Neutral Citation Number: [2017] EWHC 2711 (Pat)

Case No: HP-2016-000038

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice, Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 07/11/2017

Before :

THE HON. MR JUSTICE BIRSS

- -

Between :

ACCORD HEALTHCARE LIMITED	**Claimant**
- and -	
RESEARCH CORPORATION TECHNOLOGIES, INC	**Defendant**

- -

- -

Piers Acland QC and Will Duncan (instructed by **HGF Law**) for the **Claimant**
Tom Mitcheson QC and Stuart Baran (instructed by **Powell Gilbert**) for the **Defendant**

Hearing dates: 19th - 22nd, 27th-28th September 2017

- -

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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THE HONOURABLE MR JUSTICE BIRSS

Mr Justice Birss :

Introduction

1. This is a patent action. It relates to EP (UK) 0 888 289. The patent covers an anti-epileptic drug called lacosamide. The lacosamide compound is (R) -N-benzyl-2-acetoamido-3-methoxypropionamide. Lacosamide is a successful medicine, with annual worldwide sales projected for next year to reach €1 billion. The patent application was filed on 17th March 1997 claiming priority from a US filing on 15th March 1996. The patent expired on 18th March 2017. There is a supplementary protection certificate (SPC/GB09/007) which means that protection for lacosamide in this jurisdiction continues until 2022.

2. The claimant (Accord) is a generic pharmaceutical company. It contends that the patent is invalid. If it is right then the SPC will be revoked, clearing the way for generic competition. The defendant (RCT) is a technology investment and management company based in the USA. In effect the defendant works as a technology transfer office for a number of universities. This case concerns work done at the University of Houston by Professor Harold Kohn and his group. Prof Kohn and his group had been working on anticonvulsant compounds since the 1980s. The patent came out of that work. It is exclusively licensed to the pharmaceutical company UCB, who sell lacosamide to treat epilepsy under the brand name VIMPAT. A share of the licence fees paid to RCT under the licence goes back to the university and to Prof Kohn and the other relevant workers in the group.

3. Accord contend the patent is invalid on two grounds. Accord challenges the patentee's legal entitlement to claim priority from the 1996 priority document. If that challenge is successful then a paper by Choi becomes relevant prior art since it was published after the priority date but before the filing date. That paper makes lacosamide available to the public and there is no dispute that if priority is lost, the patent is invalid.

4. Accord's second challenge is obviousness. This is based on the state of the art before the priority date, which included a number of papers and other publications from Prof Kohn's group relating to their work on anticonvulsant compounds. Accord relies on

two starting points for the obviousness analysis. One is a master's thesis by a student called Philipe Le Gall. It is entitled *2-Substituted-2-acetamido-N-benzylacetamides Synthesis. Spectroscopic and Anticonvulsant Properties*. It was made available to the public in December 1987. Le Gall was a student of Prof Kohn. The other attack is based on a paper referred to as "Bardel" the full citation of which is given below. That also came from the work of Prof Kohn's group.

5. The attack based on Le Gall was originally put in two ways but by the closing Accord had narrowed its case over Le Gall to a single approach. Accord submits that it would be obvious for the skilled team given Le Gall at the priority date in 1996 to do a literature search to find what had come out of Prof Kohn's group in the nine years since the thesis. They would find a number of publications from the group. Accord contends that lacosamide is obvious over Le Gall taking that supplementary information into account. The other approach to Le Gall which had been part of Accord's case until closing was to rely on the thesis alone and not the supplementary information. That case was abandoned.

6. RCT denies the allegation of lack of entitlement to priority and denies that the invention is obvious.

7. There had been further points or squeezes on insufficiency and substantive priority concerning chronic toxicity but by the closing it was common ground they did not need to be addressed.

The witnesses

8. Accord called two technical experts: Professor Brian Cox, a medicinal chemist and Mr Reece Jones, a toxicologist.

9. Professor Cox is Professor of Pharmaceutical Chemistry at the School of Life Sciences, University of Sussex. Professor Cox received his PhD at the University of Manchester in 1986. He then had extensive experience in industry first at Schering-Plough and then at Glaxo Research Group from 1990. Whilst at Glaxo Research Group, Professor Cox worked on various of their medicinal chemistry programs, and was promoted to Research Leader in 1995. One of his projects was a study starting in September 1995 to look for analogues of the anticonvulsant sodium-channel blocker lamotrigine, seeking a treatment with improved tolerability. Around the same time, he was also lead chemist on a project to identify the molecular target of a competitor anticonvulsant product, retigabine and also worked on a project concerning calcium channel agonists as potential anticonvulsants. His Professorship at the University of Sussex started in 2014.

10. RCT levelled a number of criticisms of Professor Cox. The major ones were that: his positions were at odds with the textbooks, his views were influenced by hindsight, and he gave long answers which did not answer the questions put. I reject all of RCT's criticisms, for the following reasons. Professor Cox did not accept certain points in textbooks but that was an expression of his genuine views which he explained clearly. On hindsight, I do not accept Accord's case that Professor Cox's opinions on what is obvious over the prior art were fully formed without any reference to the patent. If it matters (and I believe it does not) the evidence did not establish that. However I also reject RCT's corollary that at some overall level the

fact that his views were formed after he had read the patent means they are necessarily tainted with hindsight. Professor Cox understood that the court's task in trying an obviousness case is to work out what would be obvious, without hindsight. He sought to help the court by explaining his opinions about that. As for long answers not answering the question, Professor Cox did give quite long answers but that was borne of his desire to ensure that the court understood his full opinions on the topic. Also it was not helped by occasions on which a question was put by presenting a summary of what the Professor's report was said to say but which missed out relevant details.

11. Professor Cox was a good witness, seeking to help the court resolve the issues in this case.

12. Mr Reece-Jones is a consultant toxicologist who trained as a toxicologist following receiving his HND in Applied Biology from Manchester Polytechnic. He started training at Hazleton in 1979, and he has worked both in-house in industry and at consulting toxicology companies. He worked as a study director since 1988. He has worked on a wide variety of compounds antibiotics, antihistamines, and central nervous system (CNS) compounds. He is a highly experienced toxicologist and was well placed to give evidence as to toxicology in 1996.

13. Mr Reece-Jones was barely cross-examined. By closing the point to which his evidence went had been dropped. I thank him for his attendance at court.

14. RCT called two technical experts: Professor Wolfgang Löscher, a pharmacologist and Professor Simon Ward, a medicinal chemist.

15. Professor Löscher is Professor and Director of Pharmacology, Toxicology and Pharmacy at the University of Veterinary Medicine, Hannover. He is also the founder of the Centre of Systemic Neurosciences there. He has worked in the field of anticonvulsant drugs since the 1970s. He has worked primarily as an academic but his work has always involved close links with industry and drug development.

16. Accord submitted that Professor Löscher's experience with drug development was primarily as a consultant brought in only when the drugs were already at a stage of pre-clinical development or later. The contrast was between that and experience of an earlier stage of drug development. Part of Professor Löscher's extensive work in this field did involve the tasks referred to by Accord, but I reject the submission that this qualifies his expertise. He knew very well how the *in vivo* pharmacological assays such as the MES test (see below) were used in early stage drug development and was well qualified to express opinions about all the issues he covered in this case.

17. Accord submitted he was an ardent advocate of criticism of the MES test in particular especially for its tendency, as he saw it, to produce "me too" drugs. So he was. I was not satisfied that this view of the MES test represented the common general knowledge at the relevant time. He also had strong views about the need to address drug resistant epilepsy in particular as opposed to treating epilepsy in general and again I am not persuaded those views represented the common general knowledge of a drug development team in 1996. He also had worked with and visited the NIH and had personal knowledge about the results of a comprehensive programme of testing

putative anticonvulsant compounds for drug developers which the NIH had been running for a number of years by 1996. I will deal with that in context if need be.

18. Professor Löscher was an excellent witness, seeking to help the court at all times.

19. Professor Ward is Visiting Professor of Medicinal Chemistry in the School of Life Sciences at the University of Sussex and is also Sêr Cymru Professor in Translational Drug Discovery and Director of Medicines Discovery Institute at Cardiff University. After graduating in chemistry in 1993 Professor Ward worked at the pharmaceutical company Chiroscience for a year and then went back to Cambridge to do his PhD (1994-1997). He then worked at the pharmaceutical company Cerebrus until moving to Knoll in 1999 and on to GSK in 2001 where he remained until taking up his Professorship at the University of Sussex.

20. Professor Ward was another good witness, seeking to help the court.

21. At the priority date (1996) Professor Ward was studying for his PhD. Accord submitted he was not in a position to assist the court about the attitudes, interests and common general knowledge of those in the field at the relevant date. Accord submitted his evidence about this could not be relied on. I do not accept the full extent of that submission. I distinguish between two different things. In my judgment Professor Ward was able and was well qualified to assist the court in relation to medicinal chemistry itself, in other words the way medicinal chemists apply their chemical knowledge and skill to the problems presented by pharmaceutical drug development. He is an expert medicinal chemist and was close enough to the field at the time to be able to assist the court. He was good at explaining things. Medicinal chemistry as a discipline did not change over the relevant period in a manner which would undermine Professor Ward's ability to assist. The fact he did not work on anticonvulsant or CNS drugs until much later does not matter. Medicinal chemists would routinely be called upon to work in a new field. Despite hints to the contrary by Accord, I find that Professor Ward's work since he graduated in 1993 has all been in or closely related to medicinal chemistry, with some synthetic chemistry as many medicinal chemists would also undertake particularly at the start of their careers.

22. However where the nature and timing of Professor Ward's personal experience is relevant and does qualify his ability to help is in addressing evidence about the general approaches of drug development teams in anticonvulsant medicine in 1996. He was not there.

23. The parties also called experts on US federal and state law. They were not cross-examined.

24. Accord relied on Professor Robert Merges for US federal law; and Judge Leonard Davis for the law of the state of Texas.

25. Professor Merges is the Wilson Sonsini Goodrich & Rosati Professor of Law and Technology at US Berkeley School of Law, a position he has held since 1995. He teaches Intellectual Property, Patent Law and Contracts and his research focusses on the economic aspects of intellectual property rights, with a focus on patents.

26. Judge Davis was the Chief Judge of the United States District Court for the Eastern District of Texas. That court is famous for its experience of patent law. From 2002-2015 Judge Davis managed one of the busiest dockets in the United States handling over 1700 patent cases a year, and personally tried as many as eleven jury trials in one year. The judge was also the Chief Judge of the Twelfth Court of Appeals of the State of Texas. He has now retired from the bench and works as Of Counsel at the law firm Fish & Richardson.

27. RCT's US law experts are: Professor Donald Chisum on US federal law and Judge David Folsom on Texas state law.

28. Professor Chisum has held various professorships at Stanford University, the University of Washington and Santa Clara University, each of which being Professor of Law. He is the author of Chisum on Patents, the well known text book on US patent law.

29. Judge Folsom is currently a partner in the law firm Jackson Walker LLP. From 1995 till 2012 he served as a United States District Court Judge, Eastern District of Texas (as Chief Judge from 2009-2012). During this time he heard over 250 trials and has presided over hundreds of patent cases.

30. Rightly, neither side suggested the US law experts were not qualified to give the evidence they did.

31. RCT also called a number of fact witnesses, who were not cross-examined. Their evidence related to the entitlement to priority issue. The witnesses were Professor Kohn himself, Dr Ramanan Krishnamoorti of the University of Houston and Mr Timothy Reckart formerly of RCT.

The skilled team and the common general knowledge

32. In this case the person skilled in the art is a team. The team will include a medicinal chemist and a pharmacologist as well as other disciplines.

33. The only aspect of chemistry worth mentioning at this stage is chirality. Many of the compounds in this case are chiral. Chiral compounds exist in two non-superimposable mirror image forms known as enantiomers. The compounds have a carbon atom with four bonds in a tetrahedral shape and different substituents attached to each of the four bonds. Chirality is common in biological systems and in many cases one enantiomer may have a completely different effect from another enantiomer. A racemate is an equal mixture of the two enantiomers.

34. Turning to clinical issues, the skilled team would know that epilepsies can be categorised by reference to the types of seizure that the patient suffers from. These can be broadly classed as partial or generalised seizures. The former arise in a localised area of the brain and are further classified as: "simple" (where consciousness is maintained); "complex" (where consciousness is lost or impaired); and "secondarily generalised" (involving convulsions). Generalised seizures arise in all or large parts of both cerebral hemispheres and comprise two main categories: "tonic-clonic"/"grand mal" (involving widespread convulsive activity); and "absence"/"petit mal" (where consciousness is impaired with little or no motor disturbance).

35. The treatment of epilepsy involves the administration of an anticonvulsant drug or cocktail of drugs. These are given chronically, with a view to preventing or reducing the incidence of seizures.

36. Various anticonvulsant drugs had been identified by the Priority Date including the "first generation" anticonvulsants phenytoin, phenobarbital and ethosuximide which had been discovered in the 1930s/1940s using animal models. Phenytoin remained a mainstay of the treatment of epilepsy at the priority date. Various other drugs were discovered in the "second generation" of anti-epileptic drugs, in the 1950's and 60's, including carbamazepine, sodium valproate and benzodiazepines. These too were found using animal models.

37. In the early 1990s, a number of new anticonvulsant drugs came on the market including vigabatrin, gabapentin, lamotrigine, clobazam, topiramate, felbamate, tiagabine, oxcarbazepine, zonisamide and progabide. Nevertheless, for the skilled team there remained a need for new and better anticonvulsants at the priority date.

38. To a pharmacologist interested in anticonvulsant drugs, there were various assays based on animal models which could be performed to evaluate the possible activity of candidate compounds. One was the MES test. MES stands for Maximum ElectroShock. It was a test in mice or rats in which a seizure is induced using a standardised electric shock, and the ability of a compound to prevent the seizure is measured. The effect of the drug is measured at a time after delivery called TPE (time of peak effect). The seizure is determined by HLE (hind limb extension) in the test animal. For a compound which is effective, the MES test produces an ED50 value. That is the dose in mg/kg require to protect 50% of the animals challenged. So a low ED50 is more desirable as it represents a higher potency.

39. Other kinds of assay used involved a chemically induced seizure instead of a seizure induced by an electric shock. An example is the sc Met test. The term sc Met refers to the subcutaneous (sc) administration of the compound Metrazol (pentylenetetrazol). That compound induces the seizures. The test is not the same as the MES test but it still produces an ED50 value. Other similar tests using a chemically induced seizure are the sc Bic and sc Pic tests. These use different compounds to induce seizures.

40. A different kind of animal test which was also routine was to see if the compound caused undesirable neurological symptoms. Put simply the point is that one may be able to treat seizures by giving a drug which acts as a sedative to the patient; however what is wanted is a drug which can treat the seizures without a major sedative effect. The possible sedative effect is assessed using these tests. One of them was the rotarod test, in which rodents which are trained to balance upon a rotating rod, are given the drug, and the unwanted neurotoxicity assessed by monitoring the extent to which the animal can stay on the rod. The other major test used was the horizontal screen test, in which the animals are placed upon a wire mesh that is slowly rotated 180^{o}. If the animals are unable to climb to the top of the screen in a certain period of time, this also demonstrates neurological impairment. Using these kinds of neurotoxicity tests it is possible to calculate the toxic dose which causes neurological impairment. This is calculated as a TD50 value.

41. The ratio of a compound's ED50 value to its TD50 value is known as its protective index (PI). The skilled team would want a compound with a good protective index, to

reduce the neurological toxicity issues with the compound – this was a key selection criterion.

42. The skilled team looking for promising new anticonvulsant compounds would gauge the putative compound's test results (ED50, TD50 and PI) in animal models such as the MES test against the results for known compounds, such as phenytoin. If the results were promising the team would screen good compounds in further animal models such as sc Met. Over time the ED50 levels in the MES test which a team would consider worth pursuing were dropping. Recognising that it is an over simplification to pick a value and state that the team would focus on that, nevertheless by 1996 a fair picture is presented by considering a team looking for ED50 values in the MES test of around 10 mg/kg or less along with a good PI.

The lacosamide patent

43. The patent starts with a statement that the invention relates to novel enantiomeric compounds and pharmaceutical compositions useful for treating epilepsy and other CNS disorders. The background section describes the use of anticonvulsant drugs to treat seizures, and summarises the two main kinds of seizures. Various existing drugs such as phenytoin and phenacemide are mentioned and there is a reference to a prior patent from the Kohn group. At paragraph [0006] the patent refers to problems with the existing agents including poor management of the disease and disturbing side effects. A particular point is made about the difficulty that these agents are administered chronically and this is associated with liver toxicity. In paragraph [0007] four criteria for an ideal anticonvulsant drug are set out:

> "(1) has a high anticonvulsant activity, (expressed as a low ED_{50});
>
> (2) has minimal neurological toxicity, (as expressed by the median toxic dose (TD_{50})), relative to its potency;
>
> (3) has a maximum protective index (sometimes known as selectivity or margin of safety), which measures the relationship between the doses of a drug required to produce undesired and desired effects, and is measured as the ratio between the median toxic dose and the median effective dose (TD_{50}/ED_{50}); and
>
> (4) is relatively safe as measured by the median lethal dose (LD_{50}) relative to its potency and is non-toxic to the animal that is being treated, e.g., it exhibits minimal adverse effects on the remainder of the treated animal, its organs, blood, its bodily functions, etc. even at high concentrations, especially during long term chronic administration of the drug. Thus, for example, it exhibits minimal, i.e., little or no liver toxicity."

44. The paragraph continues by explaining why, although not so critical for short term administration, the fourth criterion is extremely important for an anticonvulsant which is to be taken over a long period of time or in high dosage as follows:

> "It may be the most important factor in determining which anti-convulsant to administer to a patient, especially if chronic dosing is required. Thus, an anti-convulsant agent which has a high anti-convulsant activity, has minimal neurological toxicity and maximal P.I. (protective index) may unfortunately exhibit such toxicites which appear upon repeated high levels of administration. In such an event, acute dosing of the drug may be considered, but it would not be used in a treatment regime which requires chronic administration of the anti-convulsant. In fact, if an anti-convulsant is required for repeated dosing in a long term treatment regime, a physician may prescribe an anti-convulsant that may have weaker activity relative to a second anti-convulsant, if it exhibits relatively low toxicity to the animal. An anti-convulsant agent which meets all four criteria is very rare."

45. Next is a summary of the invention section which corresponds to claim 1. Although the patent is drafted on the basis of a class of compounds defined in claim 1, the extent of the class in claim 1 does not matter because claims 8 to 10 relate to lacosamide specifically. The remainder of the summary of the invention section states that administering the compounds of the invention provide an excellent regime for the treatment of epilepsy and some other CNS disorders.

46. The detailed description section starts with the general synthesis of the compounds. The synthesis described at Scheme 1 starts from the amino acid D serine and preserves the chirality of the starting material. A racemic serine can be used instead and the final product resolved to produce the relevant R isomer (paragraph [0030]). Wide general statements are made about dosing, route of administration, dosage forms and excipients (paragraphs [0031] – [0042]).

47. The examples start at paragraph [0044]. Examples 1, 2 and 5 provide alternative syntheses for lacosamide. Examples 3 and 4 relate to other compounds in the class of claim 1 (they are fluorinated). Comparative examples 1 – 13 relate to other similar compounds which are not within the claimed class.

48. Pharmacology is dealt with from paragraph [0077] and the results of various animal studies are in Table 1. They show testing of lacosamide and two other compounds within the claimed class along with a number of comparative example compounds. The tests are in mice (ip) and rats (po). The tests are MES and neurological toxicity via the rotarod test. The results report ED_{50} and TD_{50} values with some 95% confidence intervals. PI values are stated. The values for lacosamide are:

Compound	mouse (ip)			Rat (po)		
	MES ED_{50}	Tox TD_{50}	PI	MES ED_{50}	Tox TD_{50}	PI
Lacosamide	4.5 (3.7-5.5)	26.8 (25.5-28.0)	6.0	3.9 (2.6-6.2)	>500	>128.2

49. The patent summarises the data in Table I as a whole from paragraph [0079]-[0085] as showing that the R enantiomers of the invention have quite potent anticonvulsant activity and an excellent drug profile while the comparative compounds tested (save

for the furyl derivative) are significantly inferior drugs. Even if the level of neurotoxicity is low and the PI is satisfactory, the patent explains that one wants to administer as little drug as possible and so a low potency value is advantageous (paragraph [0085]).

50. Turning to chronic liver toxicity, in paragraphs [0086]-[0087] the patent explains that while both the furyl derivative and the compounds of the invention have a good drug profile, the furyl compound is more toxic to the animal, making it less suitable for chronic administration. The compound called BAMP (which is lacosamide) exhibited little if any toxicity to the animal. The animal toxicity tests on lacosamide are reported in [0089] to [0105]. There is a short term, 48 hour, study in rats in which minimal liver toxicity was shown. Then a longer term, 30 day, study in rats was run, which showed no histological evidence of an adverse effect at the highest doses. Toxicity studies are run on other compounds outside the invention. The results for those compounds and for BAMP/lacosamide are summarised in Table 6. The comparison favours BAMP/lacosamide.

51. The description ends at paragraph [0141] with a statement that the compounds of the invention have an excellent drug profile, meet all the four characteristics outlined before and can be used for chronic administration.

52. Claim 8 is a claim to lacosamide itself, in other words (R) -N-Benzyl 2-Acetoamido-3-methoxypropionamide. Claim 9 is to the "substantially enantiopure" compound of claim 8. Claim 10, as dependent on claim 9, is to the therapeutic composition of an anticonvulsant effective amount of substantially enantiopure lacosamide and a pharmaceutically acceptable carrier.

Priority

53. The right to claim priority is in section 5 of the Patents Act 1977. That section is one of the sections to which section 130(7) applies and so it is intended to have the same effect as the relevant parts of the EPC. In the EPC priority is governed by Art 87. This in turn gives effect to Article 8 of the PCT which in turn gives effect to Article 4(A)(1) of the Paris Convention. The Paris Convention is the origin of the international priority right.

54. Before getting into the law any further it is convenient to state the problem which arises in this case. The underlying facts are not in dispute.

55. For lacosamide the inventor was Prof Kohn. The US filing from which priority was claimed was made by Prof Kohn on 15th March 1996. The international application under the Patent Cooperation Treaty (PCT) filing number PCT/US97/04579, which matured into the patent in suit, was filed by RCT on 17th March 1997 claiming priority from that earlier filing. There is on the face of it a properly executed written assignment of the invention from Prof Kohn in favour of RCT dated 4th February 1997. The assignment expressly includes the right to claim priority at clause 5. In the context of priority it is convenient to refer to the relevant invention as lacosamide rather than refer to the whole subject matter of the patent in suit but nothing turns on that difference.

56. So is everything in order? Accord say it is not. Accord took a wide range of points prior to the trial but by the opening its case came down to a single point. Accord contends that the assignment of 4th February 1997 only took effect as an assignment of the bare legal title to the invention and priority claim. What it did not do was assign the equitable or beneficial title to that property to RCT. That equitable or beneficial title was with the University of Houston ("Houston"). It may (or may not) have ended up with RCT later but that does not matter. Accord submits that as a matter of law, what is required for the priority claim to be accepted in this court at this trial is that the substantive right to priority, also known as the equitable or beneficial title to that right, was with the correct party on the correct day. The correct party was RCT and the correct day was 17th March 1997 when the international application was filed. Accord contends that this did not happen and so the claim to priority should fail.

57. The reason the substantive right to priority might have been in the wrong place at the wrong time (if it was) is as follows. The first step is that for inventions made by faculty members or other university staff such as associates and employees at Houston, those individuals are obliged as a result of the contractual arrangements between them and the university to assign them to Houston (or to a person appointed by Houston such as RCT). That applies to all the relevant individuals here such as Prof Kohn and the others. This is common ground.

58. The second step is that Houston had a long standing agreement with RCT relating to inventions and patents. It started as an agreement in 1966 between Houston and RCT's predecessor. This is also common ground.

59. By that agreement Houston had the right but not the obligation to offer inventions to RCT. For any relevant invention made by its faculty/staff, Houston would make a decision whether or not to offer that invention to RCT. As between Houston and RCT it did not matter what internal Houston process was used to make that decision. What matters is that at all relevant times under the contract between Houston and RCT, Houston was not obliged to offer inventions to RCT. From RCT's point of view it was a decision in Houston's discretion. Conversely once Houston had disclosed and offered an invention to RCT, RCT was not obliged to accept it, RCT could choose to accept it or not. Again how the party (now RCT) made the decision was up to that party (RCT). If RCT decided to accept the invention it would notify Houston of that acceptance.

60. From now on pursuant to the contract, RCT would file and prosecute patent applications to protect the invention in its own name and Houston would ensure it could do so and execute or have executed all necessary assignments. A share of any revenue would be passed back to Houston. In fact under the arrangement some payments of modest sums such as $3,000 at one early stage would be made by RCT to Houston. Note that the disclosure and offering were all confidential so none of this makes anything available to the public and references to disclosure in this context have to be understood that way.

61. There was clear evidence of this arrangement working as described for some work by the Kohn group prior to lacosamide. The project was called "FAA" which means Functionalised Amino Acid. Compounds would be identified and tested by Prof Kohn and his group. For this purpose a group of related compounds is an invention.

Houston would consider whether to offer that invention to RCT. In fact it did decide to do so on a number of occasions. RCT would take the invention disclosure documents and consider them in order to decide whether to accept them. RCT in fact did decide to accept them and file patent applications. The compounds developed by Prof Kohn (not lacosamide) were licensed to Eli Lilly by RCT as licensor under these patent applications. The Lilly licence had come to an end before lacosamide.

62. The problem, says Accord, is that there is no evidence the proper process took place for lacosamide. There is no evidence of a disclosure by Prof Kohn to Houston of this invention in order for Houston to make its choice. Nor is there evidence of Houston, rather than Prof Kohn, offering the invention to RCT having decided to do so. So, says Accord, what seems to have happened is the following.

63. Prof Kohn made the invention. At that stage Prof Kohn was obliged by his obligations to the university to assign it to Houston or to their order. So analytically (says Accord) while Prof Kohn held the legal title, Houston held the equitable title since they had a legally enforceable right to call for an assignment of the legal title. Accord says this analysis is correct under US law (Federal and Texas state law). In fact Prof Kohn disclosed the invention to RCT and RCT did apply for patents. Prof Kohn also did execute the assignment mentioned already before the international PCT application was filed. But, says Accord, at the point in time before Prof Kohn signed the assignment to RCT, the equitable title was with Houston. The written assignment was not effective to move the equitable title from Houston to RCT and so the priority claim fails.

64. Accord's case rests on two points: first the legal requirements to establish a priority right and second the factual question of what actually happened in Texas in 1996/97 and what are the legal consequences in terms of legal and equitable ownership of property.

65. In order to address the first point it is necessary to understand where English law on entitlement to priority has got to. In ***Edwards Lifesciences v Cook Biotech*** [2009] EWHC 1304 (Pat) Kitchin J held as follows:

> "In my judgment the effect of Article 4 of the Paris Convention and section 5 of the Act is clear. A person who files a patent application for an invention is afforded the privilege of claiming priority only if he himself filed the earlier application from which priority is claimed or if he is the successor in title to the person who filed that earlier application. If he is neither the person who filed the earlier application nor his successor in title then he is denied the privilege. *Moreover, his position is not improved if he subsequently acquires title to the invention.* It remains the case that he was not entitled to the privilege when he filed the later application and made his claim. Any other interpretation would introduce uncertainty and the risk of unfairness to third parties."
>
> (my emphasis)

66. In the large majority of cases, including this one, a patent applicant starts the process of obtaining a patent by filing a patent application in their home state (e.g. here the USA). Then a year later an international application is filed under the PCT designating all states and claiming priority from that earlier regular national filing. The real importance of this passage from ***Edwards v Cook*** is in the sentence emphasised. In the normal case described its effect is that the applicant's title to the priority claim must be in place by the time the international application is filed. That is because it is that application which makes the priority claim, claiming as the priority date the filing date of the earlier application. If the applicant's entitlement to priority has not been secured by that time then the position cannot be fixed after the event. This is a critical aspect of Accord's case. The fact that the university and RCT today are making common cause does not help. Perhaps (and this is pure speculation) that common cause is the result of some accommodation reached after 17th March 1997 and therefore too late to save the priority claim.

67. ***Edwards v Cook*** has been followed and applied at first instance on a number of occasions including at least the following: Arnold J in ***KCI Licensing v Smith & Nephew*** [2010] EWHC 1487 (Pat) and ***Idenix v Gilead*** [2014] EWHC 3916 (Pat), Henry Carr J in ***Fujifilm v Abbvie*** [2017] EWHC 395 (Pat); and me in ***HTC v Gemalto*** [2013] EWHC 1876 (Pat). In ***KCI Licensing v Smith & Nephew*** and ***HTC v Gemalto*** the judges (Arnold J and myself respectively) accepted a significant softening to what otherwise might have been the rigour of the rule that the title must be secured by the time the international application is made, by accepting an analysis based on common law principles distinguishing the equitable and legal title to property. If the relevant local law meant that the equitable or beneficial title to the priority right was in the hands of the person making the priority claim in the international application, that was held to be good enough even though that person did not then hold the legal title under the local law and could only perfect their title after the event.

68. The critical passage in ***KCI*** is as follows. Arnold J had held that on its true construction the relevant agreement there did convey the legal title to the applicant but he went on to hold that even if that was wrong, the agreement was effective to transfer the entire beneficial interest. The applicant had an enforceable legal right to call for a conveyance of the bare legal title and that made the applicant the "successor in title" for the purposes of a claim to priority under Article 87(1) of the EPC and Article 4(A)(1) of the Paris Convention even if KC Inc had not acquired the bare legal title at the relevant date. After referring to a decision of the EPO Case J19/87 ***Burr-Brown /Assignment*** [1988] EPOR 350, Arnold J held:

> "71. To my mind, this makes sense. Article 4(A) of the Paris Convention and Article 87(1) of the EPC are provisions in international treaties whose operation cannot depend upon the distinction drawn by English law, but not most other laws, between legal and equitable title. *When determining whether a person is a "successor in title" for the purposes of the provisions, it must be the substantive rights of that person, and not his compliance with legal formalities, that matter*."
>
> (Accord's emphasis)

69. In ***HTC*** I referred to ***Edwards v Cook*** and noted in paragraph 132 that no-one in argument before me had challenged the proposition that a later acquisition of title to the invention was not enough. I referred to the above passages from Arnold J's judgment in ***KCI*** and stated at paragraph 134:

> "134. Mr Mellor submitted that this [*Arnold J's reasoning in KCI*] showed that as long as an applicant had, at the relevant date, what English law would characterise as a beneficial title to the invention, even if the bare legal title had not been acquired, then the applicant was a successor in title in the relevant sense. I did not understand Mr Tappin to dispute that and I think he was right not to. In my judgment if the relevant person has acquired the entire beneficial interest in the invention at the relevant time then that should be enough to satisfy the law."

70. When ***Idenix*** reached the Court of Appeal Kitchin LJ did not have to express a concluded view on the subject but expressed a provisional view that ***KCI*** and ***HTC*** were correct. Floyd LJ and Patten LJ agreed. ***Fujifilm*** came after ***Idenix*** in the Court of Appeal and Henry Carr J took the same approach.

71. To return to ***Idenix***, the reasoning of Kitchin LJ was the following. He noted that Arnold J had held that equitable title was sufficient, referring to his own ***KCI*** judgment and to mine in ***HTC***. Kitchin LJ then noted that a critical part of the reasoning was the EPO decision in ***Burr Brown*** and then said the following:

> "265. Mr Acland submits as follows. The judge's analysis starts correctly but jumps to the wrong conclusion. The signatories to the Paris Convention have a diversity of legal traditions and it is only the common law that distinguishes between equitable and legal ownership. Accordingly, the treatment of equitable interests in English law cannot have any bearing on what the signatories to the Paris Convention meant by the expression 'successor in title' in Article 4(A). Instead, one must search for and identify a notion of ownership and transfer of ownership that is common to all of those signatories.
>
> 266. It is my provisional view that the decisions on this issue in *KCI* and *HTC* are correct, that the Paris Convention does not purport to identify the requirements for the effective transfer of title to an invention and that these matters are left to the relevant national law. Indeed this appears to be the approach of the Boards of Appeal of the EPO: see, for example, T 0205/14 of 18 June 2015. In these circumstances the notion that it is the transfer of the substantive right and title to the invention which is important makes eminently good sense. Nevertheless, it emerged during argument that there may be other materials and decisions which bear on this issue and to which our attention has not been drawn. Accordingly and having regard also to the fact that it is not necessary in this appeal to express a final view

> on this issue, it seems to me that it is better left to be decided in another case."

72. Although obviously personalities do not come into it, one can see a personal tinge to Mr Acland's submissions in this case. In ***Idenix*** his argument which failed is effectively the converse of his argument before me. Before me his case is that the outcome of applying local law to the facts is that the substantive right and title to the invention were with Houston on the day Prof Kohn signed the assignment. So while I do not believe it is disputed that RCT has those rights today, there is no evidence RCT had them when it made the application. If, instead of RCT, Houston had filed the application on 17th March 1997, the assignment assigning the invention to RCT before the filing date would not have mattered, applying this line of cases, because even though the bare legal title was with RCT, the substantive right remained with Houston. Houston could have then filed an application making a valid priority claim. All Accord's case amounts to is the logical consequence of the decisions above.

73. RCT's response to this submission has two aspects. First is on the facts. RCT submits that the court should hold that in fact the assignment by Prof Kohn was effective to ensure that RCT acquired the substantive priority right. This factual argument is put on two bases. One that as a matter of fact I should infer that all the relevant steps did take place and the state of the evidence is explained by the 20 year time gap. I am invited to hold that Houston did decide to offer lacosamide to RCT before the assignment and RCT accepted it and Houston directed Prof Kohn to transfer it to RCT such that the assignment was therefore effective to assign both legal and equitable title. The other approach on the facts is to argue that in any event RCT is equity's darling, the bona fide purchaser for value without notice (which under the relevant US law is provided for by statute) and therefore the assignment was effective to leave RCT with full title despite Houston's equitable rights.

74. Second RCT submitted that even if either of those points were not right, there was nevertheless a transfer of the equitable title to RCT. However its case on this was incoherent. RCT did submit that the proposition that a person with full equitable title but no legal title can claim priority is not "reversible" and does not imply that the person with legal title may not claim priority unless they prove they also hold the full equitable interest, but there was no analysis to back this up. There was a suggestion by RCT that in ***KCI*** it was held by Arnold J at paragraph 68 that the legal title was sufficient. That is not accurate. By "sufficient" RCT must mean to suggest that the judge had held that legal title was sufficient even if the equitable title was elsewhere. That is not what Arnold decided. In ***KCI*** the relevant company held the equitable title anyway. RCT's submissions on principles also contained references to a number of equitable maxims such as "equity does not assist a volunteer" but the submission did not make sense and the point was not pursued. I will approach this aspect of the case as a submission that under US law (Federal and Texas law) an implied in fact agreement to assign the equitable interest to RCT should be found to exist and was effective to assign the interest at the same time as the February 1997 assignment. The US law aspects of this submission are addressed below.

75. I find that the legal principles applicable to priority entitlement are settled at this first instance level. They are:

i) Usually the right to claim priority goes with the right to the invention. That is uncontroversial.

ii) The right to claim priority must be with the person making the patent application in which that right is claimed when they make that claim, i.e. when the application is filed. A later acquisition of that right cannot make good a lack of it on the relevant date. If the right was not in place at the time then the right is lost for all time. That is ***Edwards v Cook***.

iii) But if the local law applicable to rights of the applicant and the patent application at the place and time when it was made allows for a splitting of property rights into legal and equitable interests, then it will be sufficient to establish an entitlement to priority if the applicant holds the entire equitable interest at the relevant date. That is ***KCI***, ***HTC*** and ***FujiFilm*** and was held in the Court of Appeal in ***Idenix*** provisionally to be correct.

iv) A person with a legally enforceable right to call for the assignment of the legal title to a piece of property such as an invention (or a right to claim priority) has the equitable title to that property. When the cases refer to the applicant holding the substantive right and title to the invention, they are referring to this legal/equitable distinction.

76. In my judgment Accord is right in law that following from those principles, a person who at the relevant time and under the relevant applicable law, acquired only the bare legal title to an invention and not the equitable title, when the equitable title is held by another, does not then hold the substantive right and title to the claim to priority.

77. However I cannot help but observe that if priority is lost this patent would be revoked over a publication by the inventor in the period between the priority date and the filing date which I infer was assumed to be a safe thing to do because it was assumed by everyone involved that priority would be successfully claimed. There will be many cases like this. There is no obvious public interest in striking down patents on this ground, unlike all the other grounds of invalidity. The difficulty starts with the point that the title cannot be fixed retrospectively. If I may say so the reasons given by Kitchin J in ***Edwards v Cook*** are compelling reasons why that should be so. However the legal/equitable analysis chips away at that principle since what is happening in those cases is that the equitable owner's imperfect title on the relevant date is only perfected after the event. No doubt that is why, in the Court of Appeal, Kitchin LJ declined to get into the issue any further since he did not have to.

78. I offer the following tentative suggestions. One approach could be that the effect and devolution of the priority right has to be purely governed by a *sui generis* law applicable to priority rights in all signatory states to the Paris Convention equally and applicable in all those states regardless of whether those states recognise a legal/equitable distinction. Flaws in the title cannot be fixed retrospectively. That is one way of interpreting ***Edwards v Cook*** and there are good reasons for it. However it does not sit happily with the equitable/legal distinctions made in the later cases. An alternative could be to apply the same approach and the same applicable law to the priority claim as applies to ownership of the invention and the right to the patent. In a case in which there is some doubt about the claimant's title to the patent itself, that title has to be perfected by the judgment e.g. by assignment or the legal owner must

be joined to the proceedings (see e.g. ***Baxter v NPB*** [1998] RPC 250). The moment the title to the patent matters is judgment. In this case the moment the priority claim matters could be said to be the judgment. As far as the applicable law is concerned, under English private international law, the law applicable to the devolution of the rights to the invention in Texas in 1996/97 is US law, which is in fact a mix of Federal and Texan state law. Nevertheless regardless of these tentative suggestions, I will apply the law as it is settled at this level.

Assessment – priority

79. It was common ground between the US law experts that there existed between Prof Kohn and Houston an agreement whereby the professor would assign his rights in any relevant inventions to Houston or its designee. The parties helpfully prepared a set of agreed principles of US law. Agreed Principle 14 was that:

> "Where there is a valid and enforceable promise to assign in the future all rights in a future invention, patent application or patent, the promise holds equitable title in the invention, patent application or patent. Upon the invention being made, the patent application being file or the patent being issued the promisee is entitled to demand the transfer of the legal title and to compel the same by way of civil proceedings. Where a promisee holds such an equitable interest, to gain legal title to an invention, patent application or patent the promisor must transfer legal title by a written assignment from the promisor-assignor after the invention is made, the patent application is filed or the patent is issued."

80. Applying that principle leads to the conclusion that when Prof Kohn made the lacosamide invention, Houston held the equitable interest in it.

81. The only dispute about US law was or seems to be about whether the transfer of equitable title to a patent requires a "clear and unmistakable act of assignment" in order to part with the rights. In his first report Prof Merges refers in both paragraphs 40 and 58 to the need for a clear and unmistakable act of assignment to transfer an equitable interest. Prof Chisum did not agree, expressing the view in his second report (paragraph 21) that such a requirement was inconsistent with the principle that an "implied-in-fact" contract could convey an equitable title, which principle had been expressed by Judge Davis and which Prof Chisum agreed with. Accord submitted there was no inconsistency between the view that an "implied-in-fact" contract could convey an equitable interest and Prof Merges' opinion, because the implied-in-fact contract was simply an example of the necessary clear and unmistakable intent required by Prof Merges being found to exist evinced by conduct.

82. RCT relied on findings of US law in the judgment of Henry Carr J in ***Fujifilm*** under s4(2) of the Civil Evidence Act 1972. The point is that although foreign law is a question of fact, under s4(2)(b) the foreign law can be taken in this trial to be in accordance with the earlier judgment unless the contrary is proved. The two points decided by Henry Carr J as US law were:

i) That there are no special requirements under US law for: (i) a person or company to be nominated under an agreement to be the beneficiary of rights; or (ii) that party to be expressly identified in a contract providing for assignment to a nominee before the agreement can take effect (***FujiFilm*** paragraph 49); and

ii) implied-in-fact contracts are not limited to the field of employed to invent (***FujiFilm*** paragraph 55).

83. I accept both propositions. RCT says that the first proposition is contrary to Prof Merges' opinion. Accord's submission is that it is not because the first proposition from ***Fujifilm*** is concerned with formalities, or rather the absence of them whereas, as Accord puts it in its closing:

> "262. *[...]* The issue is not whether there are special requirements for a person to be nominated, but the standard of proof necessary to show that a person has been nominated (regardless of the means by which that nomination occurs). This is particularly important where the method by which the nomination is said to have occurred is by an implied contract. There is no extra "requirement" upon them to nominate in a particular way (for example in writing, etc.), merely to prove to the Court's satisfaction that there was in fact a nomination (by any means) which demonstrated the necessary clear intent to part with the patent rights.

84. This is an accurate reflection of the way Accord puts its case. Neither side addressed the question whether the standard of proof is a matter for the *lex fori* and I will not do so either.

85. My findings on this point are the following. An implied in fact contract, inferred from matters such as the conduct of the parties is capable under US law of transferring an equitable interest. There are no special requirements, in the sense of formalities, under US law for a person to be nominated as the beneficiary of rights. What must be proved is a clear intention by the parties that a person was in fact nominated. In that sense it must be clear and unmistakable.

The evidence

86. RCT's case is based on witness statements from Professor Kohn, Mr Reckart and Dr Krishnamoorti. Accord did not seek to cross-examine the latter two witnesses at all. At the pre-trial review Accord raised the question of cross-examination of Professor Kohn. I refused to permit Accord to cross-examine the witness on case management grounds. At that stage Accord's challenge to priority was much broader than the single point now taken. Importantly Accord only advanced one reason why they wanted to cross-examine the professor; it was about his awareness in 1997 of a policy document from the university. That did not justify cross-examination and so it was refused. The point on Professor Kohn's awareness of a policy document has nothing to do with the issue I now have to decide.

87. Professor Kohn's general evidence comes down to the following:

i) He does not recall having, or signing, any formal employment contract on joining Houston or subsequently.

ii) Throughout the FAA Project, Professor Kohn understood that he would not own the rights in his inventions, nor any patents in those inventions. Moreover, he understood he would assign any rights to RCT if required by Houston.

iii) In return, upon commercialisation of any of his work by RCT, Professor Kohn and Houston (together with members of his laboratory group) would receive payment from RCT.

iv) The work described was all part of a single project, the FAA Project. The various strands of work, including the work on lacosamide, all fell within the FAA Project.

v) Professor Kohn understood that the arrangement between Houston, RCT and himself was the same for lacosamide as it had been agreed to be for all the other work within the FAA Project. He started the work which led to the FAA project in 1973. Six patent applications were assigned to RCT under the FAA project before lacosamide.

88. Pausing there, two matters can be mentioned. One relates to paragraph (ii). Professor Kohn's witness statement is clear in this respect that he understood he would assign to RCT if required by Houston. A question is whether he ever was required by Houston to assign lacosamide.

89. The other matter is that RCT submitted that these points and point (iv) in particular meant that it was therefore a reasonable assumption of any party that the same arrangements that had applied to the previous work within the FAA Project would apply equally to the lacosamide work. It depends what you mean. I accept that lacosamide was governed by the terms which governed the FAA project, in effect the 1966 agreement. However what is clear, as Accord submitted, is that the proper process required a decision by Houston to offer to RCT (and so on) as was followed for other inventions in the FAA project. There is no basis for assuming that a previous decision by Houston to offer a particular invention made in the FAA project (i.e. a particular set of compounds) applied to another different invention made later in the same project (i.e. lacosamide). Moreover there is no evidence that Professor Kohn made such an assumption on that basis. He does not say that is what he did.

90. Turning to lacosamide specifically, Professor Kohn's evidence is that in 1993 he identified twelve FAA compounds (including lacosamide) as worth testing. He does not mention the work reported in the earlier Le Gall thesis but nothing turns on that.

91. No invention disclosure document is now in the possession of RCT. Professor Kohn explains he told RCT about lacosamide (and the corresponding racemate) in correspondence. He used the same FAA project number as before. There were pharmacological tests run on the compounds at an organisation called NINDS which is in effect the NIH. There is evidence of discussions between the professor and RCT in 1993/94 about RCT being authorised by the professor to discuss those results with NINDS. Professor Kohn's evidence about this is clear that he was working on the basis that RCT were responsible for patenting these compounds. What is not said is

why. There is no reference to Houston having made a decision to offer the compounds to RCT. A fair reading of this evidence is that Professor Kohn simply assumed that RCT were responsible for patenting all FAA compounds.

92. By October 1994 Professor Kohn had obtained "neat test results" from the NIH for lacosamide. That expression comes from a letter from him to RCT which discussed RCT taking action on licensing. Neither this letter nor the previous letters show on their face that they were copied to Houston. That of course does not mean they were not.

93. An issue arose in early 1996 to delay publication of Daeock Choi's PhD thesis pending filing of the first priority application in March. Professor Kohn wrote to Dr Bear, the Dean of the College of Natural Sciences and requested the delay, as he put it to Dr Bear because "it is very important to protect the university's interests". Publication was delayed and the priority application was filed by Professor Kohn in March 1996 with the assistance of RCT.

94. A week later Professor Kohn wrote to Dr Robbins, the Director of Technology at Houston because RCT had made a payment under the FAA project. The letter was concerned with identifying which members of the Professor's group were entitled to a share. It is not clear what exactly this payment was for. I do not accept the suggestion (if made) that this was a stage payment arising from a decision by RCT to accept an offer of lacosamide by Houston.

95. On 4th February 1997 Professor Kohn completed the assignment in favour of RCT which has been referred to already. In his statement Professor Kohn states that he felt that assigning his rights in the lacosamide invention made sense to him in light of the relationship between Houston and RCT, and the manner in which previous FAA inventions had been dealt with. This makes sense but note that here the Professor is referring to assigning his own rights to RCT and not to assigning Houston's rights.

96. Professor Kohn refers to the FAA project as a whole, the fact that payments were made by RCT, and that there was regular communication and annual reports from RCT. He says he kept in close contact with Houston about the inventions and that he took care to keep Houston informed of his dealings with RCT. The contacts included telephone calls as well as carbon copies of letters. Professor Kohn says that all three parties (Professor Kohn, Houston and RCT) were in contact throughout and Houston never once suggested that they were anything other than fully content with Professor Kohn's co-operation with RCT pursuant to arrangements described. He said that Houston never once suggested to him that it did not fully endorse his passing of information about the FAA inventions to RCT or assigning his rights in these inventions to them.

97. Professor Kohn states that one of his relevant contacts at Houston's Office of Sponsored Research and Technology Transfer Department was Mrs Judy Johncox. That matters because (and I find) that department would be the correct part of the university to make a decision to offer an invention to RCT and because (and I find) Mrs Johncox would be one of the relevant individuals to participate in such decision making. I will return to Mrs Johncox below.

98. The professor ends his witness statement by summarising that his understanding was that he would not own the rights in the inventions but that he would assign them to RCT in accordance with Houston's wishes.

99. Turning to Dr Krishnamoorti's evidence, this can be addressed much more briefly. He was not at Houston until well after the relevant events. He explains that lacosamide is the most successful technology transfer undertaken by Houston and has earned the university over $50 million to date with more to come. He is not aware of any disputes about ownership arising out of the FAA project or any suggestion that Houston does not or did not consider that RCT was entitled to the rights it has. He says that based on current practice, which as far as he is aware is the same now as it was then, either Houston would have assigned the intellectual property to RCT or to the extent that Professor Kohn had not executed an assignment in favour of Houston, Houston would have required Professor Kohn to assign their interests directly to RCT.

100. Mr Reckart's evidence explains the origins of RCT. He was RCT's general counsel from 1986 to 2001 and therefore can speak from first hand experience. He explains how the FAA project ran and explains the usual procedure of notification to RCT of the inventions and acceptance. In this respect (paragraphs 23-35) he is talking about the time before lacosamide.

101. In relation to lacosamide Mr Reckart's evidence deals with the same correspondence between Professor Kohn and RCT in 1993/94 discussed by Professor Kohn. In relation to the filing of the priority document by Professor Kohn in March 1996 with RCT's assistance, Mr Reckart points out that as part of that filing a declaration was filed which he signed on 8th March 1996. The declaration is about the "small business" status of RCT. It states that the rights in the invention have been conveyed to RCT. The form includes a statement that the signing person is aware that willful false statements are punishable by a fine or imprisonment. The timing of this declaration implies that if there had been a decision by Houston to offer the invention to RCT and an acceptance of that offer by RCT, it most probably happened before 8th March 1996.

102. Mr Reckart refers to an agreement for a joint collaboration signed in September 1996 by Houston, RCT and Queens University of Kingston, Ontario, Canada. He says that this arose following Professor Kohn's invention of lacosamide and was to look into new CNS active agents. On behalf of Houston the agreement is signed by Dr Arthur C. Vailas, the Vice Provost of Research. The agreement records that RCT has patents arising from inventions made at Houston and gives a project number which is the FAA project number. There is no express reference to lacosamide.

103. On 10th January 1997 Mr Reckart wrote to Ms Johncox at Houston (copied to Dr Vailas). The letter refers to the priority application from a year before, that is the one which includes lacosamide, and informs her that a PCT application was going to be filed. I am not aware of any reply to that letter. RCT emphasises that Ms Johncox was in the department of the university which would make or would have made a decision to offer inventions to RCT. That would also explain why Ms Johncox is the person to whom Mr Reckart was writing about patent applications.

104. In relation to the February 1997 assignment, Mr Reckart states that in his view it is consistent with the 1966 agreement whereby the university may recommend to faculty

members to assign their inventions to RCT. I accept that the assignment is consistent with the agreement (see clause 3 which is addressed below).

105. Mr Reckart explains that RCT kept Houston up to date on patent prosecution after this.

106. Finally, in closing RCT produced a disclosure list from which it submitted that one can infer many documents from the relevant period have been lost.

Inferences

107. That concludes my summary of the evidence. RCT submitted I should infer from this evidence that the procedure under the 1966 agreement had been complied with and therefore Houston had decided to offer lacosamide to RCT and the Professor's assignment to RCT had been done because Houston had required him to do it. Alternatively I should infer the existence of an implied in fact contract effective to assign the equitable interest. Finally and in any case I should find that RCT were in the position of a bona fide purchaser for value without notice and so took good title under the 1997 assignment even if Houston still had equitable title at the time it was executed.

108. Accord submitted that the principles identified by the Court of Appeal in ***Wisniewski v Central Manchester Health Authority*** (unreported 1st April 1998 Roch, Aldous and Brooke LJ) and by the Supreme Court in ***Prest v Petrodel*** [2013] UKSC 34 meant that the court was precluded from drawing the relevant inferences.

109. The leading judgment in ***Wisniewski*** was given by Brooke LJ, which whom Roch and Aldous LJJ agreed. After citing a number of authorities including ***Herrington v BRB*** [1972] AC 877 the judge summarised the principles as follows:

> "(1) In certain circumstances a court may be entitled to draw adverse inferences from the absence or silence of a witness who might be expected to have material evidence to give on an issue in an action.
>
> (2) If a court is willing to draw such inferences they may go to strengthen the evidence adduced on that issue by the other party or to weaken the evidence, if any, adduced by the party who might reasonably have been expected to call the witness.
>
> (3) There must, however, have been some evidence, however weak, adduced by the former on the matter in question before the court is entitled to draw the desired inference: in other words, there must be a case to answer on that issue.
>
> (4) If the reason for the witness's absence or silence satisfies the court then no such adverse inference may be drawn. If on the other hand there is some credible explanation given, even if it is not wholly satisfactory, the potentially detrimental effect of his/her absence or silence may be reduced or nullified."

110. Accord then referred to paragraphs 43-45 of the judgment of Lord Sumption in ***Prest v Petrodell***. In the first paragraph Lord Sumption explains that what is in issue depends on what presumptions may properly be made against a husband given that the defective nature of the material is down to his own persistent obstruction and mendacity. There are then references to ***Herrington***, to ***R v IRC ex parte Coombs*** [1991] 2 AC 283 and to ***Wisniewski***. Subject to an irrelevant caveat about matrimonial cases, Lord Sumption states the principle in paragraph 44 as being that:

> "There must be a reasonable basis for some hypothesis in the evidence or the inherent probabilities, before a court can draw useful inferences from a party's failure to rebut it."

111. The reliance by Accord on ***Prest v Petrodell*** and on some of the statements in ***Wisniewski*** seeks to portray Professor Kohn as an absent witness or to portray RCT as a litigant who elected to call no relevant witnesses. That would be unfair. I have addressed the pre-trial review already.

112. Nor is it really fair to say that any of RCT's witnesses are "silent" given their extensive evidence directed to the issues. However the real point Accord is making is that Professor Kohn does not state in terms that he disclosed lacosamide to Houston first before disclosing it to RCT, nor that (regardless of when his disclosure to Houston took place) in any event the university actually did make a specific decision to offer lacosamide to RCT and then directed Professor Kohn to execute an assignment in RCT's favour. None of the other witnesses say that either. Therefore, the argument goes, given this absence of evidence, the court should not infer that something happened when the witnesses do not say that it did.

113. I have no doubt that from his own point of view, Professor Kohn at all times did what he did because he thought he was obliged to the university to do so and because he thought the university thought he should. However reading Professor Kohn's evidence as a whole, it seems to me that by the time lacosamide was identified he also thought or assumed that the university was obliged to assign any FAA invention to RCT. The heart of the problem is that this has not been established (and I find would not be correct). However this assumption on the professor's part may explain where the problem arises.

114. I am not satisfied I can draw the inferences of fact necessary to support RCT's primary case that the procedure under the 1966 agreement had been complied with before 4th February 1997. This depends on what did or did not happen as between Professor Kohn and the university. For example one approach which RCT's case invites me to take is to infer that Professor Kohn must have completed an invention disclosure document for lacosamide for delivery to the department in Houston in order for them to make the decision whether to offer that invention to RCT and for the document to then be passed to RCT. The fact such a document is not available in disclosure today from either RCT or Houston must therefore be simply because it has been lost. But Professor Kohn does not say that is what did happen nor does he even say that it is what must have happened albeit he now has no recollection of it. The most he says is that RCT does not today have any formal invention disclosure document but he does not even state in terms that such a document ever existed. He is simply silent on that point. In my judgment it would be wrong to infer that such a document must have existed but has been lost, without at least some statement to that

effect by a witness or in a disclosure list. RCT referred to a list of what has been disclosed in closing but that list does not help. It does not, for example, include an invention disclosure document as a document which did exist but has now been lost.

115. The same problem arises with the other inferences necessary to support this part of the case. I cannot infer that the university made a decision to offer lacosamide to RCT. Neither Professor Kohn or Dr Krishnamoorti say that is what happened nor, again, does Professor Kohn say that it must have happened albeit he has forgotten. All Professor Kohn does is give generalised evidence, which I accept, that the university was aware of what he was doing. That does not mean that they had made a specific decision about lacosamide. The same problem also arises for an inference that the university instructed Professor Kohn to execute the assignment on 4th February 1997. He does not say that that is what happened.

116. Similarly I cannot make the findings necessary to infer the existence of an implied in fact contract to assign the equitable interest. That fails for the same reasons. There is nothing from which to infer that the university actually did intend that the lacosamide invention should be patented by RCT. There is no evidence the university thought about it at all.

117. I find that on the date Professor Kohn executed the assignment to RCT, he held the bare legal title to the invention (including the priority right) but Houston held the beneficial or equitable title. The Professor thought he was doing what he was supposed to do in executing that assignment but the assignment was not an assignment of Houston's equitable interest.

118. RCT made a submission based on agency but I do not see how that would work on the facts in this case.

119. I turn to the bona fide purchaser argument. Professor Chisum explained that in the USA the common law concept of a bona fide purchaser for value without notice had been codified in statute at 35 USC §261. This was not in dispute. The only issue is notice.

120. Here attention switches from Houston to RCT. RCT clearly knew what the terms of the 1966 agreement were. Mr Reckart does not say that RCT received a formal offer of lacosamide from Houston directly. Accordingly for the same reasons as before I decline to infer that that must have happened. However the invention was clearly disclosed to RCT and by the time Professor Kohn filed the priority document in March 1996, RCT believed it was entitled to the invention (see Mr Reckart's declaration to that effect), albeit a formal assignment would be needed to perfect its title. That assignment came in February 1997 and Mr Reckart explains that he considers that the terms of the assignment are consistent with the 1966 agreement under which Houston may recommend to faculty members that they assign their inventions to RCT.

121. Mr Reckart's evidence here is supported by the terms of the February assignment itself. Clause 1 notes that the inventor is obliged to assign his rights in the application to Houston or its designee. Clause 2 describes what is the 1966 agreement and states that RCT has evaluated the invention, is now attempting to commercialise it and is obliged to pay Houston a share of the revenues. Clause 3 states in terms that

the inventor wishes to assign his interests to RCT in furtherance of his obligations to Houston and Houston's obligations to RCT. Thus although the document states in terms it is an assignment of Professor Kohn's interest (rather than, say, any interest of Houston's) the document also makes clear that this is the inventor assigning to RCT as Houston's designee and pursuant to Houston's obligations to RCT. That must be on the footing that the invention has already been offered by Houston to RCT and has been accepted by RCT.

122. From RCT's point of view the February assignment was the assignment RCT would be expecting to perfect its title. Its context was that shortly afterwards RCT would be filing an international application under the PCT. Also relevant is the 10th January 1997 letter from Mr Reckart to Ms Johncox about the forthcoming PCT application.

123. Accord submitted that the circumstances and the recitals in the assignment were such that RCT were on notice that they at least needed to enquire about the university's rights. I reject that submission. The evidence works the other way round. All the indications available to RCT were that the university was aware of what was going on and that Professor Kohn was executing the assignment because he was obliged to do so pursuant to his obligations to the university. Those indications do not only derive from Professor Kohn but also from the university itself, by Dr Vailas' signature on the Queen's University contract in mid 1996. While that document does not name lacosamide, it is concerned with the FAA project for which the patents were being prosecuted by RCT and, from RCT's point of view, by then that included lacosamide. I find that on 4th February 1997 RCT was not on notice of any possible conflicting interest held by the university. Therefore RCT acquired good title to the invention including any priority right. Any equitable interest in the invention which the university did hold prior to the assignment was destroyed or overridden by the assignment to RCT.

124. Accordingly RCT had the substantive priority right when the PCT application was filed.

Obviousness

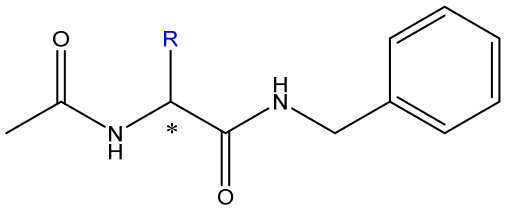
125. The only point of law arising relating to obviousness is the idea of "supplementary information". This term was used by Accord to refer to information which was not common general knowledge but which would be obvious to acquire. Recent cases on this are ***KCI Licensing v Smith & Nephew*** [2010] EWCA Civ 1260 at paragraph 6 (endorsing Arnold J at first instance [2010] EWHC 1487 (Pat)) and ***Richter v Generics*** [2014] EWHC 1666 (Pat) (Sales J) upheld at [2016] EWCA Civ 410. ***KCI*** states the principle that that sort of information can be relevant and ***Richter*** is a case in which it led to a finding of obviousness. Mind you there is a notable contrast on the facts between this case and ***Richter***. In ***Richter*** the supplementary information was a single fact (that something reported as 1.5g was actually 1.5mg). In this case Accord rely on the distillation of what is said to be an obvious literature search.

Le Gall

126. Le Gall is a Master's thesis, describing work undertaken under the supervision of Professor Kohn in the Chemistry Department at the University of Houston. The study

describes work carried out on functionalised amino acids (FAA), both synthesising them and evaluating them in the MES test for their anticonvulsant drug potential.

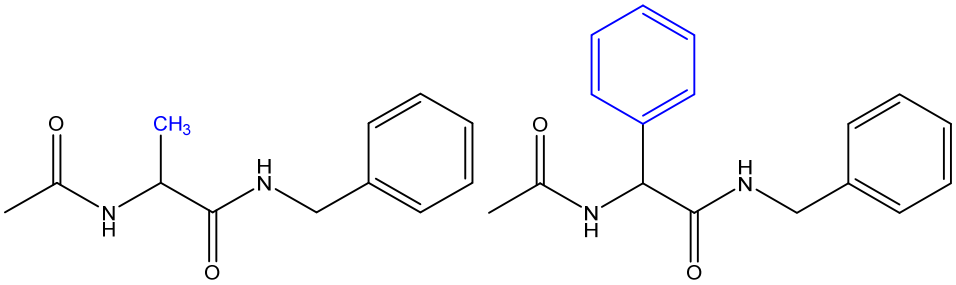
127. Le Gall built on work already carried out by the Kohn group. He had two compounds around which he sought to develop a SAR, both of which were previously discovered by the Kohn group. The base structure used by Le Gall is shown below, with the variable R group in blue:



Le Gall base structure

128. Le Gall only modified the R side chain. The starred (*) carbon is a chiral carbon atom.

129. The two starting compounds used by Le Gall are derivatives where the R group is a methyl or a phenyl respectively. The compounds are referred to in Le Gall as 68a and 68b:



68a 68b

130. In his work Le Gall produced three different sets of derivatives, each set with related but different R groups; one set numbered 69a-h, one numbered 86a-b (which were intermediates in the synthesis of 69a-h but were still tested for activity) and the other numbered 107a-e. Some data for other compounds, not made by Le Gall, are also given and addressed in the thesis.

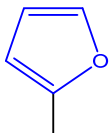
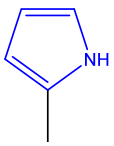
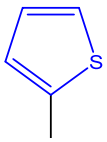
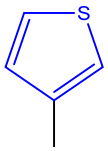
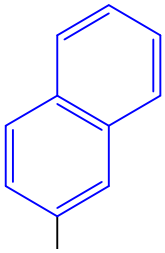
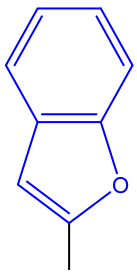
131. Following an abstract which summarises the work, the thesis is split into three sections: an introduction, and Chapters I and II. The introduction summarises the state of research into anticonvulsant drugs at the relevant date and the previous work of the Kohn group. At page 42 (using the document's own page numbers) the following passage appears:

> "Recently, Kohn and co-workers[68,102,103] described the anticonvulsant properties of several N-benzyl amino acids. Compounds 68 contained many of the structural elements (i.e. 46b, 46c) present in phenytoin (13a) and the benzodiazepines (24). Recent evidence has indicated that these compounds

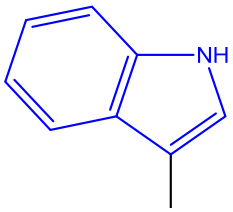
> possess an unique mode of action, suggesting that they may be a new class of anticonvulsant drugs.[68] Interestingly, the D-enantiomer of 68a was thirteen times more active than the L-isomer when tested orally in mice in the MES seizure test. A comparable difference in activity was also noted for the two stereoisomers of 68b. This information coupled with the stringent structure-activity relationship observed for this class of compounds[68] has led to the speculation that the anticonvulsant properties of these compounds may be related to interactions with specific receptor sites."

132. The base structure set out above is then shown in the thesis with compounds 68a and 68b shown (along with 68 c, d and e). Accord places emphasis on the comparison to phenytoin, the reference to a possibly unique mode of action and the statement about the relative potency of enantiomers. On the last point one needs to take care not to mix up the difference between the relative potency of two enantiomers as opposed to the potency of the racemate as compared to one active enantiomer. Even if one enantiomer is entirely inactive and the other is active such that the ratio of their activities is not thirteen times but effectively infinite, the difference in potency between the racemate and the active enantiomer in this idealised example is only half. That would be common general knowledge.

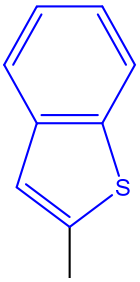
133. The compounds synthesised in chapter I are analogues where the R group is replaced by various different aromatic side chains. The rationale given by Le Gall is that these are analogues of the phenyl compound 68b. In particular Le Gall makes and tests the following derivatives (showing the R groups):

name	structure	name	structure
2-furan (69a):		2-pyrrole (69b):	
2-thienyl (69c):		3- thienyl (69d):	
β-napthyl (69e):		2-benzofuryl (69f):	

3-indoyl (69g):



2-benzo-[b]thienyl (69h):



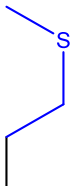
134. These eight compounds can be considered in two groups of compounds – the one group of the smaller single ring structures (the first four), and the second with larger benzo-fused ring structures (the second four). Strictly compounds 69a and 69b should be called furyl and pyrryl above but I have called then furan and pyrrole for consistency with the rest of this judgment and the way in which the arguments at trial were expressed. The 2 in "2-furan" refers to the point in the furan or pyrrole ring which is attached to the backbone of the structure.

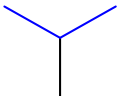
135. The pharmacological evaluation of these compounds begins at page 102, and the data are shown on pages 104-105. The values obtained are described as having been generated using the MES test to create the ED50's, with the compounds first being administered to groups of four mice at 300, 100 and 30 mg/kg, and then effective compounds being further tested in groups of 12 mice to determine an ED50. The TD50's were generated using the horizontal screen test.

136. Compounds 69a and 69b have ED50's of 10.3 mg/kg (with 95% confidence limits of 9.1-11.6 mg/kg) and 16.1 (with 95% confidence limits of 13.2-19.9 mg/kg) respectively. The TD50 values are also given for these compounds with 69a having a TD50 of about 40, and 69b having a TD50 of 30-100.

137. In Chapter I Le Gall also shows data for a series of other compounds, some synthesised by Le Gall as intermediates, and others whose data are gathered from other members of the Kohn team. These are numbered 68c, 68d, 86a and 86b. The compounds are the following derivatives (showing just the R groups):

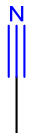
name	structure	name	structure
Methoxy (86a)		Ethoxy (86b)	

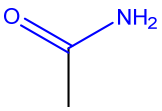
2-methylthio ethyl (68c) 

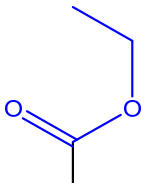
Iso-propyl (68d) 

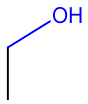
138. These compounds were not as highly active, with the ethoxy (86b) showing the highest activity of 62.0 mg/kg. The activity of the methoxy derivative (86a) was 98.3 mg/kg.

139. Chapter II is concerned with a series of analogues of the methyl compound 68a. Several of the compounds in this group were unsaturated and had a polar substituent at the α-position (page 132). The five compounds are 107a-e. The first four were made and tested. Showing the R group only they are:

Cyano (107a) 

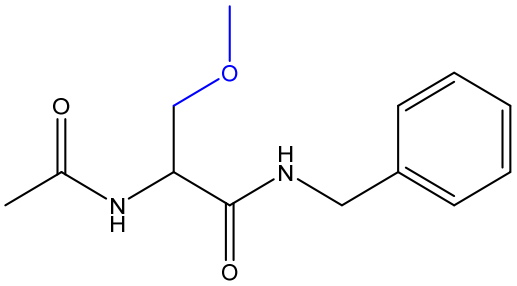
Amido (107b) 

Ethylcarboxylate (107c) 

Hydroxymethyl (107d) 

140. Compounds 107a, 107b and 107C have ED50s in the MES test of >300 mg/kg while 107 has an ED50 of ">100, <300" mg/kg. The TD50s for 107a and 107b are >300 mg/kg while the TD50 for compounds 107c and 107d are <300 mg/kg.

141. The fifth compound 107e was made but never tested. This has the following structure:



142. This is the structure for which lacosamide is the R enantiomer. Compound 107e is the racemate.

143. Le Gall discusses these compounds at p153-155 as follows:

> "Compounds 107a-c did not exhibit significant activity in the MES seizure test. The lack of anticonvulsant properties of these adducts was interesting in light of the pronounced activity of the methyl analogue 68a. A tentative explanation for this dichotomy of results can be offered. In a first approximation compounds 68a and 107a-c all contain relatively small substituents. The primary difference between the two sets of compounds is the presence of an electron-donating (68a) or an electron-withdrawing (107a-c) moiety at the α-carbon. Our previous studies have indicated that the activity of the drug candidate in the MES seizure test is enhanced by the presence of electron-donating groups at the a-carbon. The negligible activity of 107a, b and c is in agreement with this trend.
>
> The serine derivative 107d exhibited only slight anticonvulsant activity in the MES seizure test. The activity of this compound was considerably diminished from the corresponding isomeric methoxy ether 86a (Table 33). This result may reflect the inability of 107d to readily pass through the blood-brain barrier. The more lipophilic methoxy ether 107e has not been evaluated yet. The close structural analogy of this compound with 86b suggest that this adduct may have good anticonvulsant activity."

144. In this passage Le Gall seeks to explain the weak activity of the compounds tested and draws an analogy between 107e and the compound 86b which had been tested. Note that the activity of the ethoxy compound 86b is 62.0 mg/kg and that provides an indication of what the author regards as good activity (in 1987).

145. The thesis ends with general conclusions at p164-165. Amongst other things the conclusions draw attention to the activity of the five membered ring heteroaromatic analogues of 68b (such as the furan 69a and pyrrole 69b) and describe their activities as being similar to phenytoin and diazepam. The idea that the enantiomers may be more active than the racemates is mentioned. There is then a reference to stringent electronic and steric requirements and the statement that the study supports the notion that the α-carbon substituent interacts with an electrophilic site on the receptor. Various suggestions for future work are made. None of the suggestions are about doing anything with compound 107e.

What to do with Le Gall

146. Accord no longer rely on a case that the claimed invention is obvious over Le Gall alone. I am not surprised. Assume the skilled team thought it was worth considering taking compound 107e forward at all, despite the quality of Le Gall's reasoning and despite the poor performance of 107 a-d; that would be based on the last two sentences of the passage from p155 quoted above which links the possible activity of

compound 107e to the activity of compound 86b. Given Le Gall alone and the common general knowledge the best that could be said in terms of expectation of success based on this, is that the activity of the 107e racemate might be comparable to compound 86b, which was 62.0 mg/kg. The thesis was written in 1987 but by 1996 that level of activity would not be good enough to make it obvious to try with a fair prospect that a useful anticonvulsant drug might be the result. For the argument to have any traction considering a skilled team in 1996, the expectation would have to be of a much lower activity than that. Even halving it, based on the best you can get from Accord's racemate/ enantiomer argument, it is still not worthwhile.

147. Accord's case is that given the Le Gall thesis in 1996, the first thing the skilled team would do is a literature search into the work of the Kohn group. I agree that would be the conventional thing for a skilled team to do given Le Gall in 1996 if they wanted to do anything at all. Although RCT contended that the skilled team having read Le Gall in 1996 with interest would then decide they were not interested, I do not accept that. I find that the skilled team in 1996 would find the chemical reasoning in Le Gall over-simplified and unconvincing but the pharmacological data on the compounds tested is sufficiently interesting for a skilled team to do the next conventional thing, which would be a literature search. The search would include searching using the named authors. The thesis is clearly the product of work in Prof Kohn's group at the University of Houston and the names Kohn and Le Gall would be searched as well as other names appearing such as Conley (Conley papers are cited by Le Gall). The thesis also shows that the major pharmaceutical company Eli Lilly have been involved and the names Leander and Robertson would be seen in the thesis as linked to Lilly (see the acknowledgement). The conventional search would also involve not only searching by author name but also searching by reference to some of the compounds such as the furan.

148. The team would find many papers. I have not had my attention drawn to a single comprehensive list of the material which would emerge from this exercise. It would include the following:

i) *Functionalized DL-Amino Acid Derivatives. Potent New Agents for the Treatment of Epilepsy* by Judith Conley and Harold Kohn, published in J Med Chem 1987 Vol 30 567-574 ("Conley 1987")

ii) *LY274959 - A Potent, Stereoselective Anticonvulsant against Maximal Electric Shock (MES) Seizures* by Leander et al published as an abstract submitted to the Princeton Drug Research Symposium on Current and future trends in anticonvulsant, anxiety and stroke therapy May 21-23, 1989 – Princeton NJ ("Leander")

iii) *Preparation and Anticonvulsant Activity of a Series of Functionalised α-Aromatic and α-Heteraromatic Amino Acids* by Kohn et al published in J Med Chem 1990 Vol 33 pp919-926 ("Kohn 1990")

iv) *Preparation and Anticonvulsant Activity of a Series of Functionalised α - Heteroatom-Substituted Amino Acids* by Kohn et al published in J Med Chem 1991 Vol 34 pp2444-52 ("Kohn 1991")

v) *Synthesis and anticonvulsant activities of α -heterocyclic α -acetamido-N-benzylacetamide derivatives* by Kohn et al published in J Med Chem 1993 Vol 36 pp3350-60 ("Kohn 1993")

vi) *Anticonvulsant Properties of N-Substituted α,α-Diamino Acid Derivatives* by Kohn et al published in J Pharmaceutical Sciences 1994 Vol 83 pp689-91 ("Kohn 1994")

vii) *Synthesis and Anticonvulsant Activities of α-Acetamido-N-benzylacetamide Derivatives Containing an Electron-Deficient α-Heteroaromatic Substituent* by Patrick Bardel et al published in J Med Chem 1994 Vol 37 pp4567-71 ("Bardel).

149. There are more papers from the Kohn group than this and the conventional literature search by the skilled team would turn up more papers than the seven listed above but I find it would include those seven. Conley 1987 is referred to in the Le Gall thesis and would be obtained even though it predates Le Gall. Prof Cox's own searches conducted for the purpose of this case did not turn up the Leander abstract but it was published and available and I find that in 1996 it would be identified.

150. Conley 1987 is reference 68 in Le Gall. It is the reference for the statement that the new class of compounds have a unique mode of action in the passage quoted above from p42 of the thesis. It was put to Professor Löscher that if the skilled team followed this up they would read Conley 1987 and see the profile of activities in the various pharmacological assays in that paper of two compounds mentioned in Le Gall. The compounds are 68a (methyl) and 68b (phenyl) in Le Gall while in Conley 1987 they are 1a and 1d. In cross-examination a table was produced of those results to show the activities of these two. The tests are all in mice. They are the MES test, four tests using chemical convulsants (sc Met, sc Bic, sc Pic and sc Strych) and the neurotoxicity rotarod test. Professor Löscher did not agree with the way Le Gall had put it based on these data. Professor Löscher's way of expressing what would emerge from this was that the compounds had a different pharmacological profile in seizure models from known antiepileptic drugs, although he thought the phenyl compound (68b) was quite similar to phenytoin and would be more confident that the methyl compound (68a) was potentially interesting.

151. The pharmacologist and the medicinal chemist would review the results of the literature search as a whole. The team would see the work that the Kohn group had done over an extended period of about ten years in this class of compounds. A large number of compounds with the same basic structure have been synthesised and tested. The vast majority are different substitutions at the R position described above in what I have called (but they did not) the Le Gall base structure. There are some substitutions elsewhere too. I am not aware that they have been counted but there must be well over fifty different compounds spread over about ten years, all of which were new chemical entities and were synthesised and tested at least in the MES and neurotoxicity tests. That is a huge body of pharmacology and medicinal chemistry work.

152. If the team was going to take things forward they would look for the best compounds arising from this work. There are two ways of looking at this. One is the Leander Abstract. The authors are from Lilly and the Kohn group. As an abstract it is very

brief. Its compound is called LY274959 (LY obviously refers to Lilly). It is the R enantiomer of the furan compound (Le Gall's 69a). The abstract shows that this compound has been taken further down the development process than many of the others and is showing promising results. Leander reports MES and neurotoxicity (horizontal screen) test results both ip (intraperitoneal) and po (oral) in mice and po in rats as well as some chemical convulsant results in mice (sc Met, sc Bic and sc Pic). The conclusion is that "*LY274959 has a preclinical profile that suggests it would be a therapeutically useful anticonvulsant in humans*." The skilled team would be very interested in that despite the limitations in the detail of the information available.

153. So one obvious thing for the team to do could be to work on LY274959 and take it forward. But that is not the only thing a skilled team might do.

154. In his evidence Professor Löscher had pulled together a table of the compounds from this material which had ED50s in the MES test of about 10 mg/kg or lower. I find that the skilled team (really the pharmacologist) would pull together a list of what they thought were the best compounds. Of course that is not all that would come out of the significant work of reviewing all these papers but producing such a list would be conventional.

155. An expanded version of Professor Löscher's table (expanded not to add compounds but to add more data) is the following:

Table 1: Kohn group compounds with potential MES ED_{50} values < 10 mg/kg

Compound	Side Chain	Other modification	Where reported	MES ED50 (mg/kg)	TD50 (mg/kg)	PI
(R,S)-**2g**			Kohn 1990	10.3	~40	3.9
(R)-**2g** (LY274959)			Kohn 1990	3.3	23.8	7.2
(R)-**30**		Para-F on benzyl ring	Kohn 1993	3.5	14.4	4.1
(R,S)-**3l**	$NH(OCH_3)$		Kohn 1991	6.2	46	7.4
Phenytoin (NIH data)			White et al	6.5	42.8	6.6
(R,S)-**3n**	$N(CH_3)OCH_3$		Kohn 1991	6.7	50.5	7.5
(R,S)-**13**			Bardel	8.1	56.7	7.0
Phenytoin (NIH data)			Porter et al	9.5	65.5	6.9
(R,S)-**18**			Kohn 1993	10.4	38.6	3.7
(R,S)-**11**			Bardel	10.8	25-100	2.3-9.2
(R,S)-**19**			Kohn 1993	12.1	69.1	5.7

(I have edited Professor Löscher's table in two further ways: the reference to LY274959 is added to (R) -2g and the entry for (R,S)-11 is edited to reflect the range of TD50 values rather than expressing it as a footnote as in the original table.)

156. Note that Professor Löscher's table includes two entries for phenytoin. They show slightly different MES ED50s. In reality the team would probably have more comparator compounds, not just phenytoin, and put them elsewhere but nothing turns on that. In this table compound (R)-2g is the R enantiomer of Le Gall's furan compound 69a. In other words it is LY274959.

157. Now before going any further a point arises on the quality of the data. A conventional skilled team would not make major decisions based simply on reported data. It would not be practical to rerun the whole of the Kohn group's work but they would seek to reproduce any results on which they were going to place any significant weight. Repeating all the results just in this table would be very substantial albeit routine work. It would not just involve synthesising and testing the compounds but running various internal standards and controls. For the purpose of the analysis I will assume the repetition of results would be identical, although that is not really a credible assumption given these are tests in a biological system and using a small number of subjects.

158. For the team to move forward from this sort of information would involve the team taking a phenotypic screening approach to drug development rather than a target based approach or one based on modifying an existing clinically approved compound (such as Professor Cox's work on lamotrigine). If Professor Löscher was involved personally I doubt that is the approach which would have been taken but in 1996 phenotypic screening was one of the conventional approaches taken by skilled teams.

159. Professor Cox's evidence was that 3n and 3l would stand out as the most active. I do not accept that the skilled team's approach would be quite as simple as that. Professor Cox is a medicinal chemist albeit with a wealth of experience in liaising with pharmacologists. The pharmacologist member of the skilled team would be familiar with the various tests such as the MES test. They would not attribute much significance to small differences in the test results reported in this way. Professor Löscher's evidence was that this sort of early phase phenotypic screening is relatively crude and uses small cohorts of animals. He said the pharmacologist would not make fine distinctions between ED50 values in the MES test and gave an example that no distinction would be drawn between values of approximately 10 mg/kg and 25 mg/kg. The point of the example was a relative one.

160. Nevertheless the skilled team taking the approach of moving forwards from a table of best compounds would indeed be interested in 3n and 3l from the above table but also in other compounds. I doubt they would dismiss any of the nine compounds in Professor Löscher's table. To a pharmacologist an ED50 of 6.2 in the MES test conducted this way is not materially different from an ED50 of 10.4 (and that is irrespective of 95% confidence intervals).

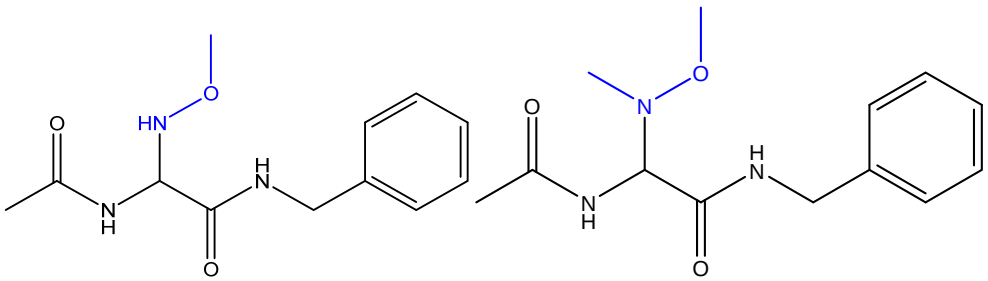
161. Compounds 3l and 3n are racemates. Accord contends that this means the team would expect the activity to be in a single enantiomer and that enantiomer (most likely R rather than S given the other data) would have an ED50 value twice as good as the value for the racemate – so 6.3 mg/kg for compound 3l would be expected to be

just over 3 mg/kg. That is too simplistic. The skilled team would expect the activities of the two enantiomers to differ and expect that the useful activity would probably reside in one of the enantiomers, although it may not and both enantiomers may have relevant effects (one may even have a negative effect). They would think it probable that the more active enantiomer had a better ED50 than the racemate to some degree (but it might not) but they would not think it was reasonable to expect the active enantiomer to have twice as good a value as the racemate. The same racemate point also applies to compounds 13, 18, 11 and 19. Note that compound (R)-30 is a single enantiomer. It differs from LY274959 in that it has a fluorine on the benzene ring (shown in the right of the Le Gall base structure above).

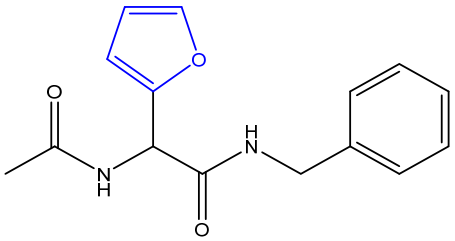
162. So the racemate point is relevant but it does not go as far as Accord contends.

163. Now the next step involves analogues. It was common ground that the development program is a kind of funnel, starting with many compounds, coming up with a lead and some back up compounds and gradually coming down to fewer and fewer as the project advances. The team would be interested in thinking about analogues of whatever lead compounds it chose. The team would also know from the Kohn work that a wide variety of compounds which can be regarded as analogues of whatever compounds the team selected had already been tested.

164. Thinking about analogues the focus turns away from the pharmacologist and towards the medicinal chemist. Accord's case is that at this stage the skilled team would identify a few lead compounds from this work. They would be or include the following three: compound LY274959 as well as compounds 3n and compound 3l. Their structures are:



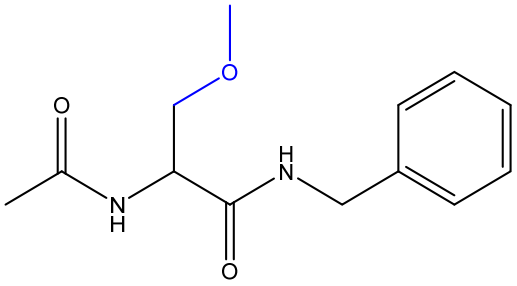
3l 3n



LY274959 (strictly what is drawn is the racemate)

165. The key question is the following. Accord contends that thinking about analogues would take the skilled team, now led by the medicinal chemist, to consider a

methoxymethyl derivate of the base structure compounds as an analogue worth making and testing. The compound is:



166. This is Le Gall's 107e. Its R enantiomer is lacosamide. Accord says the team would test both the racemate and the two enantiomers (expecting the R enantiomer to be the good one). I will refer to it as lacosamide although of course that name was not used at the time.

167. Accord's case is that once the team had conceived of what is compound 107e the team's expectations about its activity in tests would be a sufficient expectation of a good result, in the standard screening tests (MES and neurotoxicity), that claimed invention is obvious. There is an intermediate step in that logic in that what really has to happen is the team tests the racemate, likes it, and then tests the enantiomers and finds lacosamide. However for the purposes of analysis this intermediate step is not a major issue. I find that if the team did test the racemic compound 107e in the standard screening tests (MES and neurotoxicity) they would find a good enough ED50/TD50 and PI that it would then be obvious to test both enantiomers, one of which is lacosamide, in the same sort of tests. That would be obvious to do with a fair expectation that the useful activity which had already been identified resides in one of the two enantiomers. Those results would in turn be good enough for the skilled team to then make a reasonable prediction that lacosamide would be a useful anticonvulsant medicine for the treatment of epilepsy – at least for tonic-clonic seizures – and that is enough to invalidate the relevant claims. This analysis of the intermediate step is fair whether all the tests are run in mice or in rats.

168. The issues in this case about thinking of testing compound 107e and the relevant expectation are primarily matters of medicinal chemistry. Professor Cox's opinion, maintained in cross-examination, was that there were solid grounds for expecting good activity for lacosamide based on the information available to the skilled team and their common general knowledge. Prof Ward's opinion, also maintained in cross-examination, was to the contrary. Save for one point, this is not a topic on which Professor Cox's longer experience in the field as at 1996 is of significance because the issue is about chemical reasoning, not drug development programme approaches.

169. The exception is about what was called a "reductionist" approach to analogue design. The point is that if you look at the furan and the methoxymethyl parts of lacosamide respectively, you can notionally cut away the two carbons on the left of the furan ring as it is drawn above and if you do you get the methoxymethyl compound. In fact some hydrogens need to be put on the terminal carbon to make it methyl. One needs to be a bit careful about this for reasons addressed below, but this step is what Accord call the result of taking a "reductionist" approach.

170. Professor Cox explained that this approach of cutting away and reducing a starting compound down to the key parts was a method medicinal chemists who trained before the 1990s had been trained in. He referred to the training whereby very often the approach would be applied to a complex natural product in order to identify its pharmacophore. The term pharmacophore refers to effectively the active core of the molecule responsible for the effect you are interested in – consisting of the functional groups which are required for activity and their relative positions in space. Professor Cox gave an example of the analgesic morphine to which this approach was applied over many decades to produce numerous simpler successful drugs.

171. Professor Ward did not disagree that this approach was taken but he did not agree that it justified, as he put it "literally with a pair of scissors cutting out 107e from 69a". His reference to the pair of scissors metaphor in cross-examination was to acknowledge the existence of the similarity Accord relies on while he then went on in his answer to explain why he did not agree it was a step the skilled person would take.

172. I accept Professor Cox's evidence, which was not challenged, that one of the things medicinal chemists were trained to do was take a "reductionist" approach of the kind he described, such as paring down a large complex natural product to a putative pharmacophore. But that general technique, which perhaps older medicinal chemists were more familiar with in 1996 than younger ones, is different from the very specific step in the context of analogue design of going from one analogue (the furan) to another (the methoxymethyl). Neither analogue is a large complex natural product. I was not persuaded that the thinking about a change of that kind would be influenced by the age or training of a medicinal chemist in 1996. Professor Ward said that there was no step change in how medicinal chemists had been trained and that considering shape and electronics of the molecule, reducing complexity and having simpler pharmacophores was what every medicinal chemist deals with. I accept that.

173. Therefore the fact Professor Cox's training started before the 1990s is not a reason to give his opinion greater weight than Professor Ward's on this issue.

174. However despite RCT's case that they would not, I think one of the analogues the skilled team would at least conceive of would be the methoxymethyl as a racemate. That would arise from their thinking about analogues of what are clearly the best compounds revealed by the literature search. I am not convinced it would be conceived by cutting away at the furan, since as Professor Ward pointed out that "cutting away" involves a significant change to the three dimensional structure and the electronics because it removes a planar aromatic ring with π-electrons. But I think it could well be conceived from thinking about the compound 3l in particular. The team would have drawn up a full list of the compounds found in the literature search. The thing about 3n and 3l is that they are not aromatic, unlike the other compounds in the table above and unlike the large majority of compounds the Kohn group had tested. The team would see that a number of other non-aromatic substituents had been tested. Results for about 20 non-aromatic compounds are reported in the Kohn 1991 paper. They include the Le Gall compound 86a (methoxy) which is compound 3a in Kohn 1991 and include some compounds similar to 3n and 3l such as 3k (in which R is -NHOH) and 3m (in which R is -N(CH_3)OH). However an analogue of compound 3l in which the nitrogen in the substituent group is replaced with a carbon had not been tested in any of the results shown in the literature search. The team would probably have noted it was in Le Gall as compound 107e and never tested but

even if they had forgotten that, I think they would conceive of the compound as one possible analogue to consider, for which they had no data.

175. Bioisosterism is the idea that certain atoms or groups in a molecule can be replaced with certain others in such a way that the molecule is not altered very much and so the two molecules may behave the same way. It was part of the medicinal chemist's common general knowledge as part of analogue design. However bioisosteric reasoning cannot be taken too far. Professor Ward pointed out that the table of substitutions which was to be found in the current textbook and derived from a paper by Thornber in 1979, if read literally, would suggest that a carbon could simply be replaced with an arsenic (replacing -CH= with -As=). The manner in which Professor Ward expressed himself about that indicated that he did not see it as a serious suggestion.

176. On the other hand I accept that a medicinal chemist in 1996 could regard replacing a linkage -NH- with a $-CH_2-$ as a possible change. That is the change which would turn compound 3l into compound 107e. They would not see it as a change with no possible consequences but then the medicinal chemist would not think that about any change. The question is always about what the possible consequences might be and their likelihoods. Unlike a carbon, the nitrogen atom has an electron lone pair. That can be responsible for differences in the behaviour of two otherwise identical molecules.

177. A further possible difference would be in relation to interaction between the adjacent oxygen and the nitrogen, as opposed to the oxygen and the new carbon atom. Professor Ward referred to an effect called the alpha effect, which can arise when there is a nitrogen-oxygen bond. I do not believe the skilled medicinal chemist would think the alpha effect itself was relevant to the activity of compound 3l since the alpha effect is about forming covalent bonds. However, it is an example of the fact that interactions between adjacent atoms can be relevant. I find that the skilled medicinal chemist would have in mind that changing the nitrogen to a carbon could make a difference given the adjacent oxygen. Given the strong electronegativity of the oxygen it might be a small difference or even a positive difference but then again it might not be. I was not satisfied the skilled team would be confident they could make a reasonable prediction what difference the change would make either based on bioisosteric considerations alone (i.e. just swapping C for N) or taking account of the adjacent oxygen as well.

178. Professor Cox said that on the basis of the bioisosteric switch from 3n or 3l, the medicinal chemist would expect the activity of the methoxymethyl compound to be "the same or better" and that such a switch was very highly likely to be successful. Similarly he said that comparing to the furan, the skilled person would also expect the methoxymethyl compound to be very similar in activity.

179. In order to make such a prediction the scientist needs to have a hypothesis, a theory which makes predictions which can then be tested. This is the basis for a structure activity relationship or SAR. The SAR allows the chemist to predict what the effect of a change to the structure might be in order to enhance the properties of the compound. This is core medicinal chemistry. The literature search would show that by 1996 the Kohn group had two related theories for the basis on which the compounds showed good activity - aromaticity and the effect of a β-heteroatom.

180. Professor Ward gave evidence that looking across all the compounds found in the literature search, the results show cases in which aromatic substituents work and some in which they do not, as well as cases in which substituents with a β-heteroatom work and some in which they do not. It is also clear that the Kohn group spent by far the bulk of its energy on aromatic substituents. So for Professor Ward the skilled team would not have a fair expectation that 107e would give a good result in the tests. Professor Cox did not agree. In order to grapple with this I need to take a step back and explain the hypotheses in more detail.

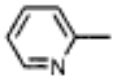
181. Aromaticity refers to the aromatic systems in many of these molecules such as phenyl rings. They have a π-electron cloud above and below the ring. The concept of a β-heteroatom is as follows. The oxygen in the R group of compounds 3l and 3n is at the β position. It is called a "hetero" atom in the context of organic chemistry because it is different from carbon. So a furan is called a heterocyclic structure because instead of being all carbon atoms around the ring, one of them is different. Equally a pyrrole is a heterocycle but this time the different atom is the nitrogen.

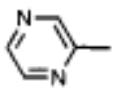
182. So just as the oxygen in 3l is a β-heteroatom so the oxygen in the methoxymethyl group in 107e is also a β-heteroatom.

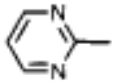
183. The skilled team would see from the Kohn group's papers that two hypotheses were being advanced to explain the activity of the compounds. One theory was that having an aromatic system in the R group was responsible for good activity and another was that it was the presence of a β-heteroatom which was responsible for good activity. Since the R group in LY274959 is a furan, that has both aromaticity and a heteroatom. Linking the furan to the backbone at the 2 position locates the oxygen heteroatom at the β position.

184. The latest paper from the Kohn group turned up by the literature search at the priority date would be Bardel. The following explanation of Bardel is put in the language used in this judgment. The abstract of Bardel states that the group's work has shown that compounds using the Le Gall base structure and with various R groups have displayed excellent anticonvulsant activities in mice. It then states that analysis of the SAR for this series of compounds has shown that what makes for good activity in the MES test is "*the presence of small, electron-rich aromatic and heteroaromatic groups*" in R. The examples of that used in Bardel are Le Gall's furan compound 69a (numbered 2 in Bardel and marked as (R,S)-2g in Professor Löscher's table above) and Le Gall's pyrrole compound 69a (3 in Bardel). The abstract continues by explaining that three new compounds have been synthesised (11, 12, and 13) and all three have potencies comparable to or better than phenytoin. The abstract ends by explaining that these findings mean that the group has to "modify in part" its previous SAR hypothesis.

185. Compound 11 is compound "(R,S)-11" in Professor Löscher's table above. The R groups for the three compounds 11 – 13 are:

11[i] 

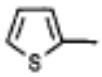
12[i] 

13[i] 

186. These structures have R groups which are aromatic rings (a pyridine, pyrazine and pyrimidine ring respectively), but Bardel explains that these three compounds are electron-deficient aromatic analogues in contrast to the furan and pyrrole which in Bardel's terms are electron-rich aromatic analogues. All five compounds (the furan and pyrrole and the three new compounds) are aromatic and they all have at least one β-heteroatom. The β-heteroatom in the furan is an oxygen whereas in the three new compounds and the pyrrole it is a nitrogen.

187. The ED50s in the MES test for new compounds 11-13 are from 8.1 – 14.8 mg/kg. Bardel points out that the group's theory had previously proposed that using an electron rich aromatic group for R would result in improved activity. The significance of the good activity of electron deficient aromatic rings is that it is not consistent with the electron rich aromatic theory.

188. Bardel also points out that the Kohn group had also presented evidence that *"placement of a substituted heteroatom two atoms removed from the C(α) site*" gave enhanced activity in the MES test, referring to compounds 4 and 5 in Bardel with ED50s of 44.8 mg/kg and 87.8 mg/kg. This is the β-heteroatom theory. Compounds 4 and 5 have sulphur atoms substituted in the ring (they are Le Gall's thienyl compounds 69c and 69d). They are:

4[f,g] 

5[f,g] 

189. Bardel then states that in agreement with the β-heteroatom theory, the trend in activity as between 11, 12 and 13 was that 13 was more potent than either 11 or 12 (because it has two β-heteroatoms).

190. Then Bardel states that the findings indicate that "*of these two structural determinants the latter was the more important factor for anticonvulsant activity. Consistent with this theory was the notable protection observed for the C(α)-heteroatom adducts 24 (ED50 = 6.2 mg/kg) and 25 (ED50 = 31.4 mg/kg) in the MES test*". The two structural determinants referred to are the aromaticity theory (or at least the electron rich aromaticity theory) on the one hand and the β-heteroatom theory on the other. So this is a clear statement that the authors are proposing here that the β-heteroatom theory is the more important structural determinant. Compounds 24 and 25 referred to in support of this proposal are aliphatic (that is in contrast to being aromatic). Compound 24 is the compound in Professor Löscher's table labelled as compound 3l, while compound 25 is the following:

(This compound was compound 3o in Kohn 1991)

191. This proposal in favour of the β-heteroatom theory and the evidence leading to it are the high point of Accord's case. The case is that armed with that endorsement of the β-heteroatom theory in favour of aromaticity, the team would have a fair expectation that 107e with its β-heteroatom in a structure which is in effect a carbon analogue of Bardel's compound 24 (i.e. compound 3l in Professor Löscher's table) would have good activity.

192. However I do not believe the argument reflects the skilled team's thinking about the issue. Bardel does not say that any compound with a β-heteroatom will work and the team would not understand Bardel in that way. The Kohn group's work shows examples of compounds with β-heteroatoms which do not work. They include compounds in Kohn 1991 such as 3k (-NHOH) and 3m (-N(CH_3)OH).) In Le Gall's thesis compounds 107a (-CN), 107b (-$CONH_2$), 107c (-COOEt) and 107d (-CH_2OH) all include a β-heteroatom and have poor or no activity.

193. Conversely there are compounds with no β-heteroatom at all which have reasonable activity, such as the phenyl compound, Le Gall's 68b. Moreover the compounds with good activity reported by the Kohn group mostly have an aromatic ring structure. That can be seen just by looking at Professor Löscher's table above. So the idea of going forward with a non-aromatic compound would be to divert from the thrust of the Kohn group's published work.

194. Also one needs to take care not to equate "aromatic" with "electronic rich aromatic". All aromatic compounds have a π cloud of electrons, it is just that some are more electron rich than the others. It is a matter of degree. The new evidence in Bardel was not that aliphatic compounds could be active, since, as the reader would understand, the papers show the Kohn group already knew that. The new evidence in Bardel was about aromatic compounds which worked even though they were electron deficient.

195. Possible explanations for the failures of compounds with a β-heteroatom to work may be based on what is called ADME (Absorption, Distribution, Metabolism, Excretion). These are pharmacokinetic effects which relate to what happens to the drug after it is administered to a living system. Absorption is the process of the drug entering the systemic circulation after it has been administered. Distribution is the dispersion of the drug through the fluids and tissue of the body. It could include the ability to cross the blood brain barrier. Metabolism is the conversion of the drug into other molecules by enzymes in the body (such as the enzyme family cytochrome P-450 in the liver and in other places). Excretion is the removal of the drug from the body. It is not difficult to see how these effects can be very significant. If all the drug substance is metabolised to an inactive metabolite shortly after it has been administered and before it can act, then no activity will show up in the test irrespective of whether the molecule could interact with the target. Equally if the target is in the brain and the drug cannot cross the blood brain barrier, it will never interact with that target.

196. I reject the suggestion that Professor Cox'a opinions about this topic were of more weight than Professor Ward's. Consideration of ADME effects is fundamental to drug development and both experts were well qualified to discuss it. There were no relevant changes in that field over time. A point arose about the presence of cytochrome P-450 in the gut as well the liver. I do not accept that was common general knowledge in 1996 but it is a minor issue. Also Professor Ward gave credible evidence that his work on *in vitro* target based assays also involved an analogous issue in that to interpret results one needed to take into account whether the drug had actually reached the target concerned.

197. It was common general knowledge that ADME can cause unexpected and unpredictable changes in activity. All the same it was common ground that the team might think that compound 3k (-NHOH) as well as its carbon analogue 107d (-CH_2OH) were susceptible to being metabolised owing to the terminal hydroxyl group and that might be the explanation for the poor activity of 107d and the lower activity of 3k relative to 3n. But then again it might not. The available information does not include any studies on metabolism which might show that that is what has happened.

198. Furthermore the team would also think that replacing the hydrogen of the hydroxyl with a methyl (which turns 3k into 3l and turns 107d into 107e) might reduce the tendency of the compound to be metabolised. However the team would regard both the hydroxy and methoxy compounds as having possible sites of metabolism, albeit without any data their guess would be that hydroxy would be metabolised more readily than methoxy.

199. I will not chase down every example of this sort of argument in the case. They are all instances of a general difficulty. The problem is concerned with the interpretation of negative results. Accord submitted that a negative data point could easily be caused by ADME properties, and have nothing to do with the binding to whatever target the team believed was relevant. I agree. Accord then went on to submit that:

> "as such, negative data does not necessarily prove anything about the active site, and certainly cannot invalidate a hypothesis that is built upon positive data. The negative data must be given much less weight, although the quantity of negative data could ultimately require refinement of the SAR hypothesis, if sufficiently overwhelming."

200. This submission was supported by a contention by Accord that Professor Cox and Professor Ward were fundamentally at odds about this point and that that was due to their different experience in work based on animal models (Cox) as opposed to in vitro assays (Ward). I have already rejected the latter point about their difference in experience.

201. As for the former point I do not believe the experts were as far apart as Accord's submission suggests. That is because as far as I am aware Professor Cox did not say that "*negative data ... certainly cannot invalidate a hypothesis that is built upon positive data*" and I would not have accepted it if he had. A hypothesis which cannot be falsified by negative data is not a scientific hypothesis at all and I am sure Professor Cox understood that as all scientists do. The point Professor Cox was making is best seen in a passage in cross-examination from Day 3 p337 line 10 to 341

line 18. He accepted that it was standard medicinal chemistry to build hypotheses based on active and inactive compounds but also explained that the team would not put all its energy into explaining why inactive compounds do not work. That is because their focus would be the active compounds. I accept that. It does not mean that negative data "is given much less weight" nor does it mean that the quantity of negative data has to be "overwhelming" to justify changing the SAR hypothesis. What is the case, as Professor Cox's evidence explained, was that the weight of evidence does matter. A body of results pointing one way or another will be given more weight than a few results.

202. In the end the issue comes down to the following. As I have said before Professor Ward's opinion was essentially that looking at the results as a whole, positive and negative, the skilled team would not predict that an aliphatic compound such as 107e, albeit with a β-heteroatom, would have good activity. That was for two fundamental reasons. First because so much of the data related to aromatic rather than aliphatic compounds and second because he thought that while ADME and other effects might be the explanation for the negative results, then again they might not and in any case the same effects might just as well apply to compound 107e. To the contrary Professor Cox's opinion was that the β-heteroatom theory was supported by a lot of evidence and where it is not supported there were very realistic ways in which you can explain why the negative result does not fit.

203. In my judgment a critical factor is a point emphasised by Professor Ward, that so much of the Kohn group's work is on aromatic rather than aliphatic compounds. Much of the evidence which supports the β-heteroatom theory is in aromatic compounds. I am not convinced the skilled team, acting without invention, would be comfortable making predictions about the behaviour of an aliphatic compound with a β-heteroatom (such as compound 107e) based on reasoning derived from results achieved using aromatic compounds, even if those aromatic compounds also had a β-heteroatom. Making predictions based on comparing aromatic and aliphatic compounds does not compare like with like. The team considering compound 107e would focus primarily on evidence relating to the β-heteroatom theory in aliphatic compounds alone. Taking that approach the weight of positive evidence for β-heteroatomic aliphatic compounds to set against the negative results for β-heteroatomic aliphatic compounds makes the position much more equivocal. I find that the team would not think there was sufficient evidence from which they could make a reasonable inference that 107e would give good activity in whichever in vivo test they were going to use.

204. Although I have focussed on the β-heteroatom theory, it is right to point out that there were other ways of making the same essential point. Professor Cox also referred to the need for electron richness in this location instead of focussing on the β-heteroatom theory. In my judgment this alternative approach comes to the same point in the end, because in compound 107e the electron richness would be provided by the lone pairs on the oxygen. If the electron rich approach is not the same as the β-heteroatom approach then I do not accept that the electron rich way of thinking would justify a finding of obviousness if the arguments based on the β-heteroatom approach fails. That is because discussion about a β-heteroatom is the way in which the authors of the Kohn papers express themselves and is the way the skilled team acting without invention would think. If electron richness is different (e.g. because it would be a

way of trying to pull together aromatic and aliphatic results) then I was not satisfied it was an obvious way to reinterpret the information available to the skilled team.

205. Putting it all another way, there are just too many uncertainties to justify a finding of obviousness. Even if the team got as far as deciding to make and test 107e they would know that the uncertainties meant that either outcome, good or bad, could just as easily be rationalised after the event as the other. That is not a fair prospect of success.

206. So I reject the obviousness case over Le Gall either alone or with the supplementary information on the primary ground that I am not satisfied that even if the skilled team did decide to try the relevant tests (using the 107e racemate in MES and neurotoxicity tests ip in mice or rats), they would have a sufficient prospect of success to lead to the conclusion that the claim lacks inventive step.

207. The arguments delved into further points of detail on a number of issues – such as: how much the skilled team would know about the results of the NIH compound testing programme, toxic furan metabolites and ease of synthesis of enantiomers, what the team might make of the effect of basicity and Kohn 1994, but I have not found it necessary to decide those questions.

208. Having reached that conclusion I will also say that I was doubtful that the whole step by step analysis was indicative of obviousness. The series of steps from Le Gall involved a full literature search, the distillation of all that work, numerous other avenues which could be considered and the conception of the methoxymethyl compound as something to consider. Although they are all apparently easy steps and many of them are conventional individually, looked at as a whole they did not strike me as supportive of obviousness but I did not decide the case on that point.

Bardel

209. Accord's alternative case was over Bardel plus supplementary information. This time the supplementary information relied on is the express references in the paper. I agree it would be conventional for a team given Bardel to acquire and read those further papers. They are Kohn 1990, Kohn 1991 and Kohn 1993. I am bound to say on the evidence I would have thought the team would do essentially the same full literature search as over Le Gall (because I really doubt such a literature search in 1996 would happen just because of the age of Le Gall) but this turned out to be contentious and Accord submitted it was not established. I think Accord's forensic objective was that this approach allowed Accord to say that the skilled team did not have the Leander abstract or Kohn 1994 before them when they make the relevant decisions. The Leander abstract might inconveniently send the team off an alternative avenue of chasing LY 274959 while Kohn 1994 might suggest than the nitrogen in compound 3l was important and should not be replaced. Neither issue has been part of my reasoning and so the literature search point does not matter and I will not decide it.

210. Given the prominence of the Bardel paper in the case advanced over Le Gall, there is no material difference between the case I have rejected and the one starting from Bardel. The biggest difference is a point which makes the case more difficult for Accord because the team would not have Le Gall. At least starting from Le Gall the team would have seen compound 107e at one stage even if they had forgotten it after

completing and distilling the literature search. Over Bardel the team would have to think of 107e with no prior contact with the compound at all.

211. In any case my findings over Le Gall mean the claims are not obvious over Bardel either.

Conclusion

212. The priority date for the relevant claims in the patent is 15th March 1996. The claims of the patent involve an inventive step and are not obvious. The action will be dismissed.