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Datasheet for the decision of 23 August 2021

Case Number: T 2049/19 - 3.3.01

Application Number: 07794121.9

Publication Number: 2056832

IPC: A61K31/519, A61K9/20, A61K9/48

Language of the proceedings: EN

Title of invention:
COMPOSITIONS, SUITABLE FOR ORAL ADMINISTRATION, COMPRISING A TRIAZOLO [4, 5-D]PYRIMIDIN DERIVATE

Patent Proprietor:
AstraZeneca AB

Opponents:
Wittkopp, Alexander
Hexal AG
Generics [UK] Limited (trading as Mylan)

Headword:
Ticagrelor formulation/ASTRAZENECA

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - no (all requests)

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Case Number: T 2049/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 23 August 2021

Appellant: (Opponent 1)	Wittkopp, Alexander Bogenallee 5 20144 Hamburg (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Appellant: (Opponent 2)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
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Representative:	Gill Jennings & Every LLP The Broadgate Tower 20 Primrose Street London EC2A 2ES (GB)
Respondent: (Patent Proprietor)	AstraZeneca AB 151 85 Södertälje (SE)
Representative:	Potter Clarkson The Belgrave Centre Talbot Street Nottingham NG1 5GG (GB)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 22 May 2019 rejecting the oppositions filed against European patent No. 2056832 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chair R. Hauss
Members: J. Molina de Alba
R. Romandini

Summary of Facts and Submissions

I. The decision under appeal is the opposition division's decision rejecting the three oppositions filed against European patent No. 2 056 832 (hereinafter "the patent").

The patent had been granted with nine claims. Independent claim 1 reads as follows.

"*1. A pharmaceutical composition comprising:*

{11S-[1α,2α,3β(1S,2R*),5β]}-3-(7-{[2-(3,4-difluorophenyl)cyclopropyl]-amino}-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol;*
a filler which is a mixture of mannitol and dibasic calcium phosphate dihydrate;
a binder which is hydroxypropyl cellulose;
a disintegrant which is sodium starch glycollate; and one or more lubricants."

During the opposition and appeal proceedings, the parties referred to the compound in claim 1 as granted as the active ingredient "ticagrelor", disclosed in paragraphs [0001] and [0002] of the patent specification. The board sees no reason to differ and assumes that the mention in claim 1 of the configuration "11S" instead of ticagrelor's configuration "1S" is merely a typing error. The error was reproduced in claim 1 of each of auxiliary requests 1 to 7 but was corrected in claim 1 of auxiliary request 8 (see point VI below). In any case, the typing error has no bearing on the outcome of this decision.

II. The following documents are referred to in the present decision.

D3 WO 01/92262 A1

D9 Handbook of Pharmaceutical Excipients, R. Rowe et al., Fifth Edition, 2006, pages 96-9, 132-5, 211-3, 336-43, 385-98, 430-3, 449-53, 611-6 and 701-4

D11 Remington. The Science and Practice of Pharmacy, 20th Edition, 2000, pages 654-8, 713-4, 858-61, unnumbered pages on glidants, disintegrants, coloring agents and flavoring agents, pages 884-5 and 1114-5

D12 Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Eighth Edition, 2005, pages 233-9 and 253-4

D13 Respondent's letter dated 7 June 2013

D25 Declaration by M. Thomson dated 24 May 2018

III. The oppositions had been filed on the grounds that the claimed subject-matter did not involve an inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed (Article 100(a), (b) and (c) EPC).

IV. In the decision under appeal, the opposition division concluded that none of these grounds prejudiced the maintenance of the patent as granted. It held, among other things, that starting from document D3, which taught tablet formulations of ticagrelor, and taking into consideration the comparative data provided in post-filed documents D13 and D25, the subject-matter of claim 1 as granted was inventive.

V. Opponents 1 and 2 (appellants 1 and 2 respectively) each filed an appeal and requested that the opposition division's decision be set aside and that the patent be revoked.

Opponent 3 (party as of right) also filed an appeal, which it later withdrew.

VI. In its reply to the statements setting out the grounds of appeal, the patent proprietor (respondent) requested that the appeals be dismissed and that the patent be maintained as granted (main request). In addition, it filed eight sets of claims as auxiliary requests 1 to 8.

Claim 1 of auxiliary request 1 differs from claim 1 as granted in that it specifies that the pharmaceutical composition is oral.

Claim 1 of auxiliary request 2 differs from claim 1 as granted in that it specifies that ticagrelor is present in an amount of 20 to 45% by weight.

Claim 1 of auxiliary request 3 differs from claim 1 as granted in that it specifies that mannitol is present in an amount of 20 to 45% by weight and dibasic calcium phosphate dihydrate is present in an amount of 10 to 30% by weight.

Claim 1 of auxiliary request 4 differs from claim 1 as granted in that it combines the amendments of auxiliary requests 1 and 2.

Claim 1 of auxiliary request 5 differs from claim 1 as granted in that it combines the amendments of auxiliary requests 1 and 3.

Claim 1 of auxiliary request 6 differs from claim 1 as granted in that it combines the amendments of auxiliary requests 2 and 3.

Claim 1 of auxiliary request 7 differs from claim 1 as granted in that it combines the amendments of auxiliary requests 1, 2 and 3.

Claim 1 of auxiliary request 8 reads as follows.

"*1. A pharmaceutical composition comprising:*

{1S-[1α,2α,3β(1S,2R*),5β]}-3-(7-{[2-(3,4-difluorophenyl)cyclopropyl]-amino}-5-(propylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)-cyclopentane-1,2-diol in an amount of 20 to 45% by weight;*
mannitol in an amount of 20 to 45% by weight;
dibasic calcium phosphate dihydrate in an amount of 10 to 30% by weight;
hydroxypropylcellulose in an amount of 3 to 6% by weight;
sodium starch glycolate in an amount of 2 to 6% by weight; and
one or more lubricants in an amount of 0.5 to 3% by weight."

VII. The board scheduled oral proceedings in line with the parties' requests. In its preliminary opinion, the board focused on the issue of inventive step: it expressed doubt on the validity of Formulation 1 of D13 as a reference for comparison, and mentioned that it

was inclined to agree with the appellants that the objective technical problem had to be formulated in terms of an alternative.

VIII. On 23 August 2021, oral proceedings before the board were held by videoconference. Appellant 2 and the party as of right (opponent 3) did not attend the oral proceedings. Appellant 2 had informed the board of its absence in advance of the oral proceedings.

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

X. The appellants' arguments, where relevant to the present decision, can be summarised as follows.

The composition of claim 1 as granted did not involve an inventive step. The closest prior art was represented by the tablets in Example 2 of D3, especially Tablet II. The claimed composition differed from Tablet II in its particular combination of excipients.

This difference did not produce any technical effect. The improvements in bioavailability and stability alleged by the respondent were not rendered plausible in the application as filed, so post-filed evidence could not be taken into account.

Even if post-filed evidence were to be considered, the comparative examples in D13 and D25 did not demonstrate that the improvements observed were due to any feature distinguishing the claimed composition from the disclosure of D3: these improvements had been shown over Formulation 1 of D13, which was not a suitable comparator. This was because Formulation 1 of D13 and

Tablet II of D3 differed in several features and, contrary to the respondent's allegation, it could not be inferred that Formulation 1 must necessarily be superior to Tablet II.

First, Tablet II had less than one fifth of the binder content of Formulation 1 and a different filler composition. Regarding the differences in the filler, the respondent's reasoning was inconsistent: the respondent claimed on the one hand that the differences between Tablet II and Formulation 1 as regards the filler components were immaterial, while arguing on the other hand that the differences between the filler components of Formulations 2 and 1 of D13 resulted in a surprising increase in bioavailability.

Second, the argument that Formulation 1 must be superior to Tablet II because it had been prepared by the respondent for its use at a more advanced stage in the development of ticagrelor formulations was flawed. The modification of pharmaceutical formulations across their development stages was not necessarily driven by improvements in bioavailability and stability. Other factors were also considered, such as production and cost.

Thus, even though the respondent was itself the applicant for the patent application D3, the respondent had failed to prove its own allegation that Formulation 1 was a suitable comparator.

Regarding the higher stability of Formulation 3 over Formulation 2 that was reported in D13, and the improved disintegration rate of the composition in D25 comprising hydroxypropyl cellulose, neither D13 nor D25

showed conclusively that these technical effects had been achieved in relation to Tablet II.

Thus, the objective technical problem to be solved was the preparation of an alternative pharmaceutical formulation of ticagrelor.

The excipients in Tablet II and in claim 1 as granted had all been well known on the priority date, e.g. from handbooks/textbooks such as D9 and D11. As exchanging excipients and adjusting their quantities was a routine step in the development of tablet formulations (D12, pages 253 and 254), it would have been an obvious measure for the skilled person to replace the excipients in Tablet II by those of claim 1 having the same functions. Furthermore, the quantitative limitations included in the dependent claims were within the standard ranges disclosed in D9.

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

The composition in claim 1 as granted was inventive over the closest prior art, represented by Tablet II in Example 2 of D3. It differed from that closest prior art in its combination of the key excipients mannitol, dibasic calcium phosphate dihydrate, hydroxypropyl cellulose and sodium starch glycolate. This difference resulted in increased bioavailability and improved stability (shelf life). As these technical effects were plausible on the basis of the application as filed, the post-filed comparative data in D13 and D25 demonstrating the effects had to be taken into account.

Regarding the data presented in D13, Formulation 1 was a valid comparator. Although Formulation 1 was not

identical to the formulation of the closest prior art (Tablet II of D3), it was sufficiently similar. It was also expected to have comparable or even superior dissolution properties and bioavailability, as it contained twice as much disintegrant and its active compound was micronised. Furthermore, Tablet II of D3 and Formulations 1 to 3 of D13 represented the timeline of the development of ticagrelor formulations by the respondent. Formulation 1 was the formulation used for Phase I/IIa studies and had resulted from the optimisation of Tablet II. Consequently, Formulation 1 was necessarily superior to Tablet II of D3 and was a valid comparator.

As shown in D13 (figure on page 6), Formulation 3, which conformed to claim 1, showed improved dissolution in comparison with Formulation 1. This implied that Formulation 3 was also superior to Tablet II of D3. The difference between Tablet II and Formulation 1 as regards the filler components was immaterial.

D13 also showed that the binder/disintegrant combination according to claim 1 (represented by Formulation 3) resulted in higher stability than that in Formulation 1. This could be seen from a comparison of Formulations 2 and 3, which differed essentially in that the combination binder/disintegrant in Formulation 2 corresponded to that of Formulation 1. This improvement in terms of stability had been achieved without compromising the dissolution properties, which were equivalent to those of Formulation 2. Moreover, test report D25 showed that the binder according to claim 1 (hydroxypropyl cellulose) achieved a faster disintegration rate than the binder in Formulation 1 and Tablet II (povidone).

Thus, given that drug release (disintegration and dissolution) and the stability of a formulation correlated with its bioavailability, the comparative tests demonstrated that Formulation 3 had improved bioavailability over Tablet II. This had been confirmed by the *in vivo* pharmacokinetic tests carried out by the respondent when moving from Phase I/IIa to Phase IIb studies. These tests had shown that Formulation 2 provided a considerably higher C_{max} and AUC than Formulation 1. As Formulations 1 and 2 differed essentially only in their fillers, the test results demonstrated that the filler in Formulation 2, which conformed to claim 1 as granted, produced a surprising improvement in ticagrelor bioavailability.

Consequently, the objective technical problem solved by the composition of claim 1 was the provision of a ticagrelor composition which had an improved bioavailability profile while maintaining shelf life.

The solution proposed in claim 1 was not obvious. The skilled person would have had many options for modifying Tablet II and would not have found any incentive in the prior art to replace the excipients of Tablet II by those in claim 1 to increase the bioavailability of ticagrelor. First, D3 did not deal with any issue relating to bioavailability. Second, developing pharmaceutical formulations was a complex process; excipients were not simply replaced routinely (D11, page 858, left-hand column and D12, passage bridging pages 238 and 239). Third, the fact that ticagrelor was a BCS Class IV compound rendered it even more difficult to predict the effect that a change of excipient could bring about *in vivo*.

The compositions in the auxiliary requests were defined more narrowly and were closer to Formulation 3 of D13, for which improved bioavailability had been demonstrated. Thus, the compositions of auxiliary requests 1 to 8 were inventive for the same reason as claim 1 as granted.

XII. The parties' final requests were as follows.

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

- The respondent requested that the appeals be dismissed and that the patent be maintained as granted; or in the alternative that the patent be maintained in amended form on the basis of the claims according to one of auxiliary requests 1 to 8, all of which had been filed with the reply to the statements setting out the grounds of appeal.

- The party as of right did not make any request in these proceedings.

Reasons for the Decision

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

2. Absence of parties at the oral proceedings - Rule 115(2) EPC and Article 15(3) RPBA 2020

The oral proceedings before the board took place in the absence of appellant 2 and the party as of right (opponent 3). Both had been duly summoned. Therefore, in accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020, the board decided to continue the proceedings in the absence of those parties.

The party as of right (opponent 3) had not presented any submissions in the course of the appeal proceedings. Appellant 2 was treated as relying on its written case. Hence, the board was in a position to announce a decision at the conclusion of the oral proceedings, in accordance with Article 15(6) RPBA 2020.

3. Inventive step (Article 56 EPC) - claim 1 as granted

3.1 The patent (paragraphs [0001], [0004] and [0006]) seeks to provide ticagrelor formulations for oral administration which release substantially all of the active ingredient.

3.2 The parties agreed that the tablets in Example 2 of document D3, especially Tablet II, constituted the closest prior art. The board sees no reason to differ.

D3 is cited in the patent (paragraph [0003]) and the corresponding passage of the application as filed. It concerns the preparation of crystalline and amorphous forms of ticagrelor, and pharmaceutical compositions comprising them (D3: abstract and page 1, lines 2-6; claims 1, 15, 18 and 29). In Example 2, D3 discloses Tablet II, which contains ticagrelor, lactose, croscarmellose sodium, maize starch, polyvinyl pyrrolidone and magnesium stearate.

3.3 Thus, the pharmaceutical compositions of claim 1 as granted and Tablet II of D3 differ in respect of their excipients.

3.4 It was a matter of dispute what technical effect(s) could be attributed to these differences. The respondent, relying on the comparative examples in post-filed test reports D13 and D25, asserted that the composition of claim 1 had improved stability and bioavailability. The appellants maintained that the improvements alleged by the respondent were not plausible from the application as filed. Therefore, post-filed evidence could not be taken into consideration. Moreover, they argued that the comparative tests described in D13 and D25 were not conclusive as they did not constitute a suitable comparison with the closest prior art.

3.5 Irrespective of whether the improvements alleged by the respondent were plausible on the basis of the application as filed and common general knowledge, the board agrees with the appellants that the comparative tests presented in D13 and D25 are not suitable for the purpose of showing any effect over the closest prior art, for the reasons set out below.

3.5.1 The following data (percentages calculated from the data on file) relate to the composition (tablet core) of Tablet II of D3 and Formulations 1 to 3 in D13. Tablet II is the formulation of the closest prior art. Formulation 3 of D13 is a composition according to claim 1. Formulations 1 and 2 are the comparative compositions used according to D13.

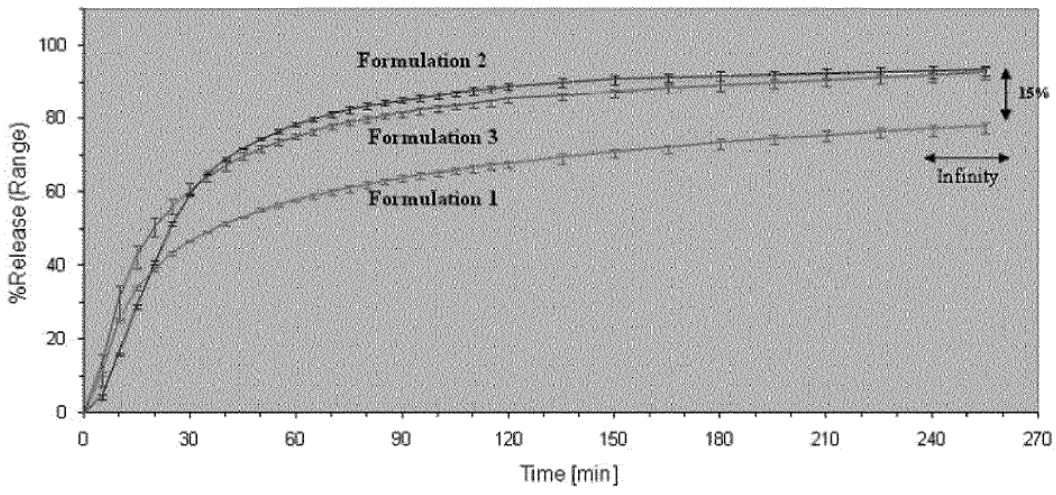
Function	**Tablet II (D3)**	**Formulation 1 100 mg (D13)**	**Formulation 2 (D13)**	**Formulation 3 (D13)**
Pharm. active agent	Ticagrelor 16.7%	Ticagrelor (micronised) 28.6%	Ticagrelor (micronised) 30.0%	Ticagrelor 30.0%
Filler	Lactose Ph. Eur. 74.6%	Lactose monohydrate 40.0% MCC 22.6%	Mannitol 42.3% DCPD 18.0%	Mannitol 42.0% DCPD 21.0%
	Maize starch 5.0%			
Binder	PVP 0.8%	PVP 4.3%	PVP "K30" 5.0%	HPC 3.0%
Disinte-grant	Croscarmellose sodium 2.0%	Croscarmellose sodium 4.0%	Croscarmellose sodium 4.0%	Sodium starch glycolate 3.0%
Lubricant	Magnesium stearate 1.0%	Magnesium stearate 0.5%	Magnesium stearate 0.8%	Magnesium stearate 1.0%

In this table, MCC stands for microcrystalline cellulose, HPC for hydroxypropyl cellulose, DCPD for dibasic calcium phosphate dihydrate and PVP for polyvinyl pyrrolidone (povidone).

It was a subject of discussion whether the maize starch used in Tablet II should be included in the category of filler rather than binder. As pointed out by the respondent, Example 2 of D3 does not indicate that the maize starch in Tablet II was pre-gelatinised ("starch paste"), a required step for it to act as a binder (reply to the statements setting out the grounds of appeal: page 10, paragraph 1, and D11: page 861, left-hand column, paragraph 3).

3.5.2 The respondent relied on the following data.

(a) D13 describes *in vitro* dissolution tests of Formulations 1 to 3 in a dissolution medium, presumed to correlate with the bioavailability of ticagrelor (see D13, page 4, paragraph 1). According to the results shown in the figure below, Formulations 2 and 3 release ticagrelor to a similar extent, which is greater than that achieved with Formulation 1.

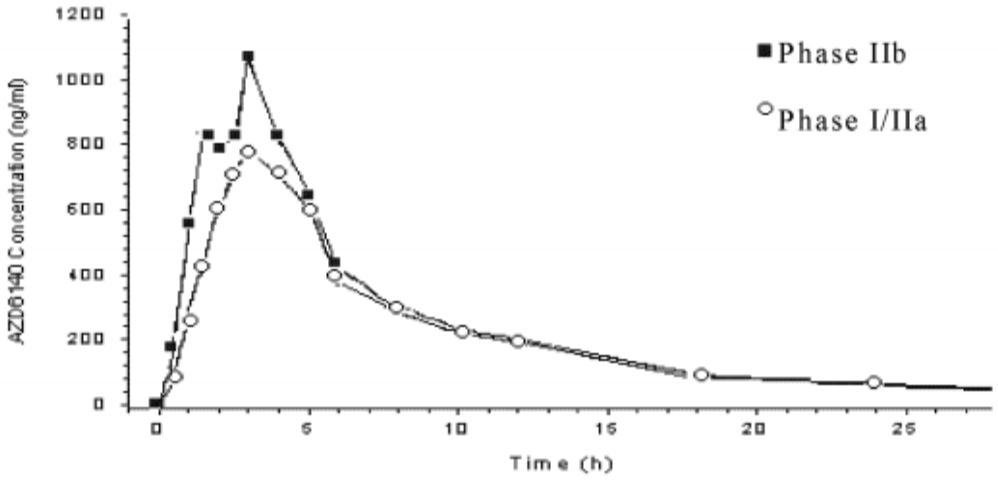


(b) The respondent stated furthermore that the thus predicted higher bioavailability of Formulations 2

and 3 was confirmed *in vivo* in a bioequivalence study (D13: paragraph bridging pages 4 and 5).

Formulation 2 achieved higher values of C_{max} and AUC than Formulation 1, as shown in the following figure (included on page 15 of the respondent's reply to the statements setting out the grounds of appeal). The curve designated Phase IIb corresponds to Formulation 2, and that designated Phase I/IIa to Formulation 1.

Figure 1 Mean plasma concentration levels of ticagrelor following oral administration of phase I/IIa and Phase IIb formulations



(c) Lastly, it is mentioned in D13 (page 5, last full paragraph) that accelerated stability studies showed that Formulation 3 had a superior stability profile to Formulation 2.

3.5.3 The respondent argued that although Formulation 1 differed in several technical features from Tablet II of D3, it was suitable as a comparator for showing an improvement over the closest prior art for the following reasons.

(i) Ticagrelor in Formulation 1 was micronised, so it should dissolve faster than in Tablet II, where it was not micronised (D11, right-hand column, paragraph 3).

(ii) Formulation 1 contained double the concentration of disintegrant of Tablet II, so it should also disintegrate faster.

(iii) Other differences between Formulation 1 and Tablet II, especially those relating to the filler, were immaterial.

Regarding points (i) and (ii), as the disintegration and dissolution rates were directly linked to bioavailability, Formulation 1 could be expected to provide higher ticagrelor bioavailability than Tablet II. Thus, as the bioavailability of the formulation according to claim 1 (Formulation 3) was superior to that of Formulation 1, it was also superior to Tablet II.

Furthermore, the sequence Tablet II > Formulation 1 > Formulation 2 > Formulation 3 depicted the timeline in the development of ticagrelor formulations by the respondent, which led to the commercialisation of the product Brilique®. Formulation 1 had resulted from the optimisation of Tablet II, to be used in Phase I/IIa tests. Formulation 2 was used for Phase IIb clinical studies, and Formulation 3 was the optimised formulation for Phase III studies and commercialisation. Hence, it was evident that Formulation 1 must be superior to Tablet II.

Regarding point (iii), the appellants had not shown that differences between Tablet II and Formulation 1 other than (i) and (ii) were relevant.

3.5.4 These arguments cannot succeed for the following reasons.

While this was not shown for the actual formulations in question, the assumption that micronisation and an increase in the amount of disintegrant may result in higher dissolution and disintegration rates appears plausible (points 3.5.3(i)-(ii) above).

However, it cannot be assumed without any evidence that the other remaining differences between Formulation 1 and Tablet II (point 3.5.3(iii) above) are immaterial.

The respondent argued that replacing the filler material of Tablet II by the filler of Formulation 1, i.e. an equivalent excipient having the same function in the formulation, would not make a difference.

Yet when comparing Formulations 1 and 2, which both contain micronised ticagrelor and essentially the same combination of binder and disintegrant, the respondent came to the conclusion (D13, page 4, last full paragraph, and reply to the statements of grounds of appeal, page 15, last paragraph) that replacement of the filler lactose/microcrystalline cellulose by the filler mannitol/DCPD resulted in an unexpectedly superior formulation. In other words, the respondent attributed the enhanced dissolution rate and bioavailability of Formulation 2 to the filler composition and considered that this effect could not have been predicted.

Given the unpredictable effect of a modification of the filler on dissolution and bioavailability, it is uncertain what would have been the impact of reducing the total filler content in Tablet II from 79.6% to 62.6%, removing maize starch, and replacing a

considerable proportion of the lactose by microcrystalline cellulose.

In addition, the effect of increasing the povidone content to more than five times the amount, from 0.8% to 4.3%, is also unknown.

Therefore, the board cannot conclude that Formulation 1 necessarily provides higher bioavailability than Tablet II. Consequently, the conclusions drawn from comparative tests relating to Formulation 1 cannot be extended to Tablet II; the tests reported in D13 do not show that the claimed composition exhibits higher bioavailability than the composition of the closest prior art.

3.5.5 The respondent's argument that Formulation 1 necessarily had superior bioavailability to Tablet II because it represented a more advanced stage in the development of ticagrelor formulations is not convincing. As argued by appellant 1 at the oral proceedings before the board, the use of Formulation 1 in Phase I/IIa tests rather than Tablet II was not necessarily linked to improved bioavailability; it could have been due to other factors, for instance the cost of the preparation process. In the absence of supporting evidence, attributing the selection of Formulation 1 to higher bioavailability than Tablet II is a speculative exercise. Therefore, the related argument cannot be taken into consideration.

3.5.6 Regarding the aspect of stability, the respondent observed that replacing the binder and disintegrant of Formulation 2 by those in Formulation 3 resulted in an improvement. Although the nature of the binder and disintegrant in Tablet II is the same as in Formulation 2, their proportions are different. But

more importantly, a comparison between Formulations 2 and 3 does not take account of the impact of the filler on tablet stability. Hence, this comparison is not suitable for establishing any improvement over Tablet II either.

3.5.7 The comparative tests in D25 show that replacing polyvinyl pyrrolidone by hydroxypropyl cellulose in a specific formulation results in improved disintegration times. As in D13, this comparative test was not carried out in relation to Tablet II of D3, and fails to establish the effect of replacing components other than the binder, e.g. the filler, and of their different amounts. Therefore, the tests in D25 are also inconclusive.

3.6 It follows from the above that the respondent failed to prove the alleged technical effects of the subject-matter of claim 1 over the composition of the closest prior art (Tablet II of Example 2 of D3).

Hence, the objective technical problem to be solved has to be formulated as the provision of an alternative formulation of ticagrelor. In this context, an alternative formulation means a further formulation suitable for the oral administration of ticagrelor.

3.7 The board is satisfied that the pharmaceutical composition of claim 1 as granted solves the objective technical problem. This was never contested by the appellants.

3.8 It was common ground that the fillers, binders and disintegrants in Tablet II of D3 and in claim 1 as granted were generally known on the priority date of the patent. This was apparent from the handbook

excerpts collected in documents D9 and D11, which in the board's view represent common general knowledge.

Lactose, starch, mannitol and dibasic calcium phosphate dihydrate were widely used as tablet fillers (D9: page 385, section 7, page 389, section 7, page 449, section 7, and page 96, section 7; D11: page 860, left-hand column, last paragraph). Polyvinyl pyrrolidone and hydroxypropyl cellulose were widely used as tablet binders (D9: page 611, section 7, and page 336, section 7; D11: page 861, left-hand column, paragraphs 5 and 6). Moreover, croscarmellose sodium and sodium starch glycolate were known as tablet "super disintegrants" (D11: page 882, left-hand column, paragraph 5; D9: page 211, section 7, and page 701, section 7).

Taking into account common general knowledge, it would thus have been obvious, to the skilled person searching for another formulation suitable for the oral administration of ticagrelor, to replace some or all of the excipients in Tablet II of D3 by excipients known to fulfil the same function. Thus, replacement of the filler lactose/maize starch by mannitol/DCPD, the binder polyvinyl pyrrolidone by hydroxypropyl cellulose and the disintegrant croscarmellose sodium by sodium starch glycolate did not require inventive efforts.

3.9 Consequently, the subject-matter of claim 1 as granted does not involve an inventive step and the ground for opposition of Article 100(a) EPC in combination with Article 56 EPC prejudices the maintenance of the patent as granted.

4. Inventive step (Article 56 EPC) - auxiliary requests

In the written proceedings, the inventive-step arguments put forward by the respondent in relation to the auxiliary requests were based on an alleged improvement of the claimed compositions over the closest prior art (see the annex filed with the reply to the statements of grounds of appeal, section 4).

At the oral proceedings, the board announced its conclusion that the comparative examples in D13 and D25 were not conclusive and that the subject-matter of claim 1 as granted did not involve an inventive step. It then expressed its preliminary opinion that these conclusions also applied to auxiliary requests 1 to 8. The respondent nevertheless chose not to present any arguments as to why the auxiliary requests would overcome the lack of inventive step of the main request.

Compared to claim 1 as granted, the corresponding independent claims of the auxiliary requests (see point VI above) indicate as further restrictions that the composition is for oral administration (auxiliary requests 1, 4, 5 and 7) and specify concentration ranges for some or all of the ingredients in the composition (auxiliary requests 2 to 8).

Tablet II in Example 2 of D3 is a tablet for oral administration (D3, page 12, lines 16-21). Hence, the limitation to oral administration in claim 1 of auxiliary requests 1, 4, 5 and 7 does not constitute an additional difference to the closest prior art and cannot contribute to inventive step.

Regarding the concentration ranges specified in the respective claim 1 of auxiliary requests 2 to 8, they appear to fall within the customary concentration ranges known for each of the ingredients when fulfilling their respective function in tablet formulations (see for example D9), and have not been shown to produce any unexpected effect. The concentration range indicated for ticagrelor is also a customary modification with no associated unexpected effect.

Hence, the amendments made to claim 1 in the respective auxiliary requests do not overcome the lack of inventive step of the composition of claim 1 as granted. Consequently, none of auxiliary requests 1 to 8 meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

M. Schalow R. Hauss

Decision electronically authenticated