Neutral Citation Number: [2014] EWHC 3916 (Pat)

Case No: HP14D01069

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 1 December 2014

Before :

THE HON MR JUSTICE ARNOLD

- -

Between :

IDENIX PHARMACEUTICALS, INC.	**Claimant**
- and -	
(1) GILEAD SCIENCES, INC. **(21) GILEAD SCIENCES LTD** **(3) CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE** **(4) UNIVERSITÀ DEGLI STUDI DI CAGLIARI** **(5) L'UNIVERSITÉ MONTPELLIER II**	**Defendants**

And between :

(1) GILEAD SCIENCES, INC. **(2) GILEAD SCIENCES LTD**	**Part 20 Claimants**
- and -	
(1) IDENIX PHARMACEUTICALS, INC.	**Parts 20 Defendants**
(4) CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE **(3) UNIVERSITÀ DEGLI STUDI DI CAGLIARI** **(4) L'UNIVERSITÉ DE MONTPELLIER II**	

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Andrew Waugh QC, **Piers Acland QC** and **Stuart Baran** (instructed by **Jones Day**) for **Idenix**
Justin Turner QC, **Andrew Lykiardopolous QC**, **Thomas Moody-Stuart** and **William Duncan** (instructed by **Herbert Smith Freehills**) for **Gilead**

Hearing dates: 3, 7-10, 14-16, 21-23 October 2014

- -

Judgment

MR JUSTICE ARNOLD :

Contents

Introduction

1. Idenix Pharmaceuticals, Inc. ("IPI"), Centre National de la Recherche Scientifique, Università degli Studi di Cagliari and L'Université Montpellier II (collectively, "Idenix") are the joint registered proprietors of European Patent (UK) No. 1 523 489 entitled "Modified 2' and 3' –Nucleoside Produgs [*sic*] for Treating Flaviridae [*sic*] Infections" ("the Patent"). The application for the Patent, International Patent Application No. WO 2004/002999 ("the Application"), was filed on 27 June 2003. The Patent was granted on 12 March 2014. Although the Patent on its face claims priority from four United States priority documents dating from 28 June 2002 to 14 May 2003, no claim to priority is made by Idenix in these proceedings.

2. Idenix claim that Gilead Sciences, Inc and Gilead Sciences Ltd (collectively, "Gilead") have infringed the Patent by the keeping and disposal of sofosbuvir, which Gilead market under the trade mark Sovaldi. Sovaldi represents a significant breakthrough in the treatment of Hepatitis C virus ("HCV"). A standard course of treatment of Sovaldi takes from only 12 weeks (a significant reduction compared to previously available HCV treatments), has a high efficacy rate and few, if any, side effects when compared with other treatments. Sovaldi received a marketing authorisation from the European Medicines Agency in January 2014. In the UK it is in the process of approval by the National Institute for Clinical Excellence ("NICE"). On 15 August 2014 NICE published draft guidance on Sovaldi which contained positive recommendations based *inter alia* on the cost-effectiveness of the treatment. By contrast, Idenix has no product either on the market or near to receiving a marketing authorisation which is covered by the Patent.

3. Gilead deny infringement and counterclaim for revocation of the Patent on the grounds of lack of novelty over Gilead's own International Patent Application PCT/US2004/012472 ("the Pharmasset PCT"), lack of inventive step, insufficiency and added matter. Somewhat unusually, there is an issue as to the entitlement to priority, not of the Patent, but of the Pharmasset PCT. As explained below, this involves issues both of fact and US law. In support of their allegation of insufficiency, Gilead rely upon work done by a number of Idenix scientists. As part of their answer to Gilead's case on this point, Idenix rely upon certain experiments conducted for the purposes of these proceedings. Idenix contend that claims 1, 5-7, 21 and 24 are independently valid and infringed. Idenix have also made a conditional application to amend the Patent. As a result, there are a considerable number of issues to be determined, on which the parties adduced a large body of evidence.

4. Idenix's claim was issued within hours of the Patent being granted. On 17 March 2014, Gilead filed its Defence and Counterclaim. Gilead applied to expedite the trial, and on 16 April 2014 Birss J gave directions for an expedited trial. As a result, the case came on for trial in less than seven months from the grant of the Patent and the commencement of the proceedings. The parties and their representatives are to be congratulated on having brought such a complex patent case on for trial so swiftly and so efficiently.

The parties and their respective patent applications

5. For reasons that will appear, it is necessary to say a little more about the parties to this dispute and their respective patent applications. IPI was founded (as Novirio

Pharmaceuticals Inc) by Dr Jean-Pierre Sommadossi in May 1998. On 31 March 2003 it was announced that Novartis was to acquire a majority stake in IPI, together with the right jointly to develop IPI's HCV drug candidate NM283. As noted above, the Application was filed on 27 June 2003. As their names indicate, IPI's co-applicants, and co-proprietors of the Patent, are academic institutions. In August 2014 IPI was acquired by Merck & Co Inc.

6. At around the same time as Dr Sommadossi founded IPI, Dr Raymond Schinazi founded Pharmasset Ltd, a company incorporated in Barbados ("Pharmasset Barbados") and Pharmasset, Inc, a company incorporated under the law of the State of Georgia, USA ("Pharmasset Georgia"). Pharmasset Barbados was incorporated on 29 May 1998. Pharmasset Georgia was incorporated on 5 June 1998. Pharmasset Georgia was a wholly-owned subsidiary of Pharmasset Barbados. Curiously, Dr Sommadossi was a director of Pharmasset Barbados for a period, and I understand that Dr Schinazi was likewise a director of IPI for a period. On 8 June 2004 Pharmasset Barbados was "redomesticated" and became Pharmasset, Inc, a company incorporated under the law of the State of Delaware, USA ("Pharmasset Delaware"). On 23 July 2004 Pharmasset Georgia merged into Pharmasset Delaware. In January 2012 Pharmasset Delaware was acquired by Gilead.

7. Pharmasset Georgia employed a chemist called Jeremy Clark. On 30 May 2003 Mr Clark and Lieven Stuyver filed US Provisional Patent Application 60/474,368 ("US 368"). On 21 April 2004 Pharmasset Barbados filed the Pharmasset PCT claiming priority from US 368. US 368 and the Pharmasset PCT disclose *inter alia* the synthesis of a 2'-fluoro-2'methyl cytosine compound and the activity of this compound against HCV in a replicon assay. This work was published in Clark *et al*, "Design, Synthesis and Antiviral Activity of 2'-Deoxy-2'-fluoro-2'-C-methylcytidine, a Potent Inhibitor of Hepatitis C Virus Replication", *J. Med. Chem.*, 48, 5504-5508 (2005) ("the Clark Paper"). In 2005 Dr Stuyver was removed as an inventor from the Pharmasset PCT.

The witnesses

Technical experts

8. Each side called two technical experts, a virologist and a medicinal chemist. As I shall explain, however, the two pairs of experts did not have expertises that precisely corresponded to each other. Furthermore, whether because of the differing expertises of their witnesses, or for other reasons, the parties divided the labour between their experts in different ways.

9. *The virologists*. Idenix's virology expert was Professor Jeffrey Glenn. Prof Glenn is an Associate Professor of Medicine (Division of Gastroenterology and Hepatology) and Microbiology and Immunology at Stanford University School of Medicine in California, a position he has held since 2008. He received a BA in biochemistry and French civilization from the University of California, Berkeley in 1984, a PhD degree in biochemistry from the University of California, San Francisco in 1992 and a MD from the same institution in 1993. From 1993 to 1995, he completed an internal medicine residency and from 1995 to 1999, he completed a gastroenterology fellowship, both at Stanford University Medical Center. From 1999 to 2008, he was an Assistant Professor at Stanford University School of Medicine. From 2006 until

the present, he has held the position of Director, Center for Hepatitis and Liver Tissue Engineering at Stanford University School of Medicine. From 2008 until the present, he has been first Associate Director and then Co-Director of the Stanford University Digestive Disease Center. From 1999 until the present, he has also served as Staff Physician, Palo Alto Veterans Administration. He is also a member of the Executive Committee of the Stanford Institute of Chemical Biology. Prof Glenn has authored or co-authored more than 50 publications in peer-reviewed journals, many of which are in the field of viral diseases and in particular HCV.

10. The only evidence which Idenix led from Prof Glenn in his first report concerned the common general knowledge of the skilled virologist and the ability of the skilled virologist to asses the antiviral activity of the compounds and compositions claimed in the Patent using that knowledge. In his second report Prof Glenn commented briefly on two points raised by Prof Götte, but said that he regarded a number of other matters as falling within the province of the medicinal chemist. No doubt for this reason, counsel for Gilead only cross-examined Prof Glenn briefly. Very little reference was made to Prof Glenn's evidence by either side in their closing submissions. Without intending any disrespect to Prof Glenn, I shall follow their example in this judgment. I have, however, taken his evidence into account.

11. Gilead's virology expert was Professor Matthias Götte. He is Chair of the Department of Medical Microbiology and Immunology at the University of Alberta in Canada, a position he has held since July 2014. He studied chemistry at undergraduate level at the University of Kiel and then the Technical University of Munich from 1984-1991, and obtained the equivalent of an MSc degree in 1991. He obtained a PhD from the Ludwig Maximilian University of Munich in 1997 for studies on the reverse transcriptase (RT) enzyme of HIV-1, a multifunctional enzyme that possesses DNA polymerase and ribonuclease H activities and is critical for replication of HIV. He was a postdoctoral researcher at the Lady Davis Institute for Medical Research at the Jewish General Hospital, Montreal, Canada between 1997 and 2000. During this time, he turned his attention to mechanisms of action and resistance associated with nucleoside analogue RT inhibitors. He started his own lab at the Lady Davis Institute for Medical Research in 2000 working on HIV as well as HCV and related viruses. He studied the structure and function of RNA-dependent RNA polymerases, also referred to as NS5B, in both HCV and BVDV. Working with commercially available nucleotide analogues that lacked the 3'-hydroxyl group, his group observed in cell-free biochemical assays that chain termination with these compounds could be reversible in the BVDV model. They presented these findings at the 10th International Meeting of HCV and Related Viruses in December 2003. In 2005 Prof Götte moved to the Department of Microbiology and Immunology at McGill University, Montreal, Canada. In 2007 he was promoted to Associate Professor and in 2011 to full Professor. His interests over the last 14 years have covered a broad range of viruses, including HIV, HCV, BVDV, and human herpes viruses. Recent findings from his laboratory have contributed to the development of novel classes of viral polymerase inhibitors with antiviral activity against resistant variants. He has published his work on viral polymerases in approximately 80 peer reviewed papers. He is also the co-editor/co-author of a number of books and book chapters.

12. Counsel for Idenix submitted that it was curious that Prof Götte had been asked by Gilead to address many of the chemical aspects of the case. I disagree. Prof Götte was

qualified to address the chemical aspects of the case that he considered, although it is true that Prof Boons could have been asked to address some of them. One might equally well say that it was curious that Dr Brancale was asked by Idenix to go as far as he did into the virological aspects of the case, when I am sure that Prof Glenn could have said more about them. I shall return to this point when discussing the composition of the skilled team.

13. Counsel for Idenix also submitted that Prof Götte had considered the question of plausibility on an entirely erroneous basis, namely without consideration of what the skilled team would know from their common general knowledge. I do not accept this. Prof Götte quite properly considered the matter of the basis of reading the Patent in the light of what he considered the relevant common general knowledge to be. Much of counsel's cross-examination was devoted to trying to persuade Prof Götte to accept that the level of common general knowledge was higher and that this impacted on the question of plausibility, but that does not establish that Prof Götte proceeded on the wrong basis. More generally, counsel for Idenix submitted that Prof Götte's approach was extreme and in several respects unsatisfactory. I do not accept this either. I found Prof Götte to be a very careful, precise and balanced witness.

14. *The medicinal chemists*. Idenix's medicinal chemistry expert was Dr Andrea Brancale. He is Senior Lecturer in Medicinal Chemistry at the School of Pharmacy and Pharmaceutical Sciences in the University of Cardiff, a position he has held since 2011. He received an undergraduate degree in Medicinal Chemistry from the University of Rome "La Sapienza" in 1996. In 2001 he was awarded a PhD from the University of Cardiff for a thesis on a new group of nucleosides with antiviral activity. From February 2001 to September 2002 he undertook post-doctoral research in Professor Chris McGuigan's group. This research focussed on phosphorylation of, and chemical modifications to, nucleoside analogues that might have activity against HBV and HIV. In particular, it included modifications to the 5'-phosphate group of such nucleotides. As part of that work, he investigated prodrugs, including masked phosphate prodrugs, of such nucleoside analogues. During his PhD and post-doctoral work, he personally synthesised a considerable number of nucleosides. He also used the fluorinating agent diethylaminosulphur trifluoride (DAST). In September 2002 he was appointed to a lectureship in the School of Pharmacy and Pharmaceutical Sciences. He is an author on approximately a hundred peer-reviewed journal articles in a variety of journals concerned with medicinal chemistry and allied fields.

15. Counsel for Idenix submitted that Dr Brancale was the best qualified of all the experts to assist the court due to his experience in synthesising nucleoside analogues, whereas Counsel for Gilead submitted that Dr Brancale was not as well qualified as Prof Götte and Prof Boons. Counsel for Gilead gave three reasons for this. First, Dr Brancale was not actively working in the field of nucleoside analogues against HCV, and in particular NS5B inhibitors, at the date of the Patent. When he took up his lectureship, he started work on a project on HCV helicase which was not published until 2009. He did not become interested in NS5B until 2009. By contrast, Prof Götte was working on NS5B in 2003. Secondly, Dr Brancale had not carried out any fluorination reactions on a sugar ring during his career. Indeed, he had only once fluorinated a primary carbon and had not fluorinated a tertiary carbon. By contrast, Prof Boons had considerable experience in fluorinating sugars, including for the purpose of synthesising modified nucleotides, although he had little experience of synthesising

nucleoside analogues. Thirdly, Dr Brancale's particular interest since 2006, when he ceased doing wet chemistry in the laboratory, has been in computer modelling of biological problems and drug design. I agree with counsel for Gilead that each of these three points, and particularly the first two, constitute significant limitations in Dr Brancale's expertise. Nevertheless, he did have the most experience of nucleoside synthesis of all the experts, and that experience was gained during the period prior to the date of the Patent.

16. Counsel for Gilead also submitted that Dr Brancale's evidence was unsatisfactory in five respects, the first three of which stemmed from the nature of his instructions. First, Dr Brancale prepared his expert reports with the understanding that the common general knowledge included anything that turned up on a literature search. Secondly, Dr Brancale was not provided with the Application before preparing his first expert report. Thus he only considered it after he had read, and formed his opinions as to the disclosure of, the Patent. Thirdly, Dr Brancale was not asked to consider the allegation that the Patent fails to disclose a technical contribution over the prior art. Fourthly, Dr Brancale had what counsel characterised as an eccentric view of the disclosure of a patent or patent application. By contrast with his approach to scientific papers, he did not focus on the technical information they contained. Rather, he approached such documents as an exercise in detecting the commercial intentions of the proprietor. He thought that a patentee "will keep some hidden cards" by holding back data, and that by focussing on the claims one could deduce what the patentee regarded as the most promising compounds despite the absence of supporting data or a scientific rationale from the patent. Fifthly, counsel submitted that Dr Brancale's evidence about the use of DAST was tainted with hindsight.

17. I agree with the first two points, although it is fair to observe in relation to the second point that Gilead expanded its plea of added matter during the course of the proceedings in a way which made the disclosure of the Application more significant than it was originally. The third point is not accurate. As to the fourth point, I did find Dr Brancale's approach to patents and patent applications somewhat unusual for a scientist, but it is right to acknowledge that he made it clear that he was not saying that the scientific content of the document should be disregarded. I will address the fifth point below.

18. Gilead's medicinal chemistry expert was Professor Geert-Jan Boons. He has been the UGA Foundation Distinguished Professor in Biochemical Sciences at the Franklin College of Arts and Sciences at the University of Georgia since 2012. He was awarded his first degree in chemistry by the State University of Leiden, the Netherlands, in 1987. Between 1987 and 1988 he worked as a research scientist in the Department of Research and Development of Organon International in the Netherlands. His work was focused on the chemical synthesis of modified nucleotides with the aim of developing novel antiviral drugs. He obtained a PhD in synthetic carbohydrate chemistry in 1991. From 1991 to 1993 he worked as a post-doctoral research assistant to Professor Steven Ley, first at Imperial College in London and then at the University of Cambridge. From 1993 to 1997 he was a Lecturer, and from 1997 to 1998 a Professor, in Bioorganic Chemistry at the University of Birmingham. While working at Birmingham he focused on the development of methods for the preparation of carbohydrates and chemically modified carbohydrate, including the preparation of carbohydrates modified by fluorine, and the use of such compounds for

the preparation of nucleotides. Since 1998 he has been a Professor at the Complex Carbohydrate Research Center and the Department of Chemistry at the University of Georgia in Athens. Between 2004 and 2012 he was the Franklin Professor of Chemistry.

19. Counsel for Idenix submitted that Prof Boons was not properly qualified to assist the court because he was essentially a carbohydrate chemist who had had no experience in synthesising nucleoside analogues for antiviral use and generally lacked expertise in antiviral research. I do not accept this. It is correct that Prof Boons' focus is on carbohydrate chemistry, but this is very relevant to the synthesis of nucleoside analogues, since one of the two main routes for such syntheses involves modifying the sugar. An illustration of this point is that, as explained in paragraphs 560-563 below, Mr Clark and his colleagues published some of their synthetic work in the Journal of Carbohydrate Chemistry, a journal for which Prof Boons serves on the editorial board and acts as peer reviewer and which is on his research group's reading list. Furthermore, as discussed above, Prof Boons did have some experience of synthesising modified nucleotides. He also had some experience in antiviral research, but in any event it would not have mattered if he had not, because that part of the case was addressed by Prof Götte.

20. Counsel for Idenix also criticised Prof Boons for being evasive in his answers, of making speeches and of taking points "on the fly". I do not consider that these criticisms are justified. Prof Boons was a knowledgeable and enthusiastic expert who tried to explain some complex matters when faced with questions that were sometimes either imprecise or wrongly premised. It is true to say that some points emerged for the first time in cross-examination, but it appeared to me that the reason for this was the particular focus of the questions. I am satisfied that Prof Boons was doing his best to assist the court.

21. It follows from what I have said above that, in considering the approach the skilled team, it is necessary to take into account the differing backgrounds and perspectives of Prof Götte, Dr Brancale and Prof Boons.

Experts in US law

22. Each side called two experts on US law, one expert in US Federal patent law and one expert in Georgia State law.

23. *Federal patent law*. Idenix's expert on US Federal patent law was the Hon Paul Michel, a former Chief Judge of the United States Court of Appeals for the Federal Circuit ("CAFC"). The CAFC is the US Federal appellate court with exclusive jurisdiction over patent-related appeals. Judge Michel was appointed to the CAFC in 1988, and was its Chief Judge from 2004 until his retirement from the bench in 2010. Judge Michel heard over a thousand patent appeals during his time on the bench, and wrote some 250 decisions involving patent law.

24. Gilead's expert on US Federal patent law was Professor John Thomas. Prof Thomas is Professor of Law at Georgetown University, a position he has held since 2002. He received a BSc in Computer Engineering and Public Policy from Carnegie Mellon University in 1989, a JD from the University of Michigan in 1992, and a Master of Laws degree in Patent and Intellectual Property Law from George Washington

University in 1994. From 1992 to 1994 he served as law clerk to Chief Judge Helen Nies of the CAFC. From 1994 to 1995 he was a visiting research scholar at the Institute of Intellectual Property in Tokyo, Japan, and a visiting fellow at the Max Planck Institute for Foreign and Comparative Patent, Copyright and Unfair Competition Law in Munich, Germany. During 1995, he was an associate with Vossius & Partner in Munich. From 1996 to 1997 he practised patent law full-time as an associate attorney at Finnegan, Henderson, Farabow, Garrett and Dunner in Washington, DC. From 1997 to 2002 he was a member of the law faculty at Geoge Washington University. He has taught pharmaceutical patent law at a number of institutions, including Munich Intellectual Property Law Center and at the University of New Hampshire School of Law. From 1997 to 2003 he was an Instructor at the US Patent and Trademark Office Patent Academy. From 2012 to 2013 he was the inaugural Thomas Alva Edison Visiting Fellow for the Office of Policy and External Affairs at the USPTO. As well as numerous law review articles and book chapters on intellectual property law, he is the author of *Pharmaceutical Patent Law* (2nd edition, 2010) and a co-author of *Patent Law: Cases and Materials*, which is a leading textbook.

25. *Georgia State law*. Idenix's expert on Georgia State law was the Hon Norman Fletcher, a former Chief Justice of the Georgia State Supreme Court. Judge Fletcher was a justice on the State Supreme Court from 1990 to 2005. For the last four of those years, he was its Chief Justice, having been the Presiding Justice for the six years before that.

26. Gilead's Georgia law expert was the Hon Stanley Birch Jr. From 1974 to 1990 he practised law in the State of Georgia. From June 1990 to August 2010 he was a Circuit Judge of the 11th Circuit Court of Appeals, which hears appeals from District Courts in Georgia, Alabama and Florida.

27. I would make three general comments about the expert evidence on US law. The first is that the reports prepared by the experts not only dealt with the relevant principles of law, but also their application to the facts of the case. The evidence on the latter aspect was inadmissible. I do not blame the experts for this, but those instructing them should have known better. The second was that, at the pre-trial review on 20 September 2014, there was a dispute as to whether the experts should be cross-examined (as Idenix proposed) or whether cross-examination should dispensed with (as Gilead proposed). At my suggestion, the parties agreed a compromise under which it was ordered that the experts should be cross-examined by videolink from the USA for a maximum of 1½ hours each. By the time the experts came to give evidence, the parties had sensibly prepared an agreed statement on US law setting out a considerable number of agreed principles and a small number of disputed principles, from which it became clear that there was very little dispute as to the relevant principles of Georgia law and limited areas of dispute as to Federal patent law. Accordingly, counsel were able to keep all their cross-examinations, but particularly the cross-examinations of the Georgia experts, shorter than the time allowed. The third comment is that no one suggested that any of the experts was other than very well qualified and trying to assist the court.

Factual witnesses

28. *Idenix's witnesses*. Idenix called three witnesses of fact, each of whom gave evidence about work carried by Idenix SARL and IPI on the synthesis of various nucleoside analogues, including 2'-fluoro-2'-methyl nucleosides, between 2002 and 2005. This work is relied on by Gilead in support of its allegation of classical insufficiency.

29. Dr Jean-François Griffon is a Senior Research Scientist at Idenix SARL in Montpellier, France. He was awarded a BSc in molecular chemistry from Montpellier II University in 1991. This was followed by an MSc and Post-graduate diploma in 1992 and 1993. Between 1994 and 1998 he undertook a PhD in the laboratory of Bioorganic Chemistry of Professor Jean-Louis Imbach at Montpellier II University under the supervision of Dr Gilles Gosselin. His work focussed on the synthesis of new non-natural L-nucleosides derived from 5-fluorouracil and 5-fluorocytosine. In the course of his PhD, he prepared a number of 2' and 3' fluoro-substituted nucleosides by the following methods:

    i) epoxide ring opening using potassium hydrogenfluoride (KHF_2), hydrofluoric acid (HF) alone or a combination of HF and aluminium fluoride (AlF_3);

    ii) opening a 2,2' or 2,3'-O-anhydro nucleoside using HF or HF in the presence of certain aluminium derivatives (AlF_3, $AlFR_2$ or $AlFR_3$);

    iii) nucleophilic substitution with tetrabutylammonium fluoride (TBAF); and

    iv) using DAST to fluorinate a 2' or 3' secondary alcohol, the other hydroxyls having been protected with a benzoyl group.

30. After post-doctoral research with Professor John Secrist at the Southern Research Institute in Birmingham, Alabama from 1999 to 2000, which involved the synthesis of certain 4'-C-hydroxymethyl-α- and -ß-D-arabino-pentofuranosyl purine and pyrimidine nucleosides for the treatment of cancer, Dr Griffon joined Idenix SARL as a Research Scientist in the nucleoside analogues group working on the synthesis of potential antiviral agents in Montpellier in February 2001. In 2004 his job description was changed to Senior Research Scientist (from the French equivalent), but his position and salary remained the same.

31. Counsel for Gilead accepted that Dr Griffon has generally given his evidence fairly, but criticised two particular aspects of his testimony. I have taken those criticisms into account in assessing his evidence.

32. Dr Alistair Stewart is Director of Chemistry, Manufacturing and Controls at IPI in Cambridge, Massachusetts. He received a MChem degree in chemistry from the University of Durham in 1999. He received a Ph.D. in organic chemistry from the University of Oxford in 2003, having studied under Professor George Fleet, an expert in carbohydrate chemistry. He joined IPI in September 2003 as a Research Scientist 1 in the Process Chemistry group. He was promoted to Research Scientist 2 in 2007, Group Leader in 2008, Associate Director in 2010 and his current position in March 2012. Counsel for Gilead did not criticise his evidence.

33. Jingyang Wang is employed by IPI as a Principal Research Scientist in Cambridge, Massachusetts. She received a Bachelor of Science degree in chemistry in 1989 from Nankai University, Tianjin, China, an MSc in organic chemistry in 1995 from the University of Manchester and a Master of Science degree in organic chemistry in 1998 from the University of Maine. She joined the process chemistry department of IPI in 2002 as a Process Chemist. She was promoted to the position of Research Scientist in May 2004, to Research Scientist II in June 2007, to Senior Research Scientist in June 2010 and to her current position in March 2012. Ms Wang understandably had no independent recollection of her work at the time and her evidence was based entirely on the records in her laboratory notebooks.

34. *Gilead's witnesses*. Gilead called two witnesses in support of its case that Pharmasset Barbados was successor in title to Mr Clark in respect of the invention claimed in the Pharmasset PCT.

35. Wendell Kuhl was employed by Pharmasset Georgia as the Chief Financial Officer of Pharmasset from March 1999 to July 2004. Mr Kuhl was a good witness who gave his evidence with care and who distinguished between his direct recollection and evidence which had been prompted by his consideration of documents. I have no hesitation in relying on his evidence.

36. Bryce Roberts is an attorney admitted to the state bar of Georgia. From November 1999 to January 2012 he worked for Pharmasset. He was initially employed by Pharmasset Georgia and later by Pharmasset Delaware. For the six months after Pharmasset's purchase by Gilead he was employed by Gilead to assist in that transition. He is now in-house counsel for a start-up biotech company. Mr Roberts was again a good witness who gave his evidence with care and who distinguished between evidence that stemmed from his unassisted memory of events and evidence that had been prompted by his consideration of documents. Again, I have no hesitation in relying on his evidence.

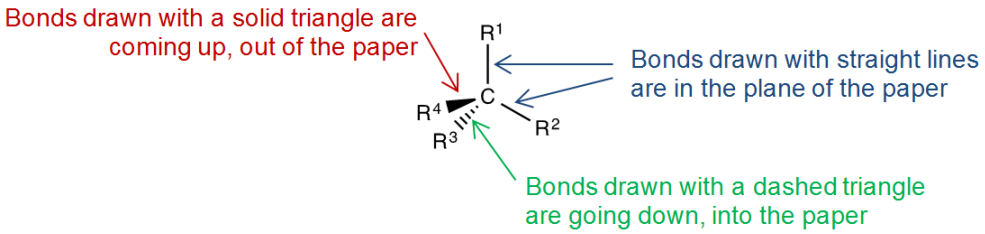
37. Counsel for Idenix drew attention to Gilead's failure to call a number of other witnesses. I shall deal with this point in context below.

Technical background

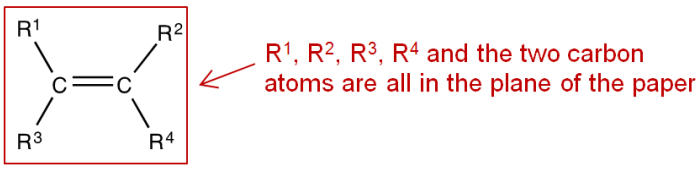
38. I have synthesised the following account of the technical background from the reports of all four experts, although I have drawn most heavily on the reports of Prof Götte and Prof Boons.

Stereochemistry

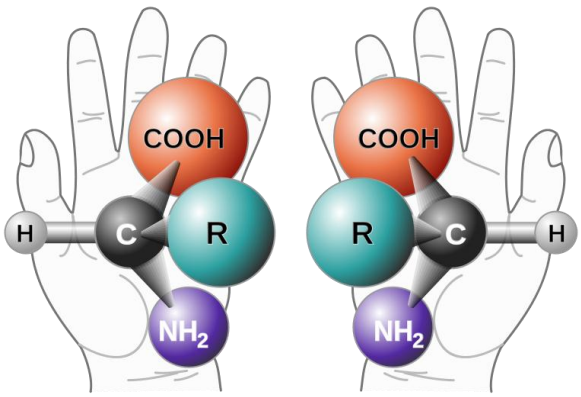
39. Stereochemistry is concerned with the three-dimensional arrangement of atoms within a molecule. Due to the fundamental properties of atoms, chemical bonds around carbon atoms can only form in certain fixed orientations. When a carbon atom is bonded to four other atoms or groups, those other atoms or groups adopt a tetrahedral arrangement around the central carbon. This can be represented in the following way.



40. When a carbon atom is bonded to three other atoms or groups, and one of those other atoms or groups is connected to the carbon by a double bond, the three other atoms or groups adopt a flat, trigonal arrangement around the carbon, as shown below.



41. One important aspect of stereochemistry is known as "chirality". A molecule which is chiral is handed, that is to say, it exists in two different forms which are mirror images of each other. A chiral molecule and its mirror image are called "enantiomers" (or "optical isomers"). A molecule is chiral when it has four different groups bonded to a carbon atom. Such a carbon atom is referred to as "chiral centre". The relationship between enantiomers is shown below.

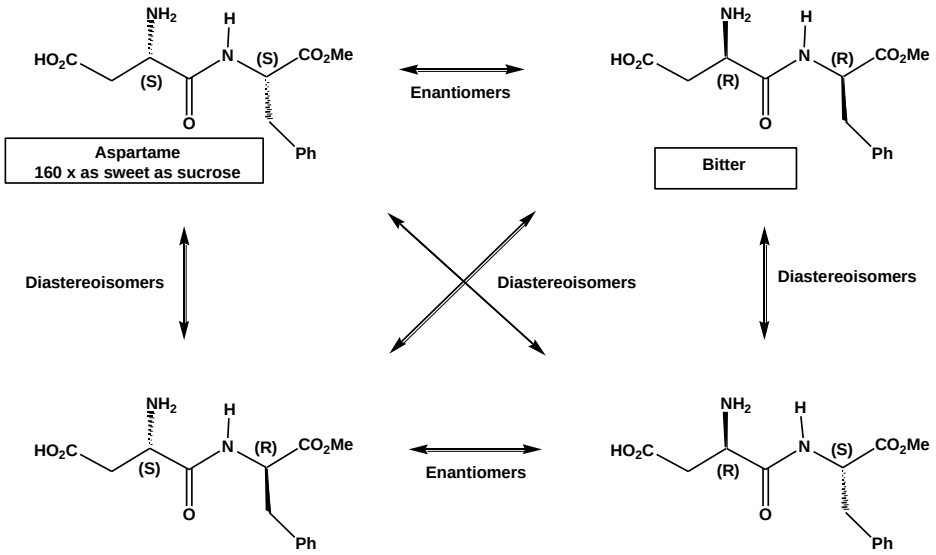


42. Enantiomers have identical chemical and physical properties except that they rotate polarised light in opposite directions. A mixture of equal quantities of enantiomers is termed a "racemic mixture", and overall will not rotate polarised light.

43. Chiral centers are described in a number of ways. The official (International Union of Pure and Applied Chemistry, IUPAC) method is to employ the R/S system, in which R denotes *rectus* (straight) and S denotes *sinister* (left). This system involves assignment of priority of substituents by the Cahn Ingold Prelog rules. In this approach, the chiral center is viewed from the side opposite the lowest ranking group (based on the atomic number of the atom, so in the above picture the hydrogen atom has the lowest ranking). If the priority (i.e. atomic number) of the remaining three substituents decreases in a clockwise direction, it has an R-configuration. If it decreases in a counter clockwise direction, it has an S-configuration.

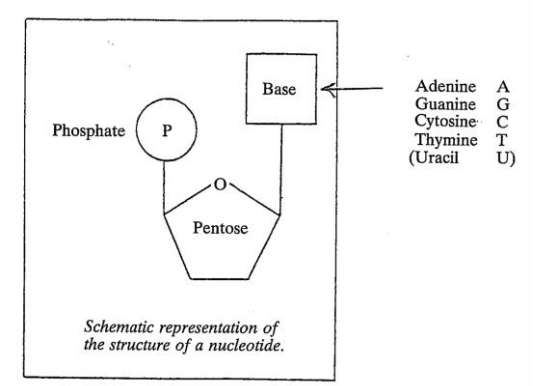
44. Another method that is used is the D/L system, in which D denotes *dexter* (right) and L denotes *laevus* (left). This system involves relating the molecule to glyceraldehyde. Glyceraldehyde is chiral itself, and its two isomers are labeled D and L. The enantiomers of other molecules are named by analogy.

45. If a molecule has more than one chiral center it has, in general, 2^n stereoisomers (where n= number of chiral centers), which cannot all be enantiomers - for example S,S is not a mirror image of S,R. Stereoisomers that are not mirror images are termed "diastereoisomers". Diastereoisomers have different properties. This is illustrated below.



Nucleic acids, nucleotides and nucleosides

46. Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are large, complex, naturally-occurring organic molecules. They encode the information which is contained in an organism's genes. Nucleic acids are polymers composed of monomers. The monomers are relatively small, naturally-occurring organic molecules called nucleotides. These consist of a five carbon (or "pentose") sugar, a heterocyclic aromatic base (or "nucleobase") and a phosphate moiety, as schematically illustrated below.

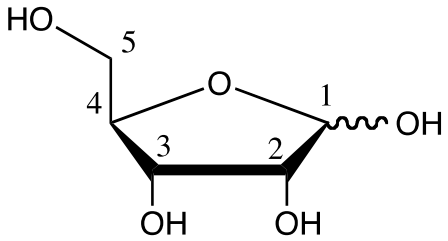


47. A pentose bonded to a nucleobase without a phosphate moiety is referred as a "nucleoside". The bond formed between the sugar and nucleobase components of

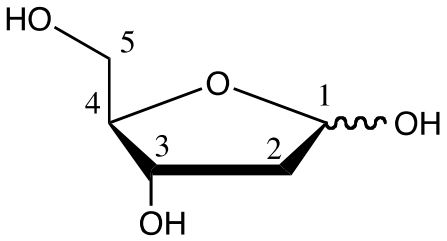
nucleosides is termed a "glycosidic" bond, and it is formed in a process known as "glycosylation".

Pentoses

48. Pentoses are carbohydrates, more specifically monosaccharides (simple sugars). The pentoses found in RNA and DNA are D-ribose and D-2-deoxy-ribose respectively. They have a ring structure of one oxygen atom and four carbon atoms, as well as one carbon atom attached to the ring. Conventionally, the carbon atoms in the ring are numbered clockwise 1 to 4, while the carbon atom attached to the ring is numbered 5, as shown below.



D-ribose

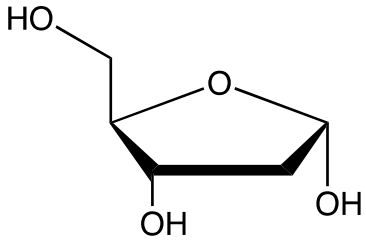


D-deoxyribose

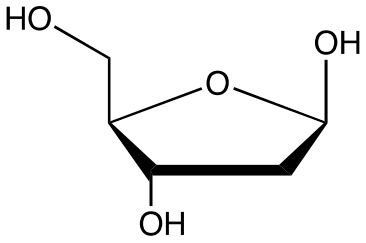
49. Pentoses have multiple chiral centres. In this form of diagram (known as a Haworth projection), the sugar ring is represented as a planar structure. The bold wedged bonds indicate that 2- and 3-carbon atoms of the sugar ring point towards the viewer whereas the oxygen atom points away from the viewer. The plain bonds pointing upwards and downwards from the sugar ring indicate that the attached substituents are respectively above and below the plane of the ring. These are commonly referred to as the "up" and "down" positions respectively.

50. In D-ribose, the 1-, 2- and 3-carbon atoms in the ring structure are each substituted with a hydrogen atom (not shown in the Haworth projection) and a hydroxyl (OH) group. The hydroxyl groups attached to the 2- and 3-carbon atoms adopt the down position ("hydroxy-down"). The 5-carbon atom, which also has a hydroxyl group attached to it, is in the up position. The wiggly lines indicate that the hydroxyl group at the 1-carbon position may be either up or down. In D-2-deoxyribose, the 2-carbon is substituted with two hydrogen atoms (missing the oxygen atom in the hydroxyl group at the corresponding position in D-ribose, hence the name "D-2-deoxyribose").

51. The 1-carbon atom in D-2-deoxyribose represented in the right-hand molecule shown below has its hydroxyl group in the up position, which is called the "β"-configuration. This hydroxyl group can also adopt the down position, as shown in the left-hand molecule below, which is called the "α"-configuration. The molecules in these two configurations are diastereomers to each other, or more specifically, in carbohydrate chemistry, "anomers". Being diastereomers, anomers have different properties to each other.



α-anomer



β-anomer

Nucleobases

52. Both DNA and RNA normally use combinations of four nucleobases each to perform their coding function. In RNA, these nucleobases are cytosine, uracil, adenine and guanine. In DNA, uracil is replaced by thymine. Adenine and guanine belong to the class of double-ringed nucleobases named purines, while cytosine, thymine, and uracil are in the class of single-ringed nucleobases named pyrimidines. These nucleobases are known respectively by their first letters, namely A, G, C, T and U. They have an important characteristic, namely that C forms hydrogen bonds ("pairs") with G, but not with A or T, and A pairs with T or (in the case of RNA) U, but not with G or C.

53. Base pairing has two main functions:

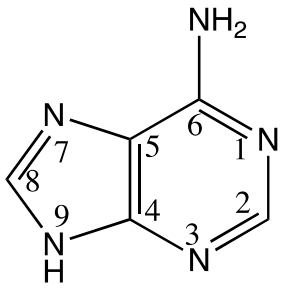
    i) in double-stranded DNA or RNA, base pairing allows the two strands to form stable intermolecular structures that can result in a double helix; and

    ii) the complementary nature of base pairing, which means that the sequence of bases on one strand dictates the sequence on the other strand, allows replication of the genetic code and its translation into proteins.

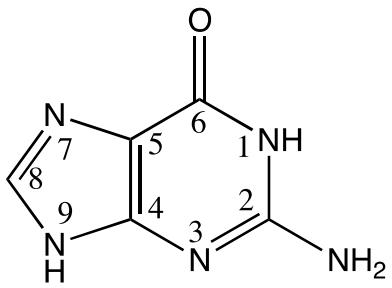
54. The sequence of bases in a strand of DNA or RNA makes up the genetic code. In simple terms, the portion of a DNA (or RNA in the case of RNA viruses) molecule that provides the code for a protein, which may comprise thousands of bases, is termed a gene. The process of "translation" converts the information of the gene from a chain of nucleotides to the corresponding chain of amino acids. A chain of amino acids is called a peptide or polypeptide. The polypeptide chain undergoes a three-dimensional folding process that results in generation of the final protein.

55. In a nucleoside, the positions in the base are numbered from 1 to 6 for pyrimidines, or 1 to 9 for purines, as shown below.

PURINES

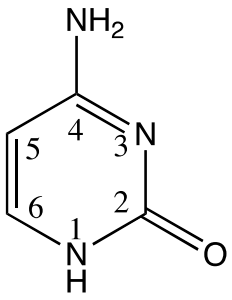


Adenine

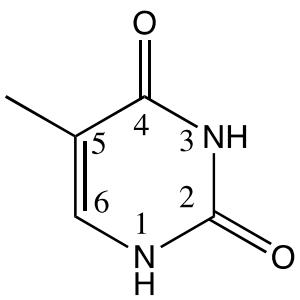


Guanine

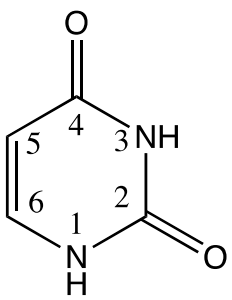
PYRIMIDINES



Cytosine



Thymine



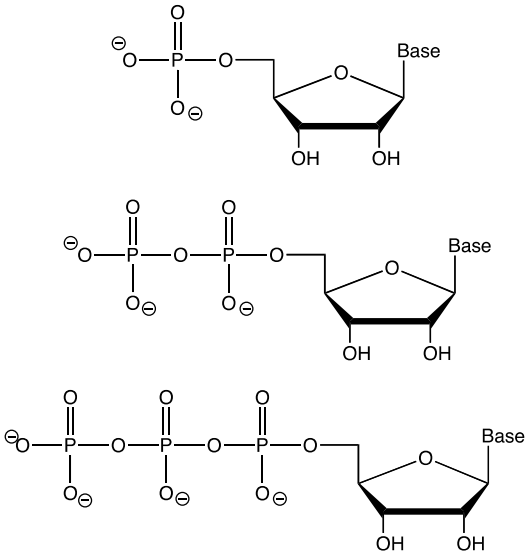
Uracil

56. When a sugar is bonded to a nucleobase and therefore forms part of a nucleoside, the carbon atoms in the sugar are numbered from 1' to 5', so that a distinction can be made between the positions in the sugar (1', 2', 3' etc) and in the nucleobase (1, 2, 3 etc).

57. When joined to the sugar via a glycosidic bond, the nucleobase adopts the up position (the β-configuration) in all naturally-occurring nucleosides.

Nucleotide formation

58. If one, two or three phosphate groups are added to a nucleoside, one has a nucleotide. Where it is necessary to distinguish the number of phosphate groups attached, the compounds are generally termed nucleoside mono, di or triphosphates. A 5'-nucleoside monophosphate, 5'-nucleoside diphosphate and 5'-nucleoside triphosphate are shown below. Due to the negative charges on the oxygen atoms in the phosphate groups, nucleotides are highly charged and polar molecules.

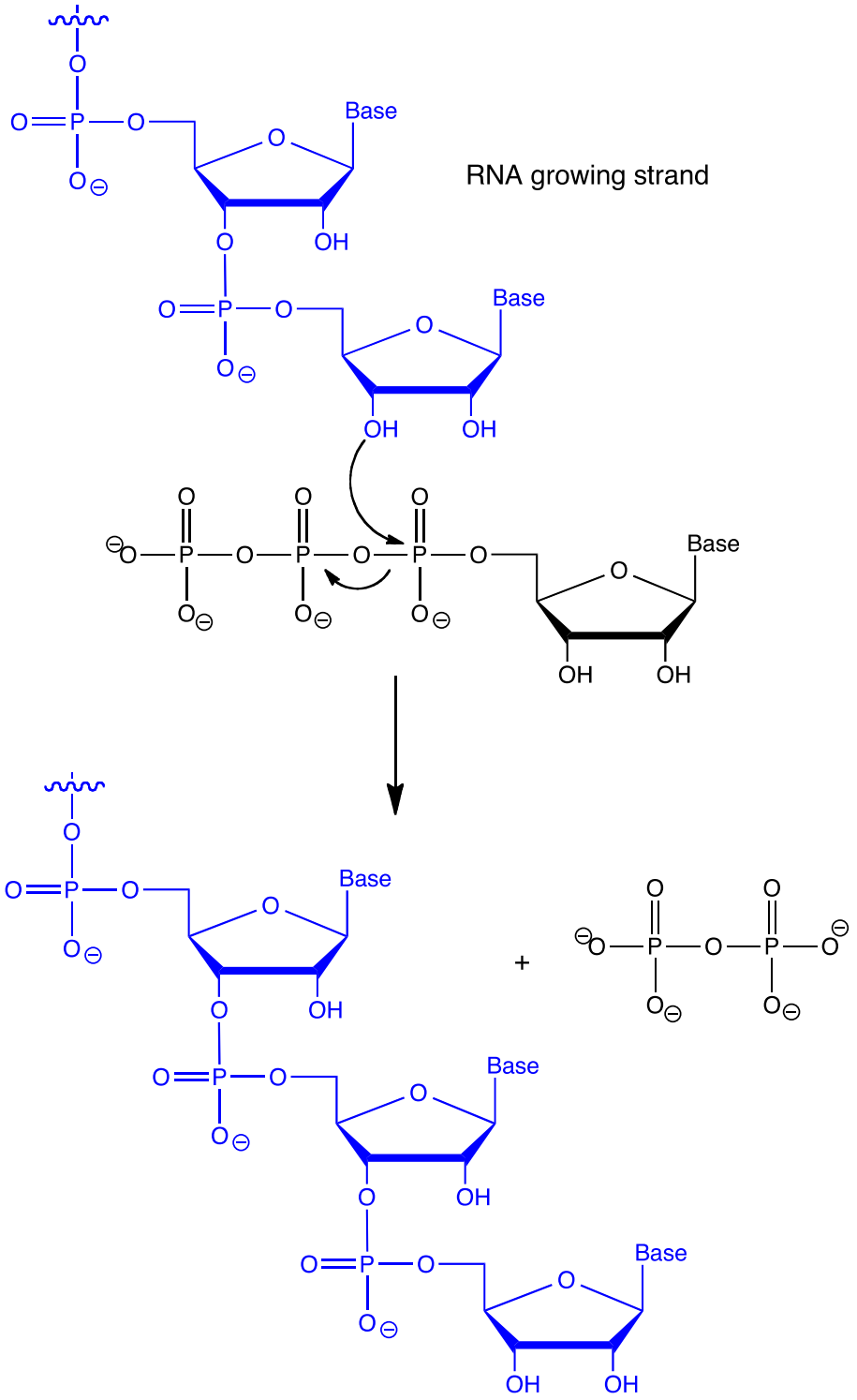


59. In nature, nucleosides undergo up to three consecutive phosphorylation steps inside the cell at the hydroxyl group attached to the 5'-carbon to form 5'-nucleoside mono-, di- and triphosphates respectively. Phosphorylation is a reaction in which a phosphate group is transferred from a phosphate donor to an organic molecule. It is catalysed by enzymes called kinases. Kinases are enzymes which are capable of bringing activated phosphate donors into close vicinity to the organic molecule, in this case a nucleoside, and facilitate the transfer of the phosphate group.

60. In general, phosphorylation of a nucleoside is catalysed by nucleoside kinases using adenosine triphosphate ("ATP") as the activated phosphate donor. ATP itself is a 5'-ribonucleoside triphosphate having adenine as the base. Again, generally the first step phosphorylation is catalysed by the nucleoside kinase and results in a 5'-nucleoside monophosphate. The 5'-nucleoside monophosphate is subsequently phosphorylated in two further phosphorylation steps to form 5'-nucleoside di- and triphosphate by nucleoside monophosphate kinase and nucleoside diphosphate kinase, respectively.

Nucleic acid formation

61. Copies of nucleic acids are made by the action of polymerase enzymes, which catalyse formation of bonds between individual nucleotides. The critical interaction in polymerase-catalyzed DNA or RNA synthesis involves the 3'-hydroxyl group of the nucleotide on the DNA or RNA of the so-called "primer" strand, which is complementary to the strand being copied (the "template"). The 3'-hydroxyl of the growing primer strand attacks the first (or α) phosphate group of the incoming 5'-nucleotide nucleoside triphosphate that forms a base pair with the template strand. This forms a 3',5'-phosphate diester linkage which builds up the backbone structure of the DNA or RNA. The other two phosphate groups form a diphosphate termed pyrophosphate which is cleaved off the nucleotide. This reaction is a nucleophilic substitution reaction (as to which, see below). The process is shown below.



Viruses

62. Viruses are small infective agents consisting of genetic material, either RNA or DNA. This is termed the viral genome. The viral genome is enclosed in a protein coat or capsid and some viruses also have a lipid-protein envelope, which can be seen as the outer "shell" of the virus.

63. Viruses are classified using a taxonomic system. At the highest level of generality, viruses are grouped on the basis of nucleic acid type. There are different groups

depending on the way the genetic information in the virus is stored, i.e. whether the nucleic acid is DNA or RNA, and whether it is single-or double-stranded.

64. Viruses are then divided into families. Members of a family share similarities in genome organisation. They are further classified into genera on the basis of genetic sequence similarity. Finally, viruses with the highest levels of genetic sequence similarity are classified as a species. The nature of disease caused by a virus, the route of transmission, the species of the host, the cells within the host that are infected and the symptoms that result are not criteria for taxonomic classification of viruses.

Flaviviridae

65. The *Flaviviridae* family is a large, diverse family of positive, single-stranded, enveloped RNA viruses. It includes a large number of viruses of significant global concern that cause disease in humans and animals. The term positive-strand RNA virus refers to viruses in which the genetic material is RNA that can be directly translated into proteins.

66. The members of the *Flaviviridae* family are evolutionarily diverse and cause a wide range of different diseases, targeting different species and different cell types. In June 2003 three genera in the *Flaviviridae* family had been recognised (subsequently a fourth genus has been recognised, Pegivirus, which includes Hepatitis G):

    i) Flavivirus – this is by far the largest genus consisting of nearly 80 virus species. They are primarily transmitted by insect vectors and cause acute self-limited infections in humans and animals. Examples include yellow fever virus ("YFV"), dengue virus ("DENV") and West Nile virus ("WNV").

    ii) Pestivirus - this includes bovine viral diarrhea virus ("BVDV"), which infects cattle.

    iii) Hepacivirus – this includes HCV, which exists in a number of distinct genotypes.

Hepatitis C

67. It has long been known that certain viruses spread by blood to blood contact caused inflammation of the liver ("hepatitis"). In the 1960s and 70s blood tests were developed which identified Hepatitis A and Hepatitis B ("HBV") viruses (neither of which are members of the *Flaviviridae* family). However, the blood samples of many patients with liver inflammation tested negative for Hepatitis A and HBV. These cases were described as non-A, non-B hepatitis. In the 1980s investigators at Chiron sought to identify this non-A, non-B virus from the blood samples of patients. This led to the identification of HCV in 1989.

68. Hepatitis C is the most important hepacivirus human disease. With about 170 million carriers of HCV worldwide and about 5-10 million in Europe, Hepatitis C is (and was in 2003) a significant global health threat.

69. Hepatitis C can be divided into four stages:

i) Initial infection or viraemia. This is the acute phase of the infection. It lasts about 2 – 26 weeks. The patient has measurable HCV levels in their blood. About 20% of patients clear the infection without treatment. Acute HCV infection is usually asymptomatic. This means that patients do not seek medical help and therefore early diagnosis of the HCV infection is rare.

ii) Chronic infection. Approximately 80% of people who become infected with HCV develop a chronic infection. There are usually no symptoms at this stage. After initial infection, it can take approximately 20-30 years until liver damage manifests and presents clinically. Therefore, infection may remain undiagnosed until serious liver damage has developed.

iii) Fibrosis. This is an overaggressive wound healing response triggered by chronic inflammation as a result of the HCV infection. It is characterised by excessive formation of connective tissue, similar to scar tissue. A fibrotic liver hardens and its function is compromised. Fibrosis itself has no symptoms but can lead to portal hypertension, which compromises blood flow to the liver, and cirrhosis. Fibrosis can be reversed by treating the underlying cause of inflammation.

iv) Cirrhosis. This is an advanced stage of fibrosis where the liver is severely and irreversibly injured. Cirrhosis can be asymptomatic for years; one third of patients never develop symptoms. If symptoms do develop they are often non-specific (e.g. loss of appetite, fatigue and weight loss). The only treatment is transplantation. The risk of cirrhosis is 15–30% within 20 years of HCV infection. Cirrhosis is also a major risk factor for development of hepatocellular carcinoma (liver cancer).

70. Untreated HCV infection is the leading cause of liver failure and liver cancer, both of which can be fatal. The World Health Organisation estimates that globally there are 350,000-500,000 deaths from HCV each year.

HCV genotypes

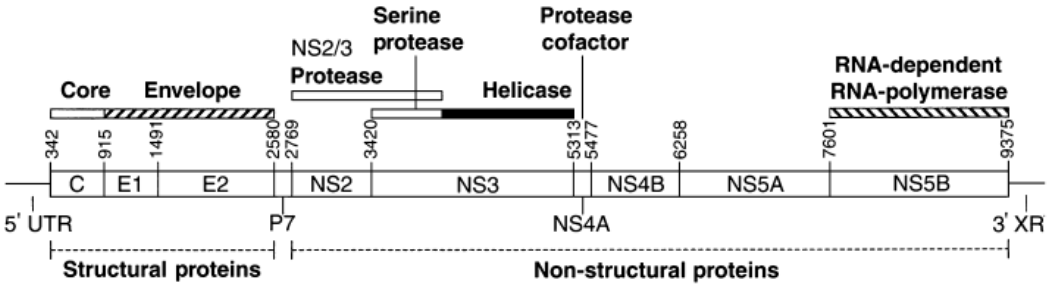
71. Within the HCV species, there are a number of different genotypes ("GTs") classified on the basis of their genetic sequence variation. The predominant genotypes are GT1-6. Within genotypes, there are distinct subtypes designated a, b, c etc. There is also some degree of genetic variation in the virus population within an infected individual due to on-going mutations caused during the process of viral RNA replication that is not entirely accurate. It is the ability of the virus to mutate that can give rise to the emergence of resistance to antiviral treatment.

72. HCV genotypes differ in their geographical spread. Currently, in the UK GT1 and GT3 are co-prevalent, each accounting for about 45% of infections. GT1b is the most prevalent subtype in Europe.

73. Different genotypes can show different responsiveness to treatment with antiviral medications. GT1 has, historically, been more difficult to treat than other genotypes.

The HCV genome

74. The HCV genome consists of a single strand of positive-sense RNA. It is about 9600 nucleotides in length. The organisation of the HCV genome is illustrated below (from A.J. Freeman *et al*, "Immunopathogenesis of Hepatitis C virus infection", *Immunology and Cell Biology*, 79, 515–536 (2001)).



75. The genome is initially translated as one long polyprotein of about 3,000 amino acids. The polyprotein is then cleaved by enzymes from the host cell called peptidases to release three structural proteins: the core protein (C), the envelope proteins (E1 and E2) and a small protein of unknown function called p7. These form the structural elements of the progeny virus particles.

76. The non-structural (NS) viral proteins are involved in protein processing and replication of viral RNA. These proteins and their functions are as follows:

    i) NS2 – forms part of the NS2/3 autoprotease that cleaves the polyprotein to release the NS segment.

    ii) NS3 protease – mediates cleavage of the NS polyprotein. It is a multifunctional protein with protease and helicase (nucleic acid unwinding) activities. NS3 forms a complex with NS4A.

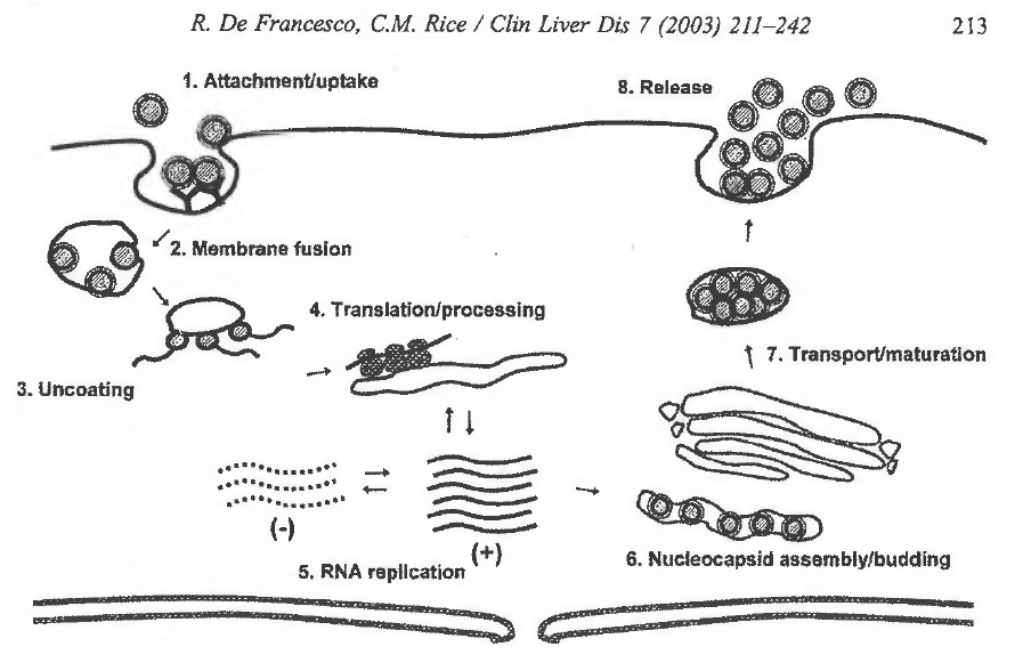
    iii) NS4A – is a co-factor of NS3 involved in protease activity.

    iv) NS4B and NS5A – the detailed functions are unknown and are not thought to include enzymatic activity.

    v) NS5B – RNA-dependent RNA polymerase activity, which is essential for mediating replication of the viral genome.

HCV replication

77. An understanding of viral replication is important for the development of antiviral therapies, since antiviral compounds often disrupt or interfere with a necessary step in the viral life cycle. The general steps in the HCV lifecycle are illustrated below.



78. These steps are as follows:

i) Virus attachment and uptake (or binding and internalisation). The HCV particle targets hepatocytes (liver cells) and attaches itself to the cell membrane.

ii) Fusion. The virus envelope and the host cell membrane fuse.

iii) Cytoplasmic release and uncoating. The protein capsid breaks down and releases viral RNA into the cytoplasm of the cell.

iv) Translation and polyprotein processing. The RNA genome is translated into a single long polyprotein. The polyprotein is cut up by host and viral enzymes called proteases into the individual structural and non-structural proteins. The latter are required for replication.

v) Viral RNA replication. The positive-stranded RNA genome is first copied to generate a complementary negative strand. The negative strand RNA then serves as a template for the production of multiple copies of the positive strand RNA. The RNA-dependent RNA polymerase, NS5B, replicates viral RNA by accepting nucleoside triphosphates present in the host cell and incorporating them into the growing viral RNA chain.

vi) Assembly. The newly synthesised positive stranded viral RNA, structural core and envelope proteins are assembled into new virus particles.

vii) Virion maturation and transport. Virus particles are transported to the cell membrane.

viii) Virion release. Virus particles are released from the host cell and go on to infect further cells.

79. A key target for those developing anti-HCV therapies is the RNA replication step. If the activity of NS5B can be disrupted, this will prevent successful replication of the HCV genome and therefore of the virus. Because of the essential function of NS5B in viral replication, it had been identified as a target for the development of antiviral therapies by June 2003.

Structures of enzymes

80. Most metabolic reactions, including replication of nucleic acids, do not take place spontaneously. Enzymes are functional proteins that are required to catalyse reactions within cells. To do this, enzymes must interact with their substrate. This takes place in the active site of the enzyme. The way in which enzymes work is closely related to their complex three-dimensional structure. Knowledge of the structure of an enzyme is an important tool in understanding how an enzyme works.

81. Crystal structures of enzymes enable visualisation of protein structures at the atomic level. Crystal structures of enzymes and substrates allow researchers to study how enzymes interact with other molecules, how they undergo changes in conformation (i.e. 3D shape), and how they perform catalysis.

RNA-dependent RNA polymerase, NS5B

82. The enzyme in HCV that copies viral RNA is the RNA-dependent RNA polymerase, also called NS5B. The reaction catalysed by NS5B is the formation of phosphodiester bonds between ribonucleoside monophosphates to make new viral RNA strands. To do this, it brings together its substrates - ribonucleoside triphosphates and the template of the viral RNA being copied -in the active site of the enzyme.

83. The crystal structure of HCV NS5B was published in 1999. The first structure of NS5B was not complexed with its substrates, meaning that it did not show the conformation of the protein in the form it takes when the nucleoside triphosphate and the template RNA are present in the active site of the enzyme.

84. In 2002 crystal structures of NS5B in complexes with nucleoside triphosphates were published. However, these crystal structures did not enable the rational design of nucleoside analogue inhibitors that targeted the active site of NS5B, because these crystal structures did not contain the viral template RNA and so gave an incomplete picture of the molecular interactions at the NS5B active site.

85. A crystal structure of the complete ternary structure (i.e. the structure of NS5B when complexed with the nucleotide and RNA template strand) was not available in June 2003. In the absence of this information, it was not known how the amino acid residues in the active site of NS5B interact with the substrates to catalyse the formation of the bond between nucleotides.

HCV treatment

86. The goal of treatment is to stop viral replication in order to eliminate the virus from the infected individual. This is termed a sustained virological response ("SVR"). If no viral RNA is detectable in a patient's blood sample several weeks after the end of treatment, this is termed a SVR and is indicative of a cure. SVR is usually measured

12 weeks after the end of treatment, in which case it is termed SVR12 (although in clinical trials it may be measured at 6 or 8 weeks termed SVR6, SVR8, respectively). Relapse after achieving a cure is rare.

87. The standard care for HCV infection in June 2003 was combination therapy with pegylated interferon alpha (“IFN”) and ribavirin (“RBV”). Treatment with IFN alone has a cure rate of about 15-25%. Therefore it is always recommended that IFN is taken in combination with RBV. Combination therapy with IFN/RBV for one year achieves cure rates of approximately 80% in GT2 and GT3 infections, but only 40-50% in GT1.

88. IFN and RBV are both indirect inhibitors of viral replication. RBV is a broad-spectrum antiviral agent that greatly improves antiviral responses. IFN is a synthetic version of a naturally occurring protein made by cells of the immune system. IFN has multiple effects on the body, some of which are antiviral. The mechanism of action of IFN is still not fully understood. RBV is described below.

89. Combination therapy with IFN/RBV involves a complex treatment regime. IFN is administered by injection once a week. RBV is taken orally twice a day. If a protease inhibitor (“PI”) is taken (as to which, see below), this is taken orally three times a day with food. Combination therapy must be administered for 24-48 weeks, depending on HCV genotype. Severe adverse side effects, especially associated with IFN, occur in almost all patients.

90. The treatment of last resort for patients with HCV is liver transplantation. HCV infection is the most common cause of liver transplantation in the US and Europe. However, the transplanted liver almost invariably becomes infected. Treating recurrent infection after liver transplantation is particularly complicated due to drug interactions between IFN/RBV with the immune suppressants administered to prevent transplant rejection.

Direct acting antivirals

91. Because of the deficiencies in the existing treatments, by June 2003 developing better treatments for HCV had long been a goal for researchers and clinicians. More targeted drugs were desirable to increase cure rates and decrease side effects. This led to research into drugs called direct acting antivirals (“DAAs”). Unlike IFN and RBV, DAAs are agents that interfere with specific steps in the viral replication cycle.

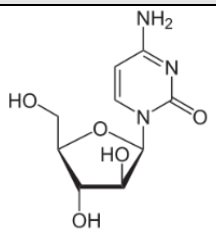
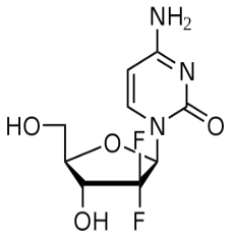
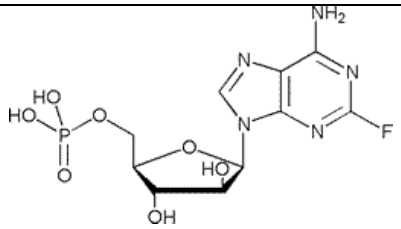
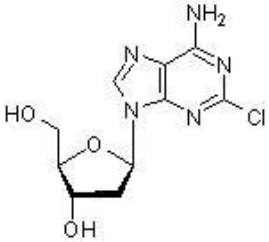
92. In developing DAAs for HCV, many research groups focused initially on PIs that targeted the NS3/4A protease. PIs work by preventing cleavage of the polyprotein into individual proteins. This prevents proper functioning of the proteins and thereby prevents virus replication. Although several potent PIs were identified, it was not until 2011 that the first DAAs were approved for treatment of HCV.

Nucleoside analogues

93. “Nucleosides analogues” are synthetic compounds which are analogues of naturally-occurring nucleosides. These differ from natural nucleosides in having one or more substituents that differ from those found in nature. As will appear, there is vast scope for devising new nucleoside analogues. It is important to appreciate that a skilled

medicinal chemist is capable of devising a new nucleoside analogue, or a class of new nucleoside analogues, purely on paper. Whether he can readily make the compound(s) is another matter.

94. *Nucleoside analogues in chemotherapy*. Outside the field of virology, cytotoxic nucleoside analogues have been used clinically for over 50 years in the treatment of cancer. By June 2003, they were an essential component of chemotherapy for many cancers including acute myeloid leukaemia (cytosine arabinoside or cytarabine), treatments of leukaemias (fludarabine, cladribine) and some solid tumors (gemcitabine). The structures of these compounds are shown below.

Name	**Structure**	**Approval date and indication**
Cytarabine		FDA approved pre-1984 Used in treatment of leukaemia.
Gemcitabine		FDA approved 1996 Used for treatment of various cancers: non-small cell lung cancer, pancreatic cancer, bladder cancer and breast cancer.
Fludarabine		FDA approved 1991 Used in treatment of B-cell chronic lymphocytic leukaemia.
Cladribine		FDA approved 1993 Used in treatment of lymphoproliferative diseases including hairy-cell leukaemia.

95. There are a number of mechanisms through which these nucleoside analogues cause cell death and therefore are of clinical benefit in treatment of cancer. These include:

i) Mimicking naturally occurring nucleosides. The nucleoside analogues act as "antimetabolites", or "decoy" metabolites, preventing the cell carrying out vital functions. As a result, the cell cannot grow and divide.

ii) Competing as an alternative substrate with naturally occurring nucleotides. The nucleoside analogues directly inhibit DNA polymerases and prevent

successful copying of cellular DNA. This prevents cell division and proliferation.

iii) Inhibiting DNA primase, an enzyme that is involved in cellular DNA replication.

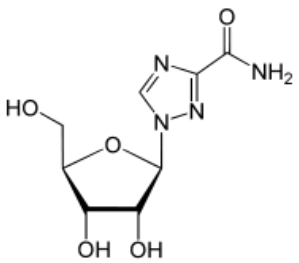
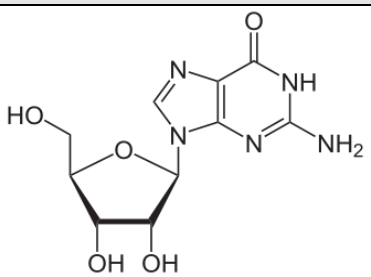
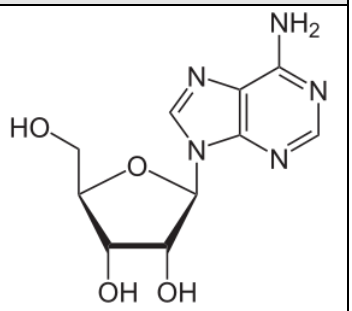
iv) Inhibiting the ability of DNA ligase I to join the incorporated nucleoside analogue to an adjacent piece of DNA.

v) Some nucleoside analogues also cause cell death in quiescent cells in the absence of their incorporation into DNA by the activation of the mitochondrial pathway of the apoptotic (or programmed cell death) cascade.

96. Individually or in combination, these actions result in inactivation of DNA synthesis followed by an initiation of apoptosis that ends in death of the cell.

97. *Nucleoside analogues to treat viral infections*. Cytotoxic effects are therapeutic in cancer, as the object of the treatment is for the nucleoside analogue to cause cell death, with a greater ultimate effect on the quickly replicating cancer cells than the other cells. Conversely, cytotoxic effects should be avoided in the development of nucleoside analogues to treat viral infections where the aim is to kill the virus rather than the host cells.

98. The antiviral activity of the nucleoside analogue RBV was discovered in 1972. RBV shows a broad spectrum of activities against unrelated RNA viruses from diverse families that share little genetic sequence homology, e.g. HCV and respiratory syncytial virus. The structure of RBV has similarities to naturally occurring nucleosides, but it contains a pseudo base that resembles A or G in their ability to base pair with U and C, respectively, depending on its rotation.

RBV	**Guanosine**	**Adenosine**
		

99. The mechanism of action of RBV is not fully understood. It may include:

i) inhibition of inosine monophosphate dehydrogenase, which can affect cellular ribonucleotide pools;

ii) immunomodulatory effects;

iii) its incorporation into RNA in place of either G or A, but without causing chain termination; and

iv) lethal hyper-mutagenesis, which, in theory, can prevent successful viral replication through error catastrophe.

100. RBV does not interfere with a specific step in the viral replication cycle, and therefore it is not considered a DAA.

101. *Direct acting nucleoside analogues for viral infections*. By June 2003, it was appreciated that therapeutic nucleoside analogues for treatment of viral infection should have the following properties. They should:

i) enter the infected target cell;

ii) be phosphorylated within the host cell to the triphosphate form (or structural equivalent);

iii) bind to the viral polymerase, ideally at the active site, although there are other nucleoside binding sites on the viral polymerase which may be targeted;

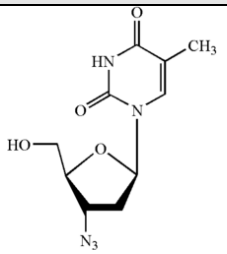
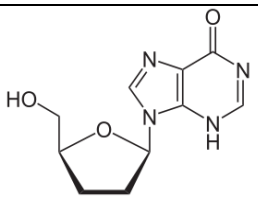
iv) ideally not be recognized by host cell polymerases (or other cellular components), which could give rise to toxicity;

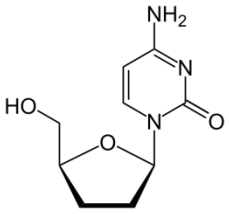
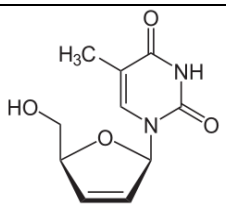
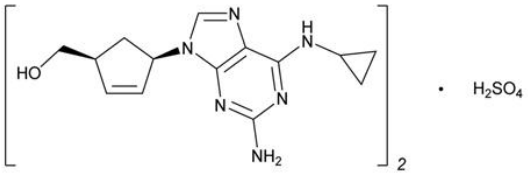
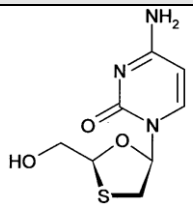
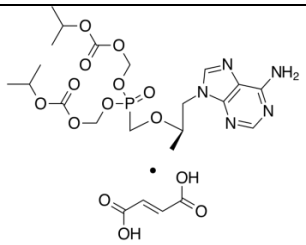
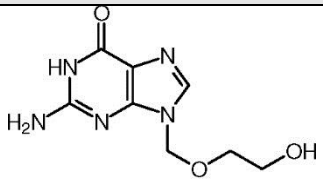
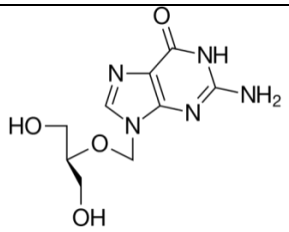
v) ideally be incorporated into the growing viral genome and possess some property that, once they are incorporated into the viral genome strand, they prevent successful replication;

vi) if not incorporated, compete with natural nucleotide pools to cause inhibition of viral replication; and

vii) ideally, selectively inhibit viral replication without cytotoxicity.

102. In June 2003 the person skilled in the art would have been aware of the antiviral activity and mechanism of action of a number of direct acting nucleoside analogues in antiviral therapy, such as AZT and 3TC for HIV. The following direct acting antiviral nucleoside analogues had been approved in the US by 2003.

Name, approval date and indication	**Structure**
HIV	
Zidovudine (**AZT**) FDA approved 1987	
Didanosine (**ddI**) FDA approved 1991	

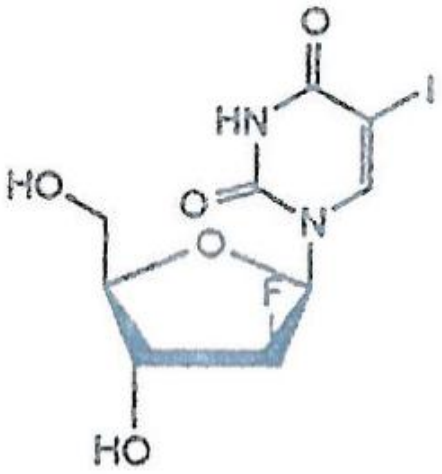
Zalcitabine (**ddC**) FDA approved 1992	
Stavudine (**D4T**) FDA approved 1994	
Abacavir sulphate (**ABC**) FDA approved 1998	
HIV and HBV	
Lamivudine (**3TC**) FDA approved 1995 for HIV, 1999 for HBV	
Tenofovir disoproxil fumarate (**TDF)** FDA approved for HIV and HBV 2001	
Other viruses	
Acyclovir FDA approved 1982 for Herpes virus infections.	
Ganciclovir FDA approved 1989 for Cytomegalovirus (CMV) and herpes virus.	

103. A structural feature of some of the antiviral nucleosides in the table above is the replacement of the 3'-hydroxyl group with a non-natural substituent. The role of the 3'-hydroxyl is particularly important in development of nucleoside analogues for

treatment of viral infections. Synthetic versions of nucleotides that lack the 3'-hydroxyl cannot mount the nucleophilic attack on the incoming nucleoside triphosphate (see paragraph 67 above). Therefore, once the nucleotide analogue has been incorporated, no further nucleotides can be added to the chain. In this way, some nucleoside analogues prevent successful viral replication by chain termination. These nucleoside analogues are referred to as "obligate chain terminators".

104. On the other hand, ganciclovir contains the structural equivalent of a 3'-hydroxyl group and is therefore referred to as a "non-obligate chain-terminator". In other words, despite the presence of the 3'-hydroxyl, the next nucleotide cannot be incorporated.

105. Another example of a nucleoside analogue developed as an antiviral agent that has a 3'-hydroxyl is fialuridine (1-(2-deoxy-2- fluoro-1-D-arabinofuranosyl)-5-iodouracil or FIAU). It has the structure shown beloe.



106. FIAU was identified *in vitro* as having anti-HBV activity. However, in 1992 it was found to cause liver and pancreatic toxicity, resulting in the deaths of five patients during clinical trials. The toxicity was probably due to poor selectivity for viral polymerase giving rise to mitochondrial toxicity.

107. *Virus specificity and selectivity of nucleoside analogues*. The skilled person in June 2003 would have known that, in general, activity of a nucleoside analogue against one virus species was not predictive of the nucleoside's activity against other virus species. Cross-reactivity of some direct acting nucleoside analogues between related viral species has been shown: for example, 3TC works against both HIV and HBV, and this has also been demonstrated for tenofovir. It is more common, however, for a nucleoside analogue that is effective therapeutically to be specific for a particular virus. For example, AZT works in HIV, but not in HBV. Furthermore, in general, if a compound is able to target structurally different viral polymerases, it may also target cellular polymerases and cause toxicities.

108. The nucleoside analogues that were active against HIV RT, which is a DNA polymerase, could not be predicted to be effective at preventing HCV replication. Deoxyribonucleosides, like the aforementioned HIV drugs, are structurally distinct from ribonucleosides that are the natural substrates for RNA polymerases.

109. *Nucleoside analogues for HCV*. By June 2003, the skilled person would have been aware that various research groups were interested in the potential of using nucleoside analogues for treating HCV by directly inhibiting NS5B activity. They would have been aware of the successful use of nucleoside analogues in the treatment of HIV, HBV, CMV and herpes virus infections. They would also have known that the efficacy of direct acting nucleoside analogues against *Flaviviridae* infections, and in particular HCV, had not been demonstrated in the clinic and that therefore no direct acting nucleoside analogues were on the market. It was not until sofosbuvir was approved that a direct acting nucleoside analogue was approved for use in the treatment of HCV.

Structure-activity relationships and the rational design of nucleoside analogues

110. In June 2003 (and still today) it was not possible to determine from a molecule's structure whether it would be effective in inhibiting HCV NS5B, and, in turn, in treating HCV. This is especially so because, as noted above, the ternary crystal structure of NS5B is not yet known and NS5B is a highly mobile molecule which undergoes conformational change as it catalyses the addition of ribonucleotides to the RNA chain. The development of nucleoside analogues to inhibit NS5B therefore was (and still is) largely empirical.

111. Generally, the approach to the discovery of novel nucleoside analogues for HCV infection involved the synthesis and testing of these compounds in order to discover which compounds had activity without toxicity. In theory, nucleoside analogues can be altered at most positions on the sugar ring and the base by the addition of a range of substituents. But to have antiviral activity, they still need to be recognised by cellular enzymes to phosphorylate the nucleoside analogue to the active triphosphate form and be recognised by the viral polymerase to catalyse its incorporation into the viral RNA chain. It was appreciated that even small changes in the nucleoside analogue can lead to significant changes in its activity. These changes can give rise to toxicity, inactivity or antiviral therapeutic potential. Once a promising candidate compound has been found, studies can be carried out to try to understand how its structure affects its mechanism of action. Typically, this involves making small changes to the structure and seeing how these affect its activity, enabling a picture to be built up of the structure-activity relationship.

Assays to test anti-HCV activity in 2003

112. The identification of antiviral agents that act against HCV has been hindered by the lack of suitable small animal models of the infection. This is because HCV is highly host-specific and only infects humans and chimpanzees. Instead, the following assays were used in 2003.

113. *Phosphorylation assay*. This is not an antiviral assay *per se*. As set out above, nucleoside analogue inhibitors need to be phosphorylated *in vivo* by the addition of three phosphate groups by cellular enzymes in order to be accepted by the active site of the polymerase. This assay is used to establish *in vitro* that it is possible for the compound to be phosphorylated. Chromatography is used to separate and to identify the different species: unphosphorylated, mono-, di- and triphosphates.

114. *Polymerase assay.* As previously described, ideally a nucleoside analogue will inhibit the activity of the polymerase. In efforts to identify and to confirm the target, purified HCV polymerase was used in cell-free biochemical assays to assess the ability of candidate compounds to inhibit the polymerase. The polymerase assay is particularly useful when used in conjunction with a cell-based assay such as replicon (described below). While the replicon assay demonstrates antiviral activity in a biologically relevant setting, the biochemical polymerase assay provides evidence that antiviral activity is due to the inhibition of the polymerase.

115. To carry out the assay, the polymerase must be purified. Purifying sufficient amounts of polymerase can be a limiting step. Engineered constructs that facilitate expression/purification of the polymerase were commonly used. The candidate nucleoside analogues must be synthesised and purified as well. Nucleoside analogues can be difficult to synthesise. Finally, the nucleoside analogue must be phosphorylated into the triphosphate form. Carrying out *in vitro* phosphorylation can be difficult and time consuming.

116. *BVDV surrogate model*. In June 2003 it was not possible to culture HCV *in vitro*. Therefore, prior to the introduction and establishment of the replicon assay, one option was to study the related virus, BVDV, as a surrogate model for identifying candidate compounds that might have anti-HCV activity. BVDV could be cultured in cell lines *in vitro*, which permitted the testing of compounds to detect inhibition of viral replication.

117. This could be done, for example, by means of a plaque reduction assay. This compares the number of viral plaques formed in cells exposed to both a virus and a candidate compound relative to cells exposed to just the virus. The reduction of plaque formation in infected cells treated with the candidate compound is indicative of its antiviral activity. Another similar type of assay is the yield reduction assay.

118. There are, however, significant differences between BVDV and HCV, although HCV and BVDV share a high degree of homology in terms of their genomic organisation, strategies of protein expression and genome replication. There are also important differences between the cell line used *in vitro* to culture BVDV (bovine kidney cells, termed MBDK cells), and the target of HCV infection *in vivo*, human hepatocytes.

119. As BVDV was an imperfect model for HCV replication, once the replicon assay had been established, the replicon assay was used preferentially over the BVDV surrogate model wherever possible.

120. *The replicon assay*. The replicon assay was first reported in 1999 in V. Lohmann *et al*, "Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line", *Science*, 285(5424), 110-3 (1999). It represented a major breakthrough in the ability to study inhibitors of HCV replication in a biologically relevant system.

121. Replicons are engineered HCV genomes that are able to replicate in cells and closely mimic replication of the HCV genome. Initially, they were made up of only a portion of the HCV genome and were therefore referred to as subgenomic replicons. A simple version of the replicon contains a portion of the HCV genome, which only codes for the non-structural proteins needed for replication of HCV RNA.

122. Using the replicon system, it was possible to measure directly whether a test compound had any anti-HCV activity. After adding a test compound to cells in which the replicon was replicating, the amount of replicon RNA in the cells was measured by polymerase chain reaction, a technique used to amplify and quantify nucleic acids.

123. The anti-HCV activity of the test compound can be determined by comparing the amount of replicon RNA in the cells incubated with the test compound with the amount of replicon RNA in cells that were not incubated with the test compound.

124. There are two important advantages of the replicon assay over the BVDV assay:

    i) in the replicon assay, the cells used are human hepatocytes (the Huh7 cell line), rather than the bovine kidney cells usually used for BVDV. It is preferable to test candidate compounds not only in cells of the same species, but also in cells of the same type that are infected *in vivo*; and

    ii) replicons are made from the HCV genome and therefore directly test the ability of candidate molecules to block HCV genome replication.

125. The replicon assay quickly became well known. By 2001, it appeared in the leading virology text book, *Fields Virology* (4th edition, chapter 32). By June 2003, it had become the gold standard for assessing anti-HCV activity.

Measures of antiviral activity and toxicity

126. In order to be identified as candidates for treatment of HCV, nucleoside analogues must show activity and lack of toxicity in appropriate *in vitro* models and there must be a sufficient difference between the efficacy and toxicity of the molecule that it has a viable "therapeutic window". A compound's antiviral activity is expressed in the following ways.

127. The effective concentration (EC) or inhibitory concentration (IC) is a measure of the ability of the test compound to show an effect on or inhibit viral replication. It is usually expressed as EC_{50} or EC_{90} (IC_{50} or IC_{90}), which is the concentration of test compound that reduces viral replication by 50% or 90% respectively. It is measured in cell-based assays by counting the number of plaques or quantifying the amount of viral RNA (inhibitory concentrations are commonly measured in cell-free, biochemical assays that involve the target enzyme). A compound with potent antiviral activity will have low EC and IC values.

128. The cytotoxic concentration (CC) is a measure of the amount of test compound needed to kill cells in the assay. Again, it is measured in terms of the amount of compound that kills 50% or 90% of the cells (expressed as CC_{50} or CC_{90} values respectively). A compound with low toxicity will have a high CC value i.e. a high concentration of the test compound is required to kill the cells.

129. A ratio of CC:EC of at least 10:1, and ideally much greater than this, indicates low toxicity and high efficacy, and therefore an effective therapeutic window. In order to assess the ratio, EC and CC values must be obtained for the same cell line as that in which the virus is tested. This is because different cell lines show different sensitivities to different nucleoside analogues.

Bioavailability

130. By June 2003, *in vitro* assays of the kind described above could be used to establish that a candidate nucleoside analogue could be phosphorylated, recognised by NS5B and potentially have a viable therapeutic window. The next step would be to assess the bioavailability of the candidate compound, i.e. its ability to get to the target cells and at sufficient concentrations to compete with naturally occurring nucleotide pools.

Prodrugs

131. One way to improve bioavailability is to create a "prodrug". In general terms, this means synthesising a modification to the molecule in the laboratory that is reversed *in vivo*, and thus will liberate the parent molecule at a certain point of time following its administration. For example, the prodrug modification might function to improve the uptake of the molecule into the target cells. The modification must be designed so that the prodrug can be metabolised back to the parent molecule in the cytoplasm of the target cells. Such modifications typically involve the use of "masking groups", groups which perform a similar function to the "protecting groups" used in synthetic organic chemistry as described below.

Retrosynthetic analysis

132. Retrosynthetic analysis is the process of planning a synthesis backwards by starting at the target compound, and working backwards a step at a time to readily available starting materials or precursors. Generally, this involves considering several possible approaches, and within each approach the skilled person might encounter a number of options, leading to a number of potential routes.

Nucleoside analogue synthesis in 2003

133. As described above, by 2003, nucleoside analogues had attracted a great deal of interest as potential candidates for the treatment of various diseases including cancer and viral infections. In general, these compounds contain chemical modifications in either the sugar or the nucleobase of the nucleoside or both. The aim of the modifications when developing antiviral compounds is to ensure that the biosynthesis of DNA and RNA of the target virus is affected, but this needs to be done without causing harm to healthy host cells (which produce their own DNA or RNA). The identification of such highly selective compounds was (and still is) a significant and challenging scientific task.

134. The skilled person approaching the synthesis of a nucleoside analogue in 2003 would have had a number of options for doing so, and the details of his approach would depend on the particular target nucleoside in question. In general, he would start by looking to see if the particular molecule was reported in the scientific literature and, if so, whether the details of its synthesis were given in any report. If there were no reports of the exact nucleoside analogue targeted, then the skilled person would examine whether related compounds had been reported, and determine whether reported syntheses of such compounds would provide guidance for a synthetic strategy. Key textbooks might also be consulted.

135. The skilled person might also carry out further, broader, literature searches relating to the structure of the desired compound. The skilled person would then use any helpful information in the key textbooks and the literature, as well as his common general knowledge, to consider how he might attempt a synthesis of the desired nucleoside analogue by carrying out a retrosynthetic analysis.

136. In very general terms, nucleoside analogue synthesis might be approached by modifying an existing nucleoside, that is, a sugar with the desired base already attached (often known as the "nucleoside route"), or by first preparing a sugar with the desired modifications before attaching the base by glycosylation (often known as the "sugar route"). The sugar route itself might involve either modifying a sugar which was already readily available, or starting with small molecules which could be used to build up the sugar with the desired modifications in place.

137. The skilled person would have known that the synthesis of nucleosides is often complicated, as a result of the number of chiral centers in the sugar ring and the number of reactive functional groups attached to the sugar (which might give rise to unwanted reactions and which would therefore need masking with suitable protecting groups, as to which see below). There would also be the need (in the case of the nucleoside route) to carry out the reaction on a molecule containing a sensitive functional group (the nucleobase) or the need (in the case of the sugar route) to carry out a glycosylation step to attach the nucleobase to the sugar and it was known in 2003 that in some circumstances this could be a difficult step.

Primary, secondary and tertiary carbons

138. Carbon atoms in organic molecules can be categorised according to the number of other carbons they are attached to:

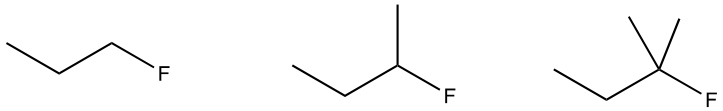
i) a "primary carbon" is attached to one other carbon atom;

ii) a "secondary carbon" is attached to two other carbon atoms;

iii) a "tertiary carbon" is attached to three other carbon atoms; and

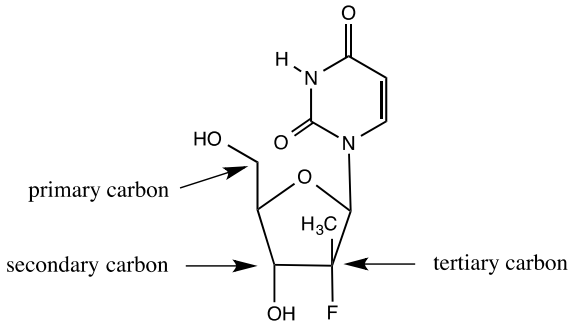
iv) a "quaternary carbon" is attached to four other carbon atoms.

139. Substituents attached to primary, secondary and tertiary carbons can be described in a similar way, by reference to the nature of the carbon which they are attached to. The following diagram shows generic examples of primary, secondary and tertiary fluorides.



primary fluoride secondary fluoride tertiary fluoride

140. The following diagram identifies primary, secondary and tertiary carbons in a 2'-fluoro-2'-methyl nucleoside:



141. Primary, secondary and tertiary carbons have different chemical and physical properties, for example in relation to:

i) the amount of space around them and, therefore, the ease with which an incoming reagent can approach them (known as "steric effects"); and

ii) the ability of the compound to stabilise the build-up of charge at the relevant carbon during a reaction (known as "electronic effects").

Nucleophilic substitution reactions

142. A "nucleophile" is a molecule or ion that can provide a pair of electrons (denoted as : below) to be shared with another atom in the formation of a new covalent bond. Nucleophilic substitutions are an important class of organic chemical reactions in which a nucleophile (Nuc) attacks a positive or partially positive charge of an atom (referred to as an "electrophile" (EL)) attached to a group or atom called the "leaving group" (LG). The overall result of the reaction is that the leaving group is replaced by the nucleophile:

$$Nuc: + EL\text{-}LG \rightarrow EL\text{-}Nuc + LG:$$

143. In other words, in nucleophilic substitutions, the attacking reagent (the nucleophile) brings an electron pair to form a new bond and the leaving group comes away with an electron pair.

144. It has been shown that a negatively charged nucleophile is more reactive than a similar nucleophile that is neutral. Furthermore, in general, the nucleophilicity decreases from left to right in the periodic table. For example, the following reactivity has been observed:

$$CH_3^- > NH_2^- > OH^- > F^-$$

145. This observation is due to an increase in "electronegativity" going from left to right in the periodic table. Electronegativity is a chemical property that describes the tendency of an atom or functional group to attract electron density to itself. The more electronegative an atom or functional group, the better it can stabilise a negative or partial negative charge, and hence such a species is less reactive (less nucleophilic). For example, fluorine is more electronegative than oxygen, making fluoride (F^-) better stabilised and less reactive as a nucleophile than hydroxide (OH^-).

146. The smaller negatively charged nucleophiles such as fluorine are more solvated by polar protic solvents, making them less reactive. Furthermore, the larger elements

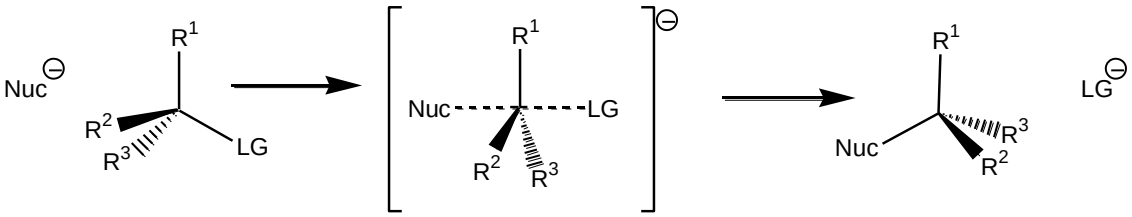
such as iodine have more diffuse, and more polarisable electron clouds, which facilitates the formation of a more effective orbital overlap in the transition state of bimolecular nucleophilic substitution reactions and will make them more reactive.

147. Going down the periodic table, nucleophilicity increases, but basicity generally decreases. "Basicity" refers to the ability of a molecule to remove a proton (hydrogen atom) from another molecule. The higher the basicity of a molecule, the better it is able to abstract a proton from a molecule. Compounds with high basicity are referred to as "strong bases".

Mechanisms of nucleophilic substitution reactions

148. In 1935 Edward Hughes and Sir Christopher Ingold reported that nucleophilic substitution reactions of alkyl halides can proceed by two different reaction mechanisms, called S_N1 and S_N2 reactions. In this terminology, S denotes chemical substitution, $_N$ refers to nucleophilic, and the number describes the kinetic order of the reaction (this can be thought of as describing the number of species involved in the rate-determining step).

149. In the case of an S_N2 reaction, the attack of the nucleophile and the departure of the leaving group take place simultaneously. In this reaction, the nucleophile attacks the electrophile from the opposite side to the leaving group involving a transition state that has trigonal bipyramidal geometry at a penta-coordinated carbon, as shown below.



Tetrahedral starting material (which is chiral if R^1, R^2 and R^3 are different)

A penta-coordinated carbon, that has a trigonal bipyramidal geometry.

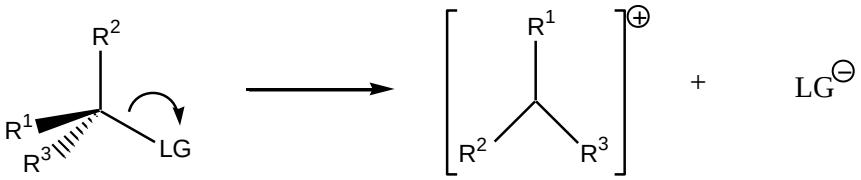
Tetrahedral product that has inverted the stereochemistry relative to the starting material.

150. This concerted displacement mechanism has important implications for the stereochemical outcome of the reaction. In particular, when the electrophilic carbon is chiral and optically pure (a single enantiomer), the product will have opposite stereochemistry compared to the starting material.

151. Structural effects have an important influence on the rate of an S_N2 reaction. In general, unfavorable steric interactions are increased at the penta-coordinated carbon (because groups around it are pushed closer together). and therefore retard the rate of the reaction. Thus, an S_N2 reaction is more facile at a primary carbon than at a secondary one, and in general this type of reaction does not take place at a tertiary carbon due to increased size of the groups around the tertiary carbon, which makes the penta-coordinated intermediate less energetically favorable.

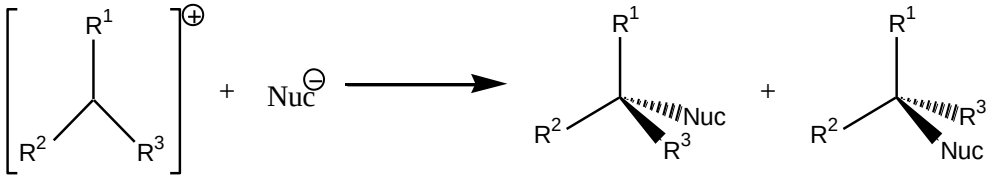
152. The S_N1 reaction involves two separate chemical steps. The first step that takes place is a heterolytic cleavage of the leaving group of the electrophile to give a trigonal

positively charged carbon (also referred to as a "carbocation") and the leaving group, as shown below.



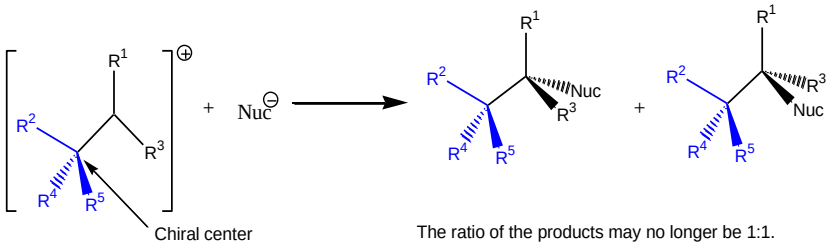
153. The rate of carbocation formation is greater for a tertiary carbon than that of a secondary carbon, which in turn is greater than that of a primary carbon. This difference in reactivity is due to differences in release of steric hindrance in the transition state, and the fact that carbon substituents are more electron donating than hydrogen and hence can better stabilise the developing positive charge.

154. This reaction is followed by a fast combination of the carbocation with the nucleophile to give a product,as shown below:



155. The S_N1 mechanism has important stereochemical implications. In particular, when the starting material is optically pure (a pure enantiomer) with only one chiral center, and the reaction takes place at that center, the resulting product will be a racemic mixture. This is due to the fact that the trigonal carbocation intermediate is achiral (planar), and so nucleophilic attack is equally likely from either face of the molecule. Regardless of the configuration of the starting material (R or S at the reactive carbon), a racemic mixture will be produced. Thus the stereochemical history of the starting material is lost.

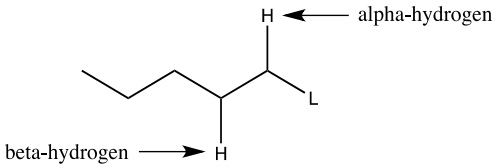
156. The stereochemical outcome of an S_N1 reaction involving multiple stereogenic centers is more difficult to predict because the two possible transition states are diastereoisomeric and hence can have different activation energies. The diagram below shows a carbocation with a neighboring chiral center (shown in blue) and the two possible diastereoisomeric products. The chiral center may block one face of the carbocation and therefore nucleophilic attack from one of the two faces of the carbocation may be preferred. As a result, the two diastereoisomers may not be formed in a ratio of 1:1.



157. Techniques were available in 2003 for driving such reactions towards to a preferred diastereoisomer. There were also techniques for separating or "resolving" different diastereisomers. The applicability of such techniques, and the ease with which they could be applied, would depend on the particular reaction in question.

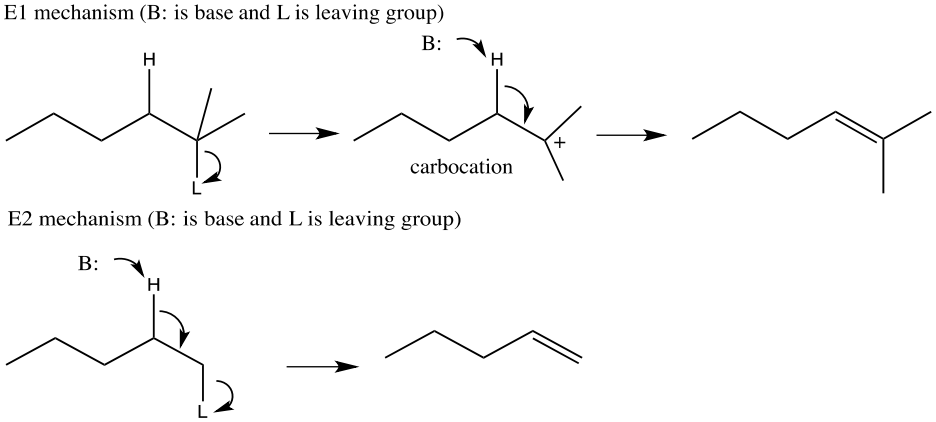
Elimination reactions

158. A substitution is not the only possible outcome under conditions suitable for nucleophilic substitution reactions. It was well known in 2003 that, if there are hydrogen atoms bonded to the carbon adjacent to the leaving group (known as beta-hydrogens), elimination can occur instead of nucleophilic substitution, resulting in the formation of a carbon-carbon double bond.



159. The likelihood of an elimination occurring will depend on various factors, including how basic the nucleophile is, the size of the nucleophile, and how sterically hindered the carbon at which substitution is desired is.

160. Like nucleophilic substitutions, elimination reactions can proceed through a one-step mechanism (known as an E2 reaction), or a two-step mechanism (known as an E1 reaction):

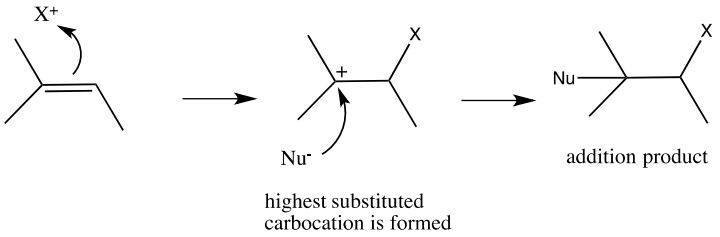


161. In general, E1 reactions compete with S_N1 reactions, whereas E2 reactions compete with S_N2 reactions.

Electrophilic addition to carbon-carbon double bonds

162. Electrophilic additions are reactions in which a carbon-carbon double bond is broken and two new bonds to other groups are formed. The driving force for these reactions is the formation of an electrophile X^+ that reacts with an electron-rich double bond. The positive charge of X is transferred to the carbon-carbon bond, forming a carbocation during the formation of the C-X bond. In the second step, the positively charged intermediate combines with a nucleophile that is electron-rich, and usually an

anion, to form the second covalent bond. The second step is similar to what is found in S_N1 nucleophilic substitutions.



163. The question of which carbon in the double bond the electrophile reacts with is an aspect of what is known as "regioselectivity". For an addition reaction, the regioselectivity is determined by Markovnikov's Rule. The chemical basis for Markovnikov's Rule is the formation of the most stable carbocation during the addition process. However, it may not always be straightforward to predict which carbocation will be the most stable in a given molecule, and mixtures of regioisomers may be possible. There will also be an issue of stereochemistry in electrophilic addition reactions, because they can result in the formation of up to two new chiral centers with the potential for the formation of enantiomers and/or diastereomers.

Fluorination

164. The term "fluorination" refers to the process of inserting fluorine into a molecule. Elemental fluorine (F_2) is a difficult compound to work with, because it is extremely toxic and reactive. Over time, a number of other reagents were developed which could be used to conduct fluorination reactions while being easier to work with.

165. By 2003, a variety of methods were known for fluorinating organic molecules. Generally speaking, two different mechanisms of fluorination had been developed, known as nucleophilic fluorination (which involves an electron-rich fluorine source (F^-)) and electrophilic fluorination (which involves an electron-poor fluorine source (F^+)).

166. The specific fluorinating reagents which the skilled person might have used for a particular nucleophilic fluorination reaction would have depended on the type of starting material being used and the functional groups it contained. Examples of nucleophilic fluorine (F^-) sources generally available in 2003 included:

i) KHF_2;

ii) KF;

iii) Et_4NF;

iv) Bu_4NF (tetrabutylammonium fluoride or TBAF);

v) $(CH_3CH_2)_2NSF_3$ (DAST); and

vi) $(CH_3OCH_2CH_2)_2NSF_3$ (bis-(2-methoxyethyl)aminosulphur trifluoride or Deoxo-Fluor).

167. Examples of electrophilic fluorination (F^+) reagents generally available in 2003 included:

i) 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate or Selectfluor;

ii) N-fluorobenzenesulfonimide ("NFSI"); and

iii) N-fluoro-o-benzenedisulfonimide ("NFOBS").

Protecting groups

168. Nucleosides and carbohydrates are polyfunctional compounds: they have several hydroxyl groups and may also contain other functional groups such as amino (NH_2) and carbonyl (C=O) moieties. During a synthetic sequence, these functionalities often need to be blocked from chemical reactions so that a selective chemical manipulation can be performed on only one particular functional group. "Protecting groups" are chemical groups that can be employed temporarily to block the reactivity of a functional group within a molecule and then subsequently removed.

169. The successful synthesis of a complex target compound typically involves selecting protecting groups based on the consideration of various issues, such as the reaction conditions required to introduce a protecting group and the fact that the installation of the group chosen should be compatible with the other functionalities in the compound. In addition, the protecting groups chosen must be stable under the conditions used during subsequent synthetic steps, and generally need to be capable of being installed and removed under mild conditions in a highly selective manner and high yield.

170. It is also important to appreciate that there are circumstances in which protecting groups are not innocent bystanders in chemical transformations and may affect the reactivity of other functionalities. For example, electron withdrawing ester functionalities reduce the nucleophilicity of neighboring hydroxy groups. Furthermore, bulky protecting groups can sterically block other functionalities, and protecting groups may affect the conformation of the molecule which can in turn affect the reactivity of the compound.

171. By 2003, many different protecting groups for hydroxy and amino groups had been described in the chemical literature. The protecting groups for hydroxyl groups included benzyl, benzoyl and tetraisopropyldisiloxanyl ether ("TIPDS"). TIPDS is useful in nucleoside analogue synthesis because it enables simultaneous protection, and then simultaneous deprotection, of the hydroxyl groups at the 3' and 5' positions.

Analysis of chemical compounds in 2003

172. By 2003, a number of techniques were available for analysing compounds produced in synthetic organic chemistry. These included the following techniques.

173. *Thin layer chromatography (TLC)*: an analytical technique commonly used in synthetic organic chemistry to monitor the progress of a reaction. It employs a sheet of glass, plastic, or aluminum foil that is coated with a thin layer of an adsorbent

material, such as silica gel or aluminum oxide. After the sample has been applied to the plate, a solvent or solvent mixture is drawn up the plate via capillary action. Often, different organic compounds interact differently with the adsorbent material and therefore ascend at different rates up the TLC plate, resulting in separation of the different organic compounds in the mixture. The location of the compounds on the TLC plate can often be determined by holding it under UV light. Additionally or alternatively, the TLC plate can be stained with a chemical which causes the "spots" of compound to become visible to the naked eye. A stain which is commonly used in the fields of carbohydrate, and hence nucleoside, chemistry is 10% sulphuric acid in methanol. The TLC place is subsequently heated, which causes carbohydrate-containing compounds to char, and hence the spots to become brown.

174. *Chromatography.* Various forms of chromatography are used to separate mixtures of different compounds either for analytical purposes or preparative purposes. These include silica gel chromotagraphy, HPLC (high performance liquid chromatography) and reverse phase HPLC. Generally speaking, HPLC is more effective at resolving mixtures than silica gel. In some circumstances, reverse phase HPLC can be more effective still.

175. *Mass spectrometry (MS)*: an analytical technique that provides the molecular weight of molecules (or fragments of molecules) and hence is used to characterise organic compounds.

176. *Nuclear magnetic resonance (NMR) spectroscopy*: an analytical technique that exploits unique magnetic properties of the nuclei of individual atoms within a molecule to determine the physical and chemical properties of those atoms. It can provide detailed information about the structure, dynamics, reaction state, and chemical environment of molecules. The intramolecular magnetic field around an atom in a molecule changes the resonance frequency, thus giving access to details of the electronic structure of a molecule. NMR spectroscopy can be used to analyse the chemical environment of a number of different types of atom, including hydrogen, carbon and fluorine. More complex experiments, including Nuclear Overhauser Effect (NOE) spectroscopy, can be carried out and may provide further information about a molecule of interest.

177. *X-ray crystallography*: an analytical technique that exploits the way in which X-rays are diffracted when passing through a crystalline compound to deduce the 3D structure of the compound from the diffraction pattern which results. This technique is only possible if a crystalline sample of a given compound can be obtained.

The Application

178. The Application is entitled "Modified 2' and 3'-Nucleoside Prodrugs for Treating *Flaviviridae* Infections". It is a remarkable document which runs to no less than 200 pages. I will outline its contents using the headings in the Application. I must do so in a little detail, for two inter-related reasons. The first is that Gilead's allegation of added matter depends upon it. The second is that, as counsel for Gilead submitted, the question of plausibility must be tested by reference to the contents of the Application. If the claimed inventions are only plausible when considered by reference to the contents of the Patent, and not when considered by reference to the contents of the Application, then it must follow that the Patent is invalid for added matter.

Field of the invention

179. In this section the Application states (at page 1 lines 10-13):

> "The invention is in the area of pharmaceutical chemistry, and is in particular, a 2' and/or 3' prodrug of a 6-modified, 1', 2', 3', or 4'-branched pyrimidine nucleoside or 8-modified 1', 2', 3' or 4'-branched purine nucleoside for the treatment of a *Flaviviridae* infection, such as a hepatitis C virus infection."

As both the title of the Application and this introduction indicate, the emphasis of the Application is on 2' and 3' prodrugs.

Background to the invention

180. In this section the Application discusses the following topics: *Flaviviridae* viruses (page 1 line 15 – page 3 line 20), HCV (page 3 line 22 – page 4 line 24), treatment of HCV infection with interferon (page 4 line 26 – page 5 line 31), ribavarin (page 6 lines 1-14), combination of interferon and ribavarin (page 6 line 16 – page 7 line 4) and additional methods to treat *Flaviviridae* infections (page 7 line 6 – page 12 line 10). The last of these passages discusses 12 "[e]xamples of classes of drugs that are being developed to treat *Flaviviridae* infections": (1) protease inhibitors: (2) thiazolidine derivatives which show relevant inhibition in a particular assay; (3) thiazolidines and benzanilides identified in two papers; (4) two compounds isolated from natural sources as discussed in two papers; (5) helicase inhibitors; (6) nucleotide polymerase inhibitors; (7) antisense phosphorothioate oligodeoxynucleotides; (8) inhibitors of IRES-dependent translation; (9) ribozymes; (10) "[n]ucleoside analogs [which] have also been developed for the treatment of Flaviviridae infections"; (11) other miscellaneous compounds and classes of compounds disclosed in 13 US patents; and (12) no less than 60 other compounds (or types of compounds or approaches) said to be currently in preclinical or clinical development by different pharmaceutical companies.

181. Since the Application's description of class (10) (at page 9 line 29 – page 10 line 24) is heavily relied on by Idenix, I shall quote it in full:

> "Idenix Pharmaceuticals discloses the use of branched nucleosides in the treatment of flaviviruses (including HCV) and pestiviruses in International Publication Nos. WO 01/90121 and WO 01/92282. Specifically, a method for the treatment of hepatitis C infection (and flaviviruses and pestiviruses) in humans and other host animals is disclosed in the Idenix publications that includes administering an effective amount of a biologically active, 1', 2', 3' or 4'-branched ß-D or ß-L nucleosides or a pharmaceutically acceptable salt or derivative thereof, administered either alone or in combination with another antiviral agent, optionally in a pharmaceutically acceptable carrier.
>
> Other patent applications disclosing the use of certain nucleoside analogs to treat hepatitis C virus include:

> PCT/CA00/01316 (WO 01/32153; filed November 3, 2000) and PCT/CA01/00197 (WO 01/60315; filed February 19, 2001) filed by BioChem Pharma, Inc. (now Shire Biochem, Inc.); PCT/US02/01531 (WO 02/057425; filed January 18, 2002) and PCT/US02/03086 (WO 02/057287; filed January 18, 2002) filed by Merck & Co., Inc., PCT/EP01/09633 (WO 02/18404; published August 21, 2001) filed by Roche, and PCT Publications Nos. WO 01/79246 (filed April 13, 2001), WO 02/32920 (filed October 18, 2001) and WO 02/48165 by Pharmasset, Ltd.
>
> PCT Publication No. WO 99/43691 to Emory University, entitled '2'-Fluoronucleosides' discloses the use of certain 2'-fluoronucleosides to treat HCV.
>
> Eldrup et al. (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International Conference on Antiviral Research (April 27, 2003, Savannah, Ga.)) described the structure activity relationship of 2'-modified nucleosides for inhibition of HCV.
>
> Bhat et al. (Oral Session V, Hepatitis C Virus, Flaviviridae, 2003 (Oral Session V Hepatitis C Virus, Flaviviridae; 16th International Conference on Antiviral Research (April 27, 2003, Savannah, GA.); p A75) describe the synthesis and pharmacokinetic properties of nucleoside analogues as possible inhibitors of HCV RNA replication. The authors report that 2'-modified nucleosides demonstrate potent inhibitory activity in cell-based replicon assays.
>
> Olsen et al. (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International Conference on Antiviral Research (April 27, 2003, Savannah, GA.) p A76) also described the effects of the 2'-modified nucleosides on HCV RNA replication."

182. Two points should be noted about this passage. First, on its face, it is simply part of a long recitation of relevant prior art. Secondly, although the Application refers to the presentations by Eldrup *et al*, Bhat *et al* and Olsen *et al* at the Savannah conference, which I shall consider below, it does not identify any publications of those presentations. The nearest it comes is the page references given for the Bhat and Olsen presentations, which are in fact the page references to the corresponding abstracts in the conference programme. Nor does the Application specify the 2'-modified nucleosides discussed in those presentations.

183. The Application goes on to state the objects of the invention in the following terms (page 12 lines 1-10):

> "In the light of the fact that HCV infection has reached epidemic levels worldwide, and has tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat hepatitis C that have low toxicity to the host.

> Further, giving the rising threat of other flaviviridae infections, there remains a strong need to provide new effective pharmaceutical agents that have low toxicity to the host.
>
> Therefore, it is an object of the present invention to provide a compound, method and composition for the treatment of a host infected with hepatitis C virus.
>
> It is another object of the present invention to provide a method and composition generally for the treatment of patients infected with *pestivirus*, *flaviviruses* or *hepaciviruses*."

Summary of the invention

184. This section of the Application extends from page 12 line 12 to page 41 line 7. It begins as follows (at page 12 lines 12-32):

> "2' and 3'-prodrugs of 1', 2', 3' or 4'-branched β-D or β-L nucleosides, or their pharmaceutically acceptable salts or pharmaceutically acceptable formulations containing these compounds are useful in the prevention and treatment of *Flaviviridae* infections and other related conditions such as anti- *Flaviviridae* antibody positive and *Flaviviridae* - positive conditions, chronic liver inflammation caused by HCV, cirrhosis, acute hepatitis, fulminant hepatitis, chronic persistent hepatitis, and fatigue. These compounds or formulations can also be used prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-*Flaviviridae* antibody or *Flaviviridae*-antigen positive or who have been exposed to a *Flaviviridae*.
>
> A method for the treatment of a *Flaviviridae* viral infection in a host, including a human, is also disclosed that includes administering an effective amount of a 2' or 3'- prodrug of a biologically active 1', 2', 3' or 4'-branched β-D or β-L nucleoside or a pharmaceutically acceptable salt thereof, administered either alone or in combination or alternation with another anti-*Flaviviridae* agent, optionally in a pharmaceutically acceptable carrier. The term 2'-prodrug, as used herein, refers to a 1', 2', 3' or 4'-branched β-D or β-L nucleoside that has a biologically cleavable moiety at the 2'-position, including, but not limited to acyl, and in one embodiment, a natural or synthetic D or L amino acid, preferably an L-amino acid. The term 3'-prodrug, as used herein, refers to a 1', 2', 3' or 4'-branched β-D or β-L nucleoside that has a biologically cleavable moiety at the 3'-position, including, but not limited to acyl, and in one embodiment, a natural or synthetic D or L-amino acid, preferably an L-amino acid."

Again it can be seen that the emphasis of the Application is on 2'- and 3'-prodrugs, and in particular those with certain cleavable moieties at those positions.

185. The Application then introduces:

i) "one embodiment" with "examples of prodrugs falling within the invention" and "additional examples of prodrugs falling within the invention" (at page 13 line 7 – page 14 line 15);

ii) "another embodiment" again with "examples" and "additional examples" of "prodrugs falling within the invention" (at page 14 line 16 – page 15 line 21); and

iii) "another embodiment" again with "examples" and "additional examples" of "prodrugs falling within the invention" (at page 15 line 22 – page 17 line 15).

186. Next there is a disclosure of various other embodiments of the invention. This part of the Application introduces:

i) "a first principal embodiment, a compound of Formula (I) or a pharmaceutically acceptable salt or a prodrug, or a stereoisomeric, tautomeric or polymorphic form thereof … as well as a method of treatment of a host infected with a *Flaviviridae* comprising administering an effective treatment amount" of the compound (at page 17 line 16 – page 18 line 27);

ii) "a second principal embodiment, a compound of Formula (II)" and its salts, prodrugs, other forms and method of treatment (at page 19 lines 1 -10);

iii) "a third principal embodiment, a compound of Formula (III), (IV) or (V)" and their salts, prodrugs, other forms and method of treatment (at page 19 line 11 – page 27 line 30);

iv) "a fourth principal embodiment, a compound of Formula (VI) or (VII)" and their salts, prodrugs, other forms and method of treatment (at page 28 line 1 – page 29 line 24);

v) "a fifth principal embodiment, a compound of Formula (VIII), (IX) or (X)" and their salts, prodrugs, other forms and method of treatment (at page 30 line 1 – page 31 line 14);

vi) "a sixth principal embodiment, a compound of Formula (XI) or (XII)" and their salts, prodrugs, other forms and method of treatment (at page 31 line 15 – page 33 line 8);

vii) "a particular aspect of the invention, a compound of Formula (XI) or (XII) [*sic* – this is clearly a typographical error and the reference should be to Formulas (XIII) and XIV)]" and their salts, prodrugs, other forms and method of treatment (at page 33 line 9 – page 34 line 22);

viii) "a second particular aspect of the invention, a compound of Formula (XV), (XVI) or (XVII)" and their salts, prodrugs, other forms and method of treatment (at page 35 lines 1-17);

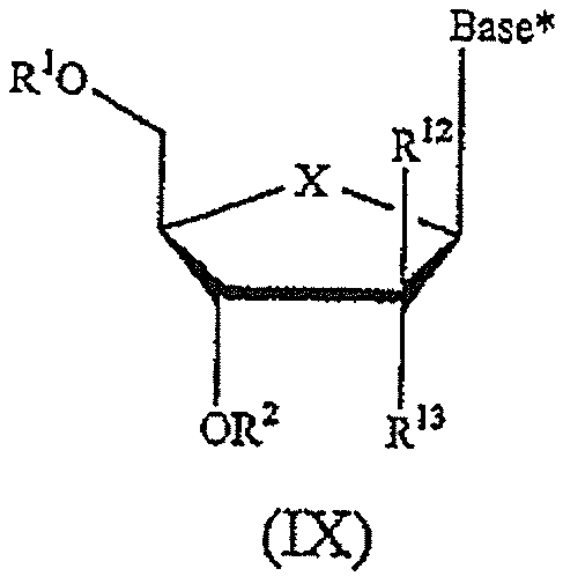
ix) "a third particular aspect of the invention, a compound of Formula (XVIII)" and its salts, prodrugs, other forms and method of treatment (at page 35 line 18 – page 36 line 1);

x) "a fourth particular aspect of the invention, a compound of Formula (XIX), (XX), (XXI), (XXII) or (XXIII)" and their salts, prodrugs, other forms and method of treatment (at page 36 line 2 – page 38 line 6);

xi) "one embodiment" where the amino acid residue has a certain formula (at page 38 lines 7-14); and

xii) "another preferred embodiment" concerning the amino acid residue (at page 38 lines 15-16).

187. Each of Formulae (I) to (XXIII) is a Markush formula with many alternative possibilities for the various substituents. It is not necessary for present purposes to set all of these out, but Formula (IX) is shown below.



(IX)

As is common ground, Formula (IX) shows substituent R^{12} in the up position and substituent R^{13} in the down position.

188. The Application then states (at page 38 lines 17-21):

> "The β -D and β -L nucleosides of this invention may inhibit *Flaviviridae* polymerase activity. Nucleosides can be screened for their ability to inhibit *Flaviviridae* polymerase activity *in vitro* according to screening methods set forth more particularly herein. One can readily determine the spectrum of activity by evaluating the compound in the assays described herein or with another confirmatory assay."

189. It should be noted that the Application only says that the nucleosides *may* exhibit *Flaviviridae* polymerase activity, not that they do so or even are likely to do so. The

screening assays described in the Application (as to which, see below) were all known in the art. Thus all this tells the reader is that he will have to screen the nucleosides to find out whether they have activity or not.

190. The Application goes on to describe a series of further embodiments of the invention (at page 38 line 22 – page 41 line 6).

Brief description of the figures

191. This section of the Application (at page 41 lines 8-18) introduces four figures, Figures 1-4, which are at to be found at pages 197 to 200. Figure 1 is headed "Chemical Structures of Illustrative Nucleosides". It sets out the structures of 14 nucleosides. All have a methyl group in the 2' up position and all have a hydroxyl or O-valine in the 2' down position. In addition, they all have an O-valine at the 3' down position. None of these nucleosides has a fluorine substitution.

192. Figures 2, 3 and 4 are some indicative outline reaction schemes for methods of preparing 2' and 3' prodrugs.

Detailed description of the invention

193. This section of the Application extends from page 41 line 20 to page 157 line 6. It begins as follows (at page 41 lines 20-30):

> "The invention as disclosed herein is a compound, a method and composition for the treatment of a *Flaviviridae* infection in humans and other host animals. The method includes the administration of an effective anti-*Flaviviridae* treatment amount of a 2' and/or 3'-prodrug of a 1', 2', 3', or 4'-branched β-D or β-L nucleoside as described herein or a pharmaceutically acceptable salt, derivative or prodrug thereof, optionally in a pharmaceutically available carrier. The compounds of the invention either possess antiviral (i.e. anti-HCV) activity, or are metabolized to a compound that exhibits such activity. HCV is a member of the *Flaviviridae* famil. HCV has been placed in a new monotypic genus, hepacivirus. Therefore, in one embodiment, the *Flaviviridae* is HCV. In an alternate embodiment, the *Flaviviridae* is a flavivirus or pestivirus."

194. After further discussion of prodrugs, particularly those with certain cleavable moieties at the 2' and/or 3' positions, the specification states (at page 43 line 20 to page 45 line 34) that "[i]n summary, the present invention includes the following features", before proceeding to list 22 such features at (a) to (v). Features (a), (p), (q) and (u) are as follows:

> "(a) a 2' and/or 3'-prodrug of a 1', 2', 3' or 4'-branched ß-D or ß-L nucleoside, as described herein, and pharmaceutically acceptable salts and compositions thereof;
>
> …

(p) use of a 2' and/or 3'-prodrug of a ß-D-2'-methyl-cytidine, or its pharmaceutically acceptable salt or composition thereof for the treatment and/or prophylaxis of a *Flaviviridae* infection in a host;

(q) use of the 3'valyl or acetyl ester of ß-D-2'-methyl-cytidine, or its pharmaceutically acceptable salt or composition thereof for the treatment and/or prophylaxis of a *Flaviviridae* infection in a host;

…

(u) use of a 2' and/or 3'-prodrug of a ß-D-2'-methyl-cytidine, or its pharmaceutically acceptable salt or composition thereof in the manufacture of a medicament for the treatment and/or prophylaxis of a *Flaviviridae* infection in a host".

195. From page 46 line 21 to page 100 line 29 the Application discloses a series of embodiments of the invention under the sub-heading "I. Active Compounds" as follows:

i) "a first principal embodiment, a compound of Formula (I) or a pharmaceutically acceptable salt or a prodrug, or a stereoisomeric, tautomeric or polymorphic form thereof … as well as a method of treatment of a host infected with a *Flaviviridae* comprising administering an effective treatment amount" of the compound (at page 46 line 22 – page 47 line 29);

ii) "a preferred subembodiment" in which Formula (I) is more restrictively defined (at page 47 line 31 - page 48 line 8);

iii) "a second principal embodiment, a compound of Formula (II)" and its salts, prodrugs, other forms and method of treatment (at page 48 lines 9-19);

iv) "a preferred subembodiment" in which Formula (II) is more restrictively defined (at page 48 line 19 - page 49 line 2);

v) "a third principal embodiment, a compound of Formula (III), (IV) or (V)" and their salts, prodrugs, other forms and method of treatment (at page 49 line 3 – page 56 line 30);

vi) "a first subembodiment", "a second subembodiment" and "a third subembodiment" in each of which Formulas (III), (IV) and (V) are more restrictively defined (at page 56 line 31 - page 57 line 1);

vii) "an even more preferred subembodiment, a compound of Formula (IV(a))" and its salts, prodrugs, other forms and method of treatment (at page 58 lines 2-31);

viii) "a fourth principal embodiment, a compound of Formula (VI) or (VII)" and their salts, prodrugs, other forms and method of treatment (at page 59 line 1 – page 60 line 25);

ix) "a particularly preferred alternative embodiment" in which Formula (VI) is more restrictively defined (at page 63 line 2 - page 64 line 19);

x) "another particularly preferred embodiment" in which Formula (VI) is restrictively defined (at page 64 line 20 - page 66 line 18);

xi) "another particularly preferred embodiment" in which Formula (VI) is restrictively defined (at page 66 line 19 - page 68 line 10);

xii) "a particularly preferred embodiment" in which Formula (VI) is restrictively defined (at page 68 line 11 - page 69 line 17);

xiii) "a particularly preferred alternative embodiment" in which Formula (VI) is restrictively defined (at page 70 line 18 - page 72 line 18);

xiv) "another particularly preferred embodiment" in which Formula (VI) is restrictively defined (at page 72 line 19 - page 74 line 19);

xv) "another particularly preferred embodiment" in which Formula (VI) is restrictively defined (at page 74 line 19 - page 76 line 10);

xvi) "a particularly preferred embodiment" in which Formula (VII) is more restrictively defined (at page 76 line 11 - page 78 line 18);

xvii) "a particularly preferred alternative embodiment" in which Formula (VII) is restrictively defined (at page 78 line 19 - page 80 line 18);

xviii) "another particularly preferred embodiment" in which Formula (VII) is restrictively defined (at page 80 line 19 - page 82 line 18);

xix) "another particularly preferred embodiment" in which Formula (VII) is restrictively defined (at page 82 line 20 - page 84 line 10);

xx) "first" through to "fourteenth subembodiment[s]" in which Formula (VI) is still more restrictively defined (at page 84 line 11 - page 90 line 19);

xxi) "even more preferred subembodiments" in which Formula (VI) is limited to one of 13 individual compounds (at page 90 line 20 - page 91 line 18);

xxii) "a fifth principal embodiment, a compound of Formula (VIII), (IX) or (X)" and their salts, prodrugs, other forms and method of treatment (at page 91 line 19 - page 92 line 33);

xxiii) "a sixth principal embodiment, a compound of Formula (XI) or (XII)" and their salts, prodrugs, other forms and method of treatment (at page 93 line 1 - page 94 line 24);

xxiv) "a particular aspect of the invention, a compound of Formula (XIII) and XIV)" and their salts, prodrugs, other forms and method of treatment (at page 95 line 1 - page 96 line 20);

xxv) "a second particular aspect of the invention, a compound of Formula (XV), (XVI) or (XVII)" and their salts, prodrugs, other forms and method of treatment (at page 96 line 21 - page 97 line 14);

xxvi) "a third particular aspect of the invention, a compound of Formula (XVIII)" and its salts, prodrugs, other forms and method of treatment (at page 97 lines 16-26);

xxvii) "a fourth particular aspect of the invention, a compound of Formula (XIX), (XX), (XXI), (XXII) or (XXIII)" and their salts, prodrugs, other forms and method of treatment (at page 98 line 1 - page 100 line 5);

xxviii) "another preferred embodiment" in which a compound of Formula (IX) is restrictively defined (at page 100 lines 6-27); and

xxix) two "subembodiment[s]" in which Formula (IX) is restricted to particular compounds (at page 100 lines 28-29).

196. Two points should be noted about this passage. First, no explanation is provided as to why certain embodiments might be preferred or particularly preferred and no data is provided to support any preference. Secondly, even embodiments in which a Formula is restrictively defined typically cover vast numbers of compounds.

197. In the last preferred embodiment and its subembodiments, the substituents in Formula (IX) are defined as follows (at page 100 lines 16-29):

> "R^1, R^2, and R^3 are independently H; phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound where R^1, R^2, and/or R^3 is independently H or phosphate;
>
> X is O, S, SO_2 CH_2;
>
> Base* is a purine or pyrimidine base;
>
> R^{12} is $C(Y^3)_3$;
>
> Y^3 is independently H, F, Cl, Br, or I; and
>
> R^{13} is fluoro.
>
> In one subembodiment X is O, and Y^3 is H. In another subembodiment, when X is O and Y^3 is H, R^1, R^2 and R^3 are also H."

198. The Application then proceeds to subsections headed "II. Stereochemistry" (at page 101 line 1 - page 103 line 8), "III. Definitions" (at page 103 line 11 - page 107 line 18), "IV. Prodrugs and Derivatives" (at page 107 line 20 - page 112 line 12), "V. Combination or Alternation Therapy" (at page 112 line 14 - page 116 line 34), "VI. Pharmaceutical Compositions" (at page 117 line 1 - page 119 line 28), "VII. Processes for the Preparation of Active Compounds" (at page 119 line 30 - page 152 line 17) and "VIII. Biological Assays" (at page 153 line 1 - page 157 line 6).

199. Section III contains a very broad definition of "purine or pymidine base" (at page 104 lines 15-32). The final definition (at page 107 lines 3-18) is as follows:

> "The term 'pharmaceutically acceptable salt or prodrug' is used throughout the specification to describe any pharmaceutically acceptable form (such as an ester, phosphate ester, salt of an ester or a related group) of a nucleoside compound which, upon administering to a patient, provides the nucleoside compound. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium and magnesium, among numerous other acids well known in the pharmaceutical art. Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form the compound of the present invention. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active compound. The compounds of this invention possess antiviral activity against a Flaviviridae, or are metabolized to a compound that exhibits such activity."

200. Section IV begins (at page 107 lines 21-30):

> "The active compound can be administered as any salt or prodrug that upon administration to the recipient is capable of providing directly or indirectly the parent compound, or that exhibits activity itself. Nonlimiting examples are the pharmaceutically acceptable salts (alternatively referred to as 'physiologically acceptable salts'), and a compound, which has been alkylated, acylated, or otherwise modified at the 5'-position, or on the purine or pyrimidine base (a type of 'pharmaceutically acceptable prodrug'). Further, the modifications can affect the biological activity of the compound, in some cases increasing the activity over the parent compound. This can easily be assessed by preparing the salt or prodrug and testing its antiviral activity according to the

> methods described herein, or other methods known to those skilled in art."

201. Subsection B of section IV is headed "Nucleoside Prodrug Formulations" and begins as follows (at page 108 lines 16-24):

> "The nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono-, di-or triphosphate of the nucleoside reduces polarity and allows passage into cells. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischoferger, Antiviral Research, 1995, 27:1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect."

202. This passage goes on to discuss the use of, among other things, "cyclic phosphoramidates" (page 110 lines 6-8) and "suitable cyclic phosphoramidate prodrugs" (page 111 line 1 – page 112 line 12).

203. Section VI contains a number of references to prodrugs. It also refers (at page 119 lines 25-26) to an "aqueous solution of the active compound or its monophosphate, disphosphate and/or triphosphate derivatives".

204. Subsection VII first describes some general methods for obtaining the nucleosides of the invention, as follows:

i) "A. General Synthesis of 1'-C-Branched Nucleosides" (at page 120 line 3 – page 122 line 20);

ii) "B. General Synthesis of 2'-C-Branched Nucleosides" (at page 122 line 21 – page 125 line 20);

iii) "C. General Synthesis of 3'-C-Branched Nucleosides" (at page 126 line 1 – page 129 line 6);

iv) "D. General Synthesis of 4'-C-Branched Nucleosides" (at page 129 line 7 – page 131 line 14);

v) "E. General Synthesis of 2' and/or 3'-Prodrugs" (at page 131 line 15 – page 132 line 8).

205. Part B describes two approaches, "1. Glycosylation of the nucleobase with an appropriately modified sugar" and "2. Modification of a pre-formed nucleoside". The first approach is described as follows (at page 123 line 1 – page 124 line 3):

> "The key starting material for this process is an appropriately substituted sugar with a 2'-OH and 2'-H, with the appropriate

leaving (LG), for example an acyl group or a halogen. The sugar can be purchased or can be prepared by any known means including standard epimerisation, substitution, oxidation and reduction techniques. The substituted sugar can then be oxidized with the appropriate oxidizing agent in a compatible solvent at a suitable temperature to yield the 2'-modified sugar. Possible oxidizing agents are Jones reagent (a mixture of chromic acid and sulfuric acid), Collins's reagent (dipyridine Cr(VI) oxide, Corey's reagent (pyridinium chlorochromate), pyridinium dichromate, acid dichromate, potassium permanganate, MnO_2, ruthenium tetroxide, phase transfer catalysts such as chromic acid or permanganate supported on a polymer, CI_2-pyridine, H_2O_2-ammonium molybdate, $NaBrO_2$-CAN, NaOCI in HOAc, copper chromite, copper oxide, Raney nickel, palladium acetate, Meerwin-Pondorf-Verley reagent (aluminum *t*-butoxide with another ketone) and *N*-bromosuccinimide.

Then coupling of an organometallic carbon nucleophile, such as a Grignard reagent, an organolithium, lithium dialkylcopper or R^6 –$SIMe_3$ in TBAF with the ketone with the appropriate non-protic solvent at a suitable temperature, yields the 2'-alkylated sugar. The alkylated sugar can be optionally protected with a suitable protecting group, preferably with an acyl or silyl group, by methods well known to those skilled in the art, as taught by Greene *et al*. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The optionally protected sugar nucleoside can then be coupled to the BASE [sic] by methods well known to those skilled in the art, as taught by Townsend Chemistry of Nucleosides and Nucleotides, Plenum Press, 1994. For example, an acylated sugar can be coupled to a silylated base with a Lewis acid, such as tin tetrachloride, titanium tetrachloride or a trimethylsilyltriflate in the appropriate solvent at a suitable temperature. Alternatively, a halo-sugar can be coupled to a silylated base with the presence of trimethylsilyltriflate.

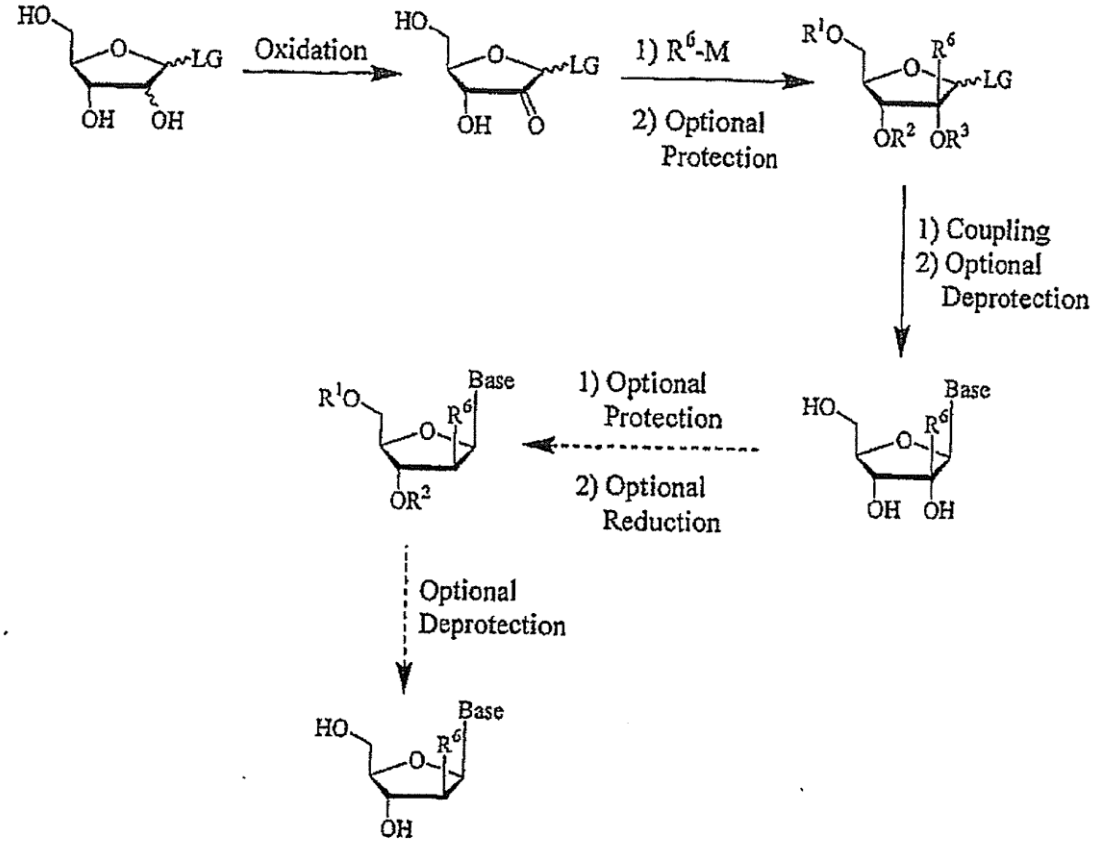
Subsequently, the nucleoside can be deprotected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition 1991.

In a particular embodiment, the 2'-C-branched ribonucleoside is desired. The synthesis of a ribonucleoside is shown in Scheme 3. Alternatively, deoxyribo-nucleoside is desired. To obtain these nucleosides, the formed ribonnucleoside can optionally be protected by methods well known to those skilled in the art, as taught by Greene et al. Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, and then the 2'-OH can be reduced with a suitable reducing agent. Optionally,

the 2'-hydroxyl can be activated to facilitate reduction; i.e. via the Barton reduction."

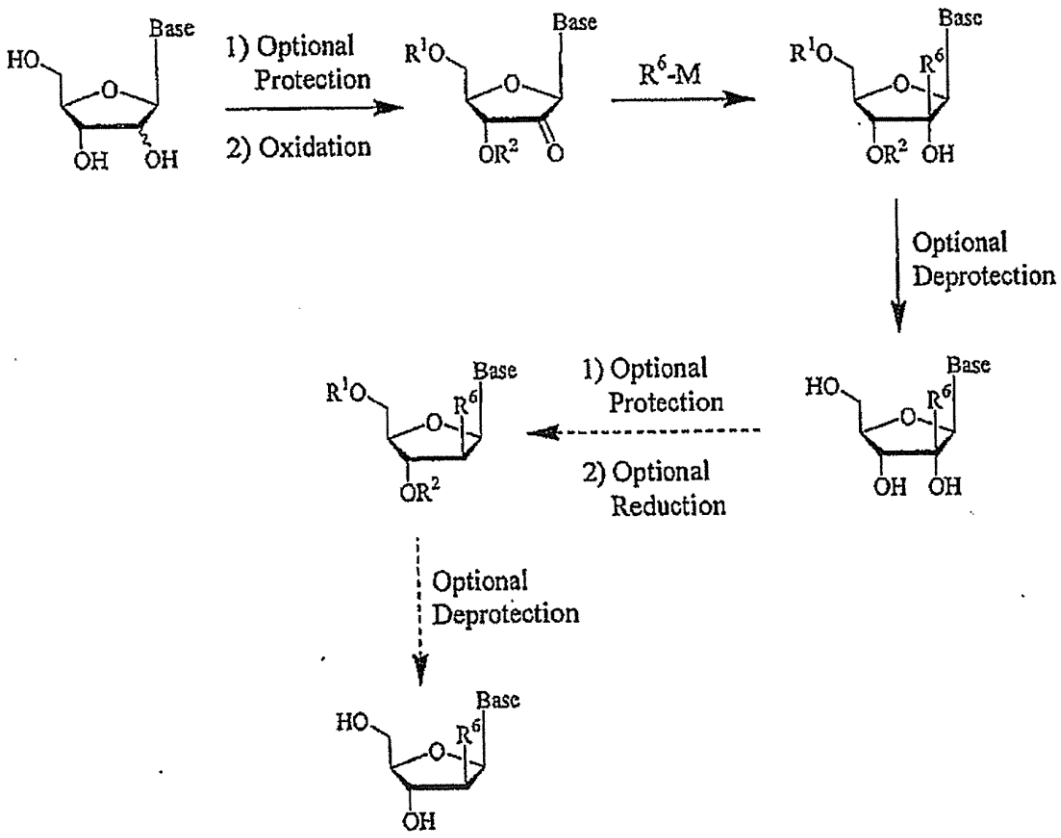
206. Scheme 3 is reproduced below.

Scheme 3



207. The second approach is described in very similar terms, except that it begins with an appropriately substituted nucleoside, which is optionally protected with suitable protecting groups, then oxidised, and deprotected (page 124 line 7 – page 125 line 13). Just as the first approach is exemplified by Scheme 3, the second approach is exemplified by Scheme 4, which is reproduced below.

Scheme 4



208. None of the general methods A-E describes the synthesis of compounds with any fluorine substitution.

209. Subsection VII then continues with Examples 1-24 (at page 132 line 10 - page 152 line 17). These examples describe the synthesis of a number of specific nucleosides. Again, none of them relate to the synthesis of compounds with any fluorine substitution.

210. Subsection VIII consists of Examples 25 and 26. Example 25 is entitled "Anti-flavivirus or pestivirus activity". It describes the following assays (at page 153 line 4 - page 156 line 17): phosphorylation assay of nucleoside to active triphosphate, bioavailability assay in Cynomolgus monkeys, bone marrow toxicity assay, mitochrondrial toxicity assay, cytotoxicity assay, cell protection assay, plaque reduction assay and yield reduction assay. All of these assays were well known in June 2003. None of the assays mentioned measures anti-HCV activity. The HCV replicon assay is not mentioned, nor is a polymerase inhibition assay.

211. Example 26 is entitled "*In vitro* anti-viral activity". It contains the only experimental data concerning anti-viral activity and toxicity in the entire Application. It reads as follows:

> "In vitro anti-viral activity was tested in the following cell lines: MT-4 for HIV; Vero 76, African green monkey kidney cells for SARS; BHK for Bovine Viral Diarrhea Virus; Sb-1 for poliovirus Sabin type-1; CVB-2, CVB-3, CVB-3, CVB-4, and

CVA-9 for Coxsackieviruses B-2, B-3, B-4 and A-9; and REO-1 for double-stranded RNA viruses. Note: BVDV = bovine viral diarrhea virus; YFV = yellow fever virus; DENV = dengue virus; WNV = West Nile virus; CVB-2 = Coxsackie B-2 virus; Sb-1 = Sabin type 1 poliomyelitis virus; and REO = double-stranded RNA Reovirus.

CC_{50} and EC_{50} Test Results for β-D-2'-C-methyl-7-methyl-6-phenyl-3,3a,5,8a-tetrahydro-1,3,4,5,7a-penta-aza-*s*-indacen-8-one (Compound F)

	CC_{50}	CC_{50}	CC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}	EC_{50}
Compound	MT-4	Vero 76	BHK	Sb-1	CVB-2	CVB-3	CVB-4	CVA-9	REO-1
F	>100	>100	>100	43	37	49	39	60	2

CC_{50} Test Results for β-D-2'-C-methyl-7-methyl-6-phenyl-3,3a,5,8a-tetrahydro-1,3,4,5,7a-penta-aza-*s*-indacen-8-one (Compound F)

	CC_{50}							
Compound		BVDV	YFV	DENV 2	WNV	CVB-2	Sb-1	REO
F	>100	10	2.5	1.3	1	37	43	2

"

212. It is common ground that it is not possible to identify Compound F on the basis of the information given about it. It is also common ground that there is no indication that Compound F contains fluorine.

213. Turning to the experimental data, this is presented in a very confusing and unsatisfactory manner. First, the Application begins by says that "anti-viral activity was tested in the following cell lines". No difficulty is caused by the first three cell lines (MT-4, Vero 76 and BHK), but it is not clear what is meant by "Sb-1 for poliovirus Sabin type 1" etc, particularly given that the Application goes on to use the same abbreviations for the viruses themselves.

214. Secondly, no information is given as to which assays were used to generate the data presented.

215. Thirdly, no units are given. Elsewhere in the Application, in Section V, it is stated that "[i]n preferred embodiments, an anti-HCV (or anti-pestivirus or anti-flavivirus) compound that exhibits an EC_{50} of 1-15 μM, or preferably less than 1-5 μM is possible" (page 112 lines 25-27). This may suggest that the EC_{50} values quoted in the tables are micromolar, and hence that the CC_{50} values are in the same units, but they could be millimolar or nanomolar. (I should say that counsel for Idenix objected in his closing submissions that Prof Götte had made this point in response to a question which I had asked the witness. It was a question which arose naturally out of counsel's cross-examination, however, and it was not put to the witness that he was factually wrong about this.)

216. Fourthly, the first table lists three CC_{50} values, which the skilled reader would understand to be a measure of toxicity, for different cell lines. It then lists EC_{50} values, which the skilled reader would understand to be a measure of antiviral activity, for a number of viruses. It does not appear, however, that the EC_{50} data have been generated for any of the same viruses or in any of the same cell lines as the CC_{50} data. In any event, none of the viruses for which EC_{50} values are quoted in this table are *Flaviviridae.*

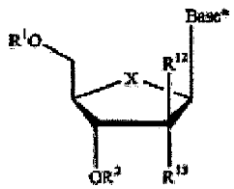
217. The second table is entitled "CC_{50} Test Results". At first blush, it appears to give a series of CC_{50} values, one for an unidentified cell line and then for (apparently) a series of cell lines called "BVDV" to "REO". It can be seen, however, that these names are the names of the viruses previously referred to. Furthermore, it can also be seen that the values given for "Sb-1" "CVB-2" and "REO" coincide with the EC_{50} values in the first table. This suggests that what the second table is in fact presenting is a single CC_{50} value from an unidentified cell line and some EC_{50} data for a number of viruses, some of which repeats what is in the first table and some of which is new, in particular data for members of the *Flaviviridae* family (but including HCV). But if so, it is wholly unclear why the data has been divided between the two tables in this way. Furthermore, the problem remains that it is not apparent that the CC_{50} value has been obtained from the same cell line as any of the EC_{50} data.

218. Prof Götte's evidence was that it could not be concluded from this data that Compound F has any potentially therapeutically useful activity. Prof Glenn disagreed with this, but I found Prof Götte's evidence on this point more persuasive.

Claims

219. There are 49 claims in the Application which extend from page 158 line 1 to 196 line 22. Claims 1-11 are compound claims, claims 12-26 are method of treatment claims, claims 27-43 are pharmaceutical composition claims and claims 44-49 are claims to compounds for the treatment of a host infected with a *Flaviviridae* virus.

220. Claim 9 is as follows:



(IX)

"A compound of Formula (IX) or a pharmaceutically acceptable salt thereof, wherein:

R^1, R^2 and R^3 are independently H; phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; a carbohydrate; a peptide; cholesterol; or a pharmaceutically

> acceptable leaving group which when administered in vivo is capable of providing a compound wherein R^1, R^2 and/or R^3 are independently H or phosphate;
>
> X is O, S, SO_2 or CH_2;
>
> Base* is a purine or pyrimidine base;
>
> R^{12} is $C(Y^3)_3$;
>
> Y^3 is independently H, F, Cl, Br or I; and
>
> R^{13} is fluoro."

221. Claim 10 is a claim to a compound of Formula (IX) in which X is O and Y^3 is H. Claim 11 is a claim to a compound of Formula (IX) in which X is O, Y^3 is H and R^1, R^2 and R^3 are all H.

Prosecution history

222. As explained below, Gilead rely upon two events which occured during the course of prosecution of the Application: first, an amendment which was made by Idenix, and secondly, the contents of a telephone conversation between Idenix's patent attorneys and the examiner.

223. The circumstances in which the amendment was made were as follows. On 10 December 2008 the examiner sent Idenix's patent attorneys a communication raising objections of lack of novelty, lack of inventive step and lack of clarity in respect of a set of claims which had been filed on 29 July 2007. Claim 1 of these claims including the expression "a pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R^1, R^2 and/or R^3 are independently H or phosphate" which can also be seen in claim 9 of the Application quoted above. The clarity objection was expressed in the following terms:

> "The term 'leaving group' used in claim 1 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 84 EPC)."

224. On 17 June 2009 Idenix's patent attorneys replied to the communication enclosing a new set of claims in which claim 1 corresponded to claim 1 of the Patent. They responded to the clarity objection as follows:

> "In reply to the clarity objection raised by the Examining Division, and solely to expedite allowance of the present claims, the term objected to by the Examining Division has been deleted."

225. Subsequently Idenix proposed a new claim 38 to the compound as claimed in earlier claims "wherein the phosphate is a lipophilically modified mono- di –or triphosphate". As a result of this request, Idenix's patent attorneys discussed the

meaning of the term "phosphate" with the examiner during a telephone conversation on 21 October 2013. In that conversation Idenix's patent attorneys argued that the term "phosphate" was "a generic term including mono-, di- and triphosphate derivatives", while the examiner took the view that "phosphate, when nothing else is mentioned, is a clear term for the skilled person meaning a monophosphate and not a derivative thereof". Accordingly, claim 38 was rejected by the examiner.

The Patent

226. The Patent is 52 pages long (excluding four pages of references cited in the description). Because the Patent is single-spaced, whereas the Application is double-spaced, the Patent is roughly half the length of the Application. As will appear, it could have been shorter still if all the material which was no longer relevant to the claimed invention had been excised.

227. The specification begins at [0001] with following statement:

> "The invention is in the area of pharmaceutical chemistry, and is in particular, a 2'-branched pyrimidine nucleoside or 2'-branched purine nucleoside as defined in the claims. The invention is also a pharmaceutical composition comprising the nucleoside, and the nucleoside for use in a method for the treatment of a *Flaviviridae* infection, such as a hepatitis C virus infection."

228. The specification then discusses the following topics: *Flaviviridae* viruses ([0002]-[0007]), HCV ([0008]-[0011]), treatment of HCV infection with interferon ([0012]-[0015]), ribavarin ([0016]-[0018]), combination of interferon and ribavarin ([0019]-[0021]) and additional methods to treat *Flaviviridae* infections ([0022]-[0024]). These passages are substantially the same as the corresponding passages in the Application. In particular, [0023] includes the passage describing class (10) quoted in paragraph 181 above.

229. The paragraphs of the Application quoted in paragraph 183 above are reproduced in the specification at [0025]-[0028].

230. The invention is then summarised in the following terms:

> "[0029] This invention relates to 2'-branched nucleosides, compositions thereof, and the nucleosides for use in methods as defined in the claims.
>
> [0030] 3'-prodrugs of 2'-branched β-D or β-L nucleosides, or their pharmaceutically acceptable salts or pharmaceutically acceptable formulations containing these compounds are useful in the prevention and treatment of *Flaviviridae* infections and other related conditions such as anti- *Flaviviridae* antibody positive and *Flaviviridae* - positive conditions, chronic liver inflammation caused by HCV, cirrhosis, acute hepatitis, fulminant hepatitis, chronic persistent hepatitis, and fatigue. These compounds or formulations can also be used

> prophylactically to prevent or retard the progression of clinical illness in individuals who are anti-*Flaviviridae* antibody or *Flaviviridae*-antigen positive or who have been exposed to a *Flaviviridae*.
>
> [0031] A method for the treatment of a *Flaviviridae* viral infection in a host, including a human, is also disclosed that includes administering an effective amount of a 3'- prodrug of a biologically active 2'-branched β-D or β-L nucleoside or a pharmaceutically acceptable salt thereof, administered either alone or in combination or alternation with another anti-*Flaviviridae* agent, optionally in a pharmaceutically acceptable carrier. The term 3'-prodrug, as used herein, refers to a 1', 2', 3' or 4'-branched β-D or β-L nucleoside that has a biologically cleavable moiety at the 3'-position, including, but not limited to acyl, and in one embodiment, a natural or synthetic D or L-amino acid, preferably an L-amino acid."

231. The specification gives "examples of prodrugs" and "additional examples of prodrugs" in [0035]-[0036] and gives "examples of prodrugs falling within the disclosure" and "additional examples of prodrugs falling within the disclosure" in [0038]-[0039].

232. At [0040] the specification describes a "principal embodiment, a compound of Formula (IX), or a pharmaceutically acceptable salt, or a tautomeric or polymorphic form thereof … as well as the compound for use in a method of treatment of a host infected with a *Flaviviridae* comprising administering an effective treatment amount" of the compound. Formula (IX) is the same as Formula (IX) in the Application, but in this embodiment the substituents are defined as set out in claim 1 quoted below.

233. At [0041] the specification identifies "another preferred embodiment" in which R^2 is an amino acid residue, and is preferably L-valinyl.

234. At [0042] the specification reproduces the paragraph from the Application quoted in paragraph 188 above.

235. At [0042]-[0057] the specification discloses various embodiments of the invention.

236. Under the heading "I. Active Compounds" the specification identifies, first, a principal embodiment which corresponds to the principal embodiment described earlier (at [0059]), secondly an embodiment in which Y^3 is H (at [0060]) and thirdly a subembodiment in which R^1 and R^2 are H.

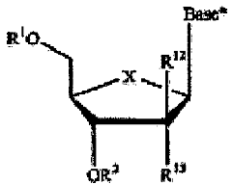
237. The specification then proceeds to subsections headed "II. Sterechemistry" (at [0062]-[0065]), "III. Definitions" (at [0066]-[0079]), "IV. Prodrugs and Derivatives" (at [0080]-[0091]), "V. Combination or Alternation Therapy" (at [0092]-[0094]), "VI. Pharmaceutical Compositions" (at [0095]-[0106]), "VII. Processes for the Preparation of Active Compounds" (at [0107]-[0182]) and "VIII. Biological Assays" (at [0184]-[0196]). Save as indicated below, these passages largely reproduce the corresponding passages in the Application.

238. Subsection VII again describes methods A-E, but methods A, C and D are now said to be "not according to the invention". Method B reproduces the paragraphs from the Application quoted in paragraph 205 above. Subsection VII also includes Examples 1-24, but these are all now described as "reference examples" either in the headings or in the text.

239. Subsection VIII again consists of Examples 25 and 26, but Example 26 is now described as a reference example.

The claims

240. Claim 1 is as follows:



(IX)

> "A compound of Formula (IX) or a pharmaceutically acceptable salt thereof, wherein:
>
> R^1 and R^2 are independently H; phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; a carbohydrate; a peptide; or a cholesterol;
>
> X is O;
>
> Base* is a purine or pyrimidine base;
>
> R^{12} is $C(Y^3)_3$;
>
> Y^3 is H; and
>
> R^{13} is fluoro."

Formula (IX) remains as set out in paragraph 187 above.

241. The other claims which Idenix contend have independent validity are as follows:

> "2. The compound of claim 1, wherein R^1 and R^2 are H.
>
> 5. The compound of any one of claims 1-4, wherein Base* is cytosine, uracil, guanine, adenine, or thymine.

> 6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, for use in a method for the treatment of a host infected with a Flaviviridae, virus.
>
> 7. The compound for use of claim 6, wherein the virus is hepatitis C.
>
> 21. A pharmaceutical composition comprising an effective amount to treat a Flaviviridae infection of a compound, or a pharmaceutically acceptable salt thereof, of any of claims 1 to 5 in a pharmaceutically acceptable carrier.
>
> 24. The composition of claim 21, wherein the Flaviviridae virus is hepatitis C."

242. Claims 20 and 37 are respectively compound for use and pharmaceutical composition claims in which the pharmaceutically acceptable salt is a hydrochloride salt.

Idenix's amendment application

243. By their amendment application, Idenix propose to amend claim 1 to delete the following from the list of possible substituents at R^1 and R^2: "straight chained, branched or cyclic alkyl" and "benzyl, wherein the phenyl group is optionally substituted with one or more substituents". The application is expressed to be conditional upon the court finding that the claims as granted are invalid. As I shall explain, however, Idenix's own evidence establishes that the granted claims are invalid. The amendment is proposed to cure this invalidity. As I shall also explain, Gilead contend that the amendment is not allowable because it would result in added matter.

The skilled team

244. A patent specification is addressed to those likely to have a practical interest in the subject matter of the invention, and such persons are those with practical knowledge and experience of the kind of work in which the invention is intended to be used. The addressee comes to a reading of the specification with the common general knowledge of persons skilled in the relevant art, and he (or she) reads it knowing that its purpose is to describe and demarcate an invention. He is unimaginative and has no inventive capacity. In some cases, the patent may be addressed to a team of persons having different skills.

245. In the present case it is common ground that the Patent is addressed to a team, and that the team comprises two scientists, a medicinal chemist and a virologist, both working in the context either of a pharmaceutical company or an appropriate academic research department. Each would be educated to undergraduate level in his or her respective subject, and probably also have a PhD or equivalent research experience.

246. The medicinal chemist would be experienced in the synthesis of organic compounds for medicinal applications. He would be likely to have some experience in the synthesis of nucleoside analogues.

247. The virologist would have expertise in the biology of the *Flaviviridae* virus family, and a particular interest in the antiviral activity of nucleoside analogues against *Flaviviridae*. He or she would be familiar with (and able to carry out) standard molecular- and cell-biological techniques, as well as activity assays.

248. The only area of disagreement concerns the division of labour between the members of the skilled team, and in particular the role of the virologist. Dr Brancale's and Prof Glenn's evidence was that the medicinal chemist would be the one who decided what compounds to synthesise next in pursuit of a particular objective, while the virologist would generally be responsible for testing the activity of given molecules, though simpler assays (such as enzymatic assays) might be carried out by the medicinal chemist. Dr Brancale agreed, however, that the medicinal chemist and the virologist would collaborate in the synthesis and testing. He also agreed that not all virologists would have the same interests: thus some might have a particular interest in viral transmission, while others might be more interested in the biochemistry of RNA polymerase. Prof Boons' and Prof Götte's evidence was that there would be a more equal dialogue between the members of the skilled team. Prof Götte accepted, however, that he had had personal experience of a team which operated in the manner described by Dr Brancale.

249. In my view the skilled team embraces partnerships which operate in both these ways. The way in which a particular partnership operated would depend on the particular backgrounds and interests of the individual members.

Common general knowledge

250. I reviewed the law as to common general knowledge in *KCI Licensing Inc v Smith & Nephew plc* [2010] EWHC 1487 (Pat), [2010] FSR 31 at [105]-[115]. That statement of the law was approved by the Court of Appeal [2010] EWCA Civ 1260, [2011] FSR 8 at [6].

251. There is little dispute that everything I have set out in the technical background section of this judgment (except where I have explicitly referred to developments after June 2003) formed part of the skilled team's common general knowledge, and in any event that is my finding. There are three main areas of dispute with regard to common general knowledge.

252. Before proceeding further, it is convenient to note three points about the issues on common general knowledge. The first is that, unusually, it is Idenix who are contending that more information formed part of the common general knowledge than Gilead. Normally it is the party attacking the validity of the patent which tries to prove a higher level of common general knowledge. It is clear that Idenix's purpose in trying to prove a higher level of common general knowledge is to attempt to remedy the deficiencies in the Patent. I shall return to this subject below.

253. The second point is that the first area of dispute, which is the most important one, lies in what Idenix contend to be province of the medicinal chemist. Hence it was addressed by Dr Brancale rather than Prof Glenn. On Gilead's side, however, it was addressed by Prof Götte rather than Prof Boons. This simply reflects the division of labour between the two pairs of experts that I have already discussed.

254. The third point is that Idenix primarily relied not on the evidence given by Dr Brancale, but upon evidence given by Prof Götte and upon a number of papers which had not been exhibited or referred to by either Dr Brancale or Prof Götte, but which were first produced shortly before the cross-examination of Prof Götte (or indeed were produced during the course of cross-examination). This is not a promising basis for a claim to common general knowledge.

Knowledge that 2'-methyl-up-2'-hydroxy-down nucleoside analogues had the potential to be efficacious in treating HCV

255. Idenix contend that it was common general knowledge that 2'-methyl-up-2'-hydroxy-down nucleoside analogues had the potential to be efficacious in treating HCV. More specifically, Idenix say that it was common general knowledge that certain 2'-methyl-up-2'-hydroxy-down nucleoside analogues which were being investigated by Merck had activity in the HCV replicon assay and acted as chain terminators of the HCV RNA-dependent RNA polymerase. Gilead dispute this. It is convenient to break consideration of this issue down into four aspects: (i) general evidence, (ii) the Carroll paper, (iii) the presentations at the Savannah conference and (iv) knowledge of NM107.

256. *General evidence*. The starting point in resolving the issue is to consider Idenix's evidence in chief on this topic. Leaving aside his evidence regarding the presentations at the Savannah conference, which I shall consider separately below, Dr Brancale dealt with this topic in a single paragraph in his first report (paragraph 51), which I shall quote in full:

> "I have read a copy of the report of Dr Glenn, in which he addresses the virology aspects of HCV. From the Medicinal Chemist's perspective, research on nucleoside analogues against HCV infection started in the late 1990s. Around the beginning of the 2000s, certain 2'-modified nucleoside analogues were known to have anti-HCV activities. The research activity in the area is reflected in International Patent Application WO 01/90121 published on 29 November 2001 which reports anti-HCV activities of 2'-methyl-up nucleoside analogues; and in WO 99/043691 published on 2 September 1999, which reports 2'-fluoro nucleoside analogues having anticancer activities and antiviral activities against several viruses including HCV. Further, other 2'-modified nucleoside analogues were reported to be active against other members of the *Flaviviridae* virus. For example, WO 01/92282 published on the 6 December 2001 reports 2'-methyl-up nucleoside analogues showing antiviral activities against BVDV and YFV. The existence of these patents illustrates the type of work that was being undertaken with respect to 2'-modified nucleoside analogues as anti-*Flaviviridae* agents."

257. As I read this, all that Dr Brancale says in terms of common general knowledge is that "certain 2'-modified nucleoside analogues were known to have anti-HCV activities". This is a very broad statement, it does not relate specifically to 2'-methyl-up-2'-hydroxy-down compounds, and no textbook or article is cited in support of it. As for

the three patent applications referred to, Dr Brancale merely says that these illustrate the type of research that was being undertaken. He does not suggest that the content of any of the applications was common general knowledge.

258. Leaving aside his evidence regarding the presentations at the Savannah conference and the Carroll paper, which again I shall consider separately below, Dr Brancale said nothing further about this topic in his second report. Nor did he address it in his third report. Thus Dr Brancale's evidence in chief did not suggest that, other than through the Savannah conference and the Carroll paper, it was common general knowledge that 2'-methyl-up-2'-hydroxy-down nucleoside analogues had the potential to be efficacious in treating HCV.

259. Counsel for Idenix nevertheless relied on a number of pieces of evidence as showing that this was the case. First, he pointed out that Prof Götte had said in his first report, and Dr Brancale had agreed in cross-examination, that a review article by Raffaele De Francesco and Charles Rice entitled "New therapies on the horizon for hepatitis C: are we close?", *Clin. Liver Dis.*, 7, 211-243 (2003) was representative of the sort of information that was common general knowledge in June 2003. In the article, the authors review various strategies for treating HCV that have been, and are being pursued, including the use of nucleoside analogues to inhibit NS5B enzymatic activity.

260. Under the heading "HCV-encoded enzymes and their inhibitors" and the sub-heading "NS5B RNA-dependent polymerase", the article states (at pages 225-226):

> "The NS5B gene product is the viral RNA-dependent RNA polymerase [65]. This enzyme is required for both of the RNA synthesis steps necessary for viral replication: the synthesis of the negative-stranded RNA intermediate, complementary to the viral genome, and the synthesis of positive-stranded RNA genomes complementary to the negative-stranded intermediate. Obviously, inhibition of this pivotal enzymatic activity would lead to suppression of the HCV replication in infected cells. The enzymatic reaction catalysed by NS5B, RNA-dependant RNA synthesis, is moreover a reaction not normally carried out in noninfected cells [119]. It is therefore possible that specific inhibitors of this enzyme could be found that block HCV replication with negligible associated toxicity."

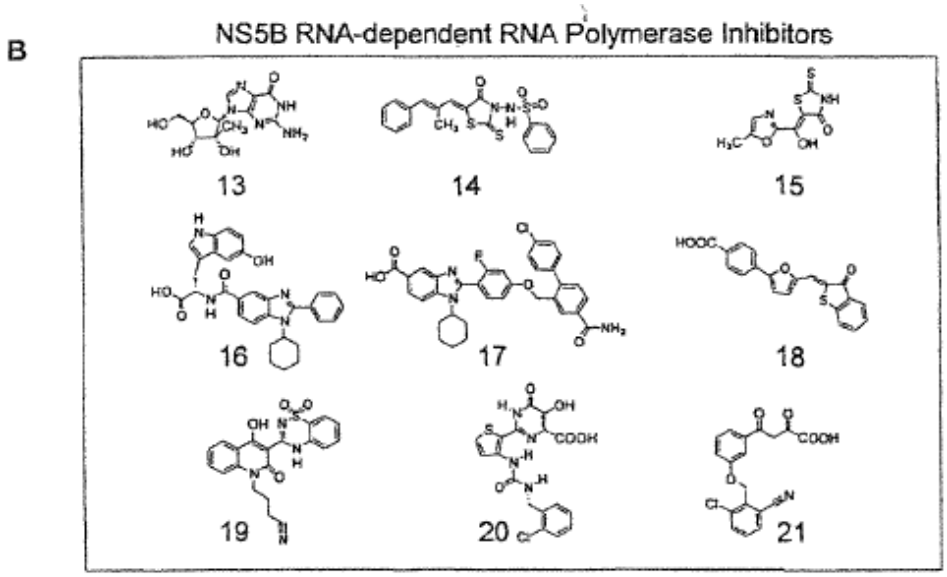
This passage confirms that, as stated in paragraph 109 above, NS5B had been identified as a target for the development of anti-HCV therapies by June 2003. It goes no further than that.

261. Under the sub-heading "Nucleoside analogues", the article states (at page 228):

> "Novel series of nucleosides that are candidates for the treatment of HCV are being developed, and some have been described in the recent patent literature [131-133]. In particular the discovery of oral, once-daily nucleosides potentially useful for the treatment of all HCV genotypes was recently reported [134]. Among these, beta-D-2'-methyl-ribofuranosyl-guanosine

> (Fig 6, compound 13) was found to be phosphorylated in cultured cells and orally bioavailable in primates [133].
>
> Interestingly, the only nucleoside analogue that thus far was shown to be therapeutically useful against HCV infection is the broad-spectrum antiviral agent D-ribavirin …"

262. I reproduce Figure 6(B), which is captioned "Chemical structures of selected inhibitors of the NS5B RNA-dependent RNA polymerase activity", below.



As the article explains (at page 229), compounds 14-21 are non-nucleoside inhibitors of NS5B.

263. The article concludes with the following assessment of "Prospects for new HCV therapies" (at page 233):

> "A myriad of new therapies for treating HCV are in various stages of preclinical and clinical development. As reviewed here, these include nucleic acid-based approaches (antisense and ribozymes), small molecule inhibitors of essential HCV-encoded enzymes (protease, helicase, and polymerase), immune modulation, and immunotherapy. As more details of the HCV life cycle are elucidated, new targets and approaches will be discovered. Drug development is difficult, expensive, and always agonizingly slow for patients in need and their physicians. Nonetheless, a broad effort has been mounted for HCV, and substantial progress has been achieved. The prospects for new HCV treatments are bright. The next few years will be very exciting as the first candidates move through clinical trials and, hopefully, into widespread clinical use."

Although this passage states that the prospects for new HCV treatments are bright, it does not identify any particular compound, or even class of compounds, as having bright prospects.

264. Idenix particularly rely on the passage which mentions compound 13, which is a 2'-methyl-up-2'-hydroxy-down nucleoside analogue. All this passage says about compound 13, however, is that it was "found to be phosphorylated in cultured cells and orally bioavailable in primates". This does not demonstrate anti-HCV activity. Furthermore, if the skilled team followed up the references quoted in this passage, they would find the following:

    i) Reference 131 is International Patent Application WO 01/32153 (Biochem Pharma Inc). This does not focus on methyl-hydroxy substitutions at the 2' position.

    ii) Reference 132 is International Patent Application WO 01/79246 (Pharmasset Barbados). Again this does not focus on methyl-hydroxy substitutions at the 2' position.

    iii) Reference 133 is International Patent Application WO 01/90121 (Novirio Pharmaceuticals Ltd and Università degli Studi di Cagliari). As is correctly reported in the review article, this contains phosphorylation and bioavailability data for beta-D-2'-methyl-ribofuranosyl-guanosine. It also contains bone marrow and mitochondrial toxicity data. No antiviral activity data is provided.

    iv) Reference 134 is an IPI website which probably did not disclose the structure of any compounds. It is not in evidence and neither party places reliance upon it.

265. It follows that, even if the skilled team took a particular interest in compound 13 in the De Francesco and Rice article and chased down the references, they would not know whether compound 13 had any anti-HCV activity. As Dr Brancale accepted, the skilled team would know that, in order to identify whether a nucleoside analogue such as compound 13 was active against HCV, it was necessary to test its activity using at least one of the *in vitro* assays that were available. I would add that WO 01/90121 is the only one of the references which was mentioned by Dr Brancale in the passage from his first report quoted above, and as previously noted, he did not suggest that the content of that application was common general knowledge.

266. Secondly, counsel for Idenix relied upon another review article by Dr De Francesco and four other authors entitled "Approaching a new era for hepatitis C virus therapy: inhibitors of the NS3-4A serine protease and the NS5B RNA RNA-dependent RNA polymerase", *Antiviral Research*, 58, 1-16 (2003), which was produced by Gilead for the cross-examination of Dr Brancale. The content of this article is very similar to that of the De Francesco and Rice article. In particular, it says almost exactly the same thing about beta-D-2'-methyl-ribofuranosyl-guanosine (referred to as compound 11, at page 11). Thus it takes Idenix no further forward.

267. Thirdly, counsel for Idenix relied upon a review article by Michelle Walker and Zhi Hong, "HCV RNA-dependent RNA polymerase as a target for antiviral development", *Current Opinion in Pharmacology*, 2, 1-9 (2002). This article was produced by Idenix during the course of Prof Götte's cross-examination. Unlike the De Francesco and Rice article, there is no evidence that the article was, or was representative of, common general knowledge as at 27 June 2003. Although Prof Götte accepted that the authors were leading scientists in the field, it was not

established that the journal was one that either a medicinal chemist or a virologist interested in developing anti-HCV therapies would routinely read.

268. Turning to the content of the article, the abstract states:

> "The lack of a highly effective and safe treatment option for the hepatitis C virus (HCV) has spurred aggressive efforts to identify new, more effective therapies. The RNA-dependent RNA polymerase encoded by HCV, which is strictly required for viral replication, has been the focus of intense drug discovery activity. This is in large measure due to successes in targeting the polymerases from other viral systems**,** coupled with recent advances in experimental systems for studying the HCV polymerase. Both nucleoside and non-nucleoside inhibitors of HCV polymerase have been identified through the innovative use of new screening tools and rational drug design. Some of these compounds have encouraging profiles and could be further developed into therapeutics. Initiation of clinical trials in the near future promises to yield exciting new information on the ability of these compounds to achieve sustained responses in suppressing HCV replication."

Again, this confirms that NS5B had been identified as a target for the development of anti-HCV therapies by June 2003

269. Under the heading "Survey of novel inhibitors", the article states (at pages 4-5):

> "The absence of a reliably efficacious cure for HCV infection has enticed numerous pharmaceutical companies to enter the frenzied sprint for compounds with superior efficacy and nominal toxicity. The result has been the identification of several compounds with the potential to inhibit various targets encoded by HCV, including the metalloprotease (NS2/3), the serine protease (NS3), the helicase (NS3) and a novel, highly conserved IRES [41●] that mediates cap-independent initiation of translation of viral proteins. However, a primary focus is currently on finding inhibitors of the NS5B polymerase, as is apparent from reviewing the numerous patents filed within the past year laying claims both to new compound entities and to new therapeutic utilities related to HCV treatment.
>
> These patents describe compounds that can logically be subdivided into the nucleoside and non-nucleoside inhibitors. These two classes generally differ in specificity, according to their mode of action. Nucleoside inhibitors directly compete with nucleoside substrates for binding to highly conserved active sites. Thus, these inhibitors generally exhibit broader spectrum activity against a class of polymerases. Greater specificity may be achieved by a non-nucleoside inhibitor, which may interact outside of the highly conserved active site

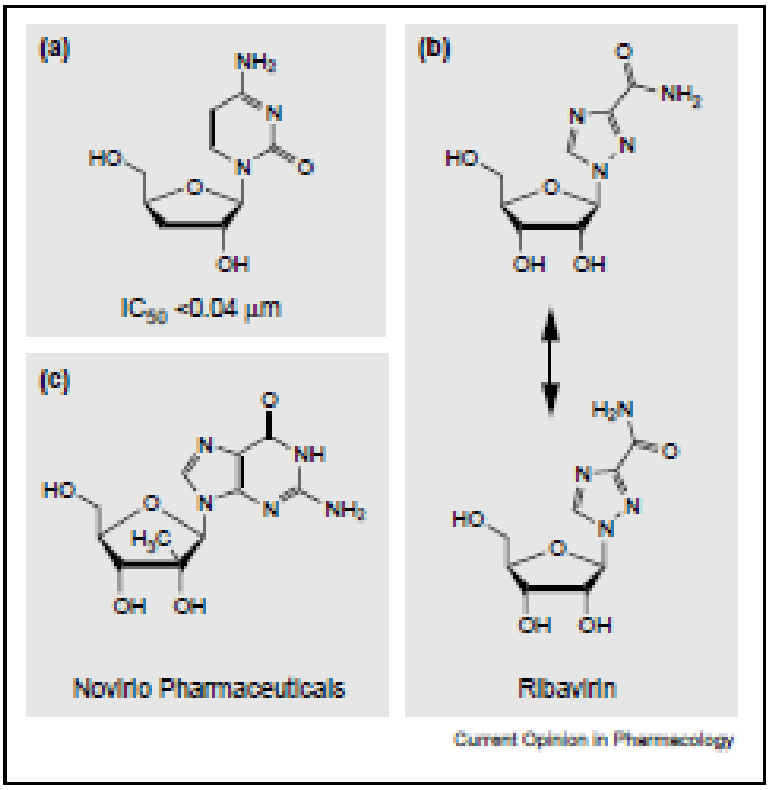
> at a unique allosteric site common only to structurally related polymerases."

270. The article goes on to discuss nucleoside and non-nucleoside inhibitors. The last paragraph of the discussion of nucleoside inhibitors states:

> "Novirio Pharmaceuticals (now Idenix Pharmaceuticals Inc., Cambridge, MA,) has also disclosed a broad series of nucleosides with extensive sugar modifications (Figure 3c; [44]). However, detailed biological information is not yet available, making it difficult to evaluate the mechanism of action of these nucleosides."

271. I reproduce Figure 3 below.

Figure 3



Nucleoside inhibitors of NS5B. **(a)** 3′-deoxycytidine, patented by Ismaili *et al.* [42]; IC_{50} <0.04mM. **(b)** Ribavirin; 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide. **(c)** 2′-β-methyl guanosine, a nucleoside inhibitor disclosed by Novirio Pharmaceuticals.

272. The compound shown in Figure 3c is the same compound as compound 13 in the De Francesco and Rice article. On its face, the Walker and Hong article is even less helpful to Idenix than the De Francesco and Rice article, since it says that "detailed biological information is not yet available" for this compound. Reference 44 is again

WO 01/90121. Thus, if the skilled team pursued the reference, they would end up with the same information.

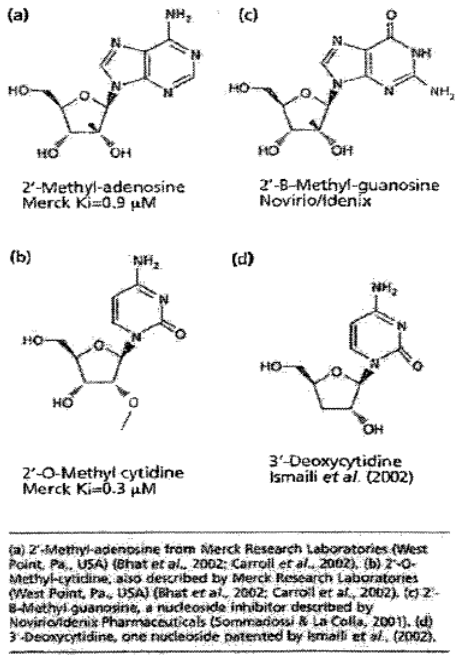
273. Fourthly, counsel for Idenix relied upon another review article by Walker and Hong and three other authors, "Hepatitis C virus therapies: current treatments, targets and future perspectives", *Antiviral Chemistry & Therapy*, 14, 1-21 (2003). This article was produced by Idenix for the purposes of Prof Götte's cross-examination. There is no dispute that it was published in early 2003, but again there is no evidence that the article was, or was representative of, common general knowledge by 27 June 2003. Although Prof Götte accepted that the authors were leading scientists in the field, and although the journal is an official publication of International Society for Antiviral Research ("ISAR"), it was not established that the journal was one that either a medicinal chemist or a virologist interested in developing anti-HCV therapies would routinely read.

274. The article discusses a number of nucleoside and non-nucleoside inhibitors of NS5B in addition to protease inhibitors. Idenix rely upon the following passage (at page 11):

> "For nucleoside inhibitors, either chain terminators or non-chain terminators could be effective. Recent studies on ribavirin suggest that some of its antiviral activity may result from the ability of NS5B to misincorporate ribavirin triphosphate into the viral genome (Maag et al., 2001). The mutagenized genome presumably decreases the fitness of progeny viruses. As such, nucleotides with this property could function as antiviral treatments, especially in combination with other drugs (Hong & Cameron, 2002; Walker & Hong, 2002). In contrast, chain terminators are proven viral DNA polymerase inhibitors and analogous RNA polymerase inhibitors are predicted. Indeed, Merck Research Laboratories (West Point, Pa., USA) recently described two ribonucleoside analogues that appear to act as chain terminators (Carroll et al., 2002). Both 2'-methyl-adenosine (2'-Me-A) (Figure 6a) and 2'-O-methyl-cytidine (2'O-Me-C) (Figure 6b) inhibit NS5B in their triphosphate forms by using the replicase complex assay or the in vitro NS5B assay with IC50 values of 2.5 and 3.5 µM (replicase complex), and 1.9 and 3.8 µM (NS5B assay), respectively (Bhat et al., 2002; Carroll et al., 2002). The 2'-Me-A was more active than 2'O-Me-C in an HB1 HCV replicon cell line (EC50 0.25 vs 21.5 µM) presumably due to inferior metabolism of 2'O-Me-C (poor conversion to the triphosphate form in vivo) (Bhat et al., 2002). It is likely that 2'-methyl-guanosine and additional nucleosides disclosed by Novirio/Idenix act in a manner similar to the Merck compounds (Figure 6c) (Somsnadossi & La Colla, 2001). In addition, a class of 3'-deoxynucleoside analogues exhibits submicromolar activity in vitro (Figure 6d) (Ismaili et al., 2002). NS5B is known to be more selective for nucleotides lacking the 3'-OH group than for nucleotides lacking the 2'-OH group, which supports the potential of these compounds (Lohmann et al.,

> 2000). The interest in inhibiting the HCV RdRp has led to the identification of new classes of compounds with great potential to serve as potent anti-HCV therapies. Hopefully, these compounds will not exhibit substantial toxicity and will enter clinical trials to expand the arsenal of therapies useful in treating chronic HCV infection."

275. I reproduce Figure 6 below.



(a) 2′-Methyl-adenosine from Merck Research Laboratories (West Point, Pa., USA) (Bhat *et al.*, 2002; Carroll *et al.*, 2002). (b) 2′-O-Methyl-cytidine, also described by Merck Research Laboratories (West Point, Pa., USA) (Bhat *et al.*, 2002; Carroll *et al.*, 2002). (c) 2′-B-Methyl-guanosine, a nucleoside inhibitor described by Novirio/Idenix Pharmaceuticals (Sommadossi & La Colla, 2001). (d) 3′-Deoxycytidine, one nucleoside patented by Ismaili *et al.*, (2002).

276. It can be seen that the compound in Figure 6(c) is the same compound as compound 13 in the De Francesco and Rice article, while the compound in Figure 6(a) is a very similar 2'-methyl-up-2'-hydroxy-down compound which has adenine as the nucleobase rather than guanine.

277. Prof Götte explained that the text and the data in Figure 6 are inconsistent: the Ki values refer to enzyme inhibition, not antiviral activity, and yet the structures shown are not triphosphates. In addition, the figures quoted in Figure 6 do not match those quoted in the text. Furthermore, Prof Götte did not consider that the general message of optimism was referable specifically to the 2'-methyl-up-2'-hydroxy-down compounds. It can be seen that no activity data is quoted for the Figure 6(c) compound, although the text suggests that it is "likely" to act "in a similar manner" to the Figure 6(a) and (b) compounds.

278. Finally, it should be noted that the references to "Bhat *et al*, 2002" and "Carroll *et al*, 2002" are references to the published abstracts of two presentations at the Savannah conference discussed below.

279. The conclusion which I draw from this evidence is that it has not been established that, leaving aside the Carroll paper and the Savannah conference, it was common general knowledge that 2'-methyl-up-2'-hydroxy-down nucleoside analogues had the potential to be efficacious in treating HCV.

280. *The Carroll paper*. This is a paper by Steven Carroll and 17 other authors, many of whom were from Merck and including Balkishen Bhat, Anne Eldrup and David Olsen, entitled "Inhibition of Hepatatis C Virus RNA Replication by 2'-Modified Nucleoside Analogues", *J. Biol. Chem.*, 278, 11979-11984. It was published online on 27 January 2003 and in print on 4 April 2003.

281. The work reported in the Carroll paper is summarised in the abstract as follows:

> "The RNA-dependent RNA polymerase (NS5B) of hepatitis C virus (HCV) is essential for the replication of viral RNA and thus constitutes a valid target for the chemotherapeutic intervention of HCV infection. In this report, we describe the identification of 2'-substituted nucleosides as inhibitors of HCV replication. The 5'-triphosphates of 2'-C-methyladenosine and 2'-O-methylcytidine are found to inhibit NS5B-catalyzed RNA synthesis in vitro, in a manner that is competitive with substrate nucleoside triphosphate. NS5B is able to incorporate either nucleotide analog into RNA as determined with gel-based incorporation assays but is impaired in its ability to extend the incorporated analog by addition of the next nucleotide. In a subgenomic replicon cell line, 2-C-methyladenosine and 2'-O-methylcytidine inhibit HCV RNA replication. The 5'-triphosphates of both nucleosides are detected intracellularly following addition of the nucleosides to the media. However, significantly higher concentrations of 2'-C-methyladenosine triphosphate than 2'-O-methylcytidine triphosphate are detected, consistent with the greater potency of 2'-C-methyladenosine in the replicon assay, despite similar inhibition of NS5B by the triphosphates in the in vitro enzyme assays. Thus, the 2'-modifications of natural substrate nucleosides transform these molecules into potent inhibitors of HCV replication."

The 2'-C-methyladenosine and 2'-O-methylcytidine compounds referred to are the same compounds as those shown in Figure 6(a) and (b) of the second Walker and Hong article.

282. The Carroll paper was not referred to by Dr Brancale in his first report. (By contrast Prof Götte did refer to it in, and exhibit it to, his first report.) In his second report, Dr Brancale said (at paragraph 47) that the Carroll paper was "very widely read and known, not least because it was a peer reviewed article in a highly regarded scientific journal". In context, Dr Brancale was clearly suggesting that the Carroll paper had become common general knowledge by 27 June 2003, but his reasons for saying this are unconvincing, and even more so given that he did not mention it in his first report.

283. Furthermore, although Prof Götte agreed that the Journal of Biological Chemistry was one of the leading journals in the field and agreed that a biochemist with an interest in nucleoside research like himself would read it, there is no evidence that it was routinely read by all medicinal chemists with an interest in anti-HCV nucleoside research. Prof Götte accepted that the Carroll paper had subsequently come to be regarded as an important paper, but he did not agree that it was regarded as important

at the time. He himself had read the Carroll paper at the time, but that was because it related to his research interests.

284. Counsel for Idenix particularly relied upon a short passage of cross-examination in which Prof Götte accepted that the skilled team would be very interested in new reports of anti-HCV nucleotide analogues which had been found using the replicon assay. When counsel suggested that the Journal of Biological Chemistry would be one of the places "you" would be looking at for reports of important new anti-HCV analogues, Prof Götte replied "The Carroll paper". Whatever Prof Götte may have meant by this answer, which counsel did not attempt to elucidate, it was not put to him in this passage that the Carroll paper or its contents had become common general knowledge by 27 June 2003. I do not consider that Prof Götte can be taken to have accepted anything more than that the skilled team would have been very interested in the Carroll paper if they came across it.

285. Counsel for Idenix also relied upon two approximately contemporaneous articles which cited the Carroll paper: (i) Lieven Stuyver *et al*, "Dynamics of Subgenomic Hepatatis C Virus Replicon RNA Levels in Huh-7 Cells after Exposure to Nucleoside Antimetabolites", *J. Virol.*, 77, 10689-10694 (received 15 May 2003, accepted 10 July 2003, published October 2003); and (ii) an article by Claudio D'Abramo, Luciano Cellai and Prof Götte, "Excision of Incorporated Nucleotide Analogue Chain-terminators can Diminish their Inhibitory Effects on Viral RNA Polymerases", *J. Molec. Biol.*, 337, 1-14 (2004) (received on 26 August 2003, received in revised form on 5 January 2004, accepted on 14 January 2004 and published online on 30 January 2004). Both these articles cite the Carroll paper, among others, as part of their introductory background. Neither draws particular attention to it. Neither gives any indication that the authors expected their readers to be familiar with the citation.

286. Considering the evidence overall, I am not satisfied that it has been established that the Carroll paper was common general knowledge by 27 June 2003. Certainly, I do not consider that it has been shown that the common general knowledge extended beyond what was in the De Francesco and Rice article.

287. *The presentations at the Savannah conference*. The 16th International Conference on Antiviral Research ("ICAR 16") was held at Savannah, Georgia, USA between 27 April and 1 May 2003. ICAR is an annual meeting organised by ISAR which is focussed entirely on research into antiviral treatments. ICAR 16 brought together academics and a significant pharmaceutical industry presence: a number of the leading scientists in the field were on the organising committee and there were 21 corporate sponsors (including Gilead). Over 400 people attended the conference. One of these was Dr Brancale, whereas none of the other technical experts attended. Prof Götte explained that he went to the 5th biennial HEP DART conference in December 2003 instead. HEP DART is more geared towards clinical work, whereas ICAR has more of a bias towards medicinal chemistry. Prof Götte also explained that there were a number of other relevant conferences that researchers might attend. As Dr Brancale accepted, ICAR 16 would not have been attended by all medicinal chemists with an interest in anti-HCV nucleoside analogues.

288. Idenix rely on the first three presentations during Oral Session V: Hepatitis C Virus, Flaviviruses given at 8:30, 8:45 and 9:00 am respectively on 30 April 2003 (the third day of the conference) by teams of authors from Merck and two other organisations:

i) Eldrup *et al*, "Structure Activity Relationship of 2' Modified Nucleosides for Inhibition of Hepatatis C Virus";

ii) Bhat *et al*, "Synthesis and Pharmacokinetic Properties of Nucleoside Analogues as Possible Inhibitors of HCV RNA Replication";

iii) Olsen *et al*, "2' Modified Nucleoside Analogs as Inhibitors of Hepatatis C RNA Replication".

289. Abstracts of these presentations were included in the Conference Programme (Abstracts 119-121). The abstracts were also published in *Antiviral Research* volume 57 issue 3 dated February 2003, a copy of which was received by the University of Minnesota Bio-Medical Library on 30 April 2003. Although the abstracts say that a number of 2'-modified nucleosides have been identified as potent inhibitors of HCV, they give no indication of the nature of the 2'-modifications.

290. Dr Brancale was sufficiently interested in all three presentations to ask for copies of the authors' slides, which he subsequently received on a CD. He was thus able to exhibit copies of these to his first report. It can be seen from the slides that the authors presented data, in particular EC_{50} data from a replicon assay, showing that 2'-C-Me-Adenosine and 2'-C-Me-Guanosine (the two compounds referred to in the abstract of the Carroll paper) were potent inhibitors of HCV.

291. Although Dr Brancale was interested in these presentations, there was no mention of them in the highlights of the conference published in *ISAR News* volume 13 number 1 dated July 2003. There is no other evidence that they attracted any particular attention.

292. Dr Brancale's evidence was that, although the precise data presented in these presentations would not have been common general knowledge, he thought that the general message conveyed by them, namely that 2'-methyl-up-2'-hydroxy-down nucleoside analogues were showing very promising anti-HCV activity, would have been. Prof Götte disagreed. In my judgment the evidence falls a long way short of showing that even the general message conveyed by these presentations was common general knowledge by 27 June 2003.

293. *Knowledge of NM107.* Counsel for Idenix attempted during his cross-examination of Prof Götte to establish that it was common general knowledge that an Idenix compound identified as NM107 (or rather its prodrug NM283) had entered clinical trials by March 2003. Although this point was only mentioned in passing in Idenix's closing submissions, I shall deal with it for completeness. NM107 is in fact 2'-C-methyl-cytidine i.e. another 2'-methyl up-2'-hydroxy-down nucleoside analogue which is very similar in structure to the two Merck compounds discussed above.

294. The only evidence in support of the proposition that NM107/NM283 was in clinical trials by March 2003 is a statement in a publication called *the pharmaletter* dated 31 March 2003 that NM283 "is currently in Phase I/II trials". On the other hand, an abstract of a presentation by D.N. Stranding *et al* from IPI and collaborating institutions given at the 38th Annual Meeting of the European Association for the Study of the Liver on 29 March 2003 states that "regulatory filings to initiate human trials of NM283 are underway". Prof Götte disputed that NM107/NM283 was in

clinical trials by 27 June 2003. Even if Prof Götte was mistaken about this, there is no evidence that the matter was common general knowledge.

295. In any event, Prof Götte's evidence was that the structure of NM283 had not been disclosed by Idenix at this stage. Indeed, at the HEP DART conference in December 2003, the compound was referred to without disclosing its structure.

296. While on this topic, it is worth noting that (as Prof Götte discussed in an article he and two co-authors published in 2010) NM283 (also known as valopicitibine) did subsequently progress to Phase IIB clinical trials, but development of this drug was stopped due to toxicity issues and insignificant improvement with regards to treatment outcome.

297. *Overall conclusion*. Standing back and considering all four different aspects of the evidence together, I conclude that it has not been established that it was part of the skilled team's common general knowledge as at 27 June 2003 that 2'-methyl-up-2'-hydroxy-down nucleoside analogues had the potential to be efficacious in treating HCV.

The effect of substituting F for OH

298. A small, but important, issue which was explored in the evidence of Dr Brancale and Prof Boons concerns the effect of introducing a fluorine atom into a biologically active molecule such as a nucleoside, and in particular the effect of substituting F for OH.

299. Dr Brancale accepted that, in general, the introduction of a fluorine atom could seriously affect the stereoelectronic properties of a molecule and could lead to a dramatic change in the biological activity of nucleosides.

300. Counsel for Idenix suggested to Prof Boons in cross-examination, without any supporting evidence from Dr Brancale, that fluorine is an isostere of a hydroxyl group i.e. it has a similar size and therefore behaves similarly as a substituent. Prof Boons did not agree with this. As he pointed out, in terms of size, fluorine is similar to hydrogen, not a hydroxyl group. In addition, whereas a hydroxyl group can act as a hydrogen bond donor and acceptor, fluorine can only act as a hydrogen bond acceptor. It follows that changing a hydroxyl substituent to a fluorine one would be expected to affect the properties of the molecule in the ways which Dr Brancale accepted.

Predicting activity across the Flaviviridae family

301. The final area of dispute concerns the extent to which the skilled team would have regarded the activity of a nucleoside analogue against one species of the *Flaviviridae* family as predictive of its activity against another species. I do not understand it to be seriously disputed that, as stated in paragraph 107 above, the skilled team would have known that, in general, activity of a nucleoside analogue against one virus was not predictive of activity against another virus. But what if they were both members of the *Flaviviridae* family?

302. Prof Götte's evidence was that, even if activity against HCV were shown, a compound would need to be tested to see if it was active against other *Flaviviridae.* In the absence of data, it could not be assumed that it would have such activity. Although Prof Glenn suggested in his second report that a nucleoside's activity against one *Flaviviridae* virus "would be regarded as a good indication that it *might* also have activity against other viruses of this family [my emphasis]", in cross-examination Prof Glenn agreed that this was not necessarily the case, for example a nucleoside analogue could be active against HCV, but inactive against BVDV. Accordingly, although one could make an educated guess, one would need to test to find out whether a compound effective against one of the *Flaviviridae* would be effective against another.

Construction

303. I reviewed the principles applicable to the construction of patent claims at some length in *Actavis UK Ltd v Eli Lilly & Co* [2014] EWHC 1511 (Pat), [2014] 4 All ER 331 at [89]-[112]. As part of that review, I considered the law with regard to the use of the prosecution history as an aid to construction at [108]-[112].

The compound claims

304. Claims 1, 2 and 5 of the Patent are, on their face, pure compound claims. The general rule is that the validity of such claims must be assessed by reference to what is claimed and not by reference to what is said about the claimed invention in the specification: see *Conor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] RPC 28 at [17]-[19] (Lord Hoffmann) and *Eli Lilly & Co v Human Genome Sciences Inc* [2012] EWCA Civ 1185. [2013] RPC 22 at [18] (Sir Robin Jacob). In principle, it is possible for a patentee to claim a chemical compound, or a class of chemical compounds, that is novel and non-obvious and which the specification teaches the skilled person how to make. This is true even if the compound was *per se* one which was obvious to make, but there was no known way to make it and the inventor has devised a non-obvious way in which to do so: see *Generics (UK) Ltd v H. Lundbeck A/S* [2009] UKHL 12, [2009] RPC 13. Such a claim covers the compound even when made in other ways and regardless of the use to which the compound may be put (which may be quite different to that envisaged by the inventor).

305. Nevertheless, there are some cases in which the specification makes it clear to the skilled reader that, even though the claims are expressed as pure compound claims, it was not the inventor's intention to claim the compounds in the abstract and without reference to their intended use. In *Pharmacia Corp v Merck & Co Inc* [2001] EWCA Civ 1610, [2002] RPC 41 the patent in suit contained broad compound claims in Markush form (see claim 1 set out at [11]). The specification said that such compounds were anti-inflammatory, and in particular were gastric sparing by reason of their being COX II selective. Aldous LJ rejected the argument that functional limitations should not be read into the invention:

> "17. Mr Kitchin QC, who appeared for the patentees, drew attention to section 125 of the 1977 Act which provides that an invention 'shall, unless the context otherwise requires be that specified in a claim.' He then drew to our attention claims 1-12 which

claim chemical compounds. He submitted that they could be used for any purpose because they were claimed without limitation as to use. That was emphasised by the terms of claims 13 to 26 which claimed compounds which were therapeutically-effective as an anti-inflammatory and claims 21-30 which had to be effective for the particular complaints set out. It followed that the invention of claim 1 was the compounds themselves.

18. Mr Kitchin is correct that claims 1 to 12 do not include any limitation as to use. Thus when construed without recourse to the rest of the specification, the invention claimed is to the chemical compounds set out. But that construction makes the invention inconsistent with, amongst other passages, the description of the invention in the specification. It states that 'A class of compounds useful in treating inflammation-related disorders is defined by Formula 1'. I will deal with this submission and the other submissions on construction later in this judgment in the context in which they arise. But I will first decide whether the judge was right to accept Merck's submission which is set out in paragraph 42 of his judgment as to what was the 'invention' or 'technical contribution' in the specification:

> '42. On the other hand the defendants contended that the invention of the specification was a class of compounds substantially all of which were both anti-inflammatory and had significantly less harmful side effects than the existing NSAIDs. They further said that the specification taught only two mechanisms for reducing harmful side effects: to provide Cox II selectivity, and further to provide Cox I inactivity. They submitted that while gastric-sparing qualities might arise from other causes, so far as the specification was concerned the teaching was such that the addressee would understand that the inventor's contribution lay in a class of compounds which possessed Cox II/Cox I selectivity at least when assayed in the manner described in the specification. However, apart from a specific teaching in respect of the thiophenes at page 3 line 29 (see paragraph 27 above) the patent neither identifies the members of the claimed class which possess Cox II selectivity nor those which do not inhibit Cox I. The defendants contend that accordingly the teaching of the patent is that all the claimed classes, or at least all the thiophenes, possess Cox II selectivity, and moreover produce a reduced amount of side effects. This question as to the teaching of the specification is fundamental to the dispute between the parties. …'

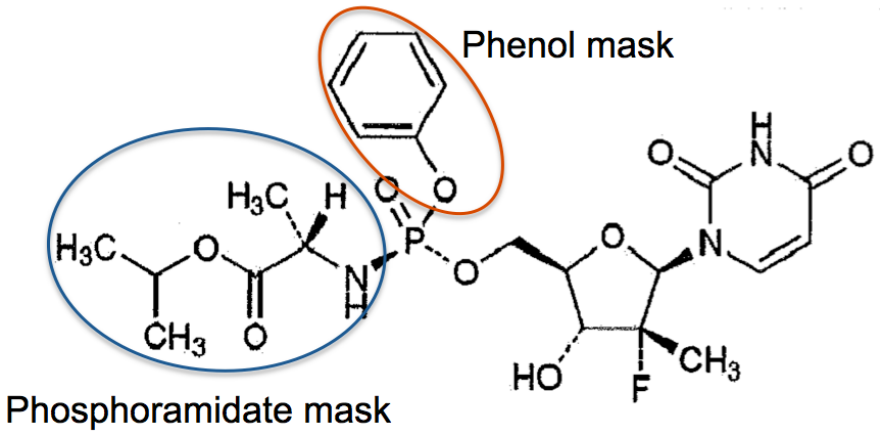
…

> 20. I agree with the judge. Nobody reading the specification could believe that the 'invention' was the compounds claimed in claim 1. The specification makes clear that the patentees had found a class of compounds that could be made which at least had anti-inflammatory action. It was that contribution that merited a 20 year monopoly. In my view the only question capable of argument is whether the compounds in the class were chosen merely for their anti-inflammatory action or because in addition they had reduced side-effects due to them being Cox II selective."

306. In the present case counsel for the parties agreed that the validity of claims 1, 2 and 5 should not be assessed on the basis that they were to be construed as pure compound claims, but rather as claims to compounds which had anti-*Flaviviridae* activity.

Phosphate

307. The first issue on construction concerns the term "phosphate" in claim 1. The dispute is only intelligible if the infringement issue which turns upon it is explained. It is common ground that sofosbuvir is a prodrug. In the case of sofosbuvir, the 5'-phosphate group is masked in order to assist the drug to permeate the cell membrane. As explained in more detail below, it is then metabolised to give the active form of the nucleoside analogue. The structure of sofosbuvir is shown below.



308. This diagram (Figure 28 in Dr Brancale's first report) identifies two masking groups: (i) one of the oxygen atoms of the phosphate group has been masked by esterification to form a phenol ester; and (ii) another oxygen atom has been masked by replacing it with an L-alanine isopropyl group to form a phosphoramidate.

309. As explained in more detail below, it is common ground that, subject to one point, the structure of sofosbuvir corresponds to Formula (IX) as defined in claim 1. The dispute concerns the R^1 substituent. Idenix contend that the phosphorous-containing part of sofosbuvir is a "phosphate", which is one of the possible R^1 substituents prescribed by claim 1. Gilead dispute this. Gilead's primary contention is that "phosphate" is limited to monophosphate, while Gilead's secondary contention is that it is limited to mono-, di- or triphosphate (see paragraph 58 above).

310. Since "phosphate" is a technical term, expert evidence is admissible as to its meaning. As always, however, what matters is not its acontextual, literal or primary meaning, but its meaning in the context of the Patent. Unlike some of the terms used in the claims, there is no definition of "phosphate" in the specification.

311. I will begin by considering Gilead's primary contention. Prof Götte's evidence was that "phosphate" meant a PO_4 group, i.e. monophosphate, and that it would not ordinarily be used as a collective term for all three phosphates. This receives support from a passage in the Recommendation on Nomenclature of Phosphorous-Containing Compounds of Biochemical Importance issued by the IUPAC-IUB Commission on Biochemical Nomenclature in 1976 (*Biochem. J.*, 171, 1-19 (1978)), which states (at page 3) that "'phosphate' means that all atoms attached to the phosphorous atom are oxygen atoms". Nevertheless, Prof Götte himself also said that the term "monophosphate" was usually used where it was necessary to draw a distinction between mono-, di- and triphosphates. This in itself suggests that "phosphate" can be used as a collective term for all three. This is indeed how the term is used in the well-known textbook by Alberts *et al*, *Molecular Biology of the Cell* (3rd ed, 1994) (at page 58), and Prof Götte accepted that this was not unreasonable. This accords with Dr Brancale's evidence.

312. More importantly, I agree with counsel for Idenix that Gilead's primary contention is at odds with the Patent. The specification refers at [0083] (corresponding to page 108 lines 16-24 of the Application, quoted in paragraph 201 above) to "alkylation, acylation or other lipophilic modification of the mono-, di- or triphosphate of the nucleoside", and then refers back to this as a replacement "on the phosphate moiety". Furthermore, the skilled team would know that the target enzyme in HCV, NS5B RNA-dependent RNA polymerase, interacts with triphosphates. The skilled team would also know that, in order to function as anti-viral drugs, nucleoside analogues generally undergo phosphorylation *in vivo* until they become triphosphates. Accordingly, the skilled team would conclude that it would make no sense for the Patent to exclude triphosphate from "phosphate".

313. Turning to Gilead's secondary contention, I think that it is reasonably clear that the term "phosphate" is ordinarily used and understood to mean a mono-, di- or tri-phosphate, and not to include a phosphoramidate (still less a phosphoramidate with a phenol ester attached). It does not necessarily follow, however, that the term cannot be used and understood in that way in a particular context. Idenix provided two examples of this happening outside the context of the Patent.

314. The first example is the substance commonly referred to as "creatine phosphate", but more correctly called "phosphocreatine". As Dr Brancale explained, creatine phosphate is a phosphoramidate. It is a phosphorylated molecule which acts as a rapidly-accessible reserve of phosphate in muscle fibres. It is used in phosphorylation of ATP after intense muscle activity, which is why some athletes take creatine-based supplements to assist their training. Counsel for Gilead put it to Dr Brancale that "creatine phosphate" was "a famous misnomer". It is true that it is strictly a misnomer, as can be seen from the IUPAC-IUB Recommendation, but that has not stopped it from being widely used, including in four scientific papers exhibited by Dr Brancale.

315. The second example is rather closer to the present context. Counsel for Idenix put to Prof Götte two papers on anti-HIV prodrug nucleoside analogues by Prof McGuigan's group in which the authors refer to phosphoramidates as "phosphates": McGuigan *et al*, "Aryl phosphate derivatives of AZT retain activity against HIV1 in cell lines which are resistant to the action of AZT", *Antiviral Research*, 17, 311-321 (1992) and McGuigan *et al*, "Phosphoramidate derivatives of d4T with improved anti-IV efficacy retain full activity in thymidine kinase-deficient cells", *Bioorg. & Med. Chem. Letters*, 6, 1183-1186 (1996). Prof Götte described this use of language as "sloppy". Strictly this is correct, but the fact remains that this is how a leading group of scientists in this field expressed themselves. I think it is tolerably clear that they were using the term "phosphate" as a form of shorthand in the expectation that, in context, that is how the reader would understand it.

316. How then would the term "phosphate" be understood by the skilled team in the context of the Patent? As usual, this requires consideration of what the skilled team would understand to be the technical purpose that lay behind the use of this term. Dr Brancale's opinion was that the skilled team would understand it to include a masked phosphate group as well as mono-, di- and triphosphates. His reasoning was that the skilled team would understand that a masked phosphate group would function as the phosphate part of the molecule, because *in vivo* it would be metabolised into a form which underwent phosphorylation to the triphosphate and then participated in the viral RNA replication. Furthermore, he pointed out that phosphoramidates and phosphate esters were well known classes of nucleoside prodrugs. Prof Götte's opinion was different, but he had no convincing answer to Dr Brancale's reasoning on this point.

317. Both counsel relied on the fact that the specification includes extensive discussions of prodrugs, and in particular makes express reference to phosphoramidates (see [0089] and [0091] corresponding to pages 110 lines 6-8 and page 111 line 1 – page 112 line 12 of the Application referred to in paragraph 202 above). Counsel for Idenix argued that the skilled team would appreciate from this the patentees could not have been intending to exclude such prodrugs from the scope of the invention and had contemplated the use of masking groups like phosphoramidates, whereas counsel for Gilead argued that the skilled team would note that the wording of the claims did not include references to "prodrugs" as opposed to "pharmaceutically acceptable salts" and that the patentees had distinguished between "phosphates" and "phosphoramidates". So far as this aspect of the issue is concerned, it seems to me that Gilead's argument is a purely linguistic one which carries little weight. Thus in the McGuigan articles referred to above, the authors use both the proper term "phosphoramidate" and the shorthand "phosphate". I consider that the skilled team would place greater weight on statements in the specification such as the statement in [0080] (corresponding to page 107 lines 21-30 quoted in paragraph 201 above) that "The active compound can be administered as any salt or prodrug that upon administration to the recipient is capable of providing directly or indirectly the parent compound" and the statement in [0083] (corresponding to page 108 lines 16-24 of the Application quoted in paragraph 200 above) that "The nucleosides described herein can be administered as a nucleotide prodrug".

318. Finally, counsel for Gilead relied on the prosecution history which I have described in paragraphs 222-225 above. So far as the amendment on 17 June 2009 is concerned, counsel pointed out that I had held in *Actavis v Lilly* at [112] that, in principle, a

limitation made to a claim to avoid an objection of lack of clarity could be relied on as aid to construction. I adhere to that view, but with the benefit of the arguments of the present case I would add that such an amendment is less likely to be a useful aid to construction than a limitation to avoid an objection of lack of support, which was the primary focus of my discussion in *Actavis v Lilly*. In the present case, the amendment relied on by Gilead is the excision of the wording referring to "a pharmaceutically acceptable leaving group" in order to meet the examiner's objection that this expression lacked clarity. In my judgment this does not assist Gilead. The clarity objection concerned the term "leaving group". The substance of the clarity objection was that this term was imprecise, so that the skilled person could not be sure whether a particular group was or was not a "leaving group". Idenix responded simply by omitting this term from the claim. The clarity objection did not concern the term "phosphate", and the amendment did not affect that term. Nor was there was any discussion of the meaning of that term or of whether the claim covered prodrugs in which the phosphate was masked. In these circumstances the amendment sheds no light on the meaning which the skilled team would understand the patentees to be conveying by use of the term "phosphate". It is neither here nor there that a masked phosphate such as a phosphoramidate would probably have constituted a leaving group falling within the excised wording. I would add that, on any view, the scope of the term "phosphate" is much narrower than that of the "leaving group" wording even if the two overlap.

319. As for the telephone conversation on 21 October 2013, this is even less helpful to Gilead's case, since Idenix's patent attorneys asserted essentially the same interpretation of "phosphate" as Idenix contend for now. The examiner took a different view, but that is immaterial.

320. Accordingly, I conclude that, purposively construed, the skilled team would interpret the term "phosphate" to include a masked phosphate group of the kind found in sofosbuvir.

Are the claims restricted to compounds which are for administration to a patient?

321. The second issue on construction only arises if Gilead are correct in their interpretation of "phosphate". Nevertheless I shall deal with it for completeness. As explained below, Gilead's answer to Idenix's claim for indirect infringement is that the claims are restricted to compounds which are for administration to a patient and do not extend to metabolites which have the structure of Formula (IX) as defined in the claims. Idenix dispute this interpretation.

322. Counsel for Gilead argued that the teaching of the Patent was to administer the compounds of Formula (IX) and that it did not teach the administration of different compounds which are metabolised to those compounds *in vivo*. I accept that, strictly speaking, this is correct. Nevertheless, as Dr Brancale pointed out, the extensive discussion of prodrugs and cleavable moieities in the specification would mean that the skilled team would have it well in mind that a substance could be administered in the form of a prodrug and then metabolised into the active form and that there could be advantages to proceeding in that way. In those circumstances I do not accept that the skilled team would understand the claims to be limited in the manner contended for by Gilead.

Priority of the Pharmasset PCT

323. Gilead can only rely on the Pharmasset PCT to attack the novelty of the Patent if the Pharmasset PCT is entitled to priority from US368. Idenix have not raised any issue concerning the disclosure of US368, but they dispute that Pharmasset Barbados was entitled to claim priority in respect of the invention disclosed in US368 at the time it filed the Pharmasset PCT. This has given rise to a complicated dispute involving disputed issues of primary fact, of foreign law and of domestic law. This part of the case amounted to a trial within a trial, involving as it did separate counsel, experts and factual witnesses to those engaged in the remainder of the case.

The right to priority: the legislative framework and earlier case law

324. The right to priority is governed by section 5 of the Patents Act 1977, which is one of the provisions declared by section 130(7) to be "so framed as to have, as nearly as practicable, the same effects in the United Kingdom as the corresponding provisions of the European Patent Convention … and the Patent Co-Operation Treaty". The corresponding provision of the EPC is Article 87 and the corresponding provision of the PCT is Article 8.

325. Prior to its amendment by the European Patent Convention 2000, paragraph 1 of Article 87 of the EPC provided:

> "Any person who has duly filed in or for any State party to the Paris Convention for the Protection of Industrial Property, an application for a patent or the registration of a utility model or for a utility certificate or for an inventor's certificate, or his successors in title, shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a period of twelve months from the date of filing of the first application."

326. Article 8 of the PCT provides:

> "(1) The international application may contain a declaration, as prescribed in the Regulations, claiming the priority of one or more earlier applications filed in or for any country party to the Paris Convention for the Protection of Industrial Property.
>
> (2)(a) Subject to the provisions of sub-paragraph (b), the conditions for, and the effect of, any priority claim declared under paragraph (1) shall be as provided in Article 4 of the Stockholm Act of the Paris Convention for the Protection of Industrial Property.
>
> (b) The international application for which the priority of one or more earlier applications filed in or for a Contracting State is claimed may contain the designation of that State. Where, in the international application, the priority of one or more national applications filed in or for a designated State is claimed, or where the priority of an international application

> having designated only one State is claimed, the conditions for, and the effect of, the priority claim in that State shall be governed by the national law of that State."

327. Article 87(1) of the EPC and Article 8 of the PCT both give effect to Article 4(A)(1) of the Paris Convention, which provides:

> "Any person who has duly filed an application for a patent, or the registration of a utility model, or of an industrial design, or of a trademark, in one of the countries of the Union, or his successor in title, shall enjoy, for the purposes of filing in the other countries, a right of priority during the periods hereinafter fixed."

328. In *Edwards Lifesciences AG v Cook Biotech Inc* [2009] EWHC 1304 (Pat), [2009] FSR 27 Kitchin J (as he then was) considered these provisions and concluded at [93]-[95]:

> "93. So art.4 specifies a person is to enjoy a right of priority if he has filed a relevant application for a patent or if he is the successor in title to such a person. Successor in title here must mean successor in title to the invention, as the parties before me agreed. Further, any person wishing to take advantage of the priority of such a filing must be required to make an appropriate declaration.
>
> 94. Both elements of art.4 are reflected in s.5 of the Act which requires a declaration made by the applicant which complies with the relevant rules and specifies one or more earlier relevant applications made by the applicant or a predecessor in title.
>
> 95. In my judgment, the effect of art.4 of the Paris Convention and s.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. In reaching this conclusion I derive a measure of comfort from the fact that the Board of Appeal of the EPO has adopted the same approach to the interpretation of art.87 EPC in two cases: J19/87 and T62/05."

329. In *KCI Licensing Inc v Smith & Nephew Plc* [2010] FSR 31 I had to consider a claim to priority from a US application filed in the name of a Mr Lina. One of the issues

was whether KC Inc had the right to claim priority by virtue of a confidentiality agreement signed by Mr Lina. Although the agreement was governed by the law of the State of Texas, USA, the parties were content to proceed on the basis that that law was the same as English law. I concluded that the agreement was effective to assign legal title to the invention to KC Inc. I went on:

> "69. I would add that, even if it was not effective to convey the legal title to the invention, paragraph 3 of the Confidentiality Agreement was plainly effective to transfer the entire beneficial interest in the invention, including the right to file patent applications in respect of it, from Mr Lina to KC Inc. KC Inc would have been entitled to demand that Mr Lina convey the bare legal title to the invention to itself at any time, and to compel Mr Lina to do so if he failed or refused to do it. If necessary, I would hold that that was sufficient to make KC Inc Mr Lina's '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.
>
> 70. I am encouraged so to hold by the decision of the Legal Board of Appeal in Case J19/87 *Burr-Brown/Assignment* [1988] EPOR 350 that an assignment of an invention and a patent application from A to B with a covenant of further assurance was sufficient to entitle B to claim priority from an application filed by A even though the assignment of the patent application was ineffective because it was not signed by B contrary to section 30(6) of the 1977 Act as it then stood. In holding that the priority claim was a good one, the Board (two of whose members were Peter Ford, later His Honour Judge Ford, and Gerald Paterson, later the author of *The European Patent System*) accepted an opinion from English counsel (Nicholas Pumfrey, later Pumfrey J) stating that (i) the assignment of the invention (which post-dated the making of the invention) was effective in law even though the assignment of the patent application was not, and (ii) although the assignment was ineffective in law B had acquired an equitable interest in the patent application which was a proprietorial interest. Although it could well be argued that point (i) was enough, the Board seems to have regarded point (ii) as significant as well.
>
> 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."

330. In *HTC Corporation v Gemalto SA* [2013] EWHC 1876 (Pat), [2014] RPC 9 at [134] Birss J expressed his agreement with the proposition that it was sufficient if the relevant person had acquired the entire beneficial interest in the invention at the relevant time.

Outline of the dispute

331. Mr Clark was employed by Pharmasset Georgia pursuant to a contract of employment dated 23 July 2001 ("the Clark Agreement"). Clause 16 of the Clark Agreement provides that it is governed by the law of the State of Georgia. There is no dispute that any invention disclosed in US368 was made by Mr Clark in the course of his employment with Pharmasset Georgia and subject to the terms of the Clark Agreement. The PCT was filed by Pharmasset Barbados. Gilead contend that Pharmasset Barbados was Mr Clark's successor in title by one of three routes:

    i) Mr Clark's rights to the invention vested in Pharmasset Georgia under the Clark Agreement. All such rights were assigned to Pharmasset Barbados by virtue of an agreement between Pharmasset Georgia and Pharmasset Barbados ("the R&D Agreement"), clause 8.12 of which provides that it is governed by the law of the State of Georgia ("Route 1").

    ii) If the R&D Agreement was not effective to transfer legal title in the invention, it was nevertheless effective to transfer the entire beneficial interest in the invention to Pharmasset Barbados ("Route 2").

    iii) All of Mr Clark's rights in the invention were assigned directly to Pharmasset Barbados as Pharmasset Georgia's "designee" under clause 6.2 of the Clark Agreement ("Route 3").

332. Gilead's case in respect of Route 1 is complicated by the fact that they have not been able to locate an executed copy of the R&D Agreement. Idenix contend that the explanation for this is that the R&D Agreement was never executed. In addition to this key factual issue, a number of other issues have arisen in relation to each of the three routes.

The facts concerning the R&D Agreement

333. Pharmasset Barbados and Pharmasset Georgia were incorporated following advice given to Dr Schinazi by PriceWaterhouseCoopers ("PWC") in a memorandum entitled "Pharmasset - Recommendations for Proposed Offshore Structure" dated 21 May 1998. PWC proposed that (what would become) Pharmasset Barbados would purchase technology (i.e. the rights in certain compounds) from universities and other sources throughout the world and engage (what would become) Pharmasset Georgia to undertake all research and development in the USA. PWC proposed two alternative arrangements as between Pharmasset Barbados and Pharmasset Georgia: (a) a costs sharing agreement, pursuant to which the development costs, intangibles and revenues would be shared between the two companies; and (b) a "costs plus" arrangement in which all of the development costs would be borne by Pharmasset Barbados. Pharmasset Barbados would acquire the intangible assets and retain the profits from licensing the same.

334. In the event, the costs plus arrangement was adopted. From the outset, it was agreed that: (i) the research and development would be undertaken by Pharmasset Georgia: (ii) the costs thereof would be paid by Pharmasset Barbados together with a 6% fee; and (iii) Pharmasset Barbados would own any intellectual property that was developed by Pharmasset Georgia. The intellectual property was to be owned by Pharmasset Barbados for tax reasons. Pharmasset Barbados would be able to sell any product that was developed, or to license any IP that was developed, and to receive the corresponding revenue and royalties. This income would be received in Barbados, where the tax rate was significantly lower than in the USA.

335. This agreement was documented in a draft of the R&D Agreement dated 9 December 1999 which was approved at a meeting of the board of directors of Pharmasset Barbados held in Maui, Hawaii on 11 December 1999. The meeting in Hawaii was also attended by representatives of Pharmasset Georgia, including Dr Schinazi (who was a director of both Pharmasset Barbados and Pharmasset Georgia), Mr Kuhl, Alan Roemer and Dr Michael Otto. Since all the important decisions relating to the conduct of the Pharmasset business were taken at the level of the Pharmasset Barbados board, and since the representatives of Pharmasset Georgia who attended the meeting agreed with the key terms of the R&D Agreement, it was probably thought unnecessary to convene a board meeting of Pharmasset Georgia to approve it.

336. A further possible reason for not convening such a meeting was that the two companies had always operated according to such terms and would continue to do so. Thus Pharmasset Barbados had paid, and continued to pay, for the research and development costs plus a 6% administrative fee; Mr Roberts had arranged, and continued to arrange, for confirmatory assignments of patent rights to be executed by Pharmasset Georgia's employee inventors in favour of Pharmasset Barbados; and patent applications had been, and continued to be, filed in the name of Pharmasset Barbados. Consistently with this, the R&D Agreement is expressed to have an Effective Date of 31 July 1998.

337. For important agreements like the R&D Agreement, Pharmasset's practice was that at least one of the Pharmasset Barbados signatures should be obtained in Barbados from a director who was located there, who was Martin Pritchard at the relevant times. The reason for this was that major contracts had to be signed outside the USA for tax purposes.

338. In early May 2000, however, it transpired that the R&D Agreement had not been signed. This oversight came to light following a request from PWC in Barbados for three documents and other information needed for a 1998 audit of Pharmasset Barbados which was faxed by PWC to Mr Kuhl on 22 April 2000. One of the documents requested was the "service fee agreement between Pharmasset Inc and Pharmasset Ltd" i.e. the R&D Agreement. Mr Kuhl asked Mr Roberts to help him gather the documents together. On 4 May 2000 Mr Roberts sent Mr Kuhl an email saying that he had a copy of the R&D Agreement, "but it has not yet been signed".

339. Neither Mr Kuhl nor Mr Roberts had a specific recollection of the steps which were taken following this discovery, but the documentary record indicates the following.

340. On 5 May 2000 Mr Kuhl sent Mr Roberts and Kathleen Metzger (Pharmasset's senior in-house lawyer at the time) an email, copied to Dr Schinazi, saying:

> "1. Let's have the PSL/PSI agreement signed and dated (December xx, 1999 – the date the B of D authorized it at the HI meeting). I suggest that it be signed for LTD in Barbados, the next time we have them sign documents. Kathleen or Alan could sign it.
>
> …
>
> Let's get all of this together early next week to be sent to PWC Barbados. We do not have to send a signed agreement to PWC, the fact that Board approved it is good enough."

341. On 15 May 2000 Mr Roberts made an electronic copy of a file entitled "Pharmasset RD 113099 Clean" which contained the draft R&D Agreement, removed the "Draft dated DATE" header from the text and printed it out. The R&D Agreement has five Exhibits identified as A to E. These exhibits have been located in a file bearing a post-it note in Mr Roberts' handwriting reading "Originals of final draft of Exhibits". Exhibit A is a list of patents and patent applications which was created in part by cutting and sellotaping tables of patents and patent applications photocopied from a Stock Purchase Agreement dated 4 June 1999 or some other source. Mr Roberts had a dim recollection of being involved in preparing these documents, perhaps assisting Ms Metzger.

342. The documentary evidence therefore suggests that preparations were made in mid May 2000 to have the R&D Agreement signed. The only evidence to support Gilead's case that the R&D Agreement was in fact executed, however, is Mr Roberts' recollection of having seen a signed copy bearing the signatures of Mr Pritchard and Dr Schinazi on behalf of Pharmasset Barbados together with two other signatures on behalf of Pharmasset Georgia made by persons whose names Mr Roberts could not recall. Mr Roberts could not recall when this happened, save that it was some time during his tenure at Pharmasset Georgia. Neither signature was particularly distinctive, nor were Mr Pritchard and Dr Schinazi identified by name in the document which Mr Roberts recalls that he saw. Mr Roberts' evidence was that the reason why this stuck in his mind was that it was the only time he could recall seeing an agreement signed on behalf of Pharmasset Georgia as well as Pharmasset Barbados. Every other document he could recall had only been signed on behalf of Pharmasset Barbados.

343. Counsel for Idenix accepted in his closing submissions that the terms of the R&D Agreement had been assented to by Pharmasset Barbados on 11 December 1999 and by Pharmasset Georgia in early-mid May 2000 (if not before). Furthermore, he did not suggest that the terms of the R&D Agreement were uncertain. Thus there is no dispute that there was a contract between the parties on those terms. Counsel submitted, however, that there were six factors which, taken together, compelled the conclusion that the R&D Agreement had never been signed.

344. First, no less than 12 versions of the R&D Agreement have been retained, spanning the period July 1998 to March 2001, some in electronic form and some in hard copy form. Furthermore, the final exhibits to the R&D Agreement have been retained, both in the original form and as a copy thereof. If the R&D Agreement had been signed, counsel submitted, an executed copy would exist, alongside the numerous drafts.

345. Secondly, the R&D Agreement was an important document for tax purposes, both prior to the merger with Pharmasset Delaware and thereafter. Accordingly, counsel submitted, if the R&D Agreement had been signed, an executed copy would have been retained.

346. Thirdly, counsel submitted that no plausible explanation has been given for the signed R&D Agreement having been lost. In his first witness statement, Mr Roberts suggested that the signed R&D Agreement could have been misplaced on one of two occasions: either during an archiving project when Pharmasset Georgia was in Atlanta or when Pharmasset Delaware moved its principal premises from Georgia to New Jersey in mid 2005. For the archiving project, a paralegal had been hired to remove documents, take them off site to be scanned and sort out the resulting electronic copies. In cross examination, Mr Roberts accepted that it was unlikely that one of the company's key documents would have been misplaced by the paralegal or the scanning service provider. If the document had not been misplaced during the archiving project, a scanned copy would exist in electronic form. Even if the original had been lost during the move to New Jersey, the electronic copy should exist.

347. Fourthly, it was Pharmasset's standard practice at the time to have two copies of every agreement signed, one for each party. No one has suggested that any documents were misplaced when Pharmasset Barbados was domesticated in June 2004. Furthermore, on Gilead's case, both originals have been lost.

348. Fifthly, Mr Roberts accepted that it was likely that, if the R&D Agreement had been signed, he would have made one or two copies and distributed them to whoever might be interested. Corporate documents were also kept by Ms Metzger, Mr Roemer, Dr Schinazi and William Brown (Ms Metzger's successor in 2002-2003). On Gilead's case, all copies of the signed R&D Agreement have also been misplaced.

349. Sixthly, Gilead did not lead evidence from anyone who might have signed the R&D Agreement. As a general principle, evidence is to be weighed according to the proof which it was in the power of one side to have produced, and in the power of the other to have contradicted: *Fairchild v Glenhaven Funeral Services Ltd* [2002] UKHL 22, [2003] 1 AC 32 at [13]. The absence of Dr Schinazi is particularly notable given that he was apparently involved in day-to-day operations and was copied in on Mr Kuhl's email dated 5 May 2000. According to Mr Roberts, if the R&D Agreement was to be signed and Dr Schinazi was involved, it would have been signed. Mr Kuhl's evidence was to the same effect. No reason has been given for Dr Schinazi's absence, however. The same is true of Mr Pritchard, Mr Roemer, Ms Metzger and Mr Brown.

350. These are powerful submissions. On the other hand, there are three factors which support the conclusion that the R&D Agreement was signed. First, as I have explained, there is documentary evidence that the R&D Agreement was prepared for signature in mid May 2000. Secondly, I found Mr Roberts' evidence that he recollected seeing a signed version of the R&D Agreement credible and persuasive. Thirdly, I have to consider the inherent probabilities: how likely is it that a document which was important for tax purposes and which had been specifically requested by PWC for the purposes of an audit was not signed? Furthermore, how likely is it that lightning struck twice i.e. that, having failed to get the R&D Agreement executed following the board meeting on 11 December 1999, Pharmasset again failed to do so following the request from PWC? Finally, how likely is it that, having gone to the

trouble of preparing the exhibits to the R&D Agreement so that it could be executed, Pharmasset nevertheless did not get it signed?

351. Although I am somewhat troubled by the absence of evidence from Dr Schinazi, Mr Pritchard, Mr Roemer, Ms Metzger and Mr Brown, I do not regard this as determinative. Let it be assumed that none of them has any recollection of either signing the R&D Agreement or seeing a signed version. I am still left with the documentary evidence, Mr Roberts' evidence and the inherent probabilities.

352. The most troubling point is the absence of any original or copy of the signed agreement. I agree with counsel for Idenix that, for the various reasons he gave, this is very hard to explain if the R&D Agreement was indeed signed. Nevertheless, it is not impossible. For example, it is possible, if unlikely, that there was only one original, that no copies were made of it and that the original was lost during the archiving project.

353. I am left to weigh the documentary evidence, Mr Roberts' evidence and the inherent probabilities which favour execution against the improbability of no copy of a signed agreement surviving if it was signed. On the balance of probabilities, I conclude that the R&D Agreement was signed.

Agreed principles of US law

354. The following principles of US law are agreed. Since they are agreed, it is not necessary for me to give authority for these principles. The numbering is that in the parties' agreement. I should explain that, as matters have turned out, not all of these principles are relevant to what is in issue. Nevertheless, I shall include them all for convenience and completeness.

355. *Application of Federal law and State law*. (1) Federal law pre-empts State law where they conflict.

356. (2) Federal law governs the requirements for a valid and enforceable assignment of present or future inventions, patents and patent applications.

357. (3) Federal law governs the question of whether contractual language effects a present assignment of patent rights or an agreement to assign such rights in the future. Basic contract issues (e.g. formation, construction, validity and enforcement) not inconsistent with Federal Law are determined by the state law that governs the agreement.

358. *Georgia State law - contractual requirements*. (4) A valid contract under Georgia Law requires:

i) parties that are able to contract;

ii) a consideration moving to the contract;

iii) the assent of the parties to the terms of the contract; and

iv) a subject matter upon which the contract can operate.

359. (5) To constitute a valid contract there must be a "meeting of the minds as to all essential terms" of the contract.

360. (6) What constitutes an essential term of a contract varies contract by contract.

361. (7) Where there has been mutual assent to all material terms, a binding agreement may be formed even in the event that immaterial terms have not yet been agreed.

362. (8) In determining whether there was mutual assent, courts apply an objective theory of intent whereby:

i) one party's intention is deemed to be the meaning a reasonable man in the position of the other contracting party would ascribe to the first party's manifestations of assent; or

ii) the meaning which the other contracting party knew the first party ascribed to his manifestations of assent.

363. Further, the circumstances surrounding the making of the contract, such as correspondence and discussions, are relevant in deciding if there was a mutual assent to an agreement.

364. (9) Assent may be given other than by signature. The presence of a signature is usually sufficient, but not necessary, to indicate mutual consent. The absence of a signature may indicate a lack of mutual assent. The ultimate answer depends on the facts.

365. (10) Signature cannot save an otherwise unenforceable agreement.

366. (11) Signature spaces in a written instrument do not in and of themselves mean that the signature of the parties is needed to form the contract, subject to the fact that it may indicate a lack of mutual assent (see paragraph 9 above).

367. *Georgia State law - contractual construction.* (12) The construction of a contract involves three steps. First, the trial court must decide whether the contract language is clear and unambiguous. If it is, the trial court simply enforces the contract according to its clear terms which are given their usual and common meaning; the contract alone is looked to for meaning. Next, if the contract is ambiguous in some respect, the court must apply the rules of contract construction to resolve the ambiguity. Finally, if the ambiguity remains after applying the rules of contract construction, the issue of what the ambiguous language means and what the parties intended must be resolved by the fact finder.

368. (13) One of Georgia's rules of contract construction is that a contract is to be construed by ascertaining the intention of the parties at the time they entered into the agreement.

369. (35) The rules of construction are applied only after it has been determined that a contract exists.

370. (14) A contract that may originally have been vague, indefinite and/or uncertain may later acquire more precision and become enforceable because of the subsequent words

or actions of the parties. Whether or not this is possible depends on the facts and how vague, indefinite and/or uncertain the Court considers the contract to be.

371. (15) The law leans against the destruction of contracts on the grounds of uncertainty and a contract will not be declared void on that ground unless, after reading it and interpreting it in the light of the circumstances under which it was made, and supplying or rejecting words necessary to carry into effect the reasonable intentions of the parties, their intention cannot be fairly collected and effectuated.

372. (16) A Court should avoid an interpretation of a contract which renders any of its terms meaningless or mere surplusage. The construction which will uphold a contract in whole and in every part is to be preferred and the whole contract should be looked to in arriving at the construction of any part.

373. (17) The existence of an unenforceable provision in a contract does not void the entire contract where a severability clause exists. Before deciding whether a contract provision is severable, a court must determine whether that provision is integral to the contract. The severance of an integral term is not allowed, even where the contract contains a severance clause. In determining whether a contract provision is severable, the question is whether the provision "is of the essence of the contract".

374. *Designee*. (18) "Designee" has not been explicitly defined nor does it have any special meaning under Georgia State law.

375. *Federal law – patent assignment requirements*. (19) To assign legal title in a patent application, patents, or any interest therein, the assignment must comply with section 261 of Title 35 of the United States Code ("35 USC §261") which reads:

> "Applications for patent, patents, or any interest therein, shall be assignable in law by an instrument in writing".

376. (20) In certain circumstances, legal title to a patent may be transferred by operation of law.

377. (21) Although no particular form of words is required to effect an immediate or automatic assignment of legal title to present or future patent rights, the instrument of transfer must be unambiguous and show a clear and unmistakable intent to part with such rights in the patent.

378. (22) Under Federal law, when considering whether there has been a valid transfer of patent rights (including the right to apply for future patents) under a given agreement, there is a distinction between wording which creates an immediate or automatic assignment (where the transfer of legal title occurs by operation of law and no further action by the holder of such rights is needed) and wording which creates an obligation to assign rights at a later date, requiring some future act by the holder of rights to transfer legal title.

379. (23) Federal statutes do not state that any particular form of words is required to effect an immediate and automatic assignment of legal title to present or future patent rights. However, the Federal Circuit has analysed particular forms of words and whether they do or do not effect an immediate and automatic assignment of legal title to present or

future patent rights. The following words have been held to create an immediate and automatic assignment of present or future patent rights:

i) "will assign and do hereby assign";

ii) "agrees to grant and does hereby grant";

iii) "agrees to and does hereby grant";

iv) "shall belong exclusively to [assignee] and [assignor] hereby conveys, transfers and assigns".

380. (24) The Federal Circuit has held that the following contractual language does not create an immediate and automatic assignment of patent rights and is instead merely an obligation to assign a future invention, patent application, or patent:

i) "shall be the property of [assignee], and all rights thereto will be assigned";

ii) "agree to assign";

iii) "will be assigned";

iv) "all such inventions which [assignee] in its sole discretion determines to be related to or useful in the business or research or development of [assignee], or which result from work performed by [assignee] shall be the sole and exclusive property of [assignee]…and [assignee] shall have the right to use and/or to apply for patents […]. [Assignor] further agrees to assist [assignee] in every proper way [..] to obtain, and from time to time to enforce, patents [..] and in enforcing the same, as [assignee] may desire, together with any assignments thereof to [assignee] or to persons designated by [assignee]".

381. (25) If an inventor chooses to assign all of his rights in an invention he no longer has any rights in the invention and he has nothing remaining to assign. Any subsequent attempt by the assignor-inventor to further assign his rights in his invention is a nullity.

382. (26) The requirements of 35 USC §261 apply to assignments between separate corporations within the same corporate structure.

383. *Equitable interest*. (27) Where there is a valid and enforceable immediate and automatic assignment of all the rights in an invention, patent application, or patent that does not yet exist, the assignee holds equitable title in the invention, patent application or patent. Upon the invention being made, the patent application being filed, or the patent being issued, the transfer of legal title occurs by operation of law without any further act being required.

384. (28) Where there is a valid and enforceable promise to assign in the future all the rights in an invention, patent application or patent that does not yet exist, the promisee holds equitable title in the invention, patent application or patent. Upon the invention being made, the patent application being filed, 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. Subject to principle (20) above, for a promisee holding

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.

385. (29) Georgia law recognises the concept of equitable rights. A party basing a claim on equitable title cannot rely on an unenforceable agreement, however an enforceable agreement gives a basis for asserting equitable title.

A disputed principle of Georgia law

386. Gilead, supported by Judge Birch, contend that the fact that the parties to a contract have a parent-subsidiary relationship is relevant to take into account when considering the circumstances surrounding the making of the contract for the purposes of determining whether there was mutual assent. Idenix, supported by Judge Fletcher, disagree. Given the concession that there was mutual assent, however, it is not necessary for me to resolve this dispute.

Disputed principles of Federal patent law

387. There are a number of principles of Federal patent law which are in dispute. For the reasons I shall explain, however, it is not necessary for me to resolve most of them. If I am wrong about that, I consider that the Court of Appeal would be in as good a position to resolve the issues as I am, since they do not turn upon the credibility of the expert witnesses.

388. The first issue is whether 35 USC §261 requires the signature of the assignor to effect the transfer of legal title in a patent application, patent or any interest therein. Having regard to my finding that the the R&D Agreement was signed, however, this issue falls away.

389. The second and third issues concern the principles regarding the assignment of a priority right and the meaning of "successor in title" under US law. In my judgment these are simply not relevant issues for me to determine. I am not concerned with the principles which US Federal patent law would apply to determine whether priority was validly claimed in the USA or to determine whether someone was a successor in title under US law. I am concerned solely with whether Gilead have a valid claim to priority in respect of the Pharmasset PCT in the United Kingdom. That question is governed by English law, albeit that English law should be interpreted consistently with the international treaties to which it is intended to give effect, namely the EPC, PCT and Paris Convention. US law only comes into the matter because (a) the agreements on which Gilead rely for their claim to priority are governed by Georgia law and (b) in certain respects, Georgia law is pre-empted by Federal patent law.

390. The fourth issue concerns the effect of 35 USC §118, which (as it applies to applications filed before 16 September 2012, when the America Invents Act came into force) provides:

> "Whenever an inventor refuses to execute an application for patent, or cannot be found or reached after diligent effort, a person to whom the inventor has assigned or agreed in writing

> to assign the invention or who otherwise shows sufficient proprietary interest in the matter justifying such action, may make application for patent on behalf of and as agent for the inventor on proof of pertinent facts and a showing that such action is necessary to preserve the rights of the parties or to prevent irreperable damage, and the Director may grant a patent to such inventor upon such notice to him as the Director deems sufficient, and on compliance with such regulations as he prescribes."

Again, however, I am not concerned with the circumstances in which applications for US patents may be filed.

391. Finally, there is a dispute regarding the question of equitable title. I shall consider this in context below.

Route 1

392. There is no dispute that, as between Mr Clark and Pharmasset Georgia, the Clark Agreement was effective to vest the rights to the invention described and claimed in US368 in Pharmasset Georgia. Having regard to my finding that the R&D Agreement was signed, there are two issues:

i) whether, on the proper construction of the R&D Agreement applying Georgia law, it amounted to an assignment, or at least an agreement to assign, as opposed to an exclusive licence of, the rights in the invention;

ii) whether, as so construed, the R&D Agreement amounted to an immediate assignment in accordance with Federal patent law.

393. The relevant terms of the R&D Agreement are as follows:

> **"WHEREAS,** [Pharmasset Barbados] is the owner of all right, title, and interest in certain intangible property in Exhibit A to this Agreement and Know-How relating to the Products (the 'Intellectual Property');
>
> …
>
> ARTICLE I
> DEFINITIONS
>
> …
>
> 1.7 Improvements. "Improvements" shall mean any findings, discoveries, inventions, additions, modifications, formulations, or changes made by either [Pharmasset Barbados] or [Pharmasset Georgia] during the term of this Agreement that relate to Intellectual Property or the Project.
>
> 1.11 Project or Projects. 'Project' or 'Projects' shall mean research project listed in Exhibit D to this Agreement.

…

ARTICLE III
GRANT OF RIGHT TO USE INTANGIBLE PROPERTY

…

3.3 Grant by [Pharmasset Georgia] [Pharmasset Georgia] grants to [Pharmasset Barbados] an exclusive, irrevocable, royalty-free right to use, develop, and enjoy any Improvements.

…

ARTICLE V
OWNERSHIP

5.1 Intellectual Property Ownership. [Pharmasset Georgia] acknowledges [Pharmasset Barbados]'s exclusive right, title, and interest in and to the Intellectual Property. [Pharmasset Georgia] shall not at any time do or cause to be done, or fail to do or cause to be done, any act or thing, directly or indirectly, contesting or in any way impairing [Pharmasset Barbados]'s right, title or interest in the Intellectual Property. Every use of any Intellectual Property by [Pharmasset Georgia] shall inure to the benefit of [Pharmasset Barbados].

5.2 Ownership of Rights. [Pharmasset Barbados] shall at all times, during or after the term of this Agreement, be the sole owner of all rights relating to or emanating from Intellectual Property, Know How, Improvements, or other matters developed in, or related to, a Project.

….

ARTICLE VIII
MISCELLANEOUS PROVISIONS

…

8.6 Further Assurances. Each party hereby covenants that it shall execute and deliver such deeds and other documents as may be required to implement any of the provisions of this Agreement.

...

8.9 Captions. Titles or captions of articles and paragraphs contaned in this Agreement are inserted only as a matter of convenience and for reference, and in no way define, limit, extend, or describe the scope of this Agreement or the intent of any provision hereof.

…"

394. Exhibit A provides as follows:

> "Pursuant to a License Agreement with the University of Georgia Research Foundation, Inc and Emory University dated June 16, 1998, [Pharmasset Barbados] was granted an exclusive right and license to the following intellectual property:
>
> [a list of patents and patent applications]
>
> Pursuant to a License Agreement with Emory University dated December 30, 1998, Emory granted to [Pharmasset Barbados] an exclusive right and license to the following intellectual property:
>
> [a list of patents and patent applications]
>
> Pursuant to a License Agreement with Emory University dated December 8, 1998, Emory granted to [Pharmasset Barbados] an exclusive right and license to the following intellectual property:
>
> [a list of patents and patent applications]
>
> Pursuant to a License Agreement with the University of Georgia Research Foundation, Inc, Emory University and the UAB Foundation, Inc, dated June 16, 1998, [Pharmasset Barbados] was granted an exclusive right and license to the following intellectual property:
>
> [a list of patents and patent applications]
>
> Pursuant to a License and Consulting Agreement with Craig Hill, Ph.D. ('Hill'), and Raymond F. Schinazi, Ph.D. ('Schinazi'), Hill granted to [Pharmasset Barbados] an exclusive sublicence and Schinazi granted to [Pharmasset Barbados] an exclusive license to the following intellectual property:
>
> [a list of patents and patent applications]
>
> Pursuant to a License and Consulting Agreement with Mahmoud H. el Kouni, Ph.D. ('el Kouni'), Fardos M.N. Naguib, Ph.D. ('Naguib') and Raymond F. Schinazi, Ph.D. ('Schinazi'), el Kouni and Naguib granted to [Pharmasset Barbados] an exclusive sublicence and Schinazi granted to [Pharmasset Barbados] an exclusive license to the following intellectual property:
>
> [a list of patents and patent applications]
>
> Pursuant to a License and Consulting Agreement with Jean-Pierre Sommadossi, Ph.D., Jean-Louis Imbach, Ph.D.

> ('Imbach'), and Gilles Gosselin, Ph.D. ('Gosselini'), Imbach and Gosselin granted to [Pharmasset Barbados] an exclusive sublicence and Schinazi granted to [Pharmasset Barbados] an exclusive license to the intellectual property related to '5-Fluorouracil Prodrugs and Derivatives of Nucleoside Anticancer Analogs."

395. Exhibit D lists six Projects, of which number 4 is as follows:

> "Hepatitis C Virus (HCV) Project:
>
> Drug discovery in nucleoside analogs to treat HCV involving:
>
> A. Development and production of novel compounds;
>
> B. Assays, active and proposed, of compounds;
>
> C. Further evaluation of promising compounds using preclinical models."

396. There is no dispute that the invention in US368 was conceived as part of Project number 4 in Exhibit D and therefore amounts to an "Improvement" within the meaning of the R&D Agreement.

397. *Construction of the R&D Agreement applying Georgia law*. Gilead contend that the R&D Agreement is an assignment of the rights to the invention, relying in particular upon clause 5.2. Counsel for Gilead submitted that the words "[Pharmasset Barbados] shall at all times … be the sole owner of all rights relating to … Improvements" were clearly intended to transfer ownership of the rights in Improvements.

398. Idenix contend that the R&D Agreement merely amounts to an exclusive licence, relying in particular upon clause 3.3. Counsel for Idenix submitted that clause 3.3 was perfectly clear: Pharmasset Georgia granted Pharmasset Barbados an exclusive licence to use, develop and enjoy any Improvements (but no more). He further submitted that there was no inconsistency between clause 3.3 and 5.2 because references to "ownership" of rights by Pharmasset Barbados in the R&D Agreement were references to it being an exclusive licensee. In support of the latter submission, he pointed out that the first preamble refered to Pharmasset Barbados as the "owner of all right, title and interest in … the Intellectual Property" and that clause 5.1 referred to Pharmasset Barbados's "exclusive right, title, and interest in and to the Intellectual Property". He submitted, however, that it was clear from Exhibit A that Pharmasset Barbados was merely an exclusive licensee in respect of the Intellectual Property.

399. So far as the last point is concerned, I should say straightaway that I do not know whether or not it is accurate to say that Pharmasset Barbados was merely an exclusive licensee in respect of the Intellectual Property. So far as I can ascertain, only one of the agreements referred to in Exhibit A is in evidence, namely the first one. While that does appear to be an exclusive licence, I do not know whether the same is true of the other agreements. This point causes me some concern, because counsel for Idenix only advanced this interpretation of Exhibit A in Idenix's closing submissions. Since it was not foreshadowed in Idenix's skeleton argument, Gilead did not have the

opportunity to adduce evidence addressing it. On the other hand, counsel for Gilead did not raise any objection on this ground. Nor did Gilead seek to put the other agreements before me. In the circumstances, I will assume that counsel for Idenix is correct about the effect of the agreements listed in Exhibit A.

400. In my judgment Gilead's construction of the R&D Agreement is the correct one, for the following reasons. First, on its face, clause 5.2 clearly and unambiguously provides that Pharmasset Barbados is to be the *sole owner* of *all rights* relating to Improvements made by Pharmasset Georgia. This is the language of ownership, not licence.

401. Secondly, this ties in with clause 5.1, which clearly provides that, at least as between Pharmasset Georgia and Pharmasset Barbados, Pharmasset Barbados has *exclusive right, title and interest in* the Intellectual Property. Again, this is the language of ownership, not licence. Given that the Improvements are ones that may relate to the Intellectual Property, as can be seen from clause 1.7, it makes sense for Pharmasset Barbados to be the owner of both the Intellectual Property and the Improvements, at least as between Pharmasset Barbados and Pharmasset Georgia.

402. Thirdly, the fact that Pharmasset Barbados may be an exclusive licensee of, rather than the owner of, the Intellectual Property, does not alter this conclusion. If Pharmasset Barbados is an exclusive licensee of the Intellectual Property, that implies that the Intellectual Property is owned by third parties who developed it. But the R&D Agreement envisages that the Improvements will be made by Pharmasset Georgia. Thus there will not be a third party owner of the Improvements.

403. Fourthly, it is fair to say that, on this interpretation of clause 5.2, clause 3.3 appears to be redundant. Agreed principle (16) indicates that the court should avoid an interpretation which renders any of a contract's provisions mere surplusage and must construe the contract as a whole. It is clear, however, that this principle is subject to the overriding principle of ascertaining and giving effect to the parties' intentions. For the reasons given above, I consider that the parties' intentions are clear from clause 5.2.

404. Fifthly, it is clear from the surrounding circumstances that it was the parties' intention that Pharmasset Barbados should own the Improvements, for tax reasons. It is also clear that the parties acted upon the understanding that this was the effect of the R&D Agreement. Thus it was Pharmasset Barbados which obtained confirmatory assignments from inventors like Mr Clark, Pharmasset Barbados which filed patent applications such as the Pharmasset PCT and Pharmasset Barbados which granted licences. Accordingly, to the extent that the R&D Agreement is ambiguous or uncertain, it should be interpreted to give effect to that intention and understanding in accordance with agreed principles (12), (13) and (14).

405. *Is the R&D Agreement an immediate assignment in accordance with Federal patent law?* In the alternative to their case that the R&D Agreement merely confers an exclusive licence of Improvements on Pharmasset Barbados, Idenix contend that it does not amount to an immediate assignment of future rights, but rather an agreement to assign in the future. This issue is governed by Federal patent law: agreed principle (3). Although I was referred to a number of decided US cases on this point, the

principles they establish are well summarised in agreed principles (22)-(24) and therefore it is unnecessary for me to cite them.

406. Counsel for Gilead submitted that the words "shall *at all times* … be the owner" in clause 5.2 clearly amounted to an immediate assignment of future rights. Counsel for Idenix submitted that it was merely an agreement to assign in future. Furthermore, he submitted that this conclusion was supported by clause 8.6.

407. In my judgment Gilead are correct that clause 5.2 amounts to an immediate assignment of future rights. If it had merely said "shall be the owner", then I would agree with Idenix. But as counsel for Gilead pointed out, the words "at all times" clearly mean that Pharmasset Barbados is to be the owner of the rights from the second that the R&D Agreement is assented to (or at least signed). This indicates that clause 5.2 is not merely binding Pharmasset Georgia to assign rights in the future, but rather is intended to have immediate effect. It is true that clause 5.2 does not use the language of assignment. As I have said, however, it uses the language of ownership, and it does so in a manner which indicates that it is intended to have immediate effect. That is sufficient to constitute an assignment.

408. Clause 8.6 does not detract from this conclusion. Covenants of further assurance of this kind are commonplace in assignments of intellectual property. They are useful even where there is no doubt about the legal effect of the assignment, for example, where there is a need to comply with particular formalities under a foreign law which the assignment may not comply with.

409. *Conclusion on Route 1*. For the reasons given above, I conclude that the R&D Agreement was effective to assign Pharmasset Georgia's rights in respect of the invention described and claimed in US368 to Pharmasset Barbados. Accordingly, Pharmasset Barbados was Pharmasset Georgia's successor in title, and hence Mr Clark's successor in title, to the invention at the time it filed the Pharmasset PCT. It follows that the Pharmasset PCT is entitled to priority from US368 in the UK.

Route 2

410. Gilead rely on Route 2 if either (a) the R&D Agreement amounts to an agreement to assign or (b) the R&D Agreement was not signed, but signature is a requirement for a valid assignment by virtue 35 USC §261. Since I have found that the R&D Agreement was signed, the later possibility falls away. I shall therefore consider Route 2 upon the assumption that the R&D Agreement is properly to be interpreted as an agreement to assign rights in Improvements in the future. On that hypothesis, Gilead contend that (i) at the date of filing the Pharmasset PCT, Pharmasset Barbados had equitable title to the invention, and (ii) that was sufficient to make Pharmasset Barbados Pharmasset Georgia's, and hence Mr Clark's, successor in title, in accordance with *KC Inc v Smith & Nephew* and *HTC v Gemalto*. Idenix take issue with both these propositions.

411. *Did Pharmasset Barbados have equitable title?* For reasons that will appear, the answer to this question may depend on what is meant by "equitable title".

412. It is convenient to start consideration of this issue by repeating that there is no dispute as to the following statements of US law (agreed principle (28)):

i) Where there is a valid and enforceable promise to assign in the future all the rights in an invention, patent application or patent that does not yet exist, the promisee holds equitable title in the invention, patent application or patent.

ii) Upon the invention being made, the patent application being filed, 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.

413. Despite the agreement on these points, Idenix contend that, under US law, the holder of equitable title in an invention in the sense covered by these points, does not own substantive rights in that invention unless and until it has obtained the legal title. Idenix say that US law is different to English law in this respect.

414. In support of this contention, Idenix argue that, by contrast with the position under English law (as to which see *Baxter International Inc v Nederlands Produktielaboratrium voor Bloedtransfusiapparatuur BV* [1998] RPC 250), under US law, the holder of equitable title in a granted US patent does not have standing to initiate infringement proceedings under 35 USC §281, which provides that "A patentee shall have remedy by civil action for infringement of his patent". Gilead disagree, but contend that this is irrelevant anyway since the issue before this court does not concern standing to sue for infringement of a granted US patent in the US courts.

415. I agree with Gilead that the question of standing to sue for infringement of a granted US patent in the US courts is irrelevant to the issue before this court. I am not concerned with a granted US patent, but with title to an invention at a time when no patent had been granted. Nor am I concerned with the ability of the (equitable) owner to bringing proceedings in a US court. Nor am I concerned with the ability of the (equitable) owner to obtain relief for infringement, particularly given that there was no question of infringement at at that time. What is relevant is the rights which Pharmasset Barbados had in respect of the invention described and claimed in US368 as at the date Pharmasset Barbados filed the Pharmasset PCT. Upon the assumption that the R&D Agreement constituted an agreement to assign all the rights in that invention in the future, it follows from agreed principle (28) that Pharmasset Barbados had equitable title to that invention and was able, if necessary, to bring proceedings to compel transfer of the legal title to it by Pharmasset Georgia.

416. In case I am wrong about that, I shall consider the relevant US law. The experts referred to four US authorities which bear upon this question: *Arachnid Inc v Merit Industries Inc* 939 F.2d 1574 (Fed. Cir., 1991); *J & J Manufacturing Inc v Logan* 24 F. Supp. 2d. 692 (E.D. Texas, 1998); *Propat International Corp v Rpost Inc* 473 F. 3d 1187 (Fed. Cir., 2007); and *Morrow v Microsoft Corp* 499 F.3d 1332 (Fed. Cir., 2007).

417. In my judgment these cases establish the following propositions:

i) The general rule is that a person seeking to recover damages for infringement of a US patent must have held the legal title to the patent during the period of the infringement.

ii) One exception to this is where an assignment of a patent is coupled with an assignment of the right of action for past infringements.

iii) Another exception is where the patentee transfers "all substantial rights in the patent", but not formal legal title, in which case the transferee has standing to sue for damages.

iv) The equitable owner of a patent may bring proceedings to compel transfer of the legal title to himself and may then bring separate proceedings for infringement of the patent, but in those separate proceedings he may only claim damages for infringement from the time he acquired legal title.

v) Once a plaintiff's claim to equitable ownership of a patent has been upheld by a court with jurisdiction over that question, the same court may then proceed to grant that plaintiff equitable relief against an infringer such as an injunction or an account of profits.

vi) Where a plaintiff claiming to be the equitable owner of a patent seeks the remedy of change of inventorship, he may also claim damages for infringement by the removed inventors.

418. Thus the equitable owner of a granted US patent does have standing to bring proceedings for infringement of the patent in US courts at least in some circumstances, but there are limitations on the remedies he can obtain. Even if standing to sue is relevant at all, I do not consider that these limitations upon the remedies which the equitable owner of a granted US patent can obtain in proceedings before US courts detract from Gilead's claim to priority.

419. *Is equitable title enough?* Counsel for Idenix submitted that I had been wrong to conclude in *KC Inc v Smith & Nephew*, and Birss J had been wrong to agree in *HTC v Gemalto*, that possession of equitable title to an invention was sufficient to make a party a "successor in title" for the purposes of a claim to priority, and that only legal title sufficed for this purpose. However, he abandoned part of his argument in support of this submission, which was based on the history of Article 4(A) of the Paris Convention, in the light of further materials concerning that history unearthed by counsel for Gilead. In those circumstances, it suffices to say that I was not persuaded by the remainder of the argument to reach a different conclusion on this issue.

420. *Conclusion on Route 2.* For the reasons given above, on the assumption that the R&D Agreement amounted to an agreement to assign the invention in US368, I conclude that Pharmasset Barbados was the equitable owner of that invention at the time of filing the Pharmasset PCT and that this was sufficient to make Pharmasset Barbados Pharmasset Georgia's, and hence Mr Clark's, successor in title for the purposes of Gilead's claim to priority.

Route 3

421. In view of my conclusions with respect to Routes 1 and 2, I shall deal with Route 3 briefly. For this purpose I shall assume that the R&D Agreement amounts to at least an agreement to assign, but nevertheless neither Route 1 nor Route 2 works for one reason or another. Clause 6.2 of the Clark Agreement provides, so far as material:

> "Employee hereby assigns and agrees to assign to [Pharmasset Georgia], its successors, assigns, or designees, all of Employee's rights to inventions …"

422. Gilead contend that Pharmasset Barbados was Pharmasset Georgia's "designee". Gilead rely primarily upon the R&D Agreement as designating Pharmasset Barbados as the owner of the invention. In the alternative, Gilead rely upon the conduct of the parties, such as the execution by Mr Clark of a confirmatory assignment in favour of Pharmasset Barbados on 16 October 2003 and the filing of the Pharmasset PCT by Pharmasset Barbados, both of which were clearly done with Pharmasset Georgia's consent.

423. Idenix's answer to Gilead's primary case is that the R&D Agreement is predicated upon Pharmasset Georgia having rights to convey to Pharmasset Barbados, whereas the effect of designation would be to divert rights directly from Mr Clark to Pharmasset Barbados.

424. As I observed earlier, however, clause 5.2 of the R&D Agreement does not use the language of assignment, it uses the language of ownership. I see no reason why this aspect of the agreement cannot take effect through the mechanism of designation rather than the mechanism of assignment. Accordingly, I would if necessary hold that the Pharmasset PCT was entitled to priority through Route 3. It is not necessary to consider Gilead's alternative case.

Novelty

425. Idenix do not dispute that, if the Pharmasset PCT is entitled to priority, then all the claims of the Patent other than claims 20 and 37 lack novelty. Since I have concluded that the Pharmasset PCT is entitled to priority, it follows that all the other claims are invalid on this ground.

Inventive step

426. Gilead contend that all of the claims of the Patent are invalid on the ground that they lack an inventive step. Gilead's case is not the more conventional kind of case that it would be obvious to take the step from a specific item of prior art to the claimed invention, but rather that the claimed invention is not inventive because it makes no technical contribution to the art.

The law

427. Although this is an area of the law which I have considered before, given that it is a relatively new and developing area of jurisprudence and given its importance in the present case, I shall review it again.

428. In the leading case of T 939/92 *Agrevo/Triazoles* [1996] EPOR 171 the patent application claimed chemical compounds consisting of a class of triazole derivatives defined by reference to a Markush formula. The specification asserted that these compounds had herbicidal activity, but it only contained test results for some of the compounds. The main issue on the appeal was whether the claims complied with the

requirement for an inventive step in accordance with Article 56 EPC. In its decision the Technical Board of Appeal began its consideration of this issue by observing:

> "2.4.2 … it has for long been a generally accepted legal principle that the extent of the patent monopoly should correspond to and be justified by the **technical contribution** to the art …. Now, whereas in both the above decisions this general legal principle was applied in relation to the extent of the patent protection that was justified by reference to the requirements of Articles 83 and 84 EPC, the same legal principle also governs the decision that is required to be made under Article 56 EPC, for everything falling within a valid claim has to be inventive. If this is not the case, the claim must be amended so as to exclude the obvious subject-matter in order to justify the monopoly.
>
> Moreover, in the Board's judgment, it follows from this same legal principle that the answer to the question what a skilled person **would have done** in the light of the state of the art depends in large measure on the technical result he had set out to achieve. In order words, the notional 'person skilled in the art' is not to be assumed to perform a particular act without some concrete technical reason; he must, rather, be assumed to act not out of idle curiosity but with some specific technical purpose in mind."

429. The Board went on to consider the position on the basis that (as the Board put it at 2.5):

> "… if the claimed compounds were to be assumed not to have any technically useful property, then it could be postulated that the technical problem which is solved by the claimed compounds … would be the minimalist one in such a situation, namely the mere provision of further (or alternative) chemical compounds as such, regardless of their likely useful properties."

430. Although the Board was not convinced that, in the absence of any technically useful properties, the claimed compounds could be regarded as being a technical invention at all, it nevertheless considered whether the person skilled in the art would have considered the claimed compounds as a solution of that problem. The applicant argued that, even on the basis of known starting compounds and known synthetic methods, the skilled person would have faced an unlimited number of possibilities for solving this problem, and that a particular selection from that unlimited number was inventive, even if it was arbitrary, unless there was a direct pointer to the preparation of these particular compounds in the prior art. The Board rejected this argument for the following reasons:

> "2.5.3 … The answer to the question as to what a person skilled in the art would have done depends on the result he wished to obtain, as explained in point 2.4.2 above. If this result is only to be seen in obtaining further chemical compounds, then all known chemical compounds are equally suitable as the starting point for structural modification, and no inventive skill needs to be exercised in selecting,

> for instance, the compound of formula XIV of D3 for this purpose. Consequently, all structurally similar chemical compounds, irrespective of their number, that a skilled person would expect, in the light of the cited prior art, to be capable of being synthesised, are equally suitable candidates for solving such a hypothetical 'technical problem' to the skilled person, and would therefore all be equally 'suggested' to the skilled person. It follows from these considerations that a mere arbitrary choice from this host of possible solutions of such a 'technical problem' cannot involve an inventive step ... In other words, the Board holds that, in view of the underlying general legal principle set out in point 2.4.2 above, the selection of such compounds, in order to be patentable, must not be arbitrary but must be justified by a hitherto unknown technical effect which is caused by those structural features which distinguish the claimed compounds from the numerous other compounds. …
>
> 2.5.4 It follows directly from these considerations that a technical effect which justifies the selection of the claimed compounds must be one which can be fairly assumed to be produced by **substantially all** the selected compounds. …"

431. The Board then proceeded to consider the position on the basis of the asserted herbicidal activity of the claimed compounds. As the Board explained at 2.6:

> "… the Board holds that, contrary to the appellant's submission, the assessment of the technical contribution to the art must take account of the actual technical reason for providing the very compounds now being claimed, as distinct from the host of other theoretically possible modified chemical compounds. In this respect, the description (see page 3, lines 1 and 2) asserts that all claimed compounds do have herbicidal activity. Herbicidally active chemical compounds which are structurally similar to the claimed ones, since they are also triazole derivatives, are known from D3, D7 and D8 (see point 2.3.1 and 2.3.2 above). Any one of these documents may therefore serve as the 'closest state of the art' in the present case.
>
> In view of this state of the art the technical problem which the present patent application **asserts** to solve is the provision of further (alternative) chemical compounds with herbicidal activity.
>
> However, in the light of the Board's finding in point 2.4.3 above, **this technical problem could only be taken into account if it could be accepted as having been solved**, that is, if, in deciding the issue under Article 56 EPC, it would be credible that substantially all claimed compounds possessed this activity (see also point 2.5.4 above). Accordingly, the Board has examined whether this requirement is fulfilled."

432. The Board concluded that it was not credible that substantially all the claimed compounds possessed herbicidal activity for the following reasons:

> "2.6.2 In the present case, the appellant's submission that the test results contained in the description show that **some** of the claimed compounds are indeed herbicidally active cannot be regarded as sufficient evidence to lead to the inference that substantially **all** the claimed compounds possess this activity. The reason for this is that there is no proven common general knowledge to show that the type of substituent that may be present in the claimed compounds would be irrelevant to the existence of the alleged herbicidal activity. On the contrary, the Board accepts the appellant's own submission that the structural differences between the compounds disclosed, for example, in D3, D7 and D8 on the one hand, and the claimed compounds on the other hand, are such that a person skilled in the art would have been unable to predict on the basis of his common general knowledge that the claimed compounds would have herbicidal activity …., and that it can therefore be accepted as undisputed common general knowledge that even small structural modifications may cause major differences in biological activity. Nevertheless, it is also well accepted that the properties of chemical compounds do indeed largely depend on their chemical structure, and that a skilled person would therefore normally expect that the properties of two compounds would become the more similar the more similar their chemical structures became …. In view of all the above considerations, the Board finds that reasonable predictions of relations between chemical structure and biological activity are in principle possible, but that there is a limit beyond which no such prediction can be validly made.
>
> 2.6.3 In the Board's judgment, this limit has to be established on the basis of the available facts and the evidence submitted for this purpose in each particular case …
>
> …
>
> 2.6.5 In the tests which are reported on pages 37 to 40 of the description, a great number of compounds was used. However, in all these compounds R^1 was always either unsubstituted phenyl or 2-pyrimidinyl optionally substituted by methyl groups and R^3 was always phenyl substituted by halogen atoms or methyl groups. Thus, despite the number of tested compounds, these test results do not support the alleged herbicidal activity of compounds in which, for example, the phenyl ring in position R^3 may be substituted by absolutely anything, having regard to the common general knowledge relied on by the appellant himself, namely that the influence of structural modifications on the desired herbicidal activity is unpredictable.

> 2.6.6 Such an allegation is likewise not supported by the content of documents D3, D7 and D8, which all disclose classes of herbicidally active compounds with limited substitution possibilities (see point 2.3.1 and 2.3.2 above).
>
> 2.6.7 The appellant had been informed about the insufficiency of the evidence submitted by him in the present case, and had also been given ample opportunity either to restrict his claims to such a group of compounds for which the Board was prepared to accept the credibility of their alleged herbicidal activity (see point III above), or to provide further evidence, either by test results or by other means, that in the present case the kind of substitution of the phenyl ring R^3 is not relevant to the herbicidal activity. Despite these clear and helpful leads, which the Board was not obliged to afford, neither appropriate amendments nor further evidence were forthcoming.
>
> 2.7 For these reasons, and on the basis of what evidence there is in the case, the Board is not satisfied that substantially **all** compounds now being claimed are likely to be herbicidally active. Since, as set out above in points 2.4.2, 2.5.4 and 2.6, only those of the claimed chemical compounds could possibly involve an inventive step which could be accepted as solutions of the technical problem of providing further **herbicidally active** compounds, the subject-matter of the main request extends to compounds which are not inventive and therefore does not meet the requirement of Article 56 EPC."

433. In T 1329/04 *Johns Hopkins/Factor-9* the application claimed a polynucleotide of a particular sequence ID encoding a polypeptide having a particular sequence ID identified as "growth differentiation factor-9" (GDF-9) which was asserted to be a member of the transforming growth factor-β (TBF-β) family (and hence to have activity as a growth differentiation factor).

434. The Technical Board of Appeal held that, starting from prior art document 3, the problem to be solved could be defined as the isolating a further member of the TBF-β family. The solution provided was the claimed polynucleotide encoding the claimed polypeptide. The question was whether this solution plausibly solved the problem i.e. whether or not it was plausible that the claimed molecule constituted a further member of the TBF-β family. The Board held that it did not for following reasons:

> "8. Furthermore, as already mentioned above, members of the TGF-Beta superfamily share sequence homology. In the part of the application as filed describing the prior art related to the invention (page 2), it is disclosed that subgroups in the family had been defined according to the percentage of homology between members, the members of a given subgroup being from 70% to 90% homologous. Here, GDF-9 is very far from fulfilling this criteria as its sequence is stated to be significantly divergent from those of other family members (cf. page 28), the maximal percentage of homology which was

observed being 34% with the bone morphogenetic protein, BMP-4. This implies that GDF-9 cannot be attributed to any subgroup and, thus, must at best be considered as the first member of a yet unidentified subgroup. This finding and that in point 7 lead to the conclusion that, contrary to GDF-1 in document (3), GDF-9 cannot be clearly and unambiguously identified as a member of the TGF-Beta superfamily by only using a 'structural approach'.

9. Of course, the situation could most probably be looked at differently if it had been demonstrated in the application as filed that GDF-9 played a role similar to that of the transforming factor-Beta (as was the case for all of the factors which initially served to define the superfamily). Yet, **there is no evidence at all in this respect**. In fact, the application only discloses that expression of GDF-9 is localised in ovarian tissues, which per se is useful but insufficient information in relation to any function the molecule might have.

10. As already pointed out above (cf. point 8), in the application (page 28), it is admitted that '..., the sequence of GDF-9 is significantly diverged from those of other family members'. Yet, functions of members of the TGF-Beta superfamily previously isolated from ovarian follicular fluid (inhibins) or shown to inhibit ovarian cancer (MIS) are recited, and tentatively and presumptively attributed to GDF-9. Further putative roles are also suggested for GDF-9 which cover some of the effects observed with TGF-Beta (paragraphs bridging pages 8 and 9). At oral proceedings, it was argued that speculations of this kind should be permitted because of the 'first to file approach' of the European patent system which forced the applicant to cover any and all subject-matter connected with its invention. The board is unable to endorse this reasoning. On the contrary, in a first-to-file system the (earlier) filing date of the application, not the date at which the invention was made determines to whom of several persons having made an invention independently of each other, the right to a European patent belongs (cf. Article 60(2) EPC). Hence, it is particularly important in such a system that the application allows to conclude that the invention had been made, i.e. that a problem had indeed been solved, not merely put forward at the filing date of the application. Therefore, the issue here is rather how much weight can be given to speculations in the application in the framework of assessing inventive step, which assessment requires that facts be established before starting the relevant reasoning. In the board's judgment, enumerating any and all putative functions of a given compound is not the same as providing technical evidence as regard a specific one.

> 11. Accordingly, as a significant structural feature fails to be identical in TGF-9 and the members of the TGF- Beta superfamily, and no functional characterisation of TGF-9 is forthcoming in the application, it is concluded that the application does not sufficiently identify this factor as a member of this family i.e. that there is not enough evidence in the application to make at least plausible that a solution was found to the problem which was purportedly solved."

435. The Board went on to hold that the applicant was not assisted by post-published evidence establishing GDF-9 was indeed a growth differentiation factor for reasons it expressed at 12 as follows:

> "This cannot be regarded as supportive of an evidence which would have been given in the application as filed since there was not any. The said post-published documents are indeed the first disclosures going beyond speculation. For this reason, the post-published evidence may not be considered at all. Indeed, to do otherwise would imply that the recognition of a claimed subject-matter as a solution to a particular problem could vary as time went by. Here, for example, had the issue been examined before the publication date of the earliest relevant post-published document, GDF-9 would not have been seen as a plausible solution to the problem of finding a new member of the TGF-Beta superfamily and inventive step would have had to be denied whereas, when examined thereafter, GDF-9 would have to be acknowledged as one such member. This approach would be in contradiction with the principle that inventive step, as all other criteria for patentability, must be ascertained as from the effective date of the patent. The definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve. Therefore, even if supplementary post-published evidence may in the proper circumstances also be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve."

436. In *Conor v Angiotech* (cited above) claim 12 was to a taxol-coated stent "for treating or preventing restenosis", which the House of Lords construed as meaning that it would prevent or treat restonsis. The issue was whether claim 12 was obvious. In holding that it was not, Lord Hoffmann said:

> "28. The question was whether [the fact that a taxol-coated stent would prevent or treat restonsis] was obvious and not whether it was obvious that taxol (among many other products) *might* have this effect. It is hard to see how the notion that something is worth trying or might have some effect can be described as

> an invention in respect of which anyone would be entitled to a monopoly. …
>
> 29. It is true that a patent will not be granted for an idea which is mere speculation, unsupported by anything disclosed in the specification. Art.84 of the EPC says that the claims must be 'supported by the description' ….
>
> 31. In this case, however, the patent had been granted by the EPO and Art.84 was therefore no longer in issue. There is also a line of authority in the EPO in which claims to broad classes of chemical compounds alleged to have some common technical effect have been rejected under Art.56 (obviousness) when there was nothing to show that they would all have that technical effect. …"

437. Having reviewed *Agrevo* and *Johns Hopkins*, Lord Hoffmann went on:

> "36. These cases are in my opinion far from the facts of this case. The specification did claim that a taxol coated stent would prevent restenosis and Conor did not suggest that this claim was not plausible. That would have been inconsistent with the evidence of its experts that taxol was just the thing to try. It is therefore not surprising that implausibility was neither pleaded nor argued. ….
>
> 37. The Court of Appeal upheld the judgment of Pumfrey J. on the ground that the patent contained no 'disclosure' saying that taxol was specially suitable for preventing restenosis. Again, I agree that the description, though offering a theory (its anti-angiogenic properties) as to why taxol would prevent restenosis, did not offer any evidence that this would turn out to be true. If it had not turned out to be true, the patent would have been insufficient. But there is in my opinion no reason as a matter of principle why, if a specification passes the threshold test of disclosing enough to make the invention plausible, the question of obviousness should be subject to a different test according to the amount of evidence which the patentee presents to justify a conclusion that his patent will work."

438. In *Dr Reddy's Laboratories (UK) Ltd v Eli Lilly & Co Ltd* [2009] EWCA Civ 1362, [2010] RPC 9 Jacob LJ said:

> "50. … The EPO jurisprudence is founded firmly around a fundamental question: has the patentee made a novel non-obvious technical advance and provided sufficient justification for it to be credible? That is the basis of all the reasoning – see e.g. [2.4.2] of *AgrEvo*. A 'selection' (by which I mean the later claimed compound or sub-class) which makes a real technical advance in the art is patentable.

> 51. More specifically Mr Carr contended that a sub-class or individual member of a prior art published class was taken to be obvious if it was a random selection from the earlier published class. I have no difficulty with that. Such a 'selection' provides no technical contribution. Mankind can learn nothing from it. Nor indeed does Lilly dispute that proposition. It said in its skeleton argument: 'Lilly does not dispute that in relation to obviousness a selection from the prior art cannot be merely arbitrary.'
>
> 52. Of course one has to consider here what is meant by an 'arbitrary selection'. The answer is to be found in the guiding principle – is there a real technical advance?"

439. In the same case Lord Neuberger of Abbotsbury MR said at [104]:

> "... the Board's approach in cases such as these is consistent and clear, and it is based on its general approach to patent validity on novelty and obviousness. There is nothing in the 1977 Act (any more than there was in the 1949 Act, it is fair to say) which recognises, or even implies, a special approach to, or even the existence of, selection patents as a special category of patent, which require a different approach when determining validity from other patents… "

440. Having reviewed these authorities in *Sandvik Intellectual Property AB v Kennametal UK Ltd* [2011] EWHC 3311 (Pat), [2012] RPC 23, I concluded at [185] as follows:

> "Where it is suggested that a claimed invention is obvious as being an arbitrary selection, the key question is whether the specification 'passes the threshold test of disclosing enough to make the invention plausible' as Lord Hoffmann put it in *Conor v Angiotech*, that is to say, to make it plausible that the selection has the technical significance claimed for it."

441. Since then, the matter has been considered by the Court of Appeal in *Generics (UK) Ltd v Yeda Research & Development Co Ltd* [2013] EWCA Civ 925, [2014] RPC 4, where Floyd LJ said at [39]:

> "As with any consideration of obviousness, the technical results or effects must be shared by everything falling within the claim under attack. This follows from the fundamental principle of patent law, which underpins many of the grounds of objection to validity, that the extent of the monopoly conferred by a patent must be justified by the technical contribution to the art. If some of the products covered by a claim demonstrate a particular property, but others do not, then the technical problem cannot be formulated by reference to that property. Either the products which do not exhibit the property must be excised from the claim by amendment, or the problem must be

> formulated by reference to some other, perhaps more mundane, technical contribution common to the whole claim."

442. Having reviewed *Agrevo*, *Johns Hopkins*, *Conor* and *Dr Reddy's*, he summarised the position at [49] as follows:

> "(i) Article 56 of the EPC is in part based on the underlying principle that the scope of the patent monopoly must be justified by the patentee's contribution to the art.
>
> (ii) If the alleged contribution is a technical effect which is not common to substantially everything covered by a claim, it cannot be used to formulate the question for the purposes of judging obviousness.
>
> (iii) In such circumstances the claim must either be restricted to the subject matter which makes good the technical contribution, or a different technical solution common to the whole claim must be found.
>
> (iv) A selection from the prior art which is purely arbitrary and cannot be justified by some useful technical property is likely to be held to be obvious because it does not make a real technical advance.
>
> (v) A technical effect which is not rendered plausible by the patent specification may not be taken into account in assessing inventive step.
>
> (vi) Later evidence may be adduced to support a technical effect made plausible by the specification.
>
> (vii) Provided the technical effect is made plausible, no further proof of the existence of the effect is to be demanded *of the specification* before judging obviousness by reference to the technical effect propounded."

443. As counsel for Idenix pointed out, the question of what is meant by "plausible" has also been considered in the context of an objection of lack of industrial applicability by the Supreme Court in *Human Genome Sciences Inc v Eli Lilly & Co* [2011] UKSC 51, [2012] RPC 6, where Lord Hope said at [149]:

> "I would not quarrel with Jacob L.J.'s comment, after consulting the *Shorter Oxford English Dictionary*, that the sense [the word 'plausibly'] conveys is that there must be some real reason for supposing that the statement is true: para. 111. The important point, however, is that the standard is not any higher than that."

The same sense is conveyed by some of the other expressions which can be found in the case law on industrial applicability, and which are mentioned by Lord Neuberger in his judgment in that case, such as "reasonably credible".

Assessment

444. I shall preface my consideration of this issue with three preliminary points. The first is that the claims of the Application were stupendously broad. They could well have covered as many as a trillion compounds. Furthermore, it was common ground between Prof Götte and Dr Brancale that it was not plausible that all the compounds claimed would be effective against *Flaviviridae*. Counsel for Gilead characterised the Application as a "land grab", and in my view that is a fair description. It does not necessarily follow that the Patent is invalid, however.

445. Secondly, for the reasons explained above, it is common ground that, so far as the compound claims are concerned, inventive step should be assessed not on the basis that they are pure compound claims, but rather on the basis that they are claims to compounds which have anti-*Flaviviridae* activity. If it were otherwise, these claims would lack inventive step on the basis that the only technical problem they solved was the provision of additional or alternative nucleoside analogues.

446. Thirdly, it is Idenix's case that substantially all the compounds covered by claim 1 can be made by the skilled team using conventional methods without undue burden. For the purposes of assessing inventive step, I shall assume that this is correct. I shall consider whether it is in fact correct when I come to consider insufficiency.

447. *Claim 1 as granted*. Claim 1 of the Patent is much narrower in scope than the claims in the Application. Nevertheless, it still covers a very large number of compounds, on a conservative estimate at least 50 billion compounds. Gilead contend that, considered as at 27 June 2003, it was not plausible that substantially all the compounds covered by claim 1 would be effective against *Flaviviridae*. I can deal with this contention quite shortly, because it is Idenix's own evidence that claim 1 covers classes of compounds which it was not plausible would be effective. Dr Brancale expressed the opinion in paragraphs 201-202 of his first report that compounds of Formula (IX) would not have been thought likely to have antiviral activity where R^1 and R^2 were either "straight chained, branched or cyclic alkyl" or "benzyl, wherein the phenyl group is optionally substituted with one or more substituents". It was for this reason that Idenix made their conditional application to amend.

448. Counsel for Idenix's only real answer to the case based on Dr Brancale's evidence was to suggest in his opening submissions that this case was not open to Gilead since they had not pleaded it. Counsel for Gilead submitted in his closing submissions that Gilead's Grounds of Invalidity did cover this case, and counsel for Idenix did not pursue the pleading point in his closing submissions. In any event I agree with counsel for Gilead. In the alternative, I would give Gilead permission to amend since the point arose out of Idenix's own evidence in chief and Idenix had a full opportunity to address it both before and at trial.

449. Accordingly, I conclude that claim 1 as granted is invalid for lack of inventive step because it covers compounds which the skilled team would not have considered plausible had anti-*Flaviviridae* activity and which therefore did not plausibly solve

the technical problem of providing compounds which did have such activity. Thus the claim covered compounds which made no technical contribution to the art.

450. *Claim 1 as proposed to be amended*. I shall assume for this purpose that the amendment is allowable (the allowability of the amendment is considered below). Gilead contend that, even as proposed to be amended, it was not plausible that substantially all the compounds covered by claim 1 would be effective against *Flaviviridae*. I accept this contention, for the following reasons.

451. First, the Patent contains no experimental data to suggest that any of the claimed compounds may be effective. The only experimental data is in Example 26, but that example (i) is expressly acknowledged to relate to a compound which falls outside the claim, (ii) relates to an unidentifiable compound which does not appear to contain fluorine and (iii) does not establish that the compound has any potentially therapeutically useful activity.

452. Secondly, the Patent contains no rationale for the assertion that the claimed compounds may be effective. On the face of the Patent, the assertion appears to be nothing more than speculation.

453. Thirdly, the specification adds nothing to the common general knowledge of the skilled team as to what nucleoside analogues might exhibit *Flaviviridae*, and in particular anti-HCV, activity. It was known in June 2003 that certain nucleoside analogues could inhibit replication in certain viruses, since such analogues had been used successfully in HIV and HBV therapy. It was also known that NS5B was a potential target for direct acting nucleoside analogues and this was an area of active research. Accordingly, as a matter of common general knowledge, it was plausible that as yet untested nucleoside analogues *might* exhibit anti-HCV activity through their effect on NS5B. The Patent contains nothing which makes this more plausible. Still less does it contain anything to make it more plausible that the compounds claimed in claim 1 – as opposed to, for example, other compounds claimed in the Application – might exhibit such activity. In particular, the passage at [0022(10)] (corresponding to page 9 line 29 – page 10 line 24 of the Application, quoted in paragraph 181 above) which is relied on by Idenix does not do so. As I have said, it is simply part of the recitation of prior art and it does not identify the 2'-modified nuclesides which were the subject of the Eldrup, Bhat and Olsen presentations at the Savannah conference.

454. Fourthly, Idenix's attempt to fill the gaps in the specification by raising the level of the skilled team's common general knowledge was unsuccessful. Idenix's case on plausibility as presented in counsel for Idenix's closing submissions started from the premise that it was common general knowledge that the 2'-methyl-up-2'-hyxroxy-down nucleoside analogues being investigated by Merck which were the subject of the Carroll paper and the presentations at the Savannah conference had activity in the HCV replicon and acted as chain terminators of the HCV RNA-dependent RNA polymerase. I have found that this was not the case.

455. Fifthly, even if Idenix's attempt to fill the gaps in the specification by raising the level of the skilled team's common general knowledge had succeeded, it would have been self-defeating. Even if it was correct that, for example, the Carroll paper was common general knowedge, and therefore the skilled team would bring that knowledge to their

reading of the Patent, it would remain the case that the Patent added nothing to their knowledge. If it was plausible in the light of the information in the Carroll paper that the claimed compounds would be effective, that would not demonstrate that the Patent had made any technical contribution to the art.

456. Sixthly, counsel for Idenix relied on the fact that Prof Götte had accepted that the compounds claimed in claims 9-11 of the Application were highly structurally related to the Merck 2'-methyl-up-2'-hydroxy-down compounds. This does not assist Idenix, however. Prof Götte was clear that this did not make it plausible that the claimed compounds would be effective against HCV, rather this had to be tested. Furthermore, it was part of the skilled team's common general knowledge that small structural changes could have a substantial effect on activity and/or toxicity. Still further, as I have explained, Idenix failed to establish that the skilled team would have regarded fluorine as an isostere for a hydroxyl group. On the contrary, the skilled team would have appreciated that substituting fluorine for hydroxyl could seriously affect the properties of the molecule, and in particular its biological activity.

457. Seventhly, counsel for Gilead pointed out that counsel for Idenix had approached his cross-examination of Professor Götte by asking whether compounds with the structure of claim 10 of the Application "would at least be plausible in the sense of worth testing". He submitted this could not be the right question and that an affirmative answer could not provide a basis for patentability. As Prof Götte explained, because the art in 2003 was largely empirical, almost any nucleoside analogue was worth testing. Thus the question was merely restating the common general knowledge. I agree with this.

458. Eighthly, when the specification tells the skilled team at [0042] (corresponding to page 38 lines 17-21 of the Application, quoted in paragraph 188 above) that the nucleosides of the invention "may inhibit *Flaviviridae* polymerase activity" and "can be screened" for such activity using known assays, the specification is simply inviting the skilled team to carry out a screening programme to find out for themselves whether the nucleosides have activity or not. If they do that and find something that works, Idenix claim it.

459. Ninthly, Dr Brancale conceded in paragraph 196 of his first report that the effectiveness of the 2'-methyl-up-2'-fluorine-down substitution which is the key feature of the claimed compounds could not have been predicted in June 2003 on the basis of what was known. Furthermore, he accepted in cross-examination that his opinion that it was plausible that compounds with that substitution would be effective anti-HCV agents was not based on anything in the Patent, but upon what other people had published. Still further, as explained above, Dr Brancale's evidence on this topic has to be approached with caution given his belief that claims could be supported by data which the patentee had kept hidden.

460. Tenthly, there is evidence that, if the skilled team did make and test the claimed compounds, they would not necessarily get a positive result if they then tested such compounds using the BVDV-based assays described in the Patent. The Clark Paper records in Table 2 that 2'-deoxy-2'-fluoro-2'-C-methylcytidine is inactive in the BVDV assay.

461. Lastly, even if a compound tested positive against BVDV in such an assay, the skilled team would know that this was not predictive of activity against other *Flaviviridae*, and in particular HCV. Thus the Clark Paper records that 2'-deoxy-2'-fluoro-2'-C-methylcytidine was active against HCV in the replicon assay.

462. *Subsidiary claims*. Although Idenix contend that claims 2, 5-6, 21 and 24 have independent validity, counsel for Idenix did not advance any arguments in his closing submissions to support the independent validity of these claims if claim 1 as proposed to be amended was invalid for lack of inventive step.

Insufficiency

The law

463. In *Lilly v HGS* (cited above) Sir Robin Jacob quoted with apparent approval at [11] the following summary of the relevant principles given by Kitchin J (as he then was) at first instance in the same case [2008] EWHC 1903 (Pat), [2008] RPC 29 at [239]:

> "The specification must disclose the invention clearly and completely enough for it to be performed by a person skilled in the art. The key elements of this requirement which bear on the present case are these:
>
> (i) the first step is to identify the invention and that is to be done by reading and construing the claims;
>
> (ii) in the case of a product claim that means making or otherwise obtaining the product;
>
> (iii) in the case of a process claim, it means working the process;
>
> (iv) sufficiency of the disclosure must be assessed on the basis of the specification as a whole including the description and the claims;
>
> (v) the disclosure is aimed at the skilled person who may use his common general knowledge to supplement the information contained in the specification;
>
> (vi) the specification must be sufficient to allow the invention to be performed over the whole scope of the claim;
>
> (vii) the specification must be sufficient to allow the invention to be so performed without undue burden."

464. Failure to enable the invention to be performed without undue burden is often referred to as "classical insufficiency" and failure to enable the invention to be performed over the whole scope of the claim is often referred to as "*Biogen* insufficiency" or "excessive claim breadth", although these are aspects of the same objection and often shade into one another.

465. *Classical insufficiency.* I reviewed the law with regard to classical insufficiency in *Sandvik v Kennametal* (cited above) at [106]-[124]. Since then, the Court of Appeal has considered the requirement that the specification enable the skilled person to perform the invention without undue burden in the context of a claim to the use of a product to make a medicine for a particular therapeutic purpose in *Regeneron Pharmaceuticals Inc v Genentech Inc* [2013] EWCA Civ 93, [2013] RPC 28, where Kitchin LJ stated at [103]:

> "… the Boards of Appeal of the EPO have recognised that in the case of a claim to the use of a product to make a medicine for a particular therapeutic purpose it would impose too great a burden on the patentee to require him to provide absolute proof that the compound has approval as a medicine. Further, it is not always necessary to report the results of clinical trials or even animal testing. Nevertheless, he must show, for example by appropriate experiments, that the product has an effect on a disease process so as to make the claimed therapeutic effect plausible. It was put this way in T609/02 *Salk* at [9]:
>
> > '… It is a well-known fact that proving the suitability of a given compound as an active ingredient in a pharmaceutical composition might require years and very high developmental costs which will only be borne by the industry if it has some form of protective rights. Nonetheless, variously formulated claims to pharmaceutical products have been granted under the EPC, all through the years. The patent system takes account of the intrinsic difficulties for a compound to be officially certified as a drug by not requiring an absolute proof that the compound is approved as a drug before it may be claimed as such. The boards of appeal have accepted that for a sufficient disclosure of a therapeutic application, it is not always necessary that results of applying the claimed composition in clinical trials, or at least to animals are reported. Yet, this does not mean that a simple verbal statement in a patent specification that compound X may be used to treat disease Y is enough to ensure sufficiency of disclosure in relation to a claim to a pharmaceutical. It is required that the patent provides some information in the form of, for example, experimental tests, to the avail that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se. Showing a pharmaceutical effect in vitro may be sufficient if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application (T 241/95, OJ EPO 2001, 103, point 4.1.2 of the reasons, see also T 158/96 of 28 October 1998, point 3.5.2 of the reasons) or, as decision

> T 158/96 also put it, if there is a "clear and accepted established relationship" between the shown physiological activities and the disease (loc. cit.). Once this evidence is available from the patent application, then post-published (so-called) expert evidence (if any) may be taken into account, but only to back-up the findings in the patent application in relation to the use of the ingredient as a pharmaceutical, and not to establish sufficiency of disclosure on their own.'"

466. *Excessive claim breadth*. I reviewed the law with regard to excessive claim breadth at some length in *MedImmune Ltd v Novartis Pharmaceuticals UK Ltd* [2011] EWHC 1699 (Pat) at [458]-[484] and summarised that analysis in *Sandvik v Kennametal* at [121]-[124]. As Kitchin LJ stated in *Regeneron v Genentech*:

> "100. It must therefore be possible to make a reasonable prediction the invention will work with substantially everything falling within the scope of the claim or, put another way, the assertion that the invention will work across the scope of the claim must be plausible or credible. The products and methods within the claim are then tied together by a unifying characteristic or a common principle. If it is possible to make such a prediction then it cannot be said the claim is insufficient simply because the patentee has not demonstrated the invention works in every case.
>
> 101. On the other hand, if it is not possible to make such a prediction or if it is shown the prediction is wrong and the invention does not work with substantially all the products or methods falling within the scope of the claim then the scope of the monopoly will exceed the technical contribution the patentee has made to the art and the claim will be insufficient. It may also be invalid for obviousness, there being no invention in simply providing a class of products or methods which have no technically useful properties or purpose."

467. For the reasons set out above, the court must undertake a two-stage enquiry. The first stage is to determine whether the disclosure of the Patent, read in the light of the common general knowledge of the skilled team, makes it plausible that the invention will work across the scope of the claim. If the disclosure does make it plausible, the second stage is to consider whether the later evidence establishes that in fact the invention cannot be performed across the scope of the claim without undue burden. In some cases, it is convenient to divide the second stage into two, first considering whether the invention can be performed without undue burden at all and then whether the claim is of excessive breadth.

468. It has been held in a number of cases that a patent will be insufficient if the specification requires the skilled person to undertake a substantial reseach project in order to perform the invention (either at all or across the breadth of the claim) and claims the results: see e.g. *Halliburton Energy Services Inc v Smith International (North Sea) Ltd* [2006] EWCA Civ 1715 at [18] (Jacob LJ), *American Home Products*

Corp v Novartis Pharmaceuticals UK Ltd [2001] RPC 8 at [41]-[47] (Aldous LJ) and *Novartis AG v Johnson & Johnson Medical Ltd* [2010] EWCA Civ 1039, [2011] ECC 10 at [50]-[92] (Jacob LJ).

Plausibility

469. For the reasons given in paragraphs 444-462 above, I conclude that the disclosure of the Patent, read in the light of the common general knowledge of the skilled team, did not make it plausible that the invention will work across the scope of the claims (whether as granted or as proposed to be amended). Accordingly, all the claims are invalid on this ground. In case I am wrong about that, and having regard to the need for me to make the necessary findings of fact, I shall consider whether the invention can be performed without undue burden either at all or across the breadth of the claims, beginning with claim 1. It is not suggested that the proposed amendment makes any material difference to this question.

Undue burden to perform the invention at all?

470. Gilead allege that the Patent does not enable the skilled team to perform the invention in claim 1 without undue burden because it does not enable them to synthesise the 2'-methyl-up-2'-fluoro down compounds claimed. The allegation is focused upon the 2'-methyl-up-2'-fluro-down substitutions on the ribose ring; Gilead do not contend that the skilled team would have any difficulty with regard to the other substitutions covered by Markush formula in claim 1. This allegation has given rise to a complex series of issues, with both parties relying on factual evidence as well as expert evidence and Idenix relying upon their Experiments. I shall consider the factual evidence and the Idenix Experiments before turning to the more general aspects of the evidence. Since this part of the case concerns the ability of the medicinal chemist to synthesise the compounds claimed, I shall refer in this part of the judgment solely to that skilled person.

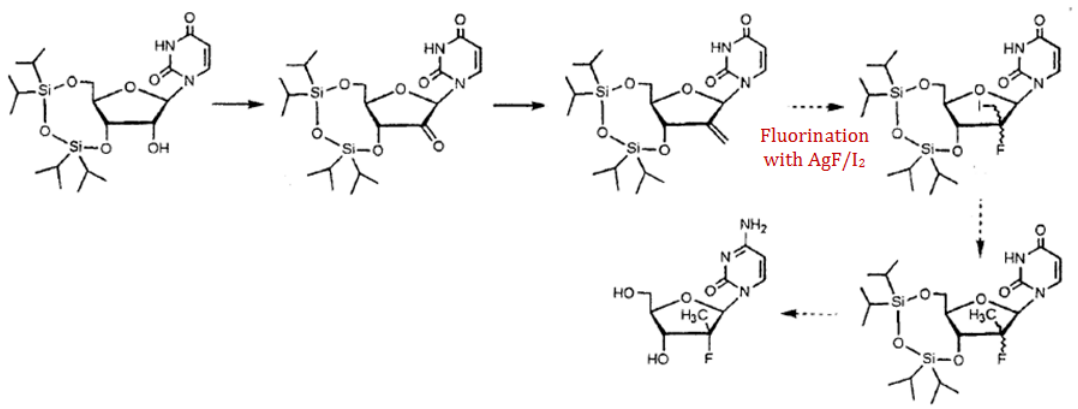
471. *Dr Griffon's work*. As explained above, Gilead relies on the work of Dr Griffon and his colleagues in support of its allegation of insufficiency. Gilead contends that Dr Griffon was a suitably-qualified medicinal chemist who failed to make a 2'-methyl-up-2'-fluoro-down nucleoside analogue despite prolonged effort and the assistance of eminent chemists both within and external to Idenix.

472. Dr Griffon was first assigned the project of making a 2'-methyl-up-2'-fluoro-down nucleoside analogue at an Idenix chemistry team meeting in Montpellier on 28 March 2002 attended by, among others, Dr Dick Storer (his supervisor and Senior Vice-President of Chemistry at Idenix) and Dr Gosselin (Dr Griffon's former PhD supervisor and the Director of Research at Idenix's Montpellier laboratory). Dr Storer and Dr Gosselin were both highly experienced research chemists. At that stage, however, a 2'-methyl-up-2'-methoxy-down compound was more of a priority.

473. Dr Griffon was given the task of undertaking a bibliographic search in relation to the 2'-methyl-up-2'-fluoro-down target at a Montpellier chemistry team meeting on 24 May 2002. Dr Griffon presented the results of the search in a report dated 27 June 2002. There were no results for a 2'-fluoro-2'-methyl substituted nucleoside/sugar, but his search using a general formula for a tertiary fluoride yielded a number of results. A subsequent refinement saw Dr Griffon search for the conversion of a tertiary

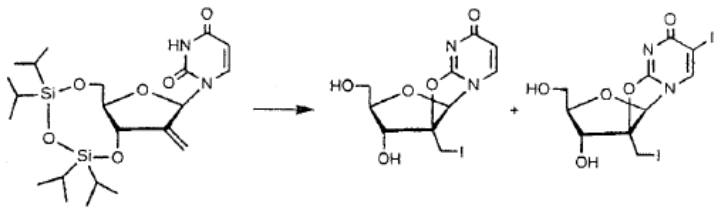
alcohol into the corresponding tertiary fluoride, but this gave only two results. An alternative refinement involving a search for the conversion of an epoxide into a tertiary fluoride also only gave two results. At the end of the report, Dr Griffon proposed a synthesis of the 2'-methyl-up-2'-fluoro-down analogue based on the literature synthesis strategy for a nucleoside with a tertiary fluoride at the 4' position derived from papers listed in the report. This strategy involved taking a "nucleoside route" (see paragraph 136 above). Dr Griffon viewed this initial proposal as a logical starting point in light of the literature references he had located during his searches. In July 2002 the project was assigned a "high priority".

474. Dr Griffon's first attempted strategy ("Strategy 1") is shown below. It involved the formation of nucleoside with a 2'-ketone from the corresponding 2'-OH nucleoside with 3'-5'-protection by TIPDS protecting groups. The 2'-ketone would subsequently be converted into a 2'-ethenyl moiety which it was intended would react with AgF and I_2 to produce a 2'-fluoro-2'-iodomethyl group. The proposal then envisaged that the 2'-iodomethyl group would be converted into a methyl group, before the protecting groups were removed.



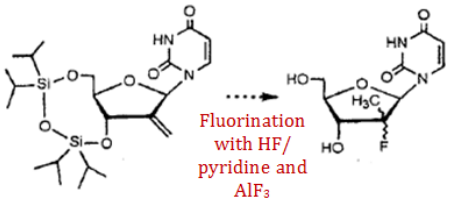
Strategy 1

475. This strategy was unsuccessful. Reaction of the 2'-ethenyl nucleoside with AgF and I_2 gave two deprotected "anhydro" compounds, instead of the desired, protected 2'-iodomethyl intermediate, as shown below.



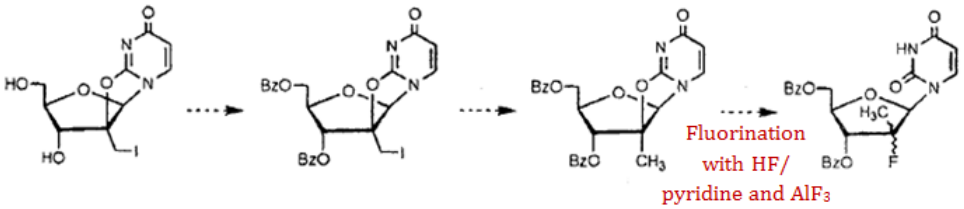
476. After this failure, Dr Griffon proposed two new strategies for the synthesis of a 2'-fluoro-2'-methyl nucleoside analogue in his monthly Progress Report for September 2002. One proposal involved the reaction of a 3'-5'-protected 2'-ethenyl nucleoside with HF/pyridine and AlF_3 ("Strategy 2"). Strategy 2 was based on a paper by G.A.

Olah *et al*, "Synthetic methods and reactions. 63: Pyrimidium poly(hydrogen fluoride) (30% pyridine-70% hydrogen fluoride): a convenient reagent for fluorination reactions", *J. Org. Chem.*, 44, 3872-3881 (1979), which was one of the papers which Dr Griffon had found during his literature search.



Strategy 2

477. The second new strategy proposed by Dr Griffon involved using one of the unwanted anhydro products of Strategy 1. The intention was to protect the 2'-iodomethyl-anhydro compound at the 3' and 5' positions with benzoyl (Bz) protecting groups, before converting the 2'-iodomethyl group into a 2'-methyl group and then opening the anhydro bond using HF/pyridine and AlF_3 ("Strategy 3"), as shown below.



Strategy 3

478. In his October 2002 Progress Report Dr Griffon noted that an attempt to convert the 2'-iodomethyl-anhydro compound to the corresponding 2'-methyl-anhydro compound (a variant on Strategy 3 above) without first installing protecting groups had failed (he recorded that "these conditions didn't allow the formation of the desired compound") and illustrated the reaction in his report with a cross on the relevant arrow.

479. In the same October 2002 Progress Report, Dr Griffon indicated that further work on Strategy 3, where the 2'-iodomethy-anhydro compound is first protected with Bz groups, was underway. Similarly, he recorded that work on Strategy 2 was also ongoing.

480. By November 2002 Dr Griffon had made several further attempts to carry out Strategy 3, but "none of the attempted experimental conditions allowed the selective reduction of the iodomethyl group". In addition, he reported that Strategy 2 had also failed after attempting the reaction using hydrogen fluoride-pyridine in a stainless steel bomb at 100°C. Dr Griffon reported that "one new compound was formed during the reaction", but NMR analysis indicated the absence of fluorine in that compound. Dr Griffon's notebooks indicate that another attempt at Strategy 2 also failed.

481. On 2 December 2002 Dr Griffon met with Dr Storer, Dr Adel Moussa and Dr Gosselin (all of Idenix) and Prof Fleet (of Oxford University). During the meeting the 2'-methyl-up-2'-fluoro-down target compound that Dr Griffon had had trouble synthesising was discussed, along with synthetic routes for the preparation of the target compound. The report of the meeting sets out the difficulties which had been encountered in attempting to reduce the iodomethyl group as part of Strategy 3 and different experimental conditions are suggested. In addition, on page 2 of the report a "proposal of synthetic strategy from G. Fleet" is set out, which involves electrophilic fluorination of a six-membered sugar ring. It may be noted that Prof Fleet did not suggest the use of DAST on the tertiary carbon.

482. By the end of December 2002, Dr Griffon had done further work on Strategy 2, attempting the "Olah" fluorination of a 2'-ethenyl nucleoside with a protected base using HF/pyridine in a stainless steel bomb at 80°C. However this reaction failed: "one compound was formed during the reaction … but this compound was identified as the [starting material but with the base protection removed]".

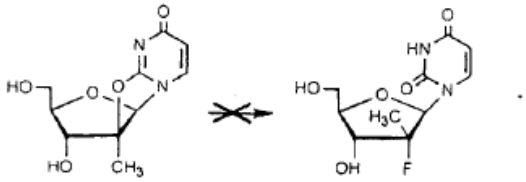
483. Dr Griffon continued to work on the synthesis of a 2'-methyl-up-2'-fluoro-down nucleoside in January 2003. In his Progress Report for that month he stated that "starting from the 2'-ethenyl derivative [i.e. Strategies 1 and 2] … all the attempted experimental conditions failed". Dr Griffon also noted that, after several failed attempts, the reduction of the 2'-iodomethyl-anhydro compound (the first step of Strategy 3) had been achieved. Looking forward, Dr Griffon stated that "several experimental conditions are going to be attempted in order to introduce the fluorine atom at the 2'-down position: HF-pyridine, AlF_3, 120°C or KHF_2, ethylene glycol, reflux".

484. In early January Prof Fleet provided another suggested route to Idenix which involved electrophilic fluorination. Meanwhile, on 8 February 2003 Dr Storer wrote to Dr Paul Coe, an organofluorine expert from the University of Birmingham who had previously collabrated with nucleoside chemists, asking for his assistance in relation to work on targets which involved fluorine. Dr Storer stated that, in relation to a number of targets, "we are OK with the nucleoside chemistry, it's the fluorine chemistry we are struggling with and where your help will be valuable". Dr Storer went on to describe a number of targets in detail, including a 2'-methyl-up-2'-fluoro-down nucleoside, which is identified in the letter as Target 9. Describing work on Target 9, Dr Storer said:

> "Target 9 is an attempt to replace the tertiary OH of the ribo analogue with fluorine. We've tried a variety of procedures from the exocyclic methylene analogue in an attempt to effectively add HF across the double bond [cf. Strategies 1 & 2]. We had no success with that. We're now looking at attempting to take the 2'-α methyl anhydro compound and open that with fluoride. I'm not too hopeful for success with that. Appendix 3 shows a summary of this. Your thoughts on how to introduce the tertiary fluoro substituent in compound 9 would be appreciated."

485. In his February 2003 Progress Report, Dr Griffon explained that "several experimental conditions have been attempted in order to introduce fluorine at the 2'-

down position". He went on to describe a number of attempts to open a 2'-anhydro nucleoside with fluoride, all of which failed.



486. The various attempts involved fluorination with:

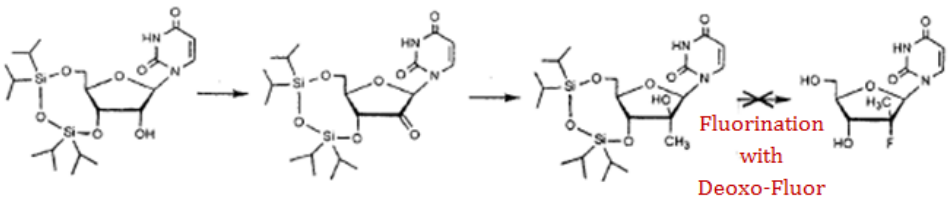
i) HF-pyridine, AlF_3 at 80˚C and 120˚C (Strategy 3 as described in paragraph 477 above, but without 3' and 5' protection)

ii) KF, Kryptofix 2.2.2, *p*TsOH, DMF, reflux ("Strategy 4"); and

iii) KHF_2 refluxed in either ethylene glycol or 2-methoxyethanol ("Strategy 5").

487. The summary of results for these reactions in Dr Griffon's February 2003 Progress Report indicated that these strategies either gave no reaction or proceeded with degradation of the starting material.

488. Having tried and failed with his first five strategies, Dr Griffon commenced a new approach in February 2003, which involved making a 3'-5'-protected 2'-hydroxy-up-2'-methyl-down nucleoside and then fluorinating it using Deoxo-Fluor ("Strategy 6"), as shown below.



Strategy 6

489. Dr Griffon had already performed the first step in Strategy 6, to make the ketone at the 2' position, in October 2002. He carried out this oxidation using chromium trioxide in acetic anhydride, pyridine and dichloromethane (also known as methylene chloride). It appears that the second step, to make the 2'-hydroxy-up-2'-methyl-down compound, had already been performed by a colleague of Dr Griffon. This was carried out using trimethylaluminium in hexane and dichlormethane.

490. Dr Griffon's evidence was that he believed that he had arrived at the proposed fluorination reaction in the light of two papers referred to in his February 2003 Progress Report:

i) R.P. Singh and J.M. Shreeve, "Recent advances in nucleophilic fluorination reactions of organic compounds using deoxofluor and DAST", *Synthesis*, 2561-2578 (2002) ("Singh and Shreeve"); and

ii) J. Wachtmeister *et al*, "Synthesis of 4-substituted carbocyclic 2,3-dideoxy-3-C-hydroxymethyl mucleoside analogues as potential ant-viral agents", *Tetrahedron*, 55, 10761-10770 (1999) ("Wachtmeister").

491. Singh and Shreeve is a review article on the use of DAST and Deoxo-Fluor. One of the references it cites, Wachtmeister, states that fluorination of a tertiary alcohol in a cyclopentanol compound with inversion of stereochemistry can be carried out with DAST with a yield of 25%, but that using Deoxo-Fluor gave a better yield of 43%. Dr Griffon decided to try Deoxo-Fluor using the method of Wachtmeister. This involved reacting the 3'-5'-protected 2'-hydroxy-2'-methyl nucleoside with Deoxo-Fluor in pyridine and chloromethane under argon, initially at -78^{o}C and then allowing the reaction mixture to warm to room temperature. Dr Griffon reluctantly admitted that he did not use DAST because he did not expect it to work, but rather to give an elimination product.

492. Dr Griffon first attempted the fluorination step on 13 February 2003. He proceeded to deprotect the hydroxyl groups before attempting to separate and analyse the reaction products. He completed his analysis of the reaction products on 17 February 2003. He monitored the reaction using TLC, first viewing the plate under UV light and then staining it with 10% sulphuric acid in methanol and heating it. He pasted into his laboratory notebook the stained TLC plates for the crude reaction mixture (i) after 5½ hours, (ii) after leaving the reaction overnight and (iii) after deprotection. The last of these three appears to show four main spots which charred with the staining and two very small spots which had been visible under UV, and had been circled in pencil by Dr Griffon, but which did not char. Dr Griffon then analysed the mixture by analytical HPLC. He then separated the crude reaction mixture using silica gel chromatography into three components. The first component he presumed to be the uracil base. The second component, which appeared to be the major product, he analysed by MS, ^{1}H and ^{19}F NMR. This turned out to be the 2' ethenyl derivative i.e. the elimination product. The third component he presumed to be the deprotected starting material. He recorded his work, including the analytical data, on pages 12 and 14 of his laboratory notebook for that period.

493. Dr Griffon repeated the reaction on 19 February 2003 using slightly different reaction conditions. This time very little remained of the starting material.The major product was the 2' ethenyl derivative, although again the TLC plate appears to show a small amount of a minor product which he did not separate or analyse. He recorded this work on pages 15 and 16 of his notebook.

494. In his February 2003 Progress Report Dr Griffon stated that "one new compound was formed during the reaction … unfortunately, based on Mass Spectrum, ^{1}H and ^{19}F-NMR spectra, this compound was identified as the 2'-ethenyl derivative…". Although Dr Griffon's conclusion at the time was that Strategy 6 had not succeeded, Idenix

contend that the products of the reaction, and in particular the products of Dr Griffon's first attempt, did in fact include the desired 2'-methyl-up-2'-fluoro-down nucleoside analogue. Idenix sought to prove this contention by their Experiments in these proceedings, which are discussed below.

495. Between 1 and 4 April 2003 Dr Griffon and one of his colleagues from Idenix, Dr Claire Pierra, attended a course in Stratford-upon-Avon entitled *Making and Using Fluoroorganic Molecules* taught by Professor Jonathan Percy and Dr Alison Stuart of the University of Leicester. After the course, Drs Griffon and Pierra produced a report summarising what they had learnt which was of interest for on-going Idenix projects. From that report, it is apparent that a number of different fluorinating reagents were discussed, including electrophilic and nucleophilic reagents. DAST was one of the fluorinating reagents discussed at the course. The report also includes a number of proposals by Dr Griffon and Dr Pierra for ways in which what was taught might be used for the synthesis of relevant Idenix targets, including 2'-methyl-up-2'-fluoro-down nucleosides. The proposals included both electrophilic and nucleophilic reagents for the formation of a tertiary fluorine at the 2'-position.

496. On or around 9 April 2003 Dr Coe replied to the letter which Dr Storer had sent him on 8 February 2003. He proposed a number of synthetic strategies for the synthesis of a 2'-methyl-up-2'-fluoro-down nucleoside. Dr Coe stated that:

> "…in our experience and indeed in that of manner other [*sic*] particularly the de Clerc group the most viable routes to fluoro nucleosides are by sugar/base condensation methods the anomer problem notwithstanding, for the very reasons you have discovered, in that the leaving groups generated in situ e.g. in DAST reactions are readily attacked by the pyrimidine ring nucleophiles or elimination and/or participation of blocking groups. Further migrations of groups can readily occur: see our papers in JFC 1993 62 145 and 1993 60 239. Having said this some of the route [*sic*] you have tried are OK except that I think you are using the wrong reagents, leaving groups and reaction conditions."

497. Dr Coe suggested four methods for the synthesis of a 2'-methyl-up-2'-fluoro-down nucleoside, which were:

i) synthesis of a 2-methyl-up-2-methoxy-down sugar, activation of the 2-hydroxyl group using SO_2Cl_2 and imidazole to form an imidazole sulfonyl leaving group, subsequent fluorination with $Et_3N.3HF$ and then glycosylation to install the base;

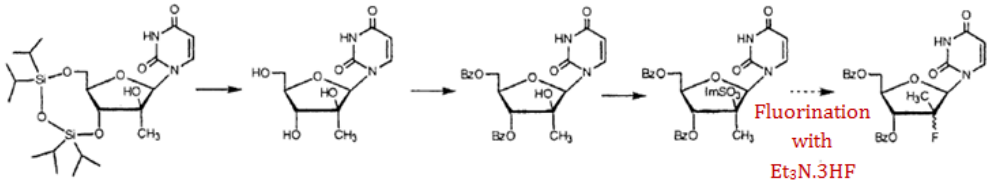
ii) a similar approach starting with a 2'-methyl-up-2'-hydoxy-down nucleoside;

iii) the opening of a 2'-anhydro nucleoside using anhydrous HF, or Bu_4NH_2F, with $Fe(AcAc)_3$ and DME; and

iv) the reaction of a 2'-methyl-up-2'-hydroxy-down nucleoside with HF-pyridine ("Olah" conditions).

498. None of the routes proposed by Dr Coe for the synthesis of a 2'-methyl-up-2'-fluoro-down nucleoside involved nucleophilic fluorination of a tertiary alcohol on a sugar with DAST.

499. During May 2003 Dr Griffon attempted routes suggested by Dr Coe. One was the strategy involving the activation of a 2'-methyl-up-2'-hydroxy-down nucleoside to form an imidazole sulfonyl ($ImSO_3$) leaving group which would then be reacted with $Et_3N.3HF$ ("Strategy 7"), as shown below.



Strategy 7

500. Strategy 7 failed. Dr Griffon recorded in his May 2003 Progress Report that when the fluorination reaction was attempted "no reaction occurred: the starting material was mainly recovered". Dr Griffon also proposed an attempt to open the 2'-anhydro nucleoside using Bu_4NH_2F with $Fe(AcAc)_3$ and DME as suggested by Dr Coe ("Strategy 8") .

501. At a chemistry team meeting held in Montpellier on 31 July 2003, it was noted in relation to the 2'-methyl-up-2'-fluoro-down nucleoside project that "up to now, all procedures starting from a nucleoside were unsuccessful". Dr Griffon agreed during cross-examination that this was his understanding at the time of the meeting. The report of the meeting also states that "a strategy starting from the corresponding fluorinated sugar might be the solution". Finally, it also proposes that "as a last alternative using a nucleoside route: need to try the method described in Fluorine Chemistry Course". This proposal appears to involve electrophilic fluorination of a 2'-methyl nucleoside containing a 2'-3' double bond.

502. During July/August 2003 Dr Griffon attempted Strategy 8, reacting the 2'-anhydro nucleoside with tetrabutylammonium dihydrogenfluoride in the presence of ferric acetylaceonate in 1,2-demethoxyethane at 110°C in a stainless steel bomb for 6.5 hours. Dr Griffon recorded in his Progress Report for this period that "no reaction occurred".

503. By November 2003, after more than a year and a half, significant external input and eight failed synthetic strategies, the 2'-methyl-up-2'-fluoro-down nucleoside target was (perhaps unsurprisingly) abandoned by Idenix. For reasons that are not clear, the project was resurrected at a chemistry team meeting held in Montpellier on 3 February 2004. The project was again assigned to Dr Griffon.

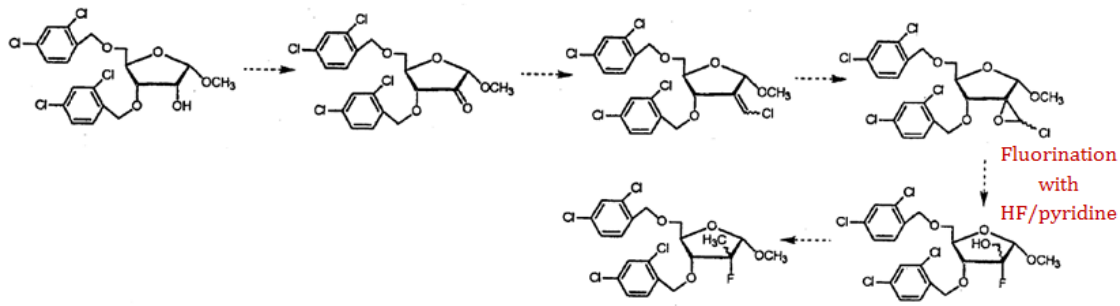
504. In his Progress Report for February 2004, Dr Griffon described renewed attempts at Strategy 1 (reaction of a 2'-ethenyl nucleoside with AgF and I_2), but this time using protected bases. These attempts failed. Dr Griffon concluded that:

> "All the strategies that were attempted to introduce the methyl group at the 2'-'up' position and the fluorine atom at the 2'-'down' position starting from different uridine derivatives failed. A 'sugar strategy' involving the synthesis of a 2'-methyl 'up'-2'-fluoro 'down'-ribofuranose derivative will be proposed."

505. In March 2004 Idenix brought even more resources to bear on the project. Dr Gosselin emailed a number of PhD chemists in the Montpellier team enclosing a report prepared by Dr Griffon summarising his work on the synthesis of 2'-methyl-up-2'-fluoro-down nucleosides and asking them to study it and contribute possible synthetic routes for discussion at a meeting to follow. Dr Griffon's report summarised his failed attempts for the synthesis of a 2'-methyl-up-2'-fluoro-down nucleoside to date, including numerous literature references relevant to the various strategies.

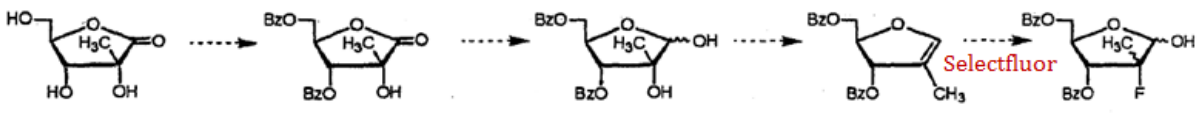
506. At least some of the Montpellier team PhD chemists responded to Professor Gosselin's request for proposed synthetic routes, for example, in March 2004 Dr Jean-Christophe Meillon proposed a route involving the electrophilic fluorination of a 2'-methyl nucleoside containing a 2'-3' double bond. Dr Pierra also provided suggestions including nucleophilic routes (opening of a 2'-3' epoxide on a 2'-methyl nucleoside, and an "Olah" type fluorodehydroxylation reaction) and electrophilic routes (reaction of NFOBS/NFSI with a 2'-methyl-3'-ketone nucleoside).

507. Dr Griffon subsequently produced a report setting out three proposed sugar routes (see paragraph 136 above) for the synthesis of a 2'-methyl-up-2'-fluoro-down nucleoside. His first proposal involved the opening of a spiro α-chloroepoxide with HF-pyridine ("Strategy 9"), as shown below.



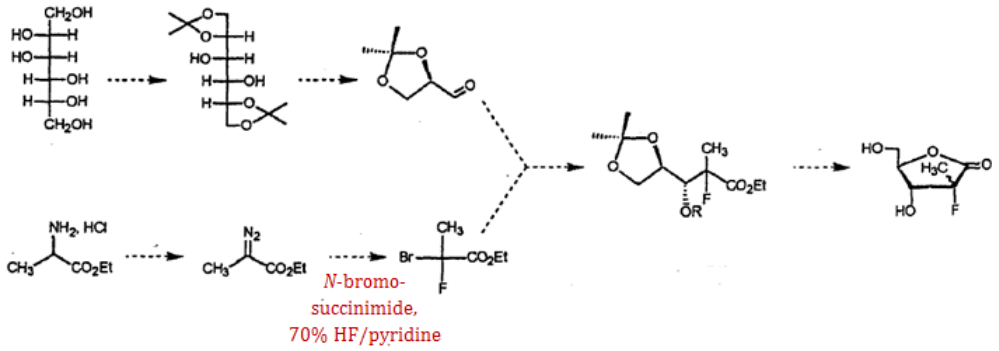
Strategy 9

508. His second proposal was to react a 2-methyl sugar containing a 1-2 double bond with Selectfluor in an electrophilic fluorination ("Strategy 10"), as shown below.



Strategy 10

509. Dr Griffon's third proposal was a "small molecules" approach (see paragraph 136 above) ("Strategy 11"), as shown below.



Strategy 11

510. Dr Griffon discussed these approaches with Dr Storer and Dr Gosselin in a meeting held on 21 April 2004, and in the report of that meeting they were described as being "in progress".

511. In his April 2004 Progress Report Dr Griffon described difficulties with the epoxidation step in Strategy 9. He proposed trying other epoxidation reagents in order to obtain the necessary intermediate. He also described an attempt at the electrophilic fluorination Strategy 10, which failed with the Selectfluor reagent - only starting material was recovered. Dr Griffon indicated in his Report that he would continue to explore alternative electrophilic fluorinating reagents. Finally, he noted that the small molecule Strategy 11 was "in progress".

512. Dr Griffon continued to work on the project during May 2004. In his Progress Report for that month he recorded that the spiro α-chloroepoxide Strategy 9 had been placed on "stand by". A further failed attempt at the electrophilic fluorination Strategy 10 with Selectfluor was recorded.

513. The May 2004 Progress Report also indicated that the small molecule Strategy 11 had also run into difficulties. Dr Griffon noted that "…cyclisation of the sugar and deprotection in acidic conditions was attempted 3 times with no success".

514. Dr Griffon stopped work on the 2'-methyl-up-2'-fluoro-down nucleoside analogue project in Summer 2004. In his annual Activity Report for September 2003-September 2004 Dr Griffon noted that "different strategies were attempted in order to synthesize the 2'-methyl 'up', 2'-fluoro 'down' nucleosides: nucleoside strategies, starting from uridine: failed. Sugar strategies that failed so far". The report went on to ask "Question: Due to the synthetic difficulties encountered, is it worthwhile to continue to consider this series as future targets?"

515. As noted above Idenix contend that, although he did not realise it, Dr Griffon did in fact succeed in making the 2'-methyl-up- 2'-fluoro-down compound as a minor

product by the route in Strategy 6. As I have said, Idenix seek to prove this by their Experiments considered below. In addition, Idenix contend that Dr Griffon's approach to his task was an idiosyncratic one which did not represent the approach which would have been adopted by the average skilled person in June 2003. Idenix say that, throughout his work on this project, Dr Griffon's thinking was driven by his desire to make a relatively large amount of the target compound. This led him to focus on reactions which produced reasonably high yields of the desired products, and to ignore minor products produced in low yields. Idenix further say that the skilled person would have analysed minor reaction products even if they were produced in low yields in case they turned out to be the desired product. Accordingly, Idenix contend that a skilled person who followed Strategy 6 would not merely have made the desired compound, but also would have detected, separated and characterised it.

516. Dr Griffon said in his witness statement that he was looking to synthesise the product in sufficient quantities to allow for (i) biological testing at Cagliari, (ii) a reference sample to be sent to Cambridge and (iii) a further quantity of material to be retained at Montpellier. For these purposes, he wanted about 100 mg of the product. In relation to the 2'-methyl up, 2'-fluoro down project, his aim was to develop a synthetic route that would deliver enough 2'-methyl-2'-fluoro uridine for these purposes and also for conversion to 2'-methyl-2'-fluoro cytidine. Thus his goal was to synthesise at least 200 mg or so of 2'-methyl-2'-fluoro uridine. This thinking influenced his approach to the project in that he was looking for reaction steps that would produce the desired product in high yields. His practice was therefore to investigate the major reaction products and ignore the others. Furthermore, if a particular reaction did not appear to give the desired product at the first attempt, he might try it again under different conditions, but he tended not to pursue the matter beyond that.

517. The picture which emerged in cross-examination was somewhat different. Although Dr Griffon repeatedly said that he was seeking yields of 20-30%, or even 30-50%, it is clear from his laboratory notebooks that he sometimes isolated and characterised products at lower yield, including ones at 15% and 16%. Furthermore, Dr Griffon started multiple experiments with amounts of starting material in the region of 50-100 mg, where getting 100-200 mg of product would simply have been impossible. Still further, Dr Griffon's Progress Reports make no mention of him only seeking high yields and do not use language which suggests that only major reaction products were considered. Yet further, Dr Griffon accepted that he had pursued his research with great persistence: his attitude to his experiments had been "never give up".

518. Above all, it is clear that Dr Griffon was not so poor a synthetic chemist that he did not ask himself what the minor products of reactions were. This is demonstrated in particular by the very evidence that Idenix rely upon and which formed the basis for their Experiments. As discussed above, Dr Griffon's TLC analysis of the crude deprotected reaction mixture revealed the presence of a number of products. Dr Griffon separated three of these. It is true that he only characterised one of them, which he hoped might be the fluorinated compound, but turned out not to be; but he still thought about what the other two were. Because he believed he knew what they were, he did not characterise them. (I should make it clear that Idenix do not suggest that Dr Griffon was mistaken in his belief as to the identity of the other two products.) I do not believe that, having got as close to his goal as he had by then, if Dr Griffon

had thought that one of the other minor products of the reaction was 2'-fluoro-2'-methyl uridine, he would not have attempted to separate and analyse it.

519. Furthermore, there is another, and in my view more plausible, reason, why at the time he did not think that the small spot which he ultimately suggested was 2'-fluoro-2'-methyl uridine was the target compound. As Prof Boons explained, that spot did not char when stained with the sulphuric acid, indicating that it did not contain a carbohydrate moiety.

520. Although Dr Brancale considered that Dr Griffon's approach did not correctly represent the approach which the skilled person would have adopted because he had not always analysed the minor reaction products, I found Prof Boons' evidence that, in a project of this nature, life was too short for a skilled person to take the time to analyse every minor reaction product more persuasive. No doubt Dr Brancale is correct that it is good science to do this, but, as Prof Boons pointed out, Dr Griffon had already spent a considerable amount of time getting to the point he had reached in mid February 2003. If he had paused to analyse every minor reaction product, it would have taken him rather longer to get to that point.

521. Accordingly, I conclude that there was nothing idiosyncratic about Dr Griffon's work. On the contrary, it represented a sustained effort by a chemist who was representative of the skilled person to synthesise 2'-fluoro-2'-methyl uridine, which at the time he reasonably believed to have been unsuccessful.

522. Furthermore, Dr Griffon was not working on his own, but received extensive advice from relevant experts. Counsel for Idenix sought to downplay the assistance Dr Griffon had received from others by arguing that there was no evidence that they were aware of his idiosyncratic approach. I do not accept this argument for two reasons. First, I do not accept that Dr Griffon's approach was idiosyncratic. Secondly, the evidence indicates that Dr Griffon explained to experts such as Prof Fleet and Dr Coe what approaches he had tried and what the results had been. If they had thought that he ought to have succeeded with a reaction that had apparently failed, I am sure they would have suggested that he try it again.

523. Finally on this topic, by the time Dr Griffon got to the point where Idenix say that he succeeded in making the target compound, albeit unknowingly, Dr Griffon had been working on the project for nearly 10 months.

524. *Dr Stewart's and Ms Wang's work*. Following Dr Griffon's substantial attempts to synthesise a 2'-methyl-up-2'-fluoro-down compound, the project was handed over to Dr Stewart and Ms Wang. Both Dr Stewart and Ms Wang received Dr Griffon's report summarising his work to date. Further, Dr Stewart was in contact with Dr Griffon by email and received his assistance. In addition to this, Dr Stewart also did a comprehensive search of the literature amounting to an average of at least two hours a day of searching for a period of six months. Dr Stewart also had regular meetings with Prof Fleet, and discussions about schemes with his colleagues on a weekly basis.

525. The route upon which Dr Stewart ultimately alighted was one suggested by Prof Fleet, involving the displacement of a triflate leaving group on a 5 or 6 membered lactone using TBAF or TSAF as a fluorinating reagent. This route was based on an azide displacement experiment carried out by Prof Fleet which Dr Stewart considered was

exciting because Prof Fleet was able to get the chemistry on the tertiary carbon to work.

526. It appears that Dr Stewart did not initially select DAST, although he had used DAST in his PhD research. It was only after it turned out that the 6 membered ring triflate was too unstable to be posted to him from Prof Fleet's laboratory that he finally attempted a DAST reaction.

527. Dr Stewart's first DAST reaction was on a 2'-methyl-up-2'-hydroxy-down lactone, and he successfully made the 2'-methyl-down-2-fluoro-up (i.e. the wrong stereoisomer of the compound). He described this as a "breakthrough", despite having made the compound with the wrong stereochemistry. However, his first attempts at trying the DAST reaction with the correct stereochemistry were all recorded as failures in his monthly reports, and an attempt on a six membered ring with DAST resulted in an inseparable mixture.

528. It was not until after Idenix received some information from a Pharmasset employee being interviewed for a role at Idenix that it was decided to shift the focus back onto the nucleoside route and lower the temperature of the DAST reaction on the nucleoside. On 12 January 2005 Dr Storer informed Dr Stewart by email that Dr Gosselin had told Dr Storer that "someone [Dr Gosselin] interviewed just after Xmas who worked at Pharmasset told him they made the compound from a nucleoside which may be good news for the other approach which Alistair [Stewart] discussed."

529. Dr Stewart replied that the information could be "very handy and might narrow things down a bit" and identified a number of potential changes to the nucleoside synthesis, including varying the fluorinating agent and changing the temperature at which DAST was being used. This information is likely to have been communicated to Ms Wang, who started an experiment using DAST at -68^{o}C (instead of room temperature) the next day.

530. Although the Pharmasset PCT was published on 13 January 2005, the documentary evidence suggests Dr Stewart first saw this on 18 January 2005.

531. Idenix contend that Ms Wang successfully made the 2'-methyl-up-2'-fluoro-down nucleoside analogue using DAST at the lower temperature, but Gilead contend that this is open to doubt. Ms Wang accepted that on the NMR spectra and in her monthly report relating to this experiment she had written a question mark, and she only did this where there was doubt. Nevertheless, I conclude on the balance of probabilities that Ms Wang did make the compound. But this was a long time after Dr Griffon had started work.

532. *The Idenix Experiments*. On 9 July 2014 Idenix served a Notice of Experiments ("the Notice") seeking to establish three facts:

    i) that the minor reaction product identified by an arrow labelled A on a photocopy of the TLC plate on page 12 of Dr Griffon's laboratory notebook from February 2003 was the compound 2'-fluoro-2'-methyl uridine;

ii) that when the experiment referred to on page 12 of that notebook is repeated, 2'-fluoro-2'-methyl uridine is obtained as a reaction product at an approximate yield of 15.7%; and

iii) that when experiments are carried out in accordance with the protocol given at Schedule 1 to the Notice, the results set out in Schedule 2 are obtained.

533. Gilead declined to admit these facts and requested the opportunity to inspect a repetition of the experiments. The repetition was inspected by Gilead over the period 25-30 August 2014. The repetition was carried out by a contract laboratory called Albany Molecular Research Inc ("AMRI") in Albany, New York State, USA, and in particular by a scientist called Dr Alex Clemens. The repetition was inspected by three representatives of Idenix and three representatives of Gilead. At trial Idenix sensibly did not attempt to prove or rely upon the original experiments which were the subject of the Notice, but only on the repetition.

534. Gilead make two complaints about the conduct of the repetition, both of which are unfounded in my view. First, Gilead complain that they were unable to ask Dr Clemens questions as he was performing the experiments. Repeating an experiment under the critical eyes of a party of inspecting scientists and lawyers is stressful for the experimenter, however. In such circumstances, it is common for the repeating party to stipulate that any questions be put in writing so as not further to distract the experimenter from his or her task. I do not consider that Idenix are to be criticised for adopting that position.

535. Secondly, Gilead complain that they were not provided with copies of the analytical and characterisation data generated during the experiments as the data were generated, but only on 3 September 2014 (together with a copy of Dr Clemens' laboratory notebook). Idenix say that AMRI did not have the facilities to provide copies on an ongoing basis. I am not particularly impressed with that excuse, but at the end of the day I cannot see what real difference it made to Gilead that they only received the copies after the repetition had been concluded.

536. On 5 September 2014 Idenix sent Gilead a draft joint report of the repetition, with various exhibits, asking for Gilead's comments by 10 September 2014. On 8 September 2014 Gilead's solicitors wrote to Idenix's solicitors saying:

> "You should not assume the experiments which were the subject of your notice are not in issue. To the extent to you wish to rely on the results obtained in the repeats or the original notice you will need to prove these experiments by serving appropriate evidence on 15 September."

On 10 September 2014 Gilead stated that they did not agree the draft joint report.

537. The only evidence served by Idenix concerning the experiments on the due date was a Report Regarding the Repetition of the Experiments ("the Report") exhibited to Dr Brancale's second report. Dr Brancale also expressed his opinion as to what the repeated experiments showed. No factual evidence was served from Dr Clemens. On 24 September 2014 Gilead's solicitors wrote to Idenix's solicitors querying this, and stating that Gilead would be content for any cross-examination of Dr Clemens to take place by video link.

538. This led to an application by Idenix which came before me on 30 September 2014. On that occasion Idenix sought a ruling that no evidence which Dr Clemens could give would be relevant. I declined to give any such ruling, and made it clear to counsel for Idenix that I considered that it was for him to decide whether to lead evidence from Dr Clemens or not. In the event, Idenix did not call Dr Clemens as a witness. Furthermore, Idenix claimed legal professional privilege in respect of their communications with AMRI regarding the Experiments.

539. In the meantime, on 25 September 2014 Idenix had served a witness statement from Indradeep Bhattacharya, an associate employed by Jones Day, Idenix's solicitors, who had attended the repetition. This was only a few days after he joined Jones Day. In his witness statement Mr Bhattacharya verified, as best he could, that the repeated experiments had been carried out in accordance with the experimental protocol set out in the Notice and that the copies of Dr Clemens' notebook and of the analytical and characterisation data exhibited to the Report were true, accurate and complete copies. In a second witness statement made on 1 October Mr Bhattacharya corrected a mistake regarding some of the exhibits. In cross-examination Mr Bhattacharya was, understandably, unable to shed light on Dr Clemens' reasons for doing what he had done.

540. So far as the first fact specified in the Notice is concerned, it is no longer suggested by Idenix that spot A is the 2'-fluoro-2'-methyl product. Dr Griffon's own evidence at trial was that he considered that spot A was probably uracil and that another, smaller spot on the TLC plate was the desired compound. This is the spot which did not char as discussed above.

541. As to the second fact specified in the Notice, there is no dispute that the repeated experiments establish that, following the protocol set out in the Notice, 2'-fluoro-2'-methyl uridine was produced as a minor product of the fluorination and deprotection reactions together with other products. There is a vigorous dispute as to the probative value of this evidence, however. Counsel for Gilead submitted that it was of no probative value for the following reasons.

542. First, the person who had designed the experimental protocol in the Notice had not been identified or called. Dr Brancale gave evidence that he was shown the protocol and asked "is that all alright?", but had no involvement in preparing it. In this regard, counsel for Gilead relied on what Pumfrey J said in *Mayne Pharma Pty Ltd v Debiopharm SA* [2006] EWHC 164 (Pat), [2006] FSR 37 at [9]:

> "This approach to the preparation of experimental evidence consisting, as it does, of presenting to the expert a fait accompli in the form of a completed experimental protocol is in my view always subject to the risk that it will be unhelpful, both in the general case and certainly in any case where anticipation by inevitable result is alleged. Indeed, it is difficult to conceive of any more effective way of leading an expert witness than to place in front of him a protocol for the performance of an experiment and ask a question of the form: That is all right, is it not?"

543. Secondly, Dr Clemens had not been called. In this regard, counsel for Gilead relied on what Kitchin J (as he then was) said in *Generics (UK) Ltd v Daiichi Pharmaceutical Co Ltd* [2008] EWHC 2413 (Pat), [2009] RPC 4 at [152]:

> "… it must be understood that if relevant questions do arise as to how experiments were designed and how they came to be conducted as they were, and if the witnesses attending court are unable to address such questions, then the weight which the court can attach to the experiments may be substantially reduced."

544. Thirdly, Prof Boons identified three main differences between the protocol followed by Dr Clemens and the procedure followed by Dr Griffon, as follows:

i) As noted above, Dr Griffon stained his TLC plates with 10% sulphuric acid in methanol. By contrast, Dr Clemens used iodine. Because of the different properties of sulphuric acid and iodine, it is possible that a different pattern of spots will be visualised.

ii) Dr Clemens used LC/MS (liquid chromatography/mass spectrum) analysis (a) to monitor the progress of the reaction and (b) to achieve an efficient separation of the reaction products by experimenting with different solvent conditions and identifying the peaks. Dr Griffon did not have access to LC/MS facilities at the relevant time, however, and therefore was not able to use it in this way.

iii) Dr Clemens used reverse phase HPLC to purify the reaction mixture where Dr Griffon used regular silica gel column chromatography. The former gives a higher level of resolution than the latter.

545. Fourthly, counsel for Gilead submitted that neither Dr Griffon's approach, nor that of Dr Clemens, represented what the average skilled person would have done in June 2003. So far as Dr Griffon's approach is concerned, Prof Boons' evidence was that the skilled person, when faced with a TLC plate that looked like Dr Griffon's TLC plate after the fluorination reaction, but before the deprotection reaction, would have stopped the reaction, since he would have thought it was a failure and that the protecting groups had probably come off and exposed the 3' and 5' hydroxyl groups which would be preferentially fluorinated over the 2' hydroxyl groups. As for Dr Clemens' approach, Prof Boons' evidence was that the average skilled person would not have used iodine, LC/MS or reverse phase HPLC.

546. Counsel for Idenix submitted that the first two matters did not matter, since the court had the evidence of what Dr Clemens did and what the results were. I do not accept this submission. The fact of the matter is that the Idenix Experiments departed from Dr Griffon's procedure in three respects, but no explanation whatsoever was given for this. In the absence of any alternative explanation, the natural inference is that the differences were thought likely to improve Idenix's prospects of getting the desired result. More specifically, the protocol followed by Dr Clemens suggests a focussed attempt to establish that the reaction mixture does contain a particular product rather than an investigation into whether the reaction had produced the desired product.

547. Turning to the materiality of those differences, counsel for Idenix submitted that the evidence showed that the differences were not material. I accept this in relation to the first difference, but not the the other two. So far as the first difference is concerned, Prof Boons said that, in nucleoside and carbohydrate chemistry, the stain commonly used was sulphuric acid, because it indicated the presence of carbohydrate-containing compounds. Although Prof Boons said that iodine was only used in specialised cases, he accepted that iodine was less likely to reveal the presence of carbohydrate-containing compounds. So far as the second difference is concerned, Dr Brancale agreed that Dr Clemens appeared to have used LC/MS to achieve an efficient separation. As to the third difference, Dr Brancale agreed that reverse phase HPLC gave better separation and this would not have been the first approach taken by a skilled person to purifying this type of reaction mixture in June 2003. Counsel for Idenix relied on the fact that these differences did not relate to the method of synthesis itself. Given that it is Idenix's case that Dr Griffon failed to detect and isolate a product which was in fact present in his crude reaction mixture, whereas a skilled person following the same procedure would have done so, however, these are potentially significant points.

548. So far as the fourth point is concerned, counsel for Idenix argued that the skilled person would have done what Dr Griffon did in one respect, but not in another: the skilled person would have proceeded with the deprotection reaction (as Dr Griffon did), but would have separated and analysed the more minor product in the way which Dr Clemens did (which Dr Griffon did not do). If one is considering what the average skilled person would have done, rather than what Dr Griffon did or might have done, then I found Prof Boons' evidence on the first aspect persuasive. As for the second aspect, I think that Dr Brancale substantially accepted that the skilled person in June 2003 would not have used LC/MS and reverse phase HPLC in the way in which Dr Clemens had.

549. Counsel for Idenix also pointed out that Gilead had had the opportunity to carry out an experiment in reply which precisely replicated the protocol followed by Dr Griffon, but had not done so. Prof Boons' evidence was this would have taken two or three days to carry out, and so Gilead had time in which to do this. There is no suggestion, however, that Gilead carried out such an experiment, but failed to put it before the court. Accordingly, there is no reason to infer that, if such an experiment had been done, it would have assisted Idenix. As it is, Idenix assumed the burden of proving the facts stated in the Notice, but in my judgment they failed to discharge it because they failed to follow the procedure followed by Dr Griffon, but deviated from it in a number of ways which (a) may have affected the result and (b) did not accord with the approach that the average skilled person would have adopted in June 2003. Furthermore, as I have explained, I am not persuaded that Dr Griffon's approach to the reaction was one that would have been followed by the skilled person in any event.

550. *Mr Clark's work.* As a counter to Gilead's reliance upon the work of Dr Griffon and his colleagues, Idenix rely upon Mr Clark's work. Idenix say that Mr Clark was able to make a 2'-methyl-up-2'-fluoro-down nucleoside analogue speedily and easily using DAST.

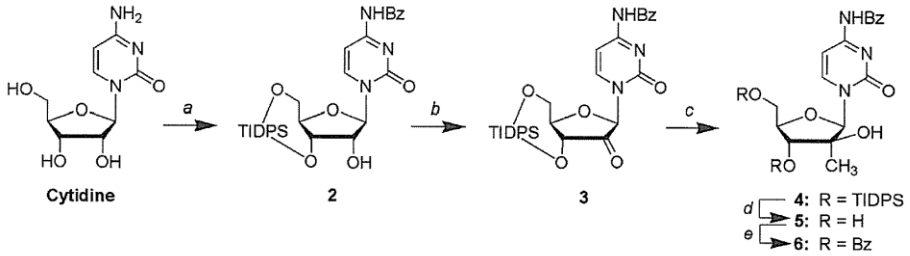
551. Neither side called Mr Clark to give evidence. Mr Clark brought proceedings against Pharmasset Delaware and Dr Schinazi in February 2008 seeking to avoid the

assignment provision in the Clark Agreement and assert ownership of a US patent. The proceedings were stayed for arbitration. After further court proceedings, Mr Clark commenced arbitration proceedings in March 2012. In June 2013 the arbitral panel issued a decision in favour of Gilead and Dr Schinazi. In those circumstances, it is understandable that Gilead did not call Mr Clark.

552. Gilead did, however, disclose Mr Clark's laboratory notebooks and other documents which Idenix adduced as hearsay evidence. The documents were considered by both Dr Brancale and Prof Boons. Both experts agreed that Mr Clark was not a very good record keeper, and therefore there is some uncertainty as to precisely what he did when.

553. It is convenient to begin with the description of the synthesis in the Clark Paper. The Clark Paper explains that N^4-benzoyl-1-(2-methyl-2,5-di-O-benzoyl-β-D-arabinofuranosyl)cytosine, compound 6, was chosen as the key intermediate. This was prepared in approximately 20% yield in six steps from cytidine by the route shown in Scheme 1, which I reproduce below.

Scheme 1[a]



[a] Reagents and conditions: (a) (i) Bz_2O, DMF, room temp, (ii) $TIDPSCl_2$, DMF; (b) DMSO, TFAA, TEA, −15 °C; (c) MeLi, −78 °C; (d) 1 M TBAF, concd HOAc, rt; (e) BzCl, pyridine, rt.

554. The six steps in this route were as follows:

i) Selective benzoylation of cytidine with benzoic anhydride in DMF to protect the amine group on the nucleobase (step (a)(i)).

ii) Treatment with $TIDPSCl_2$ in pyridine to protect the 3'- and 5'-hydroxyl groups on the sugar to produce compound 2 (step (a)(ii)).

iii) Oxidation of the 2'-alcohol to the 2'-ketone, compound 3, with trifluoroacetic anhydride in DMSO under Swern oxidation conditions (step b). Compound 3 was purified by silica gel chromatography followed by crystallisation from petroleum ether-dichloromethane.

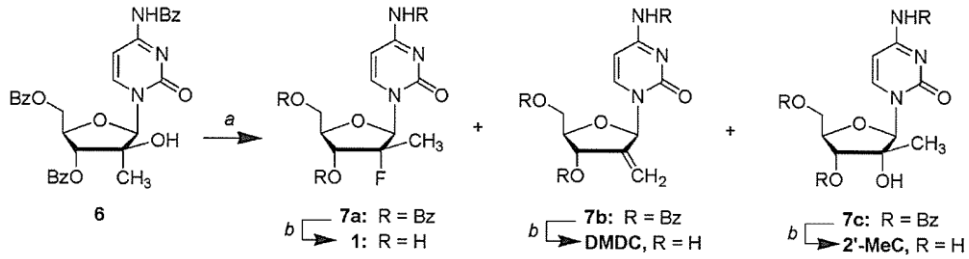
iv) Treatment of compound 3 with methyl lithium in diethyl ether at -78°C following the method of A. Matsuda *et al.*, "Alkyl addition reaction of pyrimidine 2'-ketonucleosides: Synthesis of 2'-branched-chain sugar pyrimidine nuclesides. (Nucleosides and nucleotides LXXXI.)", *Chem. Pharm. Bull.*, 36, 945-953 (1988) ("Matsuda II") gave exclusively the protected 2'-methyl-up-2'-hydroxy-down compound 4 (step c).

v) The 3',5'-silyl protecting groups were removed to give compound 5 (step d).

vi) The 3', 5'-hydroxyl groups were protected with benzoyl groups to give compound 6 (step e).

555. The intermediate compound 6 was then converted into the benzoyl-protected 2'-methyl-up-2'-fluorine-down compound 7a, together with the elimination product 7b and the 2'-methyl-down-2'-hydroxy-up compound 7c (i.e. the enantioner of compound 6) in 15-20% yield each by fluorination with DAST in toluene (step a), as shown in Scheme 2, which I reproduce below.

Scheme 2[a]



[a] Reagents and conditions: (*a*) DAST, toluene, −20 °C to rt; (*b*) MeOH/NH_3, rt.

556. The experimental section of the Clark Paper explains that compounds 7a, 7b and 7c were separated by silica gel chromatography eluting with 1:1:1 ethyl actetate-chloroform-hexanes. Each of these compounds was then deprotected with methanolic ammonia (step b), compound 7a yielding the target, title compound 1.

557. The Clark Paper comments on the fluorination reaction as follows (at page 5505):

> "The fluorination of tertiary alcohols using DAST has been reported, but the stereochemistry of such transformations is substrate-specific and often unpredictable. For instance, Yang et al. reported that the DAST fluorination of a tertiary alcohol in 2-bromomethyl-DL-*myo*-inositol proceeds with retention of configuration[14]. Wachtmeister et al. obtained a 4-fluoro-1-cyclopentanol containing a tertiary fluorine in 25% yield using DAST as a fluorinating reagent, and this transformation proceeded with inversion of configuration[15]. Furthermore, dehydrations or eliminations, rearrangements, and ring contractions are often pervading problems in the DAST fluorination of highly functionalized molecules[16]."

558. References 14, 15 and 16 are as follows:

i) Reference 14 is S.S. Yang *et al*, "Synthesis of DL-1-deoxy-I-fluro-6-O-methyl-chiro-inositol: Confirmation of a structural-DAST fluorination correlation", *Carbohydro. Res.*, 249, 259-263 (1993) ("Yang").

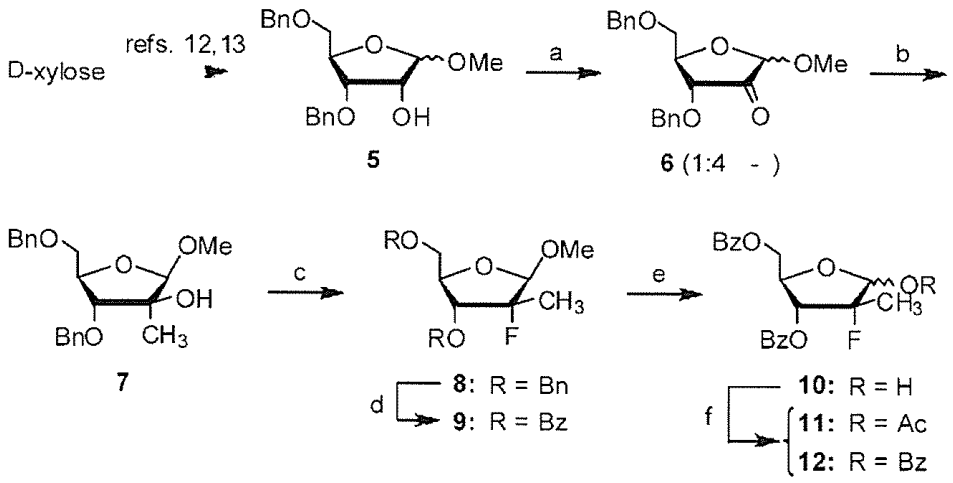
ii) Reference 15 is Wachtmeister.

iii) Reference 16 is Singh and Shreeve.

559. The Clark Paper goes on to say that the presence of the tertiary fluorine at the 2' position in compound 7a was confirmed by ^{1}H and ^{13}C NMR spectroscopy and the stereochemistry was determined by NOE ^{1}H NMR difference spectroscopy. The results of these spectroscopic examinations are set out. In addition, the Clark Paper states that the structure of compound 1 was unambiguously confirmed by X-ray crystallography.

560. In a follow-up paper by Clark and four co-authors, "Synthesis of 2-Deoxy-2-fluro-2-C-Methyl-Ribofuranoses", *J. Carbohydr. Chem.*, 25, 461-470 (2006) ("Clark II"), the authors say that, while the synthetic route described in the Clark Paper has the advantage of avoiding the glycosylation reaction to a nucleobase, it does not provide the opportunity to prepare a wide variety of base-modified nucleoside analogues. They therefore describe a more convenient approach to the synthesis of these compounds in which a protected 2-deoxy-2-fluoro-2-C-D-ribofuranose, compound 8, is prepared first and then used to glycosylate a variety of nucleobases.

561. As shown in Scheme 1, which I reproduce below, starting from D-xylose, compound 6 was prepared in a number of steps and then reacted with methyl lithium in diethyl ether at -78°C to produce the benzyl-protected 2'-methyl-up-2'-hydroxy-down sugar 7. This was then fluorinated with DAST in dicloromethane at room temperature to produce "a complex reaction mixture from which [compound 8] was isolated in 20% yield". Again, the regiochemistry of the fluorination was determined by ^{1}H and ^{13}C NMR spectroscopy and the stereochemistry by nuclear Overhauser enhancement ^{1}H NMR difference spectroscopy.



Scheme 1: Reagents and conditions: (a) TEMPO, NaOCl, 0°C; (b) MeLi, Et_2O, −78°C; (c) DAST, CH_2Cl_2, rt; (d) (i) Pd/C, cyclohexene, reflux, (ii) BzCl, pyridine; (e) ~80% HCO_2H, 60–70°C; (f) Ac_2O or BzCl, TEA, CH_2Cl_2.

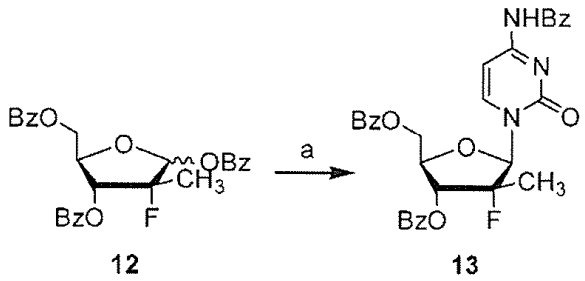
562. The authors again comment on the fluorination step, as follows (at page 463):

> "The major synthetic challenge for the synthesis of the 2-deoxy-2-fluoro-2-*C*-methyl-D-ribofuranoses (**8-12**) is the stereoselective introduction of the fluorine atom at the 2-position. In the initial synthetic planning, the number of literature examples describing the nucleophilic fluorination of tertiary alcohols, particularly those desiring stereospecificity,

> were scarce. Of the few literature examples that describe the nucleophilic fluorination of tertiary alcohols, both inversion[10] and retention of configuration[11] were reported. For the synthesis of methyl 3,5-di-*O*-benzyl-2-deoxy-2-fluoro-2-*C*-methyl-β-D-ribofuranoside (**8**), it was reasoned that the carbohydrate starting material, methyl 3,5-di-*O*-benzyl-2-*C*-methyl-β-D-arabinofuranoside (**7**), would not only serve to introduce the fluorine in the ribose configuration, but also minimize the number of stereocentres requiring assembly."

References 10 and 11 are Wachtmeister and Yang respectively.

563. After the fluorination step, the benzyl protecting groups at the 3' and 5' positions were then removed and replaced by benzoyl protecting groups, to yield compound 9. Formic acid cleavage of compound 9 yielded compound 10. This was acylated to give anomeric mixtures of compounds 11 and 12. This was then glycosylated with silylated N-benzoylcytosine to yield the protected 2'-methyl-up-2'-fluorine-down-cytidine compound 13, as shown in Scheme 2 which I reproduce below. Compound 13 produced by this route was found to be identical to that prepared by the linear approach.

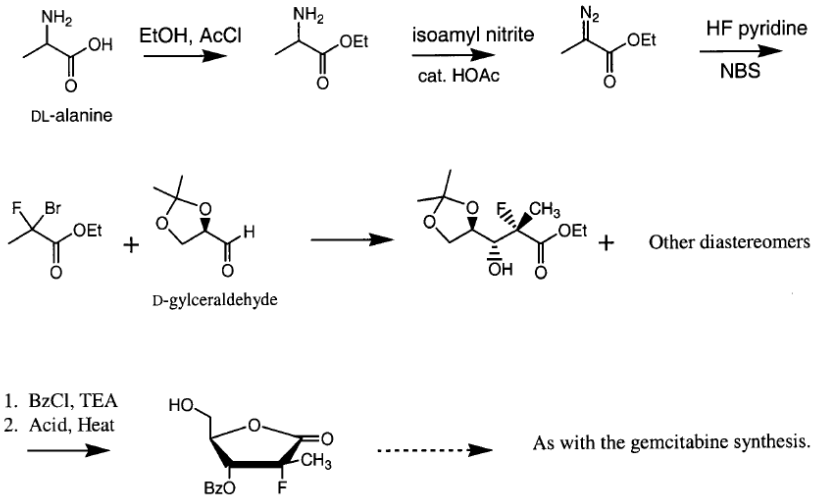


12 13

Scheme 2: Reagents and conditions: (a) bis(trimethylsilyl)N^4-benzoylcytosine, $SnCl_4$, MeCN, 50–55°C, 4 h.

564. According to the papers, Mr Clark and his colleagues first synthesised 2'-deoxy-2'-fluoro-2'-C-methylcytidine by the route described in the Clark Paper, which was a nucleoside route, and then synthesised a benzoyl-protected version of this compound by the route described in Clark II, which was a sugar route. In fact, it appears from the disclosure documents that it was the other way around. Furthermore, the sugar route was not the first route that Mr Clark attempted. Instead, it appears that he first attempted, but did not complete, the "small molecule" approach shown below, starting on 24 November 2002.

The original attempted synthesis of PSI-6130



565. By January 2003 Mr Clark was working on the sugar route. It appears that on 27 January 2003 he attempted to fluorinate the benzyl-protected 2-methyl-up-2-hydroxy-down sugar using DAST, but it is not clear what the result was. On 10 February 2003 he fluorinated the benzyl-protected 2-hydroxy-up-2-methyl-down sugar using DAST, apparently successfully. The resulting 2-methyl-up-2-fluoro-down sugar was then de-protected, re-protected with benzoyl groups, glycosylated and de-protected. He first synthesised 2'-deoxy-2'-fluoro-2'-C-methylcytidine (referred to in the documents as PSI-6130 or PSI-6120) on 10 May 2003.

566. In parallel with this work, Mr Clark seems to have been working on variants of the nucleoside route. On 28 April 2003 he attempted to fluorinate a 2'-methyl-up-2'-hydroxy-down 3'-5'-TIDPS-protected nucleoside in which the amine group at the 4 position in cytosine had been been protected by replacing it with an ethoxy group using DAST in dichloromethane, but found there was no observed product. By 21 July 2003 he appears to have been fairly well advanced with the synthesis described in the Clark Paper.

567. After this, Mr Clark and other Pharmasset chemists appear to have spent about a year and a half exploring alternative syntheses. Many of these attempts were unsuccessful.

568. Counsel for Idenix informed me, without contradiction by counsel for Gilead, that Mr Clark was a relatively junior and inexperienced chemist who did not have a PhD. On the other hand, he did not work alone, as can be seen from the fact that the Clark Paper had 14 authors, including Dr Schinazi, who counsel for Idenix not merely accepted, but asserted, was a leader in the field at that time, while Clark II had five authors, including Dr Schinazi.

569. The conclusion that I draw from Mr Clark's work is that he and his colleagues did succeed in synthesising a 2'-methyl-up-2'-fluoro-down compound much more quickly than the Idenix team. The question is why. In my view, the explanation lies in a combination of skill and luck. When Mr Clark and his colleagues carried out their retrosynthetic analysis, it evidently occurred to them at a reasonably early stage that,

if they took the sugar route, there were two key reactions to be achieved: conversion of the ketone to the 2'-hydroxy-up-2'-methyl down compound followed by S_N2 fluorination of the tertiary alcohol in that compound with inversion of the stereochemistry to give the 2'-methyl-up-2'-fluoro down compound. When planning the first reaction, it would appear that their literature searches turned up Matsuda II. As for the second reaction, it would appear from their comments in the Clark Paper and Clark II that they appreciated that stereospecific fluorination of the tertiary alcohol was likely to be challenging, but their searches turned up Singh and Shreeve, Wachmeister and Yang. Encouraged by the first two papers, they followed Wachtmeister's method, but using DAST rather than Deoxo-Fluor and omitting the pyridine. It is unclear why they used DAST and not Deoxo-Fluor. It is also unclear why they omitted the pyridine, whether this would have been expected to make any difference and whether this in fact did make any real difference. Whatever the answers to these questions, it is clear from the Clark Paper and Clark II that the success of the fluorination reaction was considered worthy of specific comment in publications in two high profile journals.

570. *To what extent does the teaching of the Patent on its own enable the skilled person to make the claimed compounds?* As is common ground, the Patent does not contain any instructions for synthesising any of the 2'-methyl-up-2'-fluoro-down compounds claimed. Idenix nevertheless contend that the specification does give the skilled person some assistance in the task, since it does disclose synthetic pathways to 2'-methyl-up-2'-hydroxy-down compounds in Schemes 3 and 4 and the accompanying text (see paragraphs 206-208 above). Idenix particularly rely upon the fact that the specification identifies "organolithium" as one of the possible reagents for making such compounds from precursors with a ketone at the 2' position.

571. In my judgment, however, the specification gives the skilled person little assistance. First, as Prof Boons pointed out, if the skilled person studied the text accompanying Schemes 3 and 4 (at [0117]-[0121] corresponding to page 123 line 1 – page 124 line 3 of the Application, quoted in paragraph 206 above, and [0122]-[0125]), he would wonder if it was written by someone who knew what they were talking about. The specification describes the production of the ketone by an oxidation step. Among the possible oxidising agents listed in the specification for this reaction, however, are Jones' reagent, an aggressive mixture of chromic acid and sulphuric acid which one would not use on a nucleoside, Collins' reagent and Corey's reagent, which again are aggressive reagents, and Raney nickel, which is a reducing agent, not an oxidising agent. I should say that counsel for Idenix objected in his closing submissions that this evidence was given in response to a question which I asked Prof Boons. I do not accept that objection, since my question arose out of counsel's cross-examination and Prof Boons' evidence. More importantly, counsel submitted that Gilead had not taken any point about the oxidation reaction. That is true, but Gilead do contend that the specification does not assist the skilled person to synthesise the claimed compounds.

572. Secondly, organolithium is just one of a list of possible reagents. Furthermore, no specific mention is made of methyl lithium, still less are appropriate reaction conditions given, nor is any reference given to Matsuda II.

573. Thirdly, even if the skilled person proceeds down this path, he is still faced with the problem of how to achieve stereospecific fluorination of the tertiary carbon. The specification gives the skilled person no assistance with this whatsoever. On their

face, where R^6 is methyl, Scheme 3 and Scheme 4 produce a 2'-methyl-up-2'-hydroxy-down compound. Fluorinating that compound would require retention of the stereochemistry, which would rule out an S_N2 reaction. In fact, however, organolithium reagents are generally not stereoselective, and so the product of the methylation reaction would be expected to be a mixture of isomers. It should then be possible to separate out the 2'-methyl-down-2'-hydroxy-up compound, which in principle it should be possible to fluorinate with inversion of the stereochemistry by an S_N2 reaction. But the specification says nothing about this, and the skilled person is left to work it out for himself. The skilled person is also left to find a fluorinating agent and reaction conditions which will achieve stereospecific fluorination of the tertiary carbon, rather than one of the competing reactions such as elimination.

574. Accordingly, I conclude that the specification on its own neither enables the skilled person to make the claimed compounds nor gives the skilled person any real assistance in doing so.

575. *Would the skilled person be able to make the claimed compounds applying his common general knowledge?* There was a difference of opinion between Dr Brancale and Prof Boons on this question.

576. Dr Brancale's opinion in summary was that the skilled person would be able to make substantially all of the claimed compounds without difficulty by routine methods, although there would have to be a degree of trial and error. The skilled person would start by carrying out a literature search and undertaking a retrosynthetic analysis. The skilled person would appreciate that, at the highest level of generality, there were two main alternative routes, the sugar route and the nucleoside route. Either way, the skilled person would conclude from his retrosynthetic analysis that the key modifications were the 2'-methyl-up and 2'-fluoro-down modifications. Dr Brancale outlined in his first report a synthetic strategy using the sugar route and a synthetic strategy using the nucleoside route. (Like him, I shall for convenience use 2' to refer to the appropriate position on the sugar in either route.) Both strategies involved conversion of a ketone at the 2' position to 2'-methyl-down-2'-hydroxy-up using methyl lithium, in the latter case following the method of A. Matsuda *et al*, "Radical Deoxygenation of Tert-Alcohols in 2'-Branched-Chain Sugar Pyrimidine Nucleosides: Synthesis and Antileukemic Acitivity of 2'-Deoxy-2' (S)-Methylcytidine", *Chem. Pharm. Bull.*, 35, 3967-3970 (1987) ("Matsuda I"), followed by nucleophilic fluorination using DAST, alternatively Deoxo-Fluor, as recommended in the the well-known textbook March, *Advanced Organic Chemistry: Reactions, Mechanisms* (5^{th} ed, 2001) and Singh and Shreeve. The skilled person would only need to make a few mg of the end product to begin with, in order to characterise it and test its activity, and the synthesis could be optimised subsequently. Dr Brancale accepted, however, that the work could take a few months.

577. Counsel for Gilead made a number of criticisms of Dr Brancale's evidence on this topic. First, Dr Brancale gave evidence that he had read the Clark Paper before he had considered the retrosynthetic analysis. Counsel for Gilead submitted that this inevitably meant that Dr Brancale's evidence was tainted by hindsight: he knew that 2'-fluoro-2'-methyl cytidine had been successfully made and he knew how it had been made. I accept this submission. In my view it is telling that, even though he expressly stated in his first report that the skilled person would undertake a retrosynthetic analysis, Dr Brancale did not go on to set out such an analysis i.e. working backwards

from the target compounds. Instead, he set out two synthetic routes working forwards from available starting materials. Both routes include the key steps in the Clark Paper, namely methylation of the 2' ketone with methyl lithium and fluorination of the resulting alcohol with DAST.

578. Secondly, Dr Brancale said nothing in his first report about the differences between primary, secondary and tertiary carbons and the difficulties of fluorinating on a tertiary carbon atom. In cross-examination, however, Dr Brancale accepted that this was difficult and challenging for the reasons explored below. Counsel for Gilead did not suggest that Dr Brancale had deliberately omitted to mention this in his report. Rather, he submitted that, because Dr Brancale had considered the retrosynthetic analysis with the benefit of the highsight gained from the Clark Paper, he had overlooked the difficulties that the skilled person would face without such hindsight. Again, I accept this submission.

579. Thirdly, although Dr Brancale gave evidence that the first thing the skilled person would have done was to undertake a literature search, he failed to consider what the outcome of such a search would have been. Rather, he seems to have simply assumed that it would have turned up the key references upon which Dr Brancale relied in his retrosynthetic analysis. Counsel for Gilead submitted that Dr Brancale had again oversimplified matters, no doubt for the same reason. Again, I accept this submission.

580. Turning to the key points in Dr Brancale's analysis, so far as the methylation step is concerned, Dr Brancale assumed that the skilled person would find Matsuda (I or II – for present purposes these papers can be treated as interchangeable). In this connection, counsel for Idenix understandably placed strong reliance upon Prof Boons' vivid evidence that, if one was trying to synthesise the 2'-methyl-down-2'-hydroxy-up compound, and carried out a literature search, Matsuda would be turned up "in a heartbeat". But this evidence has to be seen in its proper context, which was the assumption that the retrosynthetic analysis was concentrated on the route identified by Dr Brancale. Prof Boons made it clear that he did not accept that assumption. If the skilled person started with a clean sheet of paper and worked backwards from the target compound, the position would be rather different, because of the multiple possible routes that could potentially be adopted. This is graphically illustrated by Dr Stewart's evidence that he started his work by performing a literature search that took an average of two hours a day for six months (see paragraph 524 above), yet it does not appear that he turned up Matsuda. Nor does it appear that Dr Griffon had found Matsuda. I shall return to this point below.

581. So far as the fluorination step is concerned, I have no hesitation in accepting that March is a standard text which the skilled person would have on his bookshelf and would routinely consult. But what would the skilled person find if he consulted March? It must be borne in mind that it is a very long book (2112 pages including index), which is packed with detail. Dr Brancale did not explain how the skilled person would use the book, he simply cited the following passage from section 10-70 on "Formation of Alkyl Halides from Alcohols" (at page 519):

> "Hydrogen fluoride does not generally convert alcohols to alkyl fluorides.[1156] The most important reagent for this purpose is the commercially available diethylaminosulfur trifluoride (Et_2NSF_3) (DAST),[1157] which converts primary, secondary,

> tertiary, allylic, and benzylic alcohols to fluorides in high yields under mild conditions.[1158]"

582. This passage occurs in Chapter 10, which deals with aliphatic nucleophilic substitution. The skilled reader who already has DAST in their mind can quickly find this passage using the subject index, since it is indexed under "Alcohols … reaction with DAST" and "DAST … preparation of fluorides from alcohols". But the reader who does not already have DAST in their mind is forced to proceed more systematically.

583. If the skilled person started by refreshing his memory of the general principles regarding aliphatic nucleophilic substitution reactions, he would find earlier in Chapter 10 the following passage in the general section at the beginning (at page 433):

> "To sum up, primary and secondary substrates generally react by the S_N2 mechanism and tertiary by the S_N1 mechanism. However, tertiary substrates seldom undergo nucleophilic substitution at all. Elimination is always a possible side reaction of nuclephilic substitutions (wherever a β hydrogen is present), and with tertiary substrates it usually predominates. With a few exceptions, nucleophilic substitutions at a tertiary carbon have little or no preparative value."

Dr Brancale accepted that this was an accurate statement of the general position. Accordingly, the skilled person must be taken to read the passage on page 519 in this light. Read in that light, the statement that DAST converts tertiary alcohols, as distinct from primary and secondary alcohols, in high yields under mild conditions is surprising. Prof Boons' explanation was that the text was dealing with simple alcohols, not complex molecules. He did not disagree that DAST was often successful with primary and secondary alcohols, but said that tertiary alcohols were a different proposition. Again, I shall return to this point below.

584. As for Singh and Shreeve, this is not cited in March. Although Dr Griffon found this during the course of his literature searches, it seems that he did so some time after he started work on the project. There is no evidence as to precisely how he found this review. In any event, it is telling that, as noted above, the conclusion which Dr Griffon drew from Singh and Shreeve and Wachtmeister was that DAST was unlikely to work and that Deoxo-Fluor was a better bet. Furthermore, the major product of the reaction with Deoxo-Fluor was the elimination product.

585. Prof Boons' opinion in summary was that making any of the claimed compounds was a research project which represented a significant synthetic challenge and which was of uncertain outcome. He had conducted a literature search on the synthesis of 2'-methyl-2-fluoro nucleosides, and had found that no such synthesis of such a compound, regardless of stereochemistry, had been reported by June 2003. There was literature relating to 2'-methyl sugars/nucleosides and, separately, to 2'-fluoro nucleosides, but it would not have been thought possible to combine these teachings. A major difference between what had been reported and what needed to be accomplished was the nature of the fluorine at the 2' position: synthesis of a secondary fluorine at the 2' position had been reported, but not the synthesis of a

tertiary fluorine at the 2' position. The tertiary fluorine would fundamentally alter the reaction pathways compared to a nucleoside with a secondary fluorine at the 2' position. The skilled person undertaking a retrosynthetic analysis would have been confronted with a number of possible routes, all of which would have had potential difficulties associated with them, and the skilled person would not have known in advance which, if any, might have led successfully to the product. Nucleophilic substitution of a tertiary alcohol was just one possible step on one of these routes, but it was known to be difficult with competing reactions, including elimination and migration reactions. In addition to nucleophilic substitution, it was also known that fluorination could be attempted using electrophilic addition, but again this would be difficult to control. Accordingly, if asked to carry out this project, Prof Boons would have asked for a year's funding for a post-doctoral worker, would not have considered that success could be predicted and would have considered a successful synthesis worthy of publication in a peer-reviewed journal. Prof Boons formed this view before he knew about the numerous failed attempts by Dr Griffon. He subsequently reviewed various documents relating to these attempts, and concluded that they reflected a project of significant complexity with numerous failures, very much along the lines he had anticipated.

586. Counsel for Idenix advanced five main challenges to Prof Boons' evidence on this topic, apart from the question of Prof Boons' expertise, which I have already dealt with. First, he submitted that Prof Boons had raised a lot of theoretical potential difficulties which did not represent real obstacles. I do not accept this. In my judgment Dr Griffon's work demonstrates very clearly that Prof Boons' concerns were not merely theoretical and that the obstacles were real ones.

587. Secondly, counsel for Idenix submitted that Prof Boons had overstated the complexities of the retrosynthetic analysis. He argued that, as Dr Brancale's analysis demonstrated, the Patent identifies a key precursor and a method of making it, and if the skilled person needed more information, he would quickly locate Matsuda. March would then make DAST an obvious choice of reagent to fluorinate that precursor, and the skilled person would have a reasonable expectation of success. Again, I do not accept this. For the reasons given above, I do not consider that the skilled person would get any real assistance from the Patent. Furthermore, I found Prof Boons' evidence as to the complexities of the retrosynthetic analysis convincing. Yet further, it is supported by Dr Griffon's work.

588. Thirdly, counsel for Idenix criticised Prof Boons' evidence with regard to the methylation step, because Dr Brancale had clearly set out this part of his retrosynthetic analysis with its reference to Matsuda in his first report, but Prof Boons had not taken issue with it until cross-examined about it. I do not accept this criticism. As I have indicated, Prof Boons agreed that the skilled person who decided to proceed via the 2'-hydroxy-up-2'-methyl-down compound and carried out a literature search would turn up Matsuda and therefore would be able to synthesise that compound without difficulty. His point was a different one, namely that the 2'-hydroxy-up-2'-methyl-down compound is only one possible precursor and that one only arrives at that precursor working backwards in the retrosynthetic analysis if and when one has solved the problem of fluorinating the tertiary alcohol. Unless the skilled person perceives a solution to that problem, his retrosynthetic analysis will be likely to work back by other routes. This is illustrated by Dr Griffon's approach: his first strategy

was to try to fluorinate the 2'-ethenyl compound using AgF/I_2 (see paragraph 474 above).

589. Fourthly, counsel for Idenix submitted that Prof Boons had overstated the difficulty of the fluorination reaction. I do not accept this. Both Dr Brancale and Dr Griffon accepted that fluorination of a tertiary carbon was difficult and challenging. Moreover, Prof Boons gave cogent explanations as to why it was difficult and challenging. This evidence is supported by the Clark Paper and Clark II.

590. Fifthly, counsel for Idenix submitted that Prof Boons had understated the likelihood of the skilled person selecting DAST. In this regard, counsel for Idenix pointed out that Prof Boons himself had said, in a book he had written with Karl Hale, *Organic Synthesis with Carbohydrates* (Sheffield Academic Press, 2000) that "the most commonly applied reagent for direct fluorination is diethylaminosulfur trifluoride (Et_2NDF_3, DAST). In this reaction, an alcohol displaces a fluoride of DAST resulting in an activated intermediate, which in turn is displaced by the liberated fluoride (Scheme 3.2e)." Scheme 3.2e shows the fluorination of a secondary carbon, however, not a tertiary carbon. Moreover, Prof Boons did not dispute that DAST was a well-known and popular reagent. Thus I do not consider that this undermines Prof Boons' evidence.

591. In addition, counsel for Idenix cross-examined Prof Boons at some length on the scientific literature regarding DAST. The purpose of the cross-examination was to try to establish that the statement in March was supported by the literature. But counsel did not put to Prof Boons the primary reference given by March for his statement, reference 1158, which is W.J. Middleton, "New Fluorinating Reagents. Dialylaminosulfur Fluorides". *J. Org. Chem.*, 40, 574-578 (1975), even though that paper was included in the bundle produced by Idenix for Prof Boons' cross-examination. Instead, he put the following:

    i) Reference 1157, M. Hudlicky, "Fluorination with Diethylaminosulfer Trifluoride and Related Aminofluorosulfuranes", *Org. Reactions*, 35, 513-647 (1988) ("Hudlicky").

    ii) United States Patent No. 3,914,265 to Middleton, which is reference 9 in Hudlicky.

    iii) W. Dmowski, "Replacement of Oxygen by Fluorine" in Hudlicky and A.E. Pavlath (eds), *Chemistry of Organic Fluorine Compounds II: A Critical Review* (Americal Chemical Society, 1995) at 199-262.

    iv) A paper co-authored by Prof Boons, D. Noort *et al*, "Synthesis of a Potential Inhibitor of UDP-Glucuronosyltransferase", *Bioorg. & Med. Chem. Letters*, 2, 583-588 (1992).

    v) A.D. Borthwick *et al*, "Chiral Carbocyclis Nucleosides: The Synthesis and Antiviral Activity of 4'-Hydroxy and 4'-Fluorocarbocyclic-2'-Deoxyguanosines", *Bioorg. & Med. Chem. Letters*, 3, 2577-2580 (1993).

    vi) Wachtmeister.

592. Leaving aside the fact that none of these papers apart from Borthwick *et al* had been cited by Dr Brancale, it was not established a skilled person carrying out a retrosynthetic analysis in June 2003 would have conducted a literature search which would have turned up these references. Furthermore, if the skilled person had to conduct such a literature search, rather than simply relying on March, that in itself would suggest that the synthesis was far from routine.

593. In any event, I did not find the cross-examination persuasive. The question is whether the skilled person carrying out a retrosynthetic analysis would have (i) planned to follow a route in which the final step (i.e. the first step in the retrosynthetic analysis) involved nucleophilic fluorination of a tertiary alcohol, (ii) thought of using DAST to carry out that step and (iii) had a reasonable expectation that the reaction to work. Prof Boons' evidence was clear that he did not think it likely that the skilled person would plan such a route, or that the skilled person would have been likely to use DAST (he said that he himself would not have used it), or that the skilled person would have had a reasonable expectation of success. As I have indicated, I consider that Prof Boons' evidence is supported by Dr Griffon's work. But it is also supported by the fact that Prof Fleet did not suggest the use of DAST to Dr Griffon (he proposed electrophilic substitutions) and by the fact that Dr Coe's comments on the use of DAST made it clear that he expected it to lead to elimination and migration reactions.

594. *Conclusion*. Drawing these threads together, the conclusion I have reached is that the Patent does not enable the skilled person to make the claimed compounds without undue burden. The specification gives the skilled person no meaningful assistance, and so the skilled person has to rely upon his common general knowledge. The skilled person would undertake a retrosynthetic analysis, and would be immediately confronted with the problem that his target compound contained a tertiary fluorine with a particular stereochemistry. He would appreciate that making such a compound would be difficult and challenging, and there would a large number of potential routes to consider. The skilled person's prospects of success would depend on both skill and luck. If he was skilled and lucky, he could hit upon a successful synthesis fairly quickly, as Mr Clark and his colleagues did. If he was skilled but unlucky, he could spend many months on the problem without success, as Dr Griffon did.

Undue burden across the breadth of the claim?

595. I shall approach this issue on the assumptions that, contrary to my previous conclusion, the Patent when read with the common general knowledge (i) makes it plausible that the claimed compounds have anti-*Flaviviridae* activity and (ii) enables the medicinal chemist to synthesise substantially all of the claimed compounds without undue burden.

596. Even on those assumptions, Gilead contend that the Patent does not enable the skilled team to perform the invention across the breadth of claim 1 without undue burden. The basis for this contention is simple: even once the medicinal chemist has made one of the compounds, the virologist has to test it for antiviral activity. There is no dispute that testing a compound for anti-*Flaviviridae* activity would be routine work which in itself would not be unduly burdensome. But the claim covers billions of compounds and the Patent gives the skilled team no clue as to where to start. Dr Brancale accepted that it would take 3-6 days to synthesise a straightforward nucleoside analogue and that a more complicated case might take 2-3 months. As discussed

above, the Patent suggests using BVDV assays to identify active compounds, but 2'-deoxy-2'-fluoro-2'-C-methylcytidine is inactive in the BVDV assay. Admittedly, the virologist would know from his common general knowledge that the gold standard assay was the replicon assay, and 2'-deoxy-2'-fluoro-2'-C-methylcytidine turns out to be active in the replicon assay. But what this emphasises is that the Patent is setting the skilled team a substantial research project to select, synthesise and test the claimed compounds relying upon their own common general knowlege and claiming the results if they are successful.

597. Idenix's answer to this contention is that Gilead have not established that any of the claimed compounds do not work. Accordingly, Idenix say that the invention can be performed across the breadth of the claims without undue burden, because the medicinal chemist can make the compounds without undue burden and the virologist can test them without undue burden.

598. The Patent does not suggest that all of the claimed compounds have an anti-*Flaviviridae* activity, however. On the contrary, all it says is that they can be screened for such activity. Even if it is plausible that the claimed compounds do have such activity, it is clear from the evidence that they may turn not to do so when tested. Accordingly, I agree with Gilead that the Patent does not enable the skilled team to perform the invention across the breadth of the claim without undue burden because it sets the skilled team a research project and claims the results.

Subsidiary claims

599. Although Idenix contend that claims 2, 5-6, 21 and 24 have independent validity, counsel for Idenix did not advance any arguments in his closing submissions to support the independent validity of these claims if claim 1 as proposed to be amended was invalid for insufficiency.

Added matter

600. The law with regard to added matter was explained by Jacob LJ in *Vector Corp v Glatt Air Techniques Ltd* [2007] EWCA Civ 805, [2008] RPC 10 at [4]-[9]. The essential question is whether the skilled person or team would, upon reading the granted or amended patent, learn anything about the invention which he or they would not learn from the application or the unamended patent.

Claim 1 as granted

601. The Patent discards entirely 22 of the 23 general formulae disclosed in the Application, including their sub-classes, and claims only part of Formula (IX) disclosed in the Application. At first blush, this hardly amounts to added matter, but rather the subtraction of a great deal of subject matter. Furthermore, Idenix rely upon the passage at page 100 lines 16-29 (quoted in paragraph 197 above) and upon claims 9, 10 and 11 (set out in paragraphs 291-22 above) of the Application as providing a firm basis for the granted claims.

602. Gilead nevertheless contend that claim 1 as granted adds subject matter because it focuses the skilled team's attention on the sub-class of compounds of Formula (IX)

encompassed within that claim. Gilead say that no skilled team reading the Application would identify the subclass on page 100 as standing out.

603. Dr Brancale agreed that Formula (IX) did not stand out, but he said that the skilled team would pay particular attention to the subclass on page 100 of the Application because of the presence of claims 9-11. Counsel for Gilead pointed out, however, that Dr Brancale had agreed with Prof Götte that the scope of the compounds disclosed and claimed in the Application was substantial, and that it was not plausible that each compound claimed in the Application would be effective. Furthermore, counsel for Gilead drew particular attention to the following answer which Dr Brancale gave in cross-examination:

> "Q. … What else do you think the skilled man would understand to be of scientific value in [the application] that you can identify?
>
> A. The reasoning on this patent, and on the patent in general, is that very often the essence of the patent is in the claims. So clearly the good idea is there to be protected. If we have to look for science and want to know where the science – to start to look for science we have to start from the claims and I think within the claims to the more specific claims. That is what I said in the report. We have to look at the more specific claims because that is where we might find the actual needle in a haystack where the meat is in these ones. Then you can probably work your way around the patent and try to understand the connection there in terms of the science that it can offer -- well, what science is there to support it in terms of references maybe or in terms of data, if there is any data."

604. Counsel for Gilead submitted that Dr Brancale had been entirely correct to say that identifying compounds in the Application that were worth taking forward was like looking for a needle in a haystack, and that substantially altering the size of the area to be searched necessarily changed the teaching. Once 22 classes of compounds and large parts of the remaining class were discarded, leaving the subclass claimed in claim 1, the task facing the skilled team was different. The instruction "search among the compounds of claim 1 as granted to find those that have efficacy against *Flaviviridae*" was in substance a different instruction to "search among the 23 broad classes of compounds in the Application to find those that have efficacy against *Flaviviridae*".

605. I do not accept this argument. Although I agree that the Application is of stupendous breadth, one of many of the classes of compounds which it specifically identifies as a preferred embodiment of the invention is the subclass identified on page 100. Furthermore, the message that that subclass is one of the classes of particular interest is reinforced by claims 9-11. I do not consider that the skilled team would learn anything new about that embodiment of the invention as a result of claim 1 as granted being restricted to that subclass and claims to the other classes of compounds being abandoned. Accordingly, I reject the allegation of added matter in relation to claim 1.

Claims 4 and 5 as granted

606. Gilead also contend that there is added matter as result of the definition Base* in the compound of Formula (IX) as "a purine or pyrimidine base" in the Application and the narrower definition given to Base* in claims 4 and 5 of the Patent. The term "purine or pyrimidine base" is defined at page 104 of the Application by way of a non-exhaustive list encompassing a very large number of bases. In claim 4 of the Patent, Base* is limited to eight bases, namely cytosine, uracil, guanine, adenine, thymine, hypoxanthine, 5-fluorouracil and 5-fluorocytosine. In claim 5 of the Patent, the definition of Base* is still further limited to cytosine, uracil, guanine, adenine, thymine. The selections of bases in claims 4 and 5 are not disclosed as subclasses within the definition of purine or pyrimidine base in the Application. Furthermore, the particular sub-classes of compounds within the general Markush Formula (IX) claimed by claims 4 and 5 are not disclosed in the Application.

607. Counsel for Idenix had no answer to Gilead's argument on claim 4. I cannot see any basis in the Application for this particular selection of bases. Accordingly, the skilled team does learn something new about the invention from claim 4, namely that this group of bases is of particular interest. Accordingly, I conclude that claim 4 is invalid on this ground.

608. So far as claim 5 is concerned, however, counsel for Idenix pointed out that this claim is limited to the five natural bases which occur in DNA and RNA. The skilled team would be aware from their common general knowledge that those bases were of particular interest for use in nucleoside analogues with modified sugars since they were the most readily available and best characterised bases. Although this argument comes close to argument that the selection of the natural bases would be obvious, which is not enough to avoid an allegation of added matter, I am just persuaded that it would be implicit to this skilled team reading the Application that the natural bases would be of particular interest. Accordingly, I reject the added matter allegation against claim 5.

The claims as proposed to be amended

609. As explained above, it is Dr Brancale's evidence that it is not plausible that the compounds of Formula (IX) as defined in claim 1 of the Patent will be effective against *Flaviviridae* where R^1 and/or R^2 are "straight chained, branched or cyclic alkyl" or "benzyl, wherein the phenyl group is optionally substituted with one or more substituents". It follows that claim 1 is invalid at least on the ground of insufficiency. Idenix seek to meet this difficulty by amending claim 1 so to delete "straight chained, branched or cyclic alkyl" or "benzyl, wherein the phenyl group is optionally substituted with one or more substituents" from the lists of possible R^1 and/or R^2 substituents. As counsel for Idenix emphasised, the Intellectual Property Office did not raise any objection to the allowability of these amendments.

610. Nevertheless, Gilead contend that the amendments are not allowable on the ground that they will result in added matter. Counsel for Gilead submitted that, by deleting certain substituents from the list of substituents for R^1 and the list of substituents for R^2, Idenix was creating a narrower sub-class of compounds which was neither disclosed in the Application nor clearly and unambiguously derivable from it. Furthermore, to make matters worse, Idenix's own evidence was that it was plausible

that this new sub-class was effective against *Flaviviridae*, whereas this was not the case for the broader class. Accordingly, the skilled team would learn something new about the invention from the amended claim. I accept these submissions. Accordingly, I conclude that the amendment is not allowable.

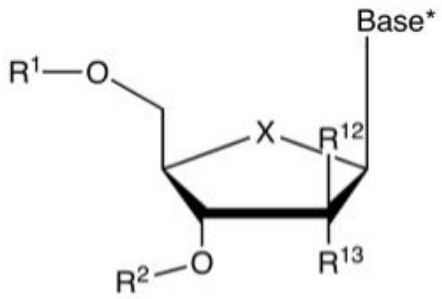
Can the granted claims be allowed to stand if they are partially invalid?

611. Perhaps realising that the amendment application was unlikely to succeed, counsel for Idenix submitted in the alternative that it was not necessary for Idenix to amend the granted claims if they were partially invalid. There is undoubtedly a line of authority that indicates that the court has a discretion to permit a patentee not to apply to amend to excise an invalid claim or an invalid combination of claims if the patent contains a valid claim or combination of claims: see *Hallen Co v Brabantia (UK) Ltd* [1990] FSR 134 at 140 (Aldous J), *Gerber Garment Technology Inc v Lectra Systems Ltd* [1994] FSR 471 at 483 (Aldous J), *Kirin Amgen Inc's Patent* [2002] EWHC 471 (pat), [2002] RPC 43 at [48] (Neuberger J, as he then was), *Zipher Ltd v Markem Systems Ltd* [2007] EWHC 154, [2007] FSR 18 at [18] (Lewison J, as he then was) and *Koninklijke Philips Electronics NV v Nintendo of Europe GmbH* [2014] EWHC 3177 (Pat) (Birss J). It is far from clear, however, that the court can permit a claim which is invalid as it stands and cannot be amended without adding matter to remain unamended on the ground that, if it could be amended, the amended claim would otherwise be valid. Even if the court has that power, this is not a case in which I would be prepared to exercise any discretion I may have in favour of Idenix, since I do not consider that it would be in the public interest to allow claim 1 to stand as it is.

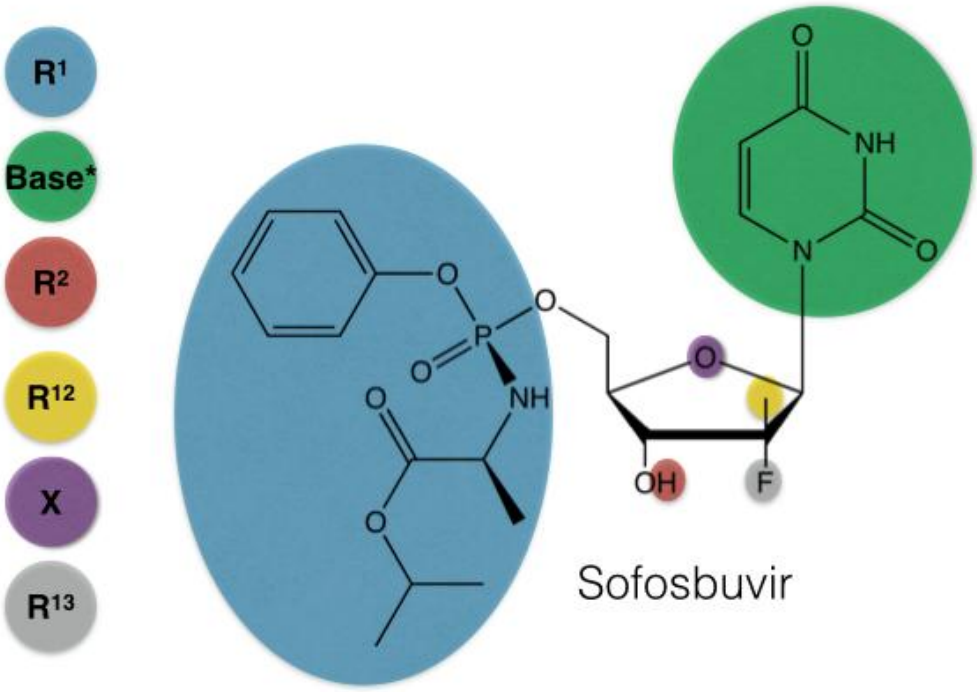
Infringement

Direct infringement

612. The following diagram compares Formula (IX) of the Patent with the structure of sofosbuvir.



Formula (IX)



Sofosbuvir

613. It is not in dispute that sofosbuvir conforms to the claimed structure in the following respects:

i) sofosbuvir has the general structure of Formula (IX), subject to the identity of the functional groups (R^1, R^2, etc);

ii) R^2 is H;

iii) X is oxygen;

iv) Base* is uracil, which is a pyrimidine base;

v) R^{12} is methyl; and

vi) R^{13} is F.

614. The dispute concerns R^1. As explained above, Idenix's case is that the masked phosphate group in sofosbuvir is "phosphate" within the meaning of the claim, so that this feature is present, while Gilead dispute this. As I have construed the term "phosphate", this requirement is satisfied. I would add that there is no dispute that sofosbuvir is useful for treating HCV. Accordingly, sofosbuvir falls within claim 1.

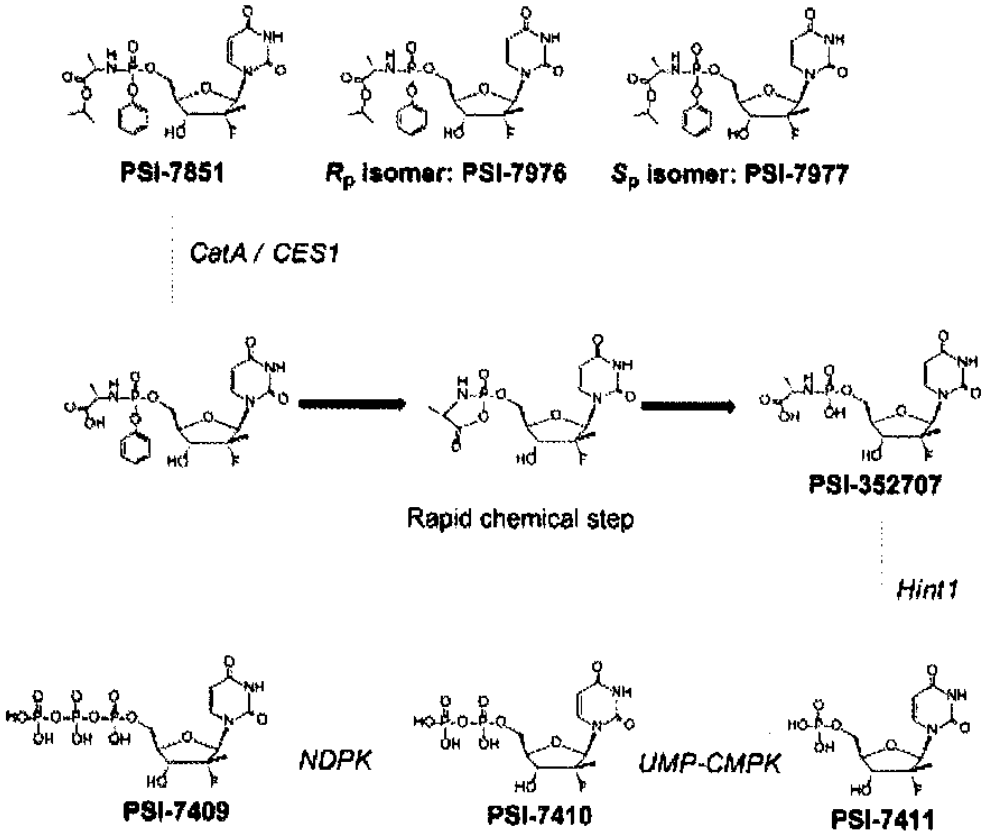
Indirect infringement

615. Idenix contend that, even if the term "phosphate" is to be construed as contended for by Gilead, and so there is no direct infringement of the claims, Gilead are nevertheless liable for indirect infringement of claim 1 pursuant to section 60(2) of the Patents Act 1977, which is one of the provisions declared by section 130(7) to be "so framed as to have, as nearly as practicable, the same effects in the United Kingdom as the corresponding provisions of the … Community Patent Convention … ". The corresponding provision of the CPC is Article 26, paragraph 1 of which provides:

> "A Community patent shall also confer on its proprietor the right to prevent all third parties not having his consent from supplying or offering to supply within the territories of the Contracting States a person, other than a party entitled to exploit the patented invention, with means relating to an essential element of that invention, for putting it into effect therein, when the third party knows, or it is obvious in the circumstances, that these means are suitable and intended for putting that invention into effect."

616. The nature and scope of the doctrine of indirect infringement was considered in detail by the Court of Appeal in *Grimme Landmaschinenfabrik GmbH v Scott* [2010] EWCA Civ 1110, [2011] FSR 7 at [70]–[131]. In *KCI Licensing Inc v Smith & Nephew pl*c [2010] EWCA Civ 1260 [2011] FSR 8 at [53] Jacob LJ summarised the key parts of the judgment of the Court of Appeal in *Grimme* with regard to the requirements of knowledge and intention.

617. The issue in the present case is a narrow one. It is common ground that sofosbuvir is metabolised as shown in the diagram below (Figure 7 from Elsuke Murakami *et al*, "Mechanism of Activation of PSI-7851 and Its Diastereoisomer PSI-7977", *J. Biol. Chem.*, 285, 34337-34347 (2010)), where PSI-7977 is sofosbuvir.



618. This sequence involves successive loss of the phenol and L-alanine isopropyl groups followed by formation of the mono-, di- and triphosphates. Accordingly, there is no dispute that metabolisation of sofosbuvir results in the production of at least one compound falling within claim 1 of the Patent. Nor is there any dispute that Gilead is well aware of this.

619. In these circumstances, Gilead accept that all the elements of section 60(2) are satisfied except the requirement that "the means are suitable … for putting that invention into effect". Gilead contend that this requirement is not satisfied because the claims are limited to compounds which are for administration to a patient and do not extend to metabolities. I do not accept this for the reasons given above. Accordingly, Gilead have indirectly infringed claim 1 by supplying sofosbuvir even if sofosbuvir does not itself fall within claim 1.

Subsidiary claims

620. There is no dispute that, if claim 1 is valid and infringed, then so too are claims 5-7, 21 and 24.

Summary of main conclusions

621. For the reasons given above, I conclude that:

i) Pharmasset Barbados was entited to claim priority from US368 at the date it filed the Pharmasset PCT;

ii) all the claims of the Patent except claims 20 and 37 lack novelty over the Pharmasset PCT;

iii) all the claims asserted to be independently valid lack an inventive step because the claimed inventions do not make any technical contribution to the art, and the same is true of the claims as proposed to be amended;

iv) all the claims asserted to be independently valid are invalid because they do not enable the claimed inventions to be performed without undue burden at all, alternatively across the breadth of the claims;

v) claim 4 is invalid on the ground of added matter, but none of the other claims;

vi) Idenix's application to amend the claims is not allowable since it would result in added matter;

vii) if they were valid, Gilead would have infringed claims 1, 5-7, 21 and 24.