of the parent application as filed set out above, they argued that starting from aspect (iii) already amounted to a first selection. In view of the further selection of

cobicistat, a double selection had to be made from the parent application as filed to arrive at the subject-matter of claim 1 of auxiliary request 2. Consequently, claim 1 did not meet the requirements of Article 76(1) EPC.

6.3 The board does not agree with this view. The above aspects are not an indication of equally preferred items, and do not constitute a list from which one specific item, here aspect (iii), would have to be selected and combined with another specific item from another list, here cobicistat. This is illustrated, for example, by the fact that these aspects cannot be subsumed under the same generic term, contrary to the case with cobicistat and the other two compounds mentioned in claims 19 to 21, all falling under the same Markush formula (see above).

Rather, the above aspects (i) to (iii) are given in the parent application as filed under the title "SUMMARY OF THE INVENTION" and describe three aspects of the invention in very general terms. The term "summary" in this title can only mean that what is in this section summarises what comes next. It is thus directly and unambiguously clear to the skilled person reading the parent application as filed that the very general definitions of the aspects of the invention given in this summary section apply to any specific embodiment described subsequently, including cobicistat.

Also from a technical point of view, the skilled person would directly and unambiguously derive from the parent application as filed that cobicistat applies to all the generally described aspects of the invention disclosed in the summary section. More specifically, each of these aspects includes a pharmaceutically active

compound and, as agreed by the parties, cobicistat is an example thereof. It would be technically nonsensical to assume that cobicistat is an example of such a compound in a pharmaceutical composition (one of the aspects described in the summary section), but not in a pharmaceutical composition with an additional therapeutic agent (another aspect described in the summary section).

Hence, from a linguistic and technical point of view, no double selection is needed to arrive at the subject-matter of claim 1.

6.4 The parent application as filed further discloses that, as required by claim 2 of auxiliary request 2, the additional therapeutic agent is preferably an agent metabolised by cytochrome P450 monooxygenase (e.g. page 191, lines 1 to 7).

6.5 Thus claims 1 and 2 of auxiliary request 2 meet the requirements of Article 76(1) EPC.

7. Amendments and priority (Article 123(2) and Articles 87 and 89 EPC)

In its communication pursuant to Article 15(1) RPBA 2020, the board had set out what it understood from the appellants' written submissions, namely

(i) that the requirements of Article 123(2) EPC are met

(ii) that the priority claimed from P2 is valid and that consequently D18 is prior art under Article 54(3) EPC and is not available for assessing inventive step

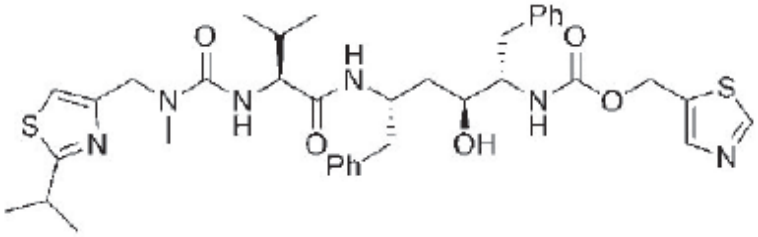
if the requirements of Article 76(1) EPC are met.

The above was not challenged by the appellants, who in fact made no further submissions under Article 123(2) and Article 87 EPC at the oral proceedings. The board is also satisfied that the claims of auxiliary request 2 meet the requirements of Article 123(2) EPC and that the priority claimed from P2 is valid.

8. Inventive step (Article 56 EPC)

8.1 The parties agreed that D3 is the closest prior art for the claimed subject-matter.

D3 (abstract; point 1) discloses the use of the HIV protease inhibitor ritonavir as a booster/ pharmacoenhancer. Ritonavir has the following structure:




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 taken on in the present case by cobicistat.

The board therefore agrees with the parties in choosing D3 as the closest prior art and ritonavir as the starting point for assessing inventive step.

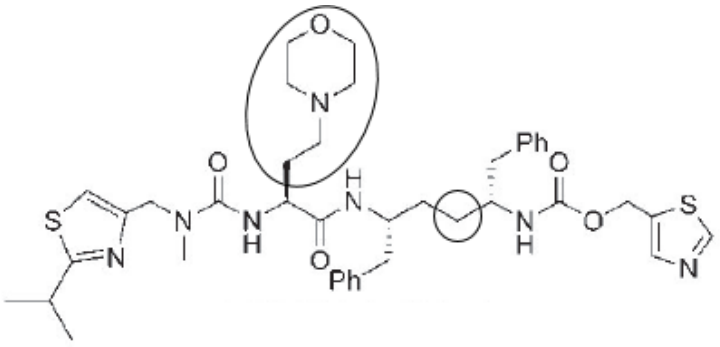
8.2 D3 (e.g. point 5 on page 408 f.) discloses regimens of ritonavir together with another HIV protease inhibitor (lopinavir, saquinavir, amprenavir, indinavir). It was common ground between the parties that this amounts to a disclosure of pharmaceutical compositions comprising ritonavir, a pharmaceutically acceptable carrier or excipient and at least one additional therapeutic agent.

8.3 On this basis, the subject-matter of claim 1 differs from D3 in that the pharmaceutical composition comprises cobicistat, i.e. a pharmacoenhancer which is different from ritonavir.

Cobicistat differs from ritonavir in that

(i) it does not contain a hydroxy group
(ii) it contains a morpholinoethyl group instead of an *iso*-propyl group.

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



8.4 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.

- 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 for 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.

8.5 In view of the above, the objective technical problem is to provide a pharmaceutical composition comprising a pharmacoenhancer

(i) which lacks HIV-1 protease inhibitory activity,
(ii) which is a potent inhibitor of CYP3A and which exhibits increased selectivity for enzymes of this subfamily relative to enzymes of other CYP subfamilies
(iii) which retains oral bioavailability

8.6 The appellants did not agree with this formulation of the objective technical problem.

8.6.1 More specifically, appellant 2 argued that the objective technical problem above considered the properties of cobicistat alone but not those of the claimed combinations which related to cobicistat and (any) additional therapeutic agent. The pharmacokinetic boost provided by cobicistat was desirable only for specific additional therapeutic agents. For other additional therapeutic agents, however, metabolism by CYP was essential for clearance, and their combination with cobicistat would cause dangerous elevated plasma concentrations. Thus the objective technical problem could only be defined as providing arbitrary combinations.

In a similar vein, appellant 1 argued that the combination of cobicistat with a therapeutic agent that was not metabolised by CYP3A4 did not solve any problem over the provision of said additional therapeutic agent alone. Accordingly, such an embodiment, which was covered by claim 1, had to be considered arbitrary.

8.6.2 In their lines of argument, both appellants disregard the fact that the assessment of inventive step has to start from the closest prior art, i.e. in the circumstances of the present case from prior-art document D3, as agreed by the appellants themselves. This document discloses ritonavir in combination with, as additional therapeutic agent, an agent the degradation of which by CYP3A is undesirable. In view of this embodiment, the objective technical problem is as formulated above (see point 8.5) and is also solved.

The appellants' argument advanced for a different formulation of the objective technical problem is, without saying so explicitly, in fact based on a different starting point, namely ritonavir in combination with, as additional therapeutic agent, an agent which is not metabolised by CYP3A or an agent the degradation of which by CYP3A is desirable. However, no closest prior art was cited in this respect by the appellants and no problem-solution approach was presented on the basis of any such prior art. This is contrary to what is required by Article 56 EPC, which makes explicit reference to an invention involving an inventive step "having regard to the state of the art". For this reason too, the appellants' argument is not convincing.

8.7 As regards the obviousness of the claimed solution to the objective technical problem above, in other words the obviousness of cobicistat over ritonavir in structural terms, the board during the oral proceedings referred to the discussion in case T 1214/18, the oral proceedings of which had been held on the previous day and concerned a similar objective technical problem (namely to provide a compound with the above three properties (i) to (iii)). Both appellant 1 and the respondent confirmed that they had nothing to add to this discussion for the present case.

Appellant 2 had never presented any argument in writing relating to the obviousness of cobicistat over ritonavir in structural terms. Appellant 2 did not submit any arguments in this respect at the oral proceedings before the board either.

The board's assessment therefore deals with appellant 1's arguments concerning the obviousness of cobicistat over ritonavir and corresponds *mutatis mutandis* to that in case T 1214/18.

8.8 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, 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.

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

8.9.1 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 in an obvious manner when 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 hydroxy 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)

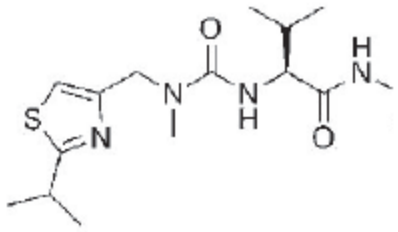
> "*Solubilization* ***with basic side chains*** *involves two essential strategies:* ***either direct binding of the amine function on a carbon atom of the parent molecule****, or linking it to a function already present: alcoholic or phenolic hydroxyl, carboxylic acid, amine or amide.*"

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 9.2.3 on pages 16 and 17) and which alone would be sufficient to acknowledge inventive step, the board cannot agree with at least the following further points from appellant 1's line of argument either:

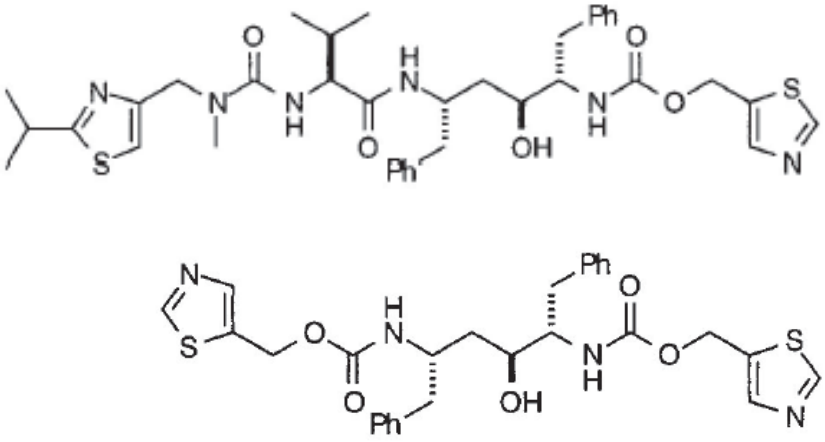
8.9.2 According to appellant 1, the skilled person would not have considered attaching the solubilising moiety to those parts of the molecule which were important for the inhibition of CYP3A. In the case of ritonavir, these were the unsubstituted 5-thiazolyl group and the hydrophobic core flanked by 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 in case T 1214/18, 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):



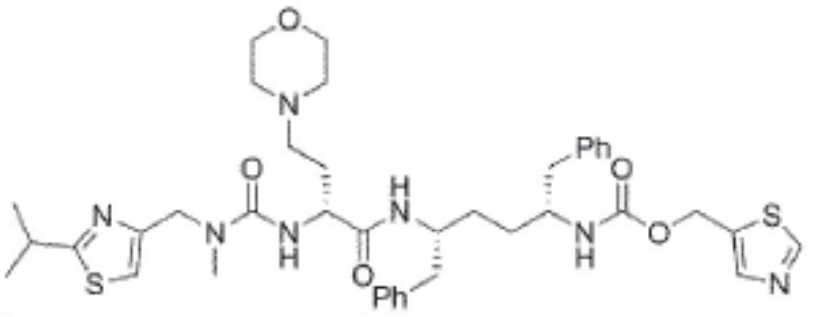
This truncated analogue differs from ritonavir only in that its left side is different. Nevertheless, contrary to appellant 1's contention suggesting no substantial inhibitory difference between ritonavir and this analogue, ritonavir ($IC_{50}$ = 0.38 µM) proved to be an inhibitor at least about 6 times 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 in case T 1214/18, 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.

8.9.3 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 for 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.

8.9.4 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 of 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 D26a (page 13566, left-hand column, second paragraph), an article published in the same issue as D26 and 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.

8.9.5 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.

8.10 Thus the subject-matter of claim 1 and by virtue of its dependency on claim 1 also that of claim 2 involves an inventive step within the meaning of Article 56 EPC. Auxiliary request 2 is 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 auxiliary request 2 filed with the reply to the statements of grounds of appeal.

The Registrar: The Chairman:

M. Schalow M. O. Müller

Decision electronically authenticated