Neutral Citation Number: [2026] EWHC 2127 (Pat)
Case No: HP-2025-000010

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS OF ENGLAND AND WALES
INTELLECTUAL PROPERTY LIST (ChD)
PATENTS COURT

The Rolls Building
7 Rolls Buildings
Fetter Lane
London EC4A 1NL
13 August 2026

Before:
MR. JUSTICE MEADE

Between:

ACCORD HEALTHCARE LIMITED **Claimant**

- and –

NOVARTIS AG **Defendant**
(a company incorporated under the laws of Switzerland)

- -
Hearing dates: 15-19 and 25-27 June 2026

APPROVED JUDGMENT

MR THOMAS HINCHLIFFE KC and MR THOMAS LUNT (instructed by **Pinsent Masons LLP**) for the **Claimant**

MR THOMAS MITCHESON KC, MR STUART BARAN and MS BETHANY HALBARD (instructed by **Bristows LLP**) for the **Defendant**

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Mr Justice Meade:

INTRODUCTION

1. In this action, the Claimant, "**Accord**", seeks a declaration of invalidity in respect of European Patent (UK) No. 1 467 728 B1 ("**the Patent**"), owned by the Defendant, "**Novartis**". The unchallenged priority date is 17 January 2002 ("the **Priority Date**")

2. The Patent expired in January 2023 but Novartis is also the proprietor of supplementary protection certificate SPC/GB16/025 ("**the SPC**"), for which the Patent was the basic patent, and which will not expire until 2028.

3. The Patent and the SPC were and are asserted by Novartis to protect its commercial product Entresto, which is a globally very successful drug for the treatment of heart failure. It also has approval in a smaller number of territories for treating hypertension.

4. Accord alleges that the Patent was always invalid on a number of grounds, which would of course automatically mean that the SPC is invalid, and also that the SPC is invalid even if the Patent was valid.

5. Accord has brought this action to try to clear the way in advance of launching an intended competing product soon after the expiry of Novartis' data exclusivity, which will be on 23 November 2026.

6. Novartis counterclaims for threatened infringement of the SPC.

7. Entresto is a combination of the angiotensin receptor blocker ("**ARB**") valsartan and the neutral endopeptidase ("**NEP**") inhibitor ("**NEPi**") sacubitril. In Entresto the valsartan and sacubitril are in the form of a co-crystal complex. In Accord's intended product they will be two separate salts, mixed together.

8. As well as asserting that the SPC is invalid, Accord denies infringement of it. Concessions made by the parties in the run-up to trial meant (as I understood it) that this denial did not have much separate significance, if any, and therefore the action was essentially all about validity.

9. As a result, Accord opened the trial and called its evidence first, even though infringement was formally in issue.

10. Mr Thomas Hinchliffe KC represented Accord and undertook the majority of the oral advocacy; he led Mr Thomas Lunt, who dealt with the SPC issues in closing oral submissions. Mr Thomas Mitcheson KC represented Novartis, leading Mr Stuart Baran, who likewise dealt with the SPC issues in oral closings, and Ms Bethany Halbard. This use of junior Counsel was in keeping with the Patents Court Guide's encouragement and I am grateful for it.

11. There have been proceedings in the Netherlands on the Dutch designation of the Patent, resulting in its being held valid. I understand some of the issues

overlapped with this case, but also that the arguments were rather differently made, and neither side relied on the decision so I say no more about it.

THE ISSUES; AN OVERVIEW

12. The issues are:

    i) The identity of the skilled addressee.

    ii) The scope of the CGK. There are disputes in relation to hypertension and in relation to heart failure.

    iii) "Classical" obviousness over:

        a) Ksander, G.M. et al., "Dicarboxylic Acid Dipeptide Neutral Endopeptidase Inhibitors", *J Med Chem*, 1995, 38, pp. 1689-1700, ("**Ksander)**";

        b) Trippodo, N.C. et al., "Repression of Angiotensin II and Potentiation of Bradykinin Contribute to the Synergistic Effects of Dual Metalloprotease Inhibition in Heart Failure", *J Pharmacology and Experimental Therapeutics*, 1995, pp. 619-627 ("**Trippodo**"), read with Ksander.

    iv) Lack of plausibility leading to insufficiency or obviousness.

    v) Obviousness based on the allegation that the invention of the Patent is a mere collocation of valsartan and sacubitril, each of which was individually known.

    vi) Obviousness for lack of technical contribution over European Patent Application No. 0 498 361 entitled "Combination of an angiotensin II antagonist or renin inhibitor with a neutral endopeptidase inhibitor" ("**Darrow**") or Trippodo.

    vii) Invalidity of the SPC even if the Patent is valid.

13. The issues interact very considerably and the dispute over the skilled addressee adds to the complexity so it will help if I provide a very high level overview, which is necessarily heavily simplified.

14. As I have mentioned already, Entresto is a combination of the ARB valsartan and the NEPi sacubitril (for the moment I leave out of account the salt forms of each, which enters the picture on the SPC issues).

15. The cardiovascular system is complex but the systems which regulate it include the renin-angiotensin-aldosterone system ("**RAAS**") and the natriuretic peptide system ("**NPS**").

16. ARBs act on the RAAS and at the Priority Date, various ARBs were approved and/or had been in advanced clinical trials (the precise picture is different for

hypertension and heart failure). Also very well known were **ACE inhibitors ("ACEis")**; they too act on the RAAS but at a different point in the system and with somewhat different consequences. Further details are the subject of the Agreed Statement of Common General Knowledge ("**ASCGK**").

17. NEPis act on the NPS. A NEPi is an inhibitor of an enzyme called neutral endopeptidase, which catalyses the breakdown of natriuretic peptides. So a NEPi would reduce such breakdown and lead to an increase in those peptides. Based on this effect, NEPis had been studied as potential therapeutics in hypertension and heart failure, but with mixed results. It is common ground that interest in drugs which had only NEPi activity had faded in the years leading up to the Priority Date, but another possibility had come along, which was to use single compounds called vasopeptidase inhibitors which combined NEP and ACE inhibition. One in particular which was topical at and around the Priority Date (though of course only events before the Priority Date are directly legally relevant to obviousness) was omapatrilat.

18. These categories of drugs have a variety of potential side-effects, but two in particular are of importance to the arguments at trial. The first is cough, thought primarily to arise from an effect on bradykinin, and the second is angio-oedema, which is a deep swelling under the skin and can be serious and even life-threatening.

19. At the very broad level at which I have just expressed them, these matters were of interest both in relation to hypertension and heart failure, and both clinically and in relation to the potential development of new treatments. But there were real differences in relation to symptoms, diagnosis, seriousness, clinical trials, what drugs were approved and what were in fact in use (including what combinations), treatment guidelines, the animal models used for testing potential compounds, and so on. For example, a persistent and annoying cough might be an acceptable trade off for effective treatment of a symptomatic and immediately life threatening case of heart failure whereas a hypertension sufferer would not readily tolerate it.

20. Novartis contends that the skilled addressee of the Patent is a skilled team interested in developing treatments, but *only* for hypertension, not heart failure at all. Accord contends that it is *also* legitimate to consider a skilled team with an interest, and corresponding CGK, in heart failure. This difference is reflected in Accord calling a single expert, Professor Wilkinson, to speak to both fields, and Novartis calling Professor Webb to address hypertension and Professor Clark to address heart failure. The dispute is a complex and rather subtle one since it is accepted that some matters would be known to both communities, at least to some, possibly differing, degree.

21. Turning to the prior art, Ksander gives pharmacokinetic/pharmacodynamic information for a range of NEPis, including sacubitril (along with its metabolite sacubitrilat) in preclinical experiments in animals.

22. Accord says that the results were promising, especially for sacubitril, and that the obvious ways forward included combining sacubitril with an ARB, specifically valsartan, which it says was as good as any other. The argument

proceeds in stages: that sacubitril was promising but NEPis on their own had not been successful; that it was appreciated, including from the vasopeptidase inhibitor/omapatrilat work that they could be made much better when combined with action on the RAAS; that action on the RAAS could be achieved with either an ARB or an ACE inhibitor; that the choice of an ARB had obvious advantages in at least some patient populations (those who could not tolerate ACE inhibitors); and that valsartan was an obvious choice since all ARBs would be thought to work in essentially the same way.

23. There are differing arguments in relation to heart failure and hypertension on Ksander. They arise mainly from alleged differences in the CGK in each field, the different treatments in use, different perspectives on side effects, and different views of the animal models used. But the arguments also have quite a lot in common.

24. Turning to Trippodo, it discloses a combination of ARB and NEPi, but (Novartis says) strictly as a tool in studying what it was really interested in, which was ACEi and NEPi combinations. Animal models of heart failure are used. Accord says that the skilled person (in heart failure or hypertension) would understand the attraction of an ARB/NEPi combination, especially for patient populations intolerant of ACEis, and would progress the work without invention, choosing valsartan as an obvious ARB (even if others were also available) and sacubitril. There is no pointer to sacubitril in Trippodo itself but Accord says it would be identified by a routine literature search. Novartis disputes all of this.

25. Again, the arguments have similarities and differences as between heart failure and hypertension. The main structural difference between the cases over Ksander and Trippodo are that on any view Ksander does not disclose an ARB/NEPi combination, so that has to come from the CGK, but it does point to sacubitril, while Trippodo does provide the ARB/NEPi combination (at least as an experimental tool) but does not disclose specifically valsartan or sacubitril.

26. Both classical obviousness attacks have to be assessed on the basis that the Patent's claims are product claims to the combination of valsartan and sacubitril. They are not first or second medical use claims, so if it was obvious to make the combination for any reason, including for animal testing, the claims are invalid. This means that the relevant expectation of success is lower than an effective treatment in man.

27. The other clutch of issues on the validity of the Patent turn on what it discloses, or contributes to the art.

28. The first of these issues is, in my view, the critical issue in the action, which is whether the Patent makes plausible that the combination of valsartan and sacubitril specifically would provide a clinically useful result in hypertension. The Patent contains a lot of description of experiments and potential uses of ARBs and NEPis, but it is common ground that much of what it describes is just proposals rather than what had in fact been done, and much of its contents is general and not linked to sacubitril specifically, or to hypertension. The

issue is whether it nonetheless contains a core disclosure about successful results in animal models of hypertension using the specific combination. Even to the extent it does, Accord says that the results are no use because they are (at most) just descriptive and do not have any hard data or specific numbers, and could have been trivially small effects.

29. The second of this group of issues is the allegation by Accord that the Patent is invalid because it is not really to a single invention but to two alleged inventions – valsartan as an ARB and sacubitril as a NEPi – which were each individually known and trivially obvious. Novartis responds that the two agents in the combination meaningfully interact and would be understood from the Patent (with CGK) to do so, so there is only one invention, so that if the classical obviousness attacks fail, this attack adds nothing.

30. Thirdly, I have to decide whether the Patent contains a technical contribution over Darrow or Trippodo; Accord says not. Darrow contains a general, conceptual disclosure of using an ARB and a NEPi in therapy (hypertension and heart failure are both mentioned). Although it does not say this renders the Patent classically obvious, Accord says that all the Patent provides over Darrow is an arbitrary choice of a particular ARB and a particular NEPi and is obvious in law. This argument has to be assessed on the assumption that the Patent passes the plausibility hurdle, since otherwise the Patent would already be invalid and it would add nothing. The argument over Trippodo is similar and has to be looked at on the same assumption, as well as the assumption that the classical obviousness case over it fails. Novartis says that the Patent's contribution is a showing that the combination of valsartan and sacubitril gives animal results showing a likelihood of being useful for therapy (and that it is in fact useful for therapy). Accord says that is not good enough in any event.

31. In the rest of this judgment I deal with the issues in a slightly different order from that above. After I assess who the skilled person(s) is or are, and set out the CGK and the teaching of the Application and of the Patent, I then deal with plausibility because it is internal to the Patent. Then I deal with all the matters which depend on the state of the art: classical obviousness first and then collocation and lack of technical contribution.

THE WITNESSES

32. Accord called one witness and Novartis called two.

33. They were:

    i) Professor Wilkinson for Accord.

    ii) Professor Webb for Novartis in relation to hypertension.

    iii) Professor Clark for Novartis in relation to heart failure.

Professor Wilkinson

34. I base the following (uncontroversial) description of Prof Wilkinson's professional qualifications and experience from Accord's written opening (I have edited it down somewhat):

    i) Professor Wilkinson is a Professor of Therapeutics at the University of Cambridge. He is Director of the Cambridge Clinical Trials Unit (since 2010), Director of the Office of Translational Research (since 2014), and has been a Fellow of Trinity Hall, Cambridge (since 2002). He is also an Honorary Consultant Physician at Addenbrooke's Hospital, Cambridge (since 2000).

    ii) Since 1997, his work and time has been split 50:50 between clinical duties and academic work. Since arriving in Cambridge in 2000, he developed and has run a specialist hypertension clinic for patients at Addenbrooke's Hospital. These outpatients are mostly hypertension patients, though if they have associated heart failure he treats that condition as well.

    iii) He has led a large number of clinical trials, including a number of formal drugs trials (CTIMPs) and first-in-man studies. He has experience of drug development in industry, including working with AstraZeneca and GlaxoSmithKline in drug development pipeline projects for a number of compounds to treat hypertension and heart failure (and other conditions).

35. Novartis did not criticise Prof Wilkinson's expertise in relation to hypertension; it is obviously profound. Novartis did say that he was less expert in relation to heart failure, and that led to a peripheral argument about how many heart failure specialists there were in the UK at the Priority Date, which I did not find helpful and do not need to resolve.

36. I agree that Prof Wilkinson's experience of heart failure was less than of hypertension, but the cross-examination revealed that he does indeed treat heart failure patients routinely, and that his research work has involved both healthy volunteers and people with heart failure. He does not have deep experience with pre-clinical drug development for heart failure specifically, however.

37. I will take this relatively lower experience into account, but I do not think it materially undermined Prof Wilkinson's ability to assist me.

38. Novartis said that Prof Wilkinson also knew about Entresto when he prepared his evidence on obviousness, as he acknowledged. That was inevitable with any heart failure expert and an inability to arrange perfect sequential unmasking is commonplace in patent actions. Again, I will bear it in mind but do not consider it detracted from his ability to give fair and helpful evidence, which he certainly did. In general his demeanour was excellent and his answers were clear, concise and fair.

39. Novartis submitted that Prof Wilkinson did not adequately deal with the fact that there was no reference in the CGK to the possibility of combining an ARB with a NEPi. I deal with this when I come to the merits but do not think it is a point that can be levelled at Prof Wilkinson personally. Novartis also said that Prof Wilkinson was too actively looking for alternatives to the active ingredients in Trippodo and was not sufficiently open to the idea of just using the agents already disclosed in it. Likewise, it said that although he was (correctly) instructed that there could be more than one obvious route, he took that to extremes. I am not sure if it was because of this, or because of knowing about Entresto, or because Prof Wilkinson is an unusually insightful scientist, which he clearly is, but I do think that he looked more deeply and saw more possibilities than the ordinary skilled person would. This is by no means a personal criticism, and he understood and tried to fulfil his role as an independent expert diligently, including by trying to avoid hindsight, but I take it into account in assessing obviousness, in particular.

Professor Webb

40. I likewise take an uncontroversial summary of Prof Webb's career from Novartis' opening skeleton argument, and have edited it down and added some points which emerged in evidence:

    i) Professor Webb is Emeritus Professor of Therapeutics & Clinical Pharmacology at the University of Edinburgh, where he was previously Christison Chair of Therapeutics & Clinical Pharmacology, between 1995 and 2021. He was also a consultant physician and clinical pharmacologist/toxicologist at the Royal Infirmary of Edinburgh, running Edinburgh's European Society of Hypertension Excellence Centre from 2007 until he retired in 2021.

    ii) As well as his practice as a clinician, he has contributed to guidelines for the treatment of hypertension, been president of the British Pharmacological Society and the European Society for Clinical Pharmacology & Therapeutics. He has also worked with several industrial pharmaceutical companies on developing and testing new hypertension treatments.

    iii) A high proportion of his time has been spent on research.

41. Accord pointed out that Prof Webb saw the Patent before he saw the Application, and that he saw Ksander after he saw the Patent. As with Prof Wilkinson, these are just consequences of the way in which he was instructed (he was instructed 2-3 years ago, probably by an EPO team) which meant that ideal sequential unmasking could not be done. I take it into account but it did not affect his ability to understand the task of describing what the ordinary skilled person would take from the prior art without knowledge of the Patent, or from the Application without knowledge of the Patent.

42. I accept also that Prof Webb had been told that patents do not have to contain actual data but may permissibly contain a qualitative statement of actual experimental results. Accord submitted that this made him too willing to

assume that in the Application where there were no data but an assertion of efficacy, there must have been results that were just being expressed qualitatively. I found the suggestion rather contorted and anyway I did not think it was cogent. I also found the point about his seeing the Patent before Ksander unpersuasive.

43. More substantively, it was put to him that he was an endothelin specialist and that that coloured his approach to some of the documents in a way which would not have been the case for the ordinary skilled person. It is only natural for someone to be affected by their specialist subjects, not a personal shortcoming. I think Prof Webb did have a tendency to emphasise endothelin more than the ordinary skilled person and I will take that into account, but it was not a major effect, at all.

44. Accord also advanced arguments about Prof Webb's evidence in relation to the choice of ARB if proceeding from the prior art. I deal with this on the merits when I come to them, and note that Prof Webb did make a small error about whether valsartan was a "surmountable" antagonist but again it was not a point which undermined the reliability of his evidence, and he quite properly corrected it in his third report when it was identified by Prof Wilkinson.

45. Overall, as with Prof Wilkinson, Prof Webb gave clear and succinct answers and understood his proper role well, and I found his evidence reliable and useful to my task.

Professor Clark

46. Prof Clark's biography is as follows (once more, on uncontroversial facts, based on Novartis' opening skeleton):

    i) Prof Clark is a professor and honorary consultant cardiologist in the Department of Cardiology at Castle Hill Hospital, part of the Hull University Teaching Hospitals NHS Trust. He is a founder member of the British Society for Heart Failure and was recently made President Elect of the British Cardiovascular Society.

    ii) Prof Clark has treated over 20,000 heart failure patients, and been involved in several clinical trials. Together with Professor John Cleland, he set up and grew the study of cardiology at the University of Hull.

    iii) Prof Clark has been involved in teaching for many years, and contributed to the European Society of Cardiology ("**ESC**") and the British Journal of Cardiology's respective heart failure training modules. He has contributed to various patient care guidelines in the NHS/Europe.

47. Accord submitted that although Prof Clark has research experience it is really as an epidemiologist and not in relation to animal models or drug development. I accept this and will bear it in mind, although I do not think it

is particularly significant. In relation to the heart failure side of the case, his lesser involvement in this type of research has to be balanced against Prof Wilkinson's lower overall clinical exposure to heart failure. The overall balance is not tilted to either side materially, in my assessment.

48. Accord submitted that Prof Clark's clinical experience was too much in evidence and given too much weight when he was describing the art's attachment to ACEis, as he saw it, and the corresponding reluctance to try something else (in particular, ARBs). I do not accept this. Prof Clark's views were sincerely held and credible as a description of the position in the field and the clinical picture would have been an important input to drug development.

49. Accord also said that Prof Clark overstated some matters, in particular the relative merits of ACEis and ARBs, and the optimism over omapatrilat. I deal with these issues below but do not think they can form a reasonable basis for criticising Prof Clark personally.

50. Lastly, Accord said that Prof Clark picked up some new points only after having heard them put to Prof Wilkinson. I agree that those points have modestly less force for not having been in his written evidence, but it was not wrong of him to mention them, in the circumstances.

51. Prof Clark was slightly less concise and more vivid in his evidence than the other two experts but I am satisfied that that is just his usual manner. As with the other experts I found his evidence helpful and reliable and he understood his proper role and did his best to satisfy it.

Overall

52. Subject to the minor points above, which are of matters of emphasis and not criticisms of their independence or integrity, all three experts were very good at their task and gave helpful and clear evidence for which I am grateful.

THE SKILLED ADDRESSEE

53. It was common ground that the skilled person would be, or be part of, a team seeking to developed new treatments, as opposed to a pure clinician treating patients. The dispute was about the area(s) of interest of that person.

54. Accord's position at one stage was that the skilled person would be an expert in relation to both hypertension and heart failure, but at trial it developed its case in line with its secondary position, which was that it was entitled to show that the Patent was obvious to either a skilled person in relation to hypertension or a skilled person in relation to heart failure.

55. Novartis' position was that the skilled person was only an expert in hypertension.

56. Novartis disputed whether it was legitimate at all for Accord to make an obviousness attack starting from a heart failure perspective. Primarily it said

that because the Patent does not materially mention heart failure (it said the few passing references did not affect this) and focused on hypertension, by definition the skilled person was not someone with an interest in heart failure; and that under s. 3 of the Patents Act 1977 there can be only one type of skilled person (because it says "a person skilled in the art").

57. Because of the way Accord developed its case at trial in line with its secondary position, to which Novartis responded in kind by dealing with the hypertension skilled person case and the heart failure skilled person case separately, including by calling two distinct expert witnesses, it is necessary and appropriate for me to make findings on both.

58. I am assisted in doing this by the fact that the written evidence and submissions and cross-examination, and the agreed and disputed CGK are all organised in separate sections. Since I conclude that the Patent is not obvious to either of the skilled persons proposed by Accord, my conclusion on the correct identification of the skilled person does not affect my overall decision on validity. In addition, the dispute does not require any factual findings from me, being essentially one of law.

59. All that being so, I am going to be brief in what I say.

Law

60. I have considered the law applicable to identifying the skilled person in a number of decisions. The basic approach can be found in *Illumina v. Latvia* [2021] EWHC 57 (Pat) ("*Illumina HC*"), a decision of Birss J (as he then was), which I considered in *Alcon v Actavis* [2021] EWHC 1026 (Pat). *Illumina HC* was upheld on appeal at [2022] EWCA Civ 1924 ("*Illumina CA*", a decision which is also relevant to the collocation argument), though the decision of Birss J on the skilled person issue was not challenged.

61. In *Illumina HC*, Birss J said (at [68]) that the approach should be to ask what problem the invention solves and to consider what was the established field in which the problem existed; the notional person or team in that field is the person skilled in the art. In *Alcon* I added that the Court must look at the real position at the Priority Date and what teams actually existed. I said that because of the twin requirements not unfairly to expand the CGK to the detriment of the patentee, or to be unfair to the public by going too broad and diluting the CGK, the exercise includes an element of value judgment.

62. Both sides mentioned these authorities, and they are useful general guidance. But in those and other similar cases the issue has primarily been how to draw the boundary around a single skilled person or team in terms of their interests and CGK, and not the legitimacy of considering two different skilled persons or teams.

63. Accord cited *Schlumberger v EMGS* [2010] RPC 33 (at [53], per Jacob LJ) for the proposition that if the claimed invention is obvious to any person then it is obvious "*And rightly so, for it would otherwise impede a class of persons who found it obvious*." Novartis pointed out, however, that that was a case

about the possibility of making an invention by the very act of combining expertise from two different fields, and that what Jacob LJ was specifically addressing was the argument that in that situation if the patent was obvious to the skilled person in either field then it was obvious overall. I agree that that has to be borne in mind and complicates the analysis a bit. A similar issue applies to *Inhale v Quadrant* [2002] RPC 21 which was considered in *Schlumberger*.

64. More directly relevant is *Philips v Nintendo* [2014] EWHC 1959 (Pat) (also Birss J). Philips, the patentee, was arguing that the patent was directed to a specialist in interactive virtual environments and not to a specialist in computer games. Accord cited the following passage:

> 33. It has been well understood in English law for over a century (see *Gillette Safety Razor v Anglo American* (1913) 30 RPC 465) that those working in industry are entitled to be sure that they are not infringing any valid patent if all they do is make obvious improvements to the prior art. If without an act of invention a person skilled in the art in 1995 would have produced a computer game system which falls within the patent then the patent lacks inventive step because the claims cover something which is obvious. It makes no difference to this conclusion if something else within the wide limits of the claim was not obvious when considered from the point of view of the developers of sophisticated virtual reality systems which were being investigated in universities. There clearly were real people or teams working on games development at the relevant time with the skills described by Prof Steed [expert for Nintendo]. Nintendo's definition of the skilled person, at least from the point of view of obviousness, is a legitimate one. This is the same as or closely related to the point made by Laddie J in *Inhale v Quadrant* [2002] RPC 21 at paragraph 42.
>
> 34. A distinct question is whether the person skilled in the art from the point of view of considering the true interpretation of the patent and how to put it into practice is the same notional person as the person skilled in the art from the point of view of assessing obviousness. In *Schlumberger v Electromagnetic Geoservices* [2010] EWCA Civ 819 the Court of Appeal held that the two did not necessarily have to be the same. The case before me is different in that it is not concerned with whether it was obvious to combine skills from different fields, it is concerned with a wide claim which covers things in at least two distinct fields. Just as there were real teams of the kind described by Prof Steed [expert for Nintendo], so too there were real teams of the kind described by Prof Darrell [expert for Philips]. They worked on interactive virtual environments and were not concerned with games.

65. In my view this hits the nail on the head. With a wide claim which covers distinct fields, there is a crucial policy consideration that workers in all the fields covered do not run into a later, valid patent if they just do what is obvious. Novartis had really no answer to this as a proposition of law and the use of the singular in s. 3 of the 1977 Act is a straw in the wind: it is a

very broad and general definition whose meaning has always been critically determined by the case law.

66. The fact that an attack can be grounded in one of a number of fields covered by a claim does not give the party attacking a patent carte blanche to define some artificial skilled person, or to distort the CGK. The skilled person in any field covered still has to be defined sensibly and in accordance with the general principles above, and the identification of the CGK has to be done appropriately.

Discussion

67. I have set out the disclosure of the Patent below. By contrast with the Application it does indeed, as Novartis submits, barely mention heart failure and focuses much more on hypertension. However, it does mention it in passing, and much more importantly the claims are product claims without any limitation to their field of use. In an objective sense the problem solved is the use of the claimed combination in medical therapy as it relates to the cardiovascular system, at least.

68. There clearly were, on the evidence, teams working on new treatments for heart failure. There is nothing artificial in positing them as one type of relevant skilled person. Accord has not used the argument as a device to artificially expand the CGK of either possible skilled person. To the extent that the exercise is a value judgment, all the above analysis and reasons point in Accord's favour.

69. Although not necessary to my decision, I observe how unattractive Novartis' position would be in the light of the trimming down of the Application. Suppose, contrary to my eventual conclusions, the claims were obvious to the heart failure expert, and that one skilled addressee of the Application was a heart failure expert (a proposition that would be hard to dispute since it mentions the condition as a use of the combinations disclosed a number of times). Could Novartis really block such a skilled heart failure expert from doing what he or she would have found obvious by the expedient of crossing out references to heart failure from the specification of the granted Patent but not narrowing the claims? That would be unjust and bad policy and does not make sense.

70. I therefore find in favour of Accord on this point. It is legitimate for it to make separate obviousness attacks from the fields of hypertension and of heart failure.

71. This all means that I have to consider the issues from the perspective of both skilled persons, in hypertension and in heart failure. This is particularly significant with CGK and the obviousness attacks. Where necessary or appropriate I have tried to specify which kind of skilled person I am talking about, but it is possible I have overlooked some instances, in which case I trust it will be apparent from the context. In addition, although I have borne the two different skilled persons in mind at all times there are quite a lot of

points where it makes really no material difference, and the parties' arguments were accordingly sometimes general to both.

THE COMMON GENERAL KNOWLEDGE

72. There was a joint document which showed the CGK that was agreed (the ASCGK mentioned above) and another identifying what was in dispute. The ASCGK was progressed between the parties both by the usual means of exchanging drafts with written comments and by the experts meeting (virtually).

73. What follows in relation to the agreed CGK is an edited down version of the ASCGK. Where I have removed material that does not mean I find that it was not CGK, just that it is not of enough importance to include in this judgment. What remains is still very long, I regret, which is largely a function of the two different skilled persons and the very wide range of points which the parties took. The ASCGK used both the present and past tenses and I have not tried to make it consistent, but unless I specifically say otherwise the matters stated relate to the situation at the Priority Date.

74. There were thirteen listed issues of CGK in dispute. In addition, some themes relevant to CGK or arising from it emerged during trial which is convenient to deal with here.

Agreed CGK

Physiology of the heart and the cardiovascular system

75. The human cardiovascular system comprises the heart and blood vessels.

76. The heart is made up of two sides: the right and left sides. The right side receives deoxygenated blood from the body, which is then pumped to the lungs, where it releases carbon dioxide and absorbs oxygen. The newly-oxygenated blood returns to the left side of the heart, whence it is pumped around the body via the aorta.

77. Each side of the heart consists of two chambers: an atrium and a ventricle. On each side, blood enters the relevant atrium and flows through an inlet valve into the relevant ventricle. On ventricular contraction, the inlet valves close and the ventricles eject the blood through an outlet valve to the relevant artery.

78. The heart pumps by contracting and relaxing (the cardiac cycle). The cardiac cycle has two phases: relaxation, or diastole, where the heart chambers relax and fill with blood, and contraction, or systole, where the heart contracts to pump blood out.

79. During contraction, the pressure in the left ventricle must be sufficient to force the blood through the aortic valve. The peak of this pressure can be measured and is called the left ventricular systolic pressure or "**LVSP**". The heart must overcome the pressure in the aorta and resistance to flow provided

by the blood vessels in the periphery. Collectively, this is known as the "**afterload**". Strictly, the LVSP and the afterload are not synonymous; the former is the pressure that the left ventricle reaches when ejecting blood and the latter is the force resisting the ejection. However, LVSP is sometimes used as a surrogate for afterload. Afterload is a theoretical construct representing the sum of resistances against which the left ventricle must eject. While LVSP and systolic blood pressure (which is measured in the periphery, see below) are strictly speaking different measures, in the context of heart failure, LVSP can be a surrogate marker of systolic blood pressure. Whether LVSP is relevant for hypertension is a matter of dispute between the parties.

80. At the end of diastole, when the left ventricle is full of oxygenated blood and just about to contract, the load in the left ventricle is called the left ventricular "**preload**", commonly measured as the left ventricular end-diastolic pressure ("**LVEDP**").

81. As the heart is a muscle, normal physiological changes to preload and afterload can impact the heart's performance:

82. Increasing preload increases the mechanical stretch of the heart muscle (called the myocardium), which increases the force of the subsequent contraction. If the preload decreases, there is less stretch, meaning less contractility.

83. If the peripheral resistance increases, so does afterload. Then, the heart has to work harder to overcome that increased resistance in order to eject blood.

84. The contractility of the heart (in other words, the strength of the myocardium) is influenced by multiple factors beyond the preload and afterload, one of which is the sympathetic nervous system. The sympathetic nervous system controls the "fight or flight" response, and increases heart rate, the speed of both contraction and relaxation, and the force of each contraction.

85. In the periphery, blood pressure is measured in mmHg (millimetres of mercury) and expressed as systolic pressure / diastolic pressure (e.g. 120/80 mmHg). Systolic pressure refers to the peak pressure that is reached during the phase of systole, and diastolic pressure refers to the minimum pressure reached during the phase of diastole.

<u>Biological systems relevant to hypertension</u>

86. Blood pressure is regulated by an interplay of a number of hormonal and other systems that feed into and counterbalance one another. These include the renin-angiotensin-aldosterone system (the RAAS), the sympathetic nervous system, and the natriuretic peptide system (the NPS).

87. Other hormones known to be involved in blood pressure regulation were:

    i) Endothelin-1 (ET-1), which is a vasoconstrictor peptide. The full extent of the physiological role of endothelin-1 was not known and as a target it was much less developed.

ii) Bradykinin, a peptide which is a potent vasodilator (and so can reduce blood pressure).

iii) Substance P. While less well understood, it might have been known to be a neurotransmitter with vasodilatory action.

The Renin-angiotensin-aldosterone system

88. The RAAS is a hormonal system which assists in the regulation of blood pressure. Activation of the RAAS promotes salt (and thus water) retention and vasoconstriction, which cause an increase in blood pressure. It is also activated in response to a fall in renal perfusion, detected by the kidneys.

89. A simple outline of the RAAS cascade system is as follows:

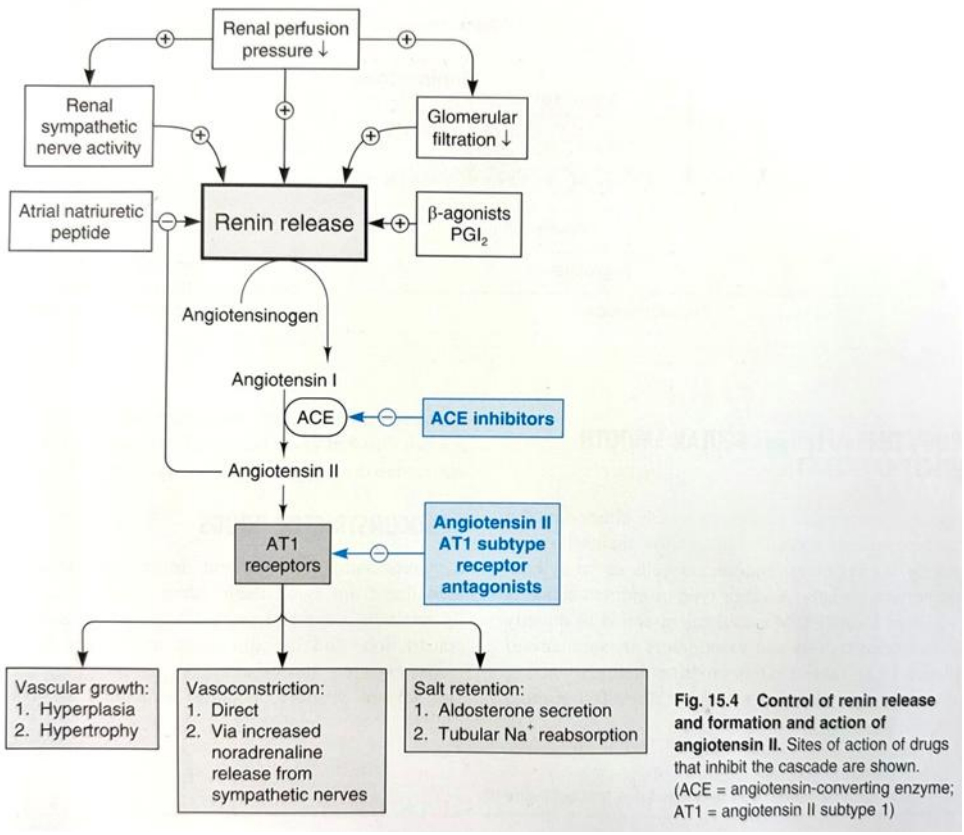


Fig. 15.4 Control of renin release and formation and action of angiotensin II. Sites of action of drugs that inhibit the cascade are shown. (ACE = angiotensin-converting enzyme; AT1 = angiotensin II subtype 1)

90. Renin is secreted in response to a number of specific stimuli, including reduction in renal perfusion in the kidneys, delivery of sodium and chloride ions to part of the kidney, activation of the sympathetic nervous system, and negative feedback from components such as Ang II, potassium and ANP.

91. Renin acts on angiotensinogen to liberate the peptide angiotensin I ("**Ang I**"). Ang I was known not to have biological activity.

92. Ang I is converted into angiotensin II ("**Ang II**") by the enzyme angiotensin converting enzyme ("**ACE**"). ACE was known to be a metalloprotease enzyme that utilises metal ions to catalyse generation of Ang II.

93. Ang II has various effects including: (a) generalised vasoconstriction; (b) sodium reabsorption; (c) secretion of aldosterone (a hormone causing retention of salt and water by the kidneys); (d) increased release of noradrenaline (i.e., activation of sympathetic nervous system); and (e) cardiac cell growth. Collectively, these effects promote salt and water reabsorption in the kidneys and increases blood volume and pressure.

94. Ang II interacts with its receptors, the AT1 receptor and the AT2 receptor. Activation of the AT1-receptor causes the effects which lead to an elevation of blood pressure, listed above. The role of the AT2-receptor in humans was less well understood but appeared to be relatively subtle.

95. The increase in blood pressure caused by the actions of Ang II and aldosterone contributes to a negative feedback loop via the kidney, which downregulates the production of renin, thus reducing the amounts of Ang I and Ang II that are produced, leading to a reduction in blood pressure. Likewise, should there be a decrease in circulating blood volume, this would lead to a reduction in blood pressure. The feedback provided as a result of this change in pressure would lead to the upregulation of renin and the activation of the RAAS to increase blood pressure. The RAAS therefore continuously regulates blood pressure through this feedback loop.

96. ACE has additional functions, including the breakdown of other peptides including bradykinin. Bradykinin is a peptide which is a potent vasodilator (so can reduce blood pressure). Bradykinin is the preferred substrate of ACE and so the breakdown of bradykinin outcompetes the activation of Ang I.

The sympathetic nervous system

97. The sympathetic nervous system acts through release of noradrenaline from nerve terminals and adrenaline from the adrenal gland, which were known to increase blood pressure, by stimulating the heart to beat harder and faster, and constricting blood vessels through the alpha-adrenergic type 1 receptor.

98. Hypertension was known to be associated with activation of the sympathetic nervous system, leading to vasoconstriction, increased heart rate, cardiac contractility, and renal vascular resistance.

The natriuretic peptide system

99. Natriuretic peptides ("**NP(s)**") are hormones that also assist in the regulation of blood pressure. Their effects reduce blood pressure. The RAAS and NP system are not direct opposites of one another, but do have largely opposing effects. The NPs trigger a number of direct effects, including (i) increased sodium and water excretion from the kidneys; (ii) increased vasodilatation of the blood vessels; and (iii) reducing renin release, ACE activity and reducing aldosterone secretion (thereby inhibiting the RAAS). Atrial (A-type) natriuretic peptides ("**ANP(s)**") are released by the heart in response to stretch or pressure in the heart.

100. In the late 1980s, attempts were made to administer exogenous ANP for the treatment of hypertension, but the approach was limited by rapid *in vivo* degradation of the peptides, mainly caused by neutral endopeptidase (also called neprilysin, "**NEP**"), the natural enzyme responsible for breaking down the NPs. This meant natriuretic peptides could not be administered orally.

101. So the limited success with administering exogenous NPs led to the alternative approach of reducing the degradation of endogenous NPs by inhibiting NEP, leading to the development of orally active NEP inhibitors ("**NEPis**"). NEPis achieve their effect by inhibiting NEP, reducing the breakdown of NPs, and so maintaining higher levels of endogenous NPs which can better achieve their diuretic and natriuretic actions. The development of NEPis is discussed further below.

102. In addition to breaking down NPs, NEP also has other effects, including breaking down Ang II, endothelin-1 and bradykinin.

Biological systems relevant to heart failure

103. The RAAS and natriuretic peptide system are also relevant to heart failure, but the CGK regarding them was slightly different in heart failure:

    i) RAAS: the outline of the RAAS above applies to heart failure.

    ii) Natriuretic peptide system: natriuretic peptides were understood to cause natriuresis, diuresis and to have vasodilatory properties. In heart failure, it was known that one of the physiological mechanisms of natriuretic peptide clearance was enzymatic cleavage by NEP. In the 1990s, clinicians explored potentiating endogenous natriuretic peptides in patients with heart failure by inhibiting NEP. NEP inhibition was known to increase levels of natriuretic peptides, as well as other vasoactive substances (for example, bradykinin).

104. In addition to the RAAS and the natriuretic peptide system, the sympathetic nervous system is overactivated in heart failure. As described above, the system can be thought of as the "fight or flight" response system.

105. Other hormone systems are also activated in heart failure. The skilled person would have known that bradykinin, substance P and other vasoactive peptides were involved in blood pressure regulation, although their precise roles in health or in heart failure were not fully understood.

Hypertension

106. Hypertension is a complex condition characterised by chronic or consistently raised blood pressure. There was no formal 'cut off' for what constituted hypertension, but it was sometimes defined as "having a blood pressure at which treatment gives more benefit than harm". The 1999 British Hypertension Society ("**BHS**") Guidelines recommended antihypertensive drug therapy for patients with sustained blood pressure at or above 160/100 mmHg, unless there were comorbidities.

107. In individuals with hypertension, the heart pumps blood through vessels under increased pressure, typically owing to small vessel vasoconstriction and remodelling which increases the resistance to blood flow.

108. Hypertension often first presents with no obvious symptoms. Lack of obvious symptoms for most people with hypertension contributes to underdiagnosis and undertreatment. In most cases patients are diagnosed with hypertension following routine check-ups or assessments done for other reasons. Rarely, patients with very severe hypertension may present with symptoms such as headache, visual disturbance, or signs of end-organ damage.

109. At the Priority Date, hypertension was a major public health concern and a leading risk factor for cardiovascular morbidity and mortality, including stroke and myocardial infarction, and can indirectly lead to heart failure.

Heart failure

110. At the Priority Date, heart failure was recognised as a syndrome rather than a specific disease. Most commonly the syndrome is caused by an abnormality of pump function due to damage to myocytes, but there are many other causes, such as heart valve disease and heart rhythm disturbance.

111. Typical symptoms of heart failure include breathlessness, fatigue, reduced exercise tolerance, and peripheral oedema (swelling of the legs and ankles).

112. At the Priority Date, due to the challenges in accurate diagnosis (described below), there was no universally accepted definition for heart failure. Accordingly, various terms were used to describe the different syndromes of heart failure although the most relevant syndrome at the Priority Date was chronic systolic heart failure. At the Priority Date, patients would present in one of two ways, which are described below.

113. One way that a patient could present is by being admitted to hospital. These patients were sometimes mistakenly described as having "acute heart failure". Patients were typically hospitalised for one of the following reasons:

    i) **Acute pulmonary oedema:** a sudden event results in an abrupt fall in left ventricular function, due to a heart attack or rapid heart rhythm.

    ii) **Cardiogenic shock**: this is a more extreme example, in which the cardiac output is so reduced that organ perfusion fails.

    iii) **Fluid retention**: this was the most common reason for heart failure hospitalisation at the Priority Date. Retention takes place over many weeks, and sometimes months, such that the patient has too much fluid in their body (in contrast to patients with acute pulmonary oedema, where the fluid is in the wrong place).

114. The other way that patients could present was with **chronic heart failure**. Chronic heart failure describes a syndrome whereby the symptoms are more controlled and the patient is stable. It is, as the name suggests, a long-term

condition, rather than acute illness. Chronic heart failure may be detected in primary care, but more commonly arises following hospitalisation for heart failure. At the Priority Date, patients with chronic heart failure were often said to be "compensated"; this meant that the medical intervention and/or their body was able to compensate for the myocardial dysfunction, such that symptoms of heart failure were stable.

115. Hospitalised heart failure syndromes are clinically distinct from chronic heart failure (described below). Different treatments are required and what is useful for acute syndromes is not necessarily useful for the chronic syndrome.

116. In 1995, the ESC implemented a simple definition for chronic heart failure to help diagnose patients, namely:

    i) Symptoms of chronic heart failure, such as breathlessness, fatigue or ankle swelling;

    ii) Objective evidence of cardiac dysfunction at rest; and

    iii) The patient responds to heart failure pharmacological treatment.

117. The definition was universally acknowledged to be unsatisfactory insofar as it was circular (patients had to respond to treatment in order to be diagnosed).

118. Chronic heart failure was further classified as:

    i) **Systolic heart failure** referred to heart failure associated with evidence of left ventricular dysfunction.

    ii) **Diastolic heart failure** was presumed to be present where the patient appeared to have the heart failure syndrome but had apparently normal left ventricular systolic function and no other cause for heart failure.

119. Diastolic heart failure was relatively uncommon in younger patients, but more common in older patients.

120. In heart failure, there is a fall in blood pressure and renal perfusion. In response, the sympathetic nervous system (which makes the heart beat faster and stronger), and the RAAS (which makes a person retain salt and water and constricts blood vessels) are activated. Further, other compensatory systems were expected to be involved.

121. The commonest cause of chronic systolic heart failure was ischaemic heart disease, also known as coronary artery disease. Relevant factors included hypertension, which on its own was thought to be related to systolic heart failure predominantly through increasing the risk of heart attack; another event was understood to be required to impair left ventricular function and cause systolic heart failure. Treatment of hypertension could reduce the risk of a cardiovascular event such as myocardial infarction, which in turn would reduce the risk of developing heart failure.

122. At the Priority Date, the prevalence of heart failure in the UK was estimated to be around 1% in those aged 45 or older but with the prevalence increasing sharply with age. The prognosis was poor: just under 40% of people diagnosed with heart failure died within a year. Over 5% of all deaths in the UK at that time were due to heart failure.

123. At the Priority Date, because of the high prevalence and poor prognosis of heart failure, there was a desire to improve outcomes for all patients with heart failure, but it was recognised to be heterogeneous in its presentation, cause, pathophysiology, prognosis and treatment, which made clinical research challenging. Research focus was on new therapies to manage chronic systolic heart failure as it was relatively easy to define and categorise.

Neurohormonal activation

124. Activation of the neurohormonal systems described above ("**neurohormonal activation**") can be thought of as the body attempting to restore the *status quo ante* by increasing blood pressure and renal perfusion, but the consequences include raised afterload (from vasoconstriction) and preload (from fluid retention). Many of the neurohormones (particularly Ang II, noradrenaline and aldosterone) have directly deleterious effects on the heart itself.

125. The compensatory mechanisms described above are beneficial for short periods of time (e.g. in response to an injury). However, *chronic* activation of the compensatory mechanisms increases the work the heart has to do, as well as directly damaging the heart further. The result is further activation of the compensatory mechanisms and the initiation of a downward spiral, and further events can occur exacerbating the situation, including:

    i) Further ischaemia or myocardial infarction causing further damage to the heart.

    ii) Atrial fibrillation.

    iii) Electrical abnormalities.

    iv) Left ventricular remodelling, the alteration of the size, structure and function of the left ventricle.

126. When the myocytes in either atria or ventricles are stretched, they release NPs. As mentioned above, at the Priority Date, the known natriuretic peptides included ANPs and BNPs. Natriuretic peptides enter the circulation and cause natriuresis (salt loss) and diuresis (water loss) as well as vasodilation. They are part of a normal body system that regulates fluid balance. If more fluid enters the circulation, the heart stretches, natriuretic peptides are produced, more urine results and the *status quo* is restored. Natriuretic peptides increase, in people with heart failure due to the heart muscle being stretched. It might be thought the effects caused by these peptides would compensate for the neurohormonal activation described above, but the natriuretic peptide system

is overwhelmed in heart failure so that vasoconstriction, as well as salt and water retention, still occurs despite the high level of natriuretic peptides.

127. Accordingly, it was thought that the body attempted to compensate for a drop in cardiac output by neurohormonal activation. However, chronic neurohormonal activation led to increased heart rate, left ventricular remodelling, salt and water retention, and a rise in preload and afterload, causing further heart damage and progression of the heart failure syndrome.

128. The neurohormonal hypothesis of heart failure was the prevalent theory of heart failure at the Priority Date and had replaced the earlier haemodynamic model (which considered the fall in cardiac function in heart failure to cause an increase in preload and afterload which in turn were the stimuli for further deterioration of cardiac function).

129. Support for the neurohormonal hypothesis came from multiple clinical trials which showed that drugs that targeted and suppressed neurohormonal activation led to better mortality and morbidity outcomes.

Diagnosis of heart failure

130. Accurate diagnosis of heart failure at the Priority Date was a significant challenge. The symptoms of heart failure were common to many disorders. There was no arbitrary cut off point or measurement of the heart that could definitively identify heart failure, nor was there any widely available clinical test that could confirm or deny the presence of heart failure. The methods which were available to image cardiac function were not particularly accurate, robust or reproducible. Haemodynamic measurements did not necessarily equate to an accurate diagnosis of heart failure.

131. At the Priority Date, accuracy of diagnosis remained an issue, and clinical researchers were trying to identify new ways to refine the diagnosis of heart failure.

Treatment of hypertension

132. Treatment of hypertension was multifaceted. The treatment pathway was dependent on a number of factors, including the severity of a patient's hypertension. Lifestyle changes (salt reduction, cessation of smoking etc) were first line methods in the treatment of mild hypertension (continued in conjunction with medical treatment). The decision to initiate pharmacologic treatment requires consideration of multiple factors including the degree of blood pressure elevation, target organ damage, and/or comorbidities.

133. The 'rule of halves' reflected the understanding that roughly half of patients with hypertension were unaware that they have it, half of those who were aware were not treated, and half of those who were treated did not have their blood pressure adequately controlled. Even when a patient was treated, control of blood pressure was poor. Partly, this was due to limitations of the available treatments to lower blood pressure across the patient population, and led to the increased use of two or more antihypertensive treatments in

combination in the run up to the Priority Date. However, poor patient adherence to treatment was also considered to be a significant factor, given patients' lack of day-to-day symptoms.

134. In broad terms, antihypertensive treatments reduce blood pressure by one or more of the following mechanisms: (i) reducing the circulating blood volume, (ii) promoting vasodilatation, or (iii) reducing the heart rate and force of contraction. However, these blood pressure lowering effects are opposed by the body's homeostatic feedback mechanisms. When blood pressure falls, systems such as the RAAS and sympathetic nervous system are activated to raise it again (i.e., to restore the *status quo*). The overall impact of any treatment therefore reflects the balance between the antihypertensive effect of the drug(s), and the body's compensatory responses.

135. The main pharmacological treatments used for the treatment of hypertension in 2002 were diuretics, beta blockers, ACEis, and calcium-channel blockers ("**CCBs**"). ARBs were also used in the treatment of hypertension, but were less preferred, as there were fewer (as compared with ACEis) clinical data available on their antihypertensive efficacy.

ACEis

136. At least the following ACEis were licensed for use in treating hypertension: captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril as well as benazepril.

137. By the mid-1980s, ACEis were widely used for the treatment of hypertension. They were viewed as sharing pharmacological effects insofar as they each inhibit ACE. They were generally effective and well-tolerated. Captopril was one of the first ACEis, although it needed to be dosed more frequently and at higher doses than later agents. Enalapril was the next ACEi to reach widespread approval and use. After captopril, enalapril and lisinopril were the most studied ACEis. Both were administered once-daily.

138. The action of ACE promotes vasoconstriction by generating the vasoconstrictor, Ang II. ACEis inhibit this action of ACE. Consequently, one way they reduce blood pressure is by promoting vasodilatation, through preventing the formation of the vasoconstrictor Ang II, and thereby reducing circulating Ang II levels. However, since ACE also breaks down bradykinin (and other vasoactive peptides, such as Substance P), ACEis elevate bradykinin levels in a patient, which further dilates blood vessels. At the Priority Date, bradykinin was known to be a vasodilatory compound. This dual effect of ACEi (preventing Ang II formation and increasing levels of the vasodilator peptides, bradykinin and Substance P) was thought to contribute to their effectiveness. A study on the short-term effects of ACEis had shown bradykinin to provide a blood pressure lowering effect of ACEis over and above that seen with ARBs. However, it was thought that a substantial part of the efficacy of an ACEi came from its prevention of the formation of Ang II. It was not known whether bradykinin potentiation was clinically significant to the long-term effect of ACEi when administered to a patient.

139. Two established side effects of ACEis were a persistent dry cough and (in rare instances) angio-oedema.

140. Approximately 5%-10% of patients given an ACEi would develop a dry cough. This is a significant issue in hypertension patients since they must take the medication indefinitely and often do not have significant symptoms, so that the persistent dry cough reduces patient compliance. These hypertension patients were considered to be intolerant of an ACEi.

141. Angio-oedema can be a far more serious side effect which causes a sudden, deep swelling under the skin, predominantly affecting the face and neck or in hands and feet, but can occur elsewhere. Angio-oedema is potentially life threatening as swelling in the throat can result in an inability to breathe and the patient may require intubation, but it typically presents as mild swelling of the lips and face. Estimates of the incidence of ACEi-associated angioedema varied between 0.1% and 2% at the Priority Date. If a patient had angio-oedema, ACE inhibitor therapy would be stopped immediately.

142. The cough was thought perhaps to have been due to elevated levels of bradykinin caused by ACEis. However, an increased sensitivity of the normal cough reflex and other mediators such as substance P were also considered as potential factors. In relation to the angio-oedema seen with ACEis, whilst the mechanism for this effect was unclear at the Priority Date, increased levels of bradykinin and increased levels of substance P had been implicated.

143. At the Priority Date, ACEis had become a mainstay of antihypertensive treatment, as the benefit of treatment with them was considered sufficient to outweigh the risk of their side effect profile.

ARBs

144. ARBs block the effects of the vasoconstrictor Ang II by preventing Ang II from binding to the AT1 receptor. ARBs entered clinical practice later than ACEis, in around the mid-1990s. At least the following ARBs were licensed for use in treating hypertension by the Priority Date: candesartan, eprosartan, irbesartan, losartan, telmisartan, and valsartan.

145. As set out above, at the Priority Date, it was understood that Ang II mediated its deleterious effects by binding to the AT1 receptor. Less was known about the function of the AT2 receptor but its role appeared to be relatively subtle. ARBs act on the RAAS further downstream than ACEis. ARBs occupy and block the AT1-receptors that Ang II binds to, and so prevent the receptor from having its effects, including its vasoconstrictive effect.

146. ARBs were not associated with a dry cough and had a much lower rate of angio-oedema than the ACEis.

Beta-adrenergic blockers

147. Beta blockers were used to treat hypertension in the UK from the 1960s onwards. Beta blockers block beta-adrenoreceptors whose activation induces renin release, which activates the RAAS. Beta blockers lower blood pressure by suppressing the RAAS and relaxing blood vessels, as well as by slowing heart rate, reducing cardiac output, and reducing sympathetic nervous system activity. These effects lower blood pressure by making it easier for the heart to pump blood around the body.

148. Beta blockers' use was supported by longstanding clinical experience and guideline recommendations. They have a range of side effects. Although beta blockers were initially used as primary treatment for hypertension, by the Priority Date other treatments were being prioritised with fewer side effects.

149. At the Priority Date, the beta blockers available in the UK were acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, celiprolol, esmolol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, pindolol, propranolol, sotalol, and timolol.

CCBs

150. CCBs were commonly prescribed, especially in older adults and those of African or Caribbean descent. They have vasodilatory effects resulting in reducing blood pressure and preventing stroke by dilating the blood vessels. CCBs interfere with the inward displacement of calcium ions through the slow channels of active cell membranes, which affects the heart and the smooth muscle.

Diuretics

151. Thiazide diuretics were considered highly effective, particularly in older patients. They lower blood pressure by causing the body to lose salt and water and relax blood vessels. Although reducing circulatory volume would lead to a compensatory increase in production of renin and so activate the RAAS, the compensatory activation did not typically prevent diuretics lowering blood pressure overall (the same applied to beta blockers). The most commonly prescribed type of diuretic for hypertension treatment was thiazide diuretics. Thiazide and thiazide-like diuretics had a range of side-effects.

Other antihypertensive drugs

152. Other antihypertensive drugs included:

    i) **Alpha blockers**.

    ii) **MRAs**

Guidelines on the approach to antihypertensive therapy

153. In 2002, the current BHS guidelines recommended starting with a low dose of a thiazide diuretic as first line treatment for hypertension, though the choice of drug depended on indications and contra-indications in the patient.

154. Some patients would be controlled on monotherapy but most would require multiple drugs; the BHS guidelines from 1999 note that less than half would be controlled on monotherapy and one third of patients would require three or more drugs to manage their hypertension.

The BPLTTC (Blood Pressure Lowering Treatment Triallists' Collaboration) meta-analysis

155. A BPLTTC meta-analysis compared the effectiveness of 'newer therapies' for the treatment of hypertension (i.e. ACEis or CCBs) with 'older therapies' (i.e. diuretics or beta blockers) and concluded that the newer therapies were as effective as the older therapies at reducing stroke, mortality and major cardiovascular morbidity. The meta-analysis also showed that the more a drug is able to lower blood pressure, the more efficacious it is i.e., the lower the patient's risk of events such as heart attack or stroke.

ACEi vs ARBs in hypertension treatment

156. ACEis had been widely available since the mid 1980s. Because ACEis had been developed earlier in time and had therefore been used clinically for longer, there was also a greater body of clinical evidence as to their effectiveness. The aim of hypertension treatment is to reduce the risk of serious events such as heart attack and stroke (such events were known as clinical outcomes) by reducing blood pressure.

157. The compelling indications for ACEis in the 1999 BHS Guidelines were heart failure, left ventricular dysfunction, type 1 diabetes and nephropathy. By contrast, the only compelling indication for ARBs was ACEi induced cough.

158. A drug being "recommended" or not being "recommended" should not be confused with "not approved for" or "only effective in". ARBs had been shown to be effective in reducing blood pressure and 6 ARBs had been approved for the treatment of hypertension. Just considering the compelling indication of ARBs for patients intolerant of ACEis due to ACEi-induced cough, given the very large number of patients taking ACEis, the 5%-10% that suffered from cough was a large number of patients for whom ARBs were recommended for hypertension.

159. However, ARBs had improved tolerability profiles with side effects not different from placebo, including in respect of a dry cough. This understanding was reflected in clinical practice, where ARBs could be substituted where an ACEi was not tolerated due to side effects. This approach was supported by national guidelines.

Development of new antihypertensive drugs at and shortly before the Priority Date

NEP inhibitors ("NEPi")

160. Before the Priority Date, there was interest in the development of a NEPi for treating hypertension. Since neprilysin breaks down NPs, a NEPi would be expected to increase the half-life of NPs and so promote natriuresis as well as vasodilatation, thereby reducing blood volume and so blood pressure. However, NEP was known to break down other vasodilating agents (such as bradykinin) and vasoconstrictors (such as Ang II and endothelin-1).

161. Animal experiments had demonstrated, for several NEPis, that an acute antihypertensive effect could be achieved. However, NEPis had shown inconsistent results in animal models – whilst they were able to lower blood pressure in some models, they had no effect on blood pressure in others.

162. Studies had been conducted in humans using various NEPis, such as candoxatril. These demonstrated increased natriuresis in healthy volunteers and hypertensive patients. However, the results for blood pressure changes were mixed and clinical success in treatment of hypertension or heart failure by NEP inhibition alone had not been established. No NEPi had demonstrated a consistent blood pressure lowering effect in clinical trials, and no NEPi had been approved for the treatment of hypertension at the Priority Date.

163. The reason(s) for the failure of NEP inhibitors were not well understood at the Priority Date, and there were competing theories as to why NEP inhibition did not lower blood pressure, despite the vasodilatory effect caused by a reduced breakdown of natriuretic peptides. It was considered that the lack of blood pressure lowering effect of NEPi monotherapy might be related to various factors or, more likely, a combination of these factors. It was not known whether NEPis were interchangeable.

Other areas of research at the Priority Date

164. Other areas of potential interest for further development at the Priority Date included renin inhibitors and attempts to target endothelin (e.g. endothelin converting enzyme inhibitors and endothelin receptor antagonists).

Treatment of heart failure

165. The goal in heart failure treatment was to reduce mortality and morbidity, by counteracting chronic neurohormonal activation. Some drugs were used to alleviate symptoms of heart failure but were not thought necessarily to impact on its progression. Disease-modifying drugs were of paramount importance for a patient with mild symptoms to prevent progression of the disease, increase duration of life and reduce hospitalisation due to cardiac events. The main disease-modifying drugs targeted neurohormonal activation.

166. ACEis were the most commonly used drugs for heart failure treatment in 2002, along with beta blockers and MRAs (mineralocorticoid receptor antagonists) . The use of these drugs had come about as the result of multiple large randomised controlled trials.

ACEis

167. In heart failure, ACEis were known to attenuate the downstream effects of Ang II. Importantly, ACEis disrupt the overactive RAAS which otherwise contributes to further damage to the vasculature and cardiac tissue. It was thought that ACEis had cardioprotective effects and could reduce the incidence of myocardial infarction and sudden death induced by arrhythmias. The increase in bradykinin as a result of ACE inhibition was understood to contribute to the beneficial effects of ACEis.

168. ACEis were the gold-standard therapy to treat heart failure, recommended as first line therapy for all patients with symptomatic heart failure by the ESC 2001 Guidelines , as they had a significant body of clinical evidence backing their ability to reduce mortality rates and hospitalisations.

169. Treatment of patients with heart failure would invariably start with an ACEi, starting with a low dose which was titrated up to the maximum dose the patient could tolerate. Once a stable maximal dose of ACEi was achieved, the same process would be replicated for a beta blocker and then an MRA.

170. The side effects associated with ACEis in the context of hypertension are described above. These side effects were known in the context of heart failure, but there are some additional considerations:

    i) Cough: given the importance of ACE inhibitors in slowing the progression of heart failure and improving prognosis, many patients were able to tolerate the cough. However, there were some for whom the cough was unbearable.

    ii) Angio-oedema: this was rare, affecting less than 1% patients taking an ACEi (but higher in Black patients with heart failure, at around 3%). Some episodes of angio-oedema can be life threatening, but not all.

171. The risk of these side effects was considered acceptable relative to the clinical benefit associated with ACEis.

172. At the Priority Date, 10 ACEis were available to treat heart failure in the UK. They were also recommended by the 2001 ESC Guidelines based on clinical trial data of their efficacy.

173. After long-term use, Ang II levels began to rise slowly, known as “ACE escape”. ACEis cause Ang I to rise as it cannot be cleaved to Ang II. When Ang I levels are very high, some Ang I can be converted to Ang II via other enzymes (i.e. non-ACE routes). This led to the investigation of a combination of ACEis and other inhibitors of the RAAS. While the theory of ACE escape was known, its clinical significance was not.

Beta blockers

174. Beta blockers have been already described above. They were recommended for the treatment of a wide range of patients on standard treatment, including diuretics and ACEi, unless there was a contraindication.

175. Historically, beta blockers were perceived to have deleterious effects on acute haemodynamic measures. However, by the Priority Date, they were understood to be helpful in heart failure for many reasons.

MRAs

176. By the Priority Date, and following the RALES trial for spironolactone, MRAs were also used with ACE inhibitors and beta blockers.

Diuretics

177. Diuretics are described above. Diuretics were recommended for use if the patient was suffering from salt and water retention. They were used to treat the symptoms of heart failure, rather than slow progression or prolong life. Nearly all patients with heart failure would be on a diuretic (usually a loop diuretic), in combination with (at least) an ACEi. Despite the widespread use of diuretics in heart failure, there had not been large randomised controlled trials to assess their effect on survival largely because loop diuretics had been in use since the 1960s with no apparent adverse safety signal.

178. There were three main classes of diuretics in use for heart failure at the Priority Date: loop diuretics, thiazide diuretics and potassium-sparing diuretics. Loop diuretics prevent the reabsorption of potassium and sodium chloride by the kidneys, meaning less water is reabsorbed and more urine is produced. Thiazide diuretics, which only prevent sodium chloride reabsorption, were thought to be less potent, particularly if the patient had impaired kidney function (which is typical in patients with heart failure). Thiazide diuretics may have been used as an add-on to loop diuretics if the patient had severe congestion, but would rarely (if ever) be used alone in patients with heart failure. In fact, by the Priority Date, thiazide diuretics were seen as first line treatment for hypertension rather than heart failure.

Drugs that were not recommended to treat heart failure

Vasodilators

179. Vasodilators were no longer generally recommended for use in heart failure following clinical trials showing no reduction in mortality, despite short term haemodynamic improvements and improvement in symptoms. Some vasodilators resulted in worsening heart failure or higher incidence of death.

CCBs

180. CCBs were not recommended for the treatment of heart failure on the basis of a series of neutral or negative clinical trial results.

NEP inhibitors

181. In the 1990s, clinicians explored potentiating endogenous natriuretic peptides in patients with heart failure by inhibiting NEP. However, no NEP inhibitors had been approved by the Priority Date. There was a lesser degree of interest in the development of NEPi monotherapy at the Priority Date.

182. Insofar as the skilled person in heart failure knew about NEPis, they would know about candoxatril. It was debatable whether other NEPis would have been known, whether there were differences between those NEPis and whether such differences mattered.

Renin inhibitors

183. Renin inhibitors inhibit the enzyme renin, which acts at the start of the RAAS and converts angiotensinogen to Ang I. Blocking renin should prevent formation of Ang II and, ultimately, aldosterone. Renin inhibitors were being investigated as another means of disrupting the RAAS at the Priority Date, potentially alongside ACEis to prevent ACE escape, but were not as advanced in terms of clinical development as vasopeptidase inhibitors and ARBs. The skilled person would be likely to be aware of renin inhibitors as an avenue of research, but they were not considered the most promising therapeutic candidate (that was reserved for vasopeptidase inhibitors).

ARBs

184. The mechanism of action of ARBs is described above. However, contrary to the position in hypertension, by the Priority Date no ARBs had been approved to treat heart failure.

185. In the 1990s, there had been much excitement about the potential of ARBs as a treatment for heart failure for two reasons: (i) as a potential replacement for ACEi in treatment for heart failure; and (ii) as an add-on therapy, to be administered on top of ACEi. Because ARBs bind to the AT1 receptor, they do not inhibit ACE activity so do not cause potentiation of bradykinin and other vasoactive peptides. In the early 1990s, this was considered a double-edged sword: the risk of cough might be lower, but potentiation of bradykinin was thought to contribute to the efficacy of ACEis in heart failure (so prolonging life). Proponents of ARBs thought that blocking the receptor for Ang II (i.e. the AT1 receptor) was a more effective mechanism of suppressing Ang II activity than blocking its formation and had the advantage of avoiding the risk of ACE escape. In addition, it was hoped that the risk of angio-oedema would be lower with use of an ARB. These differing schools of thought were widely known in (if not accepted by) the relevant scientific community at the time. Accordingly, a series of trials was undertaken in the 1990s to compare an ARB to an ACEi, and to add an ARB on top of existing ACEi therapy in heart failure. These clinical trials and their results are

described below; how the skilled person would have viewed them, and ARBs in heart failure generally at the Priority Date, is an issue in dispute.

186. Pharmacological differences between ARBs had been reported (e.g. in terms of receptor engagement) but it was not known to what extent it was clinically relevant in heart failure, due to the lack of clinical data.

187. Three clinical trials of ARBs for use in heart failure treatment had been published before the Priority Date (I note that it does not seem to me very clear that what was recorded as agreed in the ASCGK really entirely was, and these matters are subject to what I say on disputed CGK issue 11 below):

    i) Losartan: The Evaluation of Losartan in the Elderly Study, ELITE I and ELITE II trials, published in 1997 and 2000 respectively, examined losartan (ARB) vs captopril (ACEi) in heart failure. In ELITE I, the primary endpoint was renal function as measured by serum creatinine levels; there was no difference between the arms. However, a post-hoc analysis revealed an unexpected lower mortality rate in the losartan group although the study had not been powered to show an effect on mortality.

    Because the apparent superiority of losartan on morbidity and mortality was based on a small number of events and this was not the primary outcome of the study, the ELITE II trial was designed and conducted to compare the effects of losartan to captopril on mortality, morbidity, safety and tolerability The trial investigators undertook a larger study in a more representative group of patients (they looked at 3000 patients over the age of 60, rather than just over 700 patients over 65 in ELITE). ELITE II failed to show that losartan was superior to captopril in improving survival in patients with heart failure. Mortality and sudden cardiac death or resuscitated cardiac arrest did not differ significantly between groups. Losartan was better tolerated than captopril. Mortality was numerically greater in the losartan group, although the difference was not statistically significant. ELITE II also did not establish equivalence between losartan and captopril (it was not powered to).

    ii) Valsartan: the Val-HeFT trial was a Phase III trial against placebo involving over 5,000 participants, who were also taking the standard heart failure treatments (ACEi for over 90%, beta blockers, diuretics and/or digoxin), so valsartan or placebo were administered as an add-on therapy. The addition of valsartan did not improve overall mortality compared to placebo. The trial found that valsartan significantly reduced the combined end point of mortality and morbidity and improved clinical signs and symptoms in patients with heart failure who were taking prescribed therapy, but the specific combination involving valsartan, ACEi and beta blocker raised a safety concern, with an increase in morbidity and a significant increase in mortality.

    iii) Candesartan: further trials were underway involving the ARB candesartan: the CHARM trials. The results were not published at the Priority Date.

Combination therapy for hypertension

188. Using multiple different drugs in combination was common in the treatment of hypertension. Many patients needed more than one drug to control their hypertension and combination therapy was popular. Its use had several potential advantages. There was potential for reduced adverse events as, in combination, lower doses of the individual drugs could be given. There was also potential for increased efficacy, as multiple pathways for reducing blood pressure could be targeted. A combination targeting two mechanisms of action is more likely to cause a beneficial effect compared to either drug alone, although this is not guaranteed.

189. Hypertension treatment was driven by achieving a target blood pressure. A patient would be initiated on a single drug, and if their blood pressure was insufficiently controlled, the clinician would prescribe further drugs to be used in combination. Clinical trials consistently showed that about a third of patients reached target blood pressure with one drug, another third required two drugs, and the remaining third needed three or more drugs.

190. Definitively predicting the effect of a specific drug combination was very difficult as the body has mechanisms in place to maintain the *status quo* of an individual's blood pressure, and there are many different systems in the body that affect blood pressure. An effect on one system could therefore impact many other systems, and many counterbalancing effects had to be taken into account. When considering the effect of a combination, the skilled person would have known that the effect of each drug could interact with the effect of the other, which could create a difficult-to-predict effect. It is not the case that it would have been thought that any combination of antihypertensive drugs would have a beneficial therapeutic effect compared to each drug used as a monotherapy.

191. The BHS, 1999, explained at p. 580 that "*[r]ational drug combinations combine drugs with different modes of action that are additive. Such combinations include; a diuretic with beta-blocker, diuretic with ACE inhibitor, beta-blocker with calcium antagonist, calcium antagonist with ACE inhibitor*".

192. Combinations were often given by administering two (or more) different tablets, rather than co-formulating the combination into a single administration. This arose for largely practical reasons.

193. Certain therapies were formulated as fixed-dose combination pills, such as CoAprovel (for hypertension) which contained irbesartan (an ARB) and hydrochlorothiazide (a thiazide diuretic). A combination pill had benefits for patient adherence.

194. When considering combination therapies, various terms can be used to describe the effects of different drugs. Two such terms are "additive", and "synergistic". Goodman & Gilman's describes these terms as:

i) "An additive effect describes the combined effect of two chemicals that is equal to the sum of the effect of each agent given along: the additive effect is the most common."

ii) "A synergistic effect is one in which the combined effect of two chemicals is greater than the sum of the effects of each agent given alone."

Combination therapy for heart failure

195. Using multiple different drugs in combination was also common in the treatment of heart failure. The rationale for doing so was based on the clinically-backed recommendations for treatment, rather than selecting any drug from any given class. Combining therapies was only recommended if the addition of the new drug improved clinical outcomes in addition to standard therapy.

196. For ethical reasons, clinical trials typically tested drugs by layering them on top of existing proven therapies (as it would be unethical to withhold a treatment already proven to prolong life, unless there was a reasonable expectation that the new drug would be better than the standard of care).

197. In heart failure treatment, it was typical to use combination therapy rapidly after diagnosis. The aim was to get the patient on to the dosages of the three drugs that had been proven to be effective at reducing mortality and morbidity in clinical trials, in order for the patient to live longer. Treatment of patients with heart failure would start with an ACEi on a low dose which was titrated up (see above). Once a stable maximal dose of ACEi was achieved, the same process would be replicated for a beta blocker and then an MRA. However, some combinations of drugs, for example ACEis and aspirin, were viewed with suspicion.

198. Some (but not many) therapies were formulated as fixed-dose combination pills.

Vasopeptidase inhibitors

Background for hypertension and heart failure

199. It was known that both ACE and NEP broke down the vasodilator bradykinin and hence, by inhibiting both enzymes simultaneously, bradykinin levels could be potentiated by each enzyme (dual potentiation). In hypertension, it was also considered that dual inhibition of ACE and NEP could lead to efficacy in a wider patient population than existing drug classes: dual inhibition should provide a more comprehensive hormonal blockade, enhancing the antihypertensive effect, reducing cardiac workload, and enhancing diuresis. There were known to be structural similarities between the enzymes NEP and ACE, as both were zinc-dependent metalloprotease enzymes. This structural similarity was part of the rationale for attempting to develop a single molecule that would inhibit both ACE and NEP.

200. The concept of combined NEP and ACE inhibition was explored more fully with the so-called vasopeptidase inhibitors. Rather than using two separate agents, one NEPi and one ACEi, vasopeptidase inhibitors were a single molecule possessing both ACE and NEP inhibitory action. Vasopeptidase inhibitors were thought to work by reducing levels of Ang II whilst also preventing degradation of bradykinin, natriuretic peptides and other vasoactive peptides. In the mid-1990s several vasopeptidase inhibitors had been developed and, by the Priority Date, omapatrilat was the most clinically advanced example.

Omapatrilat - background for hypertension and heart failure

201. Omapatrilat is a vasopeptidase inhibitor developed by Bristol Myers Squib (BMS). Early clinical trials of omapatrilat were very promising in terms of its efficacy in treating hypertension and heart failure. Positive results had been shown in a variety of patient groups. This broad effect was likely due to omapatrilat acting via two mechanisms and therefore being a drug which could be efficacious in relation to a wider variety of patients. There was a perception that it could be a "blockbuster" drug.

202. Along with its very promising efficacy, there was a potential angio-oedema risk with omapatrilat. The precise mechanism and reasons for the angio-oedema side effect were uncertain at that time, but bradykinin and substance P were both hypothesised to be involved. There is further discussion of this issue in relation to the disputed CGK, issue 7 (and issue 13 for heart failure).

203. Therefore, at the Priority Date, the vasopeptidase inhibitors as a class were viewed as a promising potential treatment with combined effects on both the RAAS and NP systems, but there was a risk of angio-oedema with omapatrilat.

Omapatrilat in hypertension

204. By July 2000, BMS had announced the OCTAVE clinical trial, which was a phase III trial in hypertension. Participants were given 10mg omapatrilat or 5mg enalapril (an ACEi), titrated up to a maximum dose of 80mg or 40mg, respectively. The results of OCTAVE were eagerly awaited, but did not become public until after the Priority Date. A second large trial in isolated systolic hypertension was also underway at the Priority Date (OPERA). The results of OPERA did not become known until after the Priority Date.

Omapatrilat in heart failure

205. Significant interest in omapatrilat stemmed from publication of the results of the phase II trial IMPRESS in the Lancet in 2000. IMPRESS compared omapatrilat to lisinopril (an ACEi) in nearly 600 patients with heart failure with reduced ejection fraction. At the Priority Date, a phase III trial involving nearly 6000 patients with heart failure comparing omapatrilat to enalapril (OVERTURE) was underway.

Drug development

206. The first stage in drug development is early discovery and development. This could involve either screening of libraries of compounds, or the development of new compounds which would involve an iterative process of design of chemical compounds, testing *in vitro* and early *in vivo* studies, analysis of these test compounds, and re-design of compounds to improve their properties.

207. Compounds would be assessed, and preliminary results presented by way of commonly used measures of activity, such as IC_{50} values.

208. There would then be selection of lead candidates from the early stage *in vitro* and *in vivo* assays and studies. Compounds with the most promising results would be taken forward into later stage testing.

209. Pre-clinical development would screen for red flags such as toxicity, and conduct preclinical experiments in animals (e.g., in rats or dogs). The goal of this process is to identify a clinical candidate. Clinical development would focus on safety, pharmacokinetics, and efficacy. This would be followed by clinical trials in humans, with Phase I trials assessing basic safety and tolerability in a small number of usually healthy people, Phase II trials assessing efficacy, side effects and optimal dosing in people with the relevant condition, and Phase III trials confirming effectiveness, monitoring side effects and comparing compounds to standard treatment or placebo in large groups (often multinational).

Animal models of hypertension

210. It was not possible to progress a drug candidate to human clinical trials in most diseases without first having tested it in animals to obtain information on its safety profile, target engagement, and efficacy.

211. For certain conditions, animal models can be used which mimic aspects of the human disease. Accordingly, animal models are specific to the condition they mimic, i.e. animal models used to evaluate treatments for hypertension are specific to hypertension, and differ from those used to assess other conditions. The extent to which data obtained from the available animal models were considered predictive of outcome in humans varied significantly between conditions, and it was recognised that even good animal models did not correlate perfectly with outcomes in humans.

212. There were several recognised animal models for hypertension at the Priority Date. All of them were characterised by using animals with artificially elevated blood pressure and were generally considered to be helpful predictors of efficacy in humans, as the causes of hypertension in them often reflected the causes of human hypertension. For example, salt-loading animals mirrored the impact of a high-salt diet in humans. It would have been considered that a drug candidate showing a blood pressure lowering effect in an animal model of hypertension (or ideally two) would make it a good candidate for further testing in human studies.

213. There were a number of distinct animal models of hypertension. A way of characterising them was through their renin levels, which could be high, low or neutral:

    i) **The spontaneously hypertensive rat model** ("**SHR**") - hypertensive rats that have been selectively inbred over many generations to be susceptible to hypertension. The SHR is considered a reliable animal model for hypertension, as all major antihypertensive drug classes tend to show efficacy in this model. Part of the utility of the SHR was due to it being neither a high or low renin model of hypertension.

    ii) **The stroke-prone SHR model** ("**SHRsp**") – this is a subset of the SHR model, in which rats predisposed to both hypertension and stroke have been selectively bred.

    iii) **The Goldblatt model** (also known as the two-kidney, one-clip model or "**2K-1C**" model) – this is a high-renin model of hypertension, where one of the renal arteries is clipped to increase renin levels and hence increase blood pressure in the animal

    iv) **The one-kidney, one-clip model** ("**1K-1C**") – one kidney of the animal is removed, and the renal artery of the other is clipped. This model is initially characterised by transient rises in renin and Ang II, which lead to sodium and fluid retention and a long-term low renin, volume-dependent model of hypertension.

    v) **The deoxycorticosterone acetate** ("**DOCA**") **salt rat model** – a low renin model where the rat is given a powerful steroid (DOCA) that causes retention of salt and water. Further salt is then administered to raise blood pressure. The model is often utilised alongside nephrectomy of one kidney to increase the sodium load on the remaining kidney.

    vi) **The Dahl salt sensitive model** ("**Dahl SS**") – this model involves rats bred over generations to pick out those with either the least blood pressure rise with salt (salt resistant ('SR'), control rats) and the most blood pressure rise with salt (salt sensitive ('SS') rats).

214. In general, high renin models showed better results for drugs that inhibit the RAAS (e.g. ACEis and ARBs) and low renin models showed better results with drugs that do not act through the RAAS (e.g. CCBs and diuretics).

Animal models of heart failure

215. By the Priority Date, large randomised clinical trials were required to assess the efficacy of new drugs for heart failure, using mortality and morbidity as clinical endpoints. Surrogate markers such as acute haemodynamic improvements did not necessarily correlate with better patient outcomes.

216. A credible drug candidate would be expected to demonstrate target engagement, directionally coherent physiological effects, and consistency with established biology before justifying such investment.

217. Animal models are intended to approximate the relevant human condition being investigated. In some conditions, animal models can provide a reasonable indication of potential efficacy in humans (although, given the differences between animals and humans, this is not guaranteed). Animal models of heart failure were recognised as valuable for mechanistic and preclinical research, but they were not necessarily predictive of human clinical outcomes.

218. In animal models of heart failure, typically some form of myocardial dysfunction is induced so that the heart can no longer pump properly. The dysfunction can be introduced to healthy animals (i.e. is an acquired defect) or the animal can be selectively bred to increase its propensity for the dysfunction. Common animal models of heart failure were:

    i) The **rapid pacing model**: pacemakers are implanted to stimulate a fast heartbeat (tachycardia) for several weeks. The heart does not have time to fill properly and gradually fails.

    ii) The **cardiomyopathic model**: animals (typically hamsters) are selectively bred with a genetic mutation affecting heart muscle, leading to cardiomyopathy and heart failure.

219. Other models are also used, including coronary artery ligation to induce acute myocardial infarction.

220. The effects of drugs in animal models are often explored by measuring changes in haemodynamic variables, typically blood pressure, preload, afterload, and left ventricular ejection fraction. However, while acute haemodynamics represent a broad range of physiological parameters and can be indicative of target engagement, an improvement in haemodynamics does not necessarily translate into a clinical benefit. Haemodynamic changes demonstrate that a drug is engaging with a target and eliciting some kind of biological effect in the animal. However, it would be required to see whether the drug increases survival time once the animal has heart failure, because it may indicate that the progression of heart failure has been slowed. In addition, it would be required to see whether the treatment affected markers of neurohormonal activation (e.g. whether aldosterone or noradrenaline levels are reduced) or affected changes in the myocardium itself.

Prodrugs

221. Prodrugs are precursors of medicinal compounds, which are metabolised to active metabolites in the body through chemical or enzymatic reactions. A prodrug is equivalent to its active form once metabolised in the body.

Motivation for and clinical development of new hypertension drugs

222. It was generally known, and cited in guidelines that there was under-diagnosis of hypertension, discontinuance of treatment, and lack of satisfactory control. Management of hypertension remained suboptimal.

223. The general view (see above) was that around a third of people continued to remain uncontrolled even when on three different drugs. There was therefore a significant role and market for new agents that were add-ons. The market for antihypertensive treatments was significant.

224. For hypertension trials, licensing requirements focused on demonstrating a reduction in blood pressure. Typically an average of 10 mmHg reduction in systolic blood pressure was achieved by a single antihypertensive drug. Therefore, hypertension trials were not always conducted as add-on studies.

Motivation for and clinical development of new heart failure drugs

225. Despite the success of ACEis and the major market they had created, there remained significant mortality from heart failure. New heart failure treatment development followed an additive approach. Regulators like the MHRA in the UK and the FDA in the US required that new heart failure drugs demonstrate improved outcomes i.e., such as reduced mortality, not just symptom relief. Phase II trials would aim for the endpoint of improved ejection fraction and reduced breathlessness, for example. Clinical trials for new heart failure drugs were usually conducted on top of existing proven treatments (e.g. loop diuretic or an ACEi), rather than replacing them, for ethical reasons (see above).

Disputed CGK

226. There were eight disputed issues of CGK on hypertension and five on heart failure. Regrettably, they did not narrow by closings.

Issue 1 – relevance of LVSP in hypertension

227. What LVSP is, is set out in the ASCGK above. This issue concerns whether it was perceived as relevant in hypertension, and its significance is in relation to Trippodo, where LVSP is measured in the cardiomyopathic hamster model, primarily a heart failure model.

228. There was almost nothing in the hypertension literature at the Priority Date referring to LVSP, and such little as there was did not identify it as a treatment goal or useful metric.

229. Prof Webb accepted that the skilled person in hypertension would understand that LVSP is, as a matter of physiology, related to systolic blood pressure because LVSP has to rise slightly above the pressure in the aorta for the aortic valve to open. So a change in LVSP could reflect a change in systolic blood pressure.

230. Although this is true and I find that the skilled person in hypertension would understand it if they thought about it, they would not upon reading about LVSP results in an animal model attach importance to it as a matter of CGK. Therefore I find that LVSP was not, as a matter of CGK, regarded as relevant in hypertension.

Issue 2 – ACEis compared with ARBs for clinical use in hypertension

231. This issue also comprehends clinical studies comparing ACEis with ARBs, the impact on and of bradykinin, and ACE escape, which is described in the ASCGK above.

232. At the Priority Date, ACEis were better established and more deeply investigated than ARBs. It had been possible to compare their blood pressure lowering effects, which I find were known as a matter of CGK to have been essentially the same, but not to compare their relative outcomes in terms of heart attacks and strokes. The lack of outcome comparisons was also CGK. I also find that, relatedly, it was CGK that it had been possible to compare outcomes as between ACEis and other classes of drugs such as beta blockers.

233. A further part of the picture which I find was CGK (I am unclear if this was really disputed) was that ARBs had a better side effect profile than ACEis in relation to cough and angio-oedema (prevalence about 5-10% and up to about 1% respectively for ACEis, though figures as low as 0.1-0.2% were also given for the angio-oedema). A prevalent CGK theory was that bradykinin elevation caused or was involved in these side effects.

234. There was less clarity about the wider clinical implications of bradykinin elevation. There was a CGK study by a group at Vanderbilt University (Gainer et. al, 1998, published in the New England Journal of Medicine, also referred to at trial as the "Nancy Brown paper" after its eminent last author). This was a study of short term effects, and I find that the CGK in the light of it was that the longer term picture was uncertain and for further study, both with ACEis and ARBs.

235. I have mentioned ACE escape above. I do not think there was a dispute about it in itself, but find that there was similarly a known concept of ARB escape also being contemplated, so there was not a point of meaningful practical differentiation between ACEis and ARBs. The concepts did not have immediate, pressing implications, though in the longer term it was recognised to be an area that would be desirable to study.

236. These issues all feed ultimately into the obviousness case, so I will summarise by saying that the overall picture was of longer-standing use of ACEis with correspondingly stronger and clearer evidence, but not that ARBs were not worth pursuing.

Issue 3 – clinical use of ARBs in patients with ACEi-induced angio-oedema

237. To meet Accord's argument in support of obviousness that ARBs would present a lower risk of angio-oedema than ACEis, Novartis said that it was CGK that it was unsafe to give ARBs to patients who had already experienced angio-oedema when given ACEis.

238. There was some evidence of this, but it was not strong or well known (a letter to the editor of Hypertension in 2001 by Fuchs, a paper by Warner in 2000 in the Annals of Pharmacotherapy in 2000 introduced into the case only in the

cross-examination bundle for Prof Wilkinson), not rising to the level of CGK, I find.

239. Although the concrete evidence was therefore slight and not CGK, it is also fair to say that it reflects the fact that there was uncertainty, and that the proposition that ARBs actually did give beneficial results in patients who had had angio-oedema with ACEis was untested. Novartis pointed out that in hypertension there were numerous drug classes available and that if a patient had to be taken off ACEis there were various other choices (which I accept was CGK).

240. On the other hand, Accord said that none of this cut across its case that it would be desirable to have the choice to give ARBs in the first place, to reduce angio-oedema risk. I accept that there is some force in this, although it is really part of the obviousness analysis rather than a point on CGK.

Issue 4 – interchangeability within drugs classes, (i) ARBs and (ii) NEPis

241. This issue arises when it comes to obviousness, because Accord's case requires the skilled person (among other steps) when proceeding from Ksander to choose an ARB to go with sacubitril, and when proceeding from Trippodo to choose an ARB and a NEPi. Accord's case is that once the skilled person had reasoned so far as choosing a drug from the class(es) of ARBs and/or NEPis, they would regard the known drugs within each class as essentially interchangeable, so that there would be no invention in choosing specifically valsartan or sacubitril. This concept was also referred to in the evidence and argument as whether there was a "class effect".

242. In relation to ARBs, Accord relied on the evidence of Prof Wilkinson and in particular on a meta-analysis by Conlin et al. published in 2000. Prof Webb gave written evidence on two main fronts, first that ARBs differed as between those that were "surmountable" and those that were "insurmountable", and second by criticising the Conlin work.

243. I do not need to go into the (in)surmountable dispute or even explain the science underlying it because Prof Webb accepted in later reports that he had made a mistake. I regard it as an isolated error in his otherwise excellent evidence and it has no effect on my overall assessment of him as a witness, but in any event the point in substance died away, although Novartis made some half-hearted written closing submissions about it.

244. As to Conlin, I find that it was CGK as a significant piece of work in one of the CGK journals. It is true that there was some debate about it, but the more heavily critical material (a letter to the editor of the American Journal of Hypertension by Meredith and others) was only produced in the re-examination of Prof Webb, his not having raised the points in it any earlier. There was also a paper by Hansson et al. (authors also including Meredith) which was put to Prof Wilkinson, but he did not accept the points made and said the paper, which was not peer-reviewed and which recorded only some discussion at a conference, represented an outlier perspective. Also, Prof Conlin rebutted the points in the Meredith letter in the same publication.

245. Prof Webb made the point that a meta-analysis may not be as cogent as a head to head comparison; I accept this but it does not mean that the meta-analysis lacks force. In the end Prof Webb expressed what I think was a reasonable personal preference for irbesartan and candesartan based largely on their half lives, but it was no more than that and all the relevant, authorised ARBs could have the same once per day dosing interval in clinical practice.

246. So in relation to interchangeability within the class of ARBs I accept Accord's argument.

247. With NEPis the position is quite different. Prof Wilkinson never really said there was a class effect. In his written evidence he said that results from NEPis up to the Priority Date were variable and inconsistent, and in oral evidence he explicitly said that there was no class effect and that each NEPi would need to be individually tested in the relevant models; that the data in hypertension were "quite mixed" and that "whether that related to turning on RAAS, for example, or whether that was related to the individual properties of the inhibitor was not clear".

248. Prof Wilkinson also relevantly contrasted the actions of ARBs and NEPis in his oral evidence: he said that NEP was "sort of promiscuous and chewing up lots of things" and "you have a pure [ARB] which does not chew up anything, it just sits on the receptor". Prof Webb gave similar evidence that "… it is quite complicated. NEP inhibitors did lots of things.".

249. I conclude that there was no CGK expectation that NEPis were interchangeable and there was no CGK of a class effect. The CGK perception was that the effect of each different NEPi had to be studied individually. Novartis is right about this issue.

250. Sensing the problems with its position, Accord sought to retreat to a position that all NEPis inhibit NEP, so there is by definition a class effect. This was circular and not real and does not avoid the point that different NEPis would be thought to be materially different in practice and need individual testing, among other things because of the "promiscuous" point.

251. A modified version of this argument by Accord was that the whole issue was not a point over CGK but one about obviousness, since starting from Trippodo the skilled person would consider that a NEPi with good *in vitro* potency, good bioavailability and good pharmacokinetics would be considered a suitable candidate to combine with an ARB, and that these requirements would be seen to be satisfied by sacubitril as illustrated in Ksander. I return to this when I come to obviousness, but observe that any such argument has to be regarded in the light of my finding here that NEPis were not to be regarded as interchangeable and that a literature search from Trippodo would be done in the expectation that NEPis of interest had to be individually assessed, rather than all being acceptable.

Issue 5 – whether NEP inhibition monotherapy was still being considered at the Priority Date and the relative promise of other candidates (e.g. endothelin acting

drugs and renin inhibitors)

252. This issue is better divided up. Whether NEPi monotherapy was still being considered did not in the end seem to be important to the arguments, and the position was clearly that interest in it had faded very considerably by the Priority Date, and such work as was continuing was very minor.

253. The relative promise of other candidates interrelates with the perceptions about the reasons why NEPi monotherapy had not succeeded, which is the next topic, in particular because the role of endothelin bridges both.

Issue 6 – the reasons why NEPi monotherapy had not succeeded

254. I find that it was CGK that *one* prevalent theory explaining why NEPi monotherapy had had disappointing results was that NEPis reduced the breakdown of angiotensin II and/or caused compensatory activation of the RAAS, the logic being that either would counter any natriuretic and diuretic effect of the inhibition of NEP. Consistently with this, Accord took Prof Webb through a number of publications which explained the theory and I find that multiple of the publications were CGK (even if some were not).

255. However, it was also CGK that this was not the only theory and to the extent it was the most prevalent, which it probably was, that is not the same as saying that it provided a simple and unifying picture of all that was going on, and the publications put to Prof Webb did not profess certainty by any means.

256. One particular example of another theory relied on by Novartis was that the natriuretic peptides potentiated by NEPis promoted natriuresis and vasodilation but also inhibited the RAAS through the release of renin.

257. There were other effects too: NEPs were also known to break down vasoconstrictors such as endothelin, so inhibiting the enzymes could up-regulate them.

258. The potential involvement of endothelin has been a personal interest for Prof Webb and Accord said that he overstated its importance. Accord also said that if endothelin upregulation was seen as the real issue then there would have been concrete suggestions to combine a NEPi with an endothelin receptor blocker or an inhibitor of endothelin converting enzyme. Prof Webb agreed that the literature did not contain such a suggestion (the same papers as put forward the angiotensin II/RAAS theory tended to suggest a NEPi/ACEi combination), and that for overall effect on blood pressure lowering increased angiotensin II had been "much more important" than endothelin.

259. My conclusion on the endothelin point is that it was a less important part of the CGK picture, but of some significance, and this is supported by some of the line of publications relied on by Accord referring to it as well as to the angiotensin II/RAAS theory (e.g. Weber et al. 1999, Nawarskas et al. 2001); Novartis put forward other publications raising it (e.g. Ruschitzka et al. 2001). It is also another concrete illustration of the complexity of the overall

picture, and I refer again to the "promiscuous" nature of NEPs' activity which I mentioned above.

Issue 7 - the skilled person in hypertension's knowledge regarding omapatrilat and its angio-oedema risk

260. The agreed CGK included that omapatrilat had an angio-oedema risk, and that while the reasons for the side effect were uncertain, bradykinin and substance P were hypothesised to be involved.

261. Furthermore, the agreed CGK included that clinical results were very promising for hypertension and for heart failure (as to which, see further below).

262. These positive indications for omapatrilat were consistent with the CGK move away from NEPi monotherapy, mentioned above, towards vasopeptidase inhibitors.

263. Both sides argued that aspects of the omapatrilat situation were CGK; the litigation dynamic was that Novartis wanted to accentuate the positive in order to promote omapatrilat and vasopeptidase inhibitors as the most topical and promising way forward, while Accord wanted to accentuate the negative, to make an ARB/NEPi combination relatively more attractive.

264. I find that it was CGK that there had been a number of angio-oedema adverse events with omapatrilat, and that a small proportion had resulted in intubation for the patients affected. Further, although the absolute number of such events and the percentage of patients affected were both very low it would still be a really serious issue if replicated in larger patient populations. It was CGK that the drug company developing the drug, BMS, had withdrawn its fast track application to the FDA in the USA and refiled on the normal pathway, as part of which it was doing a very large phase III trial, OCTAVE, whose results were, at the Priority Date, expected to come soon (much of this is agreed CGK, some of the nuances were not agreed, hence my findings).

265. OCTAVE was designed both to study efficacy further and to test the angio-oedema risk. It needed to be a large trial partly because the angio-oedema that had been observed was a rare event. One part of the study design was to start with a low dose (10mg) in the light of the side effect issue; Novartis said this was CGK but although it was mentioned in places in the literature I was not persuaded that this point of detail of the study design was so well known, and in any case I agree with Accord that even if it was, that would just be a sign that the angio-oedema issue was a serious one.

266. Novartis' overall submission in relation to the CGK was that the results of OCTAVE were awaited with optimism. I do not accept this and I think it confuses two things. One was that the *efficacy* of omapatrilat was indeed very promising and that BMS had enough faith in in it to progress the regulatory process. Whether or not the angio-oedema *side effect* issue would turn out to be a problem was simply unknown pending the results of OCTAVE, although the fact of the trial being initiated and carried to a

conclusion implied that BMS did not have data showing that carrying on was unjustifiable. Naturally BMS and the clinical community *hoped* that the results would be positive in terms of angio-oedema, but that is a different matter.

Issue 8 – the AB/CD rule as an approach to hypertension treatment

267. The AB/CD rule was a sort of algorithm first proposed by Prof Morris Brown, a leading light in the field, in an article in the Lancet in 1999. "A" is ACEi (expanded by Prof Brown in 2001 to include ARBs), "B" is beta blocker, "C" is CCB and "D" is diuretic. A younger or white patient would be started on A or B, while older or black patients would be started on C or D. If a good enough result was not achieved, the patient would be given another drug from the other pair.

268. Neither side made much of the rule in their arguments on obviousness and each seemed somewhat perplexed that the other side was pursuing it. As to whether it was CGK or not, Accord's position was that it was not embodied into formal practice guidelines for clinicians until after the Priority Date; Novartis retorted that the skilled person is not a GP prescribing drugs but an expert working on new treatment approaches. I agree with Novartis on this: the AB/CD rule was published in an important article from a leading researcher in a very respected and widely read journal and was the subject of active discussion thereafter before the Priority Date.

269. So far as it matters, I agree with Novartis that the rule does not propose the combination of ARBs and NEPis, and that is consistent with Novartis' broader case, including the non-appearance of the combination in the CGK. Nor, on the other hand, does it actively point away. The skilled person who had otherwise followed the line of reasoning that Accord says was obvious would not then be deterred by the AB/CD rule. Accord went so far as to say that the rule gave another string to its bow on obviousness because it showed the idea that if one class of drugs activated another system that acted to oppose it, you would combine that drug with a second drug that would act on the counteracting system. This is much more abstract than the rule itself and the product of an oversimplifying hindsight, and I do not think the skilled person would derive it from Prof Brown's work as such. It does perhaps illustrate why the rule is not positively opposed to Accord's case, as I have already said, but no more than that.

270. I agree with Novartis that the rule did not change the fact that in hypertension ARBs were only positively indicated for patients intolerant of ACEis.

271. I need say no more about the AB/CD rule in analysing obviousness below. It was a sideshow and if the parties had been more pragmatic they would have just agreed that it made no difference.

Issue 9 – the relevance of improvement in haemodynamic measurements to the treatment of heart failure

272. There were two main points rolled into one on this issue.

273. The first was whether haemodynamic effects *caused* heart failure, and it was not really disputed by Accord that by the Priority Date the neurohormonal hypothesis of heart failure had taken over.

274. The second was whether changes in haemodynamic parameters were *measured* as part of the drug development process in heart failure. This was Accord's real point to advance its case of obviousness over Trippodo for the heart failure skilled person. I find that it was CGK that they were so used, on the basis of there being strong evidence that they were studied in the early development of a number of drugs relevant to heart failure, and on the basis of Prof Wilkinson's literature citations, some of which were not challenged at all.

275. Haemodynamic measurements were not however regarded as the complete picture, and Accord did not argue that they were. The skilled person would also be interested in the health and survival of animals studied, heart histology and neurohormonal signals.

Issue 10 – the perception of the side effect profile of ACEis in heart failure

276. I was not much assisted by Novartis' submissions on this topic, which tended to overlook that ACEis had side effects at all, and to repeatedly refer instead to their efficacy. There is no doubt that they were highly effective and had dramatically reduced mortality in heart failure, but that does not mean they did not have side effects, and they clearly did.

277. I find that the CGK was that ACEis were known to cause cough and angio-oedema, as is recorded in the agreed CGK along with their prevalence. Insofar as not agreed CGK, I find that the degree to which cough could be tolerated varied greatly from patient to patient and some could not tolerate it at all. The willingness to tolerate it was greater than in relation to hypertension, though, given that heart failure is more symptomatic and more life threatening (I believe this was common ground).

278. Prof Clark said that having treated 20,000 patients with heart failure he had never had anyone present with angio-oedema requiring intubation. This speaks to the rarity of that extreme degree of angio-oedema but was not suggested to mean that the side effect could be taken lightly and clearly it was taken very seriously. A finding of angio-oedema would lead to immediate withdrawal of ACEi treatment.

279. ESC Guidelines, which I find represented CGK, included recommendations for the use of ARBs in heart failure patients intolerant of ACEis; on the efficacy side their first recommendation was ACEis, however.

280. Prof Clark gave some evidence that if a patient experienced angio-oedema with ACEis they would not be given an ARB instead, but that was not borne out by the documents as being the CGK position, and there were published studies where it had happened. So this did not detract from the general position that ARBs had a role in ACEi-intolerant patients.

281. The ELITE I and II trials were agreed to be CGK and although there is a significant dispute about what they showed in relation to efficacy (see below) I find that it was CGK that they showed that ARBs had lower side effects (comparable to placebo) in relation to cough and angio-oedema, compared with ACEis. This affirmed what had been theorised for them based on the fact that they do not potentiate bradykinin (in particular).

Issue 11 – the clinical use and perception of ARBs in heart failure

282. There were three clinical trials referred to at trial that involved both ACEis and ARBs: ELITE I and II and Val-HeFT. Their interpretation is and was difficult and opinions varied. Reasons for the difficulty included that the end points differed, and that the studies were either not powered to show some differences (e.g. mortality in ELITE I), or failed to show superiority (of the ARB losartan in ELITE II) but did not show inferiority either. Val-HeFT was a complicated trial design in which either placebo or valsartan was *added* to prescribed therapy (which in most cases included ACEis).

283. Prof Clark said in his written evidence that ELITE II was a failure for losartan in not showing its superiority to the ACEi used (captopril). I do not think this was the best way to express the situation, since losartan had not come out worse, and a review by Burnier & Brunner in the Lancet in 2000, which I find represented CGK, positively said that it would be wrong to conclude from ELITE II that ARBs were less effective than ACEis in heart failure. There were other more qualitative statements in articles which I was not satisfied were CGK that ELITE II had shown the appearance of equal efficacy or that "there was really no difference in terms of mortality or other important secondary end points" but anyway approaching the matter rigorously and in terms of statistical significance the evidence did not satisfy me that that had been proven by ELITE II anyway.

284. The authors of the paper reporting ELITE II (Pitt et al., in the Lancet in May 2000) expressly said that it was not an equivalence study. They went so far as to say that their findings made "it probable that losartan resembles an ACE inhibitor in heart failure"; but they also said that "[i]t still remains to be established, however, whether [ARBs] are a fully effective substitute for [ACEis] in heart failure.". Their overall recommendation was that in view of the large body of evidence showing efficacy for ACEis they "should remain the treatment of choice in heart failure", but that in patients who could not tolerate them, an ARB "might be a useful alternative agent". I find that these statements represented the CGK.

285. Prof Clark pointed out that Figure 3 of Pitt showed captopril favoured over losartan in terms of mortality in many subgroups and that if he were presenting the results to patients they would have wanted to choose the ACEi and not the ARB. However, the differences are not statistically significant and plainly do not cut across the conclusion that ARBs might be useful where ACEis were not tolerable for the patient.

286. I do not think that Val-HeFT affects this overall position materially one way or another. The main point made by Novartis was in relation to a group in

that study who were receiving an ACEi and a beta-blocker at base line and then had added on either the ARB or placebo: the ARB recipients appeared to do worse in terms of mortality. In other subgroups who were not receiving an ACEi, the addition of the ARB gave positive results. As Accord pointed out, the fact that it was incidentally observed that the addition of an ARB on top of an ACEi was deleterious is not relevant to its case that it was obvious to combine an ARB and a NEPi without an ACEi, especially for patients who could not tolerate an ACEi. In any case, as the authors of the main paper reporting the study said (Cohn et al. New England Journal of Medicine, 2001), pending further trials it was not clear whether the adverse result was real or due to chance.

Issue 12 - whether NEP inhibition as monotherapy was still being considered for heart failure and the perception of reasons why it had not succeeded

287. As with hypertension, it is clear that interest in NEPi monotherapy had faded greatly by the Priority Date; Accord did not submit otherwise and although it put forward a little evidence of some minor continuing work it did not change the overall picture of a loss of interest.

288. As with the position in hypertension, Prof Clark and Novartis accepted that RAAS activation/upregulation of angiotensin II was CGK as one potential explanation for the monotherapy being ineffective. Prof Clark said there were others but did not support that with details, instead settling on the position that the skilled person would not think much about the reasons for failure, so the picture is less well-fleshed out than in relation to hypertension. On the other hand, Accord's evidence through Prof Wilkinson did not go so far as to say that it was CGK that RAAS activation/upregulation of angiotensin II was the only possible explanation, or that the position was uncomplicated, so overall I do not think the situation as between hypertension and heart failure was materially different for the purposes of my task.

Issue 13 – the skilled person in heart failure's knowledge regarding omapatrilat and its angio-oedema risk

289. This issue is the heart failure equivalent of issue 7 on hypertension. There had been different phase II efficacy trials in heart failure and a different phase III trial was underway (OVERTURE). It is easy to confuse these trials with the hypertension trials and they were occasionally confused by counsel during the cross-examination, but it did not matter because overall and so far as relevant for me the CGK picture is the same: efficacy had been promising, optimism remained on that front which meant there was a hope that angio-oedema would not turn out to be a problem once the further trials reported, but it was necessary just to wait and see.

"Not CGK"

290. Novartis argued that it was a facet of the CGK, or at least telling in the assessment of the obviousness arguments, that no one in the art proposed, in the CGK, an ARB/NEPi combination. It asked, forensically, if the combination was obvious, why was it not proposed?

291. Prof Wilkinson was asked in cross-examination and was not able to provide any answer. He did agree that a possible reason was that the art was distracted by the enthusiasm for omapatrilat and vasopeptidase inhibitors generally.

292. Accord responded that the combination *had* been proposed, by at least Trippodo and Darrow, and in a 1993 paper by Richardson and others (to which I attach little weight given the fact that it only appeared in the case in the cross-examination materials for Prof Webb, its age, and the fact that the combination is mentioned only in passing along with a variety of other options).

293. Accord is of course entitled to choose prior art to attack the Patent which does propose the combination, and to the extent the citations disclose it, it is not necessary to find it in the CGK. It remains relevant, however, that the combination was not proposed in any review articles or the like reflecting the mainstream thinking of the field, even though, as Novartis submitted, this was an active field of research where the literature often did suggest new combinations or drugs, or acting on multiple systems at once. It undermines Accord's case that the overall logic of the systems involved and the disease states to be treated would push towards the combination, and it is particularly significant in relation to Ksander, where the combination is not proposed.

294. So I generally agree with Novartis on this point, which I think is really one of secondary evidence rather than CGK, but it is not necessary to my rejection of the obviousness attacks.

Complexity

295. Novartis argued that both hypertension and heart failure were complex fields at the Priority Date. In relation to hypertension it referred to the RAAS with its dynamic negative feedback loop, and the multiple molecules involved in it. In relation to heart failure it made similar points and also referred to the typical elevation of ANP and BNP levels in heart failure, calling into question the use of drugs which might raise them further.

296. I agree that both were complex. Accord did not really dispute it. The separate issue is whether Accord's obviousness attack oversimplified matters, which I consider below.

THE APPLICATION

297. The contents of the Application are critical to the issue of plausibility and so it is worth setting it out in detail.

Disclosure

298. The Application begins on page 1 with a very general overview about angiotensin II and ACEis:

PHARMACEUTICAL COMPOSITIONS COMPRISING VALSARTAN AND NEP INHIBITORS

Angiotensin II interacts with specific receptors on the surface of the target cell. It has been possible to identify receptor subtypes that are termed e.g. AT 1- and AT 2-receptors. In recent times great efforts have been made to identify substances that bind to the AT 1-receptor. Such active ingredients are often termed angiotensin II antagonists. Because of the inhibition of the AT 1-receptor such antagonists can be used e.g. as antihypertensives or for the treatment of congestive heart failure, among other indications. Angiotensin II antagonists are therefore understood to be those active ingredients which bind to the AT 1-receptor subtype.

Inhibitors of the renin angiotensin system are well known drugs that lower blood pressure and exert beneficial actions in hypertension and in congestive heart failure as described, for example, in N. Eng. J. Med. 316, 23 (1987) p. 1429-1435. A large number of peptide and non-peptide inhibitors of the renin angiotensin system are known, the most widely studied being the ACE inhibitors, which includes the drugs captopril, enalapril, lisinopril, benazepril and spirapril. Although a major mode of action of ACE inhibitors involves prevention of formation of the vasoconstrictor peptide Ang II, it has been reported in Hypertension, 16, 4 (1990) p. 363-370 that ACE cleaves a variety of peptide substrates, including the vasoactive peptides bradykinin and substance P. Prevention of the degradation of bradykinin by ACE inhibitors has been demonstrated, and the activity of the ACE inhibitors in some conditions has been reported in Circ. Res., 66, 1 (1990) p. 242-248 to be mediated by elevation of bradykinin levels rather than inhibition of Ang II formation. Consequently, it cannot be presumed that the effect of an ACE inhibitor is due solely to prevention of angiotensin formation and subsequent inhibition of the renin angiotensin system.

299. On page 2 there are the following two paragraphs about hypertensive disease. The first is context for the second, which is of relevance to the plausibility/collocation/technical contribution issues:

Prolonged and uncontrolled hypertensive vascular disease ultimately leads to a variety of pathological changes in target organs such as the heart and kidney. Sustained hypertension can lead as well to an increased occurrence of stroke. Therefore, there is a strong need to evaluate the efficacy of antihypertensive therapy, an examination of additional cardiovascular endpoints, beyond those of blood pressure lowering, to get further insight into the benefits of combined treatment.

The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different mode of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need

for more efficacious combination therapy which has less deleterious side effects.

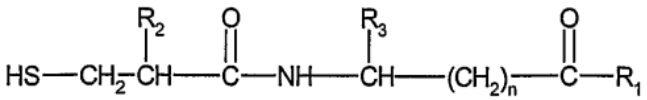
300. The idea of combining valsartan with a NEP inhibitor is then introduced in three rather similar paragraphs which bridge pages 2 and 3 (the first corresponds closely to claim 1 of the Application):

> In one aspect the present invention relates to pharmaceutical combinations comprising valsartan or pharmaceutically acceptable salts thereof and a neutral endopeptidase (NEP) inhibitor or a pharmaceutically effective salts thereof, optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.
>
> In another embodiment the present invention relates to methods of treating cardiac and renal related conditions by administration of the pharmaceutical composition comprising valsartan plus a NEP inhibitor or relates to the use of a pharmaceutical composition comprising valsartan or pharmaceutically acceptable salts thereof and a neutral endopeptidase (NEP) inhibitor or a pharmaceutically effective salts thereof.
>
> In another embodiment of the invention the present invention relates to a pharmaceutical composition comprising valsartan or pharmaceutically acceptable salts thereof and a neutral endopeptidase (NEP) inhibitor or a pharmaceutically effective salts thereof and a diuretic, especially hydrochlorothiazide.

301. Then, following the full name and structure of valsartan being given, more detail about possible NEP inhibitors is set out starting at the bottom of page 3:

> A NEP inhibitor useful in said combination is a compound of the formula (II)

(II)



> and pharmaceutically acceptable salts thereof wherein:
>
> R2 is alkyl of 1 to 7 carbons, trifluoromethyl, phenyl, substituted phenyl, -$(CH_2)_{1\text{ to }4}$" phenyl, or -$(CH_2)_{1t04}$-substituted phenyl;
>
> R3 is hydrogen, alkyl of 1 to 7 carbons, phenyl, substituted phenyl, -$(CH_2)_{1\text{ to }4}$-phenyl, or -$(CH_2)_{1t04}$-substituted phenyl;
>
> R1 is hydroxy, alkoxy of 1 to 7 carbons, or NH2;
>
> n is an integer from 1 to 15; and

> the term substituted phenyl refers to a substituent selected from lower alkyl of 1 to 4 carbons, lower alkoxy of 1 to 4 carbons, lower alkylthio of 1 to 4 carbons, hydroxy, CI, Br, or F.

302. Then some "preferred" and "even more preferred" selective NEP inhibitors are discussed (now at the top of page 4):

> Preferred selective neutral endopeptidase inhibitors of formula II include compounds wherein:
>
> R2 is benzyl;
>
> R3 is hydrogen;
>
> n is an integer from 1 to 9; and
>
> R1 is hydroxy.
>
> Even more preferred selective neutral endopeptidase inhibitors of formula II are reported in the literature as SQ 28,603 which is the compound of formula II wherein:
>
> R2 is benzyl;
>
> R3 is hydrogen;
>
> n is one; and
>
> R1 is hydroxy.

303. There follow several compendious references to NEP inhibitors "within the scope of the present invention" as including those in various identified patents. One of these (top of page 5, first paragraph) is sacubitril, described by its full chemical name of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester.

304. Two preferred salts of sacubitril are described at the bottom of page 6, with methods for their preparation.

305. On page 7 there is then a broad statement about the therapeutic use of the salts:

> The salts of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester formed with triethanolamine and tris(hydroxymethyl) aminomethane are novel and can be used as NEP inhibitors. Another embodiment of the present invention are said new salts, their use as NEP inhibitors, especially for preventing and treating of conditions and disease associated with the inhibition on NEP, pharmaceutical composition comprising these salts and their combination with valsartan, especially for the treatment of conditions and diseases as disclosed for the combinations of the present invention hereinbefore or hereinafter.

306. And there follows one of the critical passages for the purposes of assessing plausibility, on which much of the argument focused:

> It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotes less angioedema than is seen with the administration of vasopeptidase inhibitor alone. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days).
>
> Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects. The combined administration of valsartan or a pharmaceutically acceptable salt thereof and a NEP inhibitor or a pharmaceutically acceptable salt thereof results in a significant response in a greater percentage of treated patients, that is, a greater responder rate results, regardless of the underlying etiology of the condition. This is in accordance with the desires and requirements of the patients to be treated.

307. And on page 8 there is an extremely long list of possible conditions for use:

> It can be shown that combination therapy with valsartan and a NEP inhibitor results in a more effective antihypertensive therapy (whether for malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type of hypertension) through improved efficacy as well as a greater responder rate. The combination is also useful in the treatment or prevention of heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling. It can further be shown that a valsartan and NEP inhibitor therapy proves to be beneficial in the treatment and prevention of myocardial infarction and its sequelae. A valsartan plus NEP inhibitor combination is also useful in treating atherosclerosis, angina (whether stable or unstable), and renal insufficiency (diabetic and non-diabetic). Furthermore, combination therapy using valsartan and a NEP inhibitor can improve endothelial dysfunction, thereby providing benefit in diseases in which normal endothelial function is disrupted such as heart failure, angina pectoris and diabetes. Furthermore, the combination of the present invention may be used for the treatment or prevention of secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular

> hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke.

308. Page 9 also has some statements on which much argument focused:

> The person skilled in the pertinent art is fully enabled to select a relevant test model to prove the efficacy of a combination of the present invention in the hereinbefore and hereinafter indicated therapeutic indications.
>
> Representative studies are carried out with a combination of valsartan and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester [i.e. sacubitril], e.g. applying the following methodology:
>
> Drug efficacy is assessed in various animal models including the deoxycorticosterone acetate - salt rat (DOCA-salt) and the spontaneously hypertensive rat (SHR), either maintained on a normal salt diet or with salt loading (4-8% salt in rat chow or 1% NaCl as drinking water).

309. There follows a long description of the DOCA-salt test model. I will not set it all out, but pertinently it is written in the present tense. An acute and a chronic version are each described.

310. A similarly general description of SHR experiments is set out from page 11. This is also mostly described in the present tense with an exception in the middle of page 11 in the future tense which Counsel for Novartis accepted was something that the skilled reader would understand had not in fact been done.

311. Part of the description (on page 12) includes the following:

> Typical dosages for valsartan in drinking water range from 3 to 30 mg/kg/day whereas the dosage of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester is highly dependent upon the specific agent used. In most situations, a daily dose will not exceed 50 mg/kg/day when administered as the monotherapy. In combination, lower dosages of each agent are used and correspondingly, valsartan is given in the range of 1 to 30 mg/kg/day and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester in dosages below 50 mg/kg/day. However, in cases wherein the responder rate is increased with combination treatment, the dosages are identical to those used as monotherapy.

312. I return to the supposed significance of this below.

313. Throughout the procedures' descriptions the NEPi is consistently identified as sacubitril, using its full chemical name.

314. Immediately after the descriptions of the methods, the following statement is made:

> The available results indicate an unexpected therapeutic effect of a combination according to the invention.

315. Two "aspects" are then given at pages 12 to 13. They amount to much the same thing for the purposes of the arguments (the first relating to a pharmaceutical combination and the second to a method of treatment) so I will just set out the second, which was considered in the oral evidence:

> A further aspect of the present invention is a method for the treatment or prevention of a condition or disease selected from the group consisting of hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter, detrimental vascular remodeling, myocardial infarction and its sequelae, atherosclerosis, angina (whether unstable or stable), renal insufficiency (diabetic and non- diabetic), heart failure, angina pectoris, diabetes, secondary aldosteronism, primary and secondary pulmonary hypertension, renal failure conditions, such as diabetic nephropathy, glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, and also renal vascular hypertension, diabetic retinopathy, the management of other vascular disorders, such as migraine, peripheral vascular disease, Raynaud's disease, luminal hyperplasia, cognitive dysfunction (such as Alzheimer's), glaucoma and stroke, comprising administering a therapeutically effective amount of combination of (i) the AT 1-antagonists valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier to a mammal in need of such treatment.

316. There is then an extensive description of various formulation matters. Nothing was said to turn on it. It reads as a very general description of possible formulation approaches.

317. Claim 1 is as follows:

> 1. A pharmaceutical composition comprising (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

318. Claim 2, dependent on claim 1, provides a long list of NEP inhibitors to choose from.

319. Claim 3 is, and it requires that the NEPi is sacubitril (or the active metabolite sacubitrilat; nothing turns on that):

> 3. The pharmaceutical composition of claim 2, wherein the NEP inhibitor is N-(3-carboxy-l-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester [i.e. sacubitril] is a triethanolamine or tris(hydroxymethyl)aminomethane salt thereof or N-(3-carboxy-l-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-rriethylbutanoic acid or a pharmaceutically acceptable salt thereof.

THE PATENT SPECIFICATION

320. The Patent is a cut down version of the Application. It retains almost no mention of heart failure, other than in [0001] and [0002], which are the equivalents of the first two paragraphs of the Application, and [0047] in the formulation parts, which gives the dosing interval for valsartan and to which neither side attached any importance.

321. Novartis also pointed out that [0016] (the same as the "It has surprisingly …" paragraph on page 7 of the Application) by its reference to prolonged change in blood pressure, would not be of interest to the heart failure expert.

322. [0038] and [0039] were said to be relevant to the SPC issues and are as follows:

> [0038] A therapeutically effective amount of each of the component of the combination of the present invention may be administered simultaneously or sequentially and in any order.
>
> [0039] The corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

Claim in issue

323. Only claim 1 of the Patent is relevant, and it is:

> 1. A pharmaceutical composition comprising
>
> (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and
>
> (ii) N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester or N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid or a pharmaceutically acceptable salt thereof
>
> and a pharmaceutically acceptable carrier.

VALIDITY

Plausibility – the law

324. There has been a great deal of development and argument in the law of plausibility in the past decade, two landmarks being the decision of the Supreme Court in *Generics (UK) Ltd v Warner-Lambert Co LLC* [2018] UKSC 56 ("*Warner-Lambert*") and the later decision of the Enlarged Board of Appeal of the EPO in *G 2/21* ([2024] EPOR 6).

325. Both were considered by the Court of Appeal in *Sandoz Ltd v Bristol-Myers Squibb* [2023] EWCA Civ 472 ("*Apixaban CA" - G2/21* was decided between the first instance decision and the appeal in that case), and *Generics (UK) Ltd v AstraZeneca AB* [2025] EWCA Civ 903 ("*Dapagliflozin CA*").

326. In each case the Court of Appeal held that *Warner-Lambert* remained binding authority, and in the latter that the further case law in other EPC contracting states and in the TBA provided no reason to depart from *Apixaban CA*.

327. Accordingly, subject to some additional subsidiary points considered below, I can, as both sides did, take the basic law on plausibility from *Dapagliflozin CA*, citing *Warner-Lambert* but with useful emphases and paragraph breaks added:

> 16. It is common ground that the decision of the majority of the Supreme Court in *Warner-Lambert* is authority binding on this Court as to the standard to be applied when assessing the sufficiency of disclosure of a medical use invention. (The claimed invention in *Warner-Lambert* was a second medical use, but AstraZeneca does not suggest, at least in this Court, that a distinction can be made between first and second medical use claims.) The majority adopted a standard which has subsequently come to be referred to as "*ab initio* plausibility", meaning in essence that the application when read together with the common general knowledge must positively make it plausible that the invention will achieve the claimed technical effect. The minority preferred a standard which has subsequently come to be referred to as "*ab initio* implausibility", meaning in essence that the application when read together with the common general knowledge should not give rise to doubt as to whether the invention will achieve the claimed technical effect.
>
> 17. For present purposes it is sufficient to cite two passages in the judgment of Lord Sumption for the majority. The first passage sets out the principle (emphases and line breaks added in [37]):
>
> > "36. The principle is that the specification must disclose some reason for supposing that the implied assertion of efficacy in the claim is true. Plausibility is not a distinct condition of validity with a life of its own, but a standard against which that must be demonstrated. Its adoption is a mitigation of the principle in favour of patentability. It reflects the practical difficulty of

demonstrating therapeutic efficacy to any higher standard at the stage when the patent application must in practice be made. The test is relatively undemanding. But it cannot be deprived of all meaning or reduced … to little more than a test of good faith.

37. Plausibility is not a term of art, and its content is inevitably influenced by the legal context. In the present context, the following points should be made.

First, the proposition that a product is efficacious for the treatment of a given condition must be plausible.

Second, it is not made plausible by a bare assertion to that effect, and the disclosure of a mere possibility that it will work is no better than a bare assertion. ….

But, *third*, the claimed therapeutic effect may well be rendered plausible by a specification showing that something was worth trying for a reason, ie not just because there was an abstract possibility that it would work but because reasonable scientific grounds were disclosed for expecting that it might well work. The disclosure of those grounds marks the difference between a speculation and a contribution to the art. This is in substance what the Technical Board of Appeal has held in the context of article 56, when addressing the sufficiency of disclosure made in support of claims extending beyond the teaching of the patent. In my opinion, there is no reason to apply a lower standard of plausibility when the sufficiency of disclosure arises in the context of EPC articles 83 and 84 and their analogues in section 14 of the Patents Act . In both contexts, the test has the same purpose.

Fourth, although the disclosure need not definitively prove the assertion that the product works for the designated purpose, there must be something that would cause the skilled person to think that there was a reasonable prospect that the assertion would prove to be true.

Fifth, that reasonable prospect must be based on what the TBA in *Salk* (para 9) called 'a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se.'

Sixth, in *Salk*, this point was made in the context of experimental data. But the effect on the disease process need not necessarily be demonstrated by experimental data. It can be demonstrated by *a priori* reasoning. For example, and it is no more than an example, the specification may point to some property of the product which would lead the skilled person to expect that it might well produce the claimed therapeutic effect; or to some unifying principle that

> relates the product or the proposed use to something else which would suggest as much to the skilled person.
>
> *Seventh*, sufficiency is a characteristic of the disclosure, and these matters must appear from the patent. The disclosure may be supplemented or explained by the common general knowledge of the skilled person. But it is not enough that the patentee can prove that the product can reasonably be expected to work in the designated use, if the skilled person would not derive this from the teaching of the patent."

328. It was common ground at trial (the point had been made clear at the PTR) that plausibility was to be argued by reference to the Application. Counsel for Novartis briefly tried to equivocate about this in closing oral submissions, but it was far too late to try to change the agreed basis of argument, and on the strength of it Accord had not pressed an added matter plea which had been designed to prevent Novartis trying to argue plausibility from the Patent. In places below I refer to "the specification" in a general way, but without prejudice to the fact that in the present case it is plausibility from the Application that matters.

329. I turn to the various points of elaboration or detail advanced by the parties in addition to these basic principles.

A disclosure test

330. Accord emphasised that the test is about disclosure of the document, and not an exercise in trying to work out what it is likely that the patentee actually did in fact. I accept this.

331. I would add that while expert evidence is admissible to make sure the court understands the science of the document and the impact of experiments or results reported and the like, the meaning of the language used is for the judge. Quite a lot of the cross-examination was about what the words of the Application mean, and so I have not spent time on it in this judgment.

Uselessly or trivially low results

332. Accord pointed out that in the *Apixaban* case at first instance ([2025] EWHC 822 (Pat), I rejected a disclosure of a trivially low level of activity) as satisfying the plausibility threshold. I said this:

> 76. While recognising that patent specifications do not have to reach a standard of excellence or perfection, and a "working prototype" will often be good enough, there comes a point where activity loses any practical meaning and I think this argument goes beyond that point. In my view the law requires a technical contribution of some, even if low, real significance. There is no contribution in disclosing a uselessly low degree of activity so that comparisons can be made with something which is useful. BMS's argument on this point is not really different

from the sort of nihilistic argument that novel compounds with no known use can be put into service as ballast, or the like.

333. I said that in the context of the specification disclosing a K_i of 10μM or less, which on the evidence was nowhere near potent enough to be useful, and the patentee had argued that it would have utility as a sort of comparator, or example of "what not to do". I stand by what I said, but it concerned a situation where there was a positive assertion of what had been achieved, expressed numerically but at a level which was known to be useless for practical purposes.

No hard data or results

334. It is common ground that the Application does not contain any numerical results, and has at most qualitative descriptions that some combination has given positive results in tests.

335. I do not think that numerical results are necessarily needed (although they may be important if they are given). There is nothing in *Warner-Lambert* to say that they are, and it would be inconsistent with the low level of the hurdle to require them.

336. There is support for this view in *Illumina HC* at [238]-[241]. An experiment was described as going to completion but no graphs, gels or the like were provided. So it was a yes/no, descriptive assertion of success in a test, and was held good enough for plausibility. The Court of Appeal considered this part of the decision in *Illumina CA* and did not disagree with it.

337. Accord phrased its argument on this point in terms of there having to be technical information conveyed by the specification. I agree with this in the sense that a mere assertion is not technical information, but on the other hand, a statement that "I have tested a combination of x and y in a mouse model of z disease and it was better than either agent alone" is technical information.

338. I also do not think that a useful result that is said to be achievable has to be specified as to its extent by some specific value: *Gilead Sciences Inc v Nucana* plc [2023] EWHC 611 (Pat) at [338]-[339].

The mmHg point

339. Accord said that utility in hypertension requires a reduction in blood pressure of 4 or 8 mmHg (for non-inferiority in a clinical study or to be really clinically meaningful, it does not matter which), that a reduction of 1 mmHg would not be useful, and that because the Application contains no data it is possible that the combination of the Patent's claims would only provide e.g. a reduction of 1 mmHg, which would not be useful.

340. This point is a sort of hybrid of the uselessly low result point and the no data point, and is part law and part fact.

341. It needs to be understood that the various amounts of mmHg referred to by Accord are in relation to effects in *humans* but this aspect of the law requires only a showing of plausibility, which may be provided by an *animal* model. It is of course possible that an effect in humans is rendered plausible by an animal model but turns out later not to exist, and there might well then be a different insufficiency (though for obvious practical reasons these plausibility cases tend only to be fought where the effect does exist), but there is no lack of plausibility just because the specification does not show a particular level that is needed in humans.

Connection to the claimed compound(s)

342. Accord reminded me that in *Apixaban CA* and in *Dapagliflozin CA* it was fatal to plausibility that the statements in the specification about utility, such as they were, were about groups of compounds and not disclosed as being related specifically to the single compounds claimed. I accept this as a point of principle and Novartis did not dispute it; its case is that the disclosure of the application is indeed connected specifically to the valsartan and sacubitril combination.

Cannot go behind the assertions in the specification

343. Citing *Evans Medical's Patent* [1998] RPC 517, Novartis reminded me that the court should not go behind the specification, if that asserts that some particular thing was done, and conduct a factual inquiry into whether or not it really was. I accept this, although I do not think it arises on the arguments that I heard. Accord's points are all that the Application does not make the necessary disclosure, not that a disclosure which it does make is not true.

344. This is a convenient point to mention that I have no admissible evidence either way as to whether or not Novartis had done the relevant animal experiments with valsartan and sacubitril at the time of the Application, and anyway it is legally irrelevant. This did not stop Counsel for Novartis hinting that Novartis had, or Counsel for Accord from hinting that Novartis had not; I will ignore the hints on both sides.

Bare assertion is not enough

345. Accord reminded me that a bare assertion of a technical contribution is not enough. It would not be good enough for Novartis for the specification simply and without more to say "a combination of valsartan and sacubitril will treat hypertension". Novartis does not dispute the principle, but it says on the facts the Application goes beyond a bare assertion.

Patent drafting practice and conventions

346. Patents often contain predictions, sometimes across a broad scope, and what are referred to as "prophetic" statements, typically or at least frequently written in the present tense about things which might be done rather than which have been, and the expected or hoped-for results.

347. They also often contain a core of things which have been done and wider speculative statements of increasing breadth about future possibilities.

348. In addition, there is a convention for patent specifications to say "surprisingly it has been found …." simply to introduce the inventive ideas of the patent and without any implication about what is surprising or why.

349. These practices do not fit perfectly with either ordinary English writing (particularly in relation to the use of tenses) or the rigorous way a scientific publication would be written. In my view it would be unreal to determine the question of plausibility without having regard to them, however, and I think that that is consistent with the approach to the skilled person having a knowledge of patent drafting conventions as explained by the Court of Appeal in *Virgin Atlantic Airways Ltd v Premium Aircraft Interiors UK Ltd* at [6]-[15], to which Counsel for Novartis referred me.

CGK may be taken into consideration

350. It was common ground that CGK can (I would add, must) be taken into account when assessing plausibility, and *Warner-Lambert* expressly says so at the seventh proposition in Lord Sumption's paragraph [37]. Counsel for Accord additionally submitted that plausibility cannot be established from CGK alone.

351. Since Novartis' argument is that there is a disclosure of the performance of actual hypertension animal model experiments using valsartan and sacubitril in the Application and it does not rely on CGK alone (as Counsel for Novartis confirmed, pointing out also Novartis' contention that an ARB/NEPi combination was not in the CGK) I do not need to decide this point and do not do so.

352. In passing, however, I will say that I can see that Lord Sumption's seventh proposition and his use of the word "supplemented" are consistent with there having to be something in the specification to show plausibility, which could imply that CGK alone cannot be enough, but the specific point was not squarely in issue given the context, and certainly it would be over-interpreting what he said to apply it to every kind of case. I can also see that there might be cases where an idea was inventive to conceive of but where as soon as the skilled person was told it, it would be obvious from CGK alone that it would work, but that is not this case or the case in *Warner-Lambert* and I think is unlikely to happen in the biological systems that the plausibility cases have focused on.

Discussion

353. I will assess plausibility by reference to the contribution which Novartis alleges, namely the plausible disclosure that a combination of valsartan and sacubitril achieves greater therapeutic effect in hypertension than valsartan or NEPi monotherapy alone (since the contribution alleged is in relation to hypertension I will treat that as being the field of the relevant skilled person,

which is of some relevance to the animal models disclosure and some other aspects of the Application).

354. Novartis says that there is a qualitative statement of experimental results to that effect.

355. Accord says on the other hand that the skilled person would have real doubts that any experiment had been done, and there is just a bare assertion of the greater efficacy of the combination.

356. Accord also says that whatever assertion there may be does not relate specifically to valsartan with sacubitril or to hypertension.

357. It is important in my view to have regard to the teaching of the Application as a whole. So I will begin with some general observations which will involve reference to a number of parts of it, before coming back to go into individual passages in more detail.

358. First, the skilled person would think that large parts of the specification were merely descriptions of what could be done, or broad predictions or aspirations. Examples are the first full paragraph on page 8, the last paragraph on page 13, and the teaching about formulation from page 16 on.

359. Second, the skilled person would think that some things mentioned or referred to had definitely not been done, for example tests in humans and the salt modifications referred to half way up page 11 ("The manipulations will be carried out …").

360. Third, the skilled person would regard some of the predictions as inherently extremely improbable, such as efficacy across the very wide ranges of indications listed.

361. Fourth, however, the skilled person would understand that *some* work had in fact been done. This is the ordinary meaning of "It has surprisingly been found …" in the last full paragraph on page 7 and "The available results indicate …" on page 12, in their own terms and taken in the context of the description of experimental work that they bracket (expressing no view at this stage as to which of that work specifically the skilled person would understand had been or might have been or had not been done, given the differing ways they are described).

362. What the application discloses about the work that had been done is the critical question.

363. Fifth, although it does not drive a conclusion that any particular thing is disclosed as having been done, the skilled person would think it was consistent with the general approach to the drafting of patent specifications that some work had been done, from which more generalised predictions had been made by the authors.

364. I turn to the specific parts relied on.

Page 2

365. The paragraph beginning "The nature of hypertensive vascular diseases …" is really just the CGK, but Novartis relied on it in relation to plausibility. Its logic was (1) that the paragraph says that efficacious combinations cannot just be predicted based on different modes of action, and (2) that therefore the Application must be saying that it has gone further than just theory and (3) the way in which it has gone further must therefore be in terms of concrete experiments. (1) is correct but (2) and (3) are not, and do not necessarily follow at all. They are speculating far beyond what it said. I reject this argument.

Range of NEPis at pages 3 to 6

366. A variety of NEPis are described over these pages. The "[p]referred" and "[e]ven more preferred ones" at page 4 are just statements of preference among formula (II) compounds, which do not include sacubitril, so I reject Accord's argument that in some way there is a pointer away from sacubitril, which in any case is identified along with its salts shortly after, and is specifically called out repeatedly in the experimental descriptions (see below).

The "It has surprisingly.." paragraph on page 7

367. I do not think the skilled person would draw anything from the "surprisingly". It is just used in its conventional sense to indicate that the patentee is taking the position that what follows is patentably inventive.

368. Novartis said that "a combination of valsartan and a NEP inhibitor" specifically denoted sacubitril for the latter. It pointed to the focus of the document as a whole on sacubitril and contrasted the fact that "NEP inhibitor" is in the singular whereas "ACE inhibitors" and "NEP inhibitors" in the following text are plural. This is a narrow and artificial approach which I reject. The singular is used elsewhere to denote a class, for example in the second line of page 8, and where the patentee was referring to sacubitril specifically, as is done many times, the full name is used.

369. I agree with Accord that the mere number of mentions of sacubitril in the Application is not enough on its own to demonstrate that any particular results or protocols relate to it, but Novartis' case is not so limited.

370. The skilled person would also think it inherently implausible that the patentee had reached the stage of testing angio-oedema (in humans) and the use of the word "can" would be thought clearly to connote possibility for the future not what had already been done. In addition, there is no sign in the Application of a comparison with ACEis having been done.

371. The reference to change in blood pressure later in the paragraph could be a pointer to an effect in hypertension, but Novartis did not rely on it heavily, rightly in my view because it is only one of two options, the first being the much more generic return to baseline, and because of the many other

conditions than hypertension for which efficacy is proposed later in the document. The skilled person would think that hypertension was one possibility to which some emphasis is given, but not the only one.

372. So other than the fact that there is a disclosure that some work had been done with a combination of valsartan and some unspecified NEPi(s) there is not much additional in this paragraph to help Novartis. The fact that some work had been done so that the Application would not be thought completely theoretical is not a trivial point, though, as part of the overall context.

Page 8

373. As already mentioned, the middle paragraph on page 8 contains very broad statements of the scope of utility. "Can be shown" is clearly a reference to something that is possible to do, and the skilled person would understand the "is also useful" statements to be prophetic rather than actual, despite the syntax used.

Page 9

374. The second paragraph "The person skilled in the art …" is in my view just boilerplate saying that the skilled person can choose an appropriate model.

375. However, the following (third) paragraph "Representative studies are carried out with a combination of valsartan and [sacubitril]" is much more specific. A specific combination of two agents is identified, and it is said that "representative studies" are done with them. In my view the skilled person would understand that this made sense in the context of patentees doing some work and then generalising from it. On the other hand the "are carried out" formulation of words is similar to the language used elsewhere for things that merely might be done, although one should not read excessively much into this on its own.

376. Accord tended to ignore this paragraph but I think it is an important part of the picture. Accord did seem to accept that the "representative studies" mentioned are those of the kind that follow, as "applying the following methodology:" implies, and I agree that it the meaning. Accord tried to water it down by tying it to the second paragraph whose importance I have dismissed. I do not think the connection is appropriate. The second paragraph is exceptionally general and the third moves to a specific combination and a bridge to a range of experiments in hypertension models.

The experimental protocols

377. I have outlined these above and made some comments on them. They are hypertension animal experiments, and they focus exclusively on valsartan with sacubitril for the NEPi. As mentioned above, at least some of the work would be thought by the skilled person not to have been done but for the future ("will be carried out").

378. A specific argument focused on the drinking water dosage ranges given in the first 15 lines. The question of whether what is being referred to had in fact been done is complicated there by the fact that giving the drug in drinking water (compared with e.g. injection) does not allow the experimenter to know how much the animal has actually received, so it is harder to know if the dose ranges refer to what was put in the water, or what reached the animal. In my view both sides were overanalysing this, and it does not help resolve the key question for me. It is not clear but does not change whether or not the skilled person would think the combination of valsartan and sacubitril had been tested in (a) hypertension model(s).

379. There follows the reference to "the available results", which as I have said is a clear statement that results existed but only refers to "an unexpected therapeutic effect" without saying for what indication, and to "a combination according to the invention", which it is common ground would have valsartan for the ARB but is non-specific about the NEPi.

380. I agree with Accord's point that the skilled person would not know which specific experiments within the possibilities described had been done, but equally would know that they all related to hypertension.

Overall

381. Taking the Application as a whole, I conclude that there is a disclosure in a qualitative and not quantitative way that the patentee had tested the combination of valsartan and sacubitril in some animal experiments for hypertension with positive results for the combination compared with the individual components. I recognise that the results are not quantitative and that data are not given, but I have concluded above that neither is required. I also recognise that which specific tests among the ones described had been done is not disclosed.

382. This is a close call. I have borne carefully in mind what I think for present purposes is the critical distinction between disclosure of the Application on the one hand, and detective work to infer what the patentee is likely actually to have done. My view has shifted back and forth during the trial and in the preparation of this judgment but on reflection the times when I have felt there may not be a plausible disclosure have been when I have been focusing on individual parts of the Application rather than taking it as a whole.

383. Critical elements in my reasoning (though I have considered all of the Application) are what I think are a very clear disclosure that some work had been done and results were in hand, the many specific pointers to the combination, and the statement that "representative" work with it had been done, immediately preceding the description of hypertension animal experiments.

384. It might, naturally, be said that the patentee could have avoided any risk by being explicit and by including experimental details and data. One cannot know why that course was not taken, and I have to address the issue objectively in the light of what the Application contains, but in fairness to

Novartis it must be recognised that it was written over twenty years ago when the concept of plausibility and the applicable standards may have been seen differently.

Abuse of the system

385. Accord submitted that if it were enough for a patentee to achieve plausibility just by the rubric "surprisingly it has been found that X" then the way would be open for the system to be abused by patentees making purely speculative applications to monopolise wide fields of science, then to abandon all but the applications which they (or someone else) later found to be the useful inventions. I agree that would be a problem but it is not the standard the case law sets or the standard I have applied. I have found there is a limited but sufficient disclosure of some actual work meeting the modest standard for plausibility.

386. At the end of the trial, with its written closing submissions, Accord put in some patent applications which it said showed that Novartis had carried out this sort of conduct. I ruled it inadmissible because it was so late and Novartis could not fairly deal with it, but anyway on a brief read the situations did not look like they were necessarily the same as the present one anyway.

Obviousness – the law

387. The basic approach is as set out in the decision of the Supreme Court in *Actavis v. ICOS* [2019] UKSC at [52] – [73], with its endorsement at [62] of the statement of Kitchin J, as he then was, in *Generics v. Lundbeck* [2007] EWHC 1040 (Pat) at [72].

388. I was particularly reminded by Accord of the principle that more than one route can be obvious; it does not have to show that a combination of valsartan and sacubitril was the most obvious thing to do. I accept this, although of course it may be relevant to consider how many options there were available to the skilled person.

389. Accord also relied heavily on what it called "*Pozzoli* points". What it meant was the analysis by Jacob LJ in *Pozzoli v BDMO* [2007] EWCA Civ 588 at [24]-[29] where he considered whether and when there can be an inventive step in dispelling a CGK prejudice. A patentee putting forward such an argument has to show why the prejudice was wrong, and actually dispel it; it cannot rely on a perceived problem which is no different after the patent than before. I accept the principle but it can be overplayed and it is important to understand when it applies. In particular, there is a key difference between a situation where an invention is an obvious thing to think of but the patentee says that the skilled person would be put off by a prejudice (which the patent dispels), and a situation where the idea is not obvious to think of in the first place: see *Teva Pharmaceutical Industries Limited, Teva UK Limited v Astellas Pharma Inc* [2023] EWCA Civ 880 at [72]-[78]. Novartis is not saying that the idea of the combination of valsartan and sacubitril was obvious but that the Patent overcame some prejudice, but rather that it was

not obvious to think of it at all, and the upshot of my analysis of the facts is broadly that it is right.

Ksander

390. There was no material dispute about the disclosure of Ksander; the arguments were all about what the skilled person would think about it, and do next (if anything).

Disclosure

391. Ksander's abstract is as follows:

> The synthesis of three series of dicarboxylic acid dipeptide neutral endopeptidase 24.11 (NEP) inhibitors is described. In particular, the amino butyramide **21a** exhibited potent NEP inhibitory activity (IC50 = 5.0 nM) *in vitro* and *in vivo*. Blood levels of **21a** were determined using an *ex vivo* method by measuring plasma inhibitory activity in conscious rats, mongrel dogs, and cynomolgus monkeys. Free drug concentrations were 10-1500 times greater than the inhibitory constant for NEP over the course of a 6 h experiment. A good correlation of free drug concentrations was obtained when comparing values determined by the *ex vivo* analysis to those calculated from direct HPLC measurements. Plasma atrial natriuretic factor (exogenous) levels were elevated in rats and dogs after oral administration of **19a**. Urinary volume and urinary sodium excretion were also potentiated in anesthetized dogs treated with **21a**.

392. 19a is sacubitril, which is explained later to be the prodrug of 21a, the active metabolite sacubitrilat. Thus at a high level what Ksander says that it will be describing is the potency and pharmacokinetics of the compounds studied. This general thrust carries on into the introductory paragraph (footnotes omitted):

> Atrial natriuretic factor (ANF) is a potent diuretic, natriuretic, and vasorelaxant hormone. These properties have led many investigators to speculate that this peptide might be effective for treating hypertension, congestive heart failure, and renal diseases. To circumvent the inherent problems with the development of a peptide as a therapeutic agent, several approaches can be taken including the identification of nonpeptidic agonists or agents that affect the clearance of the peptide. It is generally accepted that there are two mechanisms responsible for the clearance of ANF. These are receptor-mediated internalization and degradation by so-called C-receptors and enzymatic hydrolysis. Numerous groups have independently demonstrated that kidney membrane preparations degrade ANF enzymatically. Furthermore inactivation and the loss of biological activity *in vivo*, at least in part, occur via cleavage of the Cys^{7}—Phe^{8} peptide bond by neutral endopeptidase 24.II (NEP; EC 3.4.24.11). Although the relative importance of NEP in the metabolism of endogenous ANF remains to be determined conclusively, NEP

> inhibitors have been shown to elicit ANF-like responses in animal models. Despite these encouraging experimental results, recent clinical trials have shown, at best, moderate pharmacologic activity. In these clinical studies several NEP inhibitors including sinorphan, SCH34826, and candoxatril have produced no or modest antihypertensive effects. Somewhat superior, albeit moderate, effects of these agents have been observed in patients with congestive heart failure. Since these poor clinical outcomes may arise from inferior pharmacokinetics or potency, we have sought to identify novel NEP inhibitors with superior pharmacologic properties.

393. This paragraph outlines the CGK understanding of the theory behind the use of NEP inhibitors, identifies that animal models had been encouraging but clinical results had been disappointing says that the poor clinical results could be due to inferior pK qualities or potency, and offers some new NEP inhibitors which might be better in those respects. It mentions antihypertensive effects as well as effects in patients with heart failure.

394. Thereafter the paper has a detailed description of chemical methods for making the study compounds, which is of no importance and would not be of interest to the skilled person (in hypertension or heart failure), and then presents results. It is common ground that 21a had a very good potency, as had been promised in the abstract.

395. 19a was compared with candoxatril as shown in Figure 3, in terms of ANF levels in rats:

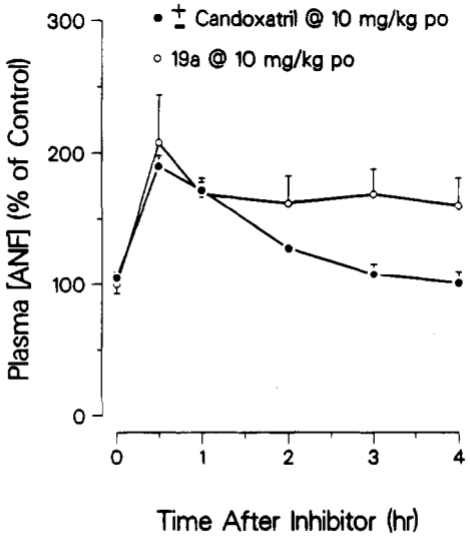


Figure 3. Effect of **19a** and (±)-candoxatril administered orally at 10 mg/kg on plasma ANF concentrations in conscious rats infused with exogenous ANF. Values are the mean ± SEM for six and three rats treated with **19a** and (±)-candoxatril, respectively.

396. This plots ANF as a percentage of control (i.e. no drug), so a positive result appears as a strong uptick shortly after the drug is given. Then there is a decline in ANF. Both candoxatril (solid circles) and sacubitril (open circles) stay above 100%, but sacubitril by more, and for longer.

397. Figure 4 tested ANF levels in dogs given sacubitril and the increase in level as a percentage of control was seen to be dose-dependent. It is not necessary to reproduce this.

398. Figure 5 tested diuresis and natriuresis with the metabolite 21a:

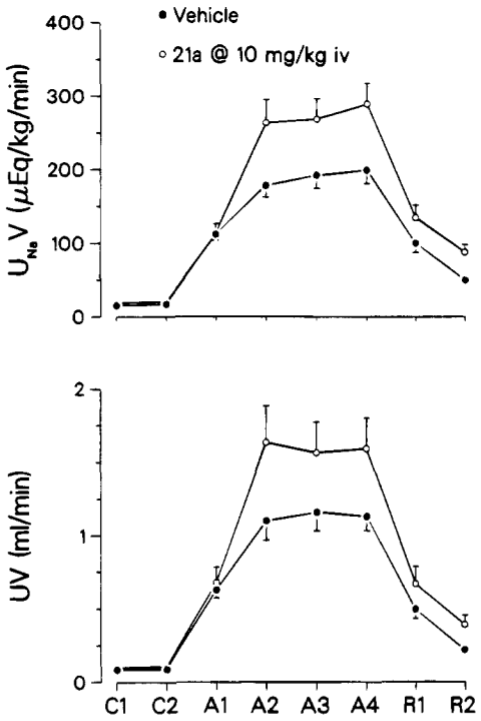


Figure 5. Effect of **21a** administered at 10 mg/kg iv on ANF-induced diuresis and natriuresis in anesthetized mongrel dogs. Values are the mean ± SEM for 11 and 15 dogs treated with **21a** and vehicle, respectively. The experiment consisted of two control periods (C_1, C_2), a period of intrarenal arterial ANF infusion alone (A_1), and three points of ANF infusion with or without **21a** (A_1–A_3) followed by two periods of recovery (termination of ANF infusion; R_1, R_2). Urine volume (UV) and urinary sodium excretion were determined for each of these collection periods.

399. The authors give the following summary:

> In summary, *in vitro* data are presented for three series of NEP inhibitors. The pharmacokinetic profile of **19a**/**21a** was determined in three species. The prodrug **19a** was also shown to increase exogenous levels of ANF and enhance ANF's natriuretic and diuretic activity. Although these experiments do not prove **21a** will enhance endogenous ANF levels and natriuretic and diuretic activity, it does demonstrate the potential to elicit these activities.

The obviousness attack - hypertension

400. Accord did not structure its submissions strictly along *Pozzoli* lines but that is not important in itself and in any case, I have identified the skilled persons (hypertension and heart failure) and the CGK above.

The parties' arguments

401. Accord's obviousness argument seemed to me to have the following elements:

i) Sacubitril is shown in Ksander to have attractive qualities as a NEP inhibitor, with, in particular, good potency, ability to potentiate ANP, effect on diuresis and natriuresis, and duration of action.

ii) Although Ksander says that the problems with NEPis may have been with inferior pharmacokinetics, the skilled person would not agree, but would attribute the problems to RAAS activation.

iii) The skilled person would therefore think that if they wanted to take sacubitril forward they would want to combine it with a RAAS blocker.

iv) This was thematically consistent with CGK suggestions to combine a NEPi with an ACEi.

v) The available options for a RAAS blocker were an ACEi or an ARB.

vi) Even if ACEis might be preferred in some respects, ARBs were also a valid option, and indeed better in terms of angio-oedema and cough, given the CGK that those side effects were associated with bradykinin elevation, which was a feature of ACEis and not ARBs.

vii) The idea of combining a NEPi with an ARB would have been thought credibly likely to give a clinical benefit and it would be worth preparing such a combination at least for animal testing, which would fall within claim 1 of the Patent.

viii) There were 6 ARBs approved for the treatment of hypertension which were equivalent to ACEis in their efficacy for hypertension, and recommended for use in patients intolerant of ACEis.

ix) Valsartan was *an* obvious ARB even if (which Accord disputed) there might be a preference for candesartan or irbesartan.

402. Novartis' main points in response were:

i) Ksander is a chemistry paper with only early stage pre-clinical data leading to an appropriately tentative conclusion.

ii) The skilled person would not be interested in NEPis, which had failed.

iii) There is no reference to the possibility of an ARB/NEPi combination, or any combination of a NEPi with something else.

iv) The art was aware of omapatrilat, which was a single-molecule ACE/NEP inhibitor, and was very topical and promising.

v) The attack over Ksander is really a CGK-only attack and it was therefore very important that the CGK contained no suggestion to combine an ARB and a NEPi.

vi) The authors of Ksander had not ruled out that sacubitril was an inhibitor of endothelin converting enzyme as well as of NEP.

vii) The successful results in animals might not read across to humans anyway and would not allow predictions about clinically useful results in blood pressure or endogenous ANP.

viii) If the skilled person did want to pursue Ksander, the first thing they would do would be to test sacubitril on its own in an animal model of hypertension, and that what the results would be is unknown.

ix) Progressing Ksander would involve filling in some gaps and, at an early stage, repeating all the work.

x) In relation to addressing the cough problem, the skilled person would not know the effect of sacubitril on bradykinin.

xi) If a RAAS blocker were to be combined with a NEPi, ACEis would be much more attractive given the much greater experience with them and because using an ARB in a combination would be to give up the dual bradykinin potentiation effect, which the skilled person would be concerned would reduce any clinical benefit.

xii) In any event, even if the point was reached of choosing an ARB the skilled person would choose the best one, candesartan (possibly irbesartan), and not valsartan.

Assessment

403. Novartis' argument that the attack over Ksander is really one from CGK alone is overstated, but only slightly. Ksander provides a specific NEPi, sacubitril, with good pharmacological properties, so Accord's attack has that concrete kernel to it. But the art did not actually think that NEPi monotherapy had failed because of a lack of potent compounds, and the experts on both sides before me agreed that Ksander's introductory statement in that respect was wrong. So in material respects Ksander really does not provide anything that had not already been in the mind of the skilled person for some years as a failure.

404. Further, and as already mentioned above, I agree with Novartis that it is striking that despite NEPis being available for years, and the reasons for their failures, too, the CGK did not contain any suggestion to combine an ARB with a NEPi, and the very occasional suggestions such as Darrow and, to the extent it does so, Trippodo, do not change this. I reject Accord's point that the CGK suggestions to combine an ACEi with a NEPi are consistent with its argument that RAAS inhibition was a natural way to go. That is just trying

to make a virtue out of a necessity and comes at the matter from the wrong end of the telescope.

405. In addition, the flow of thinking was very strongly that while combined NEPi therapy might be made to work, the way to do it was with the ACEi/NEPi combination in the single-molecule vasopeptidase inhibitors. I disagree with Novartis' argument that the notional skilled person would do nothing while they waited for the omapatrilat phase III trials, but still the thinking behind them would be strongly in the skilled person's mind.

406. It should also not be overlooked that Ksander simply does not contain any positive hint toward combination therapy, whether by RAAS inhibition or otherwise.

407. One sign that Accord's argument is very largely CGK-alone, with the typical problems that brings, is its extreme simplicity. This is most clearly seen with the part of the argument that RAAS inhibition of any kind was what was needed, but also feeds into its contentions that the potential implication of endothelin and bradykinin should be factored out. I have addressed this in relation to the CGK: these were very complicated biological cascades which were not fully understood, either on their own or as to their interactions with each other, and the art did not proceed at the very high level of abstraction of Accord's argument. I bear in mind that I have said when dealing with the CGK that e.g. endothelin was not seen as central, but it is a symptom of the complexity.

408. That said, not all Novartis' points are strong ones. The points chipping away at details of Ksander do not amount to anything, the overall conclusion from it being that within the bounds of what was being studied sacubitril was very good. And the uncertainty about an ultimately useful clinical result in humans was overplayed given that Accord only has to show that it was obvious to make a pharmaceutical composition according to claim 1 for testing in animals (allowing for the fact that the motivation to do that would have to be the investigation of the possibility of clinical use further down the line). Had all of Accord's argument otherwise succeeded, I would also have rejected Novartis' contention that some ARB other than valsartan would have been chosen, and would have concluded that it was *an* obvious choice.

409. I also reject Novartis' argument that the starting point from Ksander would have had to be repeating all the work. It may be true that that is what a real team would do, but even if it is I would regard it as just the normal burden of pursuing any publication. The argument that the skilled team would start by investigating sacubitril in an animal model of hypertension, and that the results are unknown is more significant. Accord met it by saying that the skilled person probably would do so, and would want to anyway, but would not be worried even if sacubitril had no effect, because the whole idea of taking Ksander forward would be that the ARB might make up for the ineffectiveness of the NEPi. I thought this was unrealistic and another sign of ignoring the complexities of the situation.

410. Other arguments fall somewhere in the middle between the parties' positions. Cough and angio-oedema affected a minority of patients, but still a significant number. On the other hand, the cough was not all that serious and where patients were not able to be given ACEis there were numerous other drugs types to choose for hypertension. I do not think that this potential advantage of ARBs in some patients was close to outweighing the other factors, and of course it would only come into play anyway once the skilled person conceived of the idea of the combination, which I do not think they would.

411. The oversimplified nature of Accord's argument also reflects my assessment of the expert evidence on this issue. Prof Wilkinson's opinions were honestly held and clearly expressed but they had an insight which I do not think represented the ordinary skilled person and stripped out many real world complications. I found Prof Webb's position much more persuasive.

412. Balancing all these matters together, and allowing for and/or stripping out Novartis' less good points, I do not have any hesitation in rejecting the obviousness case over Ksander in relation to hypertension.

Ksander– obviousness in relation to heart failure

413. I can deal with this more briefly because most of the key arguments are very much the same. I will focus on a few additional or different points.

414. First, I accept Prof Clark's evidence that vasodilation (if it resulted from ANP potentiation) would not be a positive sign in relation to heart failure, where the art had become more concerned with neurohormonal issues.

415. Second, the heart failure skilled person, if they did want to progress Ksander in a combined therapy, would have an extremely strong leaning towards using an ACEi, given the great success that class of drugs had had.

416. Third, there was a small cohort of patients who were intolerant of ACEis. But in my view that would not outweigh the strong and logical attachment to ACEis and the downside of replacing them for the much larger proportion of patients who could tolerate them. I say a little more about this in the context of the parallel argument with Trippodo, below. Again, this only matters if the skilled person thought of the combination.

417. Fourth, Novartis argued that if the skilled person was interested in progressing Ksander with an ARB they would use candoxatril instead of compound 21a/sacubitril and losartan not valsartan. I reject that. In this scenario (by contrast with the literature search from Trippodo) the skilled person is specifically presented with sacubitril along with positive, if very early-stage data. They would know they needed to do an appropriate animal model of disease in relation to it, but I have already held that that would be a normal part of the process.

418. Fifth, I reject Novartis' argument that the skilled person would do nothing while they awaited the results of the OVERTURE omapatrilat heart failure

trial. Although the trial was a different one for heart failure than for hypertension, the argument is the same and I reject it for the same reasons.

419. My rejection of Novartis' two points just mentioned does not make any difference to my analysis or the result. In relation to the first three points, and generally where the arguments overlapped with the hypertension points, there was a difference of opinion between Prof Wilkinson and Prof Clark and I prefer Prof Clark's approach, mainly because the considerations are clinically-focussed and he had a deeper experience of them, and because my general assessment that Prof Wilkinson's way of thinking was not that of the ordinary, uninventive worker.

420. I note that Prof Clark was taken through a series of steps from Ksander to the idea of combining a NEPi with an ARB. Accord relied on this extensively in its written closing. The steps began with choosing compound 21a as the most attractive in Ksander, which is not controversial, then proceeded by postulating that NEPis had failed as monotherapies because of RAAS activation, to the proposition that therefore the RAAS needed to be inhibited, that a RAAS blocker with a NEPi might reasonably be expected to be effective as a heart failure treatment, to the proposition that an ARB would be one possible choice as RAAS blocker. Prof Clark did not accept some of the stages very readily, and others were put on assumptions (e.g. in particular the reason for NEPi monotherapy failing), and he maintained his position that the skilled person in heart failure would not use an ARB but an ACEi if they did follow this route. I have re-read this passage of evidence in preparing this judgment and my assessment is the same as it was at the time: it was a very step-by-step approach with a heavy risk of injecting hindsight, and anyway Prof Clark was far from accepting it. I reject it.

Secondary evidence

421. Novartis sought to rely on the fact that (it said) until recently there was only one other ARB + NEPi combination (now called an "ARNi", I understand) in addition to Entresto. This argument was developed much too late and anyway there are natural commercial considerations which may have inhibited development of new combinations, including very high cost to demonstrate non-inferiority against Entresto, and the difficulty of displacing Entresto as the standard of care. I attach no weight to this, in relation to Ksander or Trippodo, to which I am coming next.

422. This is also a convenient moment to mention that Novartis repeatedly stressed what a very good drug for heart failure, and what a money-spinner, Entresto has turned out to be since the Priority Date. This is irrelevant in my view, and anyway somewhat ironic to rely on given that Novartis said that the Patent was not of interest to a heart failure skilled person, and rendered plausible in relation only to hypertension, not heart failure.

Trippodo

423. Trippodo was published in the Journal of Pharmacology and Experimental Therapeutics. Novartis submitted that this would not be a journal of interest

to the skilled person. I do not give this any weight. It is from a well known company (BMS) and the skilled person would, as the law requires, read it with interest. More significant is the fact that it was already eight years old when submitted for publication, and the art had moved on a good deal by the Priority Date.

424. As its title says, Trippodo is concerned with heart failure. It looks at haemodynamic effects in animals (hamsters) given (in various combinations) a NEPi, an ARB and an ACEi. It looks at levels of Angiotensin II ("Ang II") and bradykinin. It was thus not in dispute that in the course of the experiments a NEPi and an ARB are given together, but there was a major dispute about the significance of this, and about the implications and consistency of the results.

425. I therefore need to go through the disclosure in some detail.

Disclosure

426. Trippodo's abstract is as follows:

> **ABSTRACT**
>
> Neutral endopeptidase inhibition (NEP-I) and angiotensin converting enzyme inhibition (ACE-I) act synergistically to produce acute beneficial hemodynamic effects in models of heart failure. Blockade of the formation of angiotensin II (Ang II) acting together with potentiation of the natriuretic peptides, bradykinin and other vasoactive peptides may mediate the interaction of dual enzyme inhibition. In this study, the potential roles of Ang II repression and bradykinin potentiation were evaluated in conscious cardiomyopathic hamsters with compensated heart failure. The Ang II AT_1 receptor antagonist, SR 47436 (BMS-186295), was administered at 30 μmol/kg, i.v. followed by i.v. infusion at 1 μmol/kg/min in combination with NEP-I (SQ-28603 at 30 μmol/kg i.v.). Cardiac preload (left ventricular end diastolic pressure) and afterload (left ventricular systolic pressure) decreased significantly more after the combination of Ang II blockade and NEP-I than after either treatment alone. This indicated that repression of Ang II contributes importantly to the NEP-I/ACE-I interaction. Bradykinin B_2 receptor antagonism by Hoe 140 at 100 μg/kg, i.v. significantly blunted the decrease in left ventricular end diastolic pressure but not the decrease in left ventricular systolic pressure after dual NEP-I/ACE-I (SQ-28603 and enalaprilat each at 30 μmol/kg, i.v.). This suggests that bradykinin potentiation contributes to the pre-load-reducing, but not the afterload-reducing, acute effects of NEP-I/ACE-I. Hence, both Ang II repression and bradykinin potentiation are factors contributing to the synergistic hemodynamic effects of combined NEP-I and ACE-I in hamsters with heart failure. The bradykinin-mediated enhanced effect of combined NEP-I/ACE-I to reduce cardiac preload could improve the beneficial effects of ACE-I in the treatment of heart failure.

427. This explains in more detail that, as I have said, the authors were concerned with NEP and ACE inhibition, and refers to Ang II repression and bradykinin potentiation. It calls out the ARB to be used (SR 47436, with a BMS code) and the NEP-I (SQ-28603). It says that a hamster model will be used and that the haemodynamic effects on preload and afterload were greater with the combination than with either agent alone, showing the effect of Ang II repression. The authors also say they have used a bradykinin receptor antagonist (Hoe 140) which reduced the effect of a NEP-I/ACE-I combination (the same NEP-I with the ACE-I enalaprilat) on one of the haemodynamic markers but not the other. The bradykinin-mediated enhanced effect is stressed, and is suggested to have beneficial results on ACE-I in treatment.

428. This does not, to my mind, give any pointer at this high, introductory level, to the use of ARBs with NEP-Is in therapy. The use of the ARB is mentioned prominently, but as a way of trying to elucidate the role of bradykinin.

429. The body of the article begins as follows:

> ACE-I blocks the formation of Ang II and hence attenuates its vasoconstrictor, antinatriuretic and growth enhancement properties. NEP-I prevents the enzymatic inactivation of ANP and therefore protects or potentiates its vasodilatory, natriuretic and antiproliferative actions. Studies have shown that concurrent administration of NEP-I and ACE-I in models of hypertension and heart failure result in an interaction that leads to cardiovascular effects greater than those caused by either treatment given singly. For instance, the antihypertensive effect of ACE-I in conscious spontaneously hypertensive rats was enhanced by coadministration of selective inhibitors of NEP (Seymour *et al.*, 1991; Pham *et al.*, 1993). In dogs with pacing-induced heart failure, NEP-I potentiated the vasodilatory effects of ACE-I (Seymour *et al.* 1993); and in a similar model, subchronic treatment with ACE-I potentiated the renal hemodynamic and excretory responses to NEP-I (*Margulies et al.*, 1991). In cardiomyopathic hamsters with heart failure, the combination of the ACE inhibitor, enalaprilat, and enalaprilat, and the selective NEP inhibitor, SQ-28603, produced decreases in cardiac preload and afterload, whereas each treatment alone had minimal effects (*Trippodo et al.*, 1993). These studies support the concept that the coadministration of ACE-I and NEP-I leads to synergistic effects and could have use in the treatment of hypertension and heart failure.

430. Thus the authors discuss the combination of ACE-I and NEP-I in earlier animal work including their own. The closing sentence mentioned possible coadministration in treatment of heart failure, but of ACE-I and NEP-I, not ARB and NEP-I. The article continues:

> Possible mechanisms by which NEP-I and ACE-I interact to produce enhanced cardiovascular effects have been previously discussed (Seymour *et al.*, 1993, Trippodo *et al.*, 1993). Attenuation of the formation of Ang II by ACE-I might unmask the vasodilatory

> effects of ANP and other natriuretic peptides such as BNP and CNP. This may be particularly relevant in heart failure where the biological actions of ANP are blunted, perhaps partly because of the counteracting effects of Ang II (Raya *et al.*, 1989; Margulies *et al.*, 1991). Potentiation of the vasodilatory effects of bradykinin by both ACE-I and NEP-I might also contribute to the synergism. Although bradykinin can be potentiated by ACE-I alone, greater enhancement of the activity of this peptide may come about when two enzymes involved in its degradation, such as ACE and NEP, are inhibited. Finally, ACE and NEP have substrates in common other than bradykinin, such as substance P, and hence additional factors may play a role as well.

431. This calls out the possible role of bradykinin, pointing out that while it can be potentiated by ACE-I, greater enhancement might be possible, with NEP-I. This is just laying the theoretical ground for what follows. The authors go on:

> Any combination of two or more of these elements may interact to produce synergistic cardiovascular effects. However, currently there is no direct evidence showing whether any of these factors are important in the combined effects of dual metalloprotease inhibition. The purpose of this study was to evaluate the potential contributions of Ang II repression and bradykinin potentiation on the cardiovascular effects of combined NEP-I and ACE-I in cardiomyopathic hamsters with heart failure. These factors were studied not only because of the known effects of the inhibitors on their metabolism, but also because potent specific inhibitors of the Ang II AT_1 receptor and the bradykinin B_2 receptor were available. Ang II AT_1 receptors mediate virtually all of the known biological actions of Ang II (Timmermans *et al.*, 1993). Bradykinin B_2 receptors are likely responsible for many of the cardiovascular and renal effects of bradykinin (Regoli *et al.*, 1990). In this study we used the Ang II AT_1 receptor antagonist, SR 47436 (BMS-186295) (Cazaubon *et al.*, 1993) and the bradykinin B_2 receptor antagonist, Hoe 140 (Wirth *et al.*, 1991). The results from the use of these specific probes indicate that both the repression of Ang II and the potentiation of bradykinin contribute to the acute synergistic effects of NEP-I and ACE-I to reduce cardiac preload in cardiomyopathic hamsters with heart failure.

432. So the authors explain their overall goal, which is to look at how Ang II repression and bradykinin potentiation contribute to the combined effects of NEP-I and ACE-I in the animal models used. The ARB and the bradykinin receptor antagonist to be used are described as "specific probes". So again, the ARB is being stressed as an experimental tool, not as a potential therapy.

433. The results can be seen from figures 3 to 6, which were helpfully and uncontroversially marked up in colour and with additional labels in Prof Wilkinson's first report (he also provided a helpful narrative which I have drawn on). Starting with Figure 3:

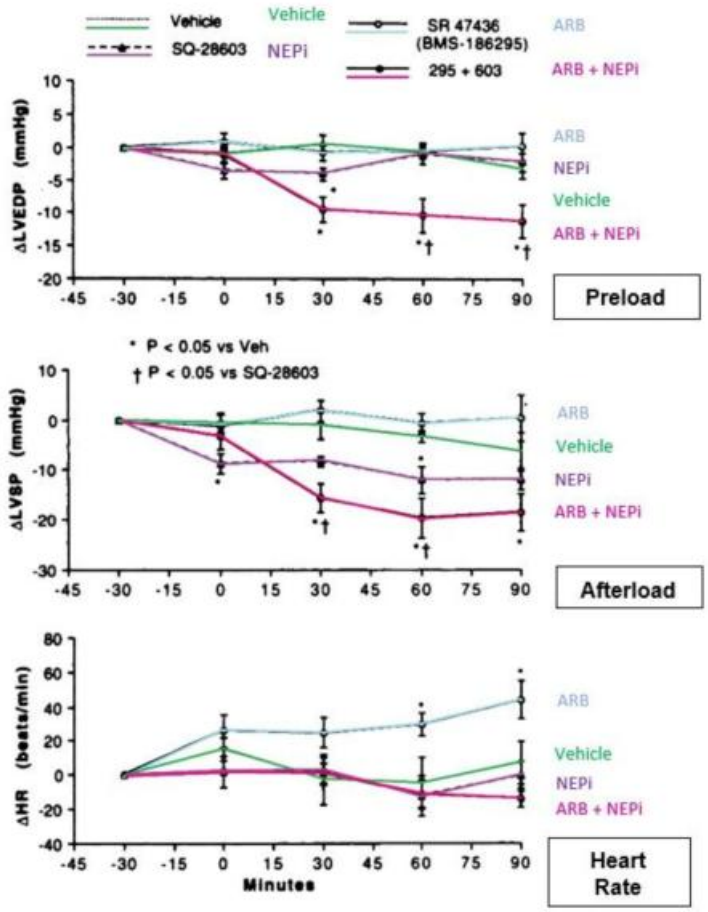


Fig. 3. Cardiovascular changes in conscious cardiomyopathic hamsters after the administration of vehicle (0.017 M KOH), SQ-28603, SR 47436 (BMS-186295) or the combination of SQ-28603 and SR 47436 (BMS-186295). The group receiving the combination treatment is designated as 295 + 603. SQ-28603 was administered as an i.v. bolus at 30 μmol/kg. SR 47436 (BMS-186295) was administered at 30 μmol/kg, i.v. followed by a continuous i.v. infusion at 1 μmol/kg/min. In the combination treatment group, SQ-28603 was administered 30 min after the bolus injection and start of infusion of SR 47436 (BMS-186295).

434. It can be seen that the effect on preload and afterload of the ARB + NEPi is greater than of either alone. Neither side attached much importance to the heart rate.

435. Figure 4 brings in the bradykinin receptor antagonist (Hoe 140) and the ACEi (enalaprilat):

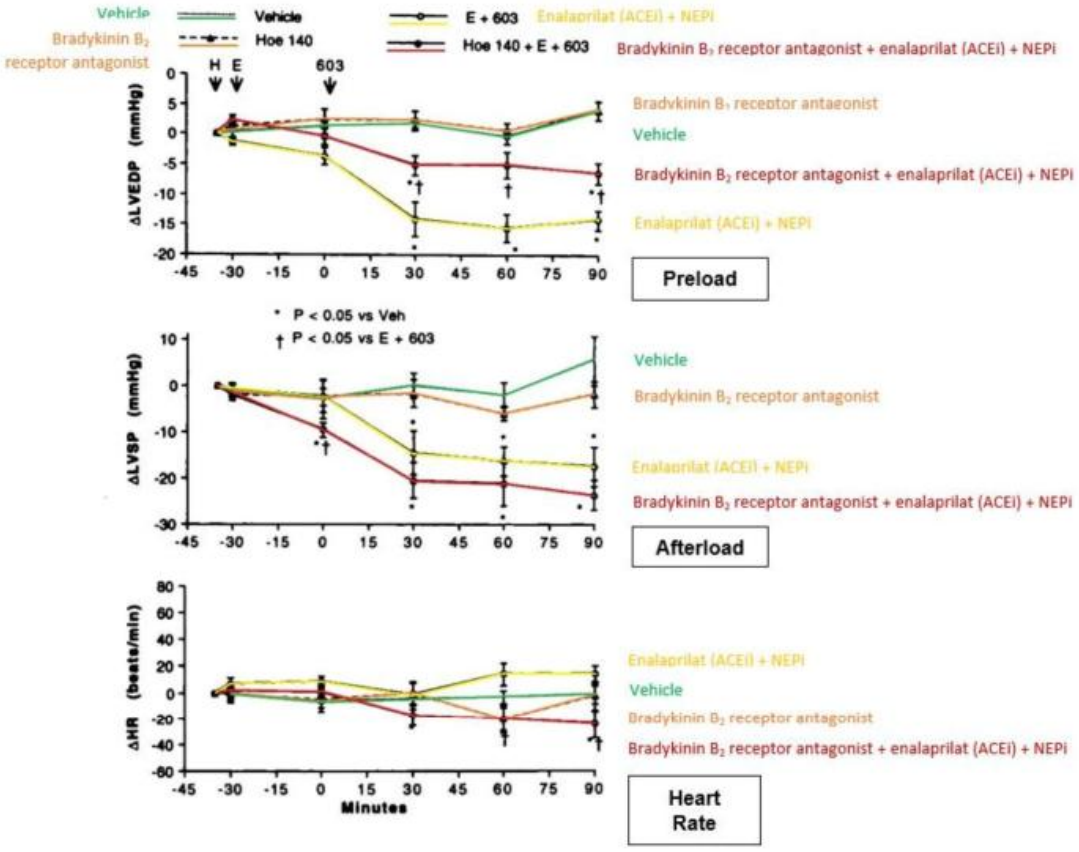


Fig. 4. Cardiovascular changes in conscious cardiomyopathic hamsters after the administration of vehicle (0.84% $NaHCO_3$), Hoe 140 (H, 100 μmol/kg, i.v.), the combination of enalaprilat (E, 30 μmol/kg, i.v.) and SQ-28603 (603, 30 μmol/kg, i.v.), or the combination of Hoe 140 plus enalaprilat and SQ-28603 (same doses as above). Arrows indicate times of administration of compounds.

436. Various combinations are used. In the top, preload chart the greatest effect is found with ACEi and NEPi, but this is significantly blunted with the addition of the Hoe 140. By contrast, in the middle, afterload chart the ACEi + NEPi combination still shows a bigger effect than either agent alone, but the addition of the Hoe 140 does not make any difference (the bottom, red line looks lower but the error bars overlap).

437. Moving on, in Figure 5 the authors test whether the addition of Hoe 140 to the ARB + NEPi combination makes a difference:

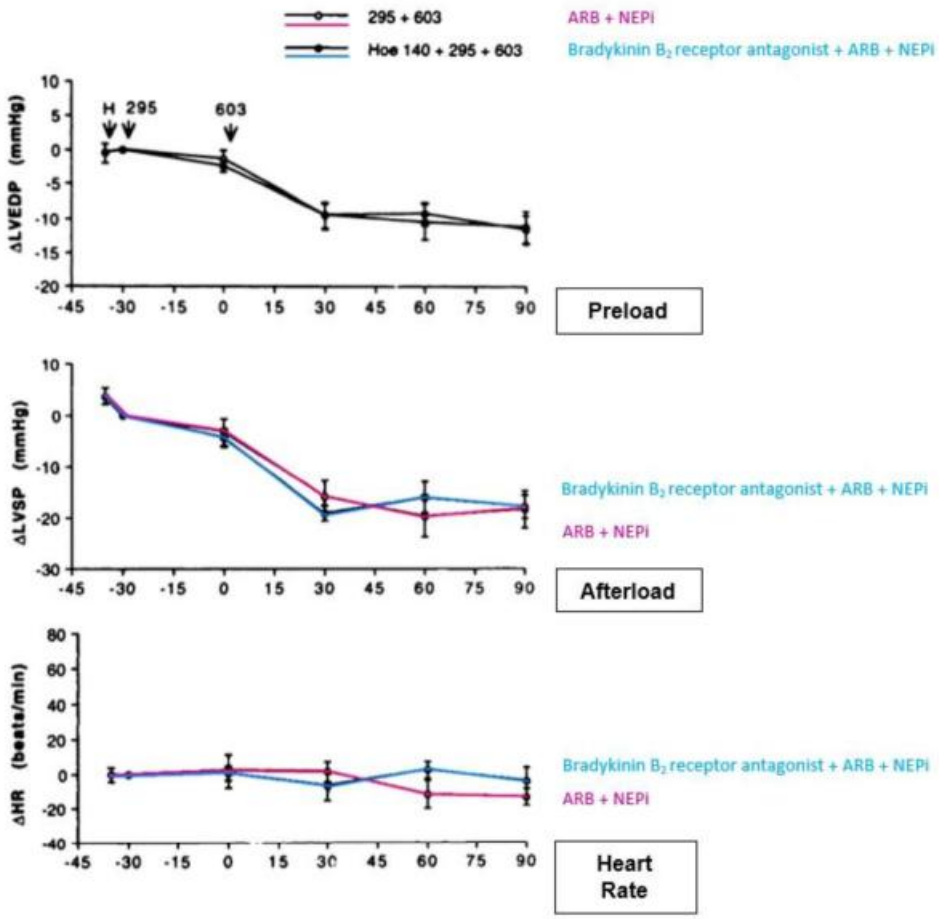


Fig. 5. Cardiovascular changes in conscious cardiomyopathic hamsters after the administration of the combination of SQ-28603 and SR 47436 (BMS-186295) or the combination of Hoe 140 plus SR 47436 (BMS-186295) and SQ-28603. The results from the combination of SQ-28603 and SR 47436 (BMS-186295) are the same as those shown in figure 3. SQ-28603 (603) was administered as an i.v. bolus at 30 μmol/kg. SR 47436 (BMS-186295) (295) was administered at 30 μmol/kg, i.v. followed by a continuous i.v. infusion at 1 μmol/kg/min. Hoe 140 (H) was administered as an i.v. bolus at 100 μg/kg. Arrows indicate times of administration of compounds.

438. And it can be seen that there was no difference. Prof Wilkinson said that this showed that the ARB + NEPi combination obtained its effect from inhibition of the AT1 receptor and the inhibition of NEP, and not from bradykinin potentiation.

439. Lastly, Figure 6:

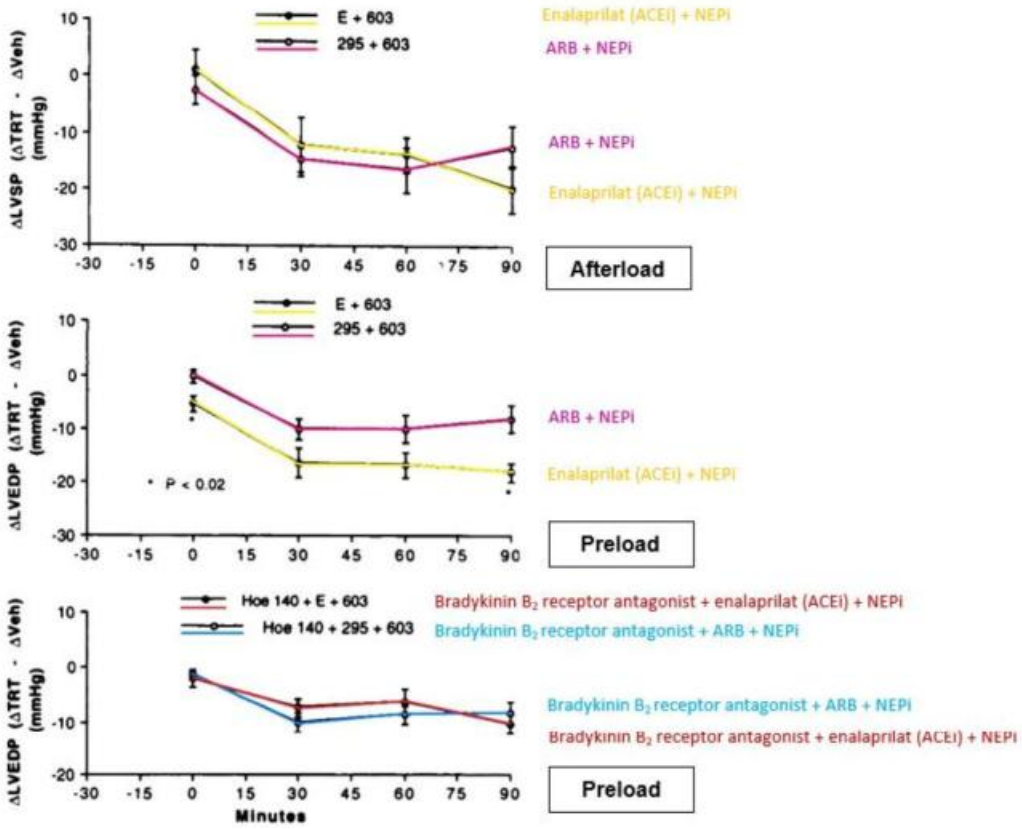


Fig. 6. Cardiovascular changes (minus vehicle effects) in conscious cardiomyopathic hamsters after the administration of the combination of enalaprilat (E, 30 μmol/kg, i.v.) and SQ-28603 (603, 30 μmol/kg, i.v.) or the combination of SQ-28603 (603, 30 μmol/kg, i.v.) and SR 47436 (BMS-186295) (295, 30 μmol/kg, i.v. + 1 μmol/kg/min, i.v.). The changes were determined from the results shown in figures 3 and 4. The bottom graph shows the changes (minus vehicle effects) in LVEDP in conscious cardiomyopathic hamsters receiving Hoe 140 in addition to the treatments indicated above; these changes were determined from the results in figures 4 and 5.

440. This shows several things. The top and middle charts compare the ARB + NEPi combination with the ACEi + NEPi combination in afterload and then preload (as Prof Wilkinson pointed out, this is in the reverse order from Figures 3 to 5). In the preload the ACEi + NEPi combination achieves a greater effect. The difference disappears when the Hoe 140 bradykinin receptor antagonist is added (bottom chart), which Prof Wilkinson said would be expected because the additional bradykinin potentiating effect of the ACEi is blunted. There is no material difference between the combinations in the afterload (top chart).

441. The authors then come on to discuss their results:

Discussion

> The findings demonstrated that in hamsters with compensated heart failure, Ang II receptor blockade acted synergistically with NEP-I to reduce cardiac preload and afterload. This interaction was similar to that previously observed with concurrent ACE-I and NEP-I in this

model and suggests that repression of Ang II is an important factor contributing to the acute synergistic effects of dual inhibition of ACE and NEP. The results also showed that blockade of bradykinin B_2 receptors blunted the synergistic effects of NEP-I and ACE-I on cardiac preload, but not on afterload, suggesting that, to some extent, potentiation of bradykinin is another contributing factor.

…

[Later, in the following paragraph:]

However, the combination of Ang II blockade and NEP-I produced significant reductions in LVEDP and LVSP that were greater than those produced by either treatment alone. These synergistic effects were similar to those observed previously with the combination of ACE-I and NEP-I. Together, the results suggest that attenuation of the formation of Ang II is an important factor contributing to the interaction of concurrent ACE inhibition and NEP inhibition in cardiomyopathic hamsters.

….

Hoe 140 did not alter the preload and afterload responses to the combination of SQ-28603 and SR 47436 (BMS-186295). Hence, potentiation of bradykinin did not appear to be a factor in the acute synergistic effects of the combination of NEP-I and Ang II receptor blockade. This suggests that NEP-I alone was not sufficient to potentiate bradykinin in this model, at least to the extent that it would interact with other vasoactive agents altered by this treatment. These results are consistent with findings in rat isolated, perfused mesenteric arteries showing that ACE-I potentiated the vasodilator effects of bradykinin, whereas NEP-I did not affect the response (Salgado *et al.*, 1992). However, although NEP-I may not have potentiated bradykinin enough for it to exert an effect during combined treatment with Ang II receptor blockade, it is possible that NEP-I could have protected bradykinin to the extent that an additive or synergistic effect of bradykinin activity could have occurred during the combined treatment with ACE-I. For instance, although the major bradykinin-degrading activity observed in intact cultured human umbilical vein endothelial cells could be attributed to ACE, nearly 20% of the activity was inhibited by phosphoramidon, indicating a significant contribution of NEP (Graf *et al.*, 1992). NEP-I also partially blocked the metabolism of bradykinin by a particulate fraction of rabbit endothelial cells of venous origin (Llorens-Cortes *et al.*, 1992). Therefore, the bradykinin potentiating effects on preload reduction observed with dual NEP-I/ACE-I in the cardiomyopathic hamsters could have been due to ACE-I alone or the combined effects of ACE-I and NEP-I.

It is interesting that bradykinin potentiation contributed to the decrease in preload but not to the decrease in afterload after dual

> metalloprotease inhibition in the cardiomyopathic hamsters. The hemodynamic events that could account for the decrease in LVEDP include: pooling of blood away from the heart due to peripheral venodilation; decreased blood volume via a fluid shift across the capillaries or via urinary fluid loss and altered left ventricular performance due to the reduction in afterload, an increase in contractility or change in diastolic function.

442. These are discussions about what has been observed and possible explanations. The authors do not claim to have a complete understanding, particularly about the differences between preload and afterload. Similarly, the authors continue to discuss possible explanations in the next column:

> If NEP-I protects CNP from inactivation in vivo, an interaction of CNP, bradykinin and decreased Ang II may have produced venodilation and a decrease in cardiac reload. Bradykinin is a potent vasodilator on both the arterial and venous sides of the circulation (Regoli and Barabé, 1980; Bönner *et al.*, 1990; Bönner *et al.*, 1992; Dachman *et al.*, 1993), and thus has the potential to decrease peripheral vascular resistance as well as to decrease venous return via pooling of blood in peripheral capacitance vessels.

443. And likewise in the following column:

> NEP-I acted synergistically with both ACE-I and Ang II blockade to reduce LVSP. Combined NEP-I/ACE-I was previously shown to reduce peripheral vascular resistance and increase cardiac output (Trippodo *et al.*, 1993). A similar hemodynamic profile of decreased vascular resistance was likely associated with reduced LVSP in this present study, although whether this is the case with NEP-I/Ang II blockade needs to be determined. Inasmuch as bradykinin was not an important factor contributing to the reduction in LVSP after either combination treatment, other factors that could have interacted with attenuated Ang II activity include potentiation of the natriuretic peptides, substance P and possibly other peptides protected by NEP-I.
>
> ….
>
> Finally, as mentioned above, the vasodilator actions of substance P (Mione *et al.*, 1990), which could be protected by both ACE-I and NEP-I (Skidgel *et al.*, 1984; Yokosawa *et al.*, 1985; Erdos and Skidgel, 1989) may have played a role. Evaluation of the importance of the natriuretic peptides, substance P and other vasoactive factors in the hemodynamic effects of dual metalloprotease inhibition will require further studies.
>
> Bradykinin potentiation appears to be involved in the synergism between NEP-I and ACE-I but not between NEP-I and Ang II receptor blockade. Therefore, we hypothesized that because of this additional influence of bradykinin potentiation, preload would be decreased to a greater extent after NEP-I/ACE-I than after NEP-I/Ang II blockade.

> However, a direct comparison of NEP-I/ACE-I with NEP-I/Ang II blockade using the data in this study would not be valid, because different vehicles were used in the two combination therapies, and small vehicle effects could obscure significant differences. Therefore, to make such a comparison without the influence of "vehicle effects," the changes due to vehicle alone were subtracted from the changes due to the therapies plus vehicle. This analysis showed that the decreases in preload were greater in the animals receiving NEP-I/ACE-I than in those receiving NEP-I/Ang II blockade. No such differences were observed in the changes in afterload and is consistent with the observation that bradykinin blockade did not alter the decrease in LVSP after NEP-I/ACE-I. This analysis was carried a step further by comparing the changes in preload in animals receiving the bradykinin antagonist in addition to the combined therapies in question. Inasmuch as the influence of bradykinin potentiation would be eliminated, there should be no differences in the changes in preload between these two groups. Indeed, consistent with the above hypothesis, the decreases in LVEDP were not significantly different between the two groups receiving the bradykinin antagonist plus NEP-I/ACE-I and those receiving the bradykinin antagonist plus NEP-I/Ang II blockade. Hence, together the results are consistent with the viewpoint that because dual NEP-I/ACE-I potentiates bradykinin in hamsters with heart failure, this form of therapy should produce a greater acute reduction in cardiac preload than the combination of NEP-I and Ang II receptor blockade which is not associated with bradykinin potentiation.

444. This is consistent with Prof Wilkinson's reasoning; it proposes a greater acute reduction in preload with the NEPi/ACEi combination explained by the difference in bradykinin potentiation, but only as a possibility.

445. The eventual and high-level conclusion is as follows:

> The bradykinin-mediated enhanced effect of combined NEP-I/ACE-I to reduce cardiac preload could improve the beneficial effects of ACE-I in the treatment of heart failure.

446. This does relate to treatment of heart failure; it is postulated merely as a possibility and it relates to a NEPi/ACEi combination, not the NEPi/ARB combination.

Obviousness

447. As with Ksander, the parties did not explicitly structure their submissions by reference to the *Pozzoli* analysis, but I have identified the skilled persons and the relevant CGK above. Trippodo discloses an ARB/NEPi combination, so to get to the claim of the Patent, Accord has to show that it would be obvious to make a further such combination in which the ARB was valsartan and the NEPi was sacubitril. As discussed above, because claim 1 of the Patent is to the combination as such (as a pharmaceutical composition, but Novartis took no point on that separately) it is not necessary for Accord to show that it was

obvious to use the combination successfully in the treatment of any condition. It would be enough to show that it was obvious to make it to test in an animal model, in particular. Since the motivation to do that would be as a first stepping stone towards potential use in treatment, however, the attractiveness and prospects as therapy are indirectly relevant, but the commitment of resources that the skilled person would be considering would be those involved in animal experiments, and while by no means trivial they would be a lot less than clinical trials in humans.

448. Accord's obviousness case over Trippodo falls broadly into two parts: first, the decision to progress an ARB/NEPi combination, and second, the decision to use sacubitril as the NEPi. The second decision depends on a literature search having made the first. In relation to the choice of valsartan as the ARB, Accord rather took it for granted on the basis that there was a recognised class effect for ARBs and that valsartan would be at least one routine choice of a known ARB. Had all the other parts of Accord's case fallen into place I would not have found the choice of valsartan as separately inventive, for those reasons, so I will say no more about it.

449. Again as with Ksander, the parties sequenced their written closing submissions on Trippodo to deal with obviousness to the hypertension skilled person first, and then heart failure. This is rather less logical than in relation to Ksander because the animal model used is a heart failure model, but I will follow the same course for convenience in relation to the main argument (I will deal with the literature search in one go, for both skilled persons).

Hypertension - Accord's case

450. Accord's case begins with the statement at the start of the Discussion, quoted above that "… Ang II receptor blockade acted synergistically with NEP-I to reduce cardiac preload and afterload." Accord points out that it is an explicit disclosure of an ARB/NEPi combination and its synergistic effect.

451. Next, Accord says that the statement would be understood to be made at the class level and to apply to other ARBs and NEPis.

452. Accord also points out that the ARB/NEPi combination is shown in Trippodo to be an improvement compared with either monotherapy, and that the ARB/NEPi combination improved afterload to a similar degree as the ACE/NEPi combination.

453. Accord recognised that the model used was a heart failure model and not a hypertension model, and that LVSP and LVEDP (afterload/preload) are not parameters used in hypertension, but argued that:

    i) The skilled person in hypertension would understand the relevance of LVSP to systolic blood pressure;

    ii) There were some hypertension papers which used cardiomyopathic hamsters in assessing omapatrilat;

iii) Prof Webb had said in his written evidence that if the skilled person had to take Trippodo forward they would repeat the work using a hypertension animal model;

iv) Prof Webb said in relation to Darrow (which proposes the ARB/NEPi combination but without data) that the skilled person in hypertension would consider it reasonable that the combination would be useful in therapy;

v) An ARB/NEPi combination was reasonable based on the CGK because ARBs were used in hypertension and NEPis had been proposed, it being understood that their mixed results were down to compensatory mechanisms;

vi) Prof Wilkinson said it was unrealistic to say that the data from Trippodo's model would not provoke interest as to use in hypertension;

vii) ARBs had better side effect profiles than ACEis.

Hypertension – Novartis' case

454. Novartis responded with the following main points:

i) Trippodo is not in a journal of interest to the skilled hypertension person. I have rejected this already.

ii) Trippodo is concerned with working out what *inhibitory* mechanisms make ACEi/NEPi combinations work, and ARBs are not inhibitors at all but receptor blockers;

iii) In Trippodo the ARB is not put forward as a therapy, even potentially, but only as one of two "tools" or "probes" (the other being the bradykinin receptor antagonist);

iv) The model used is a heart failure model not a hypertension model, and preload and (especially) afterload are not relevant parameters in hypertension;

v) Even looking at the ARB/NEPi combination it did not do better in preload;

vi) Heart failure models were not predictive of efficacy in hypertension, as (it was submitted) Prof Wilkinson accepted;

vii) The effect on blood pressure depended heavily on the animal model used;

viii) ACEis would be thought to be better than ARBs because they also potentiated bradykinin, whose importance is stressed in the discussion in Trippodo and shown by the results;

ix) An ACEi/NEPi combination would also be topical and promising because of omapatrilat (also from BMS), and indeed the skilled person in hypertension would in any event do nothing with Trippodo until the omapatrilat phase III trials were reported;

x) There was a wide variety of experiments that could be done to progress Trippodo if the skilled person chose to do that, including repeating the work, doing the work in a hypertension animal model, testing other ACEi/NEPi combinations, vasopeptidase inhibitors, and more, and all this would be "a lengthy and arduous process";

xi) NEPis had been a failure as a monotherapy in hypertension, there was no class effect for them, and they would be thought to be variable, with no comparative data available (I think this is more relevant to the choice of sacubitril, were one to get that far);

xii) Trippodo was read by others in the field but in the years from its publication to the Priority Date no one progressed it in the way that Accord said was obvious.

Hypertension - discussion

455. Although not all of Novartis' points are strong, most of them are and I find that by a considerable margin the Accord obviousness attack in this first part (the decision to progress an ARB/NEPi combination) fails.

456. Although I think the skilled person in hypertension would as a matter of fact and law take Trippodo seriously and read it with interest, I accept what I regard as Novartis' central point, that the paper is not even tangentially about the idea of using an ARB/NEPi combination in therapy for hypertension. The description of the ARB as a tool (or "probe", Trippodo's word) is entirely apt. The point about inhibitors/blockers is supportive of this.

457. Further, the skilled person in hypertension would not draw any encouragement from a heart failure model. Accord's points about LVSP possibly being seen to be relevant to hypertension, and the fact that the model was occasionally cited in relation to hypertension were unconvincing and smacked of hindsight (as did the attack generally).

458. In addition, the data are mixed and the ARB/NEPi combination does less well in some respects than the ACEi/NEPi. I appreciate that Prof Wilkinson put forward some possible explanations for why this might be, but in my view the skilled person would still see the difference, since Trippodo expressly calls it out, and even if they thought of Prof Wilkinson's explanations, which I think is not very likely, they would regard them as no more than possible. They would not dispel the question raised.

459. Then, Trippodo itself does not offer a clear or certain explanation for the results – there is no particular reason why it should have – but proposes some possible matters for further study.

460. If the skilled person in hypertension was interested in progressing Trippodo, then I agree they would have a range of options of which ARB/NEPis would be just one, and it is also important that ACEi/NEPis had better results, fitted with the bradykinin theory presented by Trippodo, and were consistent with the way of thinking in the art represented by the dual ACE/NEPi effects of the vasopeptidase idea, represented by omapatrilat. I recognise that as monotherapies in hypertension ARBs and ACEis were thought to have equivalent efficacy, but that does not answer these points. As with the argument from Ksander, however, I reject Novartis' more extreme argument that the skilled person would simply do nothing until the omapatrilat trial results came out.

461. The range of options and uncertainty of result have some weight but are not central to my decision. I was not impressed by Novartis' reliance on the "lengthy and arduous process" since it did not seem qualitatively different from any work in this field.

462. I agree with Accord that if the skilled person decided to progress Trippodo then they would repeat it in a more relevant animal model and that could be done. Prof Webb agreed to that very limited extent, but it is not a positive argument in favour of obviousness, just something that might be done.

463. I reject the analogy that Accord drew with Darrow. They are just very different teachings, but anyway and in particular Darrow explicitly proposes the ARB/NEPi combination for therapy, whereas the tool/probe point differentiates Trippodo in that respect. Trippodo also has the results and theory which point away from ARB/NEPi and towards ACEi/NEPi.

464. Once one thinks of the ARB/NEPi combination it is possible to construct an argument that the ARB part would make sense because already used for hypertension and that the relative failure of NEPis could be explained and might be remedied in the combination, but the CGK had not recognised the notion at all. To my mind Accord's reliance on this point runs it right into Novartis' argument that no one had articulated the idea, let alone tried it.

465. The better side effect profiles of ARBs has some limited weight, but not much because the prior question for the skilled person would be efficacy, and the relative attractiveness of an ARB/NEPi combination in this respect cannot come into play until it was obvious to consider as a therapy in the first place, which I do not think it was. In addition, it was not certain that an ARB/NEPi combination would not cause a cough, and Prof Webb gave written evidence which I do not think was challenged that potentiation of bradykinin by a NEPi with an ARB had the potential to also cause a cough.

466. As to the experts' evidence, Prof Wilkinson was extremely clear in his explanation of what Trippodo discloses, and I have used his account heavily above. However – and this is no criticism of him personally - I think his analysis of what the skilled person in hypertension would take from Trippodo was characterised by a clarity of thinking and perception to the point of invention and was probably affected by hindsight, or at least consistent with its involvement. I prefer Prof Webb's approach.

467. Finally, Accord said that given Trippodo discloses the ARB/NEPi combination, any alleged reason to favour the ACEi/NEPi combination "runs into a *Pozzoli* issue", by which Accord meant that the Patent does not provide a reason to disfavour ARB/NEPis. I thought this was a very convoluted and unpersuasive sort of "lion in the path" argument, but anyway Novartis' argument was not one of a positive existing prejudice against using ARB/NEPi combinations, it was that they were not obvious in the first place from Trippodo, a quite different thing.

468. As to the secondary evidence argument that Trippodo was not acted on by BMS or others in the field in the way said to be obvious, it came in only in oral evidence and I do not think there was sufficient exploration of it for me to attach weight to it.

Heart failure – Accord's case

469. Accord described the "starting point" for the argument in heart failure as similar to that for hypertension: ACEis and ARBs were both in clinical use, NEPis had been proposed, omapatrilat had shown promise and thus demonstrated that NEPis could be used successfully along with blocking the RAAS, and the Trippodo work showed positive haemodynamic results in a relevant animal model both for ACEi/NEPi and ARB/NEPi combinations.

470. Accord said that the cardiomyopathic hamster model in Trippodo was a standard one in heart failure and while not necessarily directly predictive of therapeutic effect in humans it showed target engagement.

471. Accord also said that Prof Clark accepted that for the results shown in Trippodo what mattered was that compounds had effect as ARBs and as NEPis, "i.e. a class effect". I do not agree with Accord's characterisation of the oral evidence in question, which (among other transcript references in the closings) I have re-read. In the first passage of evidence to which I was referred (T4/591) he was explaining for what the compounds were used in the "mechanistic study" being done, and rejecting the idea that the ARB and the ACEi were somehow equivalent; the passage strongly supports Novartis' tool/probe point. In the second passage (T4/610) he was just saying that other ARBs and NEPis could be used if good ones could be identified. It was not put to him, so he did not accept, that there was a class effect.

472. Accord relied on Prof Clark's acceptance that synergism was shown for the ARB/NEPi and for the ACEi/NEPi combinations. He did accept this, and I will bear it in mind, but it does not alter their relative qualities as described above.

473. In terms of Prof Clark's evidence on the haemodynamic results in Trippodo, Accord said there was a tension between his saying that the skilled person in heart failure would not be interested in them at all, and that they would be more interested in the ACEi/NEPi combination because it had a greater effect than the ARB/NEPi combination. I agree that there was such a tension and my view is that the skilled person would be interested in the haemodynamic results because although not strongly predictive the model showed relevant

target engagement. This leaves, however, the point that the ACEi/NEPi combination fared better.

474. Accord also fairly pointed out that Prof Clark put a lot of emphasis on the skilled person in heart failure progressing only the best route, rather than asking which route(s) were obvious. I agree with this, too, but feel able to allow for it.

475. Accord once more relied on the more favourable side effect profile of ARBs. Prof Clark accepted the difference in terms of side effects but said it would not be a significant factor. Accord said that he provided no reasons, but I disagree. Throughout, Prof Clark was clear that there was a very strong leaning in favour of ACEis in heart failure because they had worked so well, and said that in all drug development it was recognised that sometimes smaller patient sub-populations cannot be served at the same time as obtaining very good efficacy for the greater majority of patients. Prof Clark also said that he did not agree with the chain of reasoning towards to the conclusion that Trippodo would lead its readers to think that an ARB/NEPi combination was a useful idea for patients unable to tolerate ACEis. He said it involved too many steps to be realistic.

Heart failure - Novartis' case

476. Novartis also repeated many of the same arguments as from hypertension. I will just focus on some important additions/differences.

477. First, it said that the skilled person in heart failure would still not have any interest in Trippodo because the model, while one of heart failure, had no useful predictive effects and the haemodynamic parameters studied were not treatment goals. Prof Wilkinson agreed with this to some extent, but the model does show target engagement and I reject Novartis's argument on this point when taken to the extent that it would result in the skilled person in heart failure having no interest at all. The limitation of the model still has some relevance to prospects of success if it were decided to take the work forward.

478. Second, it said that if the skilled person did pay attention, the ACEi/NEPi combination came out better. This is correct, as I have already said in connection with the hypertension arguments.

479. Third it said that Trippodo itself promoted the ACEi/NEPi combination and used the ARB just as a tool. This is the same argument as in relation to hypertension and Prof Clark strongly supported it.

Heart failure – discussion

480. Accord's case in relation to heart failure is slightly better than in relation to hypertension, essentially because the article is aimed at heart failure, and at least the model used is recognised as one for heart failure (and I reject the attempts by Novartis entirely to sideline it).

481. The other notable differences are in the use of ACEis and ARBs in clinical practice in heart failure. This cuts both ways because I accept Prof Clark's evidence about the strong attachment to ACEis given their great success, which has to be balanced against the possible need for options in the case of patients intolerant to ACEis, but in any case as an issue it is downstream of the question of whether the ARB/NEPi combination for therapy was one which would be obvious to take forward from Trippodo, and I conclude it would not, essentially for the parallel reasons given in relation to hypertension, and especially Trippodo's lack of teaching to use ARB/NEPi combinations for therapy, the document's focus on ACEi/NEPis for heart failure, the tool/probe point, the uncertainty about the biological processes at work, and the fact that in any event the haemodynamic results are less good for ARB/NEPis.

482. I assess Prof Wilkinson's overall evidence on Trippodo for heart failure in basically the same way as in relation to hypertension, allowing for the fact that he was on ground with which he was relatively less familiar. Despite rejecting one or two facets of it identified above, and allowing for the fact that he has a much stronger clinical emphasis and less experience with research, I found Prof Clark's evidence more practical and robust and a better guide to the thinking of the ordinary skilled person in the field.

483. I also reject Accord's argument in relation to heart failure.

Getting to sacubitril – the literature search

484. As I have said, I think the skilled person in either heart failure or hypertension would regard the available ARBs as essentially interchangeable if they were intending to pursue Trippodo and I would not have found the choice of valsartan inventive, had Accord's obviousness case otherwise succeeded in respect of either skilled person. The same does not apply to the NEPi.

485. It is Accord's case that the skilled person might choose to pursue Trippodo using the very same ARB and NEPi as the authors used, if they were available. I agree that that would be one obvious way to go. I also agree with Accord that the skilled person might want to choose other compounds from the same respective classes for mundane reasons such as ease of access. So I would reject any argument by Novartis that the skilled person would only consider using Trippodo's own compounds, but I do not think it argued that.

486. Accord argues that the skilled person in either field seeking an alternative NEPi would, without invention, do a literature search. At that very high level I agree. Prof Wilkinson did one and gave evidence about it. Novartis submitted that he did not do it until told to by Accord's solicitors, but that is not quite fair: Prof Wilkinson was told early in his work on the case not to do *any* searches without prior discussion. This is entirely normal and necessary to protect the process of sequential unmasking as much as possible. Later, when the question of finding alternative NEPis to that used in Trippodo came up, he said the skilled person would do a literature search, adding that PubMed would be used, and suggesting search terms. He then did the search.

487. Novartis mounted a sustained attack on the search that was done. The main points included:

    i) Prof Wilkinson's search being ranked by "best match" and not chronologically, when the best match feature did not exist at the Priority Date;

    ii) Prof Wilkinson's being told to review only the first 20 results;

    iii) Prof Wilkinson's results might not accurately reflect what would have been returned at the Priority Date because it is not known if the phrase index existed in 2002 or what its contents were if it did;

    iv) Accordingly, it is possible far more results would have been returned;

    v) The skilled person might have used different search terms or a different database and if so then different results would have been produced, with unknown significance;

    vi) The search results omitted important review articles, an omission which the skilled person would have noticed and acted upon by refining the search, again with unknown consequences;

    vii) Other key papers including in particular one by Nawarskas et al. from 2001, which discussed multiple NEP inhibitors, were missed;

    viii) Ksander would not score particularly highly even if in a list, and there were other more attractive options, notably candoxatril.

488. As to other options, Prof Webb identified four levels of data he would be interested in, starting with human data, and said that Ksander was at the lowest level (from his perspective this was partly because it does not have data in an animal hypertension model). Prof Wilkinson accepted that there were other, potentially more interesting candidates than Ksander, even in the top 20.

489. On the other hand, the evidence was that the much larger number of papers than 20 obtained in Prof Wilkinson's search (totalling about 270) would not be unduly onerous to review, by reading just their titles and abstracts and on doing so the skilled person would see from its title that Ksander could provide an alternative NEPi. On reading the paper further, the skilled person would see the focus on compounds 21a/19a and the good results such as the IC50.

490. My assessment is as follows:

    i) As mentioned, it would not be inventive in and of itself, if the decision were taken to progress Trippodo by exploring the ARB/NEPi combination, to use alternatives and to do some kind of literature search;

    ii) Novartis' complaints about uncertainties of what exactly would have resulted at the Priority Date were overdone. With the large resources

given to this case Novartis could have tried to show that there was some material difference. Although the burden of proof is ultimately on Accord, Novartis needed to substantiate things where it could and not just point to general doubts;

iii) On the other hand the missing review papers and the omission of papers like Nawarskas cast real doubt on the completeness and robustness of the exercise;

iv) The decision to limit Prof Wilkinson to the first 20 results meant that he was not at that stage replicating what the skilled person would do, but in itself was inconsequential because of the evidence that all 270-odd could be reviewed;

v) Prof Webb's points about the different kinds of data that would be desirable had force and Ksander would score relatively low on that scale, but relatively well in relation to the pharmacological results it contains;

vi) On the balance of probabilities, a reasonable search would throw up a relatively large number of results, probably not dissimilar to Prof Wilkinson's original search, which could be reviewed with significant but not overwhelming effort, and would include Ksander;

vii) However the search would also include an unknown but significant number of other choices which were more attractive than Ksander, mainly because they would include blood pressure lowering results in animals.

491. I have rejected Accord's argument that there was a class effect for NEPis. So it is not good enough for Accord to show that a literature search would include Ksander among others so that sacubitril was an uninventive choice among some unknown number of NEPis any one of which would do. Accord would need to show that sacubitril was actually, on the facts, a "classically" obvious choice as a NEPi for tangible, specific reasons. The evidence is not good enough to do that.

Collocation – law

492. The parties were agreed that the relevant legal principles are to be found in the decision of the House of Lords in *Sabaf v MFI* [2005] RPC 10 ("*Sabaf*"), and in the decision of the Court of Appeal in *Illumina CA* at [157]-[172].

493. In *Sabaf* the House of Lords considered the domestic cases on collocation and the EPO's Guidelines (which had not materially changed by the time of *Illumina CA*), and concluded that the key question was whether the claim is concerned with a single invention or not. This was pithily summarised in *Illumina CA* at [169] as being:

> "… primarily a question of what the patent disclosed, read in the light of common general knowledge, but that evidence was admissible either

> to show that an interaction between features claimed in the specification did not occur or to show that an interaction not spelt out by the specification would be apparent to the skilled person."

494. In *Illumina CA* the invention was a single molecule, but the Court of Appeal accepted (as the trial judge had said and the patentee did not dispute), or at least assumed, that the principle was a general one, potentially applicable to chemical molecules, and not limited to mechanical inventions.

495. The critical line of reasoning of the judge, with which the Court of Appeal agreed (at [173]), was that although the molecules claimed were made of building blocks, the skilled team would know from CGK that those blocks were capable of interacting adversely with each other in various unpredictable ways, and that the patent in suit showed that they did not, so the molecules as a whole were useful. That was a technical contribution not made by either of the pieces of prior art which disclosed the individual blocks, and there was a single invention.

Collocation – assessment

496. Accord submitted that valsartan blocks the AT1 receptor and sacubitril inhibits NEP, that these are independent of each other and do the same thing with or without each other.

497. It accepted, however, that sacubitril, as a NEPi, causes compensatory activation of the RAAS, which valsartan makes up for.

498. Accord rightly anticipated that Novartis would rely on this. It said however, that there was an important distinction between (Accord's emphasis):

> "the (i) **function** of valsartan and of sacubitril (i.e. blocking angiotensin II and inhibiting NEP) versus (ii) the **effect** of valsartan and of sacubitril (i.e. their contribution to the therapeutic effect)."

499. It pointed to the interaction pleaded by Novartis:

> "The interaction or interrelationship relied upon is the achievement by the combination of valsartan and sacubitril of a greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotion of less angioedema than is seen with the administration of a vasopeptidase inhibitor alone."

500. And it said this was not an interaction between the functions of the two drugs but about their contribution to the overall therapeutic effect. It also said that a therapeutic effect being merely greater than either drug alone could cover a situation where each independently contributed but the combination was merely equal to the sum of the two effects, or even less.

501. Novartis' answer was that both valsartan and sacubitril act on the same system (the RAAS), and that at a minimum, as in *Illumina HC* and *Illumina CA*, there was the possibility of an interaction. It pointed out that the

interaction was positively part of Accord's obviousness case, which I think is correct.

502. Novartis also submitted that in the case of any combination or even mere co-administration of different drugs, there is always the possibility of interaction that needs to be considered. I think that is going too far and effectively moving back to the proposition, rejected in *Illumina CA,* that collocation only applies to some fields of science.

503. Overall, however, I think that Novartis is right in substance. Its argument paid relatively little attention to the specification of the Patent, but that too supports it. In particular paragraph [0006] says that it cannot just be assumed that putting together two drugs with different mechanisms of action will lead to combinations with advantageous effects (which was also CGK), [0016] (whose counterpart in the Application at page 7 I considered in detail in connection with plausibility) says that a combination of valsartan and a NEPi has greater effects than either alone, and the experiments are directed to showing that empirically.

504. I therefore conclude that there is no collocation objection because the invention involves the proposition, empirically demonstrated, that valsartan and sacubitril interact positively and not adversely, which would not have been known before. This is a direct parallel with the situation in *Illumina CA*. There is no direct, quantitative demonstration in the Patent of true synergy in the sense of x effect for valsartan, y effect for sacubitril and a combined effect greater than x + y but I do not think that is necessary (and it was not present in *Illumina*). Dispelling the uncertainty that there might be negative interaction and showing that the combination "works" is enough for this purpose. I accept the qualitative evidence of Prof Webb that the skilled person would think that the sacubitril is "unlocked" by the valsartan.

LACK OF TECHNICAL CONTRIBUTION

505. Accord asserts that the Patent is invalid because it lacks any technical contribution over Trippodo (discussed above), or over Darrow.

506. If, contrary to the finding I have made, the Patent was invalid because of a lack of plausibility, then this attack would not be necessary. Likewise if the Patent was classically obvious over Trippodo. So for practical purposes I will address this attack on the basis that Accord is wrong about plausibility, which means that the Application (and hence the Patent) contain a basis to think that the specific combination of valsartan and sacubitril has a beneficial effect in hypertension, and wrong about obviousness from Trippodo, which means that the choice of sacubitril was not classically obvious, and that there was no class effect when combining an ARB with a NEPi for hypertension.

Lack of technical contribution - law

507. I can take the legal principles directly from *Dapagliflozin CA*:

THE LAW CONCERNING ARBITRARY SELECTIONS

38. The judge set this out at [39]-[59]. Save in one respect, there is no dispute as to the accuracy of that account, and so I can summarise it briefly. Making an arbitrary selection from the prior art is not inventive. The question is therefore what distinguishes an arbitrary selection from an inventive selection. The answer to that question is that an inventive selection makes a technical contribution to the art, whereas an arbitrary selection does not. The leading authority on this distinction is *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly & Co Ltd* [2009] EWCA Civ 1362, [2010] RPC 9 , in which this Court adopted the principles applied by the Boards of Appeal. The test established in that case was succinctly summarised by Floyd LJ in *Generics (UK) Ltd v Yeda Research & Development Co Ltd* [2013] EWCA Civ 925, [2013] Bus LR 1329 at [49 (4)]:

> "… a selection from the prior art which is purely arbitrary and cannot be justified by some useful technical property is likely to be held to be obvious because it does not make a real technical advance …"

39. This principle has found particular application where the application or patent claims a chemical compound selected from a genus of compounds disclosed in a prior document. It is not necessary to show that the prior document contains some pointer to the later claimed compound. (If there were such a pointer, the complaint of arbitrary selection would be unnecessary because the later compound would be obvious in the conventional sense.) In order to rebut the charge of arbitrary selection in such a case, the applicant or patentee must show that the claimed compound achieves what in *Dr Reddy's* Jacob LJ at [52] called "a real technical advance" and Lord Neuberger of Abbotsbury MR at [109] called "a particular technical result".

40. The judge summarised the law at [59] as follows:

> "Overall, I do not perceive any material difference between the case law of the EPO and the UK case law (which is to be expected, given that the intention of the Court of Appeal in *Dr Reddy's* was to adopt the EPO approach). The requirement is for the claimed invention to in fact constitute a technical advance and for the patent to disclose enough to make that technical advance plausible. If the patent claims a compound selected from a previously disclosed genus of compounds which are said to have a particular property, then that requirement is not satisfied if the compound does not in fact have some different or improved property compared to those previously individually disclosed (a new effect or an increase in an effect), or the patent does not make such improved property plausible."

508. Accord also relied on how the Court of Appeal then dealt with the attack on the facts of the case:

GROUNDS 7-8: ARBITRARY SELECTION

137. It must be assumed for the purposes of considering grounds 7 and 8 that at least claim 2 of the Patent is free from objection on plausibility grounds.

138. Ground 7 is that the judge was wrong in his approach to the issue of arbitrary selection. Ground 8 is that the judge failed properly to assess the contribution of WO 128 when considering whether the Patent made a technical contribution. Although counsel for AstraZeneca argued these two grounds together, it is important to distinguish between them.

139. The starting point for ground 7 is the final sentence of [59]. For convenience I will set this out again:

> "If the patent claims a compound selected from a previously disclosed genus of compounds which are said to have a particular property, then that requirement is not satisfied if the compound does not in fact have some different or improved property compared to those previously individually disclosed (a new effect or an increase in an effect), or the patent does not make such improved property plausible."

140. AstraZeneca contends that this is wrong in law, and that the judge ought to have held that, where the prior art merely asserted that the genus had a given advantage or property without rendering it plausible, then a subsequent patent may make a technical contribution by making the same assertion in respect of a selected compound and rendering it plausible. The judge rejected this argument at [271], but AstraZeneca argues that he was in error. I disagree. As the case law discussed by the judge makes clear, a selection from the prior-disclosed genus is only inventive if the selection makes a technical contribution because the selected compound in fact has some useful property which means that the selection is a technical advance. Mere plausibility is not enough for this purpose."

509. To understand the context of what the Court of Appeal was dealing with, and saying, it is necessary to go back to the trial judgment. The facts were unusual: the relevant prior art, WO 128, contained, for material purposes, the same disclosure as the patent in suit, except that it did not individually mention dapagliflozin. Generics abandoned its case that it was classically obvious to get to dapagliflozin but said that it was a merely arbitrary selection from WO 128, within whose broader disclosure it was encompassed.

510. In support of its position, one of the things AZ said was that WO 128 did not make plausible that each compound within its disclosure had the relevant technical qualities (see [266]). The contributions that were relied on were explained at [268], and the judge's reasoning following on is also important for understanding:

268. The technical contributions relied upon by AZ at trial were, as explained earlier, that dapagliflozin was an SGLT2 inhibitor which reduced blood / plasma glucose *in vivo* (and so could be used as an experimental tool) and/or was useful in the treatment etc. of diabetes. But AZ did not advance a case that dapagliflozin was, in those regards, in fact any different in its properties to any of the other compounds of WO 128 (and in particular to the compound of Example 12).

269. For the reasons explained when considering the law above, in my judgment that means that the Patent does not make a technical contribution over WO 128. There is nothing in the Patent nor in the evidence at trial to indicate that dapagliflozin is anything other than an arbitrary selection from the genus of compounds disclosed by WO 128.

270. The argument advanced by AZ was that the Patent made it plausible that dapagliflozin was an SGLT2 inhibitor which reduced blood / plasma glucose in vivo and was useful to treat etc. diabetes, whereas that was not made plausible by WO 128. That, AZ submitted, taught the skilled person something new and so was a technical contribution.

271. In my judgment there is some sleight of hand going on here. A technical contribution needs to be both present in fact and made plausible by the specification (hence Birss J's questions in *Takeda v Roche* included "is it plausible?", "is it true?" and "is it a technical advance?" and Jacob LJ in *Dr Reddy's* said that one should ask whether the patentee had made a technical advance and provided sufficient justification for it to be credible). I do not see how making something plausible can in itself be a technical contribution. Indeed AZ did not plead a technical contribution consisting of making something plausible – it pleaded (correctly, in my judgment) actual properties of dapagliflozin as being technical contributions.

272. Even if this argument were a permissible one, in my judgment it does not work in this case. The parties were agreed that, in order for the arbitrary selection case to add anything to the plausibility case, it is necessary to assume that the Patent does make it plausible that dapagliflozin is an SGLT2 inhibitor which reduces blood / plasma glucose in vivo and/or is useful to treat etc. diabetes. That requires me to approach matters on the basis that the Patent would be understood as disclosing that dapagliflozin had been assayed and had generated an EC50 which meant that it would plausibly reduce blood / plasma glucose *in vivo* and/or be useful to treat etc. diabetes.

273. If that is so, then in my judgment WO 128 must also be understood as disclosing that compounds which it discloses had been assayed and had generated EC50s which meant that they would plausibly reduce blood / plasma glucose in vivo and/or be useful to treat etc. diabetes. Prof. Potter (whose view was that the skilled medicinal chemist reading the Patent would assume that dapagliflozin had been tested) said this:

> "While the Medicinal Chemist would not be able to identify which of the compounds encompassed by WO 128 were tested in the assay, they would not doubt that the assay had in fact been used in relation to some of them. While no biological data are provided, it would be a reasonable assumption that at least the Examples – for each of which characterisation data are provided, indicating that they were synthesised – would have been tested for activity using this assay."
>
> 274. Therefore, on this approach the skilled team would understand that the compound of Example 12 of WO 128 (amongst others) had been tested and produced an EC50 which meant that it would plausibly reduce blood / plasma glucose *in vivo* and/or be useful to treat etc. diabetes."

511. Thus the insuperable problem for the patentee was that because of the identical language, if the patent in suit was taken to mean that dapagliflozin had been tested, it followed that the same applied to the compounds in WO 128. One can therefore understand the conclusion that just naming dapagliflozin in the patent in suit was merely an arbitrary selection.

512. The Court of Appeal agreed with this (and so do I). Its judgment must be understood in this context. What the Court of Appeal said at [140] was in agreement with what the judge said at [271]. The rest of [140] is in elaboration of that. The Court of Appeal was not dealing (and nor was the judge) with a case such as the present, where, on the assumptions I am making at this stage, a patent takes a specific member of a previously disclosed broad class (in this case a previous disclosure to combine agents from each of two functionally defined classes) and tests it for the first time to demonstrate an effect. In the present case, again on the assumptions I am making, the effect found is actual (a positive result in animal models), and makes plausible the usefulness as a treatment in man.

Lack of technical contribution – assessment

513. Accord first relies on Darrow. The relevant part of its disclosure is as follows and I accept Accord's submission that it postulates the use of a combination of an ARB and a NEPi for the treatment of hypertension:

> An enhanced effect from a combination of an A II receptor antagonist or a renin inhibitor with an NEP inhibitor is, however, unexpected for several reasons. First, as discussed above, ACE inhibitors exert pharmacological effects other than inhibition of formation of A II. ACE degrades numerous substrates, including bradykinin, neurotensin, and substance P. In some instances, e.g. with bradykinin and substance P, both ACE and NEP will degrade the peptide. Since substance P and bradykinin are vasodilators, an alteration of the metabolism of either of these, or more efficient protection from degradation by inhibiting the two enzymes could account for an enhanced effect. Moreover, although nephrectomy, a manoeuvre which strikingly reduces plasma renin levels, eliminated the enhanced interaction of the ACE inhibitor and

> NEP inhibitor, the NEP inhibitor alone did not lower blood pressure in this state. Thus, the interactions of ACE inhibitors and NEP inhibitors are complex and the effect of an A II receptor antagonist or a renin inhibitor in combination with an NEP inhibitor cannot be predicted solely from data obtained from the combination of an ACE inhibitor and NEP inhibitor.

514. The authors say that the enhanced effect is unexpected and unpredictable. It is not clear whether the enhanced effect is greater than either agent alone, or additive, or more than additive but I do not think it matters to this argument and I did not detect that Novartis said it mattered. Prof Webb accepted in evidence that the assertion was credible at least to the extent of getting a better effect in combination than from either agent alone, but that acceptance was in a very general sense and does not cut across the fact that there would be no expectation of a class effect such that all NEPis would behave the same.

515. I do not accept that this makes the Patent's choice in the claims of the specific combination of valsartan and sacubitril a merely arbitrary selection. The combination is chosen and then shown to have an actual effect. This is quite different from *Dapagliflozin HC* and *CA* where, indeed, all that was different between the prior art and the patent in suit was naming a compound from a broad class. It is a misapplication of what the Court of Appeal said at [140] to try to map it to this case. The skilled person would understand from Darrow the concept that it was possible that some ARB/NEPi combinations would have a beneficial effect, but not that all possible combinations would. It is a muddle to say that the Patent merely makes the valsartan/sacubitril combination plausible and so is no different from Darrow, because in Darrow such plausibility as there may be is entirely conceptual and of uncertain application in any particular case, whereas in the Patent there is a real effect shown for the combination.

516. In even shorter terms, I am unable to accept that an experimental result showing for the first time an advantage for a specific member of a broad class is not a technical contribution. It is. Of course, the fact that the combination does indeed have a beneficial effect in humans is not in dispute.

517. Accord's case is no better over Trippodo, and if anything is worse. On my analysis of Trippodo above, the ARB/NEPi combination is disclosed as a tool and the skilled person would not drive from it the idea, which is in Darrow at the very general level above, that such a combination would be beneficial for hypertension. But even if I were wrong about that, the choice of valsartan and sacubitril is not arbitrary, not least because of the lack of any expected class effect for NEPis, and once again on the basis of my findings in relation to plausibility the Patent contains a technical contribution in relation to its testing.

VALIDITY OF THE SPC

Facts

The SPC

518. The SPC was filed on 16 May 2016 and came into effect on expiry of the Patent on 16 January 2023. It will expire on 15 January 2028.

519. The SPC is based upon the following marketing authorisations: EU/1/15/1058(NI), PLGB 00101/1041, PLGB 00101/1042 and PLGB 00101/1043 (collectively, the "**MAs**"). Each of these is dated 23 November 2015 and is a marketing authorisation for Entresto. The GB marketing authorisations are derived from the European Marketing Authorisation granted by the European Medicines Agency (EMA) for Entresto, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004.

520. The product description in the SPC is "Sacubitril/valsartan, including pharmaceutically acceptable salts thereof".

Entresto

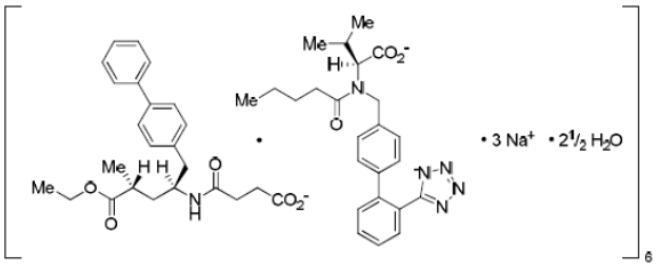
521. Entresto is described in the following way in Accord's opening skeleton:

> Entresto exists as a crystalline co-complex in which the unit cell (which is the repeating unit making up the crystal lattice) contains (i) three sodium cations (Na^+); (ii) one valsartan anion; (iii) one sacubitril anion; and (iv) 2½ waters of hydration. The chemical representation of this crystal is shown in the EMA Assessment Report (EPAR) in section 2.1.2:

2.1.2. Active Substance

General information

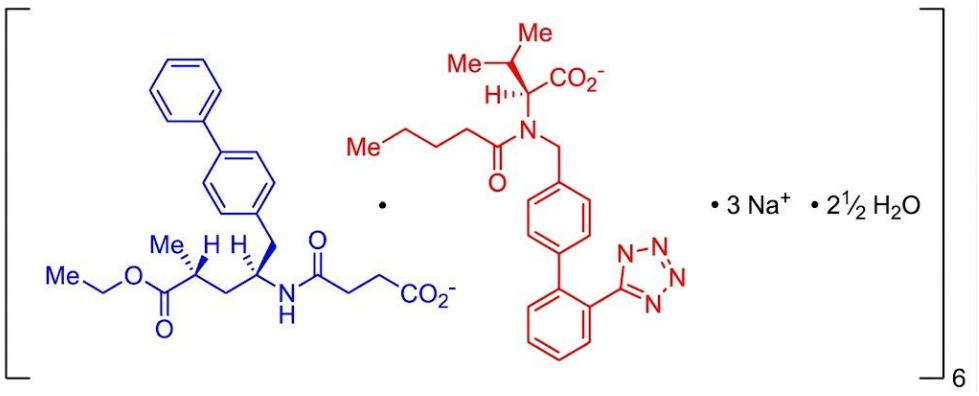
The isolated active substance is a co-crystal complex of the sodium salts of two individual active components, sacubitril and valsartan, in hydrated form. The chemical name of the sacubitril-valsartan complex is octadecasodium
hexakis-(4-{[(1*S*,3*R*)-1-([1,1'-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoate)
hexakis-(*N*-pentanoyl-*N*-{[2'-(1*H*-tetrazol-1-id-5-yl)[1,1'-biphenyl]-4-yl]methyl}-*L*-valinate)
pentadecahydrate and it has the following structure and properties:



Molecular formula of unit cell: $C_{288}H_{330}N_{36}O_{48}Na_{18}.15H_2O$ - Relative molecular mass: 5747.96 $gmol^{-1}$

The structure of the sacubitril-valsartan complex was inferred from the route of synthesis and confirmed by ^1H and ^{13}C NMR spectroscopy (solid and solution state), IR spectroscopy, UV spectroscopy, mass spectrometry, elemental analysis, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), x-ray powder diffraction (XRPD) and x-ray crystallography. The individual active substances were also characterised: the structure of sacubitril was inferred from its route of synthesis and confirmed by ^1H and ^{13}C NMR spectroscopy, IR spectroscopy, mass spectrometry and chiral HPLC; the structure of valsartan was inferred from its route of synthesis and confirmed chiral HPLC analysis compared to an authentic sample.

522. There was no dispute about that, and Novartis used the same depiction in its opening skeleton, with some helpful colouring added (showing sacubitril (blue), valsartan (red), sodium and water, from left to right):



523. Although I do not think there was any expert evidence directly addressing it, my clear understanding, reflected in Novartis' opening skeleton and not contradicted by Accord (and also stated in the Entresto SmPC), is that when a patient takes Entresto, the complex dissociates to release the valsartan and sacubitril; they do their work and the rest of the complex, namely sodium ions and water, pass into the patient's body without having any pharmacological effect of their own.

524. In crude terms, Entresto is a salt of valsartan and a salt of sacubitril physically stuck together by their inclusion in the co-complex. But it is still those two salts. Furthermore, and again in crude terms, what actually accomplishes the therapeutic effect is valsartan without the sodium counterions and sacubitril without the sodium cations.

525. Accord's intended product is a conventional (at least for present purposes) mixture of a valsartan salt and a sacubitril salt. It is a simple admixture, not a co-complex.

Other Novartis patent applications, patents, and SPCs

526. The Entresto co-complex has been the subject of patent applications and SPC applications. In the patent application process, Novartis entities (the Defendant and Novartis Pharma AG have both been involved; subject to a very minor point raised in argument it does not matter which is which) have argued that it is patentably distinct from anything disclosed in the Application, which is full prior art against the co-complex applications.

527. The distinction relied on is that the Application "relates" only to a mixture of valsartan and sacubitril. Novartis also filed some evidence about physicochemical differences between an ordinary mixture and a co-complex. I do not know in any detail what the differences relied on in prosecution were or what practical advantages Entresto has over a mixture, but they were not said to affect the point above about what happens when a patient takes Entresto.

528. Accord's opening skeleton said that a first co-complex European patent application proceeded to grant and was used as a basis for the grant of an SPC relying on the same marketing authorisations as the SPC in suit, but that Novartis withdrew the patent, invalidating the co-complex SPC. Novartis then applied for a divisional on the co-complex, also granted, which was the basis for the grant of another SPC, using the same marketing authorisations again, which was surrendered in 2025. These facts were not contradicted by Novartis and I will assume they are correct, but conclude below that they are irrelevant.

529. Novartis also made some points in written opening about Accord's various filings but they are also irrelevant and neither side made anything of them subsequently.

Regulatory approval documents

530. I deal with these separately below since they are somewhat longer and more detailed, and central to the correct definition of "the product" for the purposes of the legal issues.

Variations

531. Accord said that if Novartis wanted to market, for example, a conventional mixture of valsartan and sacubitril, it would have to apply for an extension to its MAs, under the Human Medicines Regulations 2012, Schedule 10A. This is a hypothetical situation and more a question of law than fact, but in any event I record that Novartis agreed that it was correct. Novartis said it was irrelevant however, and for reasons given below I agree.

The SPC Regulation

532. The relevant provisions are Articles 1, 3, 4 and 5 of Regulation (EC) No 469/2009 ("the SPC Regulation") as assimilated into UK law.

533. They are as follows:

> *Article 1*
>
> **Definitions**
>
> For the purpose of this Regulation:
>
> (a) 'medicinal product' means any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals;
>
> (b) 'product' means the active ingredient or combination of active ingredients of a medicinal product;

(c) 'basic patent' means a patent which protects a product as defined in (b) as such, a process to obtain a product or an application of a product, and which is designated by its holder for the purpose of the procedure for grant of a certificate";

534. Next, Article 3 provides the conditions for SPC grant:

Article 3

Conditions for obtaining a certificate

A certificate shall be granted if, in the Member State in which the application referred to in Article 7 is submitted and at the date of that application:

(a) the product is protected by a basic patent in force;

(b) a valid authorisation to place the product on the market as a medicinal product has been granted in accordance with Directive 2001/83/EC or Directive 2001/82/EC, as appropriate;

(c) the product has not already been the subject of a certificate;

(d) the authorization referred to in (b) is the first authorization to place the product on the market as a medicinal product.

535. The following articles (Articles 4 and 5) respectively provide for the subject matter of protection, and the effects of an SPC:

Article 4

Subject-matter of protection

Within the limits of the protection conferred by the basic patent, the protection conferred by a certificate shall extend only to the product covered by the authorisation to place the corresponding medicinal product on the market and for any use of the product as a medicinal product that has been authorised before the expiry of the certificate.

Article 5

Effects of the certificate

1. Subject to the provisions of Article 4, the certificate shall confer the same rights as conferred by the basic patent and shall be subject to the same limitations and the same obligations.

The pleaded attacks

536. Accord pleaded that the SPC is invalid because:

i) If the relevant "product" was the Entresto Co-Complex then it was not protected by the Patent as required under Article 3(a); or

ii) If the relevant product was something else, (in particular, if it was "a pharmaceutical composition comprising (i) AT 1-antagonist valsartan or a pharmaceutically acceptable salt and (ii) N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic—acidethylester or N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid or a pharmaceutically acceptable salt"), then it was not a product in respect of which a valid authorisation had been granted as required by Article 3(b).

Novartis' pleading

537. Novartis pleaded that "[t]he 'product' for the purposes of the SPC is the combination of sacubitril and valsartan. That product may be used in different physical/chemical forms."

Correspondence about the issues

538. The parties corresponded about the issues. In a letter of 22 May 2026, Novartis' solicitors wrote as follows:

> […] if the Court determines that the "product" for the purposes of Article 3 of the SPC Regulation is a single active ingredient being the Co-Complex (as described in your client's pleading), [Novartis] will not assert that the SPC is both valid and infringed by the Accord Product.

539. Accord's solicitors replied in a letter of 8 June 2026:

> […] if the court determines that (i) the "product" for the purposes of Article 3 of the SPC Regulation is a combination of sacubitril and valsartan (as pleaded in your client's Response 7 at B.1/8/50) and (ii) the SPC is valid, our client will accept that the Accord Product infringes the SPC.

540. This exchange served to emphasise at a broad level that a central dispute between the parties was the proper identification of the "product" for the purposes of Article 3, which I agree with, but it did not bring to the surface all the issues. In particular, it transpired in the course of trial, especially in oral closings, that "if … the SPC is valid" in Accord's reply was intended to ensure that two arguments were in play that even if the "product" was as Novartis argued, then the SPC was invalid. The arguments were:

i) If the product was as Novartis alleged then neither the co-complex nor the combination of valsartan and sacubitril expressed at the level of abstraction of Novartis' pleading were protected by the Patent, contrary to Article 3(a);

ii) If the product was as Novartis alleged then, contrary to Article 3(b), it was not authorised by the MA, which only authorised the co-complex.

Applicable law on SPCs

Identifying the product – case law

541. Novartis submitted that there is a distinction between the *medicinal product* (defined in Article 1(a)) and the *product* (defined in Article 1(b)), the former being the actual formulation authorised to be put on the market and the latter being just the active ingredients (or combination thereof). I agree with this; Jacob J (as he then was) spelled it out as long ago as *Draco's Application* [1996] RPC 417.

542. I also agree with Novartis that the "product" has to be the same for all the sub-parts of Article 3, as the Court of Appeal said in *Newron Pharmaceuticals v Comptroller-General* [2024] EWCA Civ 128 at [15]-[16], and that the critical focus is on the active ingredients "in the strict sense" – see *Santen* Case C-673/18 at [44]-[46], cited in *Newron* and later again in *Merck-Serono v Comptroller-General* [2025] EWCA Civ 45.

543. The parties agreed that the active ingredients are what the regulators concluded them to be in granting the relevant MA(s). I therefore have to look at the Commission Implementing Decision ("**CID**"), the Summary of Product Characteristics ("**SmPC**") and the European Public Assessment Report ("**EPAR**"), bearing in mind that the latter is not a decision with legal effect and from the perspective that an active ingredient is a substance that has a pharmacological, immunological or metabolic effect of its own: see e.g. Arnold J (as he then was) in *Abraxis Bioscience LLC v Comptroller-General* [2017] EWHC 14 (Pat) at [56]-[59] citing *Forsgren,* Case C-631/13.

Minor changes do not mean a new product

544. There has been a consistent line of decisions in the European and domestic case law that defining the "product" does not include aspects of the form such as the salt, the excipients, the adjuvants or the formulation. The most relevant for present purposes is the fact that a change in salt does not make for a new product: *Farmitalia* Case C-392/97. A number of these decisions are referenced in the paragraphs from *Santen* mentioned above.

545. As a result, I dismiss as irrelevant Accord's point about MA extensions. It is true, as Novartis accepts, that if it wanted to sell a simple admixture of salts of valsartan and sacubitril it would need an extension, but it is quite clear that for the purposes of the SPC Regulation the admixture would not be a different "product" from the Co-Complex.

The regulatory materials

546. The parties cited a variety of passages from the regulatory materials. Accord majored in opening on the passage from the EPAR, at 2.1.2, which I have reproduced above in explaining the facts about Entresto.

547. In closing, Accord also referred to section 2 of the SmPC which says the following (Novartis also cited this):

> **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**
>
> Entresto 24 mg/26 mg film-coated tablets
> Each film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium salt complex).
>
> Entresto 49 mg/51 mg film-coated tablets
> Each film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as sacubitril valsartan sodium salt complex).
>
> Entresto 97 mg/103 mg film-coated tablets
> Each film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as sacubitril valsartan sodium salt complex).
>
> For the full list of excipients, see section 6.1.

548. And the outer packaging, Annex III to the CID (again, also cited by Novartis who pointed out that the outer packaging is required to identify the active substances):

> **1. NAME OF THE MEDICINAL PRODUCT**
>
> Entresto 24 mg/26 mg film-coated tablets
> sacubitril/valsartan
>
> **2. STATEMENT OF ACTIVE SUBSTANCE(S)**
>
> Each 24 mg/26 mg tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium salt complex).

549. As to the "form", Accord referred to section 3 of the SmPC:

> **3. PHARMACEUTICAL FORM**
>
> Film-coated tablet (tablet)
>
> Entresto 24 mg/26 mg film-coated tablets
> Violet white ovaloid biconvex film-coated tablet with bevelled edges, unscored, debossed with "NVR" on one side and "LZ" on the other side. Approximate tablet dimensions 13.1 mm x 5.2 mm.
>
> Entresto 49 mg/51 mg film-coated tablets
> Pale yellow ovaloid biconvex film-coated tablet with bevelled edges, unscored, debossed with "NVR" on one side and "L1" on the other side. Approximate tablet dimensions 13.1 mm x 5.2 mm.
>
> Entresto 97 mg/103 mg film-coated tablets
> Light pink ovaloid biconvex film-coated tablet with bevelled edges, unscored, debossed with "NVR" on one side and "L11" on the other side. Approximate tablet dimensions 15.1 mm x 6.0 mm.

550. Accord said that this showed merely that the "form" in this context is a film-coated tablet and does not concern salts, formulation or excipients. I agree, but it is not a significant point either way.

551. In addition to the above, Novartis relied on paragraphs 5.1 and 5.2 of the SmPC:

i) 5.1 says "Entresto exhibits the mechanism of action of an angiotensin receptor neprilysin inhibitor by simultaneously inhibiting neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and by blocking the angiotensin II type-1 (AT1) receptor via valsartan."

ii) 5.2 says "Following oral administration, Entresto dissociates into valsartan and the prodrug sacubitril."

552. And from the Annexes to the CID, Novartis relied on the following from the patient information leaflets ("**PiLs**"):

> **1. What Entresto is and what it is used for**
>
> Entresto is a medicine known as an angiotensin receptor neprilysin inhibitor. It dissociates into two active substances, sacubitril and valsartan.
>
> Entresto is used to treat a type of long-term heart failure in adults.
>
> This type of heart failure occurs when the heart is weak and cannot pump enough blood to the lungs and the rest of the body. The most common symptoms of heart failure are breathlessness, fatigue, tiredness and ankle swelling.

553. And:

> **6. Contents of the pack and other information**
>
> **What Entresto contains**
> - The active substances are sacubitril and valsartan.
> - Each 24 mg/26 mg film-coated tablet contains 24.3 mg sacubitril and 25.7 mg valsartan (as sacubitril valsartan sodium salt complex).
> - Each 49 mg/51 mg film-coated tablet contains 48.6 mg sacubitril and 51.4 mg valsartan (as sacubitril valsartan sodium salt complex).
> - Each 97 mg/103 mg film-coated tablet contains 97.2 mg sacubitril and 102.8 mg valsartan (as sacubitril valsartan sodium salt complex).

554. From the EPAR, Novartis additionally relied on the International non-proprietary name ("**INN**"), which I do not think helps either way, and to the following additional statements:

> **2.1.1. Introduction**
>
> Entresto is a fixed-dose combination product presented as film-coated tablets containing sacubitril and valsartan as active substances as a trisodium hemipentahydrate co-crystal. Three strengths are proposed containing 24.3 mg sacubitril and 25.7 mg valsartan (low strength), 48.6 mg sacubitril and 51.4 mg valsartan (middle strength), and 97.2 mg sacubitril and 102.8 mg valsartan (high strength). Initially, the applicant proposed to express the strength of each tablet based on the combined content of both active substances, i.e. 50 mg, 100 mg and 200 mg respectively. However, it was judged by CHMP that since the product is a fixed-dose combination, the content of each active substance should be declared individually.

555. Novartis said this is the context for what follows at 2.1.2 and I agree (as did Accord).

556. The EPAR also contains a section on manufacturing, from which Novartis cited the following:

> ***Manufacture, characterisation and process controls***
>
> The synthesis of the individual active substances is described, along with their subsequent combination to form the co-crystal complex. Valsartan is a well-known active substance covered by a Ph. Eur. monograph.

557. And then it describes the "Finished Medical Product" at 2.1.3:

> **2.1.3. Finished Medicinal Product**
>
> ***Description of the product and pharmaceutical development***
>
> The aim of development was to identify an immediate release solid oral dosage form of sacubitril and valsartan. The co-crystal form identified by the applicant renders valsartan more bioavailable than in its standalone formulations and the dose was reduced accordingly. Both active substances are highly soluble in aqueous media above pH 5 and show medium permeability.

Assessment

558. The materials are overwhelmingly in favour of the view that the active ingredients in the sense I have described above are valsartan and sacubitril. They expressly say so, and they articulate that the co-complex/salt forms cease to be relevant after administration. It is plain that the counterions and water in the co-complex have no pharmacological effect of their own.

559. As to section 2.1.2 of the EPAR, it is not inconsistent with this view, especially not in the proper context of section 2.1.1 and all the other materials. It happens to use the form of words "isolated active substance is the co-crystal complex" but it later refers to the "individual active substances".

560. A relatively minor point which I should mention is that a number of the documents give masses in millligrams for the valsartan and sacubitril and then say "as sacubitril valsartan sodium salt complex", without a mass being given for the latter. Quite apart from the fact that the documents explicitly call out valsartan and sacubitril as the active substances, I agree with Novartis that it is consistent with their being such that masses have to be given for them, whereas the total mass of the co-complex is not relevant from a pharmacological point of view.

561. I conclude that Novartis is correct: the active ingredients are valsartan and sacubitril and not the co-complex.

The test under Article 3(a)

562. The parties agreed that the relevant (two-part) test is that set out in *Royalty Pharma*, Case C-650/17. Accord paraphrased the test in the following terms, which Novartis was content to work with:

    i) First, the product must, from the point of view of a person skilled in the art and in the light of the description and drawings of the basic patent, necessarily come under the invention covered by that patent.

    ii) Second, the person skilled in the art must be able to identify that product specifically in the light of all the information disclosed by that patent, on the basis of the prior art at the filing date or priority date of the patent concerned.

Article 3(a) - discussion

563. I have found that the product is, as Novartis contends, the combination of valsartan and sacubitril and I approach the two-part test on that basis. In addition, since Novartis conceded in correspondence that it would lose on the SPC case if the product was the co-complex, I do not need to approach it on any other basis.

564. On both parts of the test, Accord relied heavily on Novartis' applying for later, separate patent and SPC protection for the co-complex specifically. I have already said that I consider that irrelevant. There are two main reasons.

565. First, the argument made in the patent applications that the co-complex is not the same as what is disclosed in the Application relates to a completely different legal standard. The co-complex being physically different from what is disclosed in the Application could result in its being novel and inventive for the purposes of patent law, but the scope and nature of that question would not be the same as applies to SPC validity.

566. Second, I agree it was implicit in Novartis' SPC applications that the co-complex was a new and different product. That is inconsistent with what Novartis is saying now but it is also wrong in my view. I asked Counsel for Novartis if it would in fact be possible to get a further SPC for the co-complex consistently with the arguments now made, and he effectively accepted that it would not (or at least that the co-complex is not a new product – he sought to leave open the question whether a different entity could get an SPC on the same product, and this may be related to the different Novartis entities involved in the co-complex patent prosecution, not that it matters).

567. In any event, Accord did not plead or argue that what Novartis did provided a legal basis for revoking the SPC, or prevented Novartis from making the arguments it does now.

First part of the *Royalty Pharma* test

568. The combination of valsartan and sacubitril is repeatedly referred to in the description of the Patent, and in its claims. The fact that there are various references to salts, carriers and other formulation issues as well does not affect this. Assessed at the proper level, the first part of the *Royalty Pharma test* is satisfied.

Second part of the *Royalty Pharma* test

569. Accord's main argument was that the co-complex is not suggested in the description of the Patent and the person skilled in the art could not "identify" it from the Patent. This is true but irrelevant given that the co-complex is not the product.

570. By contrast and on the facts of this case, where the claim is quite specific as to the two active ingredients, essentially the same reasons as for the first part of the test lead to the conclusion that the second part of the test is satisfied, once one focuses on the product being the combination of valsartan and sacubitril.

Later inventive product

571. The CJEU referred in the second part of the *dispositif* in *Royalty Pharma* to the situation of a product covered by a functional definition in the claims only being invented after the filing date of the basic patent. Accord said that was relevant to the present case because the co-complex was inventive. I reject this. The CJEU was not adopting any different approach to what a product is, and anyway the claims of the Patent are not in functional terms as to the active ingredients; they call out valsartan and sacubitril specifically.

Is Novartis' definition too broad?

572. Accord said that if the product is defined as Novartis argued, the first part of the *Royalty Pharma* test is still not satisfied. It said that if the combination of valsartan and sacubitril is as general and abstract as Novartis argued, it is not protected by the Patent, whose claims are more specific and claim "only one specific pharmaceutical presentation of valsartan and sacubitril, namely a conventional mixture". It also pointed to the fact that the claims require a carrier whereas Novartis' definition of the product does not. I do not agree that the Patent does claim only one specific pharmaceutical presentation, but will cover that in a moment in connection with the argument on the co-complex, but in any case these arguments again proceed at the wrong level and also treat the Article 3(a) test as being a true infringement test, which is not correct.

Does the co-complex fall within claim 1 of the Patent?

573. Accord argued that the co-complex does not fall within claim 1 of the Patent. I remain rather unclear about the legal relevance of this to Accord's case in the event that it is wrong about the product, as I have found. I think the

argument was along the lines that: Novartis' definition of the product is broad, but if correct then the Patent must protect everything within the definition, including the co-complex, even if it is not the product. Yet again this proceeds at the wrong level once the product is correctly identified, but in case I have misunderstood the argument or there is an appeal, I will determine whether the co-complex falls within claim 1.

574. In my view, it does. Accord's argument is that the claim is limited to a conventional admixture of two separate salts. I agree that that is the first thing that a skilled person would think of when reading the Patent (in this instance the skilled person would be a formulator, from which discipline I have no expert evidence, but the analysis is sufficiently clear that I do not consider I need one and anyway the burden to show that the SPC is invalid is on Accord, as it accepted). But that is not the way to approach the scope of the claim. The claim does not say anything about there having to be a conventional admixture. It says that there have to be present ("comprise") a valsartan salt and a sacubitril salt, and in the co-complex there are (both sodium salts). The fact that they are physically stuck together does not change that. There is no context in the specification to suggest that a conventional admixture is *required*, either for formulation reasons or for clinical/pharmacological reasons. The skilled person would understand that what mattered was that the salts dissociated on administration. It would plainly be eccentric for the patentee to limit itself in the way suggested by Accord for no apparent reason. Such disclosure as there is in the Patent is permissive, not restrictive (see [0038] and [0039]).

Article 3(b)

575. Accord argued that what has been authorised in the MAs relied on for the SPC is the co-complex, not any combination of valsartan and sacubitril. Critical to this argument was the proposition that an extension to the MAs would be needed for Novartis to market a different form of a valsartan/sacubitril combination, but I have rejected that above as irrelevant and I agree with Novartis that once the product is correctly identified the MA authorises the two active ingredients for the purposes of Article 3(b).

Infringement of the SPC

576. Accord accepted in correspondence (see above) that if the product was as Novartis alleged and if the SPC was valid, then Accord's proposed product would infringe. I have found that Novartis is right about the product and the SPC is valid, so there is no need to make any separate finding on infringement. In the scenario I have found, Accord accepts it is shown.

CONCLUSIONS

577. My conclusions are:

i) All the attacks on the Patent fail; it was valid while in force.

ii) The separate attacks on the SPC also fail and it is valid.

iii) Accord's intended product would infringe the SPC.

578. I will hear Counsel as to the form of Order if it cannot be agreed. I direct that time for seeking permission to appeal shall not run until after the hearing on the form of Order (or the making of such Order if it is agreed). Given the timing of the giving of the judgment in draft it will not be possible to have the form of Order hearing until at least September.