



17 August 2021

Our Ref: Q40231EP CJM/JZC

STATEMENT OF GROUNDS OF APPEAL ON BEHALF OF GILEAD SCIENCES, INC.

Appeal No: T0795/21 - 3.3.01
Patent No: 2955190
Application No: 15154759.3
Patentee: NuCana plc
Opponent: Gilead Sciences, Inc.

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CONTENTS

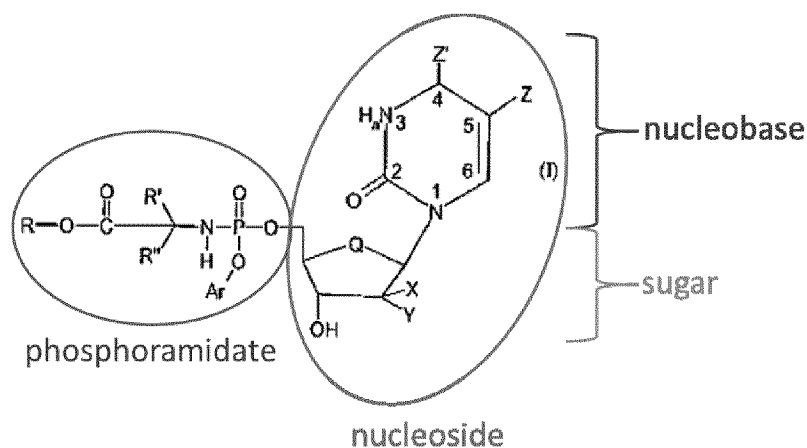
1	REQUESTS.....	3
2	INTRODUCTION AND APPEAL OUTLINE	4
3	DOCUMENTS AND ADMISSIBILITY.....	8
4	CLAIM INTERPRETATION	19
5	ADDED SUBJECT MATTER	27
6	SUFFICIENCY	39
7	INVENTIVE STEP	76
8	ANNEX A - CASE LAW RELATING TO COMPREHENSIVE SEARCHES.....	130
9	ANNEX B - SUMMARY OF ATTEMPTS BY IDENIX	133
10	ANNEX C - "ROUTE 22"	147
11	ANNEX D - D36 IS THE CLOSEST PRIOR ART	153

1 REQUESTS

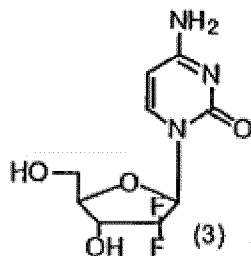
- 1.1 An opposition to European patent no. 2955190 in the name of NuCana plc (“the patentee”) was filed by Gilead Sciences, Inc. (“the opponent”) on 17 December 2018.
- 1.2 Oral proceedings were held on 8 February 2021. The main request of the patentee was for the patent to be maintained as granted, or failing that on the basis of auxiliary requests 1 to 6 filed on 6 November 2020, on the basis of auxiliary requests 7 to 12 filed on 14 January 2021 or on the basis of auxiliary request 13 filed during oral proceedings on 8 February 2021. The opponent requested that the patent be revoked in its entirety on grounds of added subject matter, lack of sufficiency and lack of inventive step.
- 1.3 The decision of the opposition division dated 7 April 2021 upheld the patent in amended form based on auxiliary request 13. The opponent requests that the decision of the opposition division dated 7 April 2021 be set aside, and that European patent no. 2955190 be revoked in its entirety.
- 1.4 In the event that the board contemplates any decision other than revocation of the patent, the opponent requests oral proceedings. Should oral proceedings be appointed, the opponent asks that interpretation into English be provided if the patentee or board of appeal wishes to speak in a language other than English.

2 INTRODUCTION AND APPEAL OUTLINE

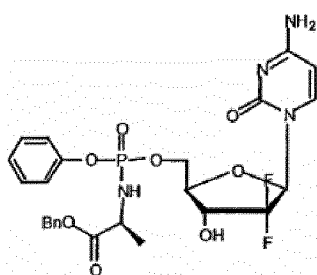
- 2.1 A brief outline of the background of the present case and the grounds and reasoning under which the opponent appeals against the decision of the opposition division is provided to assist the board.
- 2.2 The opposed patent claims a compound defined by a general formula (I), reproduced below, and its use in the treatment of cancer. The compound is a phosphoramidated derivative of a nucleoside. The compound can be conceptually considered as having two main portions: the phosphoramidate pro-group, and the nucleoside. The nucleoside itself consists of a nucleobase attached to a (deoxy)ribose sugar ring.



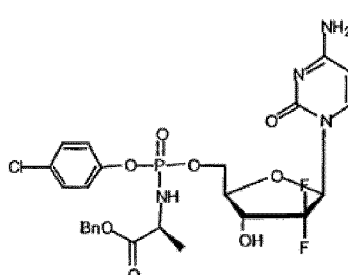
- 2.3 Arguments in the proceedings leading to the decision under appeal focussed in particular on the synthetic accessibility of the compounds claimed by the patent and their activity as anticancer agents. It is the position of the opponent that the patent does not provide sufficient information to allow one of ordinary skill in the art to synthesize compounds falling within the scope of the claims based on the teaching of the patent and their common general knowledge. It is further the position of the opponent that compounds alleged by the patentee to fall within the scope of the claims are not associated with anticancer activity. These points are contested by the patentee.
- 2.4 It is uncontested that the patent contains only three examples of compounds which fall within the scope of the claims. These compounds are referred to as CPF-31, CPF-40 and CPF-41 and are depicted on pages 40 and 41 of the patent. The structures of these compounds are highly conserved. As depicted below, all three compounds have the same nucleoside, corresponding to the commercially available compound gemcitabine, which is acknowledged in the patent to be a “well-established anticancer agent” (see paragraph [0002] of the patent). Likewise, all three compounds have the same cytosine nucleobase.



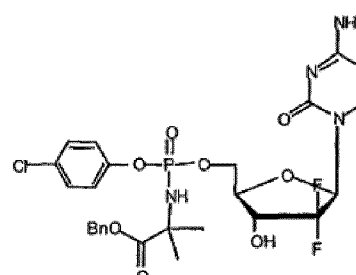
Gemcitabine



CPF-31



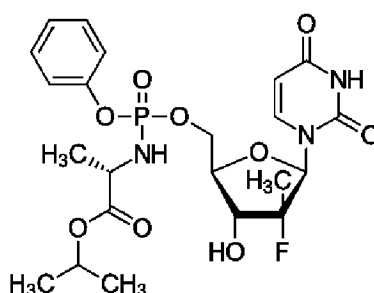
CPF-40



CPF-41

- 2.5 All of CPF-31, CPF-40 and CPF-41 have the same atoms at the positions denoted “X” and “Y” in Formula (I) of the patent. Thus, all three compounds have fluorine at each of these positions. The ring atom carrying the di-fluoro substituent in each of CPF-31, CPF-40 and CPF-41 is referred to as the 2' atom. Accordingly, each of CPF-31, CPF-40 and CPF-41 is “2'-difluoro” substituted (also written as “2'-F/2'-F”).
- 2.6 It is the position of the opponent that it was not possible for a skilled person at the priority date to synthesize compounds having certain other chemistry at the 2' position of the sugar ring. In particular, it is the position of the opponent that compounds having a 2'-Me/2'-F substituent could not be synthesized by the skilled person based on the teaching of the patent and his or her common general knowledge.
- 2.7 It is also the position of the opponent that compounds within the scope of the claims of the patent as granted and in the form maintained by the opposition division are not active as anticancer agents. In particular, it is the position of the opponent that at least compounds having 2'-Me/2'-F, 2'-Cl/2'-F and 2'-Br/2'-F substitutions are not active in treating cancer as they are not cytotoxic against cancer cells.
- 2.8 In the decision under appeal the opposition division considered that compounds having a 2'-Me/2'-F substituent could be synthesized by the skilled person based on the teaching of the patent and his or her common general knowledge. This finding was incorrect and is appealed herein.

- 2.9 The opposition division found that compounds having 2'-Cl/2'-F substitutions are not cytotoxic and accordingly held that the claims of the patent as granted as well as those of Auxiliary Requests 1-12 filed in advance of the oral proceedings lacked inventive step. However the opposition division considered that a single compound with 2'-Me/2'-F substitution was cytotoxic in a specific breast cancer cell line (that is not even mentioned in the patent) and that in the absence of data on 2'-Br/2'-F substitutions the benefit of doubt was given to the patentee that these compounds might be cytotoxic in cancer cells. This finding was incorrect, and led to the opposition division mistakenly allowing the maintenance of the patent on the basis of AR13, filed at 5:30 pm on the day of the oral proceedings.
- 2.10 The bulk of the discussion around compounds having a 2'-Me/2'-F substitution centred on the compound sofosbuvir, which is alleged by the patentee to fall within the compound definition of the patent. Sofosbuvir has the following structure:



- 2.11 Sofosbuvir differs from the claimed compounds which are exemplified in the patent at least at the 2' position on the sugar ring, at the R position of the phosphoramidate and in the base moiety. The claimed compounds exemplified in the patent all have a cyclic, aromatic benzyl group at the R position. By contrast, sofosbuvir has a non-cyclic, non-aromatic iso-propyl group at the corresponding position. The claimed compounds exemplified in the patent all have a cytosine nucleobase, whereas sofosbuvir has a uracil nucleobase. As explained below, sofosbuvir is not associated with anti-cancer activity.
- 2.12 Sofosbuvir is a revolutionary therapeutic agent, approved by the European Medicines Agency (EMA), as well as the US FDA and many other regulatory authorities around the world. Sofosbuvir is not a generic product but is an innovative product which resulted from many years of research and development by the opponent's group of companies and many hundreds of millions of US dollars in R&D and regulatory expenditure, including costly and time-consuming clinical trials. Sofosbuvir is developed and marketed by Gilead, the opponent in these proceedings, and is protected by the opponent's own patents.
- 2.13 Sofosbuvir-containing products are marketed under the tradenames SOVALDI®, HARVONI®, EPCLUSA® and VOSEVI®, all of which are approved by the EMA for

the treatment of infections of the liver by hepatitis C virus, HCV. The WHO estimates that in excess of 71 million people worldwide and more than 5 million people in Europe are infected with HCV: every year approximately 400,000 people die from HCV-related causes. In this context, sofosbuvir does not merely alleviate the symptoms of HCV, but is the first compound to offer a *cure* to most patients, whilst avoiding many of the side effects associated with previous HCV therapies. Since 2013, over 1,700,000 people around the world have been treated with a sofosbuvir-based therapy. Sofosbuvir was accordingly granted *break-through therapy* status by the US FDA in 2013 and is now listed as an *essential medicine* by the WHO.

- 2.14 The extraordinary success of sofosbuvir in treating HCV, arising solely from the opponent's research and development activities, has resulted in numerous third parties seeking to establish exclusive rights to this drug. All such attempts are without merit and have been rejected by courts around the world. In the first instance proceedings the unsuccessful attempts by one such third party (Idenix Pharmaceuticals) were discussed, as the findings of fact from the worldwide litigation between Gilead and Idenix are highly relevant to the facts of this case. Further unsuccessful attempts have been made by other third parties including (separately) Merck & Co and the University of Minnesota. In all proceedings patents which allegedly cover sofosbuvir have been found invalid and/or unenforceable for similar reasons that led to the Idenix patents being found invalid.
- 2.15 As noted above, the patentee's arguments in these proceedings rely on establishing that sofosbuvir has anticancer activity. The opposition division incorrectly agreed. However, sofosbuvir is **not** an anticancer medication and does not have anticancer activity.
- 2.16 Following the decision of the opposition division, the patentee and opponent are engaged in legal proceedings in the UK and Germany. The patentee alleges that sofosbuvir infringes the claims of the patent as maintained. The patentee has made no attempts to market sofosbuvir itself, yet has sought court injunctions against the sale of sofosbuvir in these countries by the opponent, in addition to financial relief. The opponent is rigorously defending these court actions which, despite being without merit, if successful would jeopardise the health of tens of thousands of people with HCV who would be otherwise successfully treated with sofosbuvir.

3 DOCUMENTS AND ADMISSIBILITY

3.1 During the opposition proceedings, documents D1 to D115 were relied upon by the parties. In this statement of grounds of appeal, the opponent makes reference to the following documents that were cited during the opposition proceedings:

D1: EP-B-1523489

D2: Opposition Division Decision of 18 April 2016 revoking D1

D3: Lal et al., "Electrophilic NF Fluorinating Agents", Chem. Rev. 1996, 96, 1737-1755

D4: Singh et al., "Recent Advances in Nucleophilic Fluorination Reactions of Organic Compounds Using Deoxofluor and PAST", Synthesis 2002, 17, 2561-2578

D5: WO 2005/003147

D6: 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. 2005, 48, 5504-5508

D7: Clark et al., "Synthesis and antiviral activity of 2'-deoxy-2'-fluoro-2'-C-methyl purine nucleosides as inhibitors of hepatitis C virus RNA replication", Bioorg. Med. Chem. Lett. 2006, 16, 1712-1715

D8: Clark et al., "Synthesis of 2-Deoxy-2-Fluoro-2-C-methyl-D-Ribofuranoses", J. Carbohydrate Chem. 2006, 25, 461-470

D9: Patentee letter of 29 February 2016 to Exam Division

D10: Decision of the English High Court, Decision [2014] EWHC 3916 (Pat), 01.12.14

D11: Court of Appeal Decision [2016] EWCA Civ 1089 dated 8 November 2016 on appeal from Decision D10

D12: Email of 9 December 2002 of Dr J-F Griffon and attached Progress Report for 01/11/2002

D13: Progress Report for December 2002 of Dr J-F Griffon and Audrey Chappe

D14: Email of 3 February 2003 of Dr J-F Griffon and attached Progress Report for January 2003

D15: Email of 4 March 2003 of Dr J-F Griffon and attached Progress Report for February 2003

D16: Letter of 8 February 2003 from Dr Richard Storer of Idenix to Dr Paul Coe

D17: Dr Paul Coe's letter replying to D16

D18: Email of 3 June 2003 from Dr J-F Griffon and attached Progress Report for May 2003

D19: Email of 28 August 2003 from Dr J-F Griffon and attached Progress Report for July and August 2003

D20: Prioritized Summary of Idenix meeting held on 10 May 2004

D21: Report from meeting summarized in D20

D22: Email of 11 November 2004 from Dr Alistair Stewart to Dr Richard Storer

D23: Email of 7 January 2005 from Dr Alistair Stewart to Dr Adel Moussa

D24: Deposition of Dr Alistair Stewart taken on 19 June 2013 in connection with US PTO Patent Interference 105,871

D25: Substitute Declaration of Dr Griffon from Patent Interference 105,871 before the USPTAB

D26: Notebook 1 referred to as Ex 1276 in D25

D27: Notebook 2 referred to as Ex 1282 in D25

D28: Summary of Results of a Literature Search of 27 February 2004 referred to as Ex 1289 in D25

D29: Report of Meeting on 2 December 2002 referred to as Ex 1294 in D25

D30: Report of Meeting on 3 December 2002 referred to as Ex 1295 in D25

D31: Resume of Dr Griffon referred to as Ex 1275 in D25

D32: Transcript of English High Court Trial Day 4 pp. 468-469

D33: Transcript of English High Court Trial Day 2 pp. 202-203

D34: EP-B-2332952

D35: Opposition Division Decision of 26 April 2018 revoking D34

D36: US 2003/0109697 A1

D37: Feng J.Y. et al., "Role of Mitochondrial RNA Polymerase in the Toxicity of Nucleotide Inhibitors of Hepatitis C Virus", Antimicrobial Agents and Chemotherapy, 2016, 60(2), 806-817

D38: US Patent Application No. 15/279,611, Response of 22 December 2017 to Non-Final Office Action

D39: Declaration of Hugh Griffith referred to in D38

D40: Slusarczyk M. et al., "Application of ProTide Technology to Gemcitabine: A Successful Approach to Overcome the Key Cancer Resistance Mechanisms

Leads to a New Agent (NUC-1031) in Clinical Development”, J. Med. Chem. 2014, 57, 1531-1542

D41a: Declaration of Dr Victor Marquez

D41b: CV of Dr Victor Marquez

D42a: Declaration of Professor Geert-Jan Boons

D42b: CV of Professor Geert-Jan Boons

D43: Professor Boons’ Expert Report to the English High Court referred to in D10

D43a: Expert Report of Professor Geert-Jan Boons with Section 13 unredacted

D44: Annex A: Summary of Attempts made by Idenix to make a 2’-fluoro down 2’-methyl up Nucleoside Compound

D45: [No Document]

D46: [No] Document]

D47: Mehellou, Y. et al., "The Protide Prodrug Technology: From the Concept to the Clinic", J. Med. Chem. 2018, 61, 2211-2226

D48: Declaration of Professor Stephen G Davies

D49: Declaration of Dr. Woo-Baeg Choi

D50: Declaration of Dr. Richard Bouglas

D51: Declaration of Dr. David Harrison

D52: Krenitsky et al., "An Enzymic Synthesis of Purine D- Arabinonucleosides", Carbohydrate Research, 1981, 97, 139-146

D53: Verbruggen, H. et al., "Synthesis of Nucleosides", Organic Reactions, 2000, 55, 1-630

D54: Hertel, L.W. et al., "Synthesis of 2-Deoxy-2,2-difluoro-D- ribose and 2-Deoxy-2,2-difluoro-D-ribofuranosyl Nucleosides", J. Org. Chem. 1988, 53, 2406-2409

D55: Pankiewicz, K.W. "Review of Fluorinated nucleosides", Carbohydrate Research, 2000, 327, 87-105

D56: Weigel, J. "A New Method for the Synthesis of α,α - Difluoro- β -hydroxy Esters through the Enolization of S-tert-Butyl Difluoroethanethioate", J. Org. Chem 1997, 62, 6108-6109

D57: "Halogeno-sugars" in Carbohydrate Chemistry, Volume 31, The Royal Society of Chemistry, 2000, 118-122

D58: WO 03/068164

D59: Jackson, R.F.W. et al., "A New Approach to the Synthesis of β -Hydroxy- α -amino Acids Using (Arylthio)nitrooxiranes", J. Org. Chem. 1995, 60, 6431-6440

D60: Rayner, C. M., "Synthesis of thiols, selenols, sulphides, selenides, sulfoxides, selenoxides, sulfones and selenones", Journal of the Chemical Society, Perkin Transactions 1: Organic Chemistry, 1999, 7, 737-748

D61: Bull et al., "Asymmetric alkylations using SuperQuat auxiliaries - an investigation into the synthesis and stability of enolates derived from 5,5-disubstituted oxazolidin- 2-ones", J. Chem. Soc. Perkin Trans. 1999, 1, 387-398

D62: O'Brien, P., "Stoichiometric asymmetric processes", J. Chem. Soc. Perkin Trans. 2001, 95-113

D63: Heathcock et al., "Stereochemistry of the Addition of Lithium Enolates to α -Alkoxy Aldehydes", J. Org. Chem. 1980, 45, 3846-3856

D64: Harris et al., "Complex Target-Oriented Synthesis in the Drug Discovery Process: A Case History in the dEpoB Series", J. Org. Chem. 1999, 64, 8434-8456

D65: Hayakawa, H. et al., "Reaction of Organometallic Regents with 2'- and 3'-Ketouridine Derivatives: Synthesis of Uracil Nucleosides Branched at the 2'- and 3-Positions", Chem. Pharm. Bull. 1987, 35, 2605

D66: Jorgensen et al., "Stereoselective Synthesis of C-Branched Nucleoside Analogues", Studies in Natural Products Chemistry, 1996, 19, 511-547

D67: Matsuda, A. et al., "Alkyl Addition Reaction of Pyrimidine 2'-Ketonucleosides: Synthesis of 2'-Branched-Chain Sugar Pyrimidine Nucleosides", Chem. Pharm. Bull. 1988

D68: Herdewijn, P. et al., "Synthesis of Nucleosides Fluorinated in the Sugar Moiety. The Application of Diethylaminosulfur Trifluoride to the Synthesis of Fluorinated Nucleosides", Nucleosides & Nucleotides, 1989, 8, 65-96

D69: Pankiewicz, K., and Watanabe, K., "Synthesis of 2'-B-fluoro-substituted nucleosides by a direct approach", Journal of Fluorine Chemistry, 1993, 64, 15-36

D70: Hudlicky M. "Fluorination with Diethylaminosulfur Trifluoride and related Amino fluorosulfuranes", in Organic Reactions, Vol. 35, 1998, 513-637

D70a: Hudlicky M. "Fluorination with Diethylaminosulfur Trifluoride and related Amino fluorosulfuranes", in Organic Reactions, Vol. 35. 1998. 513-637

D71: Singh et al. "Recent Advances in Nucleophilic Fluorination Reactions of Organic Compounds using Deoxofluor and PAST", Synthesis, 2002, 17, 2561-2578

D72: Substitute Clark Substantive Motion 9 from Patent Interference 105,871 before the USPTAB

D73: EP 1754710

D74: Dax et al., "Fluorinated Carbohydrates. Some New Aspects in Synthesis and Application", *Current Organic Chemistry* 1999, 3, 287-307

D75: Novo et al. "Stereocontrolled Syntheses of Fluorinated Carbohydrates", in Soloshonok, V (Ed.). *Enantiocontrolled Synthesis of Fluoro-Organic Compounds* (349-390)

D76: Pathak, T. "Azidonucleosides: Synthesis, Reactions, and Biological Properties", *Chemical Reviews*, 2002, 102.1623-1667

D77: Clark Substantive Motion 9 from Patent Interference 105,871 before the USPTAB

D78: Pharmasset Chemistry Progress Report dated January 31, 2003 referred to as Exhibit 2108 in D74 and D75

D79: Jeremy Clark Notebook No. 1058, pp. 25, 26 referred to as Exhibit 2103 in D74 and D75

D80: Ann J. Hobbs Notebook No. 1013, pp. 148, 149, 151, 153, 155, 157, 160, 161-164, 184, referred to as Exhibit 2127 in D74 and D75

D81: Pharmasset Chemistry Meeting Minutes dated January 31, 2003 referred to as Exhibit 2106 in D74 and D75

D82: Overhead Transparency labelled "Jeremy Clark: 3.28.03" referred to as Exhibit 2130 in D74 and D75

D83: Urlaub et al., "Selective Killing of Methotrexate-resistant Cells Carrying Amplified Dihydrofolate Reductase Genes", *Cancer Research* 1981, 41, 1594-1601

D84: Brox et al., "Studies on the Growth Inhibition and Metabolism of 2'-Deoxy-2'-fluorocytidine in Cultured Human Lymphoblasts", *Cancer Research* 1974, 34, 1838

D84a: Grounds of appeal filed by Gilead Pharmasset LLC in proceedings concerning its patent EP 2203462 B1 (T 2643/16)

D85: D Reference Concordance

D85a: "Chemical Principles", Fourth Edition, Dickerson et al. (pages 9-10)

D86: "Chemistry - The Central Science", Sixth Edition, Brown et al. (page 50)

D87: Declaration of Dr. Gary Allred

D88: The Merck Index, Thirteenth Edition, page 4401

D89: GB 2136425 A

D90: US 4808614

D91: Chou et al., "Stereospecific Synthesis of 2-Deoxy-2,2-difluororibonolactone and its Use in the Preparation of 2'-Deoxy-2''2'-difluoro- β -D-ribofuranosyl Pyrimidine Nucleosides: The Key Role of Selective Crystallization", *Synthesis*, June 1992, 565-570

D92: EP 0587364 A1

D93: Chemical Abstracts Service (CAS) search results for 108221-67-6

D94: Takeuchi et al., "The First General and Efficient Method for the Synthesis of Tertiary Alkyl Fluorides", *J. Org. Chem.*, 1993, 58, 3483-3485

D95: Takeuchi et al., "Chemistry of Novel Compounds with Multifunctional Carbon Structure. VI. Synthetic Studies and ^{19}F -Nuclear Magnetic Resonance Investigation of Novel α,α -Disubstituted Fluoroacetates", *Chem. Pharm. Bull.*, 1990, 38(9), 2404- D952408

D96: Takamura et al., "A simple and convenient method for preparation of α -substituted α -diazo esters", *Tetrahedron*, 1975, 31,227-230

D97: Olah et al., "Convenient Dediazoniative Hydrofluorination and Halofluorination of Diazoalkanes and Diazoketones in Pyridinium Polyhydrogen Fluoride Solution", *Synthesis*, 1974, 896

D98: CAS search results for 6087-13-4

D99: Grossel, "Alicyclic Chemistry", pages 16 and 17

D100: March's Advanced Organic Chemistry, Fifth Edition, pages 518 and 519

D101: Middleton, "New Fluorinating Reagents. Dialkylaminosulfur Fluorides", *J. Org. Chem.*, 1975, 40, 5, 574-578

D102: "Methods of Organic Chemistry", Houben-Weyl, Supplementary Fourth Edition, 2000, pages 82-118

D103: Boons et al, "Organic Synthesis with Carbohydrates", pages 59 and 60

D103a: Boons et al "Organic Synthesis with Carbohydrates" Chapter 3

D104: Lackey et al., "Enzyme-catalyzed therapeutic agent (ECTA) design: activation of the antitumor ECTA compound NB1011 by thymidylate synthase", *Biochemical Pharmacology*, 2001, 61, 179-189

D105: Second declaration of Professor Geert-Jan Boons

D106: Declaration of Dr Kathleen S. Keegan, PhD, Senior Director Tumor Immunity and Oncology Targeted Therapy Group Leader, Gilead Sciences, Inc. Dr Keegan's CV is annexed to D106 as D106a.

D107: Zhou et al, "2'-Chloro,2'-fluoro Ribonucleotide Prodrugs with Potent Pan-genotypic Activity against Hepatitis C Virus Replication in Culture", Journal of Medicinal Chemistry 60(13), 2017, 5424-5437

D108: Patentee's comments in connection with corresponding US Reissue patent, dated 22 October 2018

D109: WO 96/29336

D110: Second declaration of Professor Stephen Graham Davies, Ph.D.

D111: Furstner, "Recent Advancements in the Reformatsky Reaction", Synthesis, 1989, 571-590

D112: Kitazume, "Synthesis of optically active B-keto-γ- butyrolactones having a trifluoromethylgroup", Journal of Fluorine Chemistry, Vol. 35, 1987

D113: Schmid et al., "D-(R)-Glyceraldehyde acetonide", Organic Syntheses, 1995

D114: Decision T 177/08

D115: Second declaration of David J. Harrison, M.D., D.Sc., FRCPath

3.2 As these documents were cited during the opposition proceedings, it is our understanding that additional copies of these documents do not need to be filed during the appeal proceedings. However, if submission of further copies of the documents mentioned above would assist the board in any way, they can of course be provided.

3.3 Additionally, in response to the reasoning in the decision of the opposition division, the opponent files herewith the following further documents.

D116 Judgement of the Canadian Federal Court in Gilead Sciences, Inc et al v Idenix Pharmaceuticals, Inc et al.

D117 Judgement of the Canadian Federal Court of Appeal, upholding the first instance decision in D116.

D118 Judgement of the Federal Court of Australia in Gilead Sciences Pty Ltd v Idenix Pharmaceuticals LLC.

D119 Judgement of the Oslo District Court in Gilead Sciences Europe Ltd. v Idenix Pharmaceuticals Inc et al. (Certified English translation).

- D120 Judgement of the Borgarting Court of Appeal, upholding the first instance decision in D119.
- D120a English translation of D120.
- D121 Decision of the Düsseldorf District Court (Ref.: 4c O 5/14) in Idenix SARL v Gilead Sciences Inc et al.
- D121a English translation of D121.
- D122 Judgement of the US Court of Appeal (Federal Circuit) in Storer et al v Clark.
- D123 Third declaration of Professor Boons, including D123a (Boons et al, Tetrahedron Letters, Vol.34, No. 55, pp 5649-5652) and D123b (Michel et al, Angew. Chem. 2002, 114, Nr. 20, pp 4054-4057).
- D124 Sofia et al, J Med Chem 2010, 53, 7202-7218.
- D125 A copy of the periodic table, provided solely for the convenience of the board.
- D126 Mengshetti et al, J Med Chem 2019, 62, 1859-1874.
- D127 Quintiliani et al, Bioorg Med Chem 2011, 19, 4338-4345.
- D128 Sofia, Antivir Chem Chemother 2011, 22, 23-49.
- D129 Declaration by Professor Adrian L Harris FRCP, FMedSci, FACP, DSc, University of Oxford.
- D129a CV of Professor Adrian Harris.
- D130 Hughes et al, British Journal of Pharmacology 2011, 162, 1239-249, annexed to D129.
- D131 Declaration by Sally Shorthose, Partner, Bird & Bird LLP.
- D131a CV of Sally Shorthose.
- D132 Extract from regulatory dossier, annexed to D131.
- D133 Experimental report number PC-PSI-7851-08-0002 dated 21 October 2008.
- D134 Experimental report number PC-PSI-7977-09-0004 dated 23 July 2009.

D135 Experimental report number PC-334-2037 dated 12 August 2021, accompanied by D135a (CV of Ms Yili Xu) and D135b (CV of Dr Joy Feng).

- 3.4 D116-122 are being filed in response to the opposition division apparently disregarding the relevance of the conclusions by the EPO and the UK courts in relation to the Idenix patent, namely that synthesis of 2'-Me/2'-F nucleosides at the relevant date could not be achieved by the skilled person without undue burden. The judgments from the courts in Norway, Germany, Australia, Canada, and the USA are in line with the conclusions of the EPO and the UK courts discussed at first instance, and thus reinforce that the opposition division was incorrect to reach the conclusions it did.
- 3.5 D123 is a third declaration from Professor Boons, and is being filed in response to the second declaration of Professor Davies (D110) and the decision of the opposition division. D110 was filed by the patentee merely days before the oral proceedings before the opposition division, and as such it was not realistic for the opponent to provide a complete response to that declaration prior to the oral proceedings. D123 explains why a number of statements made in D110 are incorrect, and is thus responsive to D110. As regards the decision of the opposition division, it will be apparent from the discussion below that the opposition division apparently disregarded the first and second declarations of Professor Boons, and as a result arrived at scientifically incorrect conclusions which were not apparent from, and deviated from, their preliminary opinion. D123 is therefore also responsive to the decision of the opposition division.
- 3.6 D124 is filed in response to the conclusion of the opposition division that certain compounds having 2'-Me/2'-F substitution are cytotoxic.
- 3.7 First, D124 addresses comments from the opposition division in the decision indicating - for the first time - that numerical data in D107 proving the non-activity of the compound sofosbuvir in relevant cancer cell lines is allegedly ambiguous and should thus be disregarded in favour of *in expressis verbis* statements. D124 provides such *in expressis verbis* statements.
- 3.8 Second, D124 addresses comments from the opposition division in connection with D37 (which similarly discusses the non-cytotoxicity of sofosbuvir) and D106, which is an expert declaration from Dr Keegan on behalf of the opponent. In the decision, the opposition division for the first time indicated that despite Dr Keegan's extensive experience in the field, her comments were "unscientific", which seemingly led to D37 being disregarded by the opposition division. D124 is filed as published evidence to confirm the statements made by Dr Keegan.
- 3.9 Third, the patentee filed on 14 January 2021 an experimental report as D115 to supplement its declaration of D51, merely days before the oral proceedings on 8 February 2021. The opponent could not respond to D115 before the oral proceedings. D124 is thus also filed in direct response to D115.

- 3.10 D125 and D126 are filed in response to the conclusion of the opposition division, expressed for the first time in the decision, that compounds having 2'-Br/2'-F substitution could be cytotoxic. Discussion of such compounds only arose in connection with the filing of AR13 at 5.30 pm on the day of the oral proceedings, after the claims of the patent as granted and the claims of ARs 1-12 had been found to lack inventive step. It is only fair that, with AR13 being admitted at the very last possible moment, the opponent should have a chance to submit evidence that proves the inactivity of such compounds also.
- 3.11 D127 is filed in response to comments made by the opposition division for the first time in the decision that the phosphoramidate portion of the claimed compounds is not "a sensitive moiety for biological activity". This conclusion is contrary to the evidence on file and in particular contrary to the expert view of Dr Keegan in D106, which as noted above was critiqued by the opposition division for the first time in the decision. D127 confirms Dr Keegan's view and proves that variations in the phosphoramidate moiety are relevant to the cytotoxicity of the compounds at issue and, in particular, that compounds having small linear alkyl groups at the R position are not cytotoxic.
- 3.12 D128 is similarly filed in response to comments made by the opposition division for the first time in the decision that the phosphoramidate portion of the claimed compounds is not "a sensitive moiety for biological activity". D128 confirms that variations in the phosphoramidate moiety are relevant to the cytotoxicity of the compounds at issue.
- 3.13 D129 is filed in response to comments made by the opposition division for the first time in the decision criticising D106, the expert declaration from Dr Keegan on behalf of the opponent, as being "biased" through expressing "the opinion of a party affected by the scope of the patent". D129 sets out the opinion of an eminent and independent oncologist, Professor Adrian Harris, who is unaffected by the outcome of the present proceedings. D129 confirms Dr Keegan's views in D106. Professor Harris' CV is attached as D129a.
- 3.14 D130 is cited by Professor Harris and is annexed to and discussed in D129.
- 3.15 D131 is filed in response to comments made by the opposition division for the first time in the decision, stating that the *quantum* of the alleged cytotoxicity of sofosbuvir, as reflected by the IC50 value allegedly obtained by Dr Harrison and reported in D115, is "irrelevant". D131 comments on the relevance of cytotoxicity or the absence thereof in the process of gaining marketing authorisation, and confirms the importance of demonstrating an *absence* of cytotoxicity for a *marketed* antiviral product such as sofosbuvir. D131a is the CV of the declarant in D130, Ms Sally Shorthose.
- 3.16 D132 is cited by Ms Shorthose and is annexed to and discussed in D131.

- 3.17 D133 and D134 are filed in direct response to the data submitted in D115 and in response to the decision of the opposition division. As noted above, D115 was filed on 14 January 2021 and as such the opponent could not respond to D115 before the oral proceedings. D133 and D134 provide experimental evidence directly proving that the compound sofosbuvir (referred to as PSI-7977) (as well as its diastereomer, PSI-7976 and the racemic mixture of those compounds, PSI-7851) is not cytotoxic in the cancer cell lines Huh7, HepG2, BxPC3 and CEM. D133 and D134 are also responsive to the opposition division decision (see point 5.7.1), where the opposition division apparently gave greater weight to experimental data submitted by the patentee than other forms of evidence, and moreover criticised the opponent for not filing experimental data of its own. These views of the opposition division were not apparent until the written decision issued, and were not apparent from the preliminary opinion.
- 3.18 D135 is further filed in direct response to the data submitted in D115 and in response to the decision of the opposition division. D115 is alleged by the patentee to demonstrate that the compound sofosbuvir has an IC_{50} of $27 \pm 3 \mu M$ when assessed in an SRB assay in one specific breast cancer cell line (SKBR3, which is not mentioned in the patent). D135 provides experimental evidence proving that both sofosbuvir and analogs thereof are not cytotoxic in a panel of three different breast cancer cell lines, including both the MDA-MB-231 cell line which is used throughout the patent to support an alleged effect in breast cancer and the SKBR3 cell line tested by the patentee. D135 proves that the opposition division was wrong to conclude that compounds within the scope of the claims of the patent as granted and as maintained have meaningful anti-breast cancer activity. As with D133 and D134, D135 is also responsive to the opposition division apparently giving greater weight to experimental data than other forms of evidence and being critical of the opponent for not filing its own data. These views were not at all apparent until issue of the written decision. The CVs of the scientists who conducted the experiments reported in D135 are attached as D135a and D135b, respectively.

2'-OH group is depicted in the patent as being at exactly the same angle as the X group in Formula (I) in claim 1. Any skilled person reading the patent would thus understand that the X group in claim 1 is at the corresponding position to the -OH group in cytarabine and is thus "up", meaning that by extension the Y group must be "down".

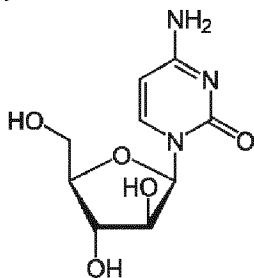
4.6 This interpretation, which would be adopted by the skilled person based on the teaching of the patent, is explicitly made by the applicant itself in the disclosure of the application as filed.

4.7 We refer to page 9, lines 26-27 and 32-33 of the application as originally filed (WO 2005/012327). These sections refer to the structure of Formula (I), and read as follows:

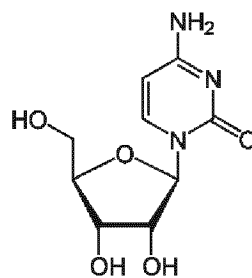
"When Z is H, Q is O, n is 0 and X is OH and Y is H, the base moiety of the compound for formula I corresponds to cytarabine i.e. compound (2) above. [...]

When Z is H, Q is O, n is 0 and X is H and Y is OH, the base moiety of the compound for formula I corresponds to cytidine."

4.8 Any skilled person would be aware of the structures of cytarabine and cytidine, shown below side-by-side for ease of reference. Cytarabine is 2'-OH "up" / 2'-H "down" (as shown on page 1 of the patent, reproduced above). By contrast, cytidine is 2'-OH "down" / 2'-H "up".



Cytarabine



Cytidine

4.9 The patentee's position that X may be other than up is thus simply not consistent with the skilled person's understanding in view of the clear statements in the application as filed that specify X as being in the "up" orientation as shown in Formula I, and Y in the "down" orientation.

4.10 We therefore submit that in view of the teaching in the patent the orientation of X and Y depicted in Formula I of claim 1 can only be X-up/Y-down.

4.11 The opposition division made a number of errors in agreeing with the patentee's interpretation of claim 1. In particular, the opposition division referred to factors a) to d) discussed below.

- 4.12 Factor a) was that in the application as filed, variables X and Y had the same scope and so it was “irrelevant” to discriminate between “up” and “down”. This reasoning entirely disregards the fact that in other parts of the application as filed X and Y have different scopes. Specifically, as noted above, the application as filed at page 9, lines 26-27 and 32-33 identifies particular values of X and Y which map onto particular compounds (i.e. cytarabine and cytidine) which have OH in the up and down positions respectively, and thus clearly link the X position to up and the Y position to down. We also note that “*particularly preferred*” definitions of the general formula of the application as filed distinguish between X and Y. We refer for example to page 10 lines 6-8 and 10-12 of the application as filed. In addition, we note that in claims 15 and 16 of the application as filed X and Y are given different, specific meanings, rather than being of the same scope or used interchangeably (in which case including both claims 15 and 16 separately would, of course, have been superfluous).
- 4.13 Factor b) was that the 3’-OH group is depicted in a conventional down position, which would suggest to the opposition division that the depiction of X and Y was intended to cover unspecific stereochemistry. The problem with that argument, however, is that it disregards the fact that elsewhere in the patent (as discussed above), a similar depiction is used to denote specific moieties in the up and down positions, respectively (for example, we refer to the structure of cytarabine in paragraph 2 of the patent, reproduced above). In fact, it is clear from the passages cited that the patent in fact intends for X to be in the up position and Y to be in the down position, as depicted.
- 4.14 Factor c) was that conventionally straight lines indicate “no specific stereochemistry”, with “bold wedges or wobble line wedges” used to depict stereochemistry. Even if that is the case conventionally, as noted above it is clear that the patent itself does not adopt that convention when depicting cytarabine. This point is therefore not relevant.
- 4.15 Factor d) was that the disclosure in the background section cannot be used as basis at the EPO to amend the claims. However, there are two problems with this argument. First, it ignores the disclosures at page 9, lines 26-27 and 32-33, page 10, lines 6-12, and claims 15-16 of the application as filed, which relate to the invention itself and not the background. Second, the question is not whether an amendment can be made to the claims, but how the claims should be interpreted. The patent as a whole, including the background section, should be used to interpret the claims, not least because the background section places the invention into the context that was intended by its authors.
- 4.16 Claim 1 should therefore be interpreted as requiring X in the up position and Y in the down position. This has consequences in relation to both added subject matter and sufficiency, as will be discussed in further detail below.

The meaning of the term “alkyl”

- 4.17 Claim 1 states that group Z is selected from H, alkyl and halogen. It was disputed during the opposition proceedings whether or not the term “alkyl”, as used in the patent, embraces substituted alkyl moieties, such as bromovinyl groups. The opposition division incorrectly concluded (see section 5.1 of the decision) that alkyl does not embrace bromovinyl.
- 4.18 The conclusion of the opposition division is incorrect because it does not take into account the way in which the term “alkyl” was used both in the application as filed and in the patent itself.
- 4.19 For example, paragraph [0015] of the patent explains that:
- “Reference in the present specification to an alkyl group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical.”* (emphasis added)
- 4.20 Paragraph [0017] further explains that:
- “The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be one to three substituents present, preferably one substituent. Substituents may include halogen atoms, by which is meant F, Cl, Br and I atoms, and halomethyl groups such as CF₃ and CCl₃; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyC₁₋₁₆alkyl, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, C₁₋₆alkylamino, diC₁₋₆alkylamino, cyano, azide and nitro; sulphur containing groups such as thiol, C₁₋₆alkylthiol, sulphonyl and sulphoxide; heterocyclic groups which may themselves be substituted; alkyl groups as defined above, which may themselves be substituted; and aryl groups as defined above, which may themselves be substituted, such as phenyl and substituted phenyl. Substituents on said heterocyclic, alkyl and aryl groups are as defined immediately above.”* (emphasis added)
- 4.21 It is therefore clear that the patent intended for the term “alkyl” in claim 1 to embrace *inter alia* bromovinyl groups.
- 4.22 Further evidence that the patentee clearly intended the claims to embrace compounds with moieties such as bromovinyl at the Z position, can be found in dependent claim 10 of the patent as granted, which *explicitly* includes these groups. Thus, claim 10 as granted specifies that:
- “Z is selected from the group H, C₁₋₆ alkyl, substituted C₁₋₆ alkyl, C₁₋₆ alkenyl, substituted C₁₋₆ alkenyl, C₁₋₆ alkynyl, and halogen.”* (emphasis added)
- 4.23 This definition was also retained in all of Auxiliary Requests 1 (claim 10), 2 (claim 4) and 3 (claim 4) filed with the patentee’s response to our Opposition. In the Auxiliary Requests submitted with the patentee’s later submissions, the

dependent compound claims were deleted. However, the mere deletion of dependent claims does not alter the scope of the independent claim. As all of the Auxiliary Requests including AR13 (on which basis the opposition division erroneously maintained the patent) retained the option for Z to be “alkyl”, all of the Auxiliary Requests embrace the option for group Z to be bromovinyl.

- 4.24 That the patentee clearly intended the claims to cover compounds with a bromovinyl moiety at the Z position is also evident from the fact that the vast majority of the data in the patent are for exactly such compounds (i.e. almost all of the compounds in the Table on pages 63 to 65 of the patent have the base (B) identified as “BVU”, i.e. bromovinyluridine).
- 4.25 Similarly, paragraph [0058] of the patent as granted (still present in the patent as amended on the basis of AR13) explains that “*compounds embodying the present invention and having variations in one or more of the ester (R), amino acid (R', R'') and aryl (Ar) region of the phosphoramidate structure compared to phenyl methoxyalaninyl phosphoramidate can give surprising and substantial potency boosts of protides derived from BVDU [bromovinyldeoxyuridine] against a range of cancer cell types*”
- 4.26 In its 14 January 2021 submissions, the patentee contented that the term “alkyl” should be construed narrowly as referring only to groups of the formula C_nH_{2n+1} , which precludes substitution. However, it is clear that the patentee does not actually hold to this position and in fact seeks to leave the option open to argue in later proceedings that such groups may be substituted. Thus, even in the amended patent specification, the option for substituted alkyl is retained for some positions. For example, we refer to paragraph [0044] of the amended specification which retains the option for substituents on group Ar to include “optionally substituted -SC₁₋₃alkyl”.
- 4.27 In considering the meaning of the term “alkyl” as used in the application as filed and the patent as granted, the opposition division correctly indicated in section 5.1 of the decision that the position is as discussed in the EPO Guidelines at section B-III-3.2.4. That section describes examples of the appropriate use of the description and/or drawings to establish definitions of clear terms given a definition different from their usual meaning. The example of this section is in fact quite instructive as it also concerns the meaning of a chemical term which is redefined by a patent. Example 1 in that section reads as follows:

“Example 1

Claim 1: Halide salt of compound A

Normally the term “halide salt” means fluoride, chloride, bromide or iodide salt.

Description: In the context of the present invention the term halide salt means fluoride, chloride, bromide, iodide or tosylate salt.

In this example, the claim at first sight appears to be clear, since it makes use of a technical term ("halide salt") with a clear and well-established meaning in the technical field of the application. However, the description defines this term in such a way that it has a meaning broader than its well-established one (here the meaning of this term is extended to include tosylate salt)."

- 4.28 This section thus highlights an established line of case law summarised in the reference text Case Law of the Boards of Appeal, 9th Ed. (hereafter "CLBA") at II-A-6.3.3:
- "In several decisions the boards have stated that terms used in patent documents should be given their normal meaning in the relevant art, unless the description gives them a special meaning (see e.g. T 1321/04, T 1089/11, T 25/15). According to the established case law, the patent document may be its own dictionary (see e.g. T 311/93, T 523/00, T 1192/02, T 61/03, T 1321/04, T 1388/09, T 2480/11, T 1817/14)"*
- 4.29 Similarly, CLBA I-C-4.1 confirms that *"it is a well-established principle laid down by the boards' case law that a non-specific definition in a claim should be given its broadest technically sensible meaning"* (see T 79/96, T 596/96). Whilst this section addresses disclosure in the prior art it is relevant to the disclosure of the patent by parity of reasoning.
- 4.30 Despite this, the opposition division held that the term "alkyl" had to be given its IUPAC meaning regardless of the clear implication to the contrary in the claims of the patent as granted, the explicit definition in the description, the extensive data in the specification relating to compounds having "alkyl" groups that are not in accordance with the IUPAC definition, and the retaining of passages in the patent clearly stating that such groups are intended to remain within the scope of the invention.
- 4.31 Whilst limited reasoning was provided by the opposition division, the patentee argued in its submissions of 14 January 2021 that decision T177/08 was relevant to deciding only that an IUPAC definition can apply when interpreting terms such as alkyl in the claims, and it seems that the opposition division agreed. However, we submit that this position does not accurately reflect *overall* EPO jurisprudence. Thus, whilst in T177/08 the term "alkyl" was construed as referring to the IUPAC definition, other decisions have reached the opposite conclusion.
- 4.32 We refer, for example, to T620/08. In that decision the Board considered a claim to a compound defined by a Markush structure and which allowed groups including alkyl and amino groups (*i.a.*) at various positions. The construction of

such terms was important in determining the validity of the claims. The Board stated at section 3.8-3.9 of the reasons for the decision:

- 3.8 *Concerning novelty of the claimed subject-matter, the Board agrees with the Opposition Division's opinion that the claims should be read giving the words the meaning and scope which they normally have in the relevant art, unless the description gives the words a special meaning by explicit definition. Being a legal document a patent may be its own dictionary. It may define technical terms and determine how a skilled person has to understand a specific word when used in the description or the claims. Thus, the description may give a word or an expression, even an unequivocally clear one, which has a generally accepted meaning, a different meaning than the generally accepted one by explicit definition (T 556/02, not published, point 5.3 of the Reasons; T 416/87, point 5 of the Reasons, OJ EPO 1990, 415; T 500/01, not published, point 6 of the Reasons).*
- 3.9 *In the present case, the description of the patent in suit contains an entire section of over two pages with the heading "Definition of terms" at the beginning of the section with the heading "Detailed Description of the Invention" in which the meaning of the terms used in the patent in suit is explicitly defined (paragraphs [0016] to [0055]), including a definition of the terms "alkyl" and "amino". It is, furthermore, made clear that these definitions apply throughout the complete patent specification, see the expression "the term as used herein" in all the paragraphs [0016] to [0054]. Alkyl, for example, is defined as C₁-C₁₂ straight or branched saturated chain radicals, amino as NH₂, both being optionally substituted (paragraphs [0016], [0040] and [0055] of the patent in suit). It would, therefore, be clear for any skilled reader that in the present case the meaning of any of these terms used in the description or the claims may differ from the meaning the skilled person would normally attribute to them. The Board sees no reason in the present case to disregard these unambiguous and explicit definitions for a proper understanding of the claims and to consider instead the generally accepted definition of alkyl, i.e. a moiety with the formula C_nH_{2n-1} with n being an integer ≥ 1 and amino, i.e. NH₂.*

Accordingly, in the present case the specific definitions given in the description of the patent in suit will be taken into account in the examination of novelty over document (7).

- 4.33 The principle to apply is thus as established by the Boards in cases such as T1646/12: *"It was nevertheless a general principle that a term could be interpreted only in context. Terms in a claim therefore had to be interpreted in the overall context of the claims set and the description (see also T 1817/14). Two extremes had to be avoided. On the one hand, limiting features mentioned in the description but not in the claims could not be read into the latter. They could not be inserted this way through interpretation,*

but only by amending the claims. On the other hand, claims could not be considered in complete isolation from the description. The skilled person interpreting the claim had to at least ascertain whether the expressions used were to be understood in their ordinary literal sense or whether they had a special meaning defined in the description.” (as summarised in CLBA at II-A-6.3.2).

- 4.34 The opposition division was therefore wrong to consider in section 5.1 of the decision that a clear definition of the term “alkyl” in the application as filed and retained in the patent as granted “has no bearing” on the interpretation of the claim, and instead to focus solely on the IUPAC definition of “alkyl”. Whilst the skilled person might recognise that there is a discrepancy between the IUPAC definition of “alkyl” and the way “alkyl” is used in the patent, that does not mean that it is appropriate simply to adopt the IUPAC definition and ignore the explicit teaching of the patent. It is noted that the opposition division neglected to consider the points above in the decision, despite such arguments being raised by the opponent both in writing and orally.
- 4.35 The term “alkyl” in claim 1 should therefore be interpreted as embracing bromovinyl. This has consequences in relation to inventive step, as will be discussed in further detail below.

5 ADDED SUBJECT MATTER

- 5.1 The opposition division incorrectly concluded in section 3 of the decision that the amendments made to the patent application as filed in arriving at the claims of the patent as granted, and those of ARs 1-13, did not add matter. The opposition division made a number of errors in this regard, which are discussed below.

Relevant legal provisions in relation to added subject matter

- 5.2 To comply with Article 123(2) EPC a European patent application or European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.
- 5.3 As is well established, the underlying idea of Art. 123(2) EPC is that an applicant should not be allowed to improve his position by adding subject matter not disclosed in the application as filed, which would give him an unwarranted advantage and could be damaging to the legal security of third parties relying on the content of the original application (see G 1/93, OJ 1994, 541). The public may not be confronted with an extent of protection, which could not have been established by a skilled person having studied the whole content of the technical disclosure of the originally filed patent application (T 157/90, see also T 187/91). (CLBA II-E-1.1)
- 5.4 The "gold standard" (G 2/10, OJ 2012, 376) for assessing compliance with Art. 123(2) EPC is that, irrespective of the context of the amendment made, such amendment can *only* be made within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of these documents as filed (G 3/89, OJ 1993, 117; G 11/91, OJ 1993, 125). (CLBA II-E-1.1).
- 5.5 After the amendment the skilled person may not be presented with new technical information (G 2/10) (CLBA II-E-1.1).
- 5.6 When amendments are made by deleting meanings of residues in a generic chemical formula, such amendment must not lead to the selection, in the respective lists, of a particular combination of single, specific but originally undisclosed meanings of residues (see T 615/95 and T 859/94). (CLBA II-E-1.6.3)
- 5.7 However, the test to be made is not merely a numerical one regarding the number of lists from which shrinkage is made, but is a substantive one. Thus, for example, in T98/09, the board held that a deletion from a list could also constitute an inadmissible extension if the singling out of one individual ingredient led to a selection of combinations which, even if conceivably covered by the application as filed, had not been specifically disclosed. It was the boards' settled case law that such a selection is to be regarded as an inadmissible extension and so as an infringement of Art. 123(2) EPC (see e.g. T

727/00 and T 686/99). The case at issue concerned two lists (six elements and 47 elements). The applicant sought to individualise one of the lists to one element. The board held that this selection was contrary to Art. 123(2) EPC. (CLBA II-E-1.6.3)

- 5.8 A complementary line of case law has established that selections of specific features from combinations of lists can lead to added matter. A leading case in this area is T12/81 although the jurisprudence of that case has been refined over the years. There is an inherent relationship between shrinking lists and selecting from lists: shrinking of a list of n original alternatives to leave p remaining alternatives is identical to selecting p alternatives from the original list of n alternatives.
- 5.9 Shrinking of lists may, in some specific circumstances be allowable. However, this is not universal. Even in cases where deletions from multiple lists were allowed, it was stressed that this required that the deletions did not lead to a particular combination of specific meanings of the respective residues which was not disclosed originally or, in other words, did not generate another invention. If another invention is created, then the amendment is not allowable.
- 5.10 We refer, for example, to T948/02 which discusses the case law in this area in detail. T948/02 was concerned with a patent claiming specific compounds defined by a generic Markush formula. Various limitations to lists of substituents defining the general formula were made by the patentee in that case, and the allowability of such amendments was discussed by the board:

2.4.1 *Reference can, in this respect, be made to T 859/94 dated 21 September 1999 (none of the decisions cited herein was published in OJ EPO, unless explicitly stated otherwise). According to this decision, the idea underlying Article 123(2) EPC "is that an Applicant should not be allowed to improve his position during the examination procedure by adding subject-matter not disclosed in the application as filed thus giving him an unwarranted advantage and possibly being detrimental to the legal security of third parties relying on the contents of the application as filed (see G 1/93, OJ 1994, 541, No. 9 of the reasons of the decision). This idea holds of course also in respect to a patent proprietor and the opposition procedure." (No. 1.1 of the reasons), and the decision continued: "To which degree deletions from lists of meanings for various substituents are admissible depends on the circumstances of the specific case." (No. 2.4.3 of the reasons).*

Furthermore, the above decision referred to T 615/95 dated 16 December 1997, which had allowed, under Article 123(2) EPC, deletions of one originally disclosed meaning from each of three independent lists of sizeable length, wherein each list specified distinct meanings for different residues in a generic chemical formula defining the subject-matter of the

main claim at issue in that case. It had been found therein that such deletions were allowable, if two conditions were fulfilled:

Firstly, these deletions did not result in singling out any hitherto not specifically mentioned individual compound or group of compounds (in the sense of a "sub- class of compounds" as referred to eg in T 859/94, above, and T 50/97 of 27 January 2000), but maintained the remaining subject-matter as a generic group of compounds differing from the original group only by its smaller size.

Secondly, these deletions did not lead to a particular combination of specific meanings of the respective residues which was not disclosed originally or, in other words, did not generate another invention. (cf. T 615/95: Catchword 1 and No. 6 of the reasons, emphasis added).

- 2.4.2 *In particular, the latter prerequisite for a limitation of the claim can, in the Board's view, only mean that a limitation of the type as discussed in those decisions and in the present case does not provide a technical contribution to the claimed subject-matter, but merely restricts the required protection in the sense as used by the Enlarged Board of Appeal with respect to the allowability of disclaimers (cf. G 1/93, above, No. 2 of the Order and No. 16 of the reasons; it is noteworthy that G 1/93 was referred to in both T 859/94, above, and in T 615/95, above, No. 4.1 of the reasons).*

In other words, if a limitation of a claim does not simply exclude certain embodiments but results in improvements or even additional effects, for which the original disclosure provides no basis, then, according to the above jurisprudence, such an amendment will not be allowable under Article 123(2) EPC.

- 5.11 Accordingly, if the amendments made by the patentee change the invention, by focussing on providing an improvement over the disclosure of the application as filed, then such an amendment is not allowable. Similar findings have been reached in, for example, T1506/13.

Claims of the Patent as granted add matter

- 5.12 The opposition division concluded in section 3 of the decision that the claims of the patent as granted were properly based on the disclosure of the patent application as originally filed. However, this conclusion was based on an incorrect application of the case law in this area as summarised above.
- 5.13 During prosecution, the patentee amended claim 1 as originally filed in order to derive claim 1 as granted.

- 5.14 Claim 1 as originally filed specified inter alia that “X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH₃)”. During examination this text was amended to specify that “X is independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH₃); Y is F.”.
- 5.15 The patentee also amended the term “pharmaceutically acceptable derivative or metabolite” to “pharmaceutically acceptable salt, ester or salt of such ester”, apparently based on page 4 lines 12 to 14 of the application as filed.
- 5.16 We address first the amendment at the 2’ position of the ring. It is clear from Formula (I) of claim 1 as filed, there are two substituents present at this position: X and Y. The patentee selected to restrict the definition at position Y and not at position X. The decision to amend the original definition at one specific position (Y) from a list of multiple possible positions (X and Y) constitutes a first selection from a first list. Thus, the original language permitted at least four conceptual alternatives: “X and Y are selected from the same list”; “X and Y are selected from different lists” “X is fixed and Y is selected from a list” and “Y is fixed and X is selected from a list”. The patentee made a first selection in choosing to specify that Y is fixed and X is selected from a list.
- 5.17 The patentee then went on to make a further selection, by specifying that Y is F. The decision to specify that Y is one specific alternative (F) from a list of multiple alternatives (H, F, Cl, Br, I, OH and methyl) constitutes a second selection from a second list.
- 5.18 The opposition division stated in section 3.2 of the decision that this amendment constitutes “nothing more than a selection from a single list” on the grounds that the definition of the X and Y substituents at the 2’ position “could equally be spelled out” in different language such that their definitions were stated separately. Such an analysis is inappropriate. It is not correct for the opposition division to base its decision on amendments that *could* have been made had the patent application been drafted differently: Article 123(2) EPC requires assessment of amendments relative to the *application as originally filed*.
- 5.19 The opposition division considered that had the patentee/applicant drafted their initial specification differently - which was not done - then the resulting subject matter could arise simply by subsequently amending Y rather than X. This latter selection is uncontested as being a selection from the list of alternatives for Y.
- 5.20 We thus submit that two selections are necessary to define the chemistry at the 2’ position as set out in the patent as granted. The opposition division started its analysis from the wrong place by considering text simply not present in the application as filed, and thus incorrectly counted only a single selection rather than a dual selection.

- 5.21 We now turn to the amendment made to alter the term “pharmaceutically acceptable derivative or metabolite” to “pharmaceutically acceptable salt, ester or salt of such ester”.
- 5.22 Claim 1 as originally filed defined the claimed compound as being of Formula (I) “or a pharmaceutically acceptable derivative or metabolite thereof”. The patentee/applicant amended this to refer to the compound of Formula (I) or “a pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I)”.
- 5.23 The original claim thus allowed for compounds in three forms: neutral compounds; pharmaceutical derivatives, and metabolites. The claim as granted restricts this to neutral compounds, salts and esters.
- 5.24 In the decision, the opposition division stated that in making the amendment “the term “pharmaceutically acceptable derivative” was replaced by the equivalent expression provided in the originally filed documents on page 4, lines 12-14. However, that is not correct.
- 5.25 Page 4, lines 12-14 of the application as filed defines “pharmaceutically acceptable derivatives” as being “any pharmaceutically acceptable salt, ester or salt of such ester or any other compound which upon administration to a recipient is capable of providing (directly or indirectly) a compound of formula (I)”.
- 5.26 The amendment made thus focusses on a subset of derivatives provided in the application as filed. The application as filed provides on the one hand derivatives which are salts and esters, and on the other hand derivatives which are necessarily other compounds capable of providing the compound of Formula (I). The applicant chose the former definition rather than the latter.
- 5.27 The applicant also deleted the option for the compound to be in the form of a metabolite.
- 5.28 The amendment made thus represents further selections: not only to select neutral compounds and derivatives from the list of neutral compounds, derivatives and metabolites; but also to select the type of derivative (salts and esters) from the broader definition provided in the application as filed.
- 5.29 Accordingly, it is simply incorrect to conclude that *only* a single selection has been made. By parity of reasoning with T98/09, the individualisation of the definition of X combined with the selections around X vs Y and the definition of the overall compound structure means that even if conceivably *covered* by the application as filed, the claimed subject matter is not specifically *disclosed*. Accordingly the amendment adds matter.

- 5.30 Furthermore, the amendments made by the patentee in deriving claim 1 as granted are not simply formal in nature. They rather represent a new technical teaching that is not present in the application as originally filed, contrary to Article 123(2) EPC, as discussed above.
- 5.31 The amendments made by the patentee are discussed in submissions of the patentee dated 29 February 2016. These submissions explain that
- “The present claims are limited to compounds having a fluorinated pentose moiety such as the compounds of the present claims. One of the ProTides mentioned in the application as filed, CPF 31 (now known as NUC-1031) is performing very well in clinical trials. It has been shown to overcome many of the key resistance mechanisms which limit the clinical efficacy of gemcitabine...*
- The present authors have shown that compounds having a fluorinated pentose moiety can be very potent anticancer agents, a result that could not have been predicted from D1”.*
- 5.32 The amendments thus present the skilled person with the information that - allegedly - fluorinated pentose compounds are potent anticancer agents with *improved* efficacy in face of resistance mechanisms. This information is not derivable from the application as filed. The application as filed discusses the effect of varying the *phosphoramidate* moiety of the compound, but is silent regarding any alleged benefit for compounds specifically having a fluorine at the 2' position of the pentose ring. The restriction to such compounds thus provides the skilled person with new technical information regarding the alleged improvement in activity that arises, and which cannot be derived from the application as filed. This is further contrary to Article 123(2) EPC (e.g. see T948/02, discussed above).
- 5.33 In considering this, the opposition division considered in section 3.4 of the decision whether the applicant's arguments in examination were *consistent* with the amendments being made. However, this reflects a mistaken reasoning on behalf of the opposition division. The fact that the opposition division “found no contradiction” between the teaching of the patent and the arguments of the applicant is irrelevant (see CLBA II-E-1.3.5): the only question is what is directly and unambiguously disclosed in the application as filed.
- 5.34 The dependent claims add matter for the same reasons as claim 1. We further note that options within, for example, claim 2 as granted lack basis in the parent (PCT) application as filed. Specifically, there is no basis in the parent (PCT) application as filed for specifying that R is selected from a limited selection of alternatives including C₁₋₆ primary or secondary alkyl and C₁₋₆ alkyl C₅₋₇ aryl: these alternatives are not disclosed in the description or claims of the PCT application as filed. Claim 2 therefore also contravenes Article 76(1) EPC.

- 5.35 The amendments made to the description during examination of the application reflect the amendments made to claim 1 and similarly add matter. However, we stress a further point here also, which is related to the issue of claim construction above in section 4.
- 5.36 As discussed above, the patentee contends that X may be other than in the “up” orientation, and Y may be other than in the “down” orientation. However, if the patentee wishes to defend this position, this relies on discarding the teaching of the description and particularly the passage at page 9, lines 26-27 and 32-33, which expressly distinguishes between compounds in which X is OH and Y is H, such as cytarabine, and those in which X is H and Y is OH, such as cytidine (quoted in paragraph 4.7, above). We submit that deleting this passage adds matter by giving claim 1 a new technical teaching that could not be derived *directly and unambiguously* from the application as filed.
- 5.37 Put another way, if deleting the passages at page 9, lines 26-27 and 32-33 does *not* present the skilled person with new information regarding the scope of claim 1 then the conclusion must be that X is up and Y is down, in order that the statements regarding cytarabine and cytidine are meaningful. If on the other hand, X and Y are to be construed to the contrary such that either group can be up and either can be down, then this can only be because a new interpretation of the claim is possible through deleting the passage highlighted above, in which case the deletion contravenes Article 123(2) EPC.
- 5.38 In view of these factors, the opposition division was incorrect to conclude that the claims and description of the patent as granted did not contravene Article 123(2) EPC. The opposition division should have concluded that the amendments made by the applicant lacked direct and unambiguous basis in the application as filed, and thus contravened Article 123(2) EPC.

Claims of ARs 1-13 add matter

AR1

- 5.39 Claim 1 of AR1 is identical to claim 1 of the patent as granted. The mere deletion of dependent claims does not and cannot alter the overall scope of the patent. Accordingly, AR1 adds matter for the same reasons as the claims of the patent as granted and contravenes Article 123(2) EPC.

AR2

- 5.40 AR2 adds matter for the same reasons as discussed above for the patent as granted.
- 5.41 In addition, in deriving the claims of AR2 the patentee deleted the option for the compound to be in the form of a pharmaceutically acceptable salt, ester or salt of such ester.

5.42 It is stated by the opposition division in section 3.3 of the decision (page 17, final paragraph) that, in connection with the amendments made in deriving the claims of the patent as granted, deletion of “metabolites” from the list of neutral compounds; pharmaceutical derivatives, and metabolites was the “*deletion of one alternative from the list of three equal embodiments*”. Accordingly, by deleting the options for the compound to be in the form of derivatives or metabolites, the patentee has correspondingly selected that the compound is in neutral form. This is a further selection of just one alternative from a list of three equal alternatives.

5.43 The claims of AR2 thus add matter by focussing on the specific combination of (i) compounds in which Y is F rather than any of the other alternatives provided in the application as filed at that position; and (ii) compounds in neutral form rather than in the form of derivatives (including but not limited to salts and esters thereof) and metabolites. Following the logic of T98/09, whilst this specific combination could have been “conceivably covered” by the application as filed, it was not *specifically disclosed*. The claims of AR2 thus contravene Article 123(2) EPC.

AR3

5.44 AR3 adds matter for the same reasons as the claims of the patent as granted.

5.45 Further amendment to claim 1 has been made by the patentee, by selecting that X is not H. The combination of the definitions of X and Y in new AR3 is not provided in the application as filed and thus AR3 contravenes Article 123(2) EPC.

5.46 AR3 also imparts a technical teaching that is not present in the application as filed. The patentee has argued in its submissions of 6 November 2020 that by focussing on two 2' substitutions (which may be asymmetrical, when the substitution is other than di-fluoro substitution), the claims focus on compounds allegedly having improved efficacy and reduced toxicity. However, there is no such teaching in the patent. In particular, the only data in the patent relate to compounds in which the chemistry at the 2' position is symmetrical - either H-up/H-down as in the vast majority of the exemplified compounds, or F-up/F-down. Accordingly, the focus on compounds having a broader range of non-symmetrical di-substitutions at the 2'-position represents a new technical teaching not present in the application as filed. AR3 thus contravenes Article 123(2) EPC for this reason also.

AR4

5.47 AR4 is a combination of new ARs 2 and 3 and similarly lacks basis in the application as filed. The selection of compounds in which (i) Y is F rather than H, Cl, Br, I, OH or methyl; (ii) X is other than H; and (iii) the compounds are in

neutral form rather than as derivatives, metabolites, salts, esters, or salts of esters of such compounds is not provided in the application as filed. AR4 thus also contravenes Article 123(2) EPC.

AR5

- 5.48 In deriving the claims of AR5, the patentee has made further selections in the definition of X, to specify that X is F, Cl, Br or methyl, and is not H, I, or OH. The combination of this new definition of group X and the definition of group Y is not present in the application as filed and represents a new technical teaching as set out above for AR3. New AR5 thus also contravenes Article 123(2) EPC for the same reasons as AR3.

AR6

- 5.49 AR6 is a combination of ARs 2 and 5 and similarly lacks basis in the application as filed. The selection of compounds in which (i) Y is F rather than H, Cl, Br, I, OH or methyl; (ii) X is F, Cl, Br or methyl, and is not H, I, or OH; and (iii) the compounds are in neutral form rather than as derivatives, metabolites, salts, esters, or salts of esters of such compounds is not provided in the application as filed. New AR6 thus also contravenes Article 123(2) EPC.

ARs 7-12

- 5.50 ARs 7-12 contain the same amendments as ARs 1-6, and consequently add matter for similar reasons.
- 5.51 In addition, in formulating ARs 7-12 the patentee deleted the option for Z to be alkyl. This is justified by the patentee on the grounds that this still does not result in singling out any compounds, but we submit that is not the case.
- 5.52 As noted below in connection with inventive step (see paragraphs 7.59-7.60), the term “alkyl” is indefinite and covers infinite possible groups here. By deleting this alternative, the patentee has focussed the claims onto compounds having just five options at this position: H, F, Cl, Br and I (see paragraph [22] of the patent for the definition of “halogen”). This is a very significant reduction in claim scope and individualises combinations of features at the Y, X and Z positions that are not directly and unambiguous disclosed in the application as filed.
- 5.53 ARs 7-12 thus all contravene Article 123(2) EPC.

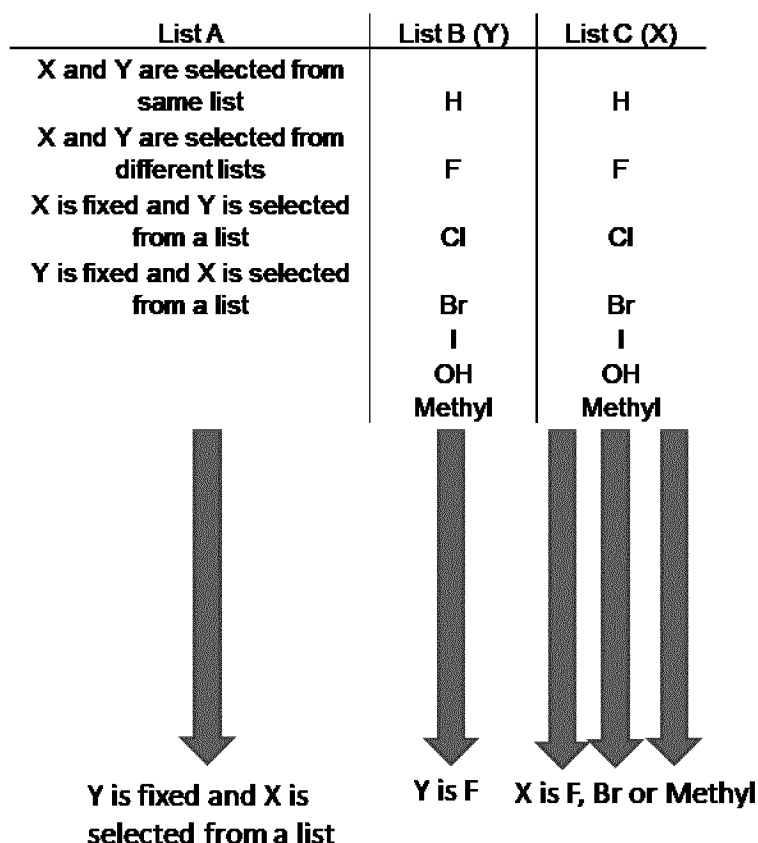
AR13

- 5.54 AR 13 is based on AR 5 and similarly adds matter as explained above. Thus, in summary, in specifying that Y is F the patentee made an initial dual selection: first by selecting to define Y from the list of X and Y; and second by selecting

that Y is F rather than any of the other alternatives at that position (as discussed in sections 5.16-5.18 above). A further selection was then made by the patentee in specifying that the compound is in the form of a salt or ester rather than in the form of a metabolite or any other form of derivative (as discussed in sections 5.21-5.28 above). Yet further selections were made within the original definition of X, as discussed in sections 5.45-5.48 above. This combination of selected subject matter is not directly and unambiguously disclosed in the application as filed and thus contravenes Article 123(2) EPC. Furthermore, the amendments made in deriving AR5 and by extension AR13 focus on compounds which comprise a necessarily 2'-disubstituted, necessarily fluorinated pentose moiety, which is alleged by the patentee to give rise to technical benefits not disclosed in the application as filed (see sections 5.46 above), and thus contravene Article 123(2) EPC for this reason also.

- 5.55 Still more significantly, however, in AR13 the patentee further deleted the alternative for X to be Cl; thus defining X to be selected from F, Br and Me only. Combined with the selections made in specifying that Y is fixed as F (discussed above), this represents a profound new technical teaching, contrary to Article 123(2) EPC.
- 5.56 In section 9.3 of the decision the opposition division stated that the amendments made to derive the claims of AR13 merely represented an “allowable shrinking of the Markush formula, that maintains the generic character of the formula”. This is incorrect.
- 5.57 We refer to the reasoning of the Board in T948/02, discussed above. As the board noted, a limitation in a claim is only permissible if it “*does not provide a technical contribution to the claimed subject-matter, but merely restricts the required protection in the sense as used by the Enlarged Board of Appeal with respect to the allowability of disclaimers (cf. G 1/93, above...) [...] In other words, if a limitation of a claim does not simply exclude certain embodiments but results in improvements or even additional effects, for which the original disclosure provides no basis, then, according to the above jurisprudence, such an amendment will not be allowable under Article 123(2) EPC.*”
- 5.58 The amendments made in deriving AR13 contravene this clear principle. Thus, in deriving the claims of AR13 the patentee deleted the option (i.a.) for X to be Cl.
- 5.59 As an initial point, we note that the application as filed provided 49 alternatives for the substitution at the 2' position on the ring. The amendments made in AR13 delete 94% of those alternatives and focus on just three very specific combinations: 2'-F/2'-F; 2'-Br/2'-F and 2'-Me/2'-F. Whilst it may be the case that (in the language of T98/09) the individualisation of these three specific combinations is *conceivably covered* by the application as filed, the now selected subject matter is not specifically *disclosed*.

- 5.60 Starting from the definitions in the application as filed, the necessary selections required to arrive at three specific combinations of substituents are summarized in the figure below:



- 5.61 Moreover, as discussed in more detail below, the reason for the amendment to form AR13 was that such compounds (i.e. those in which Y is F and X is Cl) were correctly found by the opposition division not to be associated with cytotoxicity in cancer cells, such that claims embracing such compounds were not associated with an inventive step.
- 5.62 The deletion of the option for X to be Cl in AR13 thus imparts a profound technical teaching that is not present in the application as filed, as it serves to exclude compounds proven not to be cytotoxic and therefore focusses on compounds which - in the patentee's view, which we strongly disagree with - are allegedly associated with such activity. There is no such teaching regarding the activity or otherwise of compounds having X = Cl in the application as filed.
- 5.63 We further note that the Board in T948/02 considered the reasoning in G1/93 to be of additional relevance in assessing the allowability of amendments arising from limiting lists of alternatives. G1/93 has of course been considered since by the Enlarged Board of Appeal in G1/16. G1/93 and G1/16 are

concerned with the allowability of undisclosed disclaimers in particular, but their reasoning is not limited to such amendments: after all, all amendments made are to be assessed for compliance with the same Article 123(2) EPC. Both cases reached the same essential conclusion as regards amendments which make a technical contribution to the claim: a disclaimer may not provide a technical contribution to the subject-matter disclosed in the application as filed. G1/16 further expressly confirmed that such an amendment may not be or become relevant for the assessment of inventive step.

- 5.64 The amendments made in deriving the claims of AR13 are unquestionably to address issues of inventive step. They therefore provide an (alleged) technical contribution relative to the application as filed.
- 5.65 For completeness, we further stress that to the extent the amendments made in ARs 1-12 serve to exclude inactive compounds, then *mutatis mutandis* they likewise add matter.
- 5.66 In view of this, the opposition division was wrong to find that the claims of the patent as granted, those of ARs 1-12, and those of AR13 satisfied the requirements of Article 123(2) EPC. The opposition division should have correctly applied the legal principles set out above, and in doing so concluded that the claims of the patent as granted, those of ARs 1-12, and those of AR13, all contravened the requirements of Article 123(2) EPC.

6 SUFFICIENCY

- 6.1 The opposition division incorrectly concluded in section 4 of the decision that the patent provides a sufficient disclosure. In particular, the opposition division concluded that there was a sufficient disclosure of the synthesis of compounds having a 2'-Me/2'-F substitution, despite the absence of any disclosure in the patent itself regarding how such compounds could be synthesised. In coming to this conclusion, the opposition division made a number of errors, which are discussed in further detail below.

Outline of submissions on sufficiency

- 6.2 In the submissions that follow, it will be explained why the opposition division's conclusion that the patent provides a sufficient disclosure was incorrect.
- 6.3 We will first consider the relevant legal provisions and case law, before then considering the disclosure of the application as filed and the relevance of the various Idenix proceedings.
- 6.4 We will then explain that the application as filed provided no disclosure of how to synthesise compounds having a 2'-Me/2'-F substitution pattern, and the gap in that disclosure cannot be bridged by common general knowledge.
- 6.5 The opposition division made at least the following errors in concluding otherwise. These errors included at least the following points:
1. Erroneously considering "route 22" and the "analogous gemcitabine route" without first considering all of the other routes that the skilled person would also have contemplated.
 2. Not taking into account independent, contemporaneous and highly relevant evidence of all the routes that skilled chemists at the relevant time actually did try.
 3. Apparently disregarding the expert evidence provided by Professor Boons and Dr Marquez on all of the routes that skilled chemists at the relevant time would have considered.
 4. Erroneously concluding that the skilled person was in a "one-way-street" when identifying gemcitabine to be a useful starting point for the synthesis of 2'-Me/2'-F nucleosides, and in doing so disregarding both the teaching of the application as filed and the declarations of Professor Boons.
 5. Erroneously jumping immediately from the identification of gemcitabine as a useful starting point for the synthesis of 2'-Me/2'-F nucleosides to synthesis by analogy, without first considering other options available, such as actually using gemcitabine itself as the starting material for the synthesis of 2'-Me/2'-F nucleosides.
 6. Incorrectly taking into account documents that are not common general knowledge to cure the deficient disclosure of the application as filed in relation to the known gemcitabine synthesis.

7. Not placing enough weight on the concerns identified by Professor Boons regarding adapting the “gemcitabine route” to provide the “analogous gemcitabine route”.
8. Incorrectly accepting that the starting material(s) for the “analogous gemcitabine route” could be prepared based on common general knowledge, when in fact it was necessary to rely upon primary literature references.
9. Erroneously concluding that the number of undisclosed steps and the time that would be needed to carry out those steps are not relevant factors in assessing whether the skilled person faces undue burden.
10. Placing greater weight on D49, D50 and D87, instead of contemporaneous evidence of the difficulties actually faced by two skilled chemists investigating the “analogous gemcitabine route” (see D10 and D116).
11. Applying a different standard when assessing sufficiency for the “analogous gemcitabine route” as it (correctly) did for “route 22”.
12. Not placing enough weight on decisions from multiple jurisdictions from the Idenix proceedings, which are highly pertinent to the present patent due to the similarities in dates and subject matter.

6.6 The fact that there are quite so many errors in the decision of the opposition division highlights the fundamentally deficient nature of that decision - if just one of these errors were to be reversed, it should result in the patent being found insufficient.

Relevant legal provisions in relation to sufficiency

6.7 To comply with Article 83 EPC, it must be possible to reproduce the invention on the basis of the original application documents without any inventive effort and without undue burden (T 692/05). The skilled person may use common general knowledge to supplement the information contained in the application (T 206/83, T 212/88), but information which can only be obtained after a comprehensive search is not to be regarded as common general knowledge (T 206/83, T 654/90). Documents not belonging to the common general knowledge and not referred to in the application as filed cannot be used to contribute to the clarity and sufficiency of the disclosure (T 580/88).

6.8 As noted by the Boards of Appeal (CLBA, I.C.4.11) in T 206/83, it was found that a document did not effectively disclose a chemical compound, even though it stated the structure and the steps by which it was produced if the skilled person was unable to find out from the document or on the basis of his common general knowledge how to obtain the required starting material or intermediates. Information which could only be obtained after a comprehensive search was not to be regarded as part of the common general knowledge. This need for an enabling disclosure was also in conformity with the principle expressed in Article 83 EPC. The requirements as to the sufficiency of disclosure were, therefore, identical to these considerations of disclosure for the purposes of assessing novelty.

6.9 Moreover, the Boards of Appeal have commented as follows in relation to cases where the application as filed does not disclose various steps required to carry out the invention (see CLBA, II.C.6.6.5):

“The only essential requirement is that each of those additional steps be so apparent to the skilled person that, in the light of his common general knowledge, a detailed description of them is superfluous (T 721/89).”

6.10 In other words, it is acceptable for the application as filed to omit steps that are necessary to carry out the invention, but only if those steps are so apparent to the skilled person, taking into account their common general knowledge, that it would have been *superfluous* to recite those steps explicitly in the application as filed. The test proposed by the Board of Appeal in T 721/89 was not intended to allow a patentee to omit synthetic details entirely, as is the case here, but rather to allow the omission of minor steps that are superfluous in view of common general knowledge.

6.11 It is noted for completeness that T 721/89 is only cited in five subsequent T decisions, namely T 397/02, T204/83, 871/17, T 596/04, T 394/03, none of which are concerned with complex synthetic organic chemistry. As such, none of these decisions were concerned with a complex multi-step organic synthesis comprising at least eight undisclosed steps, as in the present case.

6.12 In order to apply the rationale of T 721/89 to a particular fact pattern, it may be necessary to consider what constitutes the common general knowledge of the skilled person. There is a long line of consistent case law set on this issue from the Boards of Appeal (see CLBA, II.C.4). Principles which emerge from this case law include the following:

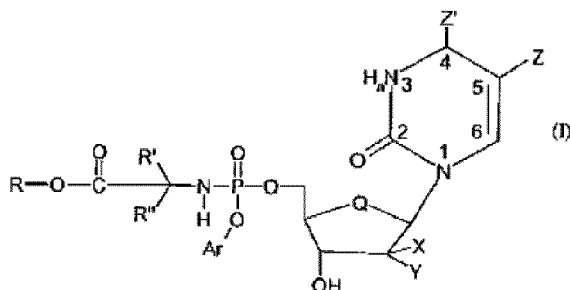
- Text books and monograph/review articles are generally considered to form part of the common general knowledge (T171/84, T51/87, T580/88 and T772/89).
- Patent publications and scientific articles are generally not common general knowledge (T475/88).
- Information that can only be obtained from a comprehensive search is not regarded as common general knowledge (T206/83, T654/90 and T924/03). This specific issue is discussed in Annex A to these grounds of appeal.
- Disputed common general knowledge requires evidence (T438/97, T329/04, T941/04 and T960/06).
- Exceptionally, information may be accepted as common general knowledge that is not in text books or monograph/review articles, but in this case the burden of proof is on the party asserting that the exceptional situation

applies and it must be such a new field that text books and review articles have not yet appeared in the field (T51/87, T772/89, T892/01, T890/02).

- 6.13 Whilst a review article or a textbook itself may form part of the common general knowledge, it is not the case that every word of every document cited in such a review article or textbook is similarly comprised in the common general knowledge. If that were the case, the outcome would be evidently absurd, as nearly all primary literature would then be considered common general knowledge. For example, many review articles cite hundreds or even thousands of primary sources, often found in disparate technical fields. It would be nonsensical to conclude that the whole disclosure of all such articles are necessarily part of the skilled person's common general knowledge. Not only would that render the concept of "common general knowledge" essentially meaningless, but also it would be contrary to the established guiding principles from the Boards of Appeal set out above.
- 6.14 Thus, it is **only** the information that is provided in the reference work that is comprised in the common general knowledge, for that is why it is included therein. In this regard, it is also well-established that he who asserts has the burden of proof. T475/88, Reasons 3.1 noted this specifically in the context of establishing what is common general knowledge.
- 6.15 Accordingly, if a party wishes to establish that more disparate information is **also** part of the common general knowledge, then evidence of that, such as the presence of the *relevant information* in a reference work, should be provided accordingly.
- 6.16 It is of course also essential that hindsight is not used to establish the common general knowledge for assessing sufficiency of invention of a patent application. The Boards of Appeal have consistently held that the correct approach is to consider (i) who is the skilled person; (ii) on what date are they reading the application; and (iii) what is their common general knowledge, defined as above.

Comparison of the claims of the main request vs the application as originally filed

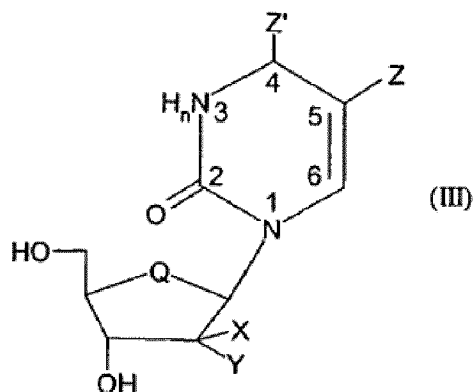
- 6.17 We will refer to the text (including page and line number references) of the application as filed, published as WO 2005/012327, in the discussion that follows, to demonstrate that the invention is insufficiently disclosed even when taking into account the original disclosure content of the application as filed before any adaptation of the description to amended claims was made.
- 6.18 Claim 1 of the main request is directed to a compound having the following general Formula I



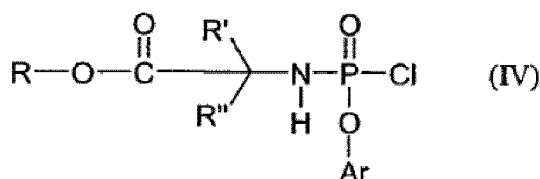
6.19 According to claim 1 of the main request, X is “*independently selected from the group H, F, Cl, Br, I, OH and methyl (-CH₃)*” and Y is “F”. However, the application as originally filed does not exemplify any claimed compound in which X is other than F. In particular, the patent does not disclose any claimed compound in which Y = F and X = -CH₃. For completeness it is noted that compounds in which Y = F and X = -CH₃ are also embraced by all of the auxiliary requests at present on file.

6.20 The description of how to prepare compounds according to claim 1 is given on page 16, line 28 to page 17, line 5 of the application as filed. This merely states that the process for preparation of a compound having Formula I is a process:

“comprising reacting of a compound of formula (III)



with a compound of formula (IV)



wherein Ar, n, Q, R, R', R'', X, Y, Z' and Z have meanings described above with respect to formula I''.

- 6.21 The skilled person is therefore required to use as the starting material a nucleoside analog of Formula III. The application as filed does not disclose how to obtain a compound of Formula III. In particular, the specification does not disclose how to obtain a compound of Formula III in which Y is F and X is -CH₃. As noted above, the only exemplified nucleoside analog in the specification in which Y is F also has X is F. This difluoro substituted compound is known as “gemcitabine”; and is commercially available.
- 6.22 According to the application as filed, if the skilled person wishes to prepare a compound of claim 1 in which Y = F and X = -CH₃, then the skilled person should use as a starting material a nucleoside analog of Formula III in which Y = F and X = -CH₃. However, at the relevant date, such nucleoside analogs of Formula III were not known or commercially available (in contrast to gemcitabine). Furthermore, the application as filed does not disclose how to synthesise such nucleoside analogs of Formula III. See the summary in paragraph 4.1 of the decision.
- 6.23 The patentee has not disputed this basic fact pattern. Rather, it seems to be accepted that there is a “disclosure gap” in the patent. A question to be answered is therefore whether this disclosure gap can be bridged based on common general knowledge without the skilled person undergoing undue burden, in contravention of Article 83 EPC.
- 6.24 It is the opponent’s position that, at the relevant date, the skilled person would have had to engage in an extraordinary amount of experimentation to synthesise such a starting material, given the fundamental lack of relevant disclosure in both the application as filed and the art at the time.
- 6.25 As discussed in paragraph 4.2 of the decision, the patentee proposed two routes by which nucleoside analogs of Formula III, in which Y = F and X = -CH₃, allegedly could have been prepared at the relevant date. These routes are denoted “route 22” and the “analogous gemcitabine route” in the decision.
- 6.26 The opposition division then went on immediately to consider whether each of these routes might be capable of bridging the disclosure gap in the patent. This was an error by the opposition division. In particular, neither “route 22” nor the “analogous gemcitabine route” are mentioned in the application as filed. When considering the disclosure of the application as filed, the skilled person would not have had the benefit (as the opposition division did) of being presented with two detailed routes which have subsequently been found to be capable of producing the desired starting material.
- 6.27 Rather, the skilled person would have had to consider ab initio how best to obtain the desired starting material. The opposition division therefore made an

error in moving directly to consideration of two routes presented by the patentee, neither of which is mentioned or suggested in the application as filed, without first considering the reality that would have been faced by the skilled person and all of the other options that would have been available to the skilled person. In this regard, it seems that the opposition division may have placed greater weight on expert evidence from the patentee's experts, whilst disregarding that provided by the opponent's experts. No explanation was provided as to why the expert reports from Professor Boons and Dr Marquez seem to have been disregarded in the decision.

- 6.28 The opposition division also made an error in not taking proper account of contemporaneous evidence (from the oppositions to D1 and D34, and judgment D10 from the related national litigation in the UK about how skilled people at the relevant time actually tried (and failed) to synthesize nucleoside analogs of Formula III in which Y = F and X = -CH₃.
- 6.29 These two points are discussed in further detail below, but before doing so it may be helpful to comment upon the relevance of the various proceedings involving Idenix Pharmaceuticals ("Idenix") to the current opposition-appeal proceedings.

Relevance of the various Idenix proceedings

- 6.30 As was discussed during the opposition proceedings, extensive evidence regarding the synthesis of 2'-fluoro-2'-methyl nucleosides was considered during the opposition of EP-B-1523489 (D1) and also its divisional which was likewise opposed, EP-B-2332952 (D34). The relevant date when assessing sufficiency for D1 and its divisional was taken by the opposition division in those proceedings as 27 June 2003 and is thus directly contemporaneous with the relevant dates for the patent opposed here (i.e. priority date of 21 July 2003, filing date of 20 July 2004).
- 6.31 In each case, the opposition division concluded that when starting from the incomplete information in the patent, the skilled person when using his common general knowledge would not have been able to produce the claimed compounds by means of routine work as of 27 June 2003 without an excessive process of trial and error. D1 was considered not to meet the requirements of Article 83 EPC. D34 was also considered not to meet the requirements of Article 83 EPC. Analogous conclusions were reached by the national courts in worldwide litigation regarding patents corresponding to D1 and D34. In particular:
- The High Court of England and Wales revoked the UK part of D1 for *inter alia* lack of sufficiency in relation to the synthesis of 2'-Me/2'-F nucleosides (see D10), and that decision was upheld by the UK Court of Appeal (see D11).
 - The Canadian Federal Court revoked the Canadian patent corresponding to D1 for lack of sufficiency in relation to the synthesis of 2'-Me/2'-F

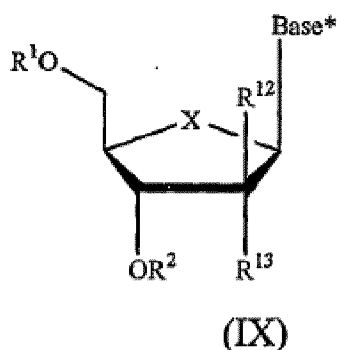
nucleosides, and that decision was upheld by the Federal Court of Appeal (see D116 and D117).

- The Australian Federal Court revoked the Australian patent corresponding to D1 for lack of sufficiency in relation to the synthesis of 2'-Me/2'-F nucleosides (see D118).
- The Oslo District court revoked the Norwegian patent corresponding to D1 for lack of sufficiency in relation to the synthesis of 2'-Me/2'-F nucleosides, and that decision was upheld by the Norwegian Court of Appeal (see D119 and D120).
- The Düsseldorf District Court on 12 March 2015 (Ref.: 4c O 5/14) stayed infringement proceedings based on the German part of D1, because of considerable doubts about the validity of the D1 patent (see D121).
- The US Court of Appeal (Federal Circuit) held, following interference proceedings, that a US patent corresponding to D1 did not enable the synthesis of 2'-Me/2'-F nucleosides (see D122).

6.32 Although EPO opposition proceedings concerning D1 and D34, and the related global litigation outlined above, related to a different patent from the present proceedings, the conclusions from those proceedings are nonetheless highly relevant to the present proceedings for a number of reasons. First, as outlined in further detail below, the subject matter at issue is very similar. Second, as discussed above, the relevant dates are nearly the same (27 June 2003 for D1/D34 vs a priority date of 21 July 2003 and filing date of 20 July 2004 for the present patent). Finally, detailed and rigorous cross examination of experts and extensive document discovery took place in various jurisdictions, the conclusions of which are highly pertinent to the present patent due to the similarities in dates and subject matter.

6.33 Claim 1 of D1 is directed to:

“A compound of Formula (IX):



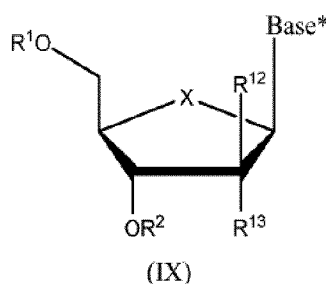
or a pharmaceutically acceptable salt thereof, wherein:

R¹ and R² 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”.

6.34 Claim 1 of D34 is directed to:

“A compound of Formula (IX):



or a pharmaceutically acceptable salt thereof, wherein:
X is O;
 R^1 and R^2 together form a cyclic 3',5'-phosphate ester;
Base* is a purine or pyrimidine base;
 R^{12} is $C(Y^3)_3$;
 Y^3 is H; and
 R^{13} is fluoro”.

6.35 It will be seen that in Formula IX in D1 and in Formula IX in D34, R^{12} is CH_3 and R^{13} is fluoro.

6.36 The compounds claimed in D1, claim 1 and in D34, claim 1 are thus 2'-methyl “up” 2'-fluoro “down” nucleosides. They have a pentose ring as shown in the compound of Formula III of the opposed patent in which Q is O, Y is F and X is - CH_3 . Thus, D1 embraces compounds that would be synthetic intermediates of Formula III in which Y is F and X is - CH_3 according to the present patent. The question of whether or not D1 contains a sufficient disclosure is therefore directly relevant to the question of whether or not the present patent provides a sufficient disclosure.

6.37 In common with the opposed patent in these proceedings, D1 does not contain any description of how to produce such 2'-methyl “up” 2'-fluoro “down” nucleosides. Nor does D34. The patentee of D1 and D34 was therefore required to argue that at the relevant date (i.e. 27 June 2003) the skilled person would have been able to prepare such compounds using information contained in D1 or D34 and the common general knowledge at the time.

However, the opposition divisions in those cases reviewed an extensive amount of evidence on this subject and concluded that the information was insufficient. The opposition division decision in relation to D1 is D2 in these proceedings, and the separately reasoned decision relating to D34 is D35 in these proceedings.

- 6.38 The opposition division in D2 (reason 17.2) when considering the 2'-methyl "up" 2'-fluoro "down" nucleosides of D1, claim 1 concluded:

"The compounds (IX) were only produced after an exhaustive process of trial and error as shown by work done by the Patentee and both the starting point and the reaction scheme required to produce (IX) were neither known nor derivable without extensive experimentation. In summary, the opposition division considers that when starting from the incomplete information in the patent the skilled person when using his common general knowledge would not have been able to produce the compounds by means of routine work without an excessive process of trial and error. The requirements of Art 83 EPC are not met by the main request".

- 6.39 The opposition division in D35 (reason 5.7, last 9 lines) when considering the 2'-methyl "up" 2'-fluoro "down" nucleosides of D34, claim 1 concluded:

"The Opposition Division is thus of the opinion that the skilled person would indeed have been confronted with common general knowledge which would have offered a large amount of options for fluorination of tertiary alcohols together with serious concerns that tertiary alcohol would represent a challenge. It is therefore considered that the skilled person, even identifying the 2'-OH(down)/2'-alkyl(up) corresponding to the intermediate compound prepared in Scheme 3 or 4, as a suitable starting compound to fluorinate would not have been able to prepare the corresponding 2'-F(down)/2'-CH₃(up) without extensive experimentation".

- 6.40 It is clear from this that 2'-methyl "up" 2'-fluoro "down" nucleosides, such as compounds of Formula III in which Y = F and X = -CH₃, were not available to the skilled person as of 27 June 2003 and it would have required an extraordinary amount of experimentation to synthesise such a compound.

An extraordinary amount of experimentation would have been required for a skilled person at the relevant date to make a compound of Formula III in which Y = F and X = -CH₃

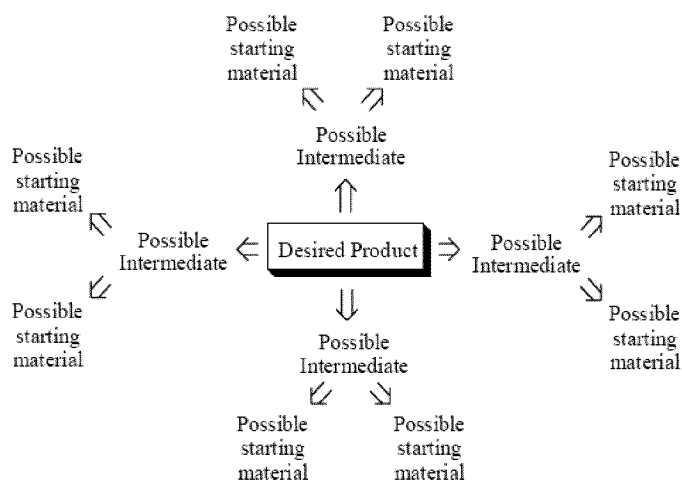
- 6.41 Using the disclosure of the application as filed and in light of the art, an extensive amount of experimentation would have been required for a skilled person as of 21 July 2003 or 20 July 2004 to attempt to synthesise a compound of Formula III in which Y = F and X = -CH₃. Given the absence of any teaching in the application as filed, the skilled person would have had to design a synthesis *ab initio*, modifying the plan based on a substantial amount of work. The

skilled person would not have had available the two “routes” proposed by the patentee and taken as a starting point by the opposition division.

- 6.42 Dr Marquez, a technical expert in an opposition to D1, explained the skilled person’s knowledge and approach as of 27 June 2003 when faced with the task of trying to make a new nucleoside, and in particular a 2’-methyl “up” 2’-fluoro “down” nucleoside. His statement is attached as D41A.
- 6.43 Dr Victor Marquez is an extremely experienced medicinal chemist. His CV at the time of making the Declaration D41A is attached as D41B. In summary, he has more than 30 years of extensive experience in the area of nucleoside chemistry, including specific experience with the chemistry of fluorinated nucleosides. In particular, his experience has involved designing and synthesising novel nucleoside compounds intended to be useful for the treatment of viral infections. Additionally, his experience has involved working with colleagues in related fields such as virology and molecular biology to assess and study the biological activity of such compounds. He is therefore well-qualified to provide an opinion regarding these subjects. Dr Marquez concludes that a skilled person as of 27 June 2003 would have had to engage in an extraordinary amount of experimentation to synthesise a compound of D1, i.e. a compound of Formula III in which Y = F and X = -CH₃, given the lack of guidance in D1 and the available art.
- 6.44 In particular, in D41A paragraphs 82 to 89, Dr Marquez explains the extraordinary amount of experimentation that the skilled person would be required to perform to make a compound of Formula III in which Y = F and X = -CH₃.
- 6.45 In a typical nucleoside synthesis, the skilled person would begin by identifying a compound to synthesise. This would include determining the substituents at each position of the compound, as well as their orientation relative to one another. For example, when planning to synthesise a compound of Formula III having Y = F and X = -CH₃, the skilled person would determine (for the reasons discussed above) that the 2’ methyl group would have an “up” orientation and the 2’ fluorine atom would have a “down” orientation. It is essential to determine the relative configuration of the groups at each position of the sugar prior to developing a reaction scheme. The synthesis of a 2’-methyl “up” 2’-fluoro “down” nucleoside would typically require different starting materials and/or a completely different reaction sequence than the synthesis of a 2’-methyl “down” 2’-fluoro “up” nucleoside (D41A, paragraph 83).
- 6.46 Having selected a nucleoside to synthesise, the skilled person would next devise one or more possible reaction schemes. Working backward from the desired final product, the skilled person would have considered how the desired product might be made from simpler precursors using chemical transformations disclosed in the literature. Such disclosures would not generally be common general knowledge. The skilled person would have worked through several iterations of this type of analysis until he or she arrived at known or

commercially available starting materials. At each step working backward, there would be multiple possibilities for precursor compounds and several possible ways to try transforming the precursor into the next intermediate. For each step, the skilled person would have had to consider factors such as which protecting groups to use and whether the reaction conditions would cause unwanted side reactions or affect the relative orientation of the different substituents (D41A, paragraphs 84 and 85).

- 6.47 A simplified, generic schematic illustrating such a process of retrosynthetic analysis is given below:



- 6.48 Myriad potential routes to making a compound of Formula III in which X = -CH₃ and Y = F - in particular to creating the 2'-methyl/2'-fluoro substitution on the sugar ring - would have been considered by a skilled person at the relevant dates. Contemporaneous evidence shows that the vast majority of such potential routes would fail. However, the application as filed provides no guidance as to which of these routes to try or how to carry out any of these methods.
- 6.49 Upon determining a reaction scheme (with no guidance from the application as filed), the skilled person would have then begun trying to synthesise the desired nucleoside according to his or her plan. Each intermediate compound synthesised would have to be purified and characterised to confirm its identity. It would likely have been necessary to optimise each step to improve the reaction yield. If a given reaction step did not occur as planned, the skilled person would have had to modify the reaction conditions. In certain cases, it could have been necessary to abandon the planned approach completely and start the entire process again using a different reaction scheme (D41A, paragraph 86).
- 6.50 The application as filed does not provide *any* teaching to guide a skilled person through the steps discussed above. For even the most skilled chemist, the

synthesis of a new nucleoside requires extensive experimentation (as is evident from, for example, D49, D50 and D87). This is particularly true where the nucleoside has a substitution pattern on the sugar ring which has not been made before. As the compounds of Formula III in which $Y = F$ and $X = -CH_3$ have such an untried substitution pattern at the 2' position, a skilled person as of the relevant dates could not have made such a compound without an extraordinary amount of experimentation (D41A, paragraph 89).

- 6.51 Dr Marquez is now retired. Technical evidence in the present opposition was therefore additionally provided by the declarations (D42A and D105) of Professor Geert-Jan Boons. Prof Boons gave technical evidence (D43) in court proceedings in the UK relating to D1 (see D10, paragraphs 18 to 20). The judge found Prof Boons to be *"a knowledgeable and enthusiastic expert"* (D10, paragraph 20, line 3). Professor Boons' CV is attached as D42B. As indicated by his CV, he has been studying and working in the field of medicinal chemistry for over thirty years. In particular, he has experience in the preparation of carbohydrates and chemically modified carbohydrates, including the preparation of carbohydrates modified by fluorine, and the use of such compounds for the preparation of nucleotides. Prof Boons is thus well placed to provide an opinion on the skilled person's understanding in these technical areas in 2003 or 2004.
- 6.52 In 2014 Prof Boons independently concluded in D43 (paragraphs 11.52-11.54) that in his opinion the synthesis of a 2'-Me/2'-F nucleoside in 2003 would have been a research project of significant complexity and uncertain outcome. He remains of this opinion (D42A, paragraph 5).
- 6.53 For this opposition Prof Boons was asked to read Dr Marquez's statement D41A. Having read D41A, Prof Boons states in D42A that he agrees with Dr Marquez's opinion concerning the knowledge and skill of a person of ordinary skill in the art as of 27 June 2003 (D42A, paragraph 6).
- 6.54 Prof Boons also read the opposed patent and was asked to consider the skilled person's knowledge and understanding at the relevant dates for the opposed patent: 21 July 2003 (the priority date) and 20 July 2004 (the filing date).
- 6.55 Prof Boons first notes that the opposed patent tells the skilled person nothing about how to prepare 2'-Me/2'-F nucleosides (D42A, paragraph 9). He also states that he is not aware of any scientific articles that were published before 26 July 2005 that described a method of synthesising a 2'-Me/2'-F nucleoside (D42A, paragraph 10).
- 6.56 With respect to the task of synthesising a 2'-Me/2'-F nucleoside as of 21 July 2003 or 20 July 2004, in Prof Boons' opinion the relevant knowledge and skill of a person of ordinary skill in the art at those dates would not be significantly changed from that as of 27 June 2003 and so the conclusions in Dr Marquez's Expert Opinion (D41A) and Prof Boons' UK High Court Report (D43) would apply in relation to the opposed patent (D42A, paragraph 10).

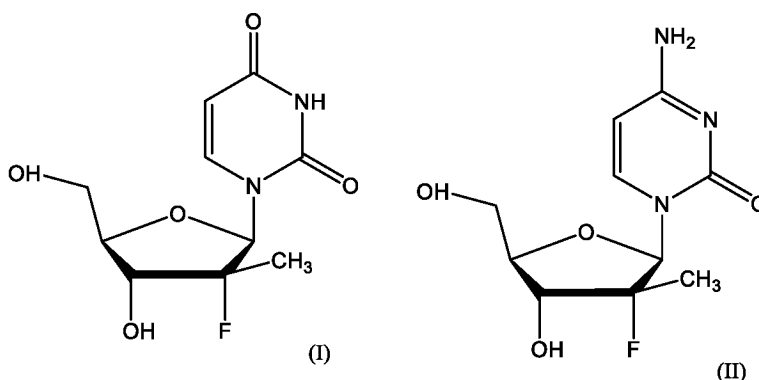
- 6.57 Prof Boons concludes that the synthesis of a 2'-Me/2'-F nucleoside in 2003 or in 2004 would have been a research project of significant complexity and uncertain outcome (D42A, paragraph 11).
- 6.58 The opposition division made an error in not taking proper account of the evidence provided by Dr Marquez and Professor Boons, and in particular their conclusion that synthesis of a 2'-Me/2'-F nucleoside in 2003 or in 2004 would have been a research project of significant complexity and uncertain outcome. Indeed, the opposition division seem to have completely ignored the evidence from Dr Marquez and Professor Boons. There is no explanation in the written decision as to why the evidence of these eminent chemists was apparently considered unpersuasive. In this regard, page 32, paragraph 1 of the decision states that "O had not provided evidence", but does not explain why the evidence of Dr Marquez and Professor Boons was not taken into account.
- 6.59 In view of the apparent disregard for the evidence of Dr Marquez and Professor Boons, a further declaration from Professor Boons (D123) is filed with these grounds of appeal. Professor Boons provides in paragraphs 5 to 9 of D123 a summary of the steps a skilled person at the relevant time would have had to take in order to devise a synthesis of 2'-Me/2'-F nucleosides. Professor Boons also explains why the opposition division and Professor Davies in D110 were incorrect to disregard the various possible routes to 2'-Me/2'-F nucleosides that a skilled person might have considered at the relevant time. Jumping directly to synthesis by analogy with the synthesis of gemcitabine without first considering other routes relies, in the view of Professor Boons, on knowledge that would not have been available to the skilled person in 2003 (or in 2004).

Contemporaneous evidence of what a skilled team of people actually did

- 6.60 Evidence of the extensive experimentation that would be required when attempting to produce a compound of Formula III in which $Y = F$ and $X = -CH_3$, at the relevant time can be seen from the actions of Idenix, a patentee of D1. This is independent, contemporaneous and highly relevant evidence of what a skilled team of people actually did. As set out below, it is evident that it was a huge challenge for a team of skilled people at the relevant date to actually make a compound of Formula III in which $Y = F$ and $X = -CH_3$. Certainly, the difficulties encountered in doing so were clearly such that overcoming them represents a burden far in excess of that allowable under Article 83 EPC.
- 6.61 Beginning in 2002, Idenix attempted to prepare a 2'-methyl "*up*" 2'-fluoro "*down*" nucleoside. This research project was carried out by a team of skilled chemists in Idenix, led by Dr Jean-François Griffon. Many experts within Idenix contributed ideas to the project. In addition, outside experts were consulted. When responsibility for leading the project passed to another individual in May 2004, more than eighteen months after the project had begun, that individual, Dr Alistair Stewart, considered it appropriate to carry out six months of literature searches (the results of which would not have been common general

knowledge) to try to identify a suitable procedure to make a 2'-methyl "up" 2'-fluoro "down" nucleoside.

- 6.62 It was only when information was available that derived from the authors of D5, that Idenix were able to produce a 2'-methyl "up" 2'-fluoro "down" nucleoside. This was more than two years after Idenix had begun the project to try to prepare such a compound.
- 6.63 The validity of D1 has been considered in the UK High Court and Court of Appeal, resulting in the Decisions D10 and D11, respectively. The work carried out by Idenix between 2002 and early 2005 was reviewed by the court; several of the scientists involved in the project were cross-examined. Based on the witness statements and extensive documentary evidence, the judgment from the UK Court, D10, paragraphs 472-523 sets out the eleven different strategies that were used or contemplated by Idenix when seeking to identify a route to synthesise a 2'-methyl "up" 2'-fluoro "down" compound. These are also set out in Annex A filed with the opposition statement and also provided for completeness with these grounds of appeal as Annex B.
- 6.64 The team of skilled chemists working for Idenix, tried many different routes to make a 2'-Me "up" 2'-F "down" nucleoside. This involved extensive trial and error and many different synthesis routes over a period of years. This period spans from 2002 (before the priority date of the opposed patent) to early 2005 (six months after the filing date of the opposed patent). Evidence of the project carried out by Idenix's chemists is provided in D12 to D33.
- 6.65 D25 is a declaration by Dr Jean-François Griffon who initially conducted experiments as part of the team in the project to make a 2'-Me "up" 2'-F "down" nucleoside. The compounds that the project sought to make are 2'-Me/2'-F uridine nucleoside (I) and 2'-Me/2'-F cytidine nucleoside (II) whose structures are depicted in D25, paragraph 6 and reproduced below:



- 6.66 These compounds are referred to in the declaration as "2'-F-2'-Me-riboU" and "2'-F-2'-Me-riboC" respectively. Dr Griffon worked under the direction of his supervisors in the chemistry group of Idenix, Dr Gilles Gosselin and Dr Richard Storer (D25, paragraph 6). D25 describes work carried out by Dr Griffon and

others in the team at Idenix and includes information about some of the other chemists with whom his team consulted.

6.67 Prior to December 2002, Dr Griffon had begun work towards the synthesis of 2'-F-2'-Me-riboU and 2'-F-2'-Me riboC (D25 paragraph 8). On 2 December 2002, Dr Griffon met with Dr Storer, Dr Gosselin and Professor George Fleet (D25, para 109). D25, paragraph 110 reports that at the 2 December 2002 meeting Dr Griffon, Dr Storer, Dr Gosselin and Professor Fleet discussed their plans to synthesise "2'-F-2'-Me-riboC and 2'-F-2'-Me-riboU", i.e. compounds that are starting materials of Formula III of the opposed patent in which Y = F and X = -CH₃.

6.68 D25, paragraphs 114 to 131 report the efforts that were made by Dr Griffon and his team over the period from December 2002 to December 2004 in their attempts to synthesise a 2'-F-2'-Me-riboU and 2'-F-2'-Me-riboC. This included monthly progress reports to Dr Storer (D25, paragraph 114); corresponding with Dr Adel Moussa (D25, paragraph 126); and discussing potential synthesis routes during various Idenix chemistry meetings and research retreats over the period from December 2002 to October 2003 (D25, paragraphs 113, 123, 127 and 130).

6.69 Clearly it was a team effort in which numerous chemists within Idenix were asked to contribute ideas as to how such compounds could be made. D14 is an example of a monthly report sent by Dr Griffon to Dr Richard Storer, copied to Dr Gilles Gosselin and Dr Jean-Louis Imbach.

6.70 The team at Idenix also consulted outside experts. As reported in D16, Dr Storer in February 2003 wrote to Dr Paul Coe, an organofluorine expert, to ask for his help. Dr Storer wrote

"I enclose herewith a summary of our current targets which involve fluorine, the first series are basically aromatic compounds and the second are nucleosides. We are okay with the nucleoside chemistry, it's the fluorine chemistry we are struggling with and where your help will be valuable". (D16, paragraph 1)

6.71 In the summary attached to the letter, the second page refers to "nucleoside analogues" and Dr Storer refers to target 9. Target 9 is a 2'-fluoro "down" 2'-methyl "up" nucleoside (D16, final page). Dr Storer states:

"Target 9 is an attempt to replace the tertiary OH of the ribo analogue with fluorine. We have tried a variety of procedures from the exocyclic methylene analogue in attempt to effectively add HF across the double bond. 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 90 would be appreciated." (D16, page 3, paragraph 2)

6.72 D17 is Dr Paul Coe's reply. Dr Coe states:

"Some of the routes you have tried are OK except that I think you are using the wrong reagents, leaving groups and reaction conditions". (D17, page 2, lines 3 to 4)

6.73 Dr Coe then suggests some possible reagents, leaving groups and reaction conditions to make the target compound 9, stating:

"Second in our experience and indeed in that of manner other 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". (D17, page 1, last paragraph)

6.74 Another outside expert, Professor George Fleet, was also consulted over a period of time including in December 2002 (D25, paragraph 109) and in May 2004 (D20, page 3, reaction scheme). He suggested various reaction schemes. These did not involve the use of DAST in nucleophilic fluorination of a 2'-Me "down" 2'-OH "up" nucleoside (D20, page 3, reaction scheme; D29, reaction schemes). In fact his initial suggestion involved electrophilic fluorination.

6.75 Idenix also brought in additional chemists to work on the project to prepare a 2'-methyl "up" 2'-fluoro "down" nucleoside. D24 is the testimony of Dr Alastair Stewart, the Idenix project leader, that was given in US proceedings. Dr Stewart began work on the synthesis of 2'-fluoro "down" 2'-methyl "up" nucleosides in May 2004 (D24, page 15, lines 21 to 23). However, his first action (after reviewing a summary of the attempts previously made in the project) was to review the literature for examples of fluorination and fluorinated nucleosides (D24, page 24, lines 2 to 4). He did not carry out an experiment until November 2004. In the period from May 2004 to November 2004, Dr Stewart was having ongoing discussions with Professor Fleet and with his colleagues in the group, meeting on a weekly basis to discuss the project (D24, page 30, lines 12 to 21) and carrying out literature searches (D24, page 31, lines 13 to 17). Dr Stewart spent at least two hours a day between May 2004 to November 2004 on the project, (D24, page 31, lines 8 to 12). This clearly shows that it was a research project for the skilled person to try to identify a route to synthesise a compound of Formula III in which Y = F and X = -CH₃.

6.76 Idenix's research team explicitly acknowledged how difficult they were finding the task of trying to prepare a nucleoside having the novel substitution pattern at the 2' position of the sugar ring (2'-methyl "up" 2'-fluoro "down"). The compounds being sought by Idenix (and the compounds of Formula III of the opposed patent in which Y = F and X = CH₃) include at the 2' position a highly congested tertiary alkyl fluoride. By November 2004, Idenix had spent over two

years trying to make such a compound. On 11 November 2004, Dr Richard Storer of Idenix wrote an email to his colleagues, Dr Stewart and Dr Moussa. In connection with the attempts to make a 2'-fluoro "down" 2'-methyl "up" nucleoside, Dr Storer commented:

"A lot of things which look simple on paper in related systems have been tried and don't work in this series. Having to make the tertiary fluoride is very different to having to make a secondary" (D22, page 1, last four lines).

- 6.77 So the work done by Idenix was undertaken over a period of at least two years and was a real team effort by numerous chemists. This team would have been aware of any relevant common general knowledge. However, for a period of at least two years, the team of skilled chemists was unable to make a compound of Formula III in which Y = F and X = -CH₃.
- 6.78 It was not until January 2005, after Idenix became aware of the teaching of D5, that their research team was able to produce a 2'-methyl "up" 2'-fluoro "down" nucleoside. This demonstrates that the starting material of Formula III of the opposed patent in which Y = F and X = -CH₃ was not available to the skilled person as of 21 July 2003 or even as of 20 July 2004, and that it would be an undue burden for the skilled person to produce it.
- 6.79 The opposition division made an error in not taking into account extensive contemporaneous evidence, independent of the patentee and the opponent in the present proceedings, showing how skilled people at the relevant time actually tried (and failed) to synthesis nucleoside analogs of Formula III, in which Y = F and X = -CH₃. This point is discussed in further below specifically in relation to the "analogous gemcitabine route".

"Route 22"

- 6.80 The opposition division discusses "route 22" in section 4.3 of its decision, before concluding that "route 22" cannot be seen as "*fulfilling the criteria as defined in CLBA edition 2019, II.C.6.6.5 describing how to deal with non-disclosed steps*". See also Section 4.9 of the decision.
- 6.81 We agree with the conclusion of the opposition division that the so-called "route 22" cannot cure the insufficient disclosure of the patent.
- 6.82 For completeness, and because these matters were discussed during the oral proceedings and written procedure prior to oral proceedings, our position on "route 22" is summarised in Annex C to these grounds of appeal. Should the patentee appeal against the decision of the opposition division in relation to "route 22", then the opponent may comment further on these matters in its response to the patentee's appeal.

"Analogous gemcitabine route"

- 6.83 The opposition division discusses the “analogous gemcitabine route” in sections 4.4 to 4.9 of its decision, before erroneously concluding that “analogous gemcitabine route” would not have presented the skilled person with undue burden at the priority date.
- 6.84 In coming to this conclusion, the opposition division made a number of errors, since there are various fundamental issues with the “analogous gemcitabine route”. These are discussed in further detail below, with reference to the errors present in the decision of the opposition division. In summary, though, there are at least the following errors in the decision of the opposition division in relation to the “analogous gemcitabine route”.
1. Erroneously concluding that the skilled person was in a “one-way-street” when identifying gemcitabine to be a useful starting point for the synthesis of 2'-Me/2'-F nucleosides, and in doing so disregarding both the teaching of the application as filed and the declarations of Professor Boons.
 2. Erroneously jumping immediately from the identification of gemcitabine as a useful starting point for the synthesis of 2'-Me/2'-F nucleosides to synthesis by analogy, without first considering other options available, such as actually using gemcitabine itself as the starting material for the synthesis of 2'-Me/2'-F nucleosides.
 3. Incorrectly taking into account documents that are not common general knowledge to cure the deficient disclosure of the application as filed in relation to the known gemcitabine synthesis.
 4. Not placing enough weight on the concerns identified by Professor Boons regarding adapting the “gemcitabine route” to provide the “analogous gemcitabine route”.
 5. Incorrectly accepting that the starting material(s) for the “analogous gemcitabine route” could be prepared based on common general knowledge, when in fact it was necessary to rely upon primary literature references.
 6. Erroneously concluding that the number of undisclosed steps and the time that would be needed to carry out those steps are not relevant factors in assessing whether the skilled person faces undue burden.
 7. Placing greater weight on D49, D50 and D87, instead of contemporaneous evidence of the difficulties actually faced by two skilled chemists investigating the “analogous gemcitabine route” (see D10 and D116).
 8. Applying a different standard when assessing sufficiency for the “analogous gemcitabine route” as it (correctly) did for “route 22”.

Gemcitabine would not have been considered a useful starting point in the synthesis of the claimed 2'-Me/2'-F nucleosides

- 6.85 There is a fundamental problem with the manner in which the “analogous gemcitabine route” was considered by the opposition division. In particular, by

immediately considering whether this route (and “route 22”) could cure the “disclosure gap” in the patent, the opposition division was necessarily presented with information that was not available to the skilled person reading the patent application at the relevant time.

- 6.86 In particular, as has been discussed above, the skilled person would in reality have been presented with a myriad different options for potentially synthesising a starting material of Formula III of the opposed patent in which Y = F and X = -CH₃, as is discussed above in relation to the expert evidence from Dr Marquez and Professor Boons. The opposition division did not take proper account of the reality that would have faced a skilled person.
- 6.87 It is certainly **not** the case that there was a “one-way-street” (see section 4.9 of the decision), whereby the only option available to the skilled person was the “analogous gemcitabine route”. Rather, the skilled person did have to make (numerous) choices, one of which was to investigate the “analogous gemcitabine route” when other options were available. The opposition division was **incorrect** to conclude that the “analogous gemcitabine route” was the only option available to the skilled person.
- 6.88 That the opposition division was incorrect is wholly supported by the independent contemporaneous evidence of how skilled people actually tried to synthesise nucleosides with a 2’-Me/2’-F substitution pattern at the relevant time: numerous routes were tried and/or suggested by a series of skilled synthetic chemists (see discussion above). Notably **none** of these scientists focussed exclusively on the “analogous gemcitabine route”, but were trying a variety of other routes.
- 6.89 The opposition division was incorrect to disregard the independent contemporaneous evidence that emerged from the various Idenix proceedings (see comments in section 4.4 b) of the decision). It has never been disputed that the Idenix patents contain a different disclosure from the present case. The opponent is not pleading, and never has pleaded, *res iudicata*. However, the contemporaneous evidence that emerged from the Idenix proceedings is nevertheless **highly relevant** to the present proceedings due to the similarity in dates and subject matter at issue (see discussion above in section 6.30 ff). In particular, contemporaneous evidence as to the strategies adopted by a number of skilled chemists when trying to synthesise nucleosides with a 2’-Me/2’-F substitution pattern in 2003 must surely be considered highly pertinent to the assessment of whether or not such compounds were sufficiently disclosed in the present patent as of 2003/2004.
- 6.90 The opposition division and patentee noted that gemcitabine is identified in the prior art section of the patent (see formula (3)) and is used in the synthesis of compounds CPF-31, CPF-40 and CPF-41. However, all this is telling the skilled person is that gemcitabine is a suitable starting material of Formula (III) when trying to synthesise particular compounds with a 2’-F/2’-F substitution pattern. That is the limit of the disclosure relating to gemcitabine’s uses as a synthetic

intermediate, and the opposition was incorrect to suggest otherwise (see point 4.4 a) of the decision).

- 6.91 In particular, gemcitabine is at no point identified as being of relevance to the synthesis of nucleosides with substitution patterns other than 2'-F/2'-F, and there is certainly no suggestion in the application as filed that it might be useful in achieving a 2'-Me/2'-F substitution pattern. Moreover, it was not common general knowledge in 2003 (or in 2004) that gemcitabine might be relevant to the synthesis of 2'-Me/2'-F nucleosides.
- 6.92 This point is entirely consistent with the comments from the opposition division in revoking D1. As noted above, the opposition division in those proceedings commented that *“both the starting point and the reaction scheme required to produce (IX) were neither known nor derivable without extensive experimentation”*. However, as noted in the opposed patent in these proceedings, gemcitabine was in 2003 a “well-established” anti-cancer agent. Its existence and structure would certainly have been known to the researchers at Idenix. Indeed, Mr Justice Arnold held in D10 that gemcitabine’s existence and structure were part of the common general knowledge of the skilled team (which he held to include a medicinal chemist) in 2003. Had the gemcitabine molecule in fact been considered a viable starting point for synthesizing a nucleoside with a 2'-Me/2'-F substitution pattern then the comments of the opposition division, confirmed in worldwide litigation, would not make sense.
- 6.93 As further evidence that the patent did not envisage gemcitabine (or its synthesis) being of relevance to the synthesis of other nucleosides, such as 2'-Me/2'-F nucleosides, it is worth noting that the application as filed provides no synthetic information for gemcitabine itself. That is because the gemcitabine used was (apparently) commercially obtained “ex. Lilly” - see page 109, line 15 of the application as originally filed.
- 6.94 In short, there is nothing in the application as filed that would *“trigger the skilled person to think what the relevancy is of this disclosure in order to make the other claimed variants”* (see point 4.4 a) of the decision). It is only with the benefit of hindsight that the skilled person would think in this manner.
- 6.95 Rather, all the skilled person could take from the synthesis of compounds CPF-31, CPF-40 and CPF-41 is that the synthesis makes use of the Formula (III) + Formula (IV) route described in the application as originally filed. The skilled person would realise that to make compounds of the invention with 2'-methyl/2'-fluoro substitution, they would first need to obtain a starting material of Formula III of the opposed patent in which X = -CH₃ and Y = F. The application as filed provides the skilled person with no guidance as to how to do that.
- 6.96 The opposition division also made an error in point 4.9 of its decision when discussing Markush formulae claims. In particular, to the extent that the application as filed contains a teaching of how various compounds can be

synthesised “by analogy”, it is merely in relation to reactions of starting materials of Formula (III) and Formula (IV). There is no disclosure or suggestion of analogous synthesis of starting materials of Formula (III). There is no disclosure or suggestion in the patent of any synthetic route to compounds having a 2'-methyl/2'-fluoro substitution pattern that could potentially be followed “by analogy”.

6.97 Professor Boons also comments on the concept of synthesis “by analogy” in paragraph 9 of D123, stating that *“unless an entirely new reaction is devised, all syntheses proceed “by analogy” with known reactions. I therefore disagree with Professor Davies (paragraph 7 of D110) that a desire to synthesise by analogy would attract the skilled person specifically to the gemcitabine synthesis in favour of other syntheses, that could also be considered “analogous” to known synthetic approaches.”* This is an important point, since the opposition division seem to have placed great weight on the so-called “analogous gemcitabine route” being “analogous”, whereas in fact virtually all syntheses are “analogous” to other known synthetic approaches.

6.98 Moreover, the only disclosure in the application as filed in relation to synthesis of starting materials of Formula (III) relates to bromo-vinyl uridine (BVU) - see page 23, line 10 to page 25, line 12 of the application as filed. So were the skilled person to even consider synthesis of starting materials of Formula III of the opposed patent in which Y = F and X = -CH₃ “by analogy”, all they would have to consult in the application as filed would be the BVU synthesis. It has not been suggested by any party in these proceedings that such a synthesis would be useful to a skilled person in deriving compounds of Formula (III) having a 2'-Me/2'-F substitution pattern.

6.99 During the opposition proceedings, the patentee argued that the skilled person would immediately consider the synthesis of gemcitabine for a number of erroneous reasons. For example, the patentee argued that replacing a fluoro moiety with a methyl moiety is a minor difference that would be expected to have little, if any, effect on the properties and synthesis of the compounds in question. This conclusion appeared to be based on the assertion that both C-Me and C-F bonds are both fairly strong (see paragraph [99] of the 6 November 2020 submissions). However, fluoro and methyl moieties have very different properties, as confirmed by Professor Boons in paragraph 5 of his declaration D105 in the following terms:

“Fluoro and methyl are very different moieties. Fluorine is the most electronegative element and is small. The presence of fluorine in a molecule or a reaction is expected to have a large electronic impact as it is strongly electron-withdrawing, but a small impact on steric hindrance. In contrast, a methyl group is a slightly electron-donating moiety. It is considerably larger than a fluorine atom and has a correspondingly-greater impact on steric factors in a molecule or a reaction. Replacing a fluorine atom with a methyl group does not constitute a minor difference and has a substantial impact on chemical transformations.” (emphasis added)

6.100 The opposition division made an error in apparently disregarding the evidence of Professor Boons on this point. Indeed, it is not apparent on what basis the opposition division reached its conclusions: if the opposition division imported their own technical knowledge rather than relying upon the clear evidence provided by an eminent expert, then that would be inappropriate and would represent another error by the opposition division. In this regard the conclusions of the opposition division at page 31, paragraph 2 of the decision are not supported by any cited document or explanation. For completeness, Professor Boons has elaborated further on this point in paragraph 14 of D123, with reference to the electronegativity of fluorine and the relative sizes of fluorine and methyl. Professor Boons remains of the view that *“a fluorine and methyl substituent will have very different impacts on chemical transformations especially when these moieties are located close to the reaction centre”*.

6.101 The patentee’s position was also based on another erroneous premise, namely that the skilled person would disregard the absence of a chiral centre at the 2’ position of gemcitabine. In reality, the skilled person would immediately identify the presence of the chiral centre at the 2’ position in the claimed 2’-Me/2’-F nucleosides, and would understand that the synthetic route selected would need to take account of this chiral centre. That being the case the skilled person would not consult a synthetic route that does not involve introduction of such a chiral centre. Rather, the skilled person would instead consider that installing the chiral centre is a key feature of the required synthesis, and consequently would instead be more likely to consult synthetic routes that involve installation of similar chiral centres. This is confirmed by Professor Boons in paragraph 6 of his declaration D105 in the following terms:

“Gemcitabine does not have a chiral centre at the 2’ position. There is a fluoro substituent both above the ring (“up”) and below the ring (“down”). In contrast a 2’-fluoro-2’-methyl nucleoside is chiral at the 2’ position, for example in the case of 2’-fluoro down and 2’-methyl up, and the skilled person seeking to make such a compound would know that he/she needs to take account of controlling the stereochemistry at that centre.”

6.102 The opposition division made an error in apparently also disregarding the evidence of Professor Boons on this point. Professor Boons has elaborated further on this point in paragraphs 11 to 13 of D123, and explains in paragraph 11 exactly why the additional chiral centre in 2’-Me/2’-F nucleosides would render synthesis by analogy with the synthesis of gemcitabine unattractive:

“[S]ynthesis by analogy with the gemcitabine approach would require the installation of three new chiral centres, each of which will have an uncertain outcome, potentially resulting the formation of 8 different stereoisomers. This would be unattractive to the skilled person, because each step in which a chiral centre is introduced will generally involve additional separation and identification steps. Rather, the skilled person

would in preference seek a starting material that has as many as possible chiral centres already in place, such as an appropriate monosaccharide or natural nucleoside”

6.103 Professor Boons goes on to conclude in paragraph 13 that in his view “*the additional chiral centre in 2’-Me/2’-F nucleosides would have rendered gemcitabine a less attractive starting point to the skilled person than many of the other routes that were potentially available*”.

6.104 In view of (at least) these two highly significant differences between gemcitabine and the claimed 2’-Me/2’-F nucleosides, it is simply not credible to suggest that the skilled person would be prompted to consult the synthesis of gemcitabine in the first place, when seeking to synthesise such 2’-Me/2’-F nucleosides.

6.105 The patentee also suggested that the existence of allegedly reliable and scalable routes to synthesise gemcitabine would have encouraged the skilled person to consider the gemcitabine route. Setting aside the fact that the application as filed does not contain any information about these allegedly reliable and scalable routes, such considerations are in any event simply not relevant. Rather, as Professor Boons explains in paragraph 9 of his declaration D105:

“Just because one particular process has, as the result of research, often quite substantial research, resulted in a scalable version, it does not follow that another, and substantially different process will be either reliable or scalable.”

6.106 In summary, the opposition division made a series of errors in concluding that the skilled person, when faced with the need to synthesise starting materials of Formula III of the opposed patent in which Y = F and X = -CH₃, would be in a “one-way-street” position. In fact, such a conclusion can only be reached with unallowable use of hindsight, and if important factors such as (a) independent contemporaneous evidence, (b) the actual disclosure of the application as filed, and (c) the evidence of Professor Boons and Dr Marquez, are disregarded.

Even if gemcitabine had been considered a useful starting point, there would still have been choices to make

6.107 Even if, which is strongly disputed, the skilled person had considered gemcitabine to be a useful starting point for synthesising starting materials of Formula III in which Y = F and X = -CH₃, then he or she still needs to decide what to do next. Of course, the application as filed provides no guidance as to how gemcitabine might be used.

6.108 The opposition division has proceeded on the basis that “synthesis by analogy” is the only option a skilled person would have considered. However, there would have been another option open to the skilled person, albeit again not

part of the common general knowledge, namely using gemcitabine as a starting material and replacing one of the fluorine atoms at the 2' position of gemcitabine with a methyl moiety. Such a synthetic pathway would potentially be attractive to the skilled person, as it would likely involve fewer steps than synthesising the sugar ring itself.

- 6.109 It is clearly not the case that the skilled person is in a “one-way-street” position, as suggested by the opposition division, where the only option that can be considered is synthesis by analogy. Once again, the opposition division has unallowably relied upon hindsight to reach that conclusion.

The patentee relies upon documents that are not common general knowledge in relation to the synthesis of gemcitabine itself

- 6.110 Even if, for sake of argument, the skilled person had considered gemcitabine to be an appropriate starting point for the synthesis of the claimed 2'-methyl/2'-fluoro nucleosides, and moreover that synthesis by analogy is the most appropriate approach, then he or she would have needed to consult documents that are not common general knowledge in order to determine how gemcitabine is synthesised.
- 6.111 First, while the Merck Index (D88) would generally be considered to constitute common general knowledge, for the reasons discussed above, it simply cannot be correct that every reference cited in the Merck Index itself also constitutes common general knowledge. If this approach were to be adopted, it would result in the common general knowledge of the skilled person being vast and clearly absurd. Nevertheless, the opposition division seems to have erroneously endorsed such an approach in point 4.4 c.2) of its decision, by characterising D54 (a primary literature article), D89 (a UK patent application), D91 (another primary literature article) and D56 (another primary literature article) as common general knowledge.
- 6.112 Even if the opposition division were correct in concluding that D54, D89, D91 and D56 are common general knowledge, due to their being cited in D88, the patentee's construction of the “analogous gemcitabine route” was not only supported by those references. In particular, the patentee identified eight separate synthetic steps in the “gemcitabine route” on pages 24 to 40 of the 6 November 2020 submissions. Step 6 also requires that a non-commercially available cytosine base is prepared (see paragraph 16 of D87). As support for each of these steps being known at the relevant date, the patentee referred on pages 16 to 41 of the 6 November 2020 submissions to at least four further documents (i.e. at least D52, D61, D90, D92,) in addition to D54, D89, D91 and D56 that do not constitute common general knowledge. The fact that some of these references were themselves cited in documents that might constitute common general knowledge is not relevant, for the reasons already provided. Further, the documents appear to have been selected to assist the patentee in arriving at the desired outcome, and those selections inevitably rely upon

knowledge that would not have been available to the skilled person in 2003/2004.

- 6.113 It is also noteworthy that even the patentee's expert, Professor Davies, accepts that a "comprehensive literature search" would be required (see paragraph 24 of D48), which would not be the case if all of the relevant documents were indeed common general knowledge. Moreover, Professor Davies suggests that this comprehensive literature review would take around a week.
- 6.114 The opposition division made an error, therefore, in asserting that all of the detail of each step in the synthetic routes to gemcitabine routes are "common general knowledge". In fact, it is evident that the patentee relied upon multiple documents that are not common general knowledge, and for this reason alone the "analogous gemcitabine route" cannot cure the disclosure gap in the application as originally filed. The fact that a "comprehensive literature search" taking around a week was considered necessary by the patentee's own expert highlights the undue burden placed on the skilled person.

Adapting the "gemcitabine route" to provide the "analogous gemcitabine route"

- 6.115 Even if the skilled person were able to determine the "gemcitabine route" without consulting documents that are not common general knowledge, then he or she would immediately identify two aspects of the "gemcitabine route" that would have been of concern.

The skilled person would have had particular concerns regarding the Reformatsky reaction

- 6.116 The Hertel synthesis to gemcitabine (step 1 in D87) involves a Reformatsky reaction using the reagent BrCFMeCO₂Et. As Professor Boons explains in paragraph 14 of his declaration D105:
- "I am not aware of any paper published before 2003 that employed BrCFMeCO₂Et in a Reformatsky reaction. A skilled person would not be confident of the results of such a reaction. Organofluorine chemistry is recognised as continuing to be an active field of research. There is a journal dedicated to it (Journal of Fluorine Chemistry); there are academics who specialise in this field and special courses are given on this topic. Once something has been done, it can be seen that it was possible. However, before carrying out a Reformatsky reaction with a new reagent, the skilled person would not be confident of succeeding."*
- 6.117 The skilled person would have no reasonable expectation of a Reformatsky reaction using the reagent BrCFMeCO₂Et proceeding in the desired manner. The fact that it is **now** known that such a reaction does work is irrelevant - at the time the untried nature of this transformation would have placed an undue burden on the skilled person.

- 6.118 In response to the comments on Professor Boons, the patentee filed a declaration from Professor Davies (D110).
- 6.119 In paragraph 9 of D110, Professor Davies summarises some results reported in D111. However, none of the results reported are for compounds that have both a methyl moiety and a fluoro moiety at the relevant position. Indeed, the general message from D111 is that Reformatsky reactions need reaction conditions, solvents and the like to be carefully controlled (see introduction). The lack of relevant disclosure in D111 is also discussed by Professor Boons in paragraph 21 of D123.
- 6.120 In paragraph 10 of D110, Professor Davies referred to D94 as providing evidence that Reformatsky reactions using the reagent BrCFMeCO₂Et do indeed work. However, the problem with D94 is that it is a primary literature article and does not represent common general knowledge (and thus would not have been something the skilled person would have known about when considering if it would be feasible to adapt the gemcitabine route). It is telling that Professor Boons was not aware of this document before it was brought to our attention by the patentee. Moreover, the main focus of this document is not the Reformatsky reaction at all. Indeed, no details are provided about reaction conditions, and it is known from D111 that reaction conditions need to be carefully controlled. The problems with D94 are confirmed by Professor Boons in paragraphs 18 to 20 of D123.
- 6.121 In paragraph 11 of D110, Professor Davies referred to D112. Again, this document is not common general knowledge, so has the same limitations as D94. Further, the reaction depicted is not with an aldehyde, as is used in the gemcitabine route. Its relevance therefore seems limited, as also confirmed by Professor Boons in paragraphs 22 and 23 of D123.
- 6.122 Professor Boons also observes in paragraph 24 of D123 that *“the selection of a reaction that is supported by only a single literature reference (which contains no reaction conditions) is rather contradictory to Professor Davies’ general position that the skilled person will want to keep things simple and avoid extensive literature searches (see paragraphs 5 to 7 of D110)”*.
- 6.123 Even if the transformation had proceeded, the skilled person would have expected the resulting product mixture to contain four diastereomers, due to the two separate stereocentres installed by the reaction. See paragraph 15 of D105. That is indeed what was observed in D87. The assertion by the patentee in paragraph [0112] of the 6 November 2020 submissions that the skilled person would be “confident of obtaining the correct diastereoselectivity” is therefore demonstrably wrong. Even if the opposition division is correct to say that such stereoisomers are “routinely separable”, it remains yet another undisclosed step that the skilled person is faced with when considering adapting the gemcitabine route.

- 6.124 It is noted that Professor Boons disagrees with the views of Professor Davies on this issue in paragraph 14 of D110. See paragraph 12 of D123. Professor Davies states that a synthesis which would result in multiple diastereomeric centres would be desirable on the grounds that such multiple products could be assessed to gain insight into the structure/activity relationship; and that it requires hindsight to conclude that such multiple products would not be wanted because it is based on the assumption that a specific compound having 2'-Me-up/2-F-down chemistry (compound 1a or 1b) is the synthetic target. However, that is exactly the challenge that would have been faced by the skilled person seeking to make specific compounds falling within the scope of the claims. Assessing a range of compounds for structure/activity relationships may possibly form part of a wider research project, but is irrelevant to the accessibility or otherwise to a skilled person of a synthetic route to a specific compound covered by the claims.
- 6.125 Moreover, as Professor Boons explained in paragraph 16 of his declaration D105, the skilled person would be well aware that the glyceraldehyde derivative is susceptible to racemisation. The fact that such racemisation did not appear to occur in reality does not mean that it would not have been a concern faced by the skilled person. It is noted that the opposition division did not comment on this point at all. Nevertheless, Professor Boons has further elaborated upon this point in paragraphs 26 and 27 of D123, particularly in response to comments made by Professor Davies in D110. Specifically, Professor Boons provides, with reference to D123a and D123b, confirmation that problems with racemisation were not only known but *"can result in severe problems"* and represent a *"long-standing problem"* (see first paragraph of D123b). The opposition division were therefore incorrect to ignore this potential problem with the proposed Reformatsky reaction step.
- 6.126 Overall, the opposition division made an error in disregarding the concerns of Professor Boons regarding the Reformatsky reaction step, and in particular in apparently placing weight on D94, which is not common general knowledge (see point 4.8 of the decision) and moreover has a number of other problems (as discussed above). Professor Boons summarises the potential problems associated with the Reformatsky reaction step in paragraph 28 of D123 in the following terms:

"In summary, the proposed Reformatsky reaction would have caused the skilled person concerns in 2003 (or in 2004) because there is almost no literature precedent for a Reformatsky reaction using BrCFMeCO₂Et. The only literature precedent (D94) describes a single reaction (when the rest of the paper focuses on other types of reactions) involving a simple aldehyde as opposed to a more complex glyceraldehyde derivative. Moreover, no experimental details are provided in D94, even though D111 confirms that the reaction conditions needed for Reformatsky reactions to succeed vary considerably according to the starting materials used. Many variations of the Reformatsky reaction have been reported, and the fact that there is almost no literature precedent for reactions involving BrCFMeCO₂Et, and

apparently no precedent at all for a reaction with a glyceraldehyde derivative, would have made this reaction unattractive to the skilled person at the relevant time.” (emphasis added)

- 6.127 The uncertainties and potential problems associated with the Reformatsky reaction would result in the skilled person undoubtedly encountering undue burden when seeking to adapt the gemcitabine synthesis.

The skilled person would also have had particular concerns regarding glycosylation of the sugar to install the base

- 6.128 Professor Boons explains in paragraph 17 of his declaration D105 that “stereoselective formation of a glycosidic linkage is one of the most challenging aspects of synthesis of a nucleoside or oligosaccharide” (emphasis added).
- 6.129 It is therefore simply not possible to generalise the parameters (e.g. protecting groups, reagents, reaction conditions) used in the glycosylation step of the synthesis of gemcitabine to other nucleosides, let alone those which have a profound structural difference (methyl in place of fluoro at the 2' position). Professor Boons summarises the position in the following terms in paragraph 17 of his declaration D105:

“The skilled person would additionally have concerns about the glycosylation step to install a base (depicted as Step 6 in D87, preceded by some preparatory steps). The stereoselective formation of a glycosidic linkage is one of the most challenging aspects of synthesis of a nucleoside or oligosaccharide. This is discussed in sections 11.46 to 11.49 of my expert report to the UK High Court, which I understand is denoted D43 in these proceedings. There are many choices to be made regarding parameters such as the leaving group, protecting groups, reagents and reaction conditions. Furanoses can adopt multiple envelope [conformations] which will affect the stereochemistry of the glycosylation differently. It is not possible to generalise such a reaction. Conditions that have been found to be adequate to install one particular base on one particular sugar cannot confidently be predicted to apply to a different combination of base/sugar.” (emphasis added)

- 6.130 The opposition division were wrong to dismiss the concerns as outlined by Professor Boons, who is an expert in sugar chemistry (see point 4.8 of the decision). Even if the opposition division are correct to say that the skilled person could separate the anomers formed by “conventional means”, it remains yet another undisclosed step that the skilled person is faced with when considering adapting the gemcitabine route. In any event, Professor Boons has provided further detail on the issues associated with the glycosylation step in paragraphs 29 to 34 of D123, in response both to the opposition division’s decision and to Professor Davies in D110.

- 6.131 Specifically, in paragraph 29 of D123 Professor Boons explains why replacing fluorine with methyl at the 2' position of a sugar ring would be expected to have an unpredictable effect on reactions to install a base. In Professor Boons' view, "[c]onsiderable experimentation is generally required to achieve the desired outcome" when seeking to install a base on a sugar with a new substitution pattern. The patent provides no guidance on this issue at all, nor were the appropriate reaction conditions for 2'-Me/2'-F nucleosides common general knowledge at the relevant time.
- 6.132 Further, in paragraphs 31 to 33 of D123, Professor Boons explains why the conclusions of Professor Davies regarding this issue in D110 are incorrect. In particular, for example, Professor Davies makes unsupported assumptions regarding the conformation that the 5-membered sugar ring will adopt, and fails to take into account any of the other conformers that might form. Professor Boons concludes in paragraph 33 of D123 that:
- "[T]he views of Professor Davies regarding the glycosylation step are not in line with my views and experiences as a chemist who has written extensively on carbohydrate chemistry and has worked in that field for 30 years (see my CV, which I understand is D42b in these proceedings)."*
- 6.133 Professor Boons is undoubtedly an expert in carbohydrate chemistry, as is clear from his CV (D42b) and, for example, the assessment of the UK judge in D110. Professor Davies, while undoubtedly also eminent, is not an expert in carbohydrate chemistry. The Board of Appeal should take that into account when assessing the relevance of their respective declarations.
- 6.134 The uncertainties and potential problems associated with the glycosylation of the sugar to install the base would result in the skilled person undoubtedly encountering undue burden.

Preparation of the starting material for the "analogous gemcitabine route"

- 6.135 The opposition division also made an error in not identifying that the starting material for the "analogous gemcitabine route" is not a commercially available compound, but instead would need to be synthesised by the skilled person. The application as filed does not, of course, provide any such synthesis. Moreover, none of the references relied upon by the patent to close that gap in the disclosure of the patent represent common general knowledge.
- 6.136 The starting material for the "analogous gemcitabine route" when proceeding via the Hertel route is BrCFMeCO₂Et (see 4.4.3.1 of the patentee's 6 November 2020 submissions). Needless to say, the patent is completely silent regarding this compound.
- 6.137 The patentee relies upon a CAS database search (see D93) to identify references that disclose the synthesis of BrCFMeCO₂Et. The documents identified were D94, D95, D96 and D97. These references were also relied

upon by Dr Allred in D87. Notably all of D94, D95, D96 and D97 are primary literature references that do not represent the common general knowledge of the skilled person. The fact that these references could have been identified by a skilled person following a comprehensive CAS database search does not render them common general knowledge.

- 6.138 Accordingly, the skilled person cannot prepare BrCFMeCO₂Et based on the disclosure of the application as originally filed and his or her common general knowledge. It is only by consulting documents that do not constitute common general knowledge that the synthesis of BrCFMeCO₂Et can be achieved.
- 6.139 Similarly, the starting material for the “analogous gemcitabine route” when proceeding via the Weigel route is HCFMeCO₂H. Needless to say, the patent is also completely silent regarding this compound. Again, it is clear that the patentee relies upon a CAS database search (D98), which identifies documents that are not common general knowledge, in an attempt to cure the lack of disclosure in the application as originally filed.
- 6.140 The skilled person cannot therefore prepare HCFMeCO₂H based on the disclosure of the application as originally filed and his or her common general knowledge. It is only by consulting documents that do not constitute common general knowledge that the synthesis of HCFMeCO₂H can be achieved. It is noted for completeness that in D49 and D50, no detail is provided as to how starting material HCFMeCO₂H was prepared.
- 6.141 Overall, it is clear that even if the skilled person did identify the “gemcitabine route” and then seek to adapt this into the “analogous gemcitabine route”, which we dispute for the reasons set out above, then the skilled person would still be faced with the problem of preparing a suitable starting material without any assistance from the application as originally filed. The common general knowledge of the skilled person would also not assist in preparing the starting material.
- 6.142 The opposition division made an error in not acknowledging this issue, and thus in concluding that the “analogous gemcitabine route” can cure the deficient disclosure of the application as originally filed.

Performing multiple undisclosed steps inevitably places a burden on the skilled person

- 6.143 The opposition division concluded that the number of undisclosed steps that needed to be carried out and time that would be needed to carry out those steps are not relevant considerations for sufficiency (see points 4.5 and 4.7 of the decision). We submit that these conclusions were erroneous.
- 6.144 In particular, it must be the case that the number of entirely new reactions that a skilled medicinal chemist needs to carry out, and the time those entirely new reactions take to complete, are factors in the burden the skilled person faces. Thus, while a single reaction that takes a few hours or a day to

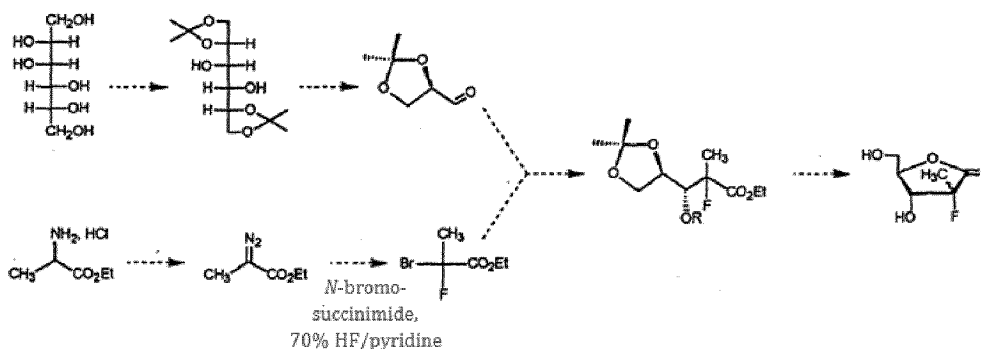
complete might in some cases not represent undue burden, an entirely new synthesis involving eight to ten steps and taking at least “several weeks” (see D49 and D50) must necessarily impose a higher burden on the skilled person. The number of undisclosed steps and the duration of the synthesis must therefore be relevant factors in assessing whether there is undue burden. When carrying out an entirely new synthesis (as is the case here), a skilled person does not know in advance whether it will work, and so each additional step inevitably imposes an increasing burden.

- 6.145 Indeed, taken together with the extensive literature search that a skilled person would have had to complete before even being in a place to commence the proposed synthesis, it is clear that the “analogous gemcitabine route” is precisely the type of “research project” that cannot be used to cure a deficient initial disclosure. It is notable that even the patentee’s own expert, Professor Davies, who describes himself as “not an ordinarily skilled person in organic synthesis” but rather “one of the leading experts in the world in organic synthesis” characterises the activity that would be involved in curing the defects of the application as filed as a “medicinal chemistry project” (see paragraph 14 of D110 and a “reasonable project” (see paragraph 18 of D48).
- 6.146 The opposition division were thus incorrect to disregard the number of steps and the time needed to complete the synthesis when assessing whether the requirements of Article 83 EPC are met. Rather, these are clearly important factors that, in the present case, are just one of many reasons why the skilled person would in fact have faced an undue burden when seeking to synthesise 2'-methyl/2'-fluoro nucleosides based on the disclosure of the application as filed and common general knowledge.
- 6.147 The opposition division was also incorrect in “decoupling” the undue burden posed by the undisclosed steps and time needed to perform those steps from other sufficiency considerations. Specifically, the opposition division stated in paragraphs that “once having the concept of an analogous Gemcitabine synthesis in mind” (see point 4.5, and similar language in point 4.7), there were no choices to be made when performing the synthesis. We submit that such a step-wise analysis is incorrect. The correct approach is to consider whether, taken as a whole, the skilled person faces undue burden. Undue burden could arise because a single aspect provides, or because multiple aspects cumulatively provided it.

Relevance of D49, D50 and D87 and actual contemporaneous evidence of investigations into an “analogous gemcitabine route”

- 6.148 The opposition division referred to D49, D50 and D87 in support of the “analogous gemcitabine route”, noting that the “the analogous synthesis proceeded with exact the same steps without adaptations” (see point 4.4 of the decision).

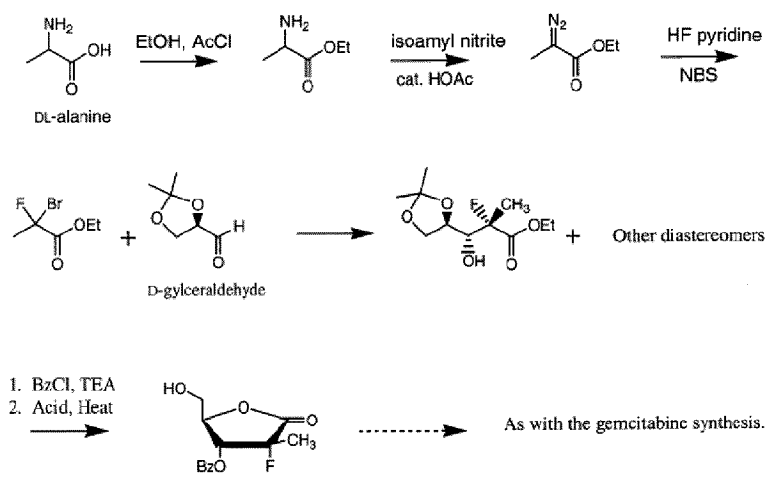
- 6.149 This comment from the opposition division illustrates a fundamental flaw in the approach adopted by the opposition division: D49, D50 and D87 do not provide any evidence as to what a skilled person would have done at the priority date.
- 6.150 That is because, according to paragraph 7 of D87, Dr Allred was presented with gemcitabine and was asked specifically to try to synthesise 2'-methyl/2'-fluoro nucleosides "by analogy" with the gemcitabine routes known in July 2003 (see paragraph 7 of D87). Notably, Dr Allred was not asked to synthesize such compounds based solely on the teaching of the patent application as filed and the common general knowledge he would have had at the priority date: in fact, there is no indication in D87 that Dr Allred has even read the patent application as filed. Similar comments are present in D49 (see paragraphs 10 and 11) and D50 (see paragraphs 6 and 7).
- 6.151 D49, D50 and D87 are therefore simply not relevant to the question of whether or not the patent is sufficient. They provide no evidence of the problems and choices that would have faced the skilled person at the priority date.
- 6.152 By contrast, the present case is unusual in that (as discussed above) we do have independent contemporaneous evidence of what skilled chemists at the relevant time actually did when faced with the same problem of seeking to synthesise 2'-methyl/2'-fluoro nucleosides.
- 6.153 "Strategy 11" discussed in Annex B to these grounds of appeal involved the following route:



- 6.154 More than 2 years after first commencing the synthesis project, Dr Griffon indicated in April 2004 that work on this route was "in progress", but then later reported in May 2004 that he had run into difficulties and that "...cyclisation of the sugar and deprotection in acidic conditions was attempted 3 times with no success". See paragraphs 509 to 513 of D11.
- 6.155 There is further evidence of contemporaneous attempts to use an "analogous gemcitabine route" in D10 and D116. In particular, paragraphs 564 and 565 of D10 explain that Jeremy Clark (author of D6) did investigate (without success) an "analogous gemcitabine route", stating at paragraph 564:

“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



(emphasis added)

- 6.156 The “small molecule” is similar to the “analogous gemcitabine route”, as is evident from the reference to “as with the gemcitabine synthesis” in the above figure.
- 6.157 Paragraph [510] of D116 confirms that Jeremy Clark did eventually synthesise 2’-Me/2’-F nucleosides “*some seven months after he first discussed the idea with Pharmasset management, and then after first trying the Gemcitabine route that proved unsuccessful*” (emphasis added).
- 6.158 The contemporaneous efforts of Dr Griffon and Jeremy Clark are highly pertinent. In particular, it is clear that two different skilled chemists at the relevant date did not in fact find it easy to perform an “analogous gemcitabine route”. On the contrary, neither chemist succeeded with an “analogous gemcitabine route”. Jeremy Clark was ultimately successful with another route, while for Dr Griffon the failure, together with similar failures with other potential routes, ultimately resulted in his ceasing work on the project altogether.
- 6.159 Clearly contemporaneous accounts of the difficulties in using an “analogous gemcitabine route” to synthesise 2’-Me/2’-F nucleosides should be taken into account, and afforded more weight than D49, D50 and D87, where the authors encountered none of the uncertainties faced by contemporary chemists.

The opposition division applied a different standard when assessing sufficiency for the “analogous gemcitabine route” as it did for “route 22”

- 6.160 When correctly concluding that “route 22” did not cure the flawed disclosure of the patent, the opposition division noted that the skilled person had to use “intellectual effort” in order both to identify compound 22 as a starting material and then to transform it. This intellectual effort was the reason that “route 22” would not have been available to the skilled person based on the application as filed and their common general knowledge.
- 6.161 However, when incorrectly concluding that the “analogous gemcitabine route” can cure the flawed disclosure of the patent, the opposition division appears to have adopted an entirely different standard. In this regard, it is inconceivable that the various steps that have to be taken by the skilled person to arrive at the “analogous gemcitabine route” would not require “intellectual effort”. On the contrary, it is clear from the discussion above that significant intellectual effort would have been required in relation to multiple aspects of the “analogous gemcitabine route”.
- 6.162 The opposition division therefore made an error in not applying a consistent standard when assessing sufficiency. The opposition division should have concluded that the “analogous gemcitabine route” requires significant intellectual effort, and thus cannot cure the insufficient disclosure of the application as originally filed.

An inventive contribution would be required to succeed with the “analogous gemcitabine route”

- 6.163 It will be evident from the above discussion that the skilled person would have to make an inventive contribution to the art in order to have succeeded with the “analogous gemcitabine route” at the relevant date. If an inventive contribution is necessary to cure a deficient disclosure in a patent, then it follows that the patent in question must necessarily be insufficient. At least the following inventive contributions would be required from the skilled person in the present case:
1. Identifying gemcitabine to be a useful starting point for the synthesis of 2'-Me/2'-F nucleosides
 2. Jumping immediately from the identification of gemcitabine as a useful starting point for the synthesis of 2'-Me/2'-F nucleosides to synthesis by analogy, instead of other options available, such as actually using gemcitabine itself as the starting material for the synthesis of 2'-Me/2'-F nucleosides.
 3. Determining how gemcitabine could be synthesised, and then determining how to adapt that synthesis to 2'-Me/2'-F nucleosides in the face of various synthetic concerns about the necessary adaptations.
 4. Actually performing the analogous gemcitabine synthesis, including synthesis of relevant starting materials, despite contemporaneous

evidence of skilled chemists attempting and failing with similar syntheses at the relevant time.

- 6.164 Each of these inventive contributions alone should be enough to render the patent insufficient, but taken together they clearly illustrate the fundamentally insufficient nature of the disclosure of the patent.

Conclusions in relation to sufficiency

- 6.165 The conclusions of the opposition division in relation to sufficiency were incorrect. The application as filed provided no disclosure of how to synthesise compounds having a 2'-Me/2'-F substitution pattern, and the gap in that disclosure cannot be bridged by common general knowledge. In concluding otherwise, the opposition division made a series of errors, as discussed above. These errors included at least the following points:
1. Erroneously considering "route 22" and the "analogous gemcitabine route" **without first considering** all of the other routes that the skilled person would also have contemplated.
 2. Not taking into account independent, contemporaneous and highly relevant evidence of all the routes that skilled chemists at the relevant time **actually** did try.
 3. Apparently **disregarding** the expert evidence provided by Professor Boons and Dr Marquez on all of the routes that skilled chemists at the relevant time would have considered.
 4. Erroneously concluding that the skilled person was in a "one-way-street" when identifying gemcitabine to be a useful starting point for the synthesis of 2'-Me/2'-F nucleosides, and in doing so **disregarding** both the teaching of the application as filed and the declarations of Professor Boons.
 5. Erroneously jumping immediately from the identification of gemcitabine as a useful starting point for the synthesis of 2'-Me/2'-F nucleosides to synthesis by analogy, **without first considering** other options available, such as actually using gemcitabine itself as the starting material for the synthesis of 2'-Me/2'-F nucleosides.
 6. Incorrectly taking into account documents that are not common general knowledge to cure the deficient disclosure of the application as filed in relation to the known gemcitabine synthesis.
 7. Not placing enough weight on the concerns identified by Professor Boons regarding adapting the "gemcitabine route" to provide the "analogous gemcitabine route".
 8. Incorrectly accepting that the starting material(s) for the "analogous gemcitabine route" could be prepared based on common general knowledge, when in fact **it was necessary to rely upon primary literature references**.
 9. Erroneously concluding that the number of undisclosed steps and the time that would have been needed to carry out those steps are not

relevant factors in assessing whether the skilled person faces undue burden.

10. Placing greater weight on D49, D50 and D87, instead of contemporaneous evidence of the difficulties actually faced by two skilled chemists investigating the “analogous gemcitabine route” (see D10 and D116).
11. Applying a different standard when assessing sufficiency for the “analogous gemcitabine route” as it (correctly) did for “route 22”.
12. Not placing enough weight on decisions from multiple jurisdictions from the Idenix proceedings, which are highly pertinent to the present patent due to the similarities in dates and subject matter.

6.166 Once the correct approach to assessing sufficiency is adopted, it is clear that the application as filed had a deficient disclosure and, even taking into account common general knowledge, would not have allowed the skilled person to synthesise 2'-Me/2'-F nucleosides without undue burden in 2003/2004. The missing information is not “superfluous”. Rather, it would have required a research programme of considerable complexity and uncertain outcome in order to synthesise 2'-methyl/2'-fluoro nucleosides starting from the disclosure of the application as filed.

7 INVENTIVE STEP

- 7.1 The opposition division concluded in section 5 of the decision that the claims of the patent as granted and the claims of Auxiliary Requests (ARs) 1 to 12 lacked inventive step. The opposition division concluded however that Auxiliary Request 13, filed at the very end of the oral proceedings, after the Opposition Division had invalidated the earlier requests, did satisfy the requirements of Article 56 EPC.
- 7.2 We agree with the conclusions of the opposition division that ARs 1 to 12 lack inventive step. However, the opposition division made a number of errors - factual, scientific and legal - in reaching this conclusion, despite the overall finding for these requests being correct. The errors of reasoning made in connection with ARs 1 to 12 led the opposition division to incorrectly conclude that the claims of AR13 satisfied the requirements of Article 56 EPC.

Relevant legal provisions for inventive step

- 7.3 We initially set out the relevant legal provisions that should apply when assessing inventive step, particularly in the pharmaceutical field.

A. The relevance of actually solving an alleged technical problem

- 7.4 To be considered as involving an inventive step, an invention must not be obvious with regard to the state of the art (Article 56 EPC).
- 7.5 The framework for assessing inventive step is the "Problem and Solution" approach (CLBA I-D-2), which involves the stages of:
- (a) identifying the "closest prior art",
 - (b) assessing the technical results (or effects) achieved by the claimed invention when compared with the "closest state of the art" established,
 - (c) defining the technical problem to be solved as the object of the invention to achieve these results, and
 - (d) examining whether or not a skilled person, having regard to the state of the art, would have suggested the claimed technical features in order to obtain the results achieved by the claimed invention.
- 7.6 In formulating the objective technical problem, alleged advantages to which the patent proprietor/applicant merely refers, without offering sufficient evidence to support the comparison with the closest prior art, cannot be taken into consideration in determining the problem underlying the invention and therefore in assessing inventive step (see T 20/81, OJ 1982, 217; T 181/82, OJ 1984, 401; T 124/84; T 152/93; T 912/94; T 284/96; T 325/97; T 1051/97). In T 1027/08, the board added that there was no reason to deviate from this case

law as it was based on the understandable rule that a patent can only properly be granted for a solution claimed as non-obvious if it actually has the alleged effect. (CLBA I-D-4.2)

- 7.7 When defining the objective technical problem an effect cannot be retained if it is not credible that the promised result is attainable throughout the entire range covered by a claim (T 741/91; T 626/90; T 939/92, OJ 1996,309; T 583/93, OJ 1996, 496). If the inventive step of a claimed invention is based on a given technical effect, the latter should, in principle, be achievable over the whole area claimed (T 939/92, OJ 1996, 309; T 694/92, OJ 1997, 408; T 583/93, OJ 1996, 496). (CLBA I-D-4.3)
- 7.8 The technical problem arising may have to be reformulated, in particular in less ambitious terms, if it appears in view of experimental evidence that the combination of features in the claim does not solve this problem over the whole area defined in the claim (T 20/81, OJ 1982, 217; T 39/93, OJ 1997, 134; see also T 2001/12). (CLBA I-D-4.4.1)
- 7.9 The above principles apply in both chemical and non-chemical fields. However, in chemical fields it is particularly recognised that actually solving the objective technical problem is essential for inventive step to be acknowledged. Accordingly, some boards of appeal in the chemical area have considered it helpful to reformulate the problem and solution approach to expressly require the step of demonstrating the success of the solution offered by the alleged invention. (CLBA I-D-9.8.1)
- 7.10 When assessing the breadth of claims (particularly in the chemical field), the boards of appeal have stressed that if the inventive step of a claimed invention is based on a given technical effect, the latter should, in principle, be achievable over the whole area claimed (T 939/92, OJ 1996, 309; T 694/92, OJ 1997, 408; T 583/93, OJ 1996, 496). (CLBA I-D-9.8.3).
- 7.11 The reasoning summarised above has been widely applied by boards of appeal to correctly deny inventive step when a particular activity alleged to exist for a claimed group of compounds is shown not, in fact, to exist. We refer, by way of example, to the headnote of T 668/94, highlighted in CLBA at I-D-9.8.3, where the board stated
- “When only some and not substantially all claimed compounds exhibit a particular technical effect, then the conclusion must be drawn that the invention as broadly defined in the independent claim is not a solution to the technical problem of achieving this particular technical effect, with the consequence that the alleged technical effect of some of the claimed compounds is to be disregarded in the determination of the objective problem underlying the invention, and thus in the assessment of inventive step, (following T 0939/92, OJ EPO 1996, 309) (point 8.1 of the reasons).”*
- 7.12 These principles apply equally in ex parte and in inter partes proceedings.

B. The burden of proof in establishing facts and evidence

- 7.13 As a general principle, each party bears the burden of proof for the facts it alleges.
- 7.14 Evidence offered by one party to prove a fact need not prove the facts with absolute certainty in order to be deemed conclusive (CLBA III-G-5.2.1). Rather, the relevant standard is the “balance of probabilities”. For example, in the widely cited decision T270/90, the board stated that *“As far as each of the parties to the proceedings is concerned, they carry the separate burdens of proof of any fact they allege. The weight of that burden is the balance of probability as distinct from “beyond all reasonable doubt” or “absolute conviction”. In the course of an appeal, therefore, each party must seek to prove facts alleged by it to this degree of proof and, as was said above, it is the function of the Board to decide, applying the same standard, which set of facts is more likely than the other to be true.”* (T270/90, Reasons §2.1)
- 7.15 In opposition proceedings, the burden of proof (that the claims of the opposed patent do not comply with the requirements of the EPC) initially rests with the opponent. However, the burden is not static but may shift constantly as a function of the weight of the evidence. For example, in T570/08 (cited in CLBA III-G-5.2.2), the opponents filed evidence in the form of comparative tests with the aim to support their argument that the claimed additive composition in the patent-in-suit did not solve the problem of improving lubricity and solubility of a diesel fuel oil. These results were in contrast to the tests which the patent proprietor had provided, so that the board was confronted with a series of tests leading to contradictory results. Therefore, the board could not share the patent proprietor’s argument that the burden of proof rested with the opponents, since the opponents’ test results cast doubts on the effect allegedly achieved by the present invention. The patent proprietor could not convincingly eliminate those doubts and the patent was revoked.

The claims of the patent as granted and ARs 1-13 lack inventive step

- 7.16 The opposition division was correct to conclude that the claims of the patent as granted, and those of ARs 1-12 lacked inventive step. However, the reasoning of the opposition division in reaching this correct conclusion was in many areas flawed.
- 7.17 The mistakes made by the opposition division in assessing the claims of the patent as granted and those of ARs 1-12 led to an incorrect finding that the claims of AR13 did possess an inventive step.
- 7.18 The opposition division should have assessed the evidence on file correctly. Doing so would have led to the correct finding that the claims of AR13, like those of the patent as granted and those of the main request and ARs 1-12, lacked an inventive step.

- 7.19 We discuss in detail the errors made by the opposition division in the following sections. First, however, we provide the framework of the correct problem/solution analysis that should have been conducted by the opposition division, in order to set the following comments in context.

1. Identifying the closest prior art

- 7.20 In section 5.2 of the decision, the opposition division concluded that D36 is the closest prior art. The opposition division considered that within D36, the compound CPF-2, namely the compound of claim 12 of D36, would be an appropriate starting point for considering inventive step.
- 7.21 We agree that D36 is the closest prior art and that the compound CPF-2 is an appropriate starting point for considering inventive step. However, because this point was discussed both in writing and orally during the first instance proceedings, arguments in favour of D36 as closest prior art are set out in Annex D to these grounds of appeal.
- 7.22 Should the patentee appeal against the decision of the opposition division in relation to inventive step and in doing so question the opposition division's decision to find D36 the closest prior art, then the opponent may comment further on these matters in its response to the patentee's appeal.

2. Assessing the technical results (or effects) achieved by the claimed invention when compared with the closest state of the art

- 7.23 The next step in the problem/solution analysis is to consider the distinguishing features between the disclosure of the closest prior art and the claimed "invention" and to assess the technical results (or effects) of these distinguishing features.
- 7.24 The Opposition Division stated in section 5.2 of the decision that, like the opposed patent, D36 is specific about the use of the disclosed compounds therein for treating cancer. We agree that D36 is directed to cancer. Accordingly, the alleged activity of the claimed compounds in that indication is not a distinguishing feature.
- 7.25 The opposition division further stated in section 5.2 of the decision that only two small molecular changes were required to get from the closest reference compounds in D36 to the compounds of the claims. The opposition division states that these two changes are at the nitrogen-heterocycle, variable "Z" in Markush Formula (I), and at the 2'-position of the sugar.
- 7.26 As explained in more detail below, the opposition division was incorrect to consider that there are structural differences between the compounds of D36 and those of the claims of the patent at both the Z position and the 2' position

of the sugar. The opposition division should have found that the claimed compounds differ from those of D36 only at the 2' position.

- 7.27 Notwithstanding this, for the purposes of this brief summary the distinguishing feature of the claimed compounds compared to the compounds of D36 may be considered to lie in the structure of the nucleoside portion of the compounds.

3. Defining the objective technical problem for the patent as granted and ARs 1-12

- 7.28 The opposition division decided in section 5.5 of the decision that the exemplified compounds do not have a consistent benefit over the compound CPF-2 disclosed in D36. We agree.
- 7.29 The only data in the patent which compares the cytotoxicity of compounds within the scope of the claims against CPF-2 is provided in Table 1, for the compounds CPF-31, CPF-40 and CPF-41. Each of these compounds is a cytidine nucleoside, di-fluoro substituted at the 2' carbon and has an aromatic benzyl ester at the R position (see the structures duplicated in paragraph 2.4 above).
- 7.30 The relevant data from Table 1 of the patent is reproduced here:

Compound	EC50/ μ M Breast MDA MB231	EC50/ μ M Colon HT115	EC50/ μ M Prostate PC-3
Claim 12 of D36 (CPF-2)	34	1.4	19
CPF-31	42.6	5.7	0.22
CPF-40	9.2	16.1	15.4
CPF-41	3.1	317.1	68.8

- 7.31 As far as the data in this table goes, all of the three exemplified 2'-fluoro up / 2'-fluoro down di-substituted compounds falling within the scope of the claims are less active than CPF-2 against colon cancer. CPF-2 has an EC50 value in HT115 cells of just 1.4 μ M, whereas all of CPF-31, CPF-40 and CPF-41 have EC50 values significantly above this, indicating significantly reduced activity compared to CPF-2. Indeed, as discussed in more detail in D130, the high EC₅₀ value for CPF-41 shows that at least this compound is effectively inactive against at least this colon cancer cell line. The data for colon cancer is relevant particularly given that the patentee has looked to this data in an attempt to establish that the claimed compounds are improved compared to gemcitabine (which, as set out above, is not the correct comparison).
- 7.32 At least CPF-31 is even less active than CPF-2 against breast cancer. CPF-2 has an EC50 value in MDA MB231 cells of 34 μ M, whereas CPF-31 has a higher

EC50 value of 42.6 μ M. Table 1 shows that CPF-31 is effectively inactive against at least this breast cancer cell line.

- 7.33 At least CPF-41 is even less active than CPF-2 against prostate cancer. CPF-2 has an EC50 value in PC-3 cells of 19 μ M, whereas CPF-41 has an EC50 value of 68.8 μ M. Table 1 shows that CPF-41 is effectively inactive against at least this prostate cancer cell line.
- 7.34 As such, no improvement compared to CPF-2 can be sustained across the scope of the claims. That is the case whether such an improvement is alleged in an “unspecified” cancer, or in just one of breast, colon or prostate cancer. Regardless of the cancer type implicated, this effect would not be demonstrated for all of CPF-31, 40 and 41, and thus would not be achieved across the scope of the claims. In fact, in each of the tested cancer types at least one of the claimed compounds is shown to be effectively inactive.
- 7.35 Accordingly, the opposition division initially considered whether the technical effect achieved by the patent could be that the claimed compounds define alternative anticancer compounds (section 5.6 of the decision).
- 7.36 The opposition division correctly held that the claims of the patent as granted and those of ARs 1-12 did not provide this technical effect across their scope (section 5.7 of the decision). Accordingly, no technical effect was to be acknowledged for the claims of the patent as granted and those of ARs 1-12. However, whilst the conclusion of the opposition division was correct in this regard, its reasoning contained multiple errors, as discussed below.
- 7.37 Because the opposition division correctly concluded that no technical effect was to be acknowledged for the claims of the patent as granted and those of ARs 1-12, the objective technical problem was reformulated to merely the provision of alternative compounds (section 5.8 of the decision).

4. Obviousness of the solution offered by the patent as granted and ARs 1-12

- 7.38 The opposition division correctly concluded that the solution to the trivial problem of providing alternative compounds is obvious and thus not inventive. Accordingly, the claims of the patent as granted and those of ARs 1-12 were correctly found to contravene Article 56 EPC.

5. AR 13

- 7.39 The distinguishing feature of the claims of AR13 vs D36 still lies in the structure of the nucleoside, as for the claims of the patent as granted and those of ARs 1-12.
- 7.40 The opposition division considered the technical effect of this distinguishing feature to be that the claims of AR13 defined alternative anticancerous phosphoramidate-nucleosides (section 9.5 of the decision).

- 7.41 The opposition division was wrong to conclude that the compounds of AR13 have anticancerous activity. As explained below, the opposition division should have found that the compounds of AR13 are not associated with anticancer activity, for the same reasons that it should have found the compounds of the patent as granted and those of ARs 1-12 not to be associated with anticancer activity.
- 7.42 In view of its incorrect formulation of the objective technical problem, the opposition division erred in concluding that the claims of AR13 did possess an inventive step. By contrast, the opposition division should have again formulated the objective technical problem as the provision of alternative compounds. The solution to this unambitious problem should have been found to be obvious in view of D36 and the other art on file.

Mistakes of the Opposition Division

- 7.43 The mistakes made by the opposition division in assessing the claims of the patent as granted and those of ARs 1-13 are discussed in more detail below. In summary, these are as follows:
1. The opposition division was wrong to decide that there are structural differences at two positions of the claimed compounds (the Z position of the base and the 2' position of the sugar) compared to the closest prior art. The opposition division should have found that at most there are structural differences at only one position (the 2' position of the sugar).
 2. The opposition division was wrong to decide that the open-ended language in the claim is consistent with biological activity being observed across its scope, contrary to the established jurisprudence of the EPO.
 3. The opposition division was wrong to decide that compounds having 2'-Cl/2'-F substitution can only be assessed in view of in *expressis verbis* statements in evidentiary documents on file. The opposition division should also have given due consideration to numerical values expressly provided in those documents which confirm this.
 4. The opposition division was wrong to decide that certain compounds having a 2'-Me/2'-F substitution have anticancer activity. The opposition division should have given due consideration to the published, peer-reviewed evidence on file demonstrating that such compounds are not associated with anticancer activity.
 5. The opposition division was wrong to give undue weight to an unsupported assertion of activity of one specific compound in one specific cell line which is not mentioned in the patent. The opposition division was wrong to give

more weight in this regard to the employee-declarant of the patentee as opposed to the employee-declarant of the opponent, and in particular was wrong to take the assertions of the employee-declarant of the patentee at face value whilst rejecting the comments of the employee-declarant of the opponent as being allegedly biased.

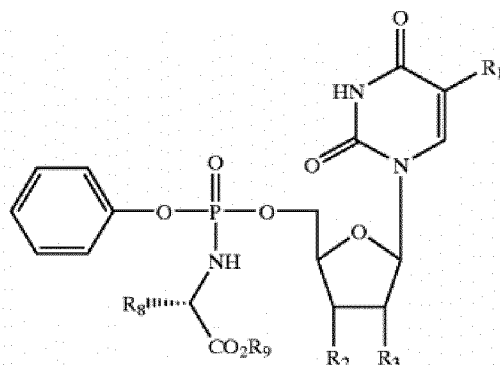
6. The opposition division was wrong to conclude that it is “irrelevant” when assessing the alleged cytotoxicity of a given compound how high an IC₅₀ or CC₅₀ value is. The opposition division was wrong to conclude that “some kind” of alleged anti-cancerous activity suffices, when this is contrary to the evidence on file.
7. The opposition division was wrong to decide that compounds having a 2'-Br/2'-F substitution are active. The opposition division should have given due consideration to the published and peer-reviewed evidence on file that such compounds are not credibly associated with anticancer activity.
8. The opposition division was wrong to decide that compounds having isopropyl groups at the R position of the phosphoramidate are cytotoxic. The opposition division should have given due consideration to the published evidence on file that such compounds are not associated with anticancer activity.

1. The claimed compounds do not differ from those of the prior art at the Z position

7.44 D36 discloses compounds defined by a general formula in claim 1:

What is claimed is:

1. A compound having the formula:



wherein R₁ is selected from the group consisting of H, alkyl, alkenyl, alkynyl, vinyl, propargyl and substituted derivatives thereof;

wherein R₂ and R₃ are independently the same or different and are selected from the group consisting of Br, Cl, F, I, H, OH, OC(=O)CH₃, —O— and —O—R_g, wherein R_g is a hydroxyl protecting group other than acetyl;

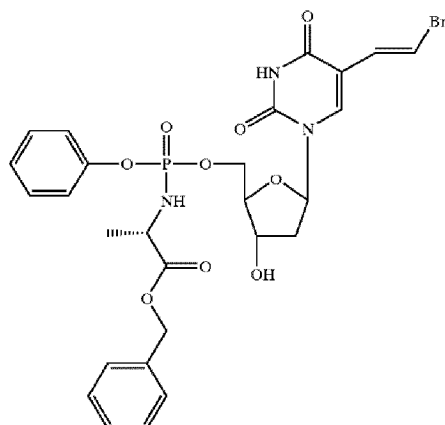
wherein R₈ is a side chain of any naturally occurring amino acid, its analogue or its isomer;

and wherein R₉ is selected from the group consisting of hydrogen, an aliphatic group, an alicyclic group, an aromatic group, a heterocyclic group and an adamantyl group and derivatives and analogs thereof;

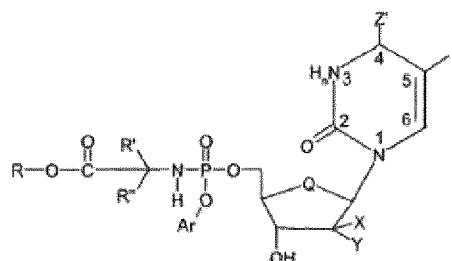
and any enantiomeric, diastereomeric, or stereoisomeric form, including D-form, L-form, α-anomeric form, and β-anomeric form, and its pharmaceutically acceptable salts.

7.45 Various exemplary compounds are set out in D36, including the compound of claim 12 which is also referred to in the patent as CPF-2.

7.46 The relationship between the compounds claimed in the patent as granted and as upheld in AR13, and the compound of claim 12 (CPF-2) in D36, is as shown in the table below. In that table, the relevant option within the definition of claim 1 of the patent is shown in bold and underlined:



CPF-2, claim 12 of D36



Claim 1 of patent

Variable position in claim 1 of the patent	CPF-2 in D36	Alternatives in claim 1 of the opposed patent as granted	Alternatives in claim 1 of the patent as maintained (AR13)
R	benzyl	alkyl, aryl, <u>alkylaryl</u>	alkyl, aryl, <u>alkylaryl</u>
R' / R''	H / methyl	each <u>H</u> , <u>alkyl</u> , alkylaryl, or together form cyclic system	each <u>H</u> , <u>alkyl</u> , alkylaryl, or together form cyclic system
Ar	phenyl	<u>aromatic: monocyclic</u> or bicyclic, <u>carbocyclic</u> or heterocyclic	<u>aromatic: monocyclic</u> or bicyclic, <u>carbocyclic</u> or heterocyclic
Q	O	<u>O</u> , CH ₂	<u>O</u> , CH ₂
Z	bromovinyl	H, " <u>alkyl</u> ", halogen	H, " <u>alkyl</u> ", halogen
n	1	0 or <u>1</u>	0 or <u>1</u>
Z'	=O	-NH ₂ when n=0 <u>=O when n=1</u>	-NH ₂ when n=0 <u>=O when n=1</u>
X	H	<u>H</u> , F, Cl, Br, I, OH, Me	F, Br, Me
Y	H	F	F

In section 5.1 of the decision, the opposition division held that the term “alkyl” at the Z position excluded the bromovinyl group of the CPF-2 compound in D36. As explained in sections 4.17-4.35 above, it is the position of the opponent that the opposition division was incorrect to do so. According to the definition provided in the patent, the term “alkyl” embraces the *same* bromovinyl groups as used in D36.

7.47

Accordingly, the opposition division should have found that the term “alkyl” embraced the groups expressly provided for this option in the patent as granted. Thus, the opposition division should have found that the option for “alkyl” at the Z position embraced the option for a bromovinyl group at this position.

2. The claim embraces open-ended definitions which are incompatible with activity

- 7.48 Claim 1 of the patent as granted is extremely broad. In fact, it is *infinitely* broad, due to the presence of a wide number of incompletely defined chemical groups. It is *prima facie* not credible that *any* technical effect can be achieved across the scope of such a claim, let alone a pharmacological effect such as anticancer activity, as alleged by the patentee.
- 7.49 Claim 1 of the patent as granted defines the compound as including features such as:
- *R is selected from the group alkyl, aryl and alkylaryl;*
 - *R' and R'' are independently selected from the group H, alkyl and alkylaryl, or R' and R'' together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system;*
 - *Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which said ring moieties is carbocyclic or heterocyclic and is optionally substituted;*
 - *Z is selected from the group H, alkyl and halogen*
 - *and being in the form of
a pharmaceutically acceptable salt, ester or salt of such ester.*
- 7.50 These definitions are all retained in claim 1 of AR13.
- 7.51 The scope of these definitions is completely without bound. For example, the claim allows for R to be infinite in length whether in the form of *any* alkyl group (branched or unbranched) or *any* alkylaryl group, and to include *any* aromatic group (monocyclic or fused; carbocyclic or heterocyclic). Similarly, R' and R'' are undefined and embrace alkyl and alkylaryl groups of *any* length. R' and R'' can similarly be attached together by an alkylene chain of *any* length to form any cyclic system. At the Ar position, *any* aromatic ring, monocyclic or bicyclic, containing zero or *any* number of *any* heteroatoms, and explicitly substituted by absolutely anything, is embraced. Finally, the compound can allegedly be esterified with *any* further compound and at *any* position.
- 7.52 As noted above, it is established EPO case law that an effect relied on to define a technical problem cannot be retained if it is *not credible* that the promised result is attainable throughout the entire range covered by a claim. As explained below, the leading decision in this area is T939/92 (AGREVO). It is also well established that in the field of drug design any structural modification of a pharmacologically active compound is, in the absence of an established correlation between structural features and activity, a priori expected to disturb the pharmacological activity profile of the initial structure (CLBA I-D-

9.8.2; citing T2402/10, T643/96 and T548/91). Applying the reasoning of such decisions, it is evident that the scope of variation permitted in the compounds claimed in the patent is such that it is not credible that any specific pharmacological activity is present across the scope of the claim.

- 7.53 The opposition division not only failed to correctly apply this established case law, but moreover concluded on page 38 of the decision (third paragraph) that such case law was “irrelevant for the present case.” The opposition division seemingly reached this incorrect view based on three factors.
- 7.54 The first factor is seemingly the inter partes nature of the opposition proceedings. The opposition division appears to have considered it relevant that the original AGREVO decision arose from a decision of the examining division rather than from the opposition division. However, this reasoning is deeply flawed. T939/92 is widely recognised (including in CLBA I-D-9.8.3), as containing “*fundamental rulings on broad claims in the field of chemistry*”. It was published in the Official Journal (OJ EPO 1996) and its reasoning has been widely applied by well over 200 decisions of the boards of appeal, many of which relate to decisions of the opposition division.
- 7.55 T939/92 has been cited far too many times to discuss each citation individually, but solely for completeness we note that the CLBA gives the example in section I-D-9.8.3 of T668/94, a decision arising from an appeal from the opposition division in revoking a patent for lack of inventive step and upholding that finding on the grounds that not all of the claimed compounds in that case credibly exerted the alleged technical effect. The headnote of that decision is quoted in paragraph 7.11 above and expressly notes that its conclusions are “following T0939/92, OJ EPO 1996, 309).”
- 7.56 The second factor is seemingly the position of the groups at issue in the structure of Formula (I) of the patent claim. The opposition division seemingly found it relevant that the open-ended language in connection with the groups R, R', R'' and (specifically) Ar appeared in the definition of the phosphoramidate moiety. The opposition division alleged that this variable had not been shown to differentiate over the prior art or to be a “sensitive” moiety for biological activity. The reasoning of the opposition division is both legally flawed and factually incorrect.
- 7.57 Legally speaking, the question is not whether the unspecified groups at issue distinguish over the prior art or not, but whether the totality of the claimed compounds credibly exert the technical effect asserted by the patentee. If the claim *necessarily* embraces inactive compounds, as here, it is irrelevant that they are inactive through variation of a residue disclosed in the art or at a new position.
- 7.58 Factually, the opposition division’s assertion that the Ar position of the phosphoramidate moiety is not sensitive for biological activity is contradicted by the patent itself. For example, passages such as paragraphs [0007]-[0008]

describe the background leading to the alleged invention as including observing “*the effect of variations in the ester... and aryl... regions of the phosphoramidate*”. More significantly, the very data relied on by the patentee to support the alleged invention proves this. We refer to the data for CPF-31 and CPF-40 in the Table on page 65 of the patent. These compounds differ **only** at the Ar position of the phosphoramidate group (CPF-31 has Ar = unsubstituted phenyl; whereas CPF-40 has Ar = para-Cl substituted phenyl) and yet they possess very different biological activity - for example, in prostate cancer, CPF-40 is effectively inactive, with an IC_{50} value of 15.41 μM , almost two orders of magnitude higher than in CPF-31 ($IC_{50} = 0.22 \mu M$). Contrary to the view of the opposition division, the identity of the Ar group and whether and how it is substituted are thus clearly of primary relevance to the alleged anticancer activity of the claimed compounds.

- 7.59 The third factor is seemingly that (in the view of the opposition division) a skilled person would interpret terms such as “alkyl” in an artificially narrow manner and would thus “self-police” the scope of the claim. The opposition division considered that viewing the claim as embracing alkyl groups with high numbers of carbons - the opposition division refers to C_{100} groups, but its reasoning is not directed to any specific value - was “construed and academic” and “that no skilled person would read [such values] into the teaching of Markush formula (I).” However, this is contrary to the established jurisprudence of the EPO, which has consistently held that (as summarised in CLBA at I-C-4.1) “*It is a well-established principle laid down by the boards’ case law that a non-specific definition in a claim should be given its broadest technically sensible meaning (see T 79/96, T 596/96).*”
- 7.60 The opposition division provides a definition of the term “alkyl” in section 5.1 of the decision. As explained in section 4 above, we consider this definition to be contrary to the definition in the patent application as filed, which we consider would be relied on by a skilled person in understanding this term. However, even adopting the opposition division’s narrow definition of the term “alkyl” as being a “*univalent group derived from alkanes by removal of a hydrogen atom from any carbon atom C_nH_{2n+1} ...*” there is no justification for assuming any particular upper limit on the value of n . The open-ended term “alkyl” necessarily embraces alkyl groups which are too large to be credibly associated with *any* biological activity, still less any anticancer activity.
- 7.61 Accordingly, the opposition division should have taken account of the established case law of the Boards of Appeal, and the teaching of the patent itself, in concluding that the claims of the patent as granted, the claims of ARs 1-12, and the claims of AR13 are all too broad for any technical effect to be achieved across their scope.

3. The claim embraces compounds having 2'-substitutions shown to be inactive

- 7.62 As noted above, in sections 5.6 and 9.5 of the decision, the opposition division framed the technical problem purported to be solved by both the claims of the

patent as granted, those of ARs 1-12, and those of AR13, to be “the provision of alternative anti-cancerous phosphoramidate nucleosides”.

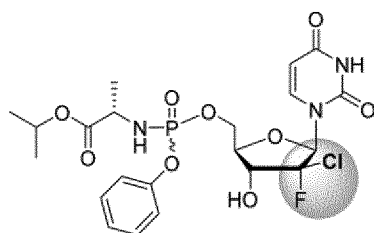
7.63 The opposition division correctly concluded that the claims of the patent as granted and those of ARs 1-12 embraced compounds proven by evidence on file to be inactive. Accordingly, the opposition division correctly concluded that the claims of the patent as granted and the claims of ARs 1-12 did not solve this problem. Whilst the overall conclusions of the opposition division as regards the claims of the patent as granted and the claims of AR12 were correct, the reasoning adopted by the opposition division was flawed. The errors in reasoning led to the finding that the claims of AR13 did involve an inventive step. That conclusion is incorrect and is contrary to the evidence on file.

7.64 In the following sections we address the following errors made by the opposition division in reaching its conclusions:

3.1 Compounds having 2'-Cl/2'-F substitution are not cytotoxic

7.65 We first briefly consider D107, which was correctly accepted by the opposition division as demonstrating that compounds having a 2'-Cl/2'-F substitution and thus being within the scope of the claims of the patent as granted and those of ARs 1-12 lacked anticancer activity.

7.66 The structure of the primary compound at issue in D107, referred to as compound 16, is set out in the abstract of that document and is reproduced below:



[Compound 16]

7.67 Cytotoxicity data for compound 16 and a related compound 20 (having defined stereochemistry at the phosphate group and a cytidine base rather than uracil, and like compound 20 falling within the scope of the claims) is provided in Table 1 of D107, reproduced below. Cytotoxicity is reported in D107 using CC₅₀ values, being the concentration of the tested compound in μM required to kill half of the cells assayed. Thus, low CC₅₀ values are associated with cytotoxicity, whilst high CC₅₀ values (e.g. >10 μM) are associated with compounds which are not cytotoxic in the tested cell line.

7.68 Cytotoxicity was assessed in four cell lines, included Huh7 and CEM cells, which are cancer cell lines.

Table 1. HCV Genotype 1b Replicon Activity and Cytotoxicity of Nucleosides 13, 19, 23, 27, 35, 36, 37, and Their Phosphoramidate Prodrugs 16, 20, 24, 28, 38, 39, and 40^a

compd	anti-HCV activity (μM)		cytotoxicity, CC_{50} (μM)			
	EC_{50}	EC_{90}	Huh-7	PBM	CEM	Vero
13	>100	>100	>100	>100	>100	>100
16	0.2 ± 0.1	0.4 ± 0.2	>10	>100	>100	>100
19	0.3 ± 0.03	0.9 ± 0.02	>10	12	>100	8.4
20	0.1 ± 0.06	0.3 ± 0.02	>10	>100	>100	>100
23	>10	>10	>10	>100	>100	>100
24	0.6 ± 0.2	2.1 ± 0.6	>33	84.8	36.3	53.9
27	19 ± 2.9	33 ± 0.5	>33	>100	>100	>100
28	0.3 ± 0.1	0.8 ± 0.2	>10	>100	>100	>100
35	>10	>10	>10	6.6	7.3	11.5
38	>10	>10	>10	>100	69.3	>100
36	>10	>10	>10	82.6	19.9	42.4
39	>10	>10	>10	99.7	55.3	60.9
37	>10	>10	>10	ND	ND	ND
40	>10	>10	>10	>100	69	>100
2'C-MeC	1.7 ± 0.8	6.5 ± 1.9	>10	>100	>100	>100
sofosbuvir	0.2	0.5 ± 0.3	>10	>100	>100	>100

^aND: not determined. All assays were performed in replicates. Only means are shown.

7.69 It can clearly be seen that in the CEM (leukemia) cells, both compounds 16 and 20 are not cytotoxic ($\text{CC}_{50} > 100 \mu\text{M}$). Discussing this data, the authors of D107 conclude that “on the basis of potency and lack of cellular toxicity in the various cell line tested, we further investigated the potential of compound 16” [as an anti-HCV agent].

7.70 The authors of D107 conclude at the end of that document under the heading “conclusions”:

“Compound 16 had excellent pan-genotypic activity with anti-HCV replicon activity similar to that of SOF [sofosbuvir]. Its nucleoside 5'-triphosphate was a specific inhibitor of HCV NS5B polymerase with no significant inhibition of human β , γ DNA polymerase and showed low incorporation by cellular mitochondrial RNA polymerase. Despite observing an IC_{50} of $20 \mu\text{M}$ versus polymerase α , we did not observe corresponding cytotoxicity nor cytostatic behaviour in five different cell lines (PBM, CEM, Vero, Huh7, and HepG2) at concentrations up to $100 \mu\text{M}$ ”.

7.71 In section 5.7 of the decision, the opposition division noted that the value for the Huh7 cell line quoted above is said to be “ $>10 \mu\text{M}$ ”, whereas the value for the CEM cell line is said to be $>100 \mu\text{M}$. The opposition division considered this to give rise to “ambiguity” as to what the actual level of cytotoxicity was in Huh7 cell lines. Accordingly, the opposition division indicated that it “*put more credit to the overall statement of the authors of D107 that in expressis verbis said that compound 16 does not have cytostatic behaviour against cancer cell lines*”.

- 7.72 Whilst the opposition division's conclusion regarding the lack of activity for compound 16 is correct, the opposition division nonetheless erred in failing to give due consideration to the data in Table 1.
- 7.73 For example, the data in Table 1 clearly indicates that in the human lymphoblastoid cancer cell line CEM, compound 16 is *expressly* inactive, having a CC₅₀ value of >100 µM. It is uncontested that a compound having a CC₅₀ value of >100 µM is manifestly non-cytotoxic. The opposition division erred in seemingly ignoring this data.
- 7.74 The opposition division also erred in failing to appreciate that the authors of D107 similarly considered a CC₅₀ value of ">10 µM" to likewise define an absence of cytotoxicity. This is relevant because this error of reasoning was similarly adopted by the opposition division in reaching an erroneous conclusion regarding other compounds within the scope of the claims of the patent as granted and those of ARs 1-13.

3.2 Compounds having 2'-Me/2'-F substitution are not cytotoxic

- 7.75 The opposition division was wrong to consider that compounds having a 2'-Me/2'-F substitution are active anticancer compounds. As explained in detail in the following sections, this finding is wholly inconsistent with the evidence on file in documents such as D37 and D107.

D37

- 7.76 The opponent filed with the Notice of Opposition D37. D37 was discussed in some detail during the oral proceedings and it is noted in the decision that "*O cited D37 [...] as evidence that the claims embrace cancer-inactive compounds*". Despite this, the opposition division seemingly failed to consider this document *at all* in the decision. Failure to give due weight to D37 is a manifest error of the opposition division that led to the incorrect finding of inventive step for AR13.
- 7.77 D37 includes the following as Table 1

TABLE 1 Cytotoxicity in human cell lines after 5-day treatment

Base	Compound	Mean CC ₅₀ ± SD (μM) in:				
		Hepatic cells		Prostate cells (PC-3)	Fibroblasts (MRC5)	T-cells (MT-4)
		Huh7	HepG2 (galactose)			
Uridine	Sofosbuvir	66 ± 17	>89	>100	>89	>100
Guanosine	IDX184	>89	>89	77 ± 14	>89	66 ± 18
	BMS-986094	0.5 ± 0.2	1.9 ± 1.0	1.0 ± 0.2	1.1 ± 0.3	1.1 ± 0.5
	PSI-938	>89	>89	>100	>89	>100
Cytidine	PSI-6130	>89	>89	>100	>89	>100
	4'-AzidoC	>89	>89	30 ± 6	>89	>100
	2'CMeC	>89	>89	49 ± 18	69 ± 1	19 ± 6
Adenosine	GS-6620 ^a	67 ± 13	66 ± 13	40 ± 0.7	8.9 ± 4.1 ^b	7.8 ± 4.3 ^b
	ddC ^c	>89	>89	0.80 ± 0.21	>89	>89
	Chloramphenicol ^c	>89	>89	16 ± 3	>89	>89
	Alpha-amanitin ^c	0.45 ± 0.16	0.81 ± 0.35	0.17 ± 0.06	0.34 ± 0.07	0.89 ± 0.10
	Puromycin ^c	0.52 ± 0.19	0.65 ± 0.18	0.22 ± 0.07	0.24 ± 0.05	0.16 ± 0.06

^a The cytotoxicity of GS-6620 in some cell types was reported previously (13).

^b Complex, multiphasic dose response was observed, with an initial drop in viability of 50% followed by a rebound to over 50% at higher concentrations. Flow cytometry studies suggested that the effect of the compound on these cells was cytostatic instead of cytotoxic.

^c Control treatment.

- 7.78 The table in D37 is similar in format to that in D107. It shows that various compounds including sofosbuvir are **inactive** in various cancer cell lines, including HepG2, PC-3 (the same cell line used in the patent), and Huh7.
- 7.79 The opposition division seemingly completely ignored the data in Table 1 of D37. As shown above, sofosbuvir has a CC₅₀ value of more than 89 μM in hepatic HepG2 cells, and more than 100 μM in prostate PC-3 cells, and is thus essentially completely inactive in each cell line. No reason for ignoring this data is provided in the decision.
- 7.80 Discussing this data, the authors of D37 comment in the first paragraph under the heading “Results” on page 809 that
- “compounds not associated with clinical toxicity generally did not show marked cytotoxicity. For example, sofosbuvir showed modest effects in only one cell line (HepG2) and the nucleoside released by mericitabine, PSI-6130, had no effects on any of the cells at the concentrations tested”.**
- 7.81 Similarly, in the section headed “Measurement of active triphosphate metabolite in PC-3 cells” on page 810 of D37, the authors state that
- “Sofosbuvir and PSI-6130 efficiently formed TP, illustrating that the **lack of toxicity** (CC₅₀ >100 μM) (Table 1) was not due to poor intracellular activation.”**
- 7.82 Dr Keegan reviewed D37 on behalf of the opponent and commented in D106 (referred to as D108 in the decision) that in her professional view, the conclusions of the authors of D37 that sofosbuvir and PSI6130 exhibit a “lack of toxicity” was entirely reasonable. The opposition division seemingly ignored this opinion, as well as the *in expressis verbis* statements in D37. No reasoning for doing so is offered in the decision.

- 7.83 In paragraph 6.15 of the submissions of 14 January 2021, the patentee alleged that D37 suggests that sofosbuvir is cytotoxic against the Huh-7 cell line due to the term “modest effects”. This is incorrect and contradicts the authors of D37, for the reasons set out above. Moreover, the patentee’s argument in this regard is misleading in the extreme. The patentee’s own declarant, Dr Harrison, opined in D51 that *“test compounds that exhibit an IC_{50} of about 5-40 μM may have potentially useful anticancer activity. In other words, a test compound with an IC_{50} of 5-50 μM would not be excluded on this basis”*. As noted above, we disagree strongly with the patentee’s position here. However, even if (*arguendo*) the patentee’s view regarding the “cytotoxicity” of such compounds were to be taken at face value (which it should not be) then it is important to note that the value for sofosbuvir in D37 of 66 μM still falls far above even the upper limit of this range.
- 7.84 The only suggestion in the decision as to why the opposition division may have failed to take account of Dr Keegan’s views regarding D37 as set out in D106 is an unfounded allegation in the first paragraph of section 5.7.1 of the decision that D106 is *“unscientific and biased”*. We discuss the unwarranted nature of this personal attack, which was advanced for the first time by the opposition division in the written decision, in section 7.127 ff below. Here, we address the substance of D37.
- 7.85 D37 has been reviewed by Professor Adrian Harris and his declaration is filed herewith as D129. As will be clear from his CV (filed as D129a), Professor Harris is a leading oncology expert and is wholly independent of both the opponent and the patentee. As such he is well placed to comment on the understanding of the skilled person in this area. Professor Harris confirms that D37 proves that the compound sofosbuvir has no meaningful anticancer activity in any of the tested cell lines, including Huh7.
- 7.86 Specifically, Professor Harris confirms in D129 that the CC_{50} values reported for the compound “sofosbuvir” in D37 in all of the tested cell lines are clear and are inconsistent with anticancer activity. Thus, in sections 25-28 of his declaration Professor Harris states:

D37 shows cytotoxicity data in Table 1 for the compound “sofosbuvir” as well as various other compounds. This data is entirely clear: the compound “sofosbuvir” is not an anticancer compound. Its CC_{50} values are far above the values that I would expect to see for any anticancer compound and this is the case in all of the cell lines tested. The values for the different cell lines are not statistically different and the compound is inactive in all of the cell lines tested.

The authors of D37 state that “Compounds not associated with clinical toxicity generally did not show marked cytotoxicity. For example, sofosbuvir showed modest effects in only one cell line (HepG2), and the nucleoside released by mericitabine, PSI-6130, had no effects on any of the cells at the concentrations tested.” I do not consider sofosbuvir to

demonstrate even “modest effects” in Huh-7 based on the data in Table 1, but even if a value of $66 \pm 17 \mu\text{M}$ were to be labelled a “modest” cytotoxic effect this does not suggest to me that the compound has meaningful anticancer activity. In my view, D37 shows that sofosbuvir does not have anticancer activity in any of the cell lines tested, and in view of that data, I would not expect sofosbuvir to have any meaningful anticancer activity in any other cancer cell line either.

In Dr Keegan’s declaration she states “In view of the data in D37, I consider the conclusions of the authors of D37 that “sofosbuvir” and “PSI-6130” exhibit a “lack of toxicity” to be entirely reasonable.” I agree, but I would go further. As I explain above, I consider D37 to clearly show that sofosbuvir does not have anticancer activity in the cell lines tested.

In D115 Dr Harrison indicates that he considers D37 to show that sofosbuvir is cytotoxic against the Huh-7 cell line. This is contrary to the data presented in D37. A value of “ $66 \pm 17 \mu\text{M}$ ” is statistically indistinguishable from a value of “ $>100 \mu\text{M}$ ”. However, even setting aside that statistical point, a value of $66 \mu\text{M}$ is far too high to be associated with anticancer activity - which even Dr Harrison seems to accept in D51.

- 7.87 The opposition division was thus wrong to ignore D37 in considering whether or not sofosbuvir is cytotoxic. Table 1 of D37 confirms it is not, and this is commented on by the authors of D37. Dr Keegan provided expert comment on D37 and confirmed that the reasonable conclusion from D37 is that sofosbuvir shows a lack of toxicity. This conclusion is agreed with by Professor Harris, who confirms that D37 proves that sofosbuvir does not have anticancer activity in any of the tested cell lines. Professor Harris also confirms that even if sofosbuvir was considered to have a “modest” cytotoxic effect in Huh7 cells specifically - which in his view is *not* the case - then that would still not imply that the compound has meaningful anticancer activity, not least as the only datapoint that is even alleged by the patentee to be associated with cytotoxicity falls outside the range alleged by the patentee’s own declarant to be of relevance to anticancer activity. It was an error of the opposition division to simply ignore this evidence in reaching their conclusion regarding the alleged activity of the compounds claimed in the patent as granted and in ARs 1-12.
- 7.88 An additional point is worth emphasizing here, which further underlines that the decision of the opposition division was manifestly wrong. Thus, the opposition division failed to appreciate that D37 stresses in the passage cited above that compounds which in the described assays “did not show marked cytotoxicity” are in practice “***not associated with clinical toxicity***”.
- 7.89 In more detail, D37 notes that sofosbuvir is an “approved” drug (see Figure 1 and the discussion in the introduction). Indeed, as noted above sofosbuvir has been approved by the regulators in Europe, the US and across the world, and has been administered to well over a million people to successfully treat HCV.

Sofosbuvir is self-evidently “*not associated with clinical toxicity*”, for it would not have been “*approved*” for administration in humans if it were. The reason it is not associated with clinical toxicity is of course at least in part because it does not show marked cytotoxicity.

- 7.90 This point is self-evident; yet for the convenience of the board we note it is also stressed in D10. We refer to paragraph 97 of D10, in which the judge sets out some basic scientific principles based on the technical evidence of the common general knowledge in the field, according to the expert witnesses in that case:

“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.”

- 7.91 Similarly, in paragraph 126 of D10, the judge stated:

“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”.”

- 7.92 The regulatory approval of sofosbuvir to treat HCV, remarked on in documents such as D37, is thus further evidence that it is not meaningfully cytotoxic. It is inconceivable that regulatory approval would have otherwise been granted.

- 7.93 In case the patentee should contest this self-evident position, we hereby file a declaration from Ms Sally Jane Shorthose, an expert in healthcare regulatory law with extensive experience of the marketing approval (MA) process and the evidence considered by the regulatory authorities prior to marketing authorisation being granted. Ms Shorthose’s declaration is filed herewith as D131.

- 7.94 Ms Shorthose discusses the MA process in some detail in D131. She explains in section 11 of D131 that, in this regard:

All information that is relevant to the evaluation of the medicinal product, whether favourable or unfavourable, must be included in the application. For example, the details and information prescribed in Article 8(3) of the EU Directive must be provided for any incomplete or abandoned pharmacotoxicological clinical trial or test relating to the medicinal product, and/or completed trials concerning therapeutic indications not covered by the application. Article 8(3) and Annex I of the EU Directive further contain the

legal requirements for submitting an MA application, including “results of pharmaceutical (physico-chemical, biological, or microbiological) tests, results of pre-clinical (pharmacological and toxicological) tests, and results of clinical trials”. In addition, proposed therapeutic indication(s), contra-indication(s), and adverse reactions, and the recommended dosing regimen or posology must also be included. The documents and information concerning the results of the pharmaceutical and pre-clinical tests and the clinical trials must be accompanied by detailed summaries in accordance with Article 12 of the EU Directive. Specifically, the summaries must be supported by the relevant scientific literature and approved by an expert.

- 7.95 Ms Shorthose confirms that such information is assessed by the EMA Committee for Medicinal Products for Human Use (CHMP) as part of the approval process, and that MA will only be granted if the overall benefit/risk profile is positive. As explained in section 14 of D131:

In summary, the key principle underpinning an MA application assessment is the balance between the benefits and risks of a medicine; a medicine can only be authorised if its benefits outweigh the risks of authorisation. This assessment differs from application to application, with the overall risk of the product being weighed against its benefits. It is, however, generally the case that for an MA to be granted, a medicament must not exhibit any significant cytotoxicity at clinically relevant concentrations.

- 7.96 Consistent with this general approach, Ms Shorthose confirms in D131 that the pre-clinical cytotoxicity test results submitted as part of the sofosbuvir MA application process with the European Medicines Agency (“EMA”) did indeed confirm that there is minimal or no significant cytotoxicity observed with sofosbuvir treatment *in vitro* for any of the cell types tested. Ms Shorthose refers in this regard to D132, entitled “Section 2.6.2 - Pharmacology Written Summary” which was filed by the applicant in the MA process for sofosbuvir and is attached herewith. D132 expressly confirms that sofosbuvir is not cytotoxic in the cancer cells tested. We refer to sections 15-16 of D131.

- 7.97 Ms Shorthose states in section 17 of D131 that:

In conclusion, the key principle underpinning an MA application assessment is the balance between the benefits and risks of a medicine; a medicine can only be authorised if its benefits outweigh the risks. Given this rigorous safety assessment undertaken by the EMA, and to the extent applicable the relevant Competent Authorities, prior to the granting of an MA, it is clear that the regulators had no concerns that sofosbuvir had any appreciable cytotoxicity, as confirmed by the data submitted during the MA application and the fact that the product’s SmPC and the product packaging do not reference any potential safety issues applicable to cytotoxicity.

7.98 The overall regulatory process would be familiar to any skilled person in the pharmacological field, as evidenced by D10. It would necessarily have been understood that the very fact that sofosbuvir is approved as an antiviral medication is strong evidence that it is not cytotoxic: this point is made in D10, confirmed in D37, and has been further confirmed now by Ms Shorthose in D131. It was a profound error of the opposition division to fail to give due weight to these considerations.

D107

7.99 D107 is discussed above and was accepted by the opposition division as proving that compounds having 2'-Cl/2'-F substitution are not active. However, the opposition division was mistaken to ignore the analogous teaching in that document regarding the compound sofosbuvir.

7.100 Table 1 of D107 is reproduced in its entirety above. An extract is reproduced here for the convenience of the board:

Table 1. HCV Genotype 1b Replicon Activity and Cytotoxicity of Nucleosides 13, 19, 23, 27, 35, 36, 37, and Their Phosphoramidate Prodrugs 16, 20, 24, 28, 38, 39, and 40^a

compd	anti-HCV activity (μ M)		cytotoxicity, CC ₅₀ (μ M)			
	EC ₅₀	EC ₉₀	Huh-7	PBM	CEM	Vero
16	0.2 $\pm$ 0.1	0.4 $\pm$ 0.2	>10	>100	>100	>100
sofosbuvir	0.2	0.5 $\pm$ 0.3	>10	>100	>100	>100

7.101 It can clearly be seen that the cytotoxicity data for sofosbuvir and compound 16 (having 2'-Cl/2'-F substitution, and for which the authors of D107 *in expressis verbis* said does not have cytostatic behaviour against cancer cell lines, as discussed above) is identical.

7.102 Despite this, the opposition division stated in section 5.7 of the decision that “OD could not accept O’s conclusion of the reported values for Sofosbuvir showing the Sofosbuvir being cancer inactive.”

7.103 The opposition division was incorrect as a matter of basic scientific reasoning in reaching this conclusion. The data for compound 16 was expressly described by the authors of D107 as meaning that neither cytotoxicity nor cytostatic behaviour was observed. Despite this the opposition division failed to even seek to interpret the identical data for the compound sofosbuvir in the absence of a corresponding *in expressis verbis* statement.

7.104 Failure to give due consideration to the data in D107 is a fundamental error by the opposition division. Seemingly, for the opposition division actual numerical data was to be afforded significantly less weight than written statements even if such statements were unsupported by any numerical disclosure.

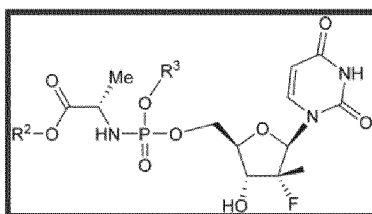
7.105 The opponent considers that D37 and D107 together more than discharge the burden on the opponent to show that sofosbuvir is *not* cytotoxic. However, in

response to the opposition division's express - albeit incorrect - consideration of the primacy of statements made *in expressis verbis*, we refer here to D124. D124 confirms the data in D37 and D107 *in expressis verbis*.

D124 - Sofia et al, J. Med. Chem. 2010

- 7.106 D124 describes the discovery and development of sofosbuvir (referred to as PSI-7977) for treating HCV.
- 7.107 Relevant compounds are shown in Table 5 of D124, reproduced below.

Table 5. HCV Replicon Activity of Phosphoramidate Prodrugs: Simultaneous Carboxylate and Phenolic Ester Modification of the Phosphoramidate Moiety



compd	R ²	R ³	EC ₅₀ cloneA (μM) ^a	inhibition of cellular rRNA replication at 50 μM (%) ^b
12	Me	Ph	1.62	0.0
24	Me	4-F-Ph	0.69	16.8
25	Me	4-Cl-Ph	0.58	62.8
26	Me	4-Br-Ph	2.11	30.8
13	Et	Ph	0.98	36.9
41	Et	4-F-Ph	0.76	55.3
42	Et	4-Cl-Ph	0.39	0.0
43	Et	4-Br-Ph	0.36	80.5
14	<i>i</i> -Pr	Ph	0.52	25.9
44	<i>i</i> -Pr	4-F-Ph	0.77	0.0
45	<i>i</i> -Pr	4-Cl-Ph	0.42	0.0
46	<i>i</i> -Pr	4-Br-Ph	0.57	0.0
18	<i>c</i> -Hex	Ph	0.25	61.1
47	<i>c</i> -Hex	4-F-Ph	0.04	52.1
48	<i>c</i> -Hex	4-Cl-Ph	0.054	66.9
49	<i>c</i> -Hex	4-Br-Ph	0.039	91.5

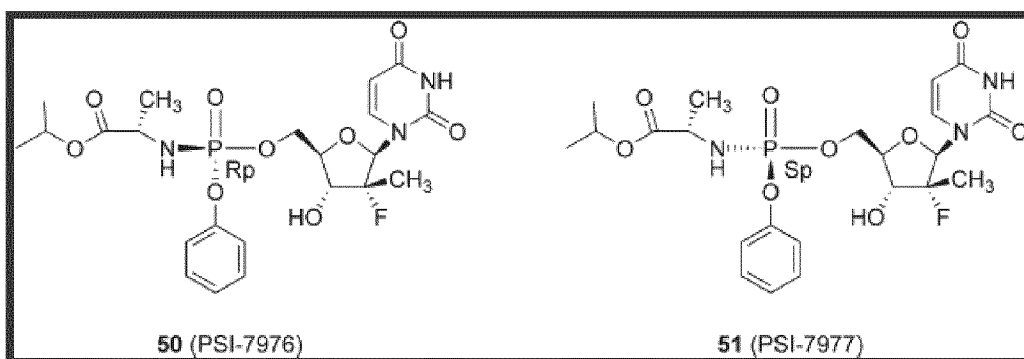
^a Each value is a result of *n* = 2 determinations. ^b Clone A cells.

- 7.108 We highlight compounds 12, 14 and 47, which along with the other compounds in this table fall within the scope of the claims of the patent as granted and the claims of ARs 1-13. On page 7209, first full paragraph, D124 states:

“Nucleos(t)ide toxicity can be correlated to several cellular effects. Mitochondrial toxicity has been reported to be associated with the long-term use of certain nucleos(t)ide analogues resulting in myopathy, peripheral neuropathy, and pancreatitis.^{33,34} Hematotoxicity, which can lead to neutropenia, severe anemia, and thrombocytopenia, has also been associated with several nucleoside analogues including the HCV polymerase inhibitor 3.^{35,36} One cause of hematotoxicity is bone marrow toxicity.^{35,36} To examine for these possible toxicities, compounds 12, 14, and 47 were evaluated for general cytotoxicity against an expanded cell panel and evaluated in vitro for both mitochondrial toxicity and toxicity to bone

marrow progenitor cells. In an expanded cell panel that included two human hepatocyte cell lines, Huh7 and HepG2, a human pancreatic cell line, BxPC3¹, and a human T lymphoblast cell line, CEM, compounds 12, 14, and 47 were found to show no cytotoxicity up to 100 µM, the highest concentration tested.”

- 7.109 The diastereomers of compound 14 are referred to in D124 as compounds 50 (PSI-7976) and 51 (PSI-7977, sofosbuvir), depicted in Figure 6 of D124:



- 7.110 D124 states at page 7201, left hand column that:

*Comparison of cytotoxicity profiles for each isomer (50 and 51) demonstrated that **both compounds were essentially devoid of cytotoxicity** when assessed in an 8-day cytotoxicity assay against an expanded cell panel (Huh7, HepG2, BxPC3, and CEM cells) at concentrations up to 100 µM.*

- 7.111 The opposition division had no need for these *in expressis verbis* statements in order to conclude that sofosbuvir is not cytotoxic in Huh7, HepG2, BxPC-3 or CEM cancer cell lines, as this data is provided in numerical form in D37, discussed in that document, confirmed by Dr Keegan in D106, and further confirmed in D107. However, given the comments of the opposition division in the decision regarding the supremacy (in its view) of conclusions presented *in expressis verbis*, D124 is filed to confirm the error in reasoning of the opposition division.

D133 and D134 - Experimental Reports regarding compounds having 2'-Me/2'-F substitution

- 7.112 At first instance the opponent filed and discussed *published, peer-reviewed* evidence showing that compounds having 2'-Me/2'-F substitution are not cytotoxic. However, the opposition division repeatedly criticized the opponent for not responding to the patentee's allegations with "data" (e.g. see section 5.7.1 of the decision).

¹ The cell line referred to is BX-PC3: see experimental protocol headed "Cell Cytotoxicity Assays" on page 7215 of D124.

- 7.113 Peer-reviewed publications do of course contain data and should have been taken as such by the opposition division. However, seemingly for the opposition division direct experimental reports were to be afforded more weight. In response to this criticism, raised for the first time in the decision, the opponent herewith files D133 and D134, consisting of direct experimental reports confirming that compounds having 2'-Me/2'-F substitution are not cytotoxic in cancer cells.
- 7.114 D133 reports on experiments conducted to assess the cytotoxicity of the compound PSI-7851 (the racemic mixture of sofosbuvir, PSI-7977 and its diastereomer, PSI-7976) in a panel of cancer cell lines. As confirmed in section 1 of D133, four different cell lines were tested: Huh7 (human hepatoma), HepG2 (human hepatoma), BxPC3 (human pancreatic cancer) and CEM (human T lymphoblast) cells.
- 7.115 The methodology employed is confirmed in section 2 of D133. Results are shown in section 3 of D133. Gemcitabine was used as a positive control. Table 1 of D133, reporting on those results, is reproduced below:

Table1. CC₅₀ (µM) of the tested compounds

	Huh 7	HepG2	BxPC3	CEM
PSI-7851	>100	>100	>100	>100
PSI-6130	>100	>100	>100	>100
Gemcitabine	<1	<1	<1	<1

- 7.116 D133 confirms in section 3 that *“Both PSI-7851 and PIS-6130 (2'-F-2'-C-methylcytidine) showed no significant cytotoxicity in Huh7, HepG2, BxPC3, or CEM cells (CC₅₀ > 100 µM). Cytotoxicity was observed at all concentrations of the positive control, Gemcitabine”*.
- 7.117 D134 similarly reports on experiments conducted to assess the cytotoxicity of PSI-7976 and PSI-7977, the diastereoisomers of PSI-7851. The same cell lines as tested in D133 were assessed.
- 7.118 The experimental methodology employed is set out in section 2 of D134. Results are shown in section 3 of D134. Again, gemcitabine was used as a positive control. Table 1 of D134 is reproduced below:

Table 1. CC₅₀ (μM) of the tested compounds

	CC50 (μM)			
	Huh7	HepG2	BxPC3	CEM
PSI-7976	>200	>200	>200	>200
PSI-7977	95.9 ± 9.8	90.6 ± 12.9	>200	>200
PSI-6130	>200	>200	>200	>200
Gemcitabine	<1	<1	<1	<1

- 7.119 D134 confirms in section 3 that “Both PSI-7976 and PSI-6130 (2’-F-2’-C-methylcytidine) showed no cytotoxicity in Huh7, HepG2, BxPC3, or CEM cells at 200 μM, the highest concentration tested (CC₅₀ > 200 μM). The CC₅₀ values for PSI-7977 were 96 μM in Huh 7 cells and 91 μM in HepG2 cells, greater than 200 μM in other two cell lines. Cytotoxicity was observed at all concentrations of the positive control, Gemcitabine”.
- 7.120 In case the patentee should contend that the values for PSI-7977 are representative of cytotoxicity in Huh7 or HepG2 cells (which is not the case), we note that the authors of D134 confirm in the summary on page 1 under the heading “Purpose/Summary” that “*this report describes the results of an eight-day cytotoxicity assay with PSI-7976 and PSI-7977 measured using the MTS assay with Huh7, HepG2, BxPC3 and CEM cells. **Both compounds did not show significant cytotoxicity in the four cell lines.***”
- 7.121 Accordingly, D133 and D134 confirm with direct experimental evidence that, in stark contrast to the positive control gemcitabine which showed cytotoxic behaviour at all tested concentrations, three different compounds having 2’-Me/2’-F substitution (PSI-7851, PSI-7976 and PSI-7977) are not cytotoxic against a panel of cancer cell lines. D133 and D134 unquestionably provide “data” and are filed herewith in direct response to the criticism of the opponent by the opposition division for relying on published peer-reviewed evidence rather than “data”.

D51 and D115 do not demonstrate cytotoxicity of sofosbuvir

- 7.122 In support of an allegation that one specific compound having 2’-Me/2’-F substitution is allegedly active in one specific cell line, the patentee filed D51. In the first paragraph of section 5.7.1 of the decision, the opposition division states that

“OD accepted D51 as evidence that Sofosbuvir was active against SKBR3 breast cancer cells, showing an IC₅₀ of 5-50 μM. [...] For opposition division it was irrelevant, how high the absolute IC₅₀ value would be [sic]. For opposition division it sufficed the Sofosbuvir shows some kind of anti-cancerous activity.”

(original emphasis)

- 7.123 The opposition division made several errors when considering D51. As explained below in more detail, D51 does not provide any data at all, is based on misleading premises, and reaches incorrect conclusions. It is also significantly deficient as regards the experiments that were allegedly carried out.
- 7.124 D51 is so brief that its entire technical disclosure can be easily reproduced as follows:
7. *I oversaw the experiments to study the anti-cancer effect of Sofosbuvir, Compound 1, against a breast cancer cell line (SKBR3 (5000) cells).*
 8. *A Sulphorhodamine B (SRB) assay was employed for the screening of anti-cancer activity of Sofosbuvir against the breast cancer line. Sofosbuvir was tested at six concentrations: 10 μ M, 25 μ M, 50 μ M, 100 μ M, 250 μ M, and 500 μ M.*
 9. *After exposure for four days, the number of cells was measured as a marker of efficacy.*
 10. *Sofosbuvir exhibited anti-cancer activity against the SKBR3 breast cancer cell and dose-dependent inhibition was observed.*
 11. *It is my experience that test compounds that exhibit an IC_{50} of about 5-40 μ M may have potentially useful anti-cancer activity through a selected route of administration, for example topical or systemic. In other words, a test compound with an IC_{50} of 5-50 μ M would not be excluded on this basis.*
- 7.125 The only alleged “data” in D51 is thus an unevidenced assertion in paragraph 10 that “anticancer activity” and “dose dependent inhibition” were observed. There is no experimental evidence *at all* in D51.
- 7.126 Despite this fundamental flaw, the opponent asked Dr Kathleen Keegan, an experienced cancer biologist, to review D51 (then referred to as D49) and to comment to the extent possible on how the comments therein should be interpreted. Her declaration is on file as D106 (referred to by the opposition division in the decision as D108). In paragraphs 13-15 of D106, Dr Keegan explained that as a professional scientist with extensive experience of performing cytotoxicity assays, she could not reproduce the assay allegedly reported on in D51. She highlighted key information missing from D51, including the composition of the medium in which the cells were assessed, the temperature used during their growth and assay, and how and under what conditions the cells were treated with SRB. It has not been disputed by the patentee that this information is missing from D51. Nor has it been disputed

that this information is relevant to the (non)-reproducibility of the assay allegedly described in D51.

- 7.127 Dr Keegan also confirmed that she could not draw meaningful conclusions from the statement regarding “anticancer activity” and “dose dependent inhibition”. She highlights that these statements would not allow her to conclude that the compound tested had any meaningful anticancer activity, still less that it would be suitable as a potential anticancer therapy.
- 7.128 The opposition division stated in section 5.7.1 of the decision that
- “Contrary to D51, wherein data is presented, D108 [sic] does not present any data, but expresses the opinion of a party affected by the scope of the patent. As opposition division saw it, D108 [sic] tries to discredit the data of D51 as being unreproducible, being “impossible to draw any meaningful conclusions therefrom”. Opposition division considers such allegations in D108 [sic] being unscientific and biased.”*
- 7.129 This statement is frankly astonishing, and could even be construed by a third party observer as implying partiality in the opposition division.
- 7.130 First, the board will appreciate that **both** D106 and D51 equally express “*the opinion of a party affected by the scope of the patent*”. **Dr Harrison, the author of D51, is the Head of Translational Medicine at Nucana, plc, the patentee in these proceedings.** The opposition division erred in law by failing to apply the principle of equal treatment of the parties, by critiquing D106 as being “biased” whereas seemingly considering D51 to be entirely “unbiased”.
- 7.131 Second, the opposition division also erred by considering the unsubstantiated statement in D51 as constituting “data” whilst dismissing the view of an experienced cancer biologist that no such conclusions could be drawn from that document. The opposition division has read far more into D51 than the text reproduced above states.
- 7.132 We stress that there is no suggestion of any specific degree of cytotoxicity *at all* in D51. The opposition division accepted D51 as evidence that sofosbuvir was active against SKBR3 breast cancer cells with an IC_{50} of 5-50 μM (section 5.7.1 of the decision, first sentence), but this is not stated in D51 and is contrary to the express view of Dr Keegan in D106. The opposition division was incorrect to consider an unsubstantiated assertion from the patentee as “data”.
- 7.133 In response to the failure of the opposition division to give due consideration to the comments from Dr Keegan in D106 and consequently to give undue weight to the unevicenced assertion in D51, Professor Harris has also reviewed D51 and he has confirmed in D129 what it does and does not disclose.

- 7.134 Professor Harris confirms the complete absence of data in D51, as previously noted by Dr Keegan. Thus, in paragraph 15 of D129 Professor Harris notes that:

"I was surprised to see that Dr Harrison does not provide any results in D51 at all."

- 7.135 Professor Harris further agrees with Dr Keegan's view that she "cannot conclude from a statement regarding dose-dependent inhibition that the compound tested had any meaningful anticancer activity, still less that it would be suitable as a potential anticancer therapy". Thus, in paragraphs 15-16 of D129 Professor Harris explains:

[Dr Harrison] states that "dose-dependent inhibition" was observed but in the absence of actual data this statement is meaningless - after all, almost all compounds will kill cells if you use high enough concentrations (even water, HCl, etc), but it would be nonsensical to suggest that all such compounds are meaningfully cytotoxic to serve as potential anticancer medications.

I have read Dr Keegan's declaration in which she comments on D51. She states "I cannot conclude from a statement regarding dose-dependent inhibition that the compound tested had any meaningful anticancer activity, still less that it would be suitable as a potential anticancer therapy". I agree, but would go further. In my view the most reasonable conclusion from D51 is that the tested compound does not possess any meaningful anticancer activity.

- 7.136 Professor Harris explains in paragraphs 18-19 of D129 why, when read correctly, D51 suggests that sofosbuvir does not possess any meaningful anticancer activity:

Dr Harrison asserts that, based on this [SRB] assay, "sofosbuvir exhibited anticancer activity". However, not only is there no data in D51 to support this assertion, but the experiments which Dr Harrison refers to are not suitable to draw this conclusion.

Dr Harrison indicates that he assayed the compound "sofosbuvir" at six concentrations from 10 μ M to 500 μ M. The use of such high concentrations is contrary to standard practice if one is seeking to identify a compound with anticancer activity that could possibly serve as a therapeutic compound. As I mention above, assays seeking to identify active compounds are usually run at concentrations not exceeding 10 μ M. If a compound shows cytotoxic activity only above this level in a test assay like the SRB assay used by Dr Harrison it cannot generally be considered to have meaningful anticancer activity. The use of concentrations from 10 μ M to 500 μ M by Dr Harrison in the SRB assay that he describes therefore suggests that the compound has no meaningful anticancer activity at any clinically relevant concentration.

- 7.137 Accordingly, it was an error of the opposition division to consider that D51 “presents data” in the first place, and a further error to conclude that the “data” in D51 suggests that sofosbuvir is cytotoxic in SKBR3 breast cancer cells. As stated by Dr Keegan in D106 and confirmed by Professor Harris in D129, no such data is present, and no such conclusions are justified from D51.
- 7.138 The opposition division stated that “OD accepted D51 as evidence that sofosbuvir was active against SKBR3 breast cancer cells, showing an IC_{50} of 5-50 μM ”. As discussed above no such data is present in D51. However, even if D51 did constitute evidence that sofosbuvir had an IC_{50} of 5-50 μM (which it does not), then this would still not prove that the compound was meaningfully cytotoxic.
- 7.139 D51 itself indicates only that that test compounds having an IC_{50} of 5-40 μM “may” have potentially useful anticancer activity. Even if the alleged value of 5-50 μM was to be considered, the only reasonable conclusion would have been that the compound may or may not lie in the range considered to be active by Dr Harrison, and even if in that range *may* (or may not) have potentially useful anticancer activity.
- 7.140 More fundamentally, however, the assertion in D51 that test compounds having an IC_{50} of 5-40 μM “may” have potentially useful anticancer activity is profoundly misleading. This is explained by Professor Harris in paragraphs 20-23 of D129:

Dr Harrison states that “test compounds that exhibit an IC_{50} of about 5-40 μM may have potentially useful anticancer activity through a selected route of administration, for example topical or systemic. In other words a test compound with an IC_{50} of 5-50 μM would not be excluded on this basis.” This statement is ambiguous and its implications are misleading.

As I have explained above, depending on the assay used, a test compound that exhibits an IC_{50} of about 5 μM in an assay may not be excluded or otherwise disregarded as being inactive (although if the assay is very sensitive then even an IC_{50} of 5 μM is rather high and in that assay may in fact indicate inactivity). However, a test compound having an activity much above this, and certainly anywhere near the upper half of the ranges indicated by Dr Harrison would mostly be considered for all practical purposes to be completely inactive. Such a test compound would generally be disregarded by any skilled person. Indeed, in my role on grant-giving committees with Cancer Research UK we have typically withdrawn support for research programmes testing compounds which can only attain activities of at best about 10 μM against their targets.

In any case, as far as D51 goes, it seems that Dr Harrison did not actually test “sofosbuvir” at 5 μM and so whatever the IC_{50} was determined to be it must exceed this value. The strong implication from D51 is that the IC_{50}

lies well above 10 μ M, which is the lowest concentration that Dr Harrison tested.

It is therefore my view that D51 does not indicate that the compound "sofosbuvir" has any meaningful anticancer activity even in the tested cell line (SKBR3 breast cancer cells), let alone in any other cancer types.

- 7.141 The position of the opponent as discussed at first instance, and informed by the expert view of Dr Keegan in D106, was and remains that D51 does *not* prove that sofosbuvir has any specific activity, let alone any meaningful cytotoxicity. Professor Harris confirms that this conclusion is correct. It was an error of the opposition division to conclude otherwise by considering D51 to constitute "evidence that sofosbuvir was active against SKBR3 breast cancer cells, showing an IC₅₀ of 5-50 μ M".
- 7.142 In addition, as noted above, Dr Keegan stated in D106 that based on the description of the assay in D51 she could not reproduce the experiments allegedly conducted. However, the opposition division alleged in section 5.7.1 of the decision that the assay described in D51 "*could have very well been reproduced by a skilled person if needed. Sulforhodamine B assay kits are commercially available e.g. from Merck. Moreover, even if there had been any uncertainties on the assay setup, a cytotoxicity value could have been measured if wanted, if not with a Sulforhodamine B assay than [sic] with any other assay that Dr. Keegan, the author of D108 [sic], is certainly capable of. However, D108 [sic] did not respond with data, but with allegations, although the party raising the allegation (i.e. O) bears the burden of proof.*"
- 7.143 The opposition division appears to have impermissibly relied on its own knowledge in asserting that such assays were standard and "*available from e.g. Merck*" (which, even if true, has not been asserted by either party). In any case, the opposition division was wrong to discount Dr Keegan's comments in D106 regarding the reproducibility of the assay referred to in D51.
- 7.144 The deficiency of the D51 disclosure is further confirmed by Professor Harris, who notes in paragraph 17 of D129 that:
- D51 refers to a sulforhodamine (SRB) assay. Such assays can indeed be used to screen anticancer compounds, although Dr Harrison does not provide many of the usual experimental parameters which I would expect to see reported and which are necessary if the assay is to be reproduced.*
- 7.145 In view of the above, it is clear that the opposition division did not correctly interpret D51. This error led the opposition division to misapply the burden of proof. As discussed above, the opponent filed with the initial Opposition *published, peer-reviewed data* including D37 proving that sofosbuvir is not cytotoxic in many cancer cell lines. This data should certainly have been enough that the burden of proving any alleged cytotoxicity of sofosbuvir lay with the patentee. D51 was the patentee's submission in this regard.

However, the absence of any data in D51, the bare reference to one cell line that is not even disclosed in the patent, and the real concerns about the reproducibility of the experiments referred to therein means that the burden should have been considered to remain with the patentee, unfulfilled.

- 7.146 In view of this, and contrary to the comments from the opposition division, there was no requirement for the opponent to respond to D51 with experimental data because there was no experimental data to respond to. The failure to provide the experimental protocol and results allegedly obtained is a failure of the patentee, who could certainly have done so - not the opponent.
- 7.147 In response to the valid criticism of D51 by the opponent and the evidence of Dr Keegan, the patentee filed D115 on 14 January 2021, well under a month before the date of the oral proceedings on 4 February 2021. For the first time D115 provided alleged data and an alleged protocol used to obtain that data.
- 7.148 D115 indicated for the first time the alleged specific cytotoxicity of the compound sofosbuvir in a specific cell line. D115 accordingly alleges sofosbuvir has an IC_{50} value of $27 \mu M \pm 3 \mu M$ in SKBR3 cells.
- 7.149 First, we note that the opposition division did not seem to give weight to the value in D115. This is expressly confirmed in section 2.5 of the decision where the opposition division states that “*The part of the document of D115 that contains the contested experimental data was not considered relevant for decision making*”. Rather, in section 5.7.1 of the decision, the opposition division stated that in its view, when assessing whether or not sofosbuvir is active as an anticancer agent “*it was irrelevant*” how high its absolute IC_{50} value was. All that mattered for the opposition division is that the compound showed “some kind of” anticancerous activity.
- 7.150 The opposition division’s conclusions in this regard are extraordinary and without justification. No skilled person would consider values such as IC_{50} or CC_{50} values to be “irrelevant” to assessing whether a compound is credibly cytotoxic. Indeed, all of the evidence on file is that such values are highly relevant in deciding whether a compound is cytotoxic, like gemcitabine, or is not cytotoxic, like the compounds discussed herein. After all, that is why such values are quoted in the primary literature (e.g. D37, D40, D107 etc) and it is these values which are relied on to support the *in expressis verbis* conclusions of the authors of those documents.
- 7.151 The issue of the *relevance* of values such as IC_{50} and CC_{50} values was raised by the opposition division for the first time in the decision, and the comments in the decision are manifestly incorrect. For example, we refer to paragraphs 10-13 of Professor Harris’ declaration D129, which explains that determination of such values allows assessment of a test compound. Compounds having high IC_{50} or CC_{50} values are not typically considered active. Professor Harris refers to D130 in this regard, and confirms that:

"I would generally consider any compound with an activity of less than 10 μ M in the relevant assay (e.g. having an IC_{50} or CC_{50} value of higher than 10 μ M) to be of no interest at all."

7.152 For this reason, Professor Harris confirms in paragraph 21 of D129 that

"in my role on grant-giving committees with Cancer Research UK we have typically withdrawn support for research programmes testing compounds which can only attain activities of at best about 10 μ M against their targets."

7.153 The opposition division was wrong to ignore the absolute value allegedly obtained by Dr Harrison in D115. Properly considered, that value confirms that sofosbuvir does **not** have meaningful anticancer activity. This point is confirmed by Professor Harris, who states in paragraphs 23-24 of D129:

It is therefore my view that D51 does not indicate that the compound "sofosbuvir" has any meaningful anticancer activity even in the tested cell line (SKBR3 breast cancer cells), let alone in any other cancer types.

My view is unchanged by Dr Harrison's declaration D115. I see that Dr Harrison reports an IC_{50} of $27 \mu\text{M} \pm 3 \mu\text{M}$. As explained above, in an assay like the SRB assay referred to in D51 and D115 this is not a value associated with meaningful cytotoxicity. If I were testing a panel of compounds for activity in SKBR3 cells in an SRB assay and obtained an IC_{50} of $27 \mu\text{M} \pm 3 \mu\text{M}$ I would disregard that compound as being inactive against such cells.

7.154 Second, the decision of the patentee to present the alleged experimental data merely days before the oral proceedings meant that there was clearly insufficient time for the opponent to conduct any verification of the data alleged in D115 prior to the hearing. However, the opponent now submits D135, in direct response to the data in D115. D135 not only calls into question the IC_{50} value reported in D115, but moreover confirms that both the compound sofosbuvir and other compounds having 2'-Me/2'-F substitution are not cytotoxic in a panel of multiple breast cancer cell lines.

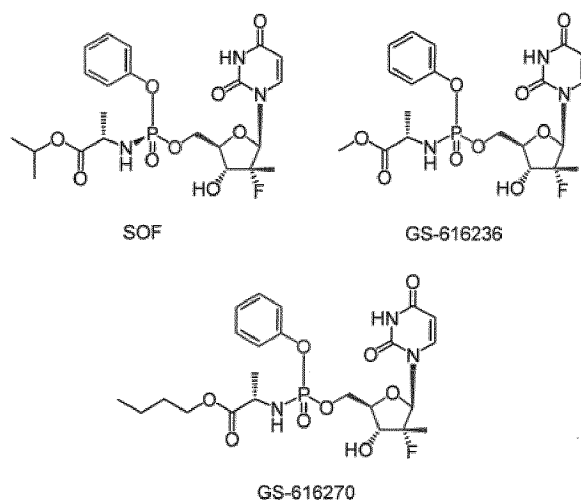
D135 - Experimental evidence that compounds having 2'-Me/2'-F substitution are not active against breast cancer cells

7.155 In direct response to D115, filed shortly before the oral proceedings, the opponent has conducted experiments to assess the alleged cytotoxicity of compounds having 2'-Me/2'-F substitution in breast cancer cell lines. The results of these experiments together with the methodology used are submitted herewith as D135.

7.156 D135 presents cytotoxicity data for three compounds having 2'-Me/2'-F substitution, referred to as sofosbuvir (SOF, GS-7977), GS-616236 and GS-616270. The structure of these compounds is shown in Figure 1 of D135,

reproduced below. As can be seen from Figure 1 of D135 the compounds differ only at the R position (with respect to the notation of claim 1 of the patent). GS-616236 has a methyl group at the R position. Sofosbuvir has an iso-propyl group at the R position. GS-616270 has an n-butyl group at the R position. GS-616236 and GS-616270 are thus analogs of sofosbuvir and fall within the scope of the claims of the opposed patent.

Figure 1. Chemical Structures of SOF and Two Analogs Used in the Study



- 7.157 A structurally unrelated compound, staurosporine, was used as the positive control. Staurosporine is routinely used as a positive control in cytotoxicity assays.
- 7.158 D135 provides cytotoxicity data in three breast cancer cell lines: MDA-MB-231 (the same cell line as used in the patent); MDA-MB-468 (a common breast cancer cell line used in cytotoxicity studies); and SKBR3 (as used in D115). The results for the three compounds in the three tested cell lines are shown in Table 1 of D135, reproduced below:

Table 1. Cytotoxicity of SOF and Analogs in Three Breast Cancer Cells after 4-day Treatment

Compounds	4-day CC ₅₀ (μM) ^a		
	MDA-MB-231	MDA-MB-468	SKBR3
Sofosbuvir (GS-007977)	>100	>100	64 ± 9
GS-616236 (PSI-7672)	>100	>100	>100
GS-616270 (PSI-7838)	>100	>100	60 ± 8
Staurosporine	2.8 ± 1.1 × 10 ⁻³	8.8 ± 2.4 × 10 ⁻³	17 ± 4 × 10 ⁻³

^a The CC₅₀ values were calculated as average ± STD of three or more independent measurements.

- 7.159 D135 confirms that none of the tested compounds, including sofosbuvir, are at all cytotoxic ($CC_{50} > 100 \mu M$) in the breast cancer cell line MDA-MB-231, which is the only breast cancer cell line tested in the patent.
- 7.160 D135 further confirms that none of the tested compounds, including sofosbuvir, are at all cytotoxic ($CC_{50} > 100 \mu M$) in the breast cancer cell line MDA-MB-468.
- 7.161 D135 further confirms that none of the tested compounds are meaningfully cytotoxic in the breast cancer cell line SKBR3, as allegedly tested by Dr Harrison. The compound GS-616236 has $CC_{50} > 100 \mu M$ confirming that it is completely non-cytotoxic. The compounds sofosbuvir and GS-616270 have CC_{50} values of 60-64 μM (which is in line with the CC_{50} value recorded for Huh7 cells in D37). As explained by Professor Harris in paragraph 28 of D129, such a high CC_{50} value is indicative of inactivity in a cytotoxicity assay. Furthermore, these CC_{50} values lie outside even the upper limit of the range of values that is alleged by Dr Harrison to be associated with anticancer activity. As noted above, we do not agree that this range is indicative of useful anti-cancer activity, but even if that were the case (which it is not) then this proves that neither the compound sofosbuvir nor its analogs GS-616236 or GS-616270 have cytotoxic activity in SKBR3 breast cancer, nor in the other tested breast cancer cell lines.
- 7.162 By contrast with the data for the sofosbuvir, GS-616236 and GS-616270, the positive control, staurosporine is confirmed to be cytotoxic in all three tested cell lines, with nanomolar CC_{50} values - many orders of magnitude lower than determined for the test compounds.
- 7.163 D135 thus summarises in section 5 the results in Table 1 as follows:
- Sofosbuvir and two analogs GS-616236 and GS-616270 showed no significant toxicity in MDA-MB-231 cells and MDA-MB-468 cells at the highest concentration tested (100 μM). For the SKBR3 cells, SOF and analog GS-616270 showed CC_{50} values of $64 \pm 9 \mu M$ and $60 \pm 8 \mu M$, respectively, while analog GS-616236 showed no significant cytotoxicity at the highest concentration tested (100 μM).*
- 7.164 D135 thus directly contradicts the alleged evidence of D115. It confirms that the compound sofosbuvir is not cytotoxic in a panel of breast cancer cell lines. It further confirms that other structurally-related compounds having 2'-Me/2'-F substitution and falling within the scope of the claims of the patent are not cytotoxic in a panel of breast cancer cell lines.
- 7.165 It is for the patentee, not the opponent, to comment on the reason as to why in D51/D115 the patentee chose to allegedly assess the compound sofosbuvir in SKBR3 cells specifically rather than, for example, the MDA-MB-231 cell line that was used in the experiments reported on in the patent. The opponent can only speculate that the patentee chose not to do so to avoid the inevitable

conclusion that sofosbuvir is completely devoid of cytotoxic activity in that cell line, as confirmed by D135.

Summary regarding lack of cytotoxicity of 2'-Me/2'-F compounds

- 7.166 In summary, it is clear that the opposition division erred in concluding that compounds having a 2'-Me/2'-F substitution were cytotoxic:
- D37 confirms that sofosbuvir is **not cytotoxic** in prostate cancer (PC-3) cells (the same cell line tested in the patent), in liver cancer HepG2 cells, and (when read correctly) in liver cancer Huh7 cells.
 - D107 confirms that sofosbuvir is not cytotoxic in CEM (leukemia) cells and in Huh-7 (liver) cells.
 - D124 confirms that the compounds numbered 12, 14 and 47 (all having 2'-Me/2'-F substitution) were found to “show no cytotoxicity at up to 100 µM” in Huh-7 or HepG2, the pancreatic cancer cell line BxPC3, or CEM. When sofosbuvir and its diastereomer were tested individually, both compounds were “essentially devoid of cytotoxicity” at concentrations up to 100 µM in these cell lines.
 - The data reported in D124 is confirmed in D132, D133 and D134.
 - The only alleged “evidence” of *any* cytotoxicity for any 2'-Me/2'-F compound is in D51/D115. However, as explained above and confirmed by Professor Harris in D129, not only does D51 fail to provide any evidence *at all*, but when moreover read by a skilled person actually implies that the compound sofosbuvir is not meaningfully cytotoxic in SKBR3 cells. D115 reports an alleged cytotoxicity which is confirmed by Professor Harris not to be associated with meaningful anticancer activity. The data in D115 is also inconsistent with the data submitted herewith in D135.
 - D135 confirms that compounds having 2'-Me/2'-F substitution are not cytotoxic against breast cancer cell lines, and in particular are not active against the only breast cancer cell line mentioned in the patent (as well as being devoid of activity against the breast cancer cell line allegedly tested in D51/D115).
- 7.167 Accordingly, for at least the reasons set out above, therefore, the opposition division was mistaken in concluding that compounds having a 2'-Me/2'-F substitution could be cytotoxic against cancer cell lines. The overwhelming preponderance of evidence is that they are not. This applies in cells deriving from all tested cancer types: prostate, liver, leukemia, pancreas, and breast. This error of reasoning applied to the claims of the patent as granted as well as those of ARs 1-12. It was similarly perpetuated when the opposition division considered the claims of AR13 and contributed to the incorrect finding in respect of that AR.

3.3 Compounds having 2'-Br/2'-F substitution are not cytotoxic

- 7.168 Only at 17:30 on the day of the oral proceedings was AR13 filed by the patentee. AR13 focusses on compounds having 2'-F/2'-F, 2'-Me/2'-F and 2'-Br/2'-F substitution.
- 7.169 In section 9.5 of the decision, the opposition division sets out its reasoning for concluding that the claims of AR13 defined compounds that are associated with anticancer activity. The opposition division's errors as regards compounds having 2'-Me/2'-F substitution are discussed above. However, further errors of reasoning were also made in reaching this conclusion.
- 7.170 A first error made by the opposition division was to apply the incorrect test when assessing the alleged activity of compounds having 2'-Br/2'-F substitution. In section 9.5 of the decision, the opposition division states that *"OD could not follow O in the view that there exist serious doubts, substantiated by verifiable facts, of claim 1 of AR-13 NOT solving the underlying problem over the whole claimed scope"*. This is not the correct test to be applied in considering inventive step.
- 7.171 The "serious doubts substantiated by verifiable facts" test is that which should be applied when considering issues of sufficiency (see the EPO GL at F-III-1 and CLBA at II-C-9).
- 7.172 In considering inventive step, it is of course the case that a finding of lack of inventive step *may* be justified in view of, for example, establishment of "serious doubts, substantiated by verifiable facts" that the claimed solution actually solves the objective technical problem. However, it is not *necessary* in law to meet this hurdle.
- 7.173 Whilst we submit that in the present case this test is anyway amply exceeded by the evidence filed by the opponent, the test that the opposition division should have applied is simply whether or not, on the balance of probabilities, it is credible that the claimed compounds have the activity alleged by the patentee (see case law discussion above). Had the opposition division applied this correct test, it should have found that it is *not* credible that this activity is present for compounds within the scope of AR13.
- 7.174 The decision states that *"OD could not follow O in the view that an objection of lack of anti-cancerous activity is credible simply because "Br" is a halogen homologue to "Cl".... as "Br" is also a halogen homologue to "F" and the patent-in-suit has without doubt demonstrated "2',2'-difluoro variant [sic] to have anti-cancerous activity"*.
- 7.175 The comments of the opposition division are scientifically fundamentally flawed.

- 7.176 It is of course basic general knowledge that F, Cl and Br are all halogens: they are found in group VIIa (also referred to as group 17) of the periodic table. To assist the Board, a copy of the periodic table is filed herewith as D125.
- 7.177 At the highest level of generality, elements within a group of the periodic table can have broadly similar properties due to the electronic configuration of their outermost “shell” of electrons. However, any skilled person (indeed, any high-school student) would be well aware that those properties are not static within a group: rather, elements within a group have different properties that vary as trends within the group.
- 7.178 Thus, for example, fluorine is in the top row of the halogen group. It is one of the smallest atoms in the periodic table. It is the most electronegative of all elements and therefore exerts a very strong inductive effect, but with a small impact on steric hindrance (see D105, paragraph 5). As any high-school student (let alone a skilled person) would be well aware, chlorine atoms are significantly larger due to their additional “shell” of electrons (e.g. see D125). Fluorine forms strong bonds with carbon. Accordingly, fluorinated sugars are very stable and typically cannot be used in, for example, substitution or elimination reactions. By contrast, the ease of displacing the halogen decreases in the order $I > Br > Cl$ (as one goes up the halogen group from the 4th row to the 1st row). Iodo-, bromo- and chloro- sugar derivatives are thus widely used in substitution and elimination reactions. (See D103, page 56, section 3.2.1.).
- 7.179 In section 9.5 of the decision, the opposition division considered it to be “equally likely that “2’-Br-2’-F” variants had anti-cancerous activity as such variants having no anti-cancerous activity”. This is nonsensical. Any skilled person would be well aware that trends in the periodic table do not oscillate in this manner, unless they have specific evidence to show the contrary.
- 7.180 To the extent that the biological activity or otherwise of a given compound is determined by the identity of the halogen X in a C-X bond, the only scientifically credible conclusion is that a compound in which $X = Br$ is more similar to a compound in which $X = Cl$ than one in which $X = F$.
- 7.181 The opposition division correctly concluded that compounds within the scope of the claims of the patent as granted and having a 2’-Cl/2’-F substitution are not active, based on D107. In view of this it is not credible that compounds having a 2’-Br/2’-F substitution would have activity. It was a fundamental error in scientific reasoning for the opposition division to reach its conclusion in respect of these compounds.
- 7.182 The opponent considers that D107, when read in a scientifically meaningful manner, more than discharges the burden on the opponent to show that it is *not credible* that compounds having 2’-Br/2’-F substitution are not cytotoxic. However, in response to the opposition division’s incorrect assessment of D107

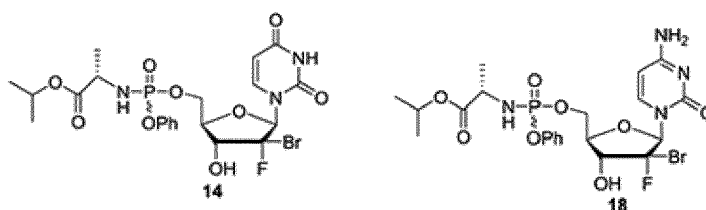
and the explicit reliance placed by the opposition division on statements made *in expressis verbis*, we refer here to D126. D126 confirms the conclusion that would be reached by any skilled person based on D107, that compounds having 2'-Br/2'-F substitution are not credibly cytotoxic.

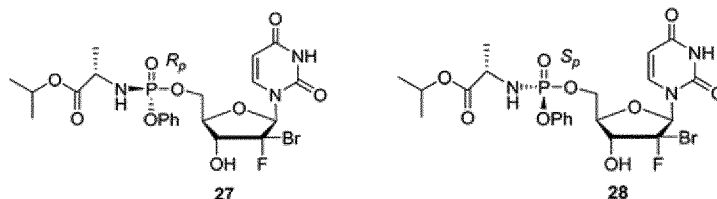
D126 - Mengshetti et al, J. Med. Chem. 2010

- 7.183 D126 describes the discovery and development of 2'- α -fluoro,2'- β -bromo-ribonucleosides and their phosphoramidate prodrugs.
- 7.184 D126 describes that, based on the author's previous work with β -D-2'-deoxy-2'- β -chloro-2'- α -fluoro uridine prodrugs (D107 in these proceedings), the synthesis and characterisation of β -D-2'-deoxy-2'- β -bromo-2'- α -fluoro nucleosides and their phosphoramidate prodrugs was conducted.
- 7.185 Relevant compounds are shown in Table 1 of D126, reproduced below:

compound	anti-HCV EC ₅₀ μ M (SD) ^a		cytotoxicity, CC ₅₀ μ M (SD) ^a			
	EC ₅₀	EC ₉₀	Huh-7	PBM	CEM	Vero
12	>10	>10	>10	>100	>100	>100
14	0.5 (0.05)	0.9 (0.01)	>10	>100	>100	>100
27	0.7 (0.1)	2.4 (0.1)	>10	>100	>100	>100
28	0.16 (0.002)	0.28 (0.003)	>10	>100	>100	>100
17	4.0 (1.6)	9.5 (0.3)	>10	>100	>100	>100
18	0.6 (0.1)	1.8 (0.2)	>10	>100	>100	>100
21	>10	>10	>10	>100	>100	>100
22	7.1 (0.2)	>10	>10	>100	>100	>100
25	>10	>10	>10	>100	>100	>100
26	0.6 (0.1)	1.8 (0.3)	>10	>100	>100	>100
2'-C-Me-C	2.8 (0.2)	9.9 (0.5)	>100	60 (20)	22 (15)	>100
SOF	0.5 (0.1)	0.9 (0.03)	>100	> 100	> 100	>100

- 7.186 We highlight compounds 14, 27 and 28 (depicted in Schemes 2 and 5, respectively), which along with other compounds in this table (e.g. compound 18) fall within the scope of the claims of the patent as granted and the claims of ARs 1-13:





7.187 The non-toxicity of these compounds in cancer cell lines can be seen in Table 1 of D126. However, in view of the opposition division's reliance on *in expressis verbis* statements in the prior art, we highlight that D126 also includes numerous statements regarding the non-toxicity of the compounds described therein in cancer cell lines such as Huh-7, CEM and HepG2. A selection follows:

"Herein, we report, the discovery of 8-D-2'-Br,2'-F-uridine phosphoramidate diastereomers 27 and 28, as nontoxic pangenotypic anti-HCV agents... Both are nontoxic by a variety of measures and display good stability in human blood and favorable metabolism in human intestinal microsomes and liver microsomes"

(D126, Abstract)

"Parent nucleosides 12, 17, 21, and 25 and their corresponding phosphoramidate prodrugs 14, 18, 22, and 26 were evaluated for inhibition of HCV genotype 1b RNA replication in Huh-7 cells using a subgenomic HCV replicon system.²² Cytotoxicity in Huh-7 cells was determined simultaneously by extraction and amplification of both HCV RNA and cellular ribosomal RNA.²³ In addition, cytotoxicity was determined in primary human peripheral blood mononuclear (PBM) cells, human lymphoblastoid cells (CEM), and African Green monkey Vero cells.^{24,25} The results are summarized in Table 1. [...] In addition, none of the compounds tested, except for reference compound 2'-C-Me-cytidine (NM-107), displayed any cytotoxicity versus our panel of cell lines.

...These properties, unique to uridine analogs, can effectively reduce systemic exposure to uridine analog phosphates and potential unwanted off-target effects. With these considerations combined with the superior potency and lack of cellular toxicity in our panel of cell lines, the uridine phosphoramidate, 14, was chosen for further study"

(D126, page 5, following heading "Antiviral Profile")

"The single diastereomers 27 and 28 were first evaluated for inhibition of HCV genotype 1b RNA replication in Huh-7 cells using a subgenomic HCV replicon system. As noted with SOF, the two diastereomers have different potencies, but again no cytotoxicity was seen in any of the four cell lines tested (Table 1)."

(D126, page 6, second paragraph)

"HepG2 cells are highly proliferative immortalized cells that derive a significant proportion of their energy from glycolysis rather than

mitochondrial oxidative phosphorylation. [...] Therefore, 14 was also tested in HepG2 cells for 3 days in glucose- and galactose-supplemented media up to 100 μ M, and no toxicity signal was observed in either media. Extending this assay to 14 days for 27 and 28 showed no significant difference between using glucose- or galactose-supplemented assay media, and again both 27 and 28 were not toxic up to 100 μ M

(D126, page 8, second paragraph)

- 7.188 The opposition division had no need for these *in expressis verbis* statements in order to conclude that compounds having a 2'-Br/2'-F substitution are not credibly cytotoxic in the cancer cell lines tested in D107, such as Huh7, HepG2, and CEM, as this is the only scientifically credible conclusion from D107. However, in view of the mistaken reasoning of the opposition division set out in section 9.5 of the decision and the comments of the opposition division regarding the supremacy (in its view) of literature conclusions presented *in expressis verbis*, D126 is filed to confirm the error in reasoning of the opposition division.
- 7.189 For completeness, we also note that D126 confirms the conclusions of D37, D107 and D124 that the compound sofosbuvir is not cytotoxic. Accordingly, D126 reports that sofosbuvir has a CC₅₀ value of >100 μ M in each of the tested cell lines, including Huh-7 cells.

4. The claim embraces compounds having phosphoramidate groups shown to be inactive

- 7.190 In addition to the errors made by the opposition division set out above, the opposition division also was mistaken to conclude that the definition of the phosphoramidate moiety of the claimed compounds did not embrace inactive compounds.
- 7.191 In the third paragraph of section 5.7 of the decision, the opposition division states that it considered "D40 proof for the problem being solved over the breadth of variable "R"." However, this conclusion is flawed. The opposition division should have concluded that variation of the variable "R" has a profound impact on the activity of the claimed compounds.
- 7.192 The patent itself accepts that the changes in the identity of the variable R has profound effects on the biological activity of the relevant compound. We refer by way of example to the following passages:

"We observed the effects of variations in the ester... regions of the phosphoramidate [...]. This work led to the optimal description of phenyl methoxyalaninyl phosphoramidate as the prototype promoiety" (paragraphs [0007]-[0008])

"Surprisingly it has now been found that other derivatives of oxyamino acid-phosphormaidate nucleoside analogs are significantly more potent in the

treatment of cancer than the phenyl methoxyalaninyl phosphoramidate” (paragraph [0011])

“Surprisingly, modifying the ester moiety in compound (7) has been found to show a marked increase in potency with respect to cancer cell lines. A compound is the benzyl ester (8). It has surprisingly been found that the benzyl ester (8) is very significantly more potent against several cancer cell lines than the methyl ester (7).” (paragraph 50)

- 7.193 The profound effect of varying the group at the R position is also confirmed in D40. D40 would be understood by those skilled in the art as showing that at least some compounds having a pentose moiety di-substituted to be 2'-fluoro down / 2'-fluoro up are not active against cancer cells.
- 7.194 D40 describes a study into phosphoramidated versions of gemcitabine.
- 7.195 D40 notes in column 2 of page 1532 (lines 4 to 8) that *“the potency of the compounds varies with the individual components (aryl, ester, and amino acid) of the phosphoramidate moiety, and therefore we examined a panel of gemcitabine ProTides”*.
- 7.196 Table 1 on page 1534 of D40 sets out the IC₅₀ (μM) of selected compounds against four cancer lines: L1210 (leukaemia), CEM (human T lymphocyte), MP-2 (pancreatic) and BxPC-3 (gemcitabine-resistant pancreatic). The IC₅₀ value is the concentration of the compound required to inhibit cellular proliferation by 50%.
- 7.197 An extract from Table 1 of D40 is given below:

entry	amino acid	ester	aryl	IC ₅₀ (μM) ^a			
				L1210	CEM	MP-2	BxPC-3
6a	L-Ala	iPrO	Ph	>5	>5	>5	>5
6b	L-Ala	Pentyl	Ph	0.024 ± 0.009	0.08 ± 0.011	N.D.	N.D.
6c	L-Ala	Hexyl	Ph	0.016 ± 0.005	0.081 ± 0.008	N.D.	N.D.
6d	L-Ala	CH ₂ tBu	Ph	0.39 ± 0.04	0.44 ± 0.04	1.41 ± 0.57	0.36 ± 0.13
6e	L-Ala	cHexyl	Ph	0.6 ± 0.06	0.42 ± 0.17	N.D.	N.D.
6f	L-Ala	Bn	Ph	0.035 ± 0.02	0.1 ± 0.03	0.44 ± 0.06	0.15 ± 0.04
dFdC (1)				0.013 ± 0.02	0.086 ± 0.003	1.04 ± 0.71	0.67 ± 0.34

- 7.198 The compound 6f is CPF-31. The only difference between compound 6a and compound 6f lies in the identity of the ester moiety. Compound 6a has an isopropyl group at this position. Compound 6f/CPF-31 has a benzyl group.
- 7.199 The compound dFdC is gemcitabine. D40 confirms at page 1533, right hand column that *“the gemcitabine IC₅₀ reference value [was] used as a positive control”*.

- 7.200 In stark contrast to the data for compounds 6b to 6f (and 6g-6l and gemcitabine) which are presented to three decimal places of accuracy, the data for compound 6a simply reads ">5 μM ".
- 7.201 It is immediately apparent that an IC_{50} of ">5 μM " is *far* higher than that of any of the other tested compounds. However, as noted by Dr Keegan in D106, the situation is in fact more complex. Thus, in paragraph 10 of D106, Dr Keegan explained:
- "It is impossible to know from D40 what the activity of compound 6a is. As I understand it, even a compound with undetectable cytotoxic activity would have an activity of ">5 μM ". It is therefore my understanding that, in the context of D40, the term ">5 μM " is an imprecise value intended to define a negative control against which activity of the other compounds could be compared. In my view, a skilled reader of D40, with no other information to guide them, would conclude that the authors of D40 considered compound 6a to be inactive."*
- 7.202 It was a profound error of the Opposition Division to ignore this view from an expert in the field. However, it is clear from section 5.7 of the decision that the opposition division did just this. In fact, the opposition division states in the decision that D40 is taken to "reflect a high threshold level for activity".
- 7.203 It is hard to see what the opposition division means by this statement. It seems to imply that an IC_{50} value of *more than* 5 μM is a "high threshold for activity", but that is nonsensical: as Dr Keegan explains, even a compound with *undetectable* cytotoxic activity would have an activity of ">5 μM ".
- 7.204 The opposition division also is mistaken to state in the decision that "D40 describes the tested compounds to be already a selection of more potent ones".
- 7.205 The opposition division has pointed to the sentence bridging the left and right columns of page 1533, but that sentence states only that "*extensive structure/activity relationship (SAR) studies and prior work suggested that the L-alanine phosphoramidates were the most potent gemcitabine ProTides*". Correspondingly, almost all of the compounds in Table 1 of D40 are based on alanine at the amino acid position (i.e. they have methyl - the side chain of alanine - and hydrogen at the R' and R'' positions). However, there is no suggestion that the isopropyl ester was considered *up front* by the authors of D40 to be a potent compound or that the compounds were *selected* from those known to be active. Furthermore, even if it had been so considered for some reason, the evidence of D40 is that compound 6a is not "potent".
- 7.206 Professor Harris has also reviewed D40, and in paragraph 29 of his declaration D129 he confirms that the data in Table 1 of D40 shows that the compound 6a is completely inactive in at least the L1210 cell line. He states:

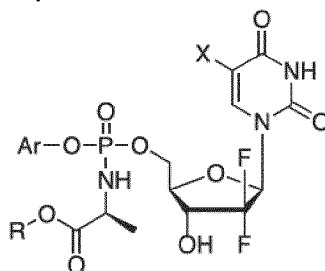
“I have been asked to comment on the paper by Slusarczyk et al, D40. It is striking to me that the compound 6a has an IC₅₀ value of more than 5 µM in all of the cell lines tested, even the L1210 cell line. L1210 is a murine leukaemia cell that has been widely used since the 1960s as a model leukaemia cell line and is notoriously sensitive to compounds such as antimetabolites. For that reason, anticancer compounds such as gemcitabine have extremely low - typically nanomolar - IC₅₀ values against L1210 proliferation - D40 reports a value of about 13 nM for gemcitabine. If a compound has an IC₅₀ value of more than 5 µM in L1210 I would generally consider it to be completely inactive”

- 7.207 The error of the opposition division is still further highlighted by the statement in section 5.7 of the decision that “OD found further evidence of a variety of esters showing activity in anti-cancerous cell lines in D39”.
- 7.208 D39 is a declaration filed by the patentee during the prosecution and reissuance examination of the corresponding US patent, and was filed to support the patentee’s accompanying arguments and amendments set out in D38.
- 7.209 On page 2 of D38 it can be seen that the patentee limited the claims not only to specify that the pentose moiety is di-fluorinated, but also to specify that the R group in the phosphoramidate portion of the molecule (i.e. the ester moiety) is selected from carbocyclic alkyl, aryl, and alkylaryl. The patentee thus excluded the option for R to be isopropyl, as in compound 6a of D40, or indeed any other linear alkyl group such as methyl or n-butyl. D39 was filed to support this amendment, and reproduces part *but not all* of Table 1 from D40. Data relating to compound 6a is notable by its absence from D39.
- 7.210 In the passage spanning pages 13 and 14 of D38, the patentee stated to the US PTO that
- “The skilled person could not predict that any given compound would be a good substrate for esterases and that the acid resulting from ester cleavage would be a good substrate for phosphoramidase-type enzymes and that the compound and its intermediates would be poor substrates for the various enzymes that could impede intracellular formation of the triphosphate active metabolite. In order to show the increased intracellular levels of the active metabolite that has been observed, the compound must be all of these things.”*
- 7.211 Clearly, compounds having an isopropyl group at the R position in the ester portion of the phosphoramidate do *not* meet all these requirements. The R group in such compounds is not within the definition set by the US claims that require the ester to be a carbocyclic alkyl, aryl, or alkylaryl group. The failure shown by compounds outside this definition is confirmed by the negative results set forth in Table 1 of D40.

- 7.212 Accordingly, the opposition division should have concluded that compounds having an iso-propyl group at position R are not credibly associated with cytotoxicity. The failure of the opposition division to conclude this despite the evidence in D40 is a further error of reasoning in the decision.
- 7.213 The opponent considers that D38, D39, and D40, together with the corresponding explanation in D106, more than discharge the burden on the opponent to show that compounds in which the R group is isopropyl are not cytotoxic. However, as confirmation of this point, we refer to D124, D127, D128 and D135. These documents confirm that compounds having short acyclic alkyl groups at the R position are not cytotoxic. Accordingly, they confirm the opponent's arguments regarding D38.
- 7.214 D124 is discussed above. We note that compounds 12 and 14, each expressly confirmed in that document as being "*found to show no cytotoxicity at up to 100 μ M*" in the tested cancer cell lines, have short alkyl groups at the R position (compound 12 has a methyl group; compound 14 has an iso-propyl group). D124 thus confirms the lack of cytotoxicity of compounds having a short alkyl group at the R position.

D127 - Quintiliani et al, Bioorg. Med. Chem. 2011

- 7.215 D127 is filed herewith and describes the design, synthesis and evaluation of 2'-deoxy-2',2'-difluoro-5-halouridine phosphoramidates.
- 7.216 Relevant compounds are depicted in Scheme 2 of D127:



- 16 X= I, Ar= Ph, R= Bn, 3%
17 X= I, Ar= Ph, R= CH₃, 5%
18 X= I, Ar= Naph, R= Bn, 6%
19 X= I, Ar= Naph, R= CH₃, 1%
20 X= Br, Ar= Ph, R= Bn, 7%
21 X= Cl, Ar= Ph, R= Bn, 4%

- 7.217 All of these compounds fall within the scope of the claims of the patent as granted and as upheld in AR13. Notably, compounds 17 and 19 each have a short acyclic alkyl group (methyl in this case) at the R position.
- 7.218 The cytotoxicity of these compounds was assessed in cancer cell lines: leukaemia (L1210), mammary (breast) carcinoma (FM3A), lymphoma (CEM) and

cervix carcinoma (HeLa). IC₅₀ data (i.e. the compound concentration required to inhibit cell proliferation by 50%) is shown in Table 4 on page 4341 of D127.

7.219 Discussing that data, the authors of D127 state on page 4340 that:

*“The 2',2'-difluoro 5-substituted uridine nucleoside derivatives 8-11 and the corresponding ProTides 16-21 have also been evaluated for their cytostatic activity against a selection of tumor cell lines (L1210, FM3A, CEM and HeLa) **and found to be virtually non-toxic** with the exception of 8 that proved cytostatic in the middle micromolar range against several cell lines (Table 4).”*

7.220 Accordingly, the authors of D127 conclude (under the heading “Conclusions” on page 4340) that:

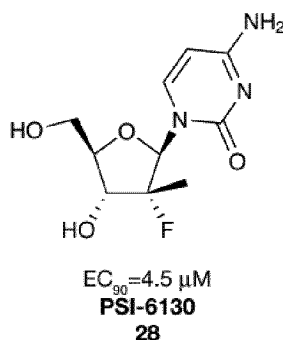
*“A series of 2'-deoxy-2',2'-difluoro-5-halouridines and their corresponding phosphoramidates were synthesized and investigated for antiviral activity and for cytotoxicity. 2'-Deoxy-2',2'-difluoro-5-iodo- and 5-bromo-uridines showed significant activity against feline herpes virus, while none of the ProTides were endowed with antiviral activity. **No appreciable antiproliferative activity against any of the cancer cell lines evaluated was found.**”*

7.221 D127 thus confirms - and states *in expressis verbis* - that compounds having a short acyclic alkyl group at the R position are not active in cancer cell lines including breast cancer.

D128 - Sofia, Antiviral Chemistry and Chemotherapy 2011

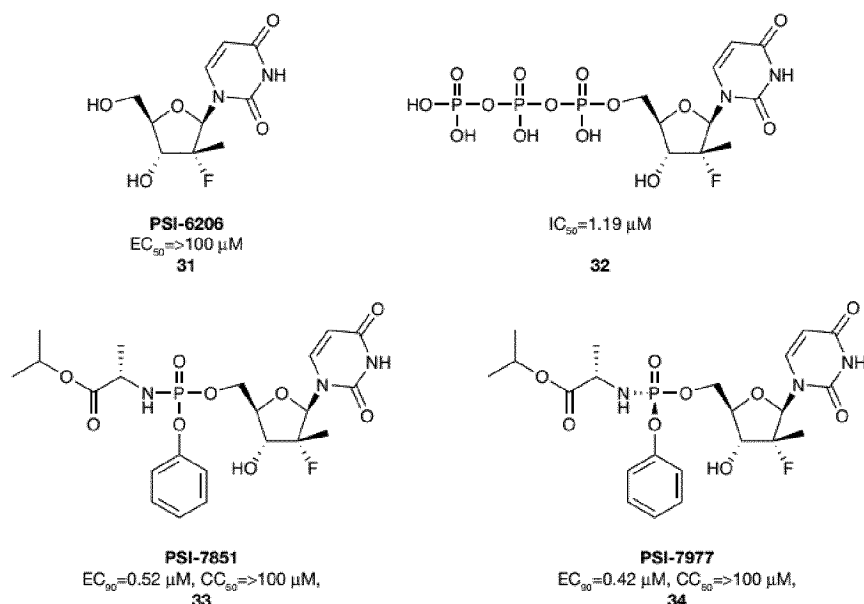
7.222 D128, filed herewith, is a review discussing nucleotide prodrugs for HCV therapy. D128 discusses compounds having a 2'-Me/2'-F substitution in the section headed “2'- α -Fluoro-2'- β -C-methyl nucleotide phosphoramidate prodrugs” beginning on page 33. D128 discusses in this context the development of the drug PSI-7977 (sofosbuvir).

7.223 D128 notes that the first disclosure of a 2'- α -Fluoro-2'- β -C-methylcytidine nucleoside was made with the publication of PSI-6130 (compound 28, depicted below).



- 7.224 D128 describes how metabolism studies on PSI-6130 showed that the compound was converted to the uridine nucleoside PSI-6206 (compound 31) in vivo. Whilst this uridine nucleoside was shown not to be active as an inhibitor of HCV replication, subsequent studies indicated that the triphosphate of PSI-6206 (compound 32) was a potent inhibitor of the HCV NS5B polymerase with a long intracellular half-life (D128, passage bridging page 35-36).
- 7.225 D128 further describes how in an attempt to take advantage of the long intracellular half-life of the uridine triphosphate (32) with the hope of potentially developing a once-daily drug, a prodrug of the uridine 5'-monophosphate was pursued. In this regard:
- “Extensive SAR around the phosphoramidate moiety showed that the preferred substitution to achieve submicromolar whole cell HCV replicon potency without cellular toxicity required a small branched alkyl ester at the terminal carboxylate ester moiety, a small alkyl group at the alpha position of the amino acid substituent and a simple phenoxy or halogenated phenoxy phosphate ester group.”*
- 7.226 This research lead to identification of PSI-7851 as a lead compound. D128 describes this at the passage bridging pages 36-37, and states that:
- “The lead compound PSI-7851 (33) was subsequently shown to be devoid of mitochondrial, bone marrow and general cellular toxicities.”*
- 7.227 Later research focussed on one of the two diastereomers of PSI-7851, namely PSI-7977 (compound 34). The structures of compounds 31-34 are depicted in Figure 12 of D128, which also confirms the lack of cytotoxicity of PSI-7851 and PSI-7977 (see figure legend):

Figure 12. 2'-α-F-2'-β-C-Methyluridine nucleoside and nucleotide phosphoramidate prodrug inhibitors of HCV replication



CC_{50} , 50% cytotoxic concentration; EC_{50} , 50% effective concentration; EC_{90} , 90% effective concentration; IC_{50} , 50% inhibitory concentration.

- 7.228 D128 thus confirms - and states *in expressis verbis* - that compounds having a short acyclic alkyl group at the R position are not compatible with cellular toxicity.
- 7.229 D124, D127 and D128 thus confirm the findings that the opposition division should have reached in view of D38, D39, D40 and D106. Clearly, the claims of AR13 (as well as those of the patent as granted and those of ARs 1-12) embrace compounds having short, acyclic alkyl groups at the R position that are not cytotoxic.

D135

- 7.230 Finally, we refer to the experimental data in D135 discussed above. Notably, the three compounds tested vary only at the R position. It is clear that variation in this position has an effect on the cytotoxicity of the compounds at issue, with compounds having short acyclic groups (methyl, iso-propyl and n-butyl) at the R position being shown to have no cytotoxic activity. D135 further confirms the relevance of this position as discussed above.

5. Summary of alleged activity

- 7.231 A summary of the position regarding alleged cytotoxicity can thus be made:

1. The only data in the patent for cytotoxicity of compounds within the scope of the claims is for the compounds CPF-31, CPF-40 and CPF-41. Each of these compounds is di-fluoro substituted at the 2' carbon and has an aromatic benzyl ester at the R position. Each of those compounds is less active than the compound CPF-2 in D36 in at least one of breast, colon and prostate cancer.

As such, no improvement compared to CPF-2 can be sustained across the scope of the claims. That is the case whether such an improvement is alleged in an "unspecified" cancer, or in just one of breast, colon or prostate cancer. Regardless of the cancer type implicated, this effect would not be demonstrated for all of CPF-31, 40 and 41, and thus would not be achieved across the scope of the claims.

2. The claims seek to define the compounds using open-ended language which necessarily embraces substituents which would deprive the compounds of activity. It is not credible that any technical effect - let alone that of providing meaningful anticancer activity - is achieved across the scope of the claim.
3. The claims embrace compounds having 2'-Me/2'-F substituents that are shown to be cytotoxically inactive against a wide variety of cancer cell lines, including those cell lines tested in the patent.
4. The claims embrace compounds having 2'-Br/2'-F substituents that are shown to be cytotoxically inactive against cancer cell lines.
5. The claims embrace compounds having small linear alkyl groups at the R position such as methyl and isopropyl which are shown to be cytotoxically inactive against cancer cell lines.
6. The difficulty of providing cytotoxic compounds was recognised by the patentee in D38 and D39 in connection with the corresponding US patent. Accordingly, the claims of that patent were limited to require 2'-F/2'-F (di-fluoro) substitution at the 2' position, and to require *carbocyclic* alkyl, aryl, or alkylaryl groups at the R position, thus excluding the option for short acyclic alkyl groups at this position. However, no such limitation is present in the claims of the patent as granted, or in any of ARs 1-13.

7.232 It is thus not credible that the claimed compounds are associated with meaningful cytotoxicity against cancer across their scope.

Objective Technical Problem

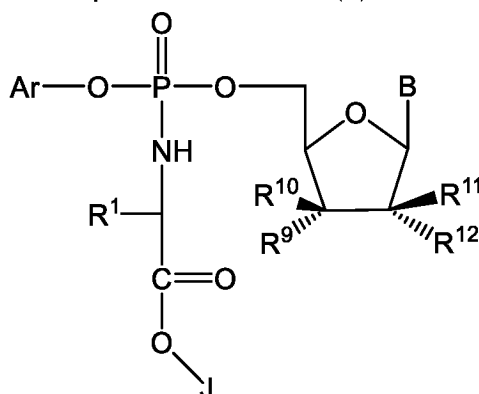
7.233 The closest prior art is D36. Specific reference is made to the compound CPF-2, being the compound of claim 12 of D36.

- 7.234 The compounds of D36 are directed to treatment of cancer, as are the compounds of the patent. The sole distinguishing feature between the claimed compounds (in the patent as granted, ARs 1-12 and AR13) and CPF-2 lies in the specific 2' substitution.
- 7.235 The claimed compounds are not credibly associated with anti-cancer activity across the scope of the claim, for the reasons discussed above. Accordingly, the alleged activity of the compounds cannot be taken into account in formulating the objective technical problem.
- 7.236 The objective technical problem can thus only be defined as the provision of alternative compounds.
- 7.237 Despite this the opposition division considered the objective technical problem for AR13 to be the provision of alternative *anti-cancerous phosphoramidate-nucleosides*. The opposition division was mistaken in reaching this conclusion, because as explained above the claimed compounds are *not* "anti-cancerous". The opposition division should have considered the claims of AR13 as similarly addressing *only* the problem of providing alternative compounds.

Claimed solution is obvious

- 7.238 The opposition division held in section 5.10 of the decision that the mere provision of alternative compounds is not inventive over D36. We agree.
- 7.239 For this reason the opposition division correctly concluded that the claims of the patent as granted and those of ARs 1-12 lacked inventive step. The opposition division should have reached the same conclusion for AR13.
- 7.240 As noted above the only difference between the structure of CPF-2 and the compounds of AR-13 is at the 2' position.
- 7.241 As regards the 2'-down position, the general disclosure of D36 specifies that this group (R₃ in claim 1 of D36; see paragraph 7.44 above) is *selected from the group consisting of Br, Cl, F, I, H, OH, OC(=O)CH₃, -O and -O-R_g, wherein R_g is a hydroxyl protecting group other than acetyl*". (emphasis added)
- 7.242 It is not inventive for the patentee to modify the compound CPF-2 by placing at the 2'-down position one of the other alternatives expressly provided for that group in D36. This is particularly the case when no technical effect is associated with doing so. An alternative way of viewing this is that the patentee has simply made arbitrary selections within the D36 general formula to arrive at the claimed compounds. As no technical effect is associated with those selections their combination cannot be seen as inventive.

- 7.243 As regards the 2'-up position, requiring a substituent selected from F, Br and Me at this position is likewise not inventive. This is particularly the case when no technical effect is associated with doing so. Such substituents are known in the art for phosphoramidated nucleosides.
- 7.244 We refer to D109, which discloses in claim 8 as dependent on claim 2 dependent on claim 1 a compound of Formula (1):



in which

- Ar is an aryl group;
 - J is selected from hydrogen, alkyl, aryl, heterocyclic and polycyclic groups;
 - R⁹ is selected from H, halogen, CN, NH₂, CO-alkyl and alkyl; and R¹⁰, R¹¹ and R¹² are independently selected from H, halogen, CN, NH₂, CO-alkyl and alkyl; and
 - B is a purine or pyrimidine base.
- 7.245 On page 8, lines 30-32, D109 explains that B may comprise a purine or pyrimidine base, such as adenine, thymine, uracil, cytosine or guanine and derivatives thereof.
- 7.246 Preferred combinations of Ar, R¹ and J are provided in Table 1 on page 11 of D109, and include the combination of compound 324, in which Ar = Ph, R¹ = Me and J = Me.
- 7.247 As regards the option for R¹¹ to be “alkyl”, page 5, lines 6-7 of D109 states that *“Where acyclic, the alkyl group is preferably C₁ to C₁₆, more preferably C₁ to C₆, more preferably methyl”*. As regards the option for R¹¹ to be “halogen”, page 6, lines 18-20 states that *“Reference in the present specification to halogen means a fluorine, chlorine, bromine or iodine radical, preferably fluorine or chlorine radical.”*
- 7.248 It is not inventive for the patentee to modify the structure of the D36 compound merely by including an alternative at the 2'-up position that is expressly provided in the art for similar compounds without that modification being associated with a technical advantage disclosed in the patent. As the claimed compounds do not have anticancer activity, as discussed above, the

objective technical problem can only be seen in the provision of alternative compounds. There is no invention in solving this unambitious problem, as correctly found by the opposition division for the claims of the patent as granted and those of ARs 1-12. Accordingly, the opposition division should have found the claims of AR13 to similarly lack inventive step.

No distinguishing feature at the Z position

- 7.249 For completeness, we note that even if the term “alkyl” in connection with the Z position of the compounds claimed in the opposed patent was to be construed as excluding the option for the bromovinyl group of CPF-2 (which we would disagree with), this would still not constitute a further distinguishing feature of the claimed compounds over the disclosure of that document.
- 7.250 The most general definition of the D36 compounds, found in claim 1 of D36, expressly provides that the relevant group (R_1 in the D36 structure) is “*selected from the group consisting of H, alkyl, alkenyl, alkynyl, vinyl, propargyl and substituted derivatives thereof*”. This matches directly onto the definition of group Z in the claims of the patent, which defines Z as being “*selected from the group H, alkyl and halogen*”.
- 7.251 It is not inventive to modify a compound of D36 by exchanging on R_1 group for another expressly provided at that position in the general definition of D36. Viewed another way, there is no invention in selecting that the R_1 position is one of the groups expressly provided at that position in claim 1 of D36. This is particularly the case when no technical effect is associated with this change.
- 7.252 Despite this, the opposition division stated in section 9.5 of the decision that in its view “*D36 teaches [the bromovinyl group] to be relevant since present in all exemplified compounds*”. However, this conclusion is incorrect and is another error made by the opposition division. In fact, compounds are exemplified in D36 which do not have a bromovinyl group at the relevant position. Moreover, such compounds are specifically called out in Table 2 of D36, referred to by the opposition division.
- 7.253 For convenience of the board, Table 2 of D36 is reproduced below:

TABLE 2

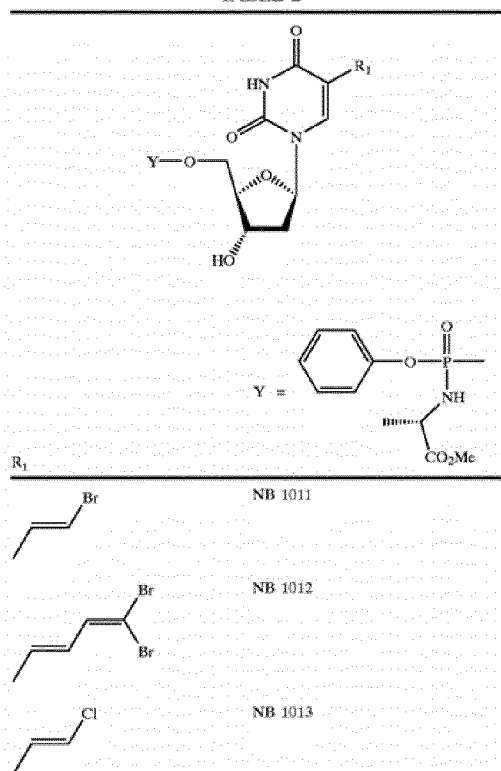
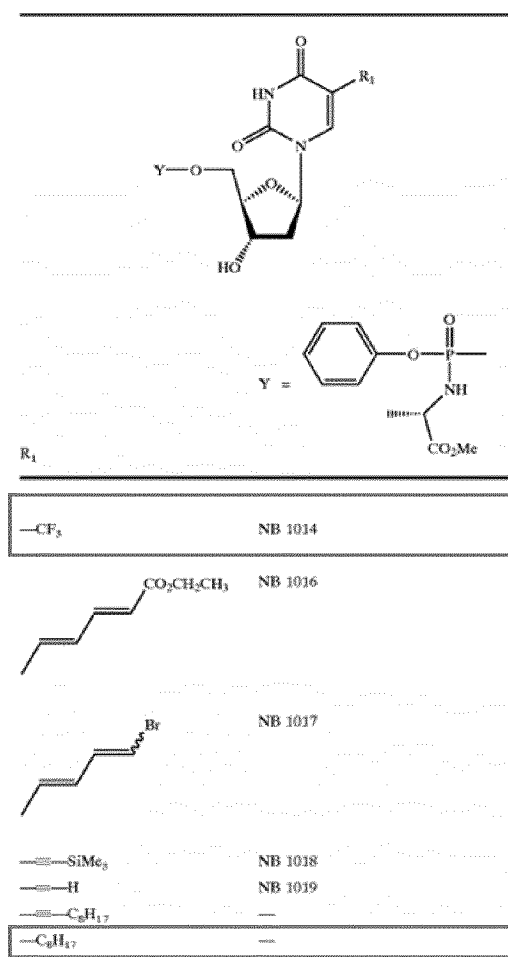


TABLE 2-continued



- 7.254 Table 2 exemplifies numerous compounds having different substituents at the R₁ position. That table includes compounds having alkyl groups which do not comprise a vinyl group. We highlight in particular the compound NB1014 which has a substituted alkane at the R₁ position (-CF₃); and the final compound in the table which has -C₈H₁₇ at the R₁ position (this being an example of the “C_nH_{2n+1} definition of an alkyl group favoured by the opposition division).
- 7.255 The overall disclosure in D36 is thus that the presence of a bromovinyl group at the R₁ position is *not* especially “relevant” as mistakenly concluded by the opposition division.

Summary of opponent's position on inventive step

- 7.256 In summary, the opponent's position on inventive step is as follows:
- 7.257 D36 is the closest prior art. A key compound within D36 is CPF-2.

- 7.258 The compounds claimed in the patent differ from the D36 compounds only at the 2' position on the sugar ring.
- 7.259 The claims of AR13 (as well as the claims of the patent as granted and the claims of ARs 1-12) are not associated with any technical effect across their scope, as many of the compounds embraced therein are not credibly cytotoxic in cancer cells. This is particularly the case for compounds having 2'-Me/2'-F substitution and/or a short acyclic group at the R position.
- 7.260 Accordingly, the objective technical problem addressed by the claims of AR13 is merely the provision of alternative compounds, as for the claims of the patent as granted and the claims of ARs 1-12.
- 7.261 The solution offered by the claims of AR13 (as well as the claims of the patent as granted and the claims of ARs 1-12) is obvious in view of D36 and D109.
- 7.262 The claims of AR13 thus lack inventive step, as do the claims of the patent as granted and those of ARs 1-12.

8 ANNEX A - CASE LAW RELATING TO COMPREHENSIVE SEARCHES

8.1 The opponent considers that the case law of the Boards of Appeal confirms that information resulting from a comprehensive search cannot be relied on as common general knowledge. Three leading decisions in this regard are T206/83, T654/90 and T924/03.

8.2 As noted above, T206/83 is cited in the Case Law of the Boards of Appeal, and also by more than 60 subsequent cases. T206/83 concerned an appeal from an examining division decision to refuse a patent directed to a herbicidal pyridine of a particular formula, on the grounds that compounds within that formula were disclosed in a prior art document, "Dow". There was no teaching in Dow regarding how to make the starting materials (referred to as CCMP and CCCMP) required to make the product at issue. Intermediates involved in the Dow synthesis (CTF and CCTF) were disclosed in other patent documents, but were not referenced in Dow itself. The question before the Board was thus whether or not Dow constituted an enabling disclosure.

8.3 In T206/83 the Board confirmed that the disclosure in Dow was not sufficiently clear and complete to constitute an enabling disclosure, reasoning as follows (see reasons 2 to 11):

"a compound defined by its chemical structure can only be regarded as being disclosed in a particular document if it has been made available to the public in the sense of Art. 54(2) EPC. In the field of chemistry this requirement is, for instance, satisfied if a reproducible method is described in the same document. This need for an enabling disclosure not only applies to documents cited under Art. 54(2) and (3) EPC but is also in conformity with the principle expressed in Art. 83 EPC for patent applications which must, accordingly, "disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art"

"The appeal concerns the question whether or not the disclosure of the Dow patent cited under Article 54(3) EPC is an enabling disclosure. The problem arises in view of the fact that no instructions are given in that patent as to the preparation of the starting materials. Although there is a process described in the document suggesting a way to convert these, viz. CCMP and CCCMP, to the corresponding intermediates, CTF and CCTF, this can only be carried out when the starting materials are available. There are no instructions either as to possible alternative routes to the intermediates suggested in the cited document, and the skilled person is therefore left to his own resources to find a route to those precursors before he can prepare the end-products.

"The Board already issued a decision on the question of sufficiency of disclosure ("Redox catalyst/AIR PRODUCTS, T 171/84, Ibid.). The Headnote of that decision suggested that "An error in the description is immaterial to the sufficiency of the disclosure if the skilled person could recognise and

rectify it using his common general knowledge". However, the decision also stated in that case that "... no undue effort was expected from the skilled man either in way of such search or experimentation, let alone any necessity to exercise his inventive skill" (Ibid, at p. 101, paragraph 12).

"The Board has come to the conclusion that the principle expressed in the cited decision should also be applicable to the present case. Basically any cure of insufficiency lies with the addressee of the document, i.e. the person skilled in the art who has common general knowledge at his immediate disposal. It would be unfair to the public if more were to be expected of him, i.e. an awareness of the whole state of the art.

[...]

"The indexes of Chemical Abstracts cover virtually the whole state of the art, and represent therefore much more than what is assumed to be the common general knowledge of the addressee of the specification. Reliance on the contents of Chemical Abstracts to rectify insufficiency might be tantamount to leave the skilled reader to carry out a search in the whole state of the art, which would be an unacceptable burden on the public.

[...]

"It is the view of the Board that a document does not effectively disclose a chemical compound, even though it states the structure and the steps by which it is produced, if the skilled person is unable to find out from the document or from common general knowledge how to obtain the required starting materials or intermediates. Information, which can only be obtained after a comprehensive search is not to be regarded as part of common general knowledge."

- 8.4 T654/90 and T924/03 follow the same approach as T206/83 in confirming that subject matter which can only be obtained as the result of a search is not part of the common general knowledge.
- 8.5 During the opposition proceedings, the patentee cited T1760/11, and argued that a skilled person is able and supposed to search chemical abstracts for specific compounds. We do not accept that proposition, and consider that it is contrary to the consistent case law discussed above.
- 8.6 In T1760/11 the patent at issue referred to making a particular magnesium salt of omeprazole. There were extensive and detailed instructions in the patent as to how this should be made from a specific, and named, starting material: 6-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole. However, no explicit synthesis of that compound was disclosed.

8.7 The Board in T1760/11 found that the patent was sufficient, because “the starting material of Example 2A” (i.e. the chloromethyl compound above) which was unambiguously disclosed as a starting material, was directly accessible in Chemical Abstracts. Thus, the Board held that a skilled person would have searched for that specific compound, and would have been led directly to a document which set out the synthesis of that compound. Only because the starting material of example 2A was retrievable in a “direct and straightforward” manner and was thus “readily available to the skilled person”, could sufficiency in that case be acknowledged.

8.8 The situation in T1760/11 is not generalizable in the manner alleged by the patentee, for reasons set out in T1760/11 itself. Thus in the paragraph immediately following that quoted by the patentee, the Board in T1760/11 stated (see reasons, paragraph 8.2):

“The present situation is not comparable with that underlying the decision T 206/83 (see OJ EPO 1987, 5). In that decision, it is apparent that the compounds in question were not traceable through the index of Chemical Abstracts (see point V.b), and it was held under the circumstances that “reliance on the contents of Chemical Abstracts to rectify insufficiency might be tantamount to leave the skilled reader to carry out a search in the whole state of the art, which would be an unacceptable burden on the public””

8.9 A clear distinction between the situation in T206/83 and T1760/11 can thus be drawn. T1760/11 permitted a skilled person to consider Chemical Abstracts only because the compound at issue was directly traceable in the index of Chemical Abstracts, and all a skilled person had to do was to consult the reference for that starting material to synthesize it without any further research. In T206/83 the compound at issue was not traceable.

9 ANNEX B - SUMMARY OF ATTEMPTS BY IDENIX

- 9.1 In early 2002 Idenix assigned the project of making a 2'-methyl-up-2'-fluoro-down nucleoside analogue to Dr Jean-François Griffon, a Senior Research Scientist at Idenix who was based on Montpellier, France. Dr Griffon's background is set out in D31 and is summarised in paragraphs 29 and 30 of D10 in the following terms:

"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. During his PhD he prepared a number of 2' and 3' fluoro-substituted nucleosides by the following methods:

- i) epoxide ring opening using potassium hydrogenfluoride (KHF₂), hydrofluoric acid (HF) alone or a combination of HF and aluminium fluoride (AlF₃);*
- ii) opening a 2,2'=' or 2,3'-O-anhydro nucleoside using HF or HF in the presence of certain aluminium derivatives (AlF₃, AlFR₂ or AlFR₃);*
- 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.*

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 - β -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".

- 9.2 The background to Dr Griffon's project is set out in paragraphs 472 to 473 of D10, and is summarised in the Table below.

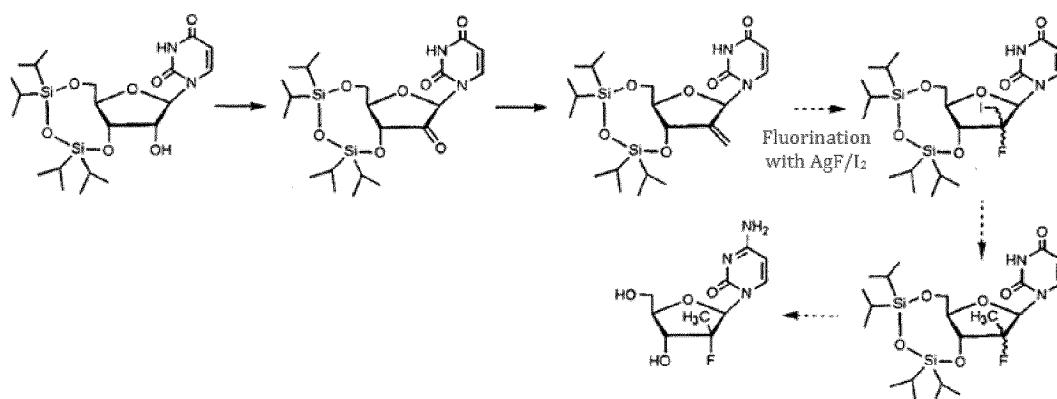
28 March 2002	Dr Griffon was first assigned the project of making a 2'-methyl-up-2'-fluoro-down nucleoside analogue at a meeting attended by, among others, Dr Richard (" <i>Dick</i> ") Storer (his supervisor and Senior Vice-President of Chemistry at Idenix) and Dr Gilles Gosselin (Dr Griffon's former 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.
24 May 2002	Dr Griffon was given the task of undertaking a bibliographic search in relation to the 2'-methyl-up-2'-fluoro-down target at a team meeting
27 June 2002	Dr Griffon presented the search results in a report - 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 " <i>nucleoside route</i> " (i.e. modifying an existing nucleoside, rather than first preparing a sugar with the desired modifications before attaching the base by glycosylation). Dr Griffon viewed this initial proposal as a logical starting point in light of the literature references he had located during his searches.
July 2002	The project was assigned a " <i>high priority</i> ".

- 9.3 As explained in paragraphs 474 to 514 of D10, over the next two years or so Dr Griffon then sought to employ a series of eleven different strategies in his quest to make a desired 2'-methyl-up-2'-fluoro-down nucleoside analogue, all without success. These eleven strategies are set out below.

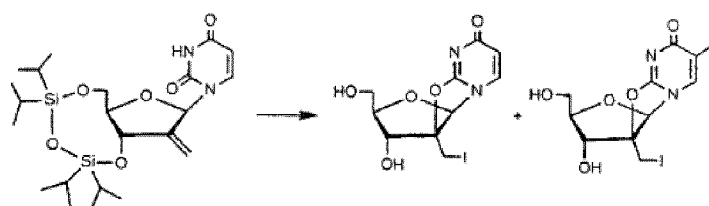
Strategy 1

- 9.4 Dr Griffon's first attempted strategy 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 I₂ 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.

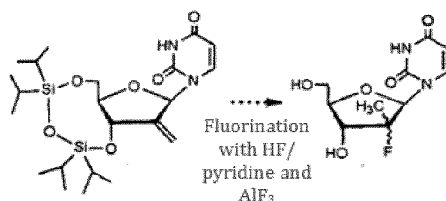


- 9.5 This strategy was unsuccessful. Reaction of the 2'-ethynyl nucleoside with AgF and I₂ gave two deprotected "anhydro" compounds, instead of the desired, protected 2'-iodomethyl intermediate, as shown below.

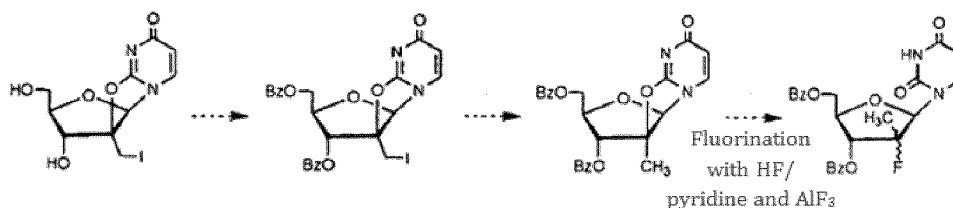


Strategies 2 and 3

- 9.6 After the failure of Strategy 1, Dr Griffon in his monthly Progress Report for September 2002 proposed two new strategies for the synthesis of a 2'-fluoro-2'-methyl nucleoside analogue. One proposal involved the reaction of a 3'-5'-protected 2'-ethynyl nucleoside with HF/pyridine and AlF₃ ("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.



- 9.7 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.



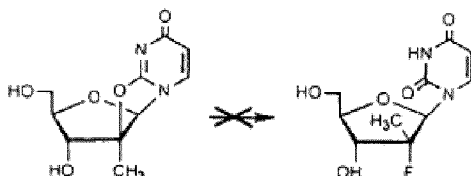
- 9.8 In his October 2002 Progress Report Dr Griffon noted that an attempt to convert the 2'-iodomethyl-anhydro compound to the corresponding 2'-methyl-anhydro compound (a variant on Strategy 3 above) without first installing protecting groups had failed (he recorded that "*these conditions didn't allow the formation of the desired compound*") and illustrated the reaction in his report with a cross on the relevant arrow.
- 9.9 In the same October 2002 Progress Report, Dr Griffon indicated that further work on Strategy 3, where the 2'-iodomethyl-anhydro compound is first protected with Bz groups, was underway. Similarly, he recorded that work on Strategy 2 was also ongoing.
- 9.10 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.
- 9.11 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 and an expert in carbohydrate chemistry). 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 (D29) sets out the difficulties which had been encountered in attempting to reduce the iodomethyl group as part of Strategy 3 (see Table on page 1 of D29) 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.

- 9.12 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]*” (D13, page 2, explanatory paragraph following Scheme 3).
- 9.13 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 (D14) he stated that “*starting from the 2'-ethenyl derivative [i.e. Strategies 1 and 2] ... all the attempted experimental conditions failed*” (D14, page 2, line 5). 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, AlF₃, 120°C or KHF₂, ethylene glycol, reflux*” 9d (D14, page 2, last two lines).
- 9.14 In early January, Prof Fleet provided another suggested route to Idenix which involved electrophilic fluorination. Meanwhile, on 8 February 2003 Dr Storer wrote (D16) to Dr Paul Coe, an organofluorine expert from the University of Birmingham who had previously collaborated 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*” (D16, page 1, lines 5 to 6). 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” (D16, page 3, paragraph 2).

Strategies 4 and 5 (plus a further variation of Strategy 3)

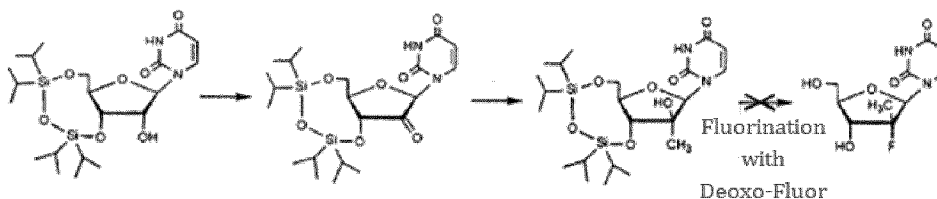
- 9.15 In his February 2003 Progress Report (D15), Dr Griffon explained that “*several experimental conditions have been attempted in order to introduce fluorine at the 2'-down position*” (D15, page 2, line 3). He went on to describe a number of attempts to open a 2'-anhydro nucleoside with fluoride, all of which failed.



- 9.16 The various attempts involved fluorination with:
- HF-pyridine, AlF_3 at 80°C and 120°C (*Strategy 3* as described above, but without 3' and 5' protection)
 - KF, Kryptofix 2.2.2, *p*TsOH, DMF, reflux (*“Strategy 4”*); and
 - KHF_2 refluxed in either ethylene glycol or 2-methoxyethanol (*“Strategy 5”*).
- 9.17 The summary of results for these reactions in Dr Griffon’s February 2003 Progress Report (D15, Table on page 2) indicated that these strategies either gave no reaction or proceeded with degradation of the starting material.

Strategy 6

- 9.18 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.



- 9.19 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 trimethylaluminum in hexane and dichloromethane.
- 9.20 In his February 2003 Progress Report Dr Griffon stated that *“one new compound was formed during the reaction ... unfortunately, based on Mass Spectrum, ^1H and ^{19}F -NMR spectra, this compound was identified as the 2'-ethenyl derivative...”* (D15, page 2, last nine lines).

Strategies 7 and 8

9.21 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.

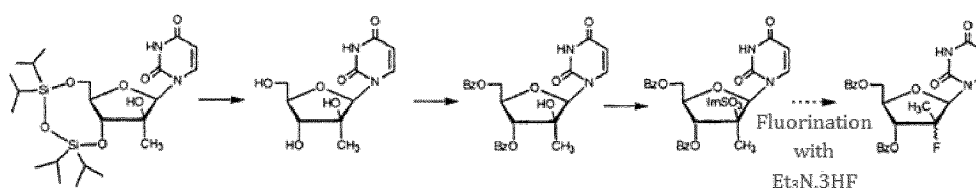
9.22 On or around 9 April 2003 Dr Coe replied to the letter which Dr Storer had sent him on 8 February 2003. Dr Coe's reply is D17. He proposed a number of synthetic strategies for the synthesis of a 2'-methyl-up-2'-fluoro-down nucleoside. Dr Coe stated that:

"...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" (D17, page 1, last five lines to page 2, line 4).

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

- 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 $\text{Et}_3\text{N} \cdot 3\text{HF}$ and then glycosylation to install the base (D17, page 2, lines 12 to 20);
- a similar approach starting with a 2'-methyl-up-2'-hydroxy-down nucleoside (D17, page 2, lines 2 to 26);
- the opening of a 2'-anhydro nucleoside using anhydrous HF, or $\text{Bu}_4\text{NH}_2\text{F}$, with $\text{Fe}(\text{AcAc})_3$ and DME (D17, page 2, line 27 to page 3, line 14); and
- the reaction of a 2'-methyl-up-2'-hydroxy-down nucleoside with HF-pyridine ("Olah" conditions) (D17, page 3, lines 15 to 20).

- 9.24 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.
- 9.25 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 $\text{Et}_3\text{N} \cdot 3\text{HF}$ ("Strategy 7"), as shown below.



- 9.26 Strategy 7 failed. Dr Griffon recorded in his May 2003 Progress Report (D18) that when the fluorination reaction was attempted "*no reaction occurred: the starting material was mainly recovered*" (D18, page 2, lines 12 to 13). Dr Griffon also proposed an attempt to open the 2'-anhydro nucleoside using $\text{Bu}_4\text{NH}_2\text{F}$ with $\text{Fe}(\text{AcAc})_3$ and DME as suggested by Dr Coe ("Strategy 8").
- 9.27 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 in the UK proceedings relating to D1 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.
- 9.28 During July/August 2003 Dr Griffon attempted Strategy 8, reacting the 2'-anhydro nucleoside with tetrabutylammonium dihydrogenfluoride in the presence of ferric acetylacetonate in 1,2-dimethoxyethane 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*" (D19, page 2, paragraph 1).

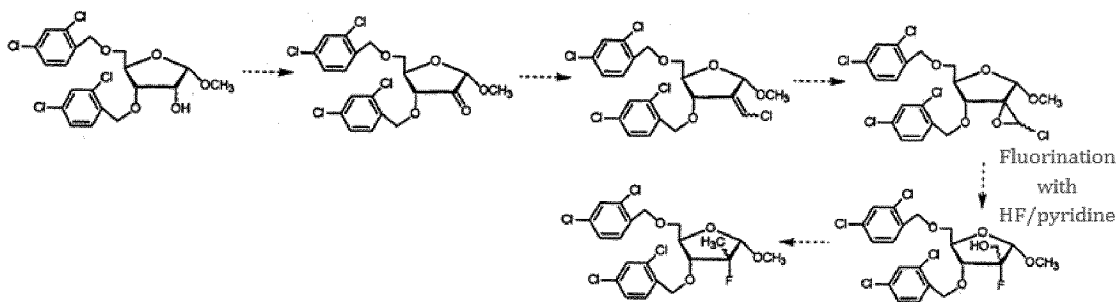
Strategies 9 to 11

- 9.29 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.

- 9.30 In his Progress Report for February 2004, Dr Griffon described renewed attempts at Strategy 1 (reaction of a 2'-ethenyl nucleoside with AgF and I₂), 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."

- 9.31 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.
- 9.32 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).
- 9.33 Dr Griffon subsequently produced a report setting out three proposed sugar routes (the sugar route involves preparing a sugar with the desired modifications before attaching the base by glycosylation) 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.



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- Chemical reaction scheme showing the synthesis of 2,3,4,6-tetra-O-methyl-2,3,5-trifluoro-6-deoxy-1-thio-beta-D-glucopyranoside. The scheme includes the starting material (D-glucose), the intermediate (cyclic acetal), and the final product. A side reaction shows the conversion of N-bromo-succinimide to N-bromo-succinimide, which is then used in the main reaction.

- Atea Pharmaceuticals, Inc.
Exhibit 1038 Page 142 of 155

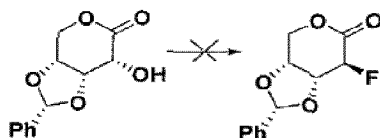
sugar and deprotection in acidic conditions was attempted 3 times with no success”.

- 9.40 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”?*
- 9.41 Dr Griffon was subjected to cross-examination during the UK proceedings based on this patent. The UK judge concluded in D10 that his work *“represented a sustained effort by a chemist who was representative of the skilled person to synthesise 2'-fluoro-2'-methyl uridine”* (paragraph 521), also noting that *“Dr Griffon was not working on his own, but received extensive advice from relevant experts”* (paragraph 522).

Further work by Idenix

- 9.42 Following Dr Griffon's substantial attempts to synthesise a 2'-methyl *“up”* 2'-fluoro *“down”* nucleoside, the project was handed over in May 2004 to Dr Alastair Stewart and Ms Jingyang Wang (D24, page 19, lines 20 to 24). Both Dr Stewart and Ms Wang received Dr Griffon's report summarising his work to date (D24, page 21, line 22 to page 22, line 5). Dr Stewart also consulted with Professor Fleet, see e.g. Report of their meeting on 10 May 2004, D20, page 3, Scheme G1, proposed route to compound 15.
- 9.43 Between May 2004 and November 2004, Dr Stewart carried out literature searches (D24, page 24, lines 9 to 24). During that period he also consulted with his colleagues Ms Wang, Ben Mayes, Adel Moussa and Narayan Chanduri (D24, page 27, lines 11 to 22).
- 9.44 By November 2004, Dr Stewart and his colleagues at Idenix were considering a *“sugar route”* that involved the displacement of a triflate leaving group on a 5- or 6-membered lactone ring using TBAF or TASF as a fluorinating reagent. This was referred to in an email on 11 November 2004 from Dr Dick Storer to Dr Stewart (D22). Dr Storer commented:
- “A lot of things which look simple on paper in related systems have been tried and don't work in this series. Having to make the tertiary fluoride is very different to having to make a secondary”.*
- 9.45 Note also that the proposed scheme referred to in D22 is followed by the comment:

Past work



Direct using DAST

- 9.46 The cross through the arrow indicates that the reaction with DAST did not result in fluorination by replacement of the OH with F.
- 9.47 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.
- 9.48 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.
- 9.49 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*" (see D10, paragraph 528).
- 9.50 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°C (instead of room temperature) the next day.
- 9.51 It is clear that during a period of more than two years Idenix made many attempts to make a 2'-methyl "*up*" 2'-fluoro "*down*" nucleoside. Both "*sugar*" routes and "*nucleoside*" routes were tried. Many different starting materials, fluorinating reagents, reaction conditions and protecting groups were tried.

Idenix had a team of skilled chemists working on the project and consulted with external experts.

- 9.52 It was not until Idenix received some information from the Applicants of D5 that Idenix directed their efforts towards a synthetic route that, as shown in D5, enables the production of a 2'-methyl "up" 2'-fluoro "down" nucleoside.

Summary of some of routes and fluorinating agents tried or contemplated by Idenix

- 9.53 A summary of some of the synthetic routes that Idenix tried or contemplated is given in the Table below.

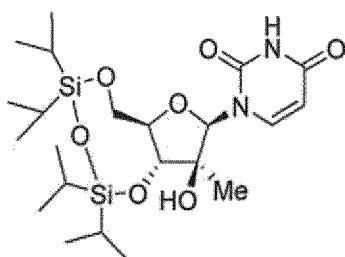
Route	Cited DOCUMENT
Routes involving various 2,2'-anhydro nucleosides	D12, p. 2 (numbered p. 1) (2002) D13, pp. 1-2 (2002) D14, p. 2 (numbered p. 1) (2003) D15, p. 2 (numbered p. 1) (2003) D19, p. 2 (numbered p. 16) (2003)
Routes involving a 2'-ethenyl nucleoside	D12, p. 2 (numbered p. 1) (2002) D23, p. 4 (numbered p. 3) (2005)
Routes involving 2'-methyl-2'-hydroxy-substituted nucleosides	D15, p. 2 (numbered p. 1) (2003) D23, p. 3 (numbered p. 2) (2005)
Routes involving 2'-methyl-2'-OSO ₂ (Imidazole) nucleosides	D18, p. 2 (numbered p. 11) (2003)
Routes involving fluorination at the 2-position of a dihydrofuranone (which would need to be followed by conversion to a dihydrofuranosyl sugar and condensation with a nucleobase)	D23, p. 2 (numbered p. 1) (2005)
Routes involving either electrophilic or nucleophilic fluorination at the 2-position of a pyranose sugar, followed by ring contraction to a 5-membered lactone (which would need to be followed by conversion of the	D21, p. 1 (Scheme G1) (2004) D22, p. 2 (2004)

lactone to a dihydrofuranosyl sugar and condensation with a nucleobase)	
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9.54 Idenix in their research project tried a number of different fluorinating reagents to make a 2'-fluoro "down" 2'-methyl "up" nucleoside. Chemists and/or consultants working for Idenix reported trying and/or contemplated trying a number of both nucleophilic and electrophilic fluorinating reagents during the period of 2002-2005 including those listed in the Table below.

Fluorinating Reagent	Cited document
HF-pyridine	D12, p. 2 (numbered p. 1) D13, pp. 1-2 D17, p. 10
HF-pyridine/AlF ₃	D14, p. 2 (numbered p. 1) D15, p. 2 (numbered p. 1)
KHF ₂	D14, p. 2 (numbered p. 1) D15, p. 2 (numbered p. 1)
KF	D15, p. 2 (numbered p. 1)
Deoxofluor	D15, p. 2 (numbered p. 1) <i>see also</i> D23, p. 3 (numbered p. 2)
Diethylaminosulfur trifluoride (DAST)	D23, pp. 2, 3 (numbered pp. 1, 2)
Et ₃ N·3HF	D18, p. 2 (numbered p. 11) D17, pp. 7, 8 (figs. a, 2)
Bu ₄ NHF ₂ / Fe(AcAc) ₃	D19, p. 2 (numbered p. 16)
Tetrabutylammonium fluoride (TBAF)	D21, p. 1 (Scheme G1)
Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)	D21, p. 1 (Scheme G1)
Tetrabutylammonium dihydrogentrifluoride (Bu ₄ NH ₂ F ₃)	D17, pp. 3, 6
Perfluoro-1-butanefluoride (PFSF)	D23, p. 3 (numbered p. 2)
SelectFluor (an electrophilic fluorinating reagent)	D23, p. 4 (numbered p. 3)
Anhydrous HF	D23, p. 4 (numbered p. 2)
HF / Fe(AcAc) ₃	D17, p. 9 (fig. 3)
Bu ₄ NH ₂ F / Fe(AcAc) ₃	D18, p. 2 (numbered p. 11) D17, p. 9 (fig. 3)

10.1 “Route 22” is characterised by a very specific compound, so-called “Compound 22”, as an intermediate in a synthesis:



10.2 The selection of Compound 22 as an “intermediate” is based entirely on hindsight and in the knowledge of the successful synthesis route that was reported in the literature in 2005 (D6). As previously noted, the Journal of Medicinal Chemistry in which D6 was published is a very prestigious, peer-reviewed journal, in which chemistry is a key focus. It is evident that the synthesis that was devised by Jeremy Clark and reported in D6 was a synthesis of some note.

10.4 It is also notable that the facts show that in the relevant period (2003/2004) a team of skilled chemists, including many chemists highly experienced in the synthesis of nucleosides and in carbohydrate or fluorine chemistry did not as a matter of fact identify “Compound 22” as a key intermediate from which it would be possible to produce the desired 2’-F down 2’-Me up nucleoside. This is discussed in our grounds of appeal and in Annex B to those grounds of appeal.

10.6 Even if the skilled person did start from a compound (i.e. compound 22) identified with hindsight, it would still be necessary then to introduce a fluorine moiety. The patentee has argued that DAST is a well-known

fluorinating agent. The opponents do not dispute that DAST was a known fluorinating agent in 2003. As the eminent nucleoside chemist Dr Marquez notes in his declaration D41a, paragraph 88:

“New compounds are often made using reagents or chemical reactions that are “known” in the sense that starting material, reagent or general type of chemical reaction was previously reported in the literature. The fact that the starting materials, reagents, or chemical reactions were “known” does not mean that it is trivial to determine which ones to use or the order in which to use them to make a new compound. The fact that a compound is reported to have been made “known” reagents and techniques does not mean that its synthesis was straightforward. An extensive amount of experimentation, including numerous unreported failures, may have been required to arrive at the ultimately successful synthetic route”.

- 10.7 The patentee has drawn attention to the comments made by Professor Boons in his textbook from which the patentee supplied an extract (D103). With the submissions we attach a copy of D103A, a complete copy of the chapter from which the patentee provided an extract. As Professor Boons explains in his attached declaration (D105), the excerpt provided by the patentee refers to the use of DAST as a fluorinating agent in the context of a secondary alcohol as depicted in Scheme 3.2. It does not refer to the use of DAST in the context of a much more difficult tertiary alcohol. The textbook also discusses other fluorination methods. It is also discussed that nucleophilic substituents as carbohydrates can be difficult due to the presence of permanent dipoles (see page 62) and that a successful nucleophilic substitution on a simple substrate does not necessarily give confidence that such a transformation can be performed on a carbohydrate derivative. This is consistent with the skilled person's knowledge as of 2003 that fluorine chemistry is unpredictable (see D41, paragraphs 79 to 81).
- 10.8 In particular, as of the relevant dates, fluorination reactions were understood to proceed by different mechanisms depending on both the fluorinating reagent selected and the particular compound with which the fluorinating reagent reacted (the “*substrate*”) (D41A, paragraph 76).
- 10.9 Generally speaking, fluorination reactions proceed by two different mechanisms known as “*nucleophilic fluorination*” and “*electrophilic fluorination*”. Nucleophilic fluorination of primary and secondary carbons often, but not always, occurs with inversion of stereochemistry in the product. In other words, the incoming fluoro atom being added to the compound ends up in the opposite orientation as the group it replaces. However, a compound of Formula III having $Y = F$, $X = -CH_3$ possesses a fluorinated tertiary carbon. The situation for tertiary carbons is much more complicated than for primary or secondary carbons. The stereochemical outcome of electrophilic fluorination reactions is also unpredictable (D41A, paragraph 76).

- 10.10 While a number of fluorinating reagents had been disclosed in the art as of the relevant dates, the application as filed fails to mention any of them. For example, nucleophilic fluorinating reagents such as hydrogen fluoride (HF), pyridine·HF, tetrabutylammonium hydrogen difluoride ($n\text{Bu}_4\text{N}^+\text{HF}_2$), activated alkali metal fluorides (e.g., KF, CsF), SF_4 , (diethylamino)sulfur trifluoride (DAST) and Deoxofluor, as well as electrophilic fluorinating reagents such as perchloryl fluoride (FClO_3), xenon difluoride (XeF_2), trifluoromethylhypofluorite (CF_3OF), and acyl and perfluoroacyl hypofluorites (RC(O)OF and $\text{R}_1\text{C(O)OF}$), and numerous “NF” reagents having nitrogen-fluorine bonds had been disclosed (see D3, page 1737, left-hand column, line 47 - right-hand column, line 6, right-hand column lines 37-45, page 1738, left-hand column lines 25-30, pages 1740-1741 (Table 1); D4, page 2561, right-hand column). (D41A, paragraph 77). The application as filed fails to mention these or any other fluorinating reagents, or provide any guidance as to which of them to use in order to synthesise a starting material of Formula III in which Y is F and X is $-\text{CH}_3$.
- 10.11 Further, different types of substrate are required to react with nucleophilic fluorinating reagents versus electrophilic fluorinating reagents. Thus, to make a starting material of Formula III in which Y is F and X is $-\text{CH}_3$, a skilled person as of the relevant dates would have had to determine whether to attempt to install the fluoro substituent via electrophilic fluorination or nucleophilic fluorination, and would have had to design and synthesise an appropriate substrate for fluorination according to the selected method (D41A, paragraph 78).
- 10.12 Accordingly, the application as filed neither suggests which general approach to take (i.e. nucleophilic or electrophilic fluorination) nor discloses any starting materials, reagents or chemical reactions that a skilled person as of the priority date or filing date could have used or modified without an extraordinary amount of experimentation to make a starting material of Formula III in which Y = F and X = $-\text{CH}_3$.
- 10.13 Even in light of the teachings in the art, a skilled person as of the relevant dates could not have known whether a particular fluorination reaction would work to produce a compound of Formula III having Y = F and X = $-\text{CH}_3$ until he or she actually tried it. This is because fluorination reactions often have surprising or unpredictable outcomes, especially when one is trying to synthesise a new compound with different chemical features from those known in the art, for example a new substitution pattern on a nucleoside sugar ring (D41A, paragraph 79).
- 10.14 A skilled person as of the relevant dates would have understood, based on the art, that various fluorinating agents could be difficult to work with and might give products other than those intended. For example, attempted fluorination reactions could result in products with the wrong stereochemistry, products resulting from undesired rearrangements or products in which no fluorination occurred. See D4, page 2563, left-hand column, line 11 - right-hand column, line 12, Schemes 5 and 6, page 2564, Scheme 9. Thus, considering the

application as filed in light of the art, a skilled person as of the relevant dates could not have expected that any particular fluorination reaction would work to make a compound of Formula III having $Y = F$ and $X = -CH_3$. Rather, a skilled person would have had to engage in a burdensome process of substantial experimentation to try to determine appropriate starting materials, reagents and chemical transformations to use to make a 2'-fluoro "down" 2'-methyl "up" nucleoside of Formula III (D41A, paragraph 80).

- 10.15 The first published synthesis of a 2'-methyl/2'-fluoro nucleoside compound was in 2005, (i.e. subsequent to the 21 July 2003 priority date and subsequent to the 20 July 2004 filing date of the opposed patent). Thus on 13 January 2005 D5 disclosed the successful synthesis of a 2'-fluoro "down" 2'-methyl "up" nucleoside (see D5, page 27, paragraph [0313] - page 30, paragraph [0326]). This synthesis was subsequently reported in journal articles subsequently published by the inventor of D5, Clark, and co-workers, such as the paper published in J. Med. Chem. in 2005 (D6). Note that the Journal of Medicinal Chemistry is a very prestigious journal, in which chemistry is a key focus. It is evident from this that the synthesis that was devised by Jeremy Clark was a synthesis of some note.
- 10.16 The synthesis disclosed in D5 and reported in D6 involves the production of 2'-fluoro "down" 2'-methyl "up" nucleosides via routes involving the reaction of the DAST fluorinating reagent with intermediate compounds having a 2' hydroxy (OH) group "up" and a 2' methyl group "down" on the sugar ring (see D6, page 5506, right-hand column, line 24 - page 5508, left-hand column, line 17; D7, page 1712, right-hand column, line 7 - page 1715, right-hand column, line 12; D8, page 461, line 17 - page 469, line 9). The synthetic route published by Clark and co-workers involves an inversion of the 2' stereochemistry to give a product with a 2' fluorine atom "down" and a 2' methyl group "up".
- 10.17 A skilled person as of 21 July 2003 or 20 July 2004 would not have had the benefit of Clark's later-published teachings regarding how to make such 2'-fluoro "down" 2'-methyl "up" nucleosides. Furthermore, none of the relevant teaching is disclosed in the application as filed.
- 10.18 The application as filed neither mentions DAST (or any other fluorinating reagent), nor suggests performing a fluorination reaction involving inversion of stereochemistry (or any other fluorination reaction), nor describes or teaches how to make a compound having 2'-methyl/2'-hydroxy substitution like the chemical intermediates reacted with DAST in D5. Rather, the application as filed requires the skilled person to obtain the compound of Formula III from a commercial source (not possible for a 2'-methyl/2'-fluoro nucleoside as of 21 July 2003 or 20 July 2004) or to devise, without any guidance whatsoever, a method to produce such a 2'-methyl/2'-fluoro nucleoside. Without the hindsight benefit of Clark *et al*'s later-published results, a skilled person as of 21 July 2003 or 20 July 2004 would not have known how to prepare a starting material of Formula III in which $Y = F$ and $X = -CH_3$.

- 10.19 Prof Boons (D42A, paragraph 11) explains that he has examined the Clark *et al* 2005 and 2006 publications (D6 and D8). The fact that the authors successfully used nucleophilic substitution on a tertiary hydroxyl group using DAST to carry out the fluorination step surprised Prof Boons when he first saw these results. He does not believe that the synthesis route reported in these documents would have been the first route that the skilled person would have tried when attempting to synthesise a 2'-methyl/2'-fluoro nucleoside in 2003 or 2004, given the difficulties which they would have foreseen (which are discussed in D43).
- 10.20 Even if, *arguendo*, a skilled person as of the relevant dates had considered using DAST to try to make a starting material of Formula III in which Y is F and X is -CH₃, the skilled person would not have had an expectation of success in making such a compound, given the unpredictable nature of fluorination reactions, including those involving DAST, particularly in the context of fluorination of a hydroxyl attached to a tertiary carbon. For example, it was known in the art that while fluorination reactions with DAST often proceeded with inversion of stereochemistry, DAST fluorinations could proceed with retention of stereochemistry due to the involvement of other chemical groups in the compound being fluorinated. In other words, the stereochemical outcome of a fluorination reaction such as one performed using DAST could not be known until one actually performed the reaction because the outcome could be affected by the unique characteristics of the specific compound being fluorinated.
- 10.21 Further, it had been reported in the literature as of 21 July 2003 that reactions with DAST could fail to result in any fluorination at all and might instead produce undesired elimination, ring expansion or dehydration products (see e.g. D4, pages 2563, Scheme 5, 2564, Scheme 9). The outcome of a reaction between the DAST reagent and a highly functionalised compound like those used by Clark and co-workers would have been particularly unpredictable given the potential for the other chemical groups in the molecule to influence the outcome.
- 10.22 Thus, even if a skilled person as of 21 July 2003 or 20 July 2004 were to have selected the DAST fluorinating reagent (of which the application as filed contains no mention, just as it lacks mention of any other fluorinating reagent), the skilled person would have had to engage in a burdensome and extensive process to design and synthesise an appropriate starting material for fluorination. Even then, the outcome of the reaction (e.g., whether fluorination would occur at all and what the stereochemistry of any fluorinated product would be) would have been unpredictable and the skilled person would not have had an expectation that a synthetic route involving DAST would work to make a starting material of Formula III in which Y is F and X is -CH₃.
- 10.23 Accordingly, a skilled person as of 21 July 2003 or 20 July 2004 could not have predicted whether particular methods known in the art for making fluorinated compounds would have worked to make a starting material of Formula III in

which Y is F and X is -CH₃. Rather, it would have been necessary to actually try such reactions to see if they gave the desired fluorinated products with the appropriate stereochemistry.

- 10.24 The patentee has extracted from D68A a list of reactions in which DAST has been used with varying degrees of success to introduce a fluorine atom. However, D68A also includes Table XII on pages 629 to 632 listing reactions that were non-fluorinating. As D68 also explains on page 543, final paragraph that:

“[i]t is difficult to list reactions in which amino fluoro sulfuranes failed to accomplish fluorinations because even if such failures are reported, they may escape indexing and a literature search”.

- 10.25 Thus, DAST is not a universal fluorination reagent; it may work or it may not work. If it does not work then it may be possible to improve the results by changing the reaction conditions, or changing the reaction conditions may prove to be fruitless. The skilled person is required to carry out research. As was commented by a senior chemist at Idenix when they had been trying for over two years to prepare a 2'-F down 2'-Me up nucleoside:

“A lot of things which look simple on paper in related systems have been tried and don't work in this series. Having to make the tertiary fluoride is very different to having to make a secondary.” (D22, page 1, last paragraph)

- 10.26 The patentee has also alleged that because Jeremy Clark at Pharmasset devised a route to synthesise a 2'-fluoro “down” 2'-methyl “up” nucleoside, it was possible to arrive at a compound having the desired substitution pattern based on common general knowledge. However, as noted above, the synthesis route devised by Jeremy Clark was considered of sufficient interest to chemists that a number of papers relating to the synthesis were published in prestigious peer reviewed articles: D6 in J. Med. Chem., D7 in Bio. Org. Med. Chem. Let. and D8 in J. Carbohydrate Chem. It does not therefore represent common general knowledge. As explained in D6, page 5505, LH column:

“The fluorination of tertiary alcohols with DAST has been reported, but the stereochemistry of such transformations is substrate-specific and often unpredictable.”

- 10.27 Indeed, Professor Boons in D43A, paragraph 13.4 comments that he was surprised when he first saw that the authors (of D6 and D8) has successfully use nucleophilic substitution on a tertiary hydroxyl group using DAST to carry out the fluorination step.
- 10.28 The opposition division similarly concluded in relation to fluorinations *that “a skilled person could contemplate using more reagents than just “DAST”, and that fluorinations are not straightforward”.*

11 ANNEX D - D36 IS THE CLOSEST PRIOR ART

11.1 As set out in section 7.21 of our Grounds of Appeal, we agree with the view of the opposition division that D36 is the closest prior art. This was contested by the patentee who considered that the compound gemcitabine should be taken as the closest prior art.

11.2 As a starting point, we note that

“the applicant or proprietor cannot refute the argument that the claimed subject-matter lacks inventive step by submitting that a more promising springboard is available: a piece of prior art on the basis of which the claimed invention is considered non-obvious cannot be “closer” than a document on the basis of which the claimed invention appears obvious, because it is evident in this situation that the former does not represent the most promising springboard from which to arrive at the invention (T 1742/12, Reasons 6.5; T 824/05, Reasons 6.2).” (Guidelines, section G-VIII-5.1)

11.3 The opposition division correctly concluded that the claims of the patent as granted and those of ARs 1-12 lacked inventive step over D36. For the reasons set out in section 7 of our Grounds of Appeal, we submit that the claims of AR13 similarly lack inventive step over D36.

11.4 Solely because the patentee has contested that gemcitabine rather than D36 should be considered the closest prior art, and because these matters were discussed at oral proceedings, we briefly summarise the reasons as to why D36 is indeed the closest prior art.

11.5 The closest prior art is that which in one single reference discloses the combination of features which constitutes the most promising starting point for a development leading to the invention. In selecting the closest prior art, the first consideration is that it must be directed to a similar purpose or effect as the invention or at least belong to the same or a closely related technical field as the claimed invention. In practice, the closest prior art is generally that which corresponds to a similar use and requires the minimum of structural and functional modifications to arrive at the claimed invention (see T 606/89). (Guidelines, section G-VIII-5.1)

11.6 As noted by the opposition division in section 5.2 of the decision, gemcitabine cannot be the closest prior art. As compared to the claimed compounds which are all phosphoramidated nucleosides, gemcitabine lacks the phosphoramidate pro-group which accounts for around half the molecular weight of the compound. Adding such a group is a significant structural modification and one that has a significant impact on the biological activity of the resulting compound.

- 11.7 Moreover, the entire focus of the patent is on providing a series of phosphoramidated nucleosides which are said to have be useful in treating cancer. Whilst we dispute that any such activity is demonstrated across the scope of the claims, it is unquestionably more reasonable to start from other phosphoramidated nucleosides provided to treat cancer than from a non-phosphoramidated compound.
- 11.8 The patentee has argued that because many of the example compounds in D36 (such as the compound of claim 12, CPF-2) have a bromovinyl group at the Z position, they act by a different mechanism to the compounds allegedly at issue in the opposed patent. As discussed in our Grounds of Appeal, the compounds claimed in the opposed patent can also have a bromovinyl group at that position and so the patentee's arguments in this regard are irrelevant. Equally, not all exemplified compounds in D36 have a bromovinyl group at the Z position, and in fact claim 1 of D36 allows for exactly the same H and alkyl groups as specified in the claims of the patent.
- 11.9 Moreover, however, the mechanism by which a compound is alleged to act is irrelevant in addressing its alleged technical effect. As both the compounds claimed in the patent and those of D36 are directed to the treatment of cancer (however unsuccessfully in the case of the compounds claimed in the patent), any alleged difference in their mechanism of action is irrelevant.
- 11.10 As regards the selection of compound 12 (CPF-2) as being a particularly suitable starting point within the broader D36 disclosure, this was contested by the patentee who suggested that a more appropriate starting point could be the compound of example 15 of D36 (corresponding to CPF-1 in the opposed patent). CPF-1 comprises a methyl group at the R position in claim 1 of the patent, whereas CPF-2 comprises a benzyl group at this position.
- 11.11 The opposition division considered that CPF-2 is a more promising starting point than CPF-1. We agree.
- 11.12 First, the CPF-1 compound is not even claimed in D36: it cannot be a more relevant starting point within that disclosure than a compound which is actually claimed. Evidence from unrelated documents that the compound has been identified elsewhere as a lead compound is utterly irrelevant. Second, the patent alleges that particular advantages arise for benzyl ester compounds (paragraph 50 of the opposed patent). Furthermore, the only examples in the patent of compounds within the scope of the claims are benzyl esters. As such, it is certainly most reasonable to start from a compound within the closest prior art document D36 which similarly has a benzyl ester at the relevant position. Third, the patent itself highlights CPF-2 as a "comparative example". It is entirely reasonable to compare the effect of the compounds of the alleged invention with a compound of the prior art when exactly such a comparison is made within the patent itself.

- 11.13 Accordingly, D36 is the closest prior art, and the compound of claim 12 of D36 (identified as CPF-2 in the opposed patent) is a reasonable starting point for assessing inventive step within that disclosure.