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**Datasheet for the decision
of 14 May 2025**

Case Number: T 0741/23 - 3.3.04

Application Number: 10176094.0

Publication Number: 2340828

IPC: A61K31/216, A61K31/41,
A61P3/10, A61P9/00, A61P9/10,
A61P9/12, A61P25/06, A61P25/28,
A61P43/00

Language of the proceedings: EN

Title of invention:
Pharmaceutical combinations of an angiotensin receptor
antagonist and a NEP inhibitor

Patent Proprietor:
Novartis Pharma AG

Opponents:
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betapharm Arzneimittel GmbH
ZAKLADY FARMACEUTYCZNE POLPHARMA S.A.
Alfred E. Tiefenbacher (GmbH & Co. KG)

Relevant legal provisions:

EPC Art. 76(1), 123(2), 83, 56

RPBA Art. 13(2)

Keyword:

Divisional application - added subject-matter (no)

Amendments - correction of errors (yes)

Sufficiency of disclosure - (yes)

Inventive step - (yes)

Decisions cited:

G 0001/03, T 0205/14



Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 0741/23 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 14 May 2025

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 16 March 2023
rejecting the oppositions filed against
European patent No. 2340828 pursuant to
Article 101(2) EPC.**

Composition of the Board:

Chairwoman M. Pregetter
Members: R. Hauss
 L. Bühler

Summary of Facts and Submissions

- I. European Patent No. 2 340 828 (patent in suit) derives from European patent application No. 10 176 094.0, which is a divisional of European patent application No. 06 827 689.8 (the earlier application, published as international application No. WO 2007/056546 A1).
- II. The patent in suit was granted with a set of 14 claims. Claim 1 reads as follows:
- "1. A compound having the sum formula [((S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionyl-amino)-2-methyl-pentanoic acid ethyl ester)]Na₃•x H₂O, wherein x is 0 to 3, and being in the solid form."*
- Claims 2 to 14 all refer back to the compound of claim 1.
- III. The patent in suit was opposed under Article 100(a), (b) and (c) EPC 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 and earlier application as filed.
- IV. In its reply to the oppositions, the patent proprietor requested as its main request that the oppositions be rejected and that the patent be maintained as granted. It also submitted amended sets of claims as auxiliary requests 1 to 22 and 12A to 22A.

V. The documents cited in the proceedings before the opposition division included the following.

- P3:** US 60/789,332
- D1:** WO 03/059345 A1
- D2:** Applicant's submissions pursuant to Rule 116 EPC, EP 06827689.8, of 11 February 2013
- D3:** US 5,217,996 A
- D4:** WO 02/06253 A1
- D7:** Journal of Pharmaceutical Sciences 66(1), 1-20 (1977)
- D9:** Pharmaceutical Research, 12(7), 945-954 (1995)
- D10:** Chem. Commun. 2004, 1889-1896
- D11:** Acta Cryst. B53, 569-586 (1997)
- D12:** Advanced Drug Delivery Reviews 56, 275-300 (2004)
- D13:** Chem. Commun. 2005, 4601-4603
- D14:** Nature Reviews 3, 42-57 (2004)
- D15:** Mc Murray et al., N. Engl. J. Med. (2014), "Angiotensin-Nepriylisin Inhibition versus Enalapril in Heart Failure", 12 pages, NEJM.org
- D18:** Prescribing Information Entresto™ (revised: 8/2015)
- D19:** J. Bernstein, "Polymorphism in Molecular crystals", 2002, pages 27, 46-49, 112, 150-151
- D20:** H. G. Brittain, Chapter 6, Polymorphism in Pharmaceutical Solids, vol. 95, ed. H. G. Brittain, 1999, 227-278
- D22:** Novartis Letter 3 October 2013, re: 10176094.0
- D23:** US 2005/0070551 A1
- D24:** EP 0034172 B1
- D25:** US 2,499,058
- D26:** US 2,534,813
- D27:** Bosnian Journal of Basic Medical Sciences 4(3), 35-39 (2004)

- D45:** Declaration R.L. Webb under 37 C.F.R §1.132
(11 May 2006)
- D48:** Tetrahedron Letters 53, 275-276 (2012)
- D50:** BGH, X ZR 126/09 (BPatG) (24 July 2012)
- D51:** BGH, X ZR 110/16 (BPatG) (7 August 2018)
- D64:** Guillory et al., "Polymorphism in Pharmaceutical Solids", 1999, Chapter 5, 183-226
- D65:** WO 2017/154017 A1
- D67:** CN 109912525 A (2017) (Translation into English included)
- D68:** CN 106905253 A (2017) (Translation into English included)
- D69:** IN 201641010897
- D70:** WO 2016/125123 A1
- D71:** IN 2018 11000274 A
- D75:** AET Interim Development Report Sacubitril and Valsartan Film-Coated Tablets (23 February 2017)

VI. The decision under appeal is the opposition division's decision rejecting the oppositions. It includes the following findings.

- (a) The grounds under Article 100(b) and 100(c) EPC did not prejudice maintenance of the patent as granted.
- (b) As claims 1 to 4 and 6 to 14 did not enjoy priority from **P3** (Article 87 EPC), document **D45** could be taken into account for the assessment of inventive step of these claims.
- (c) Document **D1**, which disclosed combinations of valsartan and a NEP (neutral endopeptidase) inhibitor, represented the closest state of the art. The objective technical problem considered by the opposition division was the provision of an

alternative dosage form of valsartan and sacubitril. Based on the cited prior art, the person skilled in the art seeking to solve this technical problem would not have arrived at the claimed subject-matter without inventive skill.

- VII. Opponents 1, 2, 4, 5, 6, 7 (the appellants) and opponent 8 all filed appeals against this decision. Opponent 8 later withdrew its appeal.
- VIII. The non-appealing opponents (opponent 3 and opponent 8) are parties to the appeal proceedings as of right (Article 107 EPC). During the appeal proceedings, opponent 3 did not present any comments regarding the substance of the case. The text of the statement setting out the grounds of appeal filed by opponent 8 is identical to that of the corresponding statements filed by appellants-opponents 6 and 7. It remained opponent 8's only submission addressing substantive issues. Thus, the parties as of right did not present any substantive comments in addition to those of the appellants.
- IX. With its reply to the appeals, the patent proprietor (respondent) requested as its main request that the appeals be dismissed. It also filed amended sets of claims as auxiliary requests 1 to 22, 12A to 22A, 12B to 22B and 12C to 22C.
- X. The following documents were submitted in the course of the appeal proceedings.
- D77:** Feng et al., "Supporting information for: LCZ696: a dual-acting sodium supramolecular complex", S1-S7 (supplementary data associated with D48)
- D78:** XPRD pattern for LCZ696

- D79:** XPRD and DSC comparison
- D80:** International Journal of Pharmaceutics 105,
125-135 (1994)
- D81:** Diovan entry, Physicians' Desk Reference, PDR 53
Edition, 1999

Documents **D77**, **D78** and **D79** were submitted (as HW11, HW12 and HW13) by appellants-opponents 6 and 7 and opponent 8 with their respective statements setting out the grounds of appeal.

Document **D80** was submitted (as D77) by appellant-opponent 1 with its statement setting out the grounds of appeal.

Document **D81** was submitted by the patent proprietor (respondent) with its reply to the appeals.

- XI. In response to a summons to attend oral proceedings, appellant-opponent 2, appellant-opponent 5 and opponent 3 advised the board that they would not be attending the oral proceedings.
- XII. Oral proceedings before the board were held on 13 and 14 May 2025, in the absence of the duly summoned opponents 3 and 8 and appellants-opponents 2 and 5 (Article 15(3) RPBA and Rule 115(2) EPC). At the start of the oral proceedings, the respondent withdrew its main request for dismissal of the appeals and made auxiliary request 1 its main request. Towards the end of the oral proceedings on 14 May 2025, the respondent filed an amended set of claims as its new main request. The board admitted this amended main request and held it allowable. The board announced its decision remitting the case to the opposition division with the order to maintain the patent on the basis of the claims of the amended main request filed on 14 May 2025 and

the description and drawing of the patent specification.

XIII. The difference between the claims of the amended main request filed on 14 May 2025 and the claims as granted is that dependent claims 4 and 6 have been deleted. The numbering and the dependencies of the remaining claims have been adapted accordingly where necessary. The claims of the amended main request read as follows:

"1. A compound having the sum formula [((S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionyl-amino)-2-methyl-pentanoic acid ethyl ester)]Na₃·x H₂O, wherein x is 0 to 3, and being in the solid form.

2. The compound of claim 1 wherein the compound is in the form of a complex.

3. The compound of claim 2 wherein the complex is a supramolecular complex.

4. The compound of any one of claims 1 to 3 wherein x is selected from the group consisting of 1, 2 and 3.

5. The compound of any one of claims 1 to 3 wherein x is 2.5.

6. The compound of claim 4 in the crystalline form.

7. A pharmaceutical composition comprising
(a) the compound of any one of claims 1 to 6; and
(b) at least one pharmaceutically acceptable additive.

8. The pharmaceutical composition of claim 7, wherein the pharmaceutically acceptable additive is selected from the group consisting of diluents or fillers,

disintegrants, glidants, lubricants, binders, colorants and combinations thereof.

9. A compound of any one of claims 1 to 6 for use in the treatment of cardiovascular and/or renal diseases.

10. A compound for use according to claim 9, wherein the use is in the treatment or prevention of hypertension.

11. A compound for use according to claim 9, wherein the use is in the treatment or prevention of heart failure.

12. A pharmaceutical composition comprising
(a) the compound of any one of claims 1 to 6;
(b) a therapeutic agent selected from an anti-diabetic, a hypolipidemic agent, an anti-obesity agent and an anti-hypertensive agent; and
(c) at least one pharmaceutically acceptable additive."

XIV. The appellants' pertinent arguments may be summarised as follows.

Claim construction

The definition of the compound in claim 1 did not cover amorphous forms as it limited the claim to crystalline hydrates due to the required precise stoichiometry. This was implied by the notation chosen for the sum formula, which used square brackets and specified a level of hydration, i.e. water of crystallisation (appellants-opponents 1 and 4).

According to a different interpretation, claim 1 also covered physical mixtures of the (amorphous) sodium

salts of valsartan and sacubitril (appellant-opponent 2).

The fact that claim 1 was directed to a "compound" whereas dependent claims 2 and 3 were directed to a "complex" and "supramolecular complex" made it clear that the scope of claim 1 was broader than that of claims 2 and 3 and was intended to cover compounds other than complexes (appellants-opponents 5 to 7).

Claim 1 also encompassed compounds with undefined geometry held together only by weak Van der Waals interactions without showing a short-range order (appellant-opponent 5).

Added subject-matter (Articles 76(1) and 123(2) EPC)

The subject-matter of claims 1 and 2 extended beyond the content of the application and earlier application as filed. The amendments in question were the following:

- the sum formula reading "5-biphenyl-4-yl-4-(3-carboxy-propionylamino)", whereas the corresponding formula on page 22 of the application as filed (penultimate paragraph) read "5-biphenyl4-yl-5-(3-carboxy-propionylamino)"
- the omission of the term "dual-acting" from claim 1
- the omission of the terms "supramolecular complex" from claim 1 and "supramolecular" from claim 2

Sufficiency of disclosure

The application and earlier application as filed did not provide any guidance for preparing the claimed compound in a form different from that of the crystalline hemipentahydrate LCZ696, i.e. as a different crystalline polymorph, in the anhydrous form (i.e. $x = 0$), with a water content other than $x = 2.5$

or in amorphous form. This placed an undue burden on the skilled person seeking to identify further working embodiments.

Since the application and the earlier application as filed did not disclose how to prepare further variants falling under claim 1, it was not permissible to take post-published evidence into account.

The "glassy" form obtained as an intermediate product in Example 1 was not disclosed as a verified amorphous form or as conforming to claim 1. As shown in **D48** (see page 276), neither an amorphous supramolecular form nor an anhydrous form or a hydrate other than a hemihydrate ($x = 0.5$), unlikely to be stable at room temperature, could be prepared by heating LCZ696.

The person skilled in the art would not have been enabled to prepare an amorphous form in any case since no analysis technique existed by which it could be verified that interaction by non-covalent forces between the sodium salts of valsartan and sacubitril resulted in providing an amorphous single compound with the sum formula of claim 1.

According to appellant-opponent 5, claim 1 covered a grey area of undefined compounds with only weak Van der Waals interactions between the components. Guidance on the identification and preparation of such compounds was lacking.

According to appellant-opponent 2, it was furthermore not made credible that the claimed compound could achieve the therapeutic effects specified in claims 9 to 11.

Entitlement to priority

Appellants-opponents 5, 6 and 7 contended that only claim 4 (which corresponds to claim 5 as granted)

was entitled to priority based on **P3**. As a consequence, **D45** was prior art under Article 54(2) EPC for all other claims.

Inventive step

Document **D1** disclosed a combination of valsartan and sacubitril. No improvement associated with the claimed compound had been shown in comparison with the combination disclosed in **D1**.

The objective technical problem could accordingly be defined as the provision of an alternative dosage form of valsartan and sacubitril. Alternatively (appellants-opponents 6 and 7), the objective technical problem could be defined as the provision of a solid unit dosage form for the oral administration of valsartan and sacubitril.

As to obviousness, first, it was argued that it would have been obvious for the person skilled in the art to make a single crystalline or amorphous compound from sacubitril monosodium and valsartan disodium in a 1:1 molar ratio.

Second, it was argued that the skilled person would inevitably have arrived at the compound of claim 1 because it would have formed during routine development of a tablet comprising a 1:1 molar ratio of valsartan disodium and sacubitril monosodium.

- XV. The respondent's pertinent arguments may be summarised as follows.

Claim construction

Claim 1 covered compounds in different hydration states and in different physical forms, namely crystalline, partially crystalline, amorphous or polymorphous, as mentioned in paragraph [0044] of the patent in suit.

As also stated in the description (see the patent in suit, paragraphs [0014] and [0045]), these forms were single chemical substances distinct from mere physical mixtures of the two active agents.

The claimed compound was a single supramolecular entity in which the valsartan and sacubitril moieties were held together only by non-covalent bonds, which could include ionic bonds, hydrogen bonds and Van der Waals forces.

Compound embodiments held together only by weak Van der Waals interactions (as hypothesised by appellant-opponent 5) did not exist as ionic bonding was inherently present in the claimed compound.

Added subject-matter (Articles 76(1) and 123(2) EPC)

The compound of claim 1 was disclosed as a preferred embodiment on page 22 of the application and the earlier application as filed. Basis for the compound of claim 1 being in the solid form was found in the first sentence of the second paragraph of page 23.

The omission of the terms "dual-acting" and "complex" did not add matter because the text passage on page 22 did not require the compound to be described as a complex, and the claimed compound was inherently dual-acting as it included the two active agents valsartan and sacubitril.

The terms "compound", "complex" and "supramolecular complex" and the relative hierarchy of these terms were the same in claims 1 to 3 and in the description of the application and earlier application as filed (e.g. on pages 9 and 22).

During pre-grant examination, a typographical error in the chemical name of sacubitril had been corrected, in claim 1 and throughout the application. The correction

of "5-biphenyl4-yl-5-(3-carboxy-propionylamino)" to "5-biphenyl-4-yl-4-(3-carboxy-propionylamino)" was permissible since it was an obvious and immediately evident correction.

Sufficiency of disclosure

It was not in dispute that the person skilled in the art could make and use the claimed compound with $x = 2.5$, i.e. the hemipentahydrate form (also known as LCZ696), on the basis of the teaching in the patent in suit. As the patent taught how to make the compound of claim 1 in solid form, this was sufficient for the skilled person to carry out the invention without undue burden.

The broader scope of claim 1 was a reasonable reflection of the technical contribution provided in the patent in suit, namely the provision of a new single compound (defined as a stoichiometric form) comprising valsartan and sacubitril. There was no requirement in patent law for the claims to be limited to the solid form exemplified in the description. Once the person skilled in the art was given a new compound, variants such as polymorphs, hydrates and amorphous forms would have been routine to make and to characterise using standard techniques and common general knowledge.

The appellants had not provided any evidence of undue burden. Post-published third-party patent applications reporting further solid, including amorphous, forms according to claim 1 confirmed that the teaching in the patent and in the common general knowledge could be applied to the claimed compound. The patent in suit was the source of all these follow-up routine implementations.

Moreover, Example 3 in the patent in suit illustrated that other solid forms could be made as it showed that the water of hydration was released in two steps from the hemipentahydrate LCZ696 upon heating, as confirmed in **D48**. Further methods for preparing alternative solid forms could be envisaged that did not start from LCZ696. The patent in suit also showed that an amorphous form could be prepared, namely the glassy solid obtained as an intermediate product in Example 1. This was confirmed in **D65**, which identified the glassy solid as an amorphous form.

As the claimed compound would always include some ionic interaction, the appellants' arguments in relation to hypothetical "undefined Van der Waals compounds" (i.e. where the components were only held together by weak Van der Waals forces) were irrelevant.

While the claimed compound itself was new, the valsartan and sacubitril moieties and their *in vivo* effects were known, in particular as being useful in combination for treating the conditions according to claims 9 to 11. The fact that the claimed compound was suitable for the claimed medical uses was furthermore confirmed by the post-published evidence in **D15**.

Entitlement to priority

In view of claim 20 of **P3**, the subject-matter of claims 4 and 6 of the main request was entitled to priority, as well as that of claims 7 to 11 when referring back to the compound of claim 4.

Inventive step

Starting from the disclosure of **D1**, the objective technical problem underlying claim 1 was the provision of an improved pharmaceutical composition for providing

valsartan and sacubitril to patients allowing ease of formulation and manufacture.

However, even if the technical problem were defined less ambitiously as the provision of an alternative dosage form of valsartan and sacubitril, the claimed compound would not have been obvious since it was not a routine technique at the priority date to combine two active pharmaceutical ingredients into a single compound. Thus, there was simply no precedent or expectation for the formation of a single compound comprising both valsartan and sacubitril, let alone in a therapeutically desirable ratio.

The person skilled in the art seeking to solve the objective technical problem would have had no motivation to choose co-formulating valsartan and sacubitril, to choose a 1:1 molar ratio of valsartan and sacubitril, and to use the salt forms of valsartan disodium and sacubitril monosodium. The appellants' arguments based on these assumptions were flawed by hindsight.

XVI. The parties' requests relevant to this decision were as follows.

- (a) All the appellants requested that the decision under appeal be set aside and that the patent be revoked. Appellant-opponent 1 also requested that document **D80** be admitted.
- (b) The respondent (patent proprietor) requested that the patent be maintained in amended form on the basis of the claims of the main request filed on 14 May 2025 and the description and drawing of the patent specification.

The respondent also requested that **D81** be admitted and that certain arguments and factual allegations presented by the appellants not be admitted.

The requests relating to admittance and the evidence and arguments in question were not crucial to this decision (see section 7. below).

(c) Opponent 3 did not file any request in the appeal proceedings.

(d) As opponent 8 withdrew its appeal (see point VII. above), it no longer maintained its initial request that the patent be revoked. Opponent 8 did not file any other requests.

XVII. Subsequent to the oral proceedings before the board and the oral announcement of the board's decision, opponents 2 and 5 withdrew their oppositions.

Reasons for the Decision

1. Oral proceedings - absent parties

1.1 In conformity with Article 15(3) RPBA and Rule 115(2) EPC, the oral proceedings before the board took place in the absence of appellant-opponent 2, appellant-opponent 5, opponent 3 and opponent 8, all of which had been duly summoned (see points XI. and XII. above).

1.2 Appellant-opponent 2 and appellant-opponent 5 were treated as relying on their written submissions (Article 15(3) RPBA). The circumstance that both these appellants withdrew their oppositions (see point XVII. above) has no impact on the board's reasoning below since these withdrawals occurred only after the appeal

proceedings were terminated by the board announcing its decision at the oral proceedings (see point XII. above and Article 15(6) RPBA).

- 1.3 Opponent 3 did not present any requests or arguments in writing (see points VIII. and XVI.(c) above)).

The statement setting out the grounds of appeal filed initially by opponent 8 was identical to the corresponding statements filed by appellants-opponents 6 and 7 (see point VIII. above). Its content was taken into consideration by the board. After withdrawing its appeal, opponent 8 did not present any requests or further comments in writing (see points VII., VIII. and XVI.(d) above).

Thus, opponents 3 and 8 (parties as of right under Article 107 EPC) chose not to avail themselves of the opportunity to present any (further) comment on the grounds and evidence in the appeal case (Article 113(1) EPC).

2. Amended main request filed on 14 May 2025 - admittance (Article 13(2) RPBA)

- 2.1 At the oral proceedings before the board, the respondent filed an amended claim request as its new main request. It differs from the previous main request (filed as auxiliary request 1 with the respondent's reply to the appeals, see points IX. and XII. above) in that dependent claim 5 has been deleted and the numbering and back-references of the subsequent claims have been adapted accordingly.

- 2.2 This amendment was occasioned by the board raising a new objection against the previous main request at the oral proceedings. The board objected that claim 5 contained added subject-matter (Articles 76(1) and

123(2) EPC). The board also indicated that this issue could be resolved by the deletion of claim 5 and that the resulting set of claims would appear allowable (see page 6 of the Minutes of the oral proceedings before the board).

2.3 This is an exceptional circumstance that justifies the presentation of the amended main request at the appeal oral proceedings. As a consequence, the amended main request filed on 14 May 2025 was admitted under Article 13(2) RPBA.

3. Claim construction

3.1 This decision is based on the claims of the amended main request filed at the oral proceedings before the board (see points XII. and XIII. and section 2. above).

3.2 The patent in suit relates to compounds containing:
- an angiotensin receptor blocker (ARB),
represented in claim 1 by: (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine,
also known as valsartan

in association with:

- a neutral endopeptidase inhibitor (NEPi or NEP inhibitor), represented in claim 1 by: (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester), also known as sacubitril or AHU-377

3.3 Using common names, the sum formula defining the compound of claim 1 of the main request can be simplified to:

$[(\text{valsartan})(\text{sacubitril})]\text{Na}_3 \cdot x \text{H}_2\text{O}$, where x is 0 to 3

- 3.4 Claim 1 is thus directed to a defined compound consisting of sodium cations, anions of valsartan, anions of sacubitril and water, at a molar ratio of 3:1:1:0 to 3:1:1:3.
- 3.5 According to the sum formula in claim 1, there is no covalent bond between valsartan and sacubitril. However, non-covalent interactions between the different moieties or components of the sum formula are present (see paragraph [0017] of the patent in suit).
- 3.6 The term "compound" used in claim 1 excludes mere physical mixtures of the components. The person skilled in the art would read it in its usual meaning as implying that the claimed form must be distinguishable by its physical properties from a physical mixture of the sodium salts of valsartan and sacubitril. This is also in line with the description in paragraph [0045] of the patent in suit, which states that the dual-acting compound of the invention is distinct from a combination of an ARB and a NEPi obtained by simply physically mixing the two active agents.
- 3.7 It was common ground that the claimed compound can be crystalline. An embodiment covered by claim 5, the crystalline hemipentahydrate, in which x equals 2.5, is also known as LCZ696 and has been marketed as a medicament under the brand name Entresto[®].
- The patent also includes a detailed characterisation of the exemplified form LCZ696 that distinguishes it from a physical mixture (see paragraphs [0045] to [0060], Figure 1 and Examples 1 to 3).
- 3.8 It was in dispute whether an amorphous form of the compound conforming to the stoichiometry of the sum formula in claim 1 exists and whether this form can be

distinguished from a physical mixture of the components.

- 3.9 On this issue, the board is of the view that the notation used for the sum formula in claim 1 in any case does not provide a restriction to a specific physical form apart from the compound being in the solid state.

The board notes, however, that, while the claim allows for any physical form in the solid state, it does not require all possible solid forms of the compound (such as generically derivable from combining different hydration levels according to claim 1 with solid form variants mentioned in the description; see paragraph [0044] of the patent in suit) to be obtainable (see also points 5.11 and 5.12 below).

- 3.10 The further question of how an amorphous compound according to claim 1 can be characterised and distinguished analytically would appear to relate to the delimitation of the claimed subject-matter and, therefore, may be regarded as an issue of clarity under Article 84 EPC, not available for objection in opposition-appeal proceedings since the current claim 1 is identical to claim 1 as granted (see G 3/14, OJ EPO 2015, A102) (see points 5.16.3 and 5.16.4 below).

- 3.11 In view of point 3.9 above, the following considerations apply in relation to anhydrous and amorphous variants.

- 3.11.1 The notation in claim 1 does not exclude an anhydrous amorphous form, if such a form exists (i.e. if it can be prepared).

- 3.11.2 Contrary to the argument presented by appellant-opponent 1, the embodiment " $\cdot x \text{H}_2\text{O}$, wherein x is 0",

i.e. [(valsartan)(sacubitril)]Na₃, merely requires the absence of water but does not imply that the compound must have the structure of a crystalline hydrate, only with the water of hydration removed.

- 3.11.3 Furthermore, it is also conceivable that a crystalline hydrate could be transformed under specific conditions into an amorphous form which - at least temporarily - preserves the same stoichiometric water content.
- 3.12 Claim 1 does not cover hypothetical compound embodiments with undefined geometry held together only by weak Van der Waals interactions. Since the compound of claim 1, by definition, contains ionic species and polar groups, there can be no such embodiment. Rather, Van der Waals forces may be present in addition to the stronger non-covalent forces (ionic bonds and polar interactions such as hydrogen bonds) that are inevitably present (see also paragraph [0017] of the description mentioning that Van der Waals forces may "also" be present, which a reader would understand as meaning in addition to the typical hydrogen and ionic bonds).
- 3.13 As set out in paragraph [0020] of the description, the term "supramolecular complex" is intended to describe an interaction between the two pharmaceutically active agents, the cations and the water molecules by means of non-covalent, intermolecular bonding between them. This interaction leads to an association of the species present in the supramolecular complex distinguishing it from a physical mixture of the species.
- 3.14 It is inherent in the definition of the compound of claim 1 that the interaction of the species in the sum formula, owing to the absence of covalent bonding, is "supramolecular". Furthermore, according to the

terminology used in the patent in suit, the type of compound defined in claim 1 is also designated as a "complex", as evidenced by paragraphs [0017], [0020] and [0045] of the patent specification. Thus, the board is of the view that claims 1, 2 and 3 have the same meaning and that, as a consequence, dependent claims 2 and 3 are redundant.

4. Amendments (Articles 123(2) and 76(1) EPC)

4.1 As previously established by the opposition division (see the decision under appeal, point 15.1), the descriptions of the application as filed and the earlier application as filed (published as WO 2007/056546 A1) are identical. Hence, it is sufficient for the assessment under Articles 123(2) and 76(1) EPC to refer to the description of the application as filed.

4.2 The respondent indicated that the subject-matter of claim 1 is based on the following passages on pages 22 and 23 of the application as filed.

4.2.1 According to page 22, lines 5 to 13:

"in a preferred embodiment of the present invention, the dual-acting compound, in particular the supramolecular complex is described by the sum formula $[ARB(NEPi)]Na_{1-3} \cdot x H_2O$, wherein x is 0 to 3, such as 2.5, preferably

$[ARB(NEPi)]Na_3 \cdot x H_2O$, wherein x is 0 to 3, such as 2.5, more preferably

$[(N\text{-valeryl-N}\{[2'\text{-}(1H\text{-tetrazole-5-yl})\text{-biphenyl-4-yl}]\text{-methyl}\}\text{-valine})(5\text{-biphenyl-4-yl-5-(3-carboxy-propionyl-amino)-2-methyl-pentanoic acid ethyl ester})]Na_3 \cdot x H_2O$, in particular

[((S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine)((2R,4S)-5-biphenyl4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester]Na₃·x H₂O, wherein x is 0 to 3, such as 2.5."

4.2.2 According to page 23, penultimate paragraph, the dual-acting compound of the invention is preferably in solid form.

4.3 The sum formula and chemical name in claim 1 of the current main request are identical to those of the particularly preferred compound in the above-cited passage on page 22 of the description, except that:

"5-biphenyl4-yl-5-(3-carboxy-propionylamino)"
has been changed to:

"5-biphenyl_4-yl_4-(3-carboxy-propionylamino)"

These modifications were carried out at the pre-grant stage and were applied throughout the text of the application. They are consequently also present in claim 1 as granted, which is identical to claim 1 of the current main request.

4.4 The board is satisfied that these modifications are permissible corrections (Rule 139 EPC) for the following reasons.

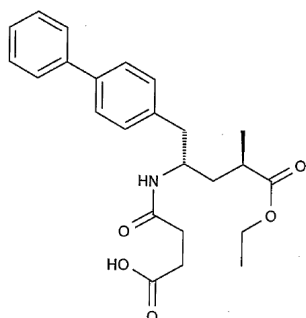
4.4.1 The addition of a hyphen between "biphenyl" and "4-yl" is an obvious correction to bring the chemical name in line with IUPAC nomenclature rules. The appellants did not object to this first modification.

4.4.2 The second modification is the replacement of "5-(3-carboxy-propionylamino)" with "4-(3-carboxy-propionylamino)".

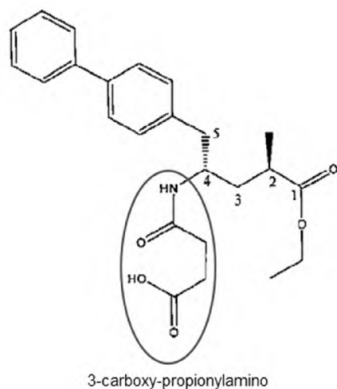
4.4.3 A person skilled in the art reading the application as filed would realise that there is an error in the

chemical name of the preferred compound on page 22 of the description (see point 4.2.1 above and the application as filed: page 22, lines 10 to 13). As the name of the second organic moiety in this compound starts with "(2R,4S)", this indicates a chiral centre on position 4 of the pentanoic acid core. This is, however, inconsistent with the attachment of the (3-carboxy-propionylamino) group at position 5 ("5-(3-carboxy-propionylamino)"), also according to the chemical name in the application as filed.

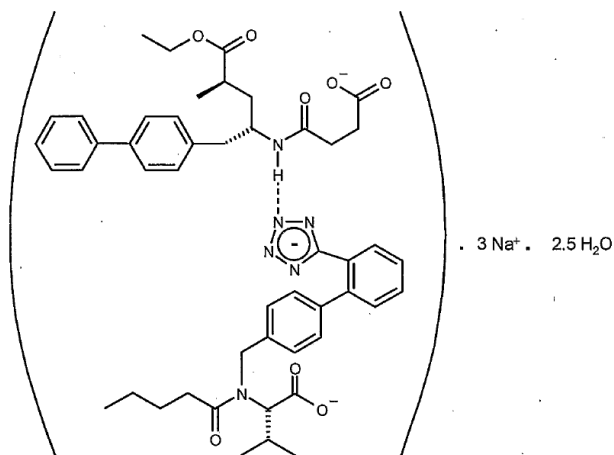
- 4.4.4 When seeking to resolve this error, the skilled person would furthermore note that the chemical name provided in the application as filed is inconsistent with the structure formula of the compound on page 18, which shows that the (3-carboxy-propionylamino) group is attached at position 4:



This was highlighted by the respondent in point 5.41 of its reply to the appellants' statements setting out the grounds of appeal:



4.4.5 The description in the application as filed explicitly mentions (see page 18, lines 5 and 6) that the structure formula on page 18 is supposed to represent "(2R,4S)-5-biphenyl-4-yl-5-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester", i.e. the same compound presented as a moiety of the preferred compound on page 22 (see points 4.2.1 and 4.4.3 above). This can also be seen in the structure formula of the preferred embodiment (with $x = 2.5$) on page 23, which shows the same structure, with the (3-carboxy-propionylamino) group attached at position 4, for the moiety in question.

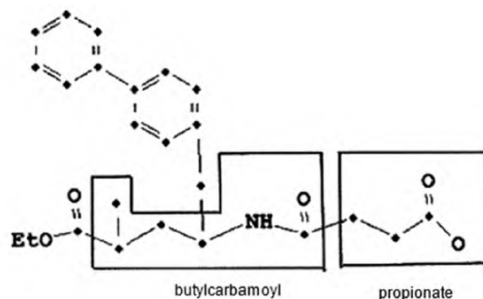


4.4.6 Furthermore, the application as filed (see page 22, lines 13 to 15) provides an alternative chemical name for the embodiment in which $x = 2.5$, namely:

"trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxy-carbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl} amino)butyrate]hemipentahydrate"

4.4.7 As highlighted by the respondent in point 5.45 of its reply to the statements setting out the grounds of appeal, this alternative chemical name also indicates

the correct structure with the (3-carboxy-propionyl-amino) group attached as shown in point 4.4.4 above.



- 4.4.8 The description furthermore refers to **D3** as describing the compound in question (see page 18, last paragraph: "The compound of formula (II) is a specific inhibitor of NEP and is described in U.S. patent No. 5,217,996"). The disclosure in **D3** is consistent with the (3-carboxy-propionylamino) group being attached at position 4 as shown in point 4.4.4 above (see, for instance, the structure of formula I(e) shown in claim 1 of **D3**).
- 4.4.9 Thus, the person skilled in the art would recognise immediately that there is an error in the original chemical name of the sacubitril moiety and that the name should be corrected by replacing the "5-" with "4-". This is the only correction that would be consistent with the chemical structures drawn in the description, with the alternative nomenclature used and with the teaching of the cross-referenced document **D3**, which is expressly cited as providing a further description of the compound in question.
- 4.4.10 In conclusion, the modification in question is deemed a permissible correction of an evident error under Article 139 EPC (see also the decision under appeal, section 15.2.1).
- 4.5 Concerning a further issue raised by the appellants, dual activity is an inherent property of the claimed

compound, which includes two drug moieties with different activities, namely valsartan (an ARB) and sacubitril (a NEPi). As a consequence, the absence of the term "dual-acting" in claim 1 does not add subject-matter extending beyond the content of the application as filed.

4.6 The appellants also objected to the omission (in comparison with claim 3) of the terms "supramolecular complex" from claim 1 and "supramolecular" from claim 2 as an inadmissible generalisation.

4.6.1 However, the meaning of "supramolecular" (see the description as filed, paragraph bridging pages 9 and 10) is in any case implicit in the definition of the "compound" of claim 1, which, according to its sum formula, includes two species of drug molecules (valsartan and sacubitril) that are not covalently linked.

4.6.2 The board is furthermore of the view that the wording "in particular the supramolecular complex" on page 22 of the description (see point 4.2.1 above) by itself does not necessarily imply that the following formulas can only define a complex. Hence, it is not necessary on the basis of the pertinent passage on page 22 itself to include the term "complex" in the definition of claim 1. See also the board's considerations in point 3.14 above.

4.7 For the reasons set out above, the board arrived at the conclusion that the claimed subject-matter does not extend beyond the content of the application and the earlier application as filed (Articles 123(2) and 76(1) EPC).

5. Sufficiency of disclosure (Article 83 EPC)

5.1 The requirement of sufficiency of disclosure has to be met on the basis of the information provided in the patent application together with the common general knowledge available at the time to the person skilled in the art. In the following, reference is made to the application as filed. All passages are also present in the patent in suit, identically or with substantially the same content.

5.2 The appellants' objections concerned:

- the accessibility of compounds as defined in claim 1 across the entire scope claimed
- their suitability for the therapeutic use defined in claims 9 to 11

Claim 1

5.3 Regarding the first issue, the appellants were of the view that while the patent in suit and the application as filed disclosed the preparation of the crystalline hemipentahydrate form LCZ696 (see Examples 1 to 3), the person skilled in the art would have faced an undue burden when seeking to identify other variants, in particular different crystalline polymorphs, forms with a water content other than $x = 2.5$, anhydrous forms or amorphous forms meeting the definition of the solid compound in claim 1.

5.4 This objection did not succeed since:

- the definition in the claim allows for limited variation only
- one way of carrying out the invention is undisputedly disclosed
- it is usually considered routine to make and characterise further variants, such as those

mentioned in point 5.3, using standard techniques and common general knowledge

- the appellants did not conclusively substantiate serious doubt or undue burden in this regard

The board's reasoning is set out in more detail as follows (see points 5.5 to 5.17 below).

- 5.5 In accordance with the criteria established in G 1/03, the application as filed, together with common general knowledge, must provide sufficient information for finding appropriate alternatives over the claimed range with reasonable effort. If this requirement is met, the inclusion of non-working embodiments is of no harm (G 1/03, OJ EPO 8-9/2004, 413; Reasons 2.5.2). Appropriate alternatives have to be understood in the context of the specific claim under consideration. For the case in hand, see section 3. above.
- 5.6 The application as filed discloses the preparation and characterisation of the crystalline hemipentahydrate form LCZ696, which conforms to claim 1. The appellants did not raise insufficiency of disclosure with regard to this compound. However, they submitted that the person skilled in the art was not provided with sufficient guidance for making the claimed compound in any solid form other than the crystalline hemipentahydrate form LCZ696, and across the range of values of $x = 0$ to 3 given in claim 1 for the level of hydration.
- 5.7 The claimed invention relates to a new single dual-acting compound comprising valsartan and sacubitril (exemplified in the application by the crystalline hemipentahydrate form LCZ696) that is suitable for administration to patients.

Accordingly, the sum formula in claim 1 defines a compound in which valsartan, sacubitril and sodium are present at a ratio of 1:1:3. Variations are possible only with regard to the hydration level (limited, however, to the range of $x = 0$ to 3) and with regard to the structure of this solid compound.

5.8 A claim may include such compound variants if these are routinely accessible without undue burden on the basis of the information provided in the application as filed and common general knowledge (see point 5.5 above).

5.9 The question is thus whether the appellants demonstrated an undue burden, or at least the existence of serious doubt substantiated by verifiable facts, with regard to the routine accessibility of variants across the scope claimed. As already mentioned, only one stoichiometrically defined compound is, in fact, claimed.

5.10 The appellants argued that there were concerns in relation to the following issues:

- (a) the lack of disclosure for "any" level of hydration between $x = 0$ and $x = 3$ (other than 2.5)
- (b) the existence/accessibility of an anhydrous form ($x = 0$)
- (c) the existence of crystalline polymorphs, in view of previous statements by the respondent that no polymorphs of LCZ696 had been identified
- (d) the existence, and means for the characterisation of, amorphous forms conforming to claim 1
- (e) the lack of guidance with regard to undefined compounds with only weak Van der Waals interactions between the components

5.11 As a first observation, current claim 1 states that the hydration level x is 0 to 3. According to a general statement in the application as filed, which is not limited to the specific compound as currently claimed, the compound of the invention can be in the crystalline, partially crystalline, amorphous or polymorphous form (see page 23, second paragraph of the application as filed).

However, it does not follow from this that variants of the compound of claim 1 with all possible combinations of these features and with any stoichiometric or non-stoichiometric hydration level must necessarily exist and that furthermore their preparation has to be disclosed for the requirement of sufficiency to be met (see also point 3.9 above).

5.12 The person skilled in the art would read claim 1, taken together with the text of the application as filed, as meaning that, in addition to the crystalline hemipentahydrate LCZ696, further existing variants within the scope of claim 1 may be identified and obtained by routine methods since no particular difficulty is mentioned and a general method for preparing compounds according to the invention is described (see the application as filed, page 36, last paragraph to page 39, penultimate paragraph). The embodiment LCZ696 itself was prepared in this way by routine techniques involving the co-crystallisation of the components from a solvent (see Examples 1 to 3 in the application as filed).

5.13 The appellants' arguments under issues (a) to (d) contesting the routine accessibility of such further variants are addressed below (see points 5.15 to 5.16.14).

5.14 As mentioned above, the information provided in the application as filed as well as common general knowledge are taken into account in the assessment of sufficiency of disclosure.

5.14.1 Application as filed

In the case in hand, the application as filed mentions different hydration states for the compound according to claim 1 (see page 22 of the application as filed), in particular 0, 1, 2 and 3, as also reflected in current claims 1 and 4, and 2.5, as reflected in current claim 5. It is also generally mentioned that the dual-acting compound of the invention can be in the crystalline, partially crystalline, amorphous or polymorphous form (see page 23, second paragraph). No reason is apparent from the content of the application as filed that could give rise to the conclusion that such forms would only be accessible with difficulty or undue burden going beyond the use of standard techniques known in the field of pharmaceutical development (see also point 5.12 above).

Indeed, a general method for preparing dual-acting compounds according to the invention is described (see the application as filed, page 36, last paragraph to page 39, penultimate paragraph).

The application as filed does not provide specific instructions for preparing individual variants of the supramolecular compound covered by current claim 1, except in the case of the crystalline hemipentahydrate LCZ696. As can be derived from Examples 1 to 3, LCZ696 was prepared by routine techniques and in accordance with the general method set out in the application as filed.

The application reports, furthermore, that water of hydration was released in two steps upon heating LCZ696. As discussed below (see point 5.15.4), the respondent contended that this may be regarded as pertinent guidance for obtaining a variant with a different hydration level.

5.14.2 Common general knowledge

The relevant common general knowledge in the pharmaceutical field extends to a wide range of techniques for screening for and preparing variants of solid compounds such as crystalline polymorphs, amorphous forms or forms varying in their hydration states, and for characterising such variants. For instance, the respondent referred to the review article **D9**, the textbook chapters **D19**, **D20** and **D64** and the journal article on amorphous solids **D27** as evidence of the pertinent common general knowledge. The content of these documents is summarised in the respondent's reply to the statements setting out the grounds of appeal (points 7.20 to 7.38).

5.15 Concerning the enablement of further crystalline polymorphs and hydration levels including anhydrous forms (issues (a) to (c) according to point 5.10 above), the following considerations apply.

5.15.1 In pharmaceutical development, it is routine practice to screen for polymorphs and hydrates. Thus, finding alternative forms by such methods is typically routine.

5.15.2 The appellants' argument that finding specific polymorph or hydrate forms is unpredictable does not change this basic premise.

Appellant-opponent 1 submitted, with reference to a piece of prior art (Chem. Comm., 2005, 2513-2514) cited as "D18" in case T 1684/16, that the discovery of

specific hydrates was unpredictable (see issue (c) above). The passage from this document cited in T 1684/16, Reasons 4.3.4, stresses that it is difficult to predict whether a new species may crystallise from solution with one or more molecules of solvent (see the statement setting out the grounds of appeal by appellant-opponent 1, points (46) and (47)).

However, in the case in hand, the issue is not whether it might have been predicted that a specific hydrate exists (as argued by appellant-opponent 1; see the statement setting out the grounds of appeal, point (47)) or that it forms under specific conditions, but whether further hydrates conforming to claim 1 would have been accessible by routine screening without undue burden. The cited passage is not pertinent to this question and cannot substantiate serious doubt in this regard (irrespective of the further question of whether the appellant's reference to new evidence should be admitted under Article 12 RPBA, see section 7. below).

The analogous reasoning and conclusion apply to the identification of further polymorphs.

5.15.3 The appellants furthermore referred to previous comments made by the respondent to the effect that no polymorphs of LCZ696 had been identified during the respondent's development screens (see issue (c) according to point 5.10 above). The appellants relied in this regard on:

- **D2**, submitted during pre-grant examination of the earlier (parent) application, stating in point 3.18 that no polymorph of LCZ696 had been identified during development in an "extensive, rigorous polymorphism screen"

- **D22**, submitted during pre-grant examination of the application as filed, stating on page 9 that LCZ696 had no polymorphs

The board concurs with the respondent and the opposition division that, even considering the statement in **D2** that the screens were "extensive and rigorous", the comments in **D2** and **D22** do not provide sufficient detail on the nature and extent of the screens that were carried out to permit the conclusion that further crystalline polymorphs of LCZ696 were not accessible without undue burden (see the respondent's reply to the statements setting out the grounds of appeal, points 7.84 to 7.86 and the decision under appeal, Reasons 16.6.2). Nothing in the cited passages from **D2** and **D22** contradicts the respondent's explanation that the screens in question were performed with the aim of detecting whether conversion to a different polymorph might occur during manufacture and formulation of LCZ696, rather than being active, exhaustive attempts to find further polymorphs. Moreover, the availability of different polymorphs for a specific hydrate is in any case not required by the terms of claim 1.

- 5.15.4 According to the application as filed (see page 45: "DSC and TGA"), as shown by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), the water of hydration was released in two steps upon heating of LCZ696 at a heating rate of 10 K/min: the first step occurred below 100°C and the second step above 120°C.

This shows that at least one other hydrate form, as obtained in the first dehydration step, may be prepared by heating the hemipentahydrate LCZ696.

According to the post-published journal article **D48** (see page 276, left-hand column), this further hydrate is the hemihydrate ($x = 0.5$):

"On heating, the waters of hydration are lost in two steps: the first step, with an onset temperature of about 65°C, is followed by a second step coinciding with the onset of melting. Both hot-stage X-ray powder diffraction and hot-stage microscopy revealed that crystalline structure is maintained up to the melting temperature, in spite of losing around 80% of water of hydration (equivalent to two water molecules) in the first dehydration step."

5.15.5 The appellants' assertion that the hemihydrate itself, as a desolvated form, would be too hygroscopic to be stable under ambient conditions remains unsupported by verifiable evidence. In the absence of evidence, any objection based on this unverified assertion cannot succeed.

5.15.6 According to a further argument by the appellants, the results reported in **D48** and in the application as filed should be taken as evidence that other hydrates, the anhydrous form and other crystalline polymorphs were not enabled. The board did not arrive at the same conclusion for the following reasons.

The fact that heating the hemipentahydrate LCZ696 at a particular rate (the application as filed specifies 10 K/min; **D48** does not disclose the heating rate) did not yield further variants does not permit the inference that such further variants, in particular other hydrates, are not accessible without undue burden by other methods (issue (a)).

In the same way, even if heating LCZ696 according to a given method might not have yielded an anhydrous form (since the second step of water loss coincided with the onset of melting), this does not permit the inference that anhydrous forms could not have been obtained by any known technique without undue burden (issue (b)).

The appellants' approach in considering only LCZ696 as a potential starting material for preparing compounds where x has a value other than 2.5 is too narrow as it is restricted to only one possible concept for synthesis. The relevant question in a more comprehensive approach would be, rather, what synthesis options would the skilled person have reasonably considered in light of common general knowledge for preparing compounds according to claim 1 other than the hemipentahydrate.

The information in **D48** that the crystalline structure of LCZ696 was maintained during dehydration in the process according to **D48** does not support the more general conclusion that other crystalline polymorphs are not accessible, or are accessible only with considerable difficulty, by any other method (issue (c)).

The common general knowledge encompassed a variety of techniques enabling the person skilled in the art to screen for, make and characterise compounds with different hydration states as well as anhydrous forms (see, for instance, **D9**: pages 948 to 951; **D64**: pages 199 to 205; **D20**: page 247). The same applies to crystalline polymorphs (see, for instance, **D9**: pages 946 to 948, **D64**: pages 184 to 202; **D20**: page 228).

For these reasons, the appellants' arguments based on **D48** are not conclusive.

5.15.7 By way of supplementary evidence illustrating the routine accessibility of other hydrates conforming to claim 1, the respondent referred to several post-published third-party patent applications that report the formation of solid forms within the scope of claim 1. The respondent submitted that the patent in suit was the source of all such follow-on implementations.

In particular, **D67** (paragraph [0020], Examples 2 and 3) disclosed a method of making a monohydrate, and **D68** (claim 10) disclosed a method of making a trihydrate form of the claimed compound along the lines of the method provided in the patent in suit.

5.15.8 Since variants according to claim 1 are encompassed in the scope covered by the application as filed and it would have appeared credible that such variants were accessible without undue burden on the basis of the generally disclosed process in the application as filed and the skilled person's common general knowledge, the respondent's reference to post-published evidence for further corroboration is not objectionable.

5.15.9 The appellants, on the other hand, relied on **D67** and **D68** in support of their view that the claimed subject-matter was insufficiently disclosed. The board did not arrive at the same conclusion for the following reasons (see points 5.15.10 and 5.15.11 below).

5.15.10 Appellant-opponent 1 contended that the preparation processes described in **D67** and **D68**, involving the use of certain solvents and temperature conditions to obtain, specifically, a monohydrate and a trihydrate, were not straightforward routine developments of the teaching of the application as filed, which did not disclose these specific processes. The process of **D67** involved crystallisation with gradient cooling for

obtaining a monohydrate form. In the case of **D68**, it involved the use of acetone as a solvent for obtaining a trihydrate rather than the hemipentahydrate form.

This argument must fail since no unreasonable effort appears to have been involved in obtaining these further hydrate forms. The preparation methods disclosed in **D67** and **D68** are within the ambit of the general method provided in the application as filed. Trying variations of solvents and process conditions to obtain further variants is a matter of routine. So it cannot be derived from the disclosure of **D67** or **D68** that it would have been particularly burdensome to find and prepare further hydrates.

5.15.11 Appellants-opponents 6 and 7 maintained (with reference to documents **D77** to **D79**) that the monohydrate according to **D67** was a desolvated form of the hemipentahydrate LCZ696 and, therefore, retained the same crystalline structure, and that the trihydrate according to **D68** also showed the same crystalline structure as LCZ696. According to appellants-opponents 6 and 7, this was proof of insufficient disclosure since claim 1 was not restricted to variants showing the same X-ray diffraction (XRD) pattern as LCZ696.

This argument does not succeed. Even if it were indeed the case that the hydrate variants described in **D67** and **D68** showed the same crystalline structure as LCZ696, this does not permit the conclusion that other crystalline polymorphs would not be accessible by routine screening and without undue burden. In any case, as the claims do not recite a particular lattice structure or XRD pattern, a demonstration of such specific technical features is not required (see also point 5.15.3 above).

- 5.16 Concerning the enablement of an amorphous variant (issue (d) according to point 5.10 above), the following considerations apply.
- 5.16.1 The application as filed states in a general way that the compound of the invention may be amorphous. While amorphous forms are not recited in claim 1, which merely defines the solid form as mandatory, the wording of claim 1 does not exclude amorphous forms (see points 3.9, 3.11.1 and 3.11.3 above).
- 5.16.2 Even if the application as filed does not point out specific measures that would lead to an amorphous product, the skilled person would have been aware that the generally described precipitation method may yield amorphous forms, depending on the chosen process conditions. Methods for preparing amorphous forms were in any case part of the skilled person's common general knowledge. In **D20**, an excerpt from a textbook about polymorphism, the amorphous form is taught to be a state available to all compounds (see **D20**, page v). Routine techniques for making amorphous forms include reduction of particle size, spray-drying, lyophilisation and drying under reduced pressure (see **D9**: pages 952 to 953; **D64**: pages 208 to 219).
- 5.16.3 Appellants-opponents 6 and 7 maintained that the person skilled in the art was not in a position to determine whether a given amorphous form was a compound conforming to claim 1, i.e. a supramolecular complex forming a single compound (see point 3.14 above on claim construction). This was because no analysis technique existed by which it could be established that an amorphous material was a supramolecular complex as required by claim 1 rather than a mixture of amorphous sacubitril monosodium and valsartan disodium salts. This differentiation was only possible for crystalline

materials like LCZ696, which could be characterised by single crystal X-ray crystallography. Reference was made to **D19** (Table 4.6, as shown below).

Table 4.6 Summary of information obtained from different physical techniques for various types of crystal modifications (From Yu *et al.* 1998, with permission.)

Type of crystal modification	Single crystal X-ray crystallography	X-ray powder diffraction	IR/Raman spectroscopy	Solid-state NMR spectroscopy	Thermal methods	Microscopy
True polymorphs	Same chemical composition. Unique unit cell parameters molecular conformation and packing.	Unique Diffraction peaks. Useful for determination of phase purity and % crystallinity.	Characteristic spectra. Sensitive to H bonding.	Unique Chemical shifts. Useful for determining phase purity, molecular mobility.	Unique mp, heat capacity, heats of fusion/transition, solubility. Useful for determining relative stability of forms.	Characteristic indices of refraction, birefringence, dispersion colour, crystal habit.
Solvates	Same as true polymorphs	Same as true polymorphs	Unique solvent bands. Shifted molecular bands. Sensitive to H bonding.	Unique solvent resonances. Shifted molecular resonances. Solvent mobility can be determined.	Low-temperature transitions due to desolvation (TGA loss)	Same as true polymorphs. Desolvation observable by hot stage microscopy.
Isomorphic desolvates	NA	Diffraction pattern only slightly changed from parents solvates.	Solvent bands disappear. Molecular bands shifted.	Solvent resonances disappear. Molecular resonances shift.	Low-temperature desolvation absent. Events due to crystallization or lattice relaxation	Birefringent microcrystalline domains, with cracks and fissures.
Amorphous solids	NA	No diffraction peaks	Broadened spectra	Broadened spectra	Glass transition seen. Often followed by crystallization and melting. 'Fragility' related to width of T_g .	No birefringence, irregular particle shape.
Polymorphic mixtures	NA	Composite pattern of crystalline components	Composite spectrum of all components	Nuclei-specific composite spectrum of all components	Thermal behaviour indicative of phase diagram (e.g. mp-depression, eutectic melting, dissolution).	Composites of distinct crystalline and amorphous particles

5.16.4 As indicated in point 3.10 above, this line of argument appears to relate to clarity and the delimitation of the claimed subject-matter rather than to sufficiency of disclosure. In addition, the reasons given were not found convincing.

5.16.5 While Table 4.6 in **D19** indicates the general type and quality of information that may be obtained by the various analytical methods for different types of solids, the content of this table does not permit the reader to infer a direct answer to the question of whether an amorphous solid material conforming to current claim 1 may be distinguished from a mixture of the (amorphous) sodium salts of valsartan and sacubitril by any of the methods shown. Thus, the cited

table does not conclusively substantiate the appellants' assertion that no analysis technique was suitable.

5.16.6 The application as filed states (see page 10, second full paragraph) that:

"Typically, the dual-acting compound, in particular the supramolecular complex, shows properties, such as melting point, IR spectrum, etc. that are different from a physical mixture [sic] of the species."

5.16.7 Amorphous forms are, by definition, non-crystalline materials which possess no long-range order (see **D27**, Abstract). Nevertheless, amorphous solids are not random at the molecular level but may possess short-range order (see **D27**: page 36, right-hand column, bullet point a).

5.16.8 The appellants did not conclusively show, by evidence or theory, that a solid material cannot, at the same time:

- have the non-covalent interactions resulting in a supramolecular compound with a sum formula as defined in claim 1
- lack a long-range crystalline structure (in which case it presents as an amorphous form)

It is not apparent why these two conditions should be mutually exclusive.

In the case in hand, specific interactions will be present in a supramolecular complex as defined in claim 1, even if it is amorphous, owing to ionic and hydrogen bonds (see point 3.13 above). These interactions and the resulting structures (absent in mere physical mixtures of valsartan disodium salt

and sacubitril monosodium salt) will have properties detectable by analytical techniques.

- 5.16.9 Based on the arguments and evidence presented, it cannot be conclusively ruled out that analytical techniques like IR spectroscopy (as relied on, for instance, in **D69**; see point 5.16.12 below) or thermal methods such as DSC, or combinations of such techniques, may permit an observer to distinguish an amorphous supramolecular compound according to claim 1 from a corresponding mixture of the amorphous sodium salts of valsartan and sacubitril based on differences in behaviour caused by these non-covalent interactions (see also point 5.16.6 above and Table 4.6 of **D19** as rendered in point 5.16.3 above).
- 5.16.10 By way of supplementary evidence illustrating the routine accessibility of an amorphous variant conforming to claim 1, the respondent relied on the post-published third-party patent applications **D69**, **D70** and **D71**, all reporting the preparation of amorphous forms of trisodium valsartan sacubitril within the scope of claim 1.
- 5.16.11 Since it would have appeared credible, on the basis of the information in the application as filed and the skilled person's common general knowledge, that amorphous variants were accessible without undue burden (see point 5.16.2 above), the respondent's reference to post-published evidence for further corroboration and in response to the appellants' arguments is not objectionable.
- 5.16.12 According to **D69**, complex formation was confirmed by IR spectrum (see **D69**: Example 10, concerning the preparation of an amorphous hydrate form of a compound conforming to the sum formula of current claim 1, and

page 19, lines 1 to 11). The board is not aware of any reason for doubting this statement in **D69**.

5.16.13 While **D70** and **D71** also claim the preparation of amorphous trisodium valsartan sacubitril (D70, D71: claims and examples), they do not include any teaching about differentiating the amorphous product from a mixture of the salts.

5.16.14 For the reasons set out in points 5.16.1 to 5.16.12 above, the appellants failed to convincingly substantiate the alleged doubts about the accessibility, including the characterisation, of amorphous variants (issue (d) in point 5.10 above).

5.17 By way of a further objection, appellant-opponent 5 maintained that compounds according to claim 1 that present only weak Van der Waals interactions as non-covalent bonds were possible embodiments of claim 1, and that these represented a "grey area" not described in the application, for which no guidance was provided for obtaining them (see issue (e) listed in point 5.10 above).

In relation to this issue, the board refers to the considerations set out in point 3.12 above. Ionic species and polar groups are by definition present in the claimed compound. These will inevitably form non-covalent bonds other than weak Van der Waals forces. Hence, the purely hypothetical embodiment restricted to just Van der Waals interactions is not covered by the definition of claim 1. For the requirement of sufficiency to be met, a patent proprietor or applicant is not required to provide guidance for evidently non-existent, artificially construed embodiments of the claimed subject-matter.

Claims 9 to 11

- 5.18 Appellant-opponent 2 furthermore asserted, without further substantiation, that the suitability of the claimed compound for the treatment of cardiovascular and/or renal diseases, as required according to claims 9 to 11 of the current main request, was not rendered credible at the filing date (see point 5.2 above and the appellant's statement setting out the grounds of appeal, points III.1 to III.3).
- 5.19 This objection must fail for the following reasons.
- 5.19.1 While the claimed compound was novel, it is composed of the active agents valsartan and sacubitril, whose pharmacological properties were already known. On a mechanistic level, it would have appeared credible to the skilled person reading the application as filed that the compound of current claim 1, in which the moieties valsartan and sacubitril are linked only by non-covalent interactions, is "dual-acting" in that it releases these two drugs to a patient upon administration. The drugs will then provide their known therapeutic benefits as an angiotensin receptor blocker and a neutral endopeptidase inhibitor (see the application as filed, page 7, third and sixth paragraphs; paragraph bridging pages 8 and 9).
- 5.19.2 The technical background on how these drug classes work, which was part of the common general knowledge, is briefly discussed on pages 1 and 2 of the application as filed. ARBs, providing the effect of lowering blood pressure, can be used as anti-hypertensives or for the treatment of congestive heart failure. Inhibitors of NEP, by increasing plasma levels of atrial natriuretic peptide, induce natriuretic and diuretic effects. This is also presented as common general knowledge in prior-art document **D1** (see pages 1

and 2). Valsartan and sacubitril had been previously described as members of the respective drug classes (see the application as filed, page 14, last paragraph and page 18, last paragraph; **D3**, **D4** and **D1**).

- 5.19.3 Furthermore, the application as filed reports that the antihypertensive effect of LCZ696, i.e. the exemplified hemipentahydrate, was shown *in vivo* in a rat model of fulminant hypertension. The inhibition of NEP *in vivo* was also shown in a rat model (see the application as filed, page 33, line 5 to page 35, line 5). The board is not aware of any reason why this dual activity should not be achieved also by any other compound variants falling within the definition of claim 1.
- 5.19.4 Thus, the suitability of the claimed compound for the therapeutic uses in claims 9 to 11 in the context of cardiovascular and/or renal disease was indeed credible at the filing date, based on technical background knowledge and the preclinical evidence reported in the application as filed.
- 5.19.5 In addition, post-published evidence in **D15** confirms that LCZ696 reduced cardiovascular death and heart failure hospitalisation in human patients with chronic heart failure and achieved better results than the comparative drug enalapril (see **D15**: abstract and results; see also **D18**, which confirms that EntrestoTM (i.e. LCZ696 tablets) received US marketing approval). **D15** also reports that clinically important increases in the serum creatinine level and discontinuation of the study drug because of renal impairment were less frequent in the LCZ696 group than in the enalapril group (see **D15**: page 11, left-hand column, last paragraph).

5.19.6 In contrast, the mere assertion of insufficiency by appellant-opponent 2 does not meet the required standard of serious doubt substantiated by verifiable facts.

Conclusion on sufficiency of disclosure

5.20 For the reasons set out above, the board concluded that the claimed subject-matter is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

6. Inventive step (Articles 100(a), 52(1) and 56 EPC)

6.1 The patent in suit seeks to provide a pharmaceutically useful combination of an ARB compound and a NEPi compound and discloses, in particular, a dual-acting compound combining valsartan and sacubitril (after correction of an evident error, see point 4.4.9 above) by non-covalent bonding according to the sum formula rendered in claim 1 of the current main request.

Starting point in the prior art

6.2 It was common ground that inventive step should be assessed starting from the disclosure of document **D1**.

6.3 **D1** relates to pharmaceutical compositions comprising valsartan and a NEPi or their pharmaceutically acceptable salts (see claim 1 and page 2, lines 26 to 30), intended for use in the known therapeutic indications of these agents, i.e. cardiac and renal related conditions (see **D1**: claim 6; paragraph bridging pages 2 and 3; page 13: last paragraph).

The active agents can be formulated in these compositions in one combined unit dose form, which may be a fixed combination, or in separate unit dose forms (see **D1**: page 13, second paragraph). Thus, the term

"composition" used in claim 1 of **D1** does not imply that valsartan and the NEPi must be present in the same dosage form in admixture. The dosing frequencies may also differ as the NEPi is to be administered once per day and valsartan up to three times per day (see **D1**: page 15, lines 19 and 28).

Formulation examples for compositions containing valsartan (but not a NEPi) are provided (see pages 16 to 21).

According to **D1**, combination therapy with valsartan and a NEPi presents advantages, in comparison with monotherapy, with regard to therapeutic efficacy and adverse effects (see page 7, lines 16 to 20).

Sacubitril is listed as an eligible NEPi compound ("N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester"; see **D1**: page 5, lines 1 to 3; claim 2, lines 6 to 7). It is the only NEPi for which a structure formula is shown in **D1** (see page 7).

The compounds to be combined can be present in the form of their pharmaceutically acceptable salts (claims 1 and 2; page 6, lines 15 to 16). The monosodium salt is among the three preferred salts of sacubitril (see page 6, line 22; by reference to **D3**, which in Examples 1 and 8 describes the synthesis of sacubitril monosodium and a capsule formulation containing it). No specific salts of valsartan are mentioned.

Efficacy studies based on rat models are proposed for the combination of valsartan with sacubitril (see **D1**: page 9, line 8 to page 12, line 29). The possible study design is described, but no experimental data from an actual study are presented.

6.4 **D1** thus discloses the combination of valsartan and sacubitril or their pharmaceutically acceptable salts,

e.g. in the form of a pharmaceutical composition as defined in claims 1 and 2 of **D1** comprising:

- valsartan or a pharmaceutically acceptable salt thereof
- sacubitril or a pharmaceutically acceptable salt thereof
- a pharmaceutically acceptable carrier

This encompasses embodiments providing valsartan and sacubitril in separate dosage units.

Objective technical problem and solution

6.5 The subject-matter of current independent claim 1 differs from this starting point in **D1** by:

- providing the desired combination of valsartan and sacubitril in a specific form as a single (supramolecular) compound according to the sum formula defined in claim 1

in which:

- valsartan and sacubitril are provided as sodium salts
- the molar ratio of these components and optional water is 3:1:1:0 to 3:1:1:3, as specified in point 3.4 above, and in particular the molar ratio of valsartan to sacubitril is 1:1
- the compound is provided in solid form

6.6 The technical effect linked to these distinguishing features is the provision of a specific combination of valsartan and sacubitril.

6.7 On this basis, the objective technical problem to be solved in view of **D1** is to provide a specific combination of valsartan and sacubitril.

- 6.8 This technical problem is solved by the compound as defined in claim 1.
- 6.9 According to the respondent, the objective technical problem should instead be formulated as providing an improved formulation of valsartan and sacubitril, based on advantages for pharmaceutical manufacturing and other favourable properties that could be attributed to the combination being available as a single compound.
- 6.10 However, since the claimed subject-matter was ultimately found to involve an inventive step on the basis of the less ambitious technical problem set out in point 6.7 above, it is not necessary to assess the merit of this argument here.

Obviousness of the solution - general considerations

- 6.11 The appellants contended that combining valsartan and sacubitril in a molar ratio of 1:1 and using the sodium salts of these compounds would have been obvious formulation choices for the person skilled in the art seeking to solve the objective technical problem.
- Furthermore, the skilled person would have been aware that co-crystallisation was a commonplace option for formulating two active ingredients in general and would have considered that valsartan and sacubitril, on account of their chemical properties, would be suitable for co-crystallisation to provide a crystalline form conforming to claim 1. The appellants referred to the disclosure of **D13** (a journal article on crystal engineering of pharmaceutical co-crystals) and a number of review articles regarded as representing common general knowledge.

Still according to the appellants, making an amorphous form would also have been obvious and arbitrary. An amorphous material could have been obtained in a conventional manner by removing the solvent from a solution of the sodium salts to obtain a glassy material, which would provide an arbitrary mixture of amorphous salts.

Moreover, no conscious decision to prepare a co-crystal or supramolecular complex from valsartan disodium and sacubitril monosodium would have been required from the skilled person since the compound of claim 1, in particular LCZ696, would have been obtained inevitably in the normal course of pharmaceutical development, e.g. using obvious routine methods for preparing film-coated tablets containing these two active ingredients. Reference was made to the test report **D75**, which, according to the appellants, showed that conversion to LCZ696 could not be avoided during the manufacture of conventional tablets or under usual storage conditions.

- 6.12 The board considers that the decisive distinguishing technical feature for establishing an inventive step is the provision of the combination of valsartan and sacubitril in the form of a single supramolecular compound.
- 6.13 Selecting a 1:1 stoichiometry for the pharmaceutically active compounds, while not the only possible option, was still a possible choice in line with the general teaching of **D1** regarding dosage.
- 6.13.1 **D1** specifies a daily dosage range of 20 to 320 mg for valsartan and 10 to 800 mg for the NEPi compound (see page 15, third and fourth paragraphs). Since valsartan and sacubitril have similar molecular weights, this translates into an approximate range for the molar ratio between 1:40 and 32:1. The set-up of the

proposed rodent study includes a dosage range from 1 to 10 mg/kg/day for valsartan and 10 to 50 mg/kg/day for sacubitril, which translates into an approximate range for the molar ratio between 1:50 and 1:1.

6.13.2 For the molar ratio, the appellants also referred to **D45**, which reports experimental data (obtained by the respondent with rodents) that purportedly point to a synergy between valsartan and sacubitril.

6.13.3 In these experiments, the agents were administered separately, at weight ratios of 1:1 and 10:3. It does not follow from the disclosure in **D45** that no other molar ratio than 1:1 would have been considered by the person skilled in the art seeking to solve the objective technical problem. Thus, **D45** does not add anything beyond what could already have been derived from **D1**, namely that a(n approximate) molar ratio of 1:1 was a possible choice.

The question of priority in relation to the status of **D45** as potential prior art (Articles 56 and 87 EPC) can, therefore, be left undecided.

6.14 The board is also of the view that selecting the sodium salts of valsartan and sacubitril was a possible option in line with the teaching of **D1** as the respondent did not show that there was a prejudice in the prior art that would under any circumstances have prevented the person skilled in the art from using the sodium salts.

6.15 However, the features specifying a molar ratio of valsartan to sacubitril of 1:1 and the presence of sodium ions making for a molar ratio of 1:1:3 should not be considered in isolation but in the context of whether the skilled person seeking to solve the objective technical problem would have chosen such features in a specific setting that would result in a

solid single compound according to claim 1 (see points 6.30.1 and 6.30.2 below).

6.16 Starting from the teaching of **D1**, and given that the objective technical problem was to provide a specific combination of valsartan and sacubitril, only solutions that the skilled person would have obtained in routine pharmaceutical development, without hindsight, i.e. without prior knowledge of LCZ696 or other variants falling within claim 1, would have been obvious.

In this aspect, the assessment of obviousness differs from the assessment of sufficiency of disclosure (see section 5. above), which, in contrast, starts from the knowledge of LCZ696 and the teaching of the application as filed.

6.17 The appellants failed to provide conclusive substantiation of their argument that crystalline or amorphous forms falling within claim 1 would have been routinely obtained by the skilled person without hindsight and knowledge of LCZ696, either because the skilled person would have sought to prepare such compounds with a reasonable expectation of success (the "single compound" argument) or because such compounds would have inevitably been obtained as the result of an obvious process choice (the "inevitable result" argument).

Obviousness - "single compound" argument

6.18 The first issue to be considered is whether the person skilled in the art, seeking to solve the objective technical problem, would have envisaged combining valsartan and sacubitril to prepare a single supramolecular compound (such as defined in current claim 1).

- 6.19 This is not a solution suggested by any passage in **D1**. According to **D1**, valsartan and sacubitril can be provided in separate unit dosage forms or in a common dosage form. This may be a fixed dosage form, but **D1** makes no suggestion as to the details of this fixed dosage form. **D1** does not require co-formulation of valsartan and sacubitril or define any interaction between these components.
- 6.20 Thus, the question to be answered is whether the person skilled in the art would nevertheless have been motivated to prepare a single supramolecular compound from valsartan and sacubitril.
- 6.21 The board came to the conclusion that this is not the case because:
- (i) forming co-crystals of two pharmaceutically active agents was not a routine approach in drug development at the time the invention was made
 - (ii) even if such an approach had been considered, the skilled person would have had no reasonable expectation of success that suitable co-crystals of valsartan and sacubitril could be prepared
 - (iii) it was not shown that the preparation of a single supramolecular compound of valsartan and sacubitril in amorphous form would have been envisaged with a reasonable expectation of success
- 6.22 Preparing co-crystals was not a routine approach
- 6.22.1 The prior art cited by the appellants, in particular **D10** to **D14**, does not demonstrate that forming co-crystals of two pharmaceutically active agents was a routine approach in pharmaceutical development at the time the invention was made.

6.22.2 **D10** to **D14** are all journal articles. With the exception of **D13**, they are review articles, most of which were published close to the priority date (**D10** and **D12** to **D14**).

Only a small part of the older document **D11** relates to co-crystals. **D11** also teaches that co-crystals are not easy to prepare and that supramolecular science was still "very much in its infancy" (see **D11**: page 572, right-hand column, second paragraph; page 582, right-hand column, second paragraph).

It can in general be taken also from the more recent articles that crystal engineering of pharmaceutical co-crystals was regarded as a new and relatively unexplored approach that required further study (**D10**: title; page 1890, left-hand column, first paragraph; page 1895, right-hand column; **D12**: abstract; **D13**: last sentence on page 4603, left-hand column; **D14**: "Afterword").

Only a limited number of examples of co-crystals is disclosed in these documents (none of which involve valsartan or sacubitril). General conclusions, if any are provided, are formulated cautiously and with the caveat that more research is needed.

Thus, these documents do not support the appellants' arguments. Instead, they confirm that the design of pharmaceutical co-crystals was not a routine part of form selection processes in pharmaceutical research and development and had up to that point in time only found limited application. General considerations found in the prior art, suggesting that co-crystallisation might in certain cases reduce polymorphism or hygroscopicity of the pharmaceutical compounds involved, are speculative (see, for instance, **D10**: point 4.3, with regard to polymorphism) and, in any case, are not specific enough to have provided an incentive for the

skilled person to try this approach for providing a combination of valsartan and sacubitril.

Hence, the person skilled in the art seeking to solve the objective technical problem would not have considered co-crystallisation, even if aiming to prepare a fixed combination of the two drugs.

6.23 No reasonable expectation of success

6.23.1 Even if the possibility of forming co-crystals and the literature relating to this option had been considered, the skilled person could at most have entertained a hope to succeed rather than a reasonable expectation of success. In the absence of pertinent data in the prior art, co-crystal formation between valsartan and sacubitril was not predictable.

6.23.2 None of **D10** to **D14** provides relevant information on the potential behaviour of valsartan, sacubitril or their salts that would allow a prediction on whether a stable co-crystal might be obtained and by which method or what the favourable or unfavourable properties of such a co-crystal might be.

6.23.3 The few examples provided in the prior-art documents cited by the appellants (which include also **D26** relating to dimenhydrinate) are isolated instances of co-crystals of different drugs (i.e. having different structures and functional groups).

6.23.4 The "acid-amide supramolecular heterosynthon" identified in **D13** involves carboxylic acid and primary amide groups (with both of the two hydrogens of the primary amide group involved in sustaining the hydrogen-bonding network in the co-crystal, see **D13**: figures; page 4601, left-hand column, first paragraph and right-hand column, first paragraph). Neither

valsartan nor sacubitril contains a primary amide group, nor are they structurally similar to piracetam disclosed in **D13**.

- 6.23.5 There is also a fundamental difference between predicting whether a single drug molecule of interest has the potential to form a co-crystal with any other agent (which could then be identified by screening with potential co-formers) and predicting whether two given molecules (in the case in hand, valsartan and sacubitril) would form a co-crystal.
- 6.23.6 Furthermore, when combining crystalline solids, there is a thermodynamic driving force towards re-formation of the two individual crystalline solids, rather than formation of a co-crystal. For example, **D11** (see page 572, right-hand column) states that a heteromeric system will form only if the non-covalent forces between two or more molecules are stronger than those between the molecules in the corresponding homomeric crystals and that, in general, it is thermodynamically more favourable to assemble similar molecules (i.e. pure A and pure B) rather than to pack dissimilar molecules into the same solid (AB).
- 6.23.7 Thus, the skilled person could not *a priori* expect that valsartan and sacubitril would be capable of forming a single supramolecular co-crystal together and could not predict under which conditions this might happen (in the current case, when in their anionic forms and in the presence of sodium cations and water molecules).
- 6.23.8 The appellants referred to further documents including **D7, D9, D23, D24** and **D25**. However, their content, like that of **D26**, does not add any further aspect that could call into question the Board's assessment based on documents **D10** to **D14**.

6.24 Amorphous single compound not envisaged

6.24.1 The appellants did not provide any evidence showing that it would have been routine to prepare a single supramolecular compound of valsartan and sacubitril in amorphous form. For analogous reasons as set out in the case of the co-crystals, there would have been no reasonable expectation of success for an amorphous form, either.

6.24.2 In so far as the appellants' reasoning was based on the premise that claim 1 includes mixtures of the amorphous sodium salts of valsartan and sacubitril and that it would have been obvious to make such mixtures, this argument is irrelevant in view of the considerations on claim construction set out above and the board's conclusion that claim 1 does not cover physical mixtures of the salts (see point 3.6 above).

Obviousness - "inevitable result" argument

6.25 The appellants' further argument that a single supramolecular compound as claimed would have been obtained inevitably did not succeed, either, for the following reasons.

6.26 The appellants maintained that the skilled person would have arrived inevitably at the compound of claim 1 because it would have formed during routine development of a tablet comprising a 1:1 molar ratio of valsartan disodium and sacubitril monosodium. Reference was made to **D75** and the jurisprudence established in **T 205/14**, **D50** and **D51**, in this regard.

6.27 However, **D1** does not convey the specific intention of developing such a tablet.

- 6.28 According to the established jurisprudence of the EPO, the concept of "inevitable result" has been used in the context of novelty assessment, but is not a known concept in the context of assessing inventive step.
- 6.29 In the current context, the board understands that the appellants' line of argument reciting an "inevitable result" appears to come down to the concept of a so-called "one-way-street" situation, in the sense that the person skilled in the art, in order to solve the objective technical problem, could only choose a particular path (such as a specific manufacturing process and/or specific parameters such as starting materials and process conditions) that would result in the claimed subject-matter, here the supramolecular compound according to claim 1.
- 6.30 In the case in hand, this argument fails because the person skilled in the art was not in that situation but, in fact, could choose from a large variety of options which would not all have provided a combination of valsartan and sacubitril conforming to claim 1, i.e. a single supramolecular compound.
- 6.30.1 Many alternative avenues were available for the skilled person starting from **D1** and seeking to provide a combination of valsartan and sacubitril. Not all of them would necessarily have resulted in the formation of a compound according to claim 1. Even if the skilled person had chosen to make a fixed dosage form containing both actives, **D1** does not require co-formulating valsartan and sacubitril in direct physical contact and in the presence of sodium ions. The drugs could still be kept physically separated also in a fixed dosage form, or they could be co-processed in the absence of sodium ions as **D1** requires neither the use of sodium salts of valsartan

or sacubitril nor the use of excipients that might be a source of sodium ions.

6.30.2 On a more general level, it was also not inevitable for the skilled person to choose a formulation approach that involved co-formulating the two drugs if, in contrast to the scenario discussed in points 6.18 to 6.24.2 above, the envisaged aim was not clearly that of providing a single compound comprising the two drug moieties together. The physical separation of the pharmaceutically active agents (e.g., in separate dosage units, in multilayer tablets, in microcapsules) would indeed be the more usual option to avoid any potentially unfavourable interaction or incompatibility.

6.31 Thus, it is precisely because certain choices would have to be made that are not suggested in combination by **D1** or by common general knowledge that the "inevitable result" argument, by definition, cannot succeed. This is illustrated by the following considerations in relation to **D75** (points 6.32 and 6.33).

6.32 The appellants relied on the experimental report **D75** to argue that the formation of LCZ696 was inevitable during attempts to formulate tablets containing the sodium salts of sacubitril and valsartan, and would occur at the latest during storage of the tablets.

6.32.1 **D75** examines three different formulation approaches for providing tablets containing equimolar amounts of valsartan and sacubitril (both used as sodium salts). The methods of manufacture adopted were direct compression, dry granulation (mono- and bilayer) and wet granulation. **D75** reports that conversion into LCZ696 was observed either in the initial product

obtained or during stability testing, i.e. in storage (see **D75**: page 2, pages 13 and 14).

6.32.2 However, the set-up of the experiments in **D75** would appear to be based on hindsight knowledge of Entresto[®] rather than on an attempt to recreate what the person skilled in the art would have done starting from **D1** at the relevant date (as confirmed by the Minutes of the oral proceedings before the opposition division, corrected version of 10 May 2023, where it is mentioned, on page 8, that **D75** was originally prepared for opponent 8 on instructions to create a generic version of the Entresto[®] tablet).

6.32.3 Valsartan and sacubitril are employed in the experiments of **D75** at, presumably, a 1:1 molar ratio, and both are provided as sodium salts. The information given is incomplete since the quantities used are indicated in mg, and it is not specified whether the respective monosodium and disodium salts were used. Entresto[®] is explicitly mentioned in Tables 3, 6 and 8 of **D75**, where its tablet parameters are compared with the corresponding parameters of the experimental tablets.

6.33 Thus, **D75** does not show that any formulation approach would inevitably result in LCZ696 (or any other variant encompassed in claim 1). Nor does it show that any attempt at formulating tablets containing valsartan and sacubitril would have this result since the process conditions and choice of components (and also the conditions for stability testing) can be varied within a much larger framework than what is covered by **D75**.

6.34 In support of their argument that the claimed compound could not be inventive as it was inevitably obtained,

the appellants also referred to the case law established in **T 205/14**, **D50** and **D51**.

- 6.34.1 As set out above, the prior art does not point to measures which result inevitably in the claimed compound. Thus, the appellants' premise that, in the case in hand, the skilled person would follow a particular path leading straight to the claimed compound is not correct and for this reason the cited judgments are not pertinent.
- 6.34.2 This applies in particular to decision **T 205/14**. In the context of novelty assessment, this decision states expressly that the claimed crystalline form is not the inevitable result of the prior-art disclosures relating to the relevant process of preparation (Reasons 4.3); in other words, the decision cannot be taken as a case in point of an inevitable result.

As to inventive step, the claimed crystalline form was known for its favourable properties. Thus the person skilled in the art had a clear incentive to search for means for providing this particular crystalline form. A general process known from the prior art but not disclosed for making this specific product turned out, after some experimentation, to be suitable for providing it, without the need for inventive skill (Reasons 5.1 to 5.5).

- 6.35 In view of these fundamental factual distinctions, the cited case law is not relevant to the case in hand.
- 6.36 Finally, for analogous reasons as discussed above, it was not the only option for the skilled person seeking to solve the objective technical problem to choose a manufacturing process that involved spray-drying a solution of the sodium salts of valsartan and sacubitril to obtain an amorphous bulk material (as

also suggested by the appellants). Nor would it have been an evident or usual choice. Spray-drying two pharmaceutically active agents together is not a routine process as it might lead to undesirable interactions. Moreover, no evidence is on file that such a process would inevitably yield a single supramolecular compound conforming to claim 1.

Obviousness - conclusion

6.37 As a consequence, the claimed compound is a non-obvious specific combination of valsartan and sacubitril (i.e. a non-obvious alternative).

6.38 The subject-matter of claim 1 of the main request therefore involves an inventive step within the meaning of Article 56 EPC. This conclusion also applies, for the same reasons, to claims 2 to 12, all of which refer back to the compound defined in claim 1.

7. Admittance of evidence and lines of argument

7.1 The respondent requested that certain lines of argument submitted by the appellants-opponents not be admitted (see the Minutes of the oral proceedings before the board, last paragraph on page 3).

7.2 The board admitted and, where necessary, considered the lines of argument in question (see points 3.8, 3.9 and 5.15.2 above). In view of the outcome in the respondent's favour, it is not necessary for the board to provide a reasoned decision regarding admittance.

7.3 The appellants did not base their objections in relation to the current main request on any of documents **D34** to **D41**.

7.4 **D80** was filed (as "D77") by appellant-opponent 1 in response to an argument made by the respondent at the oral proceedings before the opposition division about the alleged content of **D64** (see points (5) to (9) of the appellant's statement setting out the grounds of appeal). As the issue in question played no role for the board's decision, there was no need for the board to rule on the admittance of **D80**.

7.5 **D81** was filed by the respondent in response to point 18.1.7 of the decision under appeal, in order to substantiate its assertion that the only approved form of valsartan at the priority date was the free acid form and insufficient data was available for the sodium salts. As this issue was not decisive for the present outcome, there was no need to rule on the admittance of **D81**.

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 as amended in the following version:

Claims 1 to 12 of the main request filed during oral proceedings on 14 May 2025 and the description and drawing of the patent specification.

The Registrar:

The Chairwoman:



I. Aperribay

M. Pregetter

Decision electronically authenticated