Neutral Citation Number: [2016] EWCA Civ 1295

Case No: A3/2015/2032 & 2033

IN THE COURT OF APPEAL (CIVIL DIVISION)
ON APPEAL FROM THE HIGH COURT OF JUSTICE
CHANCERY DIVISION (PATENTS COURT)
THE HON MR JUSTICE ARNOLD
[2015] EWHC 1068 (Pat)

Royal Courts of Justice
Strand, London, WC2A 2LL

Date: 21/12/2016

Before:

LORD JUSTICE KITCHIN
LORD JUSTICE FLOYD
and
LORD JUSTICE HAMBLEN

- -

Between:

(1) Novartis AG **(2) LTS Lohmann Therapie-Systeme AG** **(3) Novartis Pharmaceuticals UK Ltd**	**Claimants/ Appellants**
- and -	
(1) Focus Pharmaceuticals UK Ltd **(2) Actavis Group PTC EHF** **(3) Actavis UK Ltd**	**Defendants/ Respondents**
And Between:	**Claimants/ Appellants**
(1) Novartis AG **(1) (2) LTS Lohmann Therapie-Systeme AG** **(2) Novartis Pharmaceuticals UK Ltd**	
- and -	
TEVA UK Ltd	**Defendant/ Respondent**

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- -

Thomas Hinchliffe QC (instructed by Bristows LLP) appeared for the Claimants/Appellants
Daniel Alexander QC and Henry Ward (instructed by Olswang LLP) appeared for Focus Pharmaceuticals Ltd
Daniel Alexander QC and Henry Ward (instructed by Pinsent Masons LLP) appeared for Actavis
Daniel Alexander QC and Mark Chacksfield (instructed by Bird & Bird LLP) appeared for TEVA UK Ltd

Hearing dates : 1st and 2nd November 2016

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Judgment Approved

Lord Justice Kitchin:

Introduction

1. In these actions the claimants (together "Novartis") alleged that the defendants ("Focus" and "Actavis" in action HP-2013-000011 and "Teva" in action HP-2013-000012) had infringed European Patent (UK) No. 2,292,219 entitled "Transdermal therapeutic system for the administration of rivastigmine" ("the Patent"). The Patent has a single EPC 2000 claim which is directed to rivastigmine for use in a method of preventing, treating or delaying the progression of Alzheimer's disease ("AD") in which the rivastigmine is administered in a transdermal therapeutic system ("TTS"), that is to say a patch, at a particular starting dose. The defendants denied infringement and counterclaimed for revocation of the Patent on the grounds of added matter, obviousness and insufficiency.

2. The action came on for trial before Arnold J in March 2015. In his judgment, handed down on 27 April 2015 [2015] EWHC 1068 (Pat), he found that the Patent lacked any inventive step over a single piece of prior art, US Patent No. 6,335,031 ("US 031"), and was also invalid for added matter. He rejected the allegation of insufficiency. He also held that if the Patent had been valid, the defendants would have infringed it.

3. Novartis now appeals against the judge's order revoking the Patent. Originally the defendants all supported the judge's conclusions in relation to obviousness and added matter but contended that he fell into error in construing the claim and that, if he had construed it properly, he would have found that none of their activities fell within its scope. They also contended that if the Patent was not obvious, it was insufficient. However, at the outset of the appeal we were informed that Novartis and Teva had resolved their differences and agreed a compromise of the claim and counterclaim in action HP-2013-000012. Accordingly, we proceeded to hear the appeal in action HP-2013-000011 against Focus and Actavis. We have now been informed that Novartis has also agreed confidential terms of settlement with Actavis and Focus as a result of which Novartis' claim for infringement has been compromised. However, Novartis maintains its appeal against the order for revocation.

4. There are two other matters I must mention at the outset. First, the Patent has been opposed before the European Patent Office by, at least originally, 13 opponents. The oral proceedings before the Opposition Division took place on 15 December 2015 and for reasons set out in a decision dated 15 March 2016, it decided that the Patent must be revoked for added matter. Its order for revocation has been suspended pending appeal. Secondly, other designations of the Patent and equivalent national rights have been extensively litigated in proceedings in other jurisdictions. As the judge noted, there has been a striking diversity of outcomes, with some courts and tribunals finding infringement and others not. Until the decision of the judge, there had been no final decision on validity, however.

5. I will address each of the issues which remain to be decided upon this appeal but first must say a little about the technical background and describe the relevant disclosure of the application for the Patent and of the Patent itself.

The technical background

6. The judge addressed the technical background from [11] to [33] of his judgment. The following points are material to this appeal.

7. AD is a progressive neurodegenerative disease that causes dementia and, ultimately, death. One of the key underlying mechanisms of the cognitive dysfunction associated with AD is a loss of the neurotransmitter acetylcholine ("ACh") in the brain. ACh is synthesised within presynaptic cells and, once released, interacts with receptors on postsynaptic cells. The activation of these postsynaptic receptors leads to the propagation of nerve impulses.

8. ACh is quickly inactivated by an enzyme called acetylcholinesterase ("AChE"). One way of addressing the cholinergic deficit associated with AD is therefore to inhibit AChE. Such inhibition leads to increased levels of ACh as the rate of its breakdown is attenuated.

9. Three AChE inhibitors were commonly used for the treatment of mild to moderate AD at the priority date, namely donepezil, galantamine and rivastigmine. All were administered orally and all were associated with mild to moderate cholinergic side effects such as nausea, vomiting and diarrhoea. These side effects were managed by titrating the dose administered to patients gradually upwards as their tolerance increased. However, that tolerance was quickly lost if treatment was interrupted for more than a few days.

10. At the priority date, donepezil was the UK market leader and galantamine and rivastigmine were generally considered to be second line treatments. Importantly, donepezil was perceived to have a number of significant advantages over rivastigmine: it only required a single daily dose, rather than twice daily doses, resulting in higher patient compliance and carer convenience; administration began with a clinically effective dose, whereas the initial dose of rivastigmine was sub-therapeutic; it had a less complicated treatment regime than rivastigmine; and it was perceived to have less severe side effects than rivastigmine.

11. Rivastigmine was sold under the brand name Exelon and was formulated in capsule and oral solution form. Treatment began with the administration of 1.5 mg twice daily (bis in diem or "b.i.d."). At intervals of between two and four weeks, the dose was increased in steps of 1.5 mg up to a dose of 6 mg b.i.d. The minimum effective dose was 3 mg b.i.d.

12. Various parameters are used to assess the pharmacokinetic properties of an active pharmaceutical ingredient ("API") such as rivastigmine, namely:

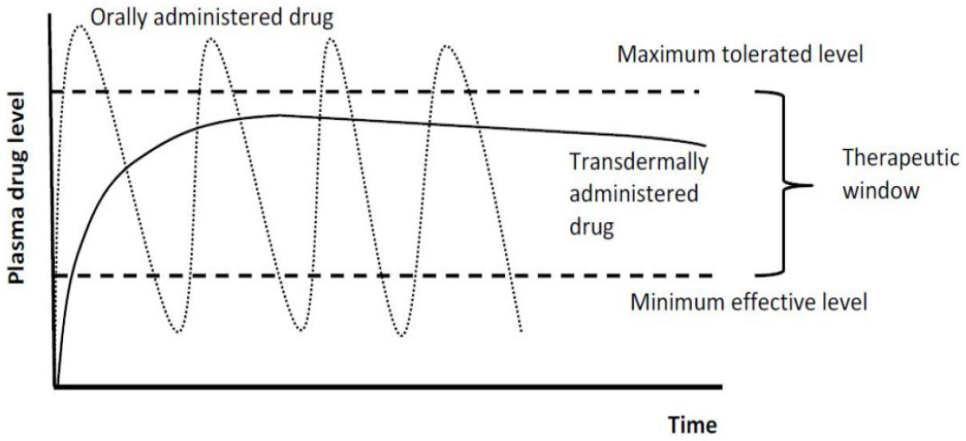
    i) "C_{max}" which is a measure of the peak plasma concentration of the API;

    ii) "t_{max}" which is the time at which C_{max} is reached; and

    iii) "AUC" or "area under the curve" which, as its name suggests, is the area under the concentration-time curve and reflects the exposure of the body to an API after administration. AUC_{24h} is the AUC over a 24 hour period.

13. The Summary of Product Characteristics ("SmPC") for Exelon capsules explained how they should be administered, gave warnings and precautions for use and detailed the drug's pharmacodynamic properties. It explained that rivastigmine should be administered b.i.d., with morning and evening meals, and that administration in this way delayed absorption assessed by reference to t_{max} by 90 minutes, lowered C_{max} and increased the AUC by approximately 30%.

14. A TTS is applied to the skin to deliver the API it contains into the bloodstream. There were, at the priority date, no available TTSs for the treatment of AD. Nevertheless, it was known that transdermal administration had a number of advantages over oral administration including the provision of a smoother delivery curve, so avoiding the rapid fluctuation and peak levels of drug plasma concentration often seen with APIs administered orally. Professor Williams, the defendants' expert witness in the area of transdermal formulation, illustrated this effect in this way in his first report:



15. Nevertheless, it was also understood that administration by transdermal means had the various disadvantages identified by the judge at [27]:

    i) only a limited number of APIs are suitable for administration in this way;

    ii) TTSs are generally more expensive and time consuming to develop than oral formulations;

    iii) the onset of treatment tends to be slower than with oral formulations; and

    iv) there is the potential for local skin irritation.

16. It was also known to be desirable to provide patients with a fixed and reproducible dose of the API over the prescribed period of application and that for this reason the rate of release should be constant. In the case of administration by TTS, this was achieved by ensuring that, so far as possible, the TTS was saturated with the API for the entire period of application.

17. The development of a TTS would begin with the provision by the clinician to the formulator of a target dose. The judge explained how matters progressed thereafter in these terms with which neither side took issue:

> "31. Once an API is identified as being suitable for delivery by a patch, a target dose would be given to the formulator by the clinician and would generally be quantified in terms of a target AUC, typically the AUC_{24h}. The target AUC_{24h} will normally correspond to the AUC_{24h} for the oral dosage form.
>
> 32. Once the target dosage is selected, prototypes will be produced and tested in short term accelerated and real time stability tests and their performance will then be assessed based upon the amount of API released from the patch. This is tested *in vitro* in a test system such as a Franz diffusion cell and, ultimately, *in vivo*, usually in humans. The Franz diffusion cell test involves measuring diffusion of the test substance across a membrane. This may be a piece of human skin or an artificial membrane such as an EVA membrane.
>
> 33. In developing a generic patch formulation (i.e. a generic version of an existing patch), a key step is to ensure that the generic patch will release the same dose as the originator patch. This would be tested in the same way as described above – *in vitro* by Franz diffusion cell and ultimately in human volunteers."

18. There was no dispute at trial that the Patent is addressed to a skilled team interested in developing a new formulation of rivastigmine and that such a team would include a formulator skilled in the transdermal administration of drugs and a clinician or neuroscientist working in the field of dementia or AD. All of the technical matters to which I have referred formed part of the common general knowledge of that skilled team. There was, however, a dispute as to the state of the common general knowledge of the clinician or neuroscientist with regard to the manner in which the tolerance of a patient could be increased. The defendants contended that it was common general knowledge that the side effects of rivastigmine were caused by sharp peaks in drug levels indicated by a short t_{max} and high C_{max}, and that the recommendation to administer with food was given to improve tolerability. This was disputed by Novartis, however.

19. In addressing this dispute, the judge had regard to the evidence of the expert clinicians called by the parties, Professor Ballard for Novartis and Professor Francis for the defendants, and to 11 papers relied upon by the defendants before expressing his conclusions in these terms at [92] to [93]:

> "92. Taking all of the evidence into account, my conclusions are follows:
>
> i) It was generally accepted that rivastigmine should be administered with food.
>
> ii) As Prof Ballard pointed out, and Prof Francis accepted, this is common practice for many drugs, and there are a number of different potential reasons for doing it.

> iii) In the case of rivastigmine, the skilled person would be aware that it was a reasonable hypothesis that administration with food increased the tolerability of rivastigmine and that this was because it increased t_{max} and reduced C_{max} which contributed to cholinergic side effects. The skilled person would also be aware, however, that there was no firm evidence to support this hypothesis.
>
> 93. I would add that, even if point (iii) was not common general knowledge, I consider that it would have been an obvious step for the skilled team, at the outset of a project to develop a new formulation of rivastigmine one of whose objects was to improve its tolerability, to undertake a short and focussed literature search into factors affecting the tolerability of rivastigmine. This would have thrown up some, if not all, of the papers considered above, from which the skilled clinician would draw the same conclusions."

20. Novartis originally sought to challenge these conclusions upon this appeal. At the hearing, that challenge melted away, however. Novartis now accept for the purposes of these proceedings that the judge was entitled to reach the conclusions that he did. As I shall explain, they have an important bearing upon the issue of obviousness.

The application for the Patent

21. Arnold J considered the disclosure of the application for the Patent ("the Application") in detail in his judgment from [34] to [61]. The following parts of the Application are particularly material to this appeal.

22. The Application is entitled "Transdermal Therapeutic System" and states in its first paragraph:

> "The present invention relates to Transdermal Therapeutic Systems comprising a backing layer, a reservoir layer and an adhesive layer, to Transdermal Therapeutic Systems having specific release profiles, to their manufacture and use."

23. The Application proceeds to identify a series of objects of the invention, three of which are as follows:

> "It is a further objective of the present invention to provide a method of treatment and controlled-release formulation(s) that substantially improves the efficacy and tolerability of rivastigmine.
>
> It is a further objective of the present invention to provide a method of treatment and controlled-release formulation(s) that substantially reduces the time and resources needed to administer rivastigmine for therapeutic benefit.

> It is a further objective of the present invention to provide a method of treatment and controlled-release formulation(s) that substantially improves compliance with rivastigmine therapy.

24. These objectives are said to be achieved by a TTS as defined in claim 1. The Application then explains on page 2:

> "Tests with active ingredients for the treatment of Alzheimer's disease have surprisingly shown that a line of silicone adhesive can be applied to a poorly adhesive reservoir matrix, thus significantly increasing the adhesive properties of the preparation without affecting the thermodynamic properties of the TTS, i.e. without reducing the release of active ingredient from the matrix and its permeation through the skin."

25. There follows a description of the first aspect of the invention:

> "The present invention provides TTS comprising a backing layer, a reservoir layer containing at least one active ingredient and a polymer, an adhesive layer comprising a silicone polymer and a tackifier.
>
> A TTS according to the invention shows improved adhesive properties. Further, and very surprisingly, the so obtained TTS has essentially the same release profile when compared with a standard TTS."

26. A second aspect of the invention is described on page 3:

> "The present invention is further related to a method for substantially improving the efficacy and tolerability of rivastigmine, comprising application of a TTS in the range of 2 to 50 cm^2, said formulation providing a mean maximum plasma concentration of about 1 to 30 ng/mL from a mean of about 2 to 16 hours after application and an AUC_{24h} of about 25 to 450 ng.h/mL after repeated "QD" (i.e., once daily) administration.
>
> A TTS according to the invention quite surprisingly shows improved tolerability, particularly gastrointestinal adverse events such as nausea and vomiting, relative to equivalent levels of exposure (AUC_{24h}) of Exelon® capsule."

As the judge noted, these pharmacokinetic data are not said to relate to the starting dose prescribed to a patient.

27. Various definitions are then set out including a definition of the term "active ingredient" which is said to mean any active ingredient suitable for transdermal administration. The most preferred active ingredients are said to be rivastigmine and rivastigmine hydrogen tartrate.

28. Various preferred embodiments are described, including this embodiment on page 7:

> "In a preferred embodiment, the TTS provides a mean maximum plasma concentration of rivastigmine of 1 to 30 ng/ml from a mean of 2 to 16 hours after application with an AUC_{24h} of 25 to 450 ng.h/ml, particularly preferred, the TTS provides a mean maximum plasma concentration of rivastigmine of 2.5 to 20 ng/ml from a mean of 4 to 12 hours after application with an AUC_{24h} of 45 to 340 ng.h/ml."

29. Further aspects of the invention are described on page 8:

> "In a further aspect, the invention provides a TTS which incorporates as active agent a cholinesterase inhibitor in free or pharmaceutically acceptable salt form, for use in the prevention, treatment or delay of progression of dementia."

30. A little later, it is explained:

> "In a further aspect, the invention provides a method for the prevention, treatment or delay of progression of Alzheimer's disease in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a TTS which incorporates as active agent a cholinesterase inhibitor in free or pharmaceutically acceptable salt form."

31. The Application continues on page 9 in these terms:

> "Little has been published in detail on rivastigmine's biopharmaceutical properties in humans. It is rapidly and completely absorbed. We have found that it is metabolised mainly through hydrolysis by esterases, e.g., acetyl and butyryl cholinesterase and has a plasma half life of 1 hour. It is subject to pre-systemic and systemic metabolism. We now have found that a TTS containing rivastigmine may be produced with advantageous properties, e.g., better tolerability."

32. After a description of further embodiments of the invention and how a TTS of the invention may be made, the Application continues on page 11:

> "The TTS of the invention allows, e.g., the manufacture of once a day pharmaceutical forms for patients who have to take more than one dose of an active agent per day, e.g., at specific times, so that their treatment is simplified. With such compositions tolerability of rivastigmine may be improved, and this may allow a higher starting dose and a reduced number of dose titration steps.
>
> A [sic] increased tolerability of rivastigmine provided by the compositions may be observed in standard animal tests and in clinical trials."

33. This is an aspect of the teaching upon which Novartis places particular reliance. However, as the judge himself observed, the reference to the "TTS of the invention" must be a reference to a TTS having the specified three-layer structure. Further, the disclosure is qualified. The Application says that the tolerability of rivastigmine may be improved and that this improvement may allow a higher starting dose and a reduced number of dose titration steps. It also says that this improvement may be observed in standard animal tests and in clinical trials. Importantly, this is the only reference in the Application to a "starting dose" and it does not say that all rivastigmine-containing TTSs of the invention will have improved tolerability and will allow a higher starting dose and a reduced number of dose titration steps, but only that some of them may do.

34. There follows a description of a single example. Section I, entitled "TTS production", describes the production of two TTSs. The first, TTS#1, has a conventional reservoir layer which is saturated with rivastigmine. The second, TTS#2, has the same reservoir layer but an additional silicone adhesive layer with a specified composition.

35. Section II describes a test to determine the adhesive force of the two TTSs and says that the use of an additional silicone adhesive layer increases the adhesive force by about five times over that of a comparable TTS without such a layer.

36. Section III describes a test to assess whether the application of the additional silicone adhesive layer affects the permeation of rivastigmine through human skin and EVA membranes. The results are illustrated graphically and it is said that they demonstrate that practically no differences with regard to permeation rates were observed between the two TTSs. Surprisingly, it continues, the application of the additional silicone adhesive layer had no influence on active ingredient permeation through the skin.

37. Section IV is concerned with pharmacokinetic properties and describes an open-label, parallel-group, four-period, ascending dose-proportionality study. It evaluated TTS#2 patches in four sizes, namely 5 cm^2, 10 cm^2, 15 cm^2 and 20 cm^2 against the four standard oral doses of rivastigmine capsules, 1.5 mg, 3 mg, 4.5 mg and 6 mg capsules b.i.d. The patients had mild to moderate AD and were put on 14 day titration steps, starting with the lowest dose and, at the time of the analysis, the number of patients completing each of the four periods was recorded. Details are set out in the table below:

Capsule	TTS#2
19 patients in the 1.5 mg bid dose	18 patients in the 5 cm^2 dose
18 patients in the 3.0 bid dose	18 patients in the 10 cm^2 dose
13 patients in the 4.5 mg bid dose	16 patients in the 15 cm^2 dose
12 patients in the 6.0 mg bid dose	11 patients in the 20 cm^2 dose

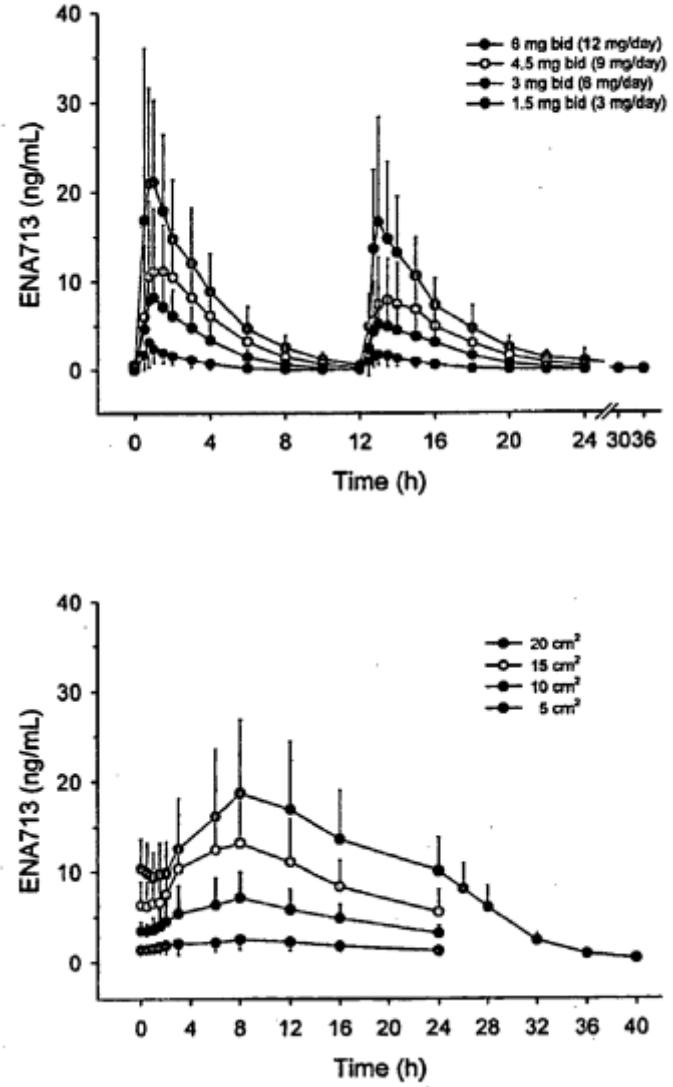
38. The pharmacokinetics of rivastigmine were investigated on the last day of treatment at each dose level, except for the highest dose level, where they were investigated on the third day. The results are set out in Table 1 (in respect of the capsule treatment) and in Table 2 (in respect of the TTS#2 treatment). The mean plasma concentration-time profiles are set out in Figure 4. The judge helpfully summarised the relevant data in

Tables 1 and 2 concerning AUC_{24h} in the following table which appears in his judgment at [58]:

Capsule	**AUC_{24h}**	**Patch**	**AUC_{24h}**
1.5 mg bid (3 mg)	12.3 $\pm$ 7.41	5 cm^2 (9 mg loaded dose)	45.6 $\pm$ 16.6
3 mg bid (6 mg)	52.7 $\pm$ 20.2	10 cm^2 (18 mg loaded dose)	123 $\pm$ 41.0
4.5 mg bid (9 mg)	90.4 $\pm$ 45.1	15 cm^2 (27 mg loaded dose)	226 $\pm$ 85.5
6 mg bid (12 mg)	150 $\pm$ 58.8	20 cm^2 (36 mg loaded dose)	339 $\pm$ 138

39. It is also useful to have in mind the graphical representations contained in Figure 4:

Fig 4:



40. The claims reflect the invention described in the body of the Application. Claims 1 to 14 concern a TTS comprising a backing layer; a reservoir layer comprising one or more pharmaceutically active ingredients and one or more polymers; and an adhesive layer comprising a silicone polymer and a tackifier. Claims 15 to 19 relate to TTSs comprising rivastigmine and which provide a C_{max} and AUC_{24h} in accordance with the various ranges disclosed in the body of the Application. No claim discloses the use of any TTS to provide a starting dose, however.

The Patent

41. The Patent begins with the following description of the invention:

> "The present invention relates to rivastigmine, in free base or pharmaceutically acceptable salt form, for use in a method of preventing, treating or delaying progression of dementia or Alzheimer's disease, wherein the rivastigmine is administered

> in a Transdermal Therapeutic System and the starting dose is as defined in claim 1."

42. I should also refer to [0016] which reads:

> "In one aspect, the present invention provides rivastigmine, in free base or pharmaceutically acceptable salt form, for use in a method of preventing, treating or delaying progression of dementia or Alzheimer's disease, wherein the rivastigmine is administered in a TTS and the starting dose is as defined in claim 1."

43. As the judge observed, the remainder of the description of the Patent is similar to that of the Application although there are a number of significant differences. The judge described these differences in concise terms from [65] to [68] of his judgment:

> "65. The remainder of the description of the Patent is broadly similar to that of the Application, but there are a number of differences. The principal differences are as follows. First, whereas the Application said that "[t]he present invention provides" a TTS comprising a backing layer, a reservoir layer and an adhesive layer, and so on, the Patent instead refers to "one embodiment [of] the present disclosure" of the Patent doing so, to "a TTS according to the disclosure" or to "a TTS as used in the invention" etc (see, for example, [0019], [0020] and [0022]). Similarly, whereas in the Application there was reference to preferred embodiments having particular characteristics in relation to e.g. the reservoir or silicone adhesive layer, in the Patent the corresponding passages now refer to preferred embodiments in which the TTS comprises such a reservoir or silicone adhesive layer (see, for example, [0032] to [0043]).
>
> 66. Secondly, the extensive definition of "active ingredient" contained in the Application has been deleted from the Patent.
>
> 67. Thirdly, the passage concerning better tolerability (at [0049] corresponding to page 9 of the Application [quoted at [31] above] is no longer followed by the consistory clauses concerning the specified pharmacokinetic profiles.
>
> 68. Fourthly, the passage referring to the starting dose (at [0057] corresponding to page 11 of the Application [quoted at [32] above] now refers to the TTS "used in", rather than "of", the invention."

44. The Patent has one claim which the parties have broken down into the following integers:

[1] Rivastigmine for use in a method of preventing, treating or delaying progression of dementia or Alzheimer's disease,

[2] wherein the rivastigmine is administered in a TTS and

[3] the starting dose is that of a bilayer TTS of 5 cm^2 with a loaded dose of 9 mg rivastigmine,

[4] wherein one layer: has a weight per unit area of 60 g/m^2 and the following composition:

- rivastigmine free base 30.0 wt %

- Durotak® 387-2353 (polyacrylate adhesive) 49.9 wt %

- Plastoid® B (acrylate copolymer) 20.0 wt %

- Vitamin E 0.1 wt %

[5] and wherein said layer is provided with a silicone adhesive layer having a weight per unit area of 30 g/m^2 according to the following composition:

- Bio-PSA® Q7-4302 (silicone adhesive) 98.9 wt %

- Silicone oil 1.0 wt %

- Vitamin E 0.1 wt %

Construction

45. There was one issue of construction before the judge and the allegation of infringement turned on it. The claim for infringement has now been compromised. However, I must still deal with the issue of construction because it bears upon the issues of validity. The judge summarised Novartis' argument in these terms at [95]:

> "Novartis' construction of the claim is that it has three components. First, it is a claim to rivastigmine for use in treating dementia or AD. Secondly, the rivastigmine is administered via a TTS. Thirdly, the "starting dose" of rivastigmine administered by the TTS is the dose released by a reference TTS which is specified in integers [3], [4] and [5] of the claim. Thus the TTS may have any structure or composition providing it can be used to deliver the same starting dose. "

46. The defendants argued that the claim is limited to the delivery of rivastigmine using a 5 cm^2 patch having the specific structure and characteristics of TTS#2 as described in integers [3] to [5]. Had the judge accepted this argument, the allegation of infringement would have fallen away because the defendants' patches have a structure which is different from that of TTS#2.

47. The judge preferred the submissions of Novartis, as he explained at [97]:

> "In my judgment Novartis' construction is the correct one. Although counsel for the Defendants advanced a number of arguments in support of the Defendants' construction, none of them really engaged with the language of the claim, and in particular the words "the starting dose is that of" in integer [3]. The natural meaning of those words is that the method of administration involves a starting dose which is the same as that of a TTS having the specified characteristics. If the patentee had intended to claim administration of rivastigmine via a TTS having the structure of TTS #2, then those words would be redundant…"

48. Upon this appeal Mr Daniel Alexander QC, who appears with Mr Henry Ward on behalf of Focus and Actavis, submits that the judge fell into error and that the defendants' interpretation of the claim is correct for four reasons which may be summarised as follows. First, where the claim refers to the starting dose of rivastigmine being "that of" the defined patch, it is using the words in the sense of the starting dose being "from" the defined patch. Secondly, the Patent is directed to the benefits obtained by the use of a three layer patch with a silicone adhesive layer. That is what it teaches and that is what the example is directed to. If the claim does not define any particular patch then this teaching is a nonsense. Thirdly, the benefits said to be associated with the invention, and in particular the provision of a patch containing a large amount of the active ingredient and having good adhesion without affecting the release profile, are inconsistent with Novartis' construction but supportive of that of the defendants. Finally, Novartis' construction means that the claim covers any patch of any structure and in any set of titration steps which start with a suitable starting dose, and this is divorced from the teaching of the Patent and would achieve none of its objectives.

49. I believe the judge was right to prefer the submissions advanced by Novartis. The opening words of integer [3] "the starting dose is that of a bilayer TTS of 5 cm^2" make it clear that this feature is directed to the starting dose in a course of treatment and that this starting dose is defined by reference to the dose administered by the particular TTS described in the claim. In short, the TTS described in the claim is a reference TTS. In my judgment the interpretation for which the defendants contend is inconsistent with the plain meaning of the words of the claim.

50. As for the other arguments advanced by the defendants, I can deal with these quite shortly. I accept, as did the judge, that the skilled team would understand from the specification of the Patent that a TTS with the three layer structure of TTS#2 would enable them to achieve the claimed starting dose but there are passages in the specification which make it clear that the invention is not limited to the use of this particular TTS and instead extends to the use of TTSs with different structures. The specification as a whole teaches the reader that the invention is directed to rivastigmine for use in a method of treating dementia or AD in which the rivastigmine is delivered by a TTS and the starting dose is that delivered by the TTS defined in the claim. Put another way, the specification teaches that with a TTS, a higher starting dose, namely the dose delivered by the TTS defined in the claim, may be used.

51. It follows that the judge construed the Patent correctly.

Added matter

52. Novartis were faced at trial with a wide-ranging and somewhat unfocused added matter attack. The judge helpfully condensed it, however. He explained that the defendants contended that the Patent presents the skilled team with information which is not directly and unambiguously derivable from the Application in three main ways:

    i) first, the skilled team is informed for the first time that the invention lies in the selection of a particular starting dose for rivastigmine administered via a TTS for the treatment of dementia or AD;

    ii) secondly, the skilled team is informed for the first time that the dose delivered by the 5 cm^2 TTS#2 should be used as the starting dose; and

    iii) thirdly, the skilled team is informed for the first time that this starting dose may be obtained using a TTS which does not have the structural and compositional features disclosed in the Application.

53. The judge dealt with these allegations in reverse order but before doing so he summarised the teaching of the Application and the Patent at [105]:

> "I have set out the disclosure of the Application in some detail above. In summary, it discloses an invention which has two main aspects. The first aspect concerns a three-layer TTS. The second aspect concerns a TTS providing C_{max} and AUC_{24h} values of rivastigmine within the broad ranges disclosed and claimed in the Application. I have also set out the disclosure of the Patent above. In summary, it discloses an invention in which rivastigmine is administered via a TTS with a starting dose which is the same as that of a reference patch, namely a 5 cm^2 TTS #2 patch."

54. As a high level summary, this is, I think, entirely fair. But Mr Hinchliffe QC, who appears on behalf of Novartis, contends that the relevant detailed teaching of the Application goes rather further, as I shall explain.

55. The third point was dealt with by the judge at [107]. Novartis treated this as an allegation of claim broadening and contended that this was permissible provided that it did not add subject matter. It continued that, although the claim covers a starting dose obtained by TTSs having different structural and compositional features, it does not disclose such TTSs. The judge accepted that neither the claim nor any other passage in the Patent discloses any particular composition of TTS other than TTS#2 but continued:

> "… in my judgment that does not meet the Defendants' point. What the Patent tells the skilled team for the first time is that it is the starting dose delivered by the TTS that matters, not the structure or composition of the TTS, whereas previously the structure and composition of the TTS was presented as the core of the invention."

56. Turning to the second point, the judge thought that this had been treated by Novartis as an allegation of an intermediate generalisation, namely that the Application disclosed a particular starting dose only in the context of TTS#2 and that it was not legitimate to take that feature from the specific embodiment in the example without the other features of that embodiment. The judge then recorded the submission made on behalf of Novartis that it would be clear to the skilled team that any TTS that released the same amount of drug as the 5 cm^2 TTS#2 would have the same therapeutic effect irrespective of the structure and composition of the patch. Finally, after addressing a particular passage in the cross examination of the defendants' expert, Professor Williams, upon which Novartis particularly relied and after referring to aspects of the teaching of the Application to which I shall come, the judge expressed his conclusion at [112]:

> "… the claim in the Patent is an intermediate generalisation because it takes the feature of the starting dose delivered by a 5 cm^2 TTS #2 stripped of its context in the example when it would not be clear to the skilled team that that feature was generally applicable or that the other features of the example were inessential to the invention."

57. That left the first point which the judge disposed of at [113]:

> "Turning to the Defendants' first point, counsel for Novartis really had no answer to this. In my judgment it encapsulates the fundamental objection to the Patent when compared with the Application."

58. Upon this appeal there was no dispute as to the applicable principles. They were explained by the Court of Appeal in *Vector Corp v Glatt Air Techniques Inc* [2007] EWCA Civ 805, [2008] RPC 10 at [4] to [9], *Napp Pharmaceutical Holdings Ltd v ratiopharm GmbH* [2009] EWCA Civ 252, [2009] RPC 18 at [98] to [99], and most recently in *Nokia Corp v IPCom GmbH & Co KG (No 3)* [2012] EWCA Civ 567, [2013] RPC 5 at [46] to [60].

59. Ultimately the key question in this case is whether the Patent presents the skilled person with information about the invention which is not directly and unambiguously apparent from the Application. There can be no doubt that the judge had the relevant principles well in mind. Nevertheless, Mr Hinchliffe submits that the judge fell into error at each stage of his analysis. In doing so, he has addressed each of the points identified by the judge and has done so in what I consider to be the most logical order, that is to say the order in which the judge originally set them out and which I have summarised at [52] above. It has also emerged during the course of these submissions that the first and second points are closely related and are conveniently dealt with together.

60. Mr Hinchliffe has developed his submissions on the first and second points as follows. He contends that there is no requirement that a patent application must identify explicitly in which parts of the application the invention resides. Further, he continues, there is a disclosure in the Application of the importance of the starting dose for rivastigmine administered via a TTS for the treatment of dementia or AD. Here he attaches particular significance to the passage on page 11 of the Application

that I have set out at [32] above and contends that this (in light of the passages on pages 1 to 3 and 8 to 11 and claims 15 to 18 to which I have also referred) teaches that a TTS is suitable for administering a higher starting dose of rivastigmine and a reduced number of titration steps.

61. Mr Hinchliffe also relies heavily on Section IV of the example, the details of which I have set out at [37] to [39] above. As I have explained, this study evaluated the use of rivastigmine delivered by TTS#2 against rivastigmine delivered orally in patients with mild to moderate AD. In the TTS#2 arm, patients were given TTSs in ascending sizes of 5 cm^2, 10 cm^2, 15 cm^2 and 20 cm^2. In the oral arm, patients were given ascending doses following the standard (approved) oral rivastigmine regimen starting at 1.5 mg b.i.d. and increasing to 3 mg, 4.5 mg and finally 6 mg b.i.d. The table in section IV sets out some of the results. For convenience, I reproduce it again below:

Capsule	TTS#2
19 patients in the 1.5 mg bid dose	18 patients in the 5 cm^2 dose
18 patients in the 3.0 bid dose	18 patients in the 10 cm^2 dose
13 patients in the 4.5 mg bid dose	16 patients in the 15 cm^2 dose
12 patients in the 6.0 mg bid dose	11 patients in the 20 cm^2 dose

62. The data in this table speak for themselves, contends Mr Hinchliffe, and show that the patch form was tolerated at least as well as, if not better than, the oral dosages. Further, although Professor Ballard, Novartis' expert, agreed in cross examination that the table had limitations from the point of view of comparing the tolerability of the two regimes, he remained of the view that it was a reasonable comparison.

63. Turning to the pharmacokinetic data, Mr Hinchliffe points out that the AUC_{24h} for the 5 cm^2 patch is almost four times higher than that for the 1.5 mg b.i.d. oral dose (mean of 45.6 ng.h/ml as compared to 12.3 ng.h/ml) and comparable to that for the 3 mg b.i.d. dose. Thus, in Example IV, a starting dose delivered by a 5 cm^2 patch was used and this produced an AUC comparable to the first therapeutic oral dose of 3 mg b.i.d. So, says Mr Hinchliffe, this shows that with a TTS, patients can, as taught by the passage on page 11, receive a higher starting dose and a reduced number of dose titration steps.

64. I am not persuaded by these submissions. I accept that the passages on page 8 of the Application to which I have referred describe in general terms a TTS for use in treating dementia or AD and a method of treating dementia or AD which comprises administering to the patient a therapeutically effective TTS which incorporates an appropriate cholinesterase inhibitor, but there is no disclosure here of any starting dose. So too, page 9 of the Application discloses that a TTS containing rivastigmine may be produced with advantageous properties, such as better tolerability, but once again, it does not disclose any starting dose. As for page 11 of the Application, the passage on which Novartis places particular reliance, I acknowledge that this does refer to a starting dose (indeed, as I have said, it is the only passage in the Application which does) but, as I have explained (see [33] above), this is qualified and says no more than that the invention *may* allow a higher starting dose and hence a reduced number of titration steps. Certainly there is nothing here by way of a disclosure of the administration of rivastigmine by a TTS with a starting dose as claimed in the Patent.

65. That brings me to the example, Tables 1 and 2 and Figure 4. I accept that TTS#2 was used and that the reader would also discern from the AUC data that the AUC_{24h} of the 5 cm^2 TTS#2 loaded with 9 mg of rivastigmine was comparable to that of the 3 mg b.i.d. capsule; and from the table reproduced at [61] above that the patients in the oral arm of the study were started on 1.5 mg b.i.d. whereas those in the patch arm were started on the 5 cm^2 TTS#2 loaded as I have described. I accept too that the reader would see the numbers of patients enrolled in each arm of the study and how many of them proceeded through the various titration steps. But I do not agree that this, together with the other passages of the Application to which I have referred, constitutes a disclosure of the use in therapy of a starting dose of rivastigmine or that such a starting dose should be that delivered by the 5 cm^2 TTS#2. As the judge observed, there is no information about the level of side effects experienced by the patients in each arm of the study and there are no data to show that the dose delivered by the 5 cm^2 TTS#2 was better tolerated as a starting dose than the dose delivered by the 3 mg b.i.d. capsule regimen would have been.

66. I am therefore satisfied the judge was right to find that the Patent does disclose matter extending beyond that disclosed in the Application in that it discloses the use of a particular starting dose for rivastigmine delivered by a TTS and that this starting dose should be the dose delivered by the 5 cm^2 TTS#2 loaded with 9 mg of the drug.

67. That brings me to the third aspect of the added matter allegation, that is to say that the Patent discloses that the claimed starting dose may be delivered by a TTS which does not have the structural and compositional features disclosed in the Application.

68. Mr Hinchliffe submits that the judge fell into error here in two respects. He argues first, that although the claim covers a starting dose obtained from a TTS of a different structure, there is no disclosure of such a TTS. This is therefore a case in which the distinction between what a claim covers and what it discloses is important. The judge wrongly held that the Patent discloses for the first time that it is the starting dose delivered by the TTS that matters, not the structure or composition of that TTS.

69. Secondly, continues Mr Hinchliffe, there was in any event no added matter because the skilled reader of the Application would understand that any TTS that released the same dose as the 5 cm^2 TTS#2 would have the same effect. In that regard Mr Hinchliffe places particular weight on the following passage in the cross-examination of Professor Williams:

> " Q. Now, if the skilled team looked at this document in 2005, they would be aware that the patch being described, the TTS2 patch, and indeed the TTS1 patch, delivered a certain dose to the skin at a certain rate.
>
> A. Yes.
>
> Q. And in so far as the starting dose produced a certain effect on the body; okay, which was deemed by the clinician to be beneficial, it would be apparent that you could make other patches also delivering the same dose at the same rate that would do the same.

> A. Yes.
>
> Q. And reading this document the skilled person would have no doubt that there would be other patches that could produce the same effect with the same starting dose.
>
> A. That is correct.
>
> Q. And they would not think that the effect can only be achieved with that particular design of patch, that particular TTS2 design of patch.
>
> A. This particular composition, no."

70. The judge considered this evidence in the context of the second point but Mr Hinchliffe submits (and I agree) that the issues it raises and the way the judge dealt with them are relevant to this, the third point. The judge held the evidence did not assist Novartis for three reasons. First, the use of the word "apparent" in the second question failed to distinguish between what the document would disclose to the reader expressly or impliedly and what would be obvious to the reader. Secondly, the second question required the witness to assume that the starting dose produced a certain effect on the body which was deemed by the clinician to be beneficial. This assumption was not justified because all that the skilled reader of the Application is explicitly told about the starting dose is that the TTS of the invention *may* allow a higher starting dose, and hence a reduced number of titration steps. As the reader would appreciate, whether this could be achieved would depend on whether the higher starting dose was tolerated, and in that regard there are no data to show that the 5 cm^2 TTS#2 was better tolerated as a starting dose than the 3 mg capsule b.i.d. would have been. Finally, the Patent claim is an intermediate generalisation because it takes the feature of the starting dose delivered by a 5 cm^2 TTS#2 stripped of its context when it would not have been clear to the skilled reader that this feature was generally applicable or that the other features of the example were inessential to the invention.

71. Mr Hinchliffe argues that each of these three reasons is misconceived. He submits that the judge's focus on the use of the word "apparent" amounted to an over-meticulous analysis of the evidence and that the question was in any event perfectly apposite. Secondly, the Application teaches that the benefit of tolerability of a higher starting dose will be obtained across the width of the claim, and this teaching is plausible. And finally, it is apparent from the evidence of Professor Williams that the skilled reader would understand that any patch delivering the same dose in the same way would have the same effect, and so would confer the same benefit in terms of tolerability.

72. In my judgment Mr Hinchliffe's characterisation of the disclosure of the Patent claim is not complete. He is right that the claim does not disclose any particular patch with a structure which is different from that of TTS#2. But that is not the case he has to meet. What is said by the defendants, correctly in my view, is that the claim discloses the administration of rivastigmine in a TTS and at a particular defined starting dose, that is to say the dose delivered by TTS#2 loaded with 9 mg of the drug. Put another way, the claim discloses the administration of rivastigmine at a particular starting dose, irrespective of the structure and composition of the TTS which is used for that purpose.

73. The next question is whether this subject matter is clearly and unambiguously disclosed in the Application. I do not believe that it is. Not only is there no disclosure in the Application of the use of any particular dose as a starting dose, a matter which I have already addressed, but there is also no disclosure that the starting dose may be delivered by a TTS which does not have the structural and compositional features of the TTS disclosed in the Application. To the contrary, the Application presents the structure and composition of the TTS it describes as the core of the invention.

74. In an attempt to meet this difficulty, Mr Hinchliffe turns to the passage in the cross-examination of Professor Williams which I have set out at [69] above and contends that this establishes that it would be implicit to the skilled person reading the Application that other TTSs could be made which would deliver the same starting dose as the 5 cm^2 TTS#2 at the same rate and in the same way. However, I believe the judge was entitled to say that this does not get Novartis home. He was in the best position to assess the evidence of Professor Williams and the context in which it was given and I believe that his conclusion that the second question failed to distinguish between what the document would clearly and unambiguously disclose to the skilled person expressly or impliedly and what would be obvious to that person is not one with which we should readily interfere. Secondly, Professor Williams was asked to assume that the starting dose produced a certain effect on the body which was deemed by the clinician to be beneficial. However, the disclosure of the Application does not support that assumption for all of the reasons I have given, and the judge was right so to hold. As for the judge's third reason, this is a consequence of his first and second reasons. The Patent teaches that other TTSs which deliver the same starting dose as the 5 cm^2 TTS#2 will have the same effect on the body when this was not clearly and unambiguously disclosed in the Application. In other words, it would not have been clear to the skilled team that the structure of TTS#2 was not necessary to produce that effect.

75. For these reasons I am satisfied the judge was also right to hold that the Patent does disclose matter extending beyond that disclosed in the Application in that it discloses that the claimed starting dose may be delivered by a TTS which does not have the structural and compositional features disclosed in the Application.

76. I would therefore dismiss the appeal against the finding that the Patent is invalid for added matter. It discloses added matter for the reasons I have explained.

Obviousness

77. As I have mentioned, the allegation of obviousness was based upon a single item of prior art - US 031 - entitled "TTS containing an antioxidant" published on 1 January 2002.

78. This publication is directed primarily to the manufacture of transdermal patches containing an antioxidant. It explains that rivastigmine (referred to as "Compound A") is susceptible to degradation, particularly in the presence of oxygen and so proposes the use of a TTS comprising Compound A and an antioxidant. There is no dispute that it describes TTSs for this purpose which have the structure and composition of TTS#2. Indeed Example 4 describes one such patch.

79. US 031 says this about dosing (column 6, line 46 to column 7, line 14):

> "The transdermal devices of the invention in general have, for example, an effective contact area of pharmaceutical composition on the skin of from 1 to about 80 square centimeters, preferably about 10 square centimetres, and are intended to be applied at intervals of about once every 1 to 7 days, preferably 1-3 days. Compound A is well tolerated at a dose of 36 mg in free base form in up to 80 cm^2 of patches according to the invention containing 36 mg compound A from which 12 mg was absorbed. Compound A may, for example be administered at a dose of 8 mg in a patch of ca. 10 cm^2, once every day. …
>
> … The exact amounts of compound A to be administered may depend on a number of factors, e.g. the drug release characteristics of the compositions, the drug penetration rate observed in vitro and in vivo tests, the duration of action required, the form of compound A, and for transdermal compositions the size of the skin contact area, and the part of the body to which the unit is fixed. The amount of and, e.g. area of the composition etc. may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of compound A in a composition according to the invention to intact skin and blood levels of Compound A observed after oral administration of a therapeutically effective dose of the compound.
>
> Orally, the Compound A is well tolerated at an initial dose of 1.5 mg twice a day orally and the dose may be stepped up to 3 mg twice a day in week 2. Higher doses are possible, for example 4.5 mg twice daily and even 6 mg twice daily. Tolerability is seen to be even better for the transdermal device, wherein 24 mg were absorbed in 24 hours."

80. It was accepted at trial that there is one difference between the Patent claim and the disclosure of US 031, namely that US 031 does not disclose a starting dose.

81. In assessing whether this step was obvious or required any degree of invention, the judge began (at [124]) by identifying four aspects of the common general knowledge about which there was really no dispute:

i) The skilled team would have been motivated to develop a formulation of rivastigmine which addressed the disadvantages of rivastigmine compared to donepezil. In particular, the skilled team would have been motivated to develop a formulation which enabled once daily administration.

ii) The skilled team would have known that a transdermal patch would be likely to enable once daily administration to be achieved.

iii) The skilled team would have ascertained, if necessary by routine testing, that the properties of rivastigmine made it suitable for administration by a transdermal patch.

iv) In developing a transdermal patch for rivastigmine, the skilled team's starting point would have been to seek to develop a patch which delivered an AUC_{24h} which matched that of an existing oral formulation, namely Exelon capsules.

82. The judge continued that, given this background, there was also no dispute that it would be obvious in light of US 031 to make a series of patches having the structure and composition of Example 4 which delivered AUC_{24h} values matching those of Exelon capsules. The real question was what dose the skilled team would select as the starting dose.

83. Novartis argued that the skilled team would try to match the AUC_{24h} values delivered by each of the daily doses in the oral regimen, starting with the 3 mg (1.5 mg b.i.d.) sub-therapeutic dose. It was accepted by the defendants that if the skilled team were to adopt that approach then they would administer a starting dose which would be less than half of that released by the 5 cm^2 TTS#2. Furthermore, they would follow the same titration steps as the oral regimen.

84. The defendants contended that it would be obvious to the skilled team to try the dose released by the 5 cm^2 TTS#2 as the starting dose in a small scale clinical trial for two reasons which may be summarised as follows. First, they would follow the teaching in US 031 that the size of the patch "may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of Compound A in a composition according to the invention to intact skin and blood levels of Compound A observed after oral administration of a therapeutically effective dose of the compound". Focusing on the words "therapeutically effective dose", they argued that the skilled team would appreciate that the lowest therapeutic oral dose of Exelon was 6 mg (3 mg b.i.d) and so would take that as the lowest dose to match. Routine bioavailability studies would then lead the skilled team to choose the dose released by the 5 cm^2 TTS#2 as the starting dose because it delivers an AUC_{24h} value approximately the same as the 6 mg daily oral dose.

85. Secondly, the skilled team would be familiar with the advantages conferred by administration of an API by a TTS to which I have referred at [14] above, that is to say the provision of a smoother delivery curve. Further, and based upon the skilled team's knowledge of the food effect, they would think it reasonably likely that the dose administered by the 5 cm^2 TTS#2 would be sufficiently well tolerated to be used as a starting dose. This would have the benefit of delivering a therapeutically effective dose from the outset and eliminating a titration step. Certainly they would think the likelihood of success was sufficient to warrant a small scale clinical trial.

86. The judge preferred the defendants' case for both of the reasons they gave. He had regard (at [132]) to evidence given by Professor Ballard that it was routine at the priority date when developing a new formulation to perform dose titration studies to determine the appropriate starting dose and the maximum dose. He also took into account that the selection of the appropriate starting dose would be a matter of judgment having regard to the balance between efficacy and side effects.

87. The judge next referred to the fact that, while the side effects of rivastigmine therapy could be unpleasant, they were generally not severe. He also explained that the inventors were not themselves put off trying the dose released by the 5 cm^2 TTS#2 as the starting dose:

> "133. It is also important to remember that, while the side effects of rivastigmine could be unpleasant for patients, they were generally not severe. The inventors of the Patent were not put off trying the dose released by the 5 cm^2 TTS #2 as the starting dose in their study by the potential side effects, and there is nothing to suggest that they were taking a risk that the skilled team would not have been prepared to countenance. On the contrary, a paper by G. Lefevre *et al*, "Pharmacokinetics and pharmacodynamics of the novel daily rivastigmine transdermal patch compared with twice-daily capsules in Alzheimer's disease patients", *Nature*, 83, 106-114 (2008), published after the priority date, which describes more fully the trial reported in the Patent, indicates that the inventors followed exactly the reasoning advanced by the Defendants (at 106):
>
> > "The incidence of centrally induced cholinergic gastro intestinal side effects with rivastigmine has been associated with the high maximum plasma concentrations (C_{max}) and short times to C_{max}, (t_{max}) provided by oral administration. Measures that prolong t_{max} and reduce C_{max} such as the administration of rivastigmine capsules with food, may improve tolerability of cholinesterase inhibitors.[8,9] For a given level of exposure, the transdermal administration of rivastigmine, by providing continuous delivery of drug with reduced fluctuations in plasma levels (i.e., lessening the rapid rise and fall of drug concentration), prolonging t_{max} and achieving a lower C_{max} is expected to reduce side effects. This may also offer additional therapeutic advantages over oral administration, such as access to higher doses, with the potential to improve compliance and treatment effects."
>
> (Reference 8 is Jann, Shirley and Small. Reference 9 is a post-priority date paper.)"

88. Finally, the judge expressed his conclusion:

> "134. In those circumstances, I conclude that it would have been obvious to try the dose released by the 5 cm^2 TTS #2 as the starting dose in a small scale clinical trial for both the reasons advanced by the Defendants. So far as the first reason is concerned, while it is true that US301 does not in terms instruct the skilled team to omit the sub-therapeutic dose, it cannot be inventive to do exactly what it does say. So far as the second reason is concerned, I consider that, having regard to the skilled team's motivation and the relative ease with which a small study could be carried out, the skilled team would have had a sufficient expectation of success to warrant trial. Accordingly, I conclude that the Patent is invalid for lack of an inventive step."

89. Mr Hinchliffe has vigorously attacked the judge's reasoning. As for the first way the defendants put their case, he submits that the particular passage in US 031 upon which the defendants focussed must be read in context and in light of the common general knowledge, and that the document, read as a whole, teaches that TTSs ought to reproduce the AUCs seen on administration of the well-known oral doses of rivastigmine, including the 1.5 mg b.i.d. dose. Moreover, he continues, it is perfectly clear that the parties' experts, Professor Ballard for Novartis and Professor Francis for the defendants, read it in exactly the same way. Mr Alexander, for the defendants, counters that the teaching of the document is plain and that the judge interpreted it entirely correctly.

90. In my judgment Mr Hinchliffe's criticisms of the judge's finding in relation to the first way the defendants put their case have substance. Professor Ballard considered the teaching of US 031 in detail in his first report and explained that, given the common general knowledge that rivastigmine had tolerability problems and the need to titrate vulnerable patients slowly from a well-tolerated starting dose, the document would not have been understood by the skilled team to be teaching the use of any particular starting dose with a TTS formulation. In his reply report, he responded to evidence given by Professor Francis in his report (and to which I shall come in a moment) and reiterated that US 031 does not refer to any starting dose, and that the fact that there is a suggestion to match the blood levels of rivastigmine observed after oral administration of a therapeutically effective dose provides no suggestion of an appropriate dosage regime or starting dose for rivastigmine when administered transdermally. Professor Ballard was not challenged upon this evidence in cross-examination. Instead it was put to him that the skilled person implementing the teaching of US 031 would do so using a range of different doses in order to try and match the AUCs of the existing oral formulation, and that that would be a routine thing to do. Professor Ballard agreed.

91. As for Professor Francis, he said in his first report that the skilled neuroscientist would note the specific suggestion in US 031 that the bioavailability testing should be carried out against therapeutically effective doses. This, he continued, would provide "some suggestion" that the patentee of US 031 did not think it necessary to produce a patch corresponding to the ineffective 1.5 mg b.i.d. formulation, presumably because the reported increase in tolerability rendered it unnecessary. In cross-examination, however, he appeared to accept that the reader would understand the document to be teaching that he should "map the oral experience".

92. The evidence on this issue was, after cross-examination and as Mr Hinchliffe submits, all one way. I am satisfied that the judge has fallen into error in failing to consider the teaching of US 031 as a whole and in the light of the common general knowledge and that he has brought hindsight to bear in considering the teaching of the particular passage in the document upon which this limb of the obviousness attack depends.

93. That brings me to the second way the defendants put their case. Mr Hinchliffe submits first, that the judge failed properly to take into account the way Professor Ballard was cross-examined and, in particular, that he was invited to assume that he had in front of him the data in the Patent. Secondly, the judge was wrong to rely upon the fact that the inventors of the Patent were not put off trying a dose released by the 5 cm^2 TTS#2 as a starting dose. Thirdly, it was apparent from the expert evidence that the skilled team would not have any expectation from the food effect that the need for the lowest

titration step could be avoided. And finally, the judge failed to take into account in his analysis a series of relevant matters including, in particular, the fact that the only known strategy for dealing with the side-effects of rivastigmine therapy was dose titration; that the mechanism causing those side-effects was complicated but thought to be the same as that which produced the desired efficacy; and that the inclusion in any treatment regime of a sub-therapeutic dose as the first titration step was highly unsatisfactory and yet considered to be essential.

94. Mr Hinchliffe has developed these submissions with care and skill but I find myself unable to accept them. The first and third of his points can be taken together because they both concern the expert evidence. We have been taken in the course of the appeal hearing to a great deal of that evidence. There are certainly passages, particularly in Professor Ballard's reports, which support the case advanced by Novartis. On the other hand, Professor Ballard accepted in cross-examination that if, in the course of a phase I dose escalation study, the initial dose looked incredibly well tolerated and had good properties then incremental attempts would probably be made to see "what doses were tolerated as a starting dose". He also accepted that dosing studies of this kind would be routine. It is true that reference was made by Mr Alexander to the data in the Patent but this was only to illustrate the kind of data that a suitable study would generate, and Professor Ballard was aware that it would not be right to "anticipate the patent". As for Professor Francis, he was clear that taking the critical step would not require a measure of creativity but would simply involve looking at the data the studies would generate. Overall, I am satisfied that there was a sufficient basis in the expert evidence to support the judge's finding that it was routine at the priority date when developing a new formulation to perform dose titration studies to determine the appropriate dose for initiating therapy, and that the claimed invention was obvious.

95. Turning to Mr Hinchliffe's second point and the judge's reasoning at [133], a court must of course be wary before attaching weight to an inventorship story in assessing obviousness for inventions may result from inspiration or serendipity. However, I believe that the judge was here doing no more than pointing to the inventors' account of their own reasoning, the fact that this was essentially the same as that said by the defendants to be obvious and the fact that the inventors observed that transdermal administration was "expected to reduce side effects". As the judge put it, there was nothing to suggest that the inventors took a risk that the ordinary skilled team would not have countenanced. As such it provided some confirmation that the defendants' approach was valid.

96. As for Mr Hinchliffe's fourth point, it is true that the judge's reasoning in this part of his judgment is concise but the matters he is said to have left out of account had all been addressed earlier in the judgment. He had no need to repeat them. Further, I am satisfied that he must have had well in mind that the oral administration of rivastigmine involved a series of dose titration steps; that the mechanisms causing side effects and efficacy were related; and that the inclusion of a sub-therapeutic dose titration step was considered to be essential.

97. At the end of the day this attack upon the Patent was entirely coherent. One of the well-known drawbacks of rivastigmine therapy was the need for a sub-therapeutic titration step to increase tolerability and minimise the cholinergic side effects. Further, it was generally accepted that rivastigmine should be administered with food and it was a reasonable hypothesis that administration in this way increased tolerability by

increasing t_{max} and reducing C_{max}. The skilled team would also have expected administration using a TTS to improve tolerability to an API because it "smooths out" the sharp peaks in blood plasma levels. It was therefore common-sense to try to administer rivastigmine by a TTS to improve tolerability, and this was in any event taught by US 031. The only question, therefore, is whether it was obvious to administer a therapeutically effective starting dose which was that of the 5 cm^2 TTS#2. It was obvious for the skilled team to try this, at least in a small scale clinical trial, because they would think it had a reasonable prospect of success in light of the food effect and the release profile of a TTS. There was also an incentive to do so because it would eliminate the therapeutically ineffective titration step. I am satisfied that the judge had ample evidence before him to support his finding that this was an obvious step to take.

98. It follows that the judge was entitled to find the Patent invalid for obviousness.

Insufficiency

99. The judge rejected the allegation that the Patent was invalid for insufficiency. By their respondents' notice the defendants contended that if Novartis were to succeed in their appeal against the finding of obviousness then the Patent would be insufficient. For the reasons I have given, I am satisfied that the judge was entitled to find the Patent invalid for obviousness and accordingly this aspect of the defendants' respondents' notice falls away.

Conclusion

100. I would dismiss the appeal.

Lord Justice Floyd:

101. I agree.

Lord Justice Hamblen:

102. I also agree.