J A • K E M P

17 December 2018

Our Ref: Q40231EP JHS/CJM/JZC

STATEMENT OF FACT AND ARGUMENTS IN SUPPORT OF OPPOSITION

Patent No:	EP 2 955 190 B1 (granted 28 March 2018)
Application No:	15154759.3
Title:	Chemical compounds
Patentee:	NuCana plc
Opponent:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City CA 94404 United States of America

PATENT ATTORNEYS • TRADE MARK ATTORNEYS
LONDON • OXFORD • CAMBRIDGE • PARIS • MUNICH

14 South Square, Gray's Inn, London WC1R 5JJ
T +44 20 3077 8600 **F** +44 20 7430 1000
mail@jakemp.com **www.jakemp.com**
A list of our partners is available at our principal place of business at the address above. Regulated by IPREG

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1 REQUESTS

1.1 Revocation of European Patent No. 2 955 190 B1 in its entirety is requested.

1.2 If the Opposition Division contemplates any outcome other than complete revocation, Oral Proceedings are requested. At any eventual Oral Proceedings, the Opponent will be represented in English and will require interpretation into English if the Patentee speaks in any other language (Rule 4 EPC).

1.3 We request that the opposition fee is debited from J A Kemp's deposit account number 2805.0038. We also request that any underpayment is deducted from, or any overpayment credited to, this deposit account.

2 SUMMARY OF THE GROUNDS OF OPPOSITION

2.1 The patent is opposed on the grounds provided by Article 100(a) EPC. The patent is opposed for lack of an inventive step under Articles 52(1) and 56 EPC.

2.2 The patent is also opposed on the grounds of Article 100(b) EPC. The patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

2.3 The patent is further opposed on the grounds provided by Article 100(c) EPC. The patent contains subject matter which extends beyond the content of the application as filed.

3 DOCUMENTS RELIED UPON

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 DAST*", 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 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 Resumé 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., 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*, 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

4 ADDED SUBJECT MATTER

Claims 1 to 15 add subject matter, contrary to the requirements of Article 123(2) EPC. There is no basis in the application as originally filed for these claims.

The description of the patent as granted also contains passages which lack basis in the application as originally filed, and similarly contravenes Article 123(2) EPC.

4.1 Claim 1

4.1.1 Claim 1 lacks basis in the application as filed.

4.1.2 During prosecution, the Patentee amended claim 1 as originally filed in order to derive claim 1 as granted. 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 (-CH_3)*". 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 (-CH_3); Y is F…*". There is no basis for making that selection in the application as filed. The restrictions necessary can only be made by selecting specific alternatives from multiple lists, contrary to Article 123(2) EPC.

4.1.3 In more detail, in deriving claim 1 of the patent, the patentee chose to limit the 2- position of the pentose ring in the Formula (I) moiety. As 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.

4.1.4 The Patentee 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.

4.1.5 Furthermore, it is stressed that the selections made by the Patentee in deriving claim 1 as granted are not simply formal in nature. As explained below, they rather represent a new technical teaching that is not present in the application as originally filed. In doing so, they further introduce new subject matter, contrary to Article 123(2) EPC.

4.1.6 The basic principle of Article 123(2) EPC is set out in section H-IV-2.1 of the EPO Guidelines for Examination. That section explains that

> *"An amendment should be regarded as introducing subject-matter which extends beyond the content of the application as filed, and therefore unallowable, if the overall change in the content of the application (whether by way of addition, alteration or excision) results in the skilled person being presented with information which is not directly and unambiguously derivable from that previously presented by the application, even when account is taken of matter which is implicit to a person skilled in the art (see G 2/10)."*

4.1.7 In the present case, the amendments made to claim 1 clearly result in the skilled person being presented with information that is not directly and unambiguously derivable from the application as filed, and thus extend beyond the content of the original application.

4.1.8 The relevance of the amendments at issue is set out in submissions of the Patentee dated 29 February 2016. The amendments made by the Patentee were not merely intended to establish novelty over documents cited by the Examiner, but were made to focus on compounds having a particular technical relevance not taught in the original application. Thus, the 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".*

4.1.9 Thus, the amendments made by the Patentee present the skilled person with the information that 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.

4.1.10 The application as filed provides the skilled person with technical teaching regarding the compounds claimed therein. In this regard, page 1 explains that anticancer drugs such as fluorodeoxyuridine, cytarabine and gemcitabine have poor membrane permeation and that phosphate prodrugs have been proposed to overcome this issue. Pages 2 and 3 state that phenyl methoxyalaninyl phosphoramidates have been described as prototype pro-moieties for intracellular delivery of bioactive nucleotides, but "surprisingly" other derivatives of oxyamino acid-phosphoramidate nucleoside analogues are more potent than the phenyl methoxyalaninyl phosphoramidate in the treatment of cancer. In this context, page 14 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 phosphoramidate can give surprising and substantial potency boosts of pro-tides derived from BVDU against a range of cancer cell types*".

4.1.11 The teaching of the application as filed is thus that by modifying the *phosphoramidate* portion of nucleoside analogues, efficacy against cancer can be improved. However, there is **no teaching** in the application as filed to show that compounds specifically having a fluorinated pentose moiety are particularly beneficial over analogues lacking such features. The restriction to such compounds thus provides the skilled person with new technical information that cannot be derived from the application as filed, contrary to Article 123(2) EPC. Claim 1 thus extends beyond the disclosure contained in the parent application as filed and thus also contravenes Article 76(1) EPC.

4.1.12 In addition to the amendments to claim 1 discussed above, 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. However, that passage relates **only** to derivatives, not to metabolites. The decision to amend the claim based on the description of one specific compound form (derivatives) from a list of multiple forms (derivatives and metabolites) constitutes a third selection from a third list, and further contravenes Article 123(2) EPC.

4.1.13 Accordingly, the selection of

(i) the limitation of Y rather than X;

(ii) the selection of F at that position, rather than any of H, Cl, Br, I, OH and methyl; and

(iii) the provision of derivative forms of the compound, rather than metabolites;

is a combination which is not directly and unambiguously disclosed in the application as filed, and further imparts a new technical teaching that is not present in the application as filed, contrary to Article 123(2) EPC.

4.2 **Claim 2**

4.2.1 Claim 2 is dependent on claim 1 and defines X and Y using the same definition as claim 1. Claim 2 contravenes Article 123(2) for the same reasons as claim 1.

4.2.2 In addition, claim 2 defines position R as being selected from a limited selection of alternatives including C_{1-6} primary or secondary alkyl; and C_{1-6}alkylC_{5-7}aryl. These alternatives were included in claim 2 as filed, but are not present anywhere in the parent application as filed. Specifically, these alternatives are not present in either claim 2 of the parent application as originally filed, or in the description at page 7 lines 16 to 23, both of which passages provide description of position R. Claim 2 thus

extends beyond the content of the parent application as filed and thus contravenes Article 76(1) EPC also.

4.3 **Claims 3 to 11**

4.3.1 Claims 3 to 11 are all dependent on claim 1 and claim 2. They define X and Y using the same definition as claim 1 and therefore likewise contravene Article 123(2) EPC. Insofar as they depend on claim 2, they likewise contravene Article 76(1) EPC for the same reasons as claim 2.

4.4 **Claim 12**

4.4.1 Claim 12 depends on any one of the preceding claims and specifies that when n is 0 each of X and Y is F. Claim 12 contains added matter for the same reason as claim 1 with respect to amendment of "*derivative or metabolite*" to "*salt, ester, or salt of such ester*". Insofar as claim 12 depends on claim 2, it likewise contravenes Article 76(1) EPC for the same reasons as claim 2.

4.5 **Claim 13**

4.5.1 Claim 13 is a medical use claim. It is directed to a compound according to any one of claims 1 to 12 for use in a method of treatment.

4.5.2 Claim 13 defines subject matter not clearly and unambiguously derivable from the application as filed. Claim 13 derives from claim 17 as originally filed, which related to a compound according to any one of original claims 1 to 16. Claims 1 to 12 of the opposed patent do not correspond to any of claims 1 to 16 of the application as filed, as explained above. Claim 13 as granted therefore likewise does not find basis in the application as originally filed and thus contravenes Article 123(2) EPC. As claim 13 relates to a compound according to claim 1 or claim 2, it likewise contravenes Article 76(1) EPC for the same reasons as claim 1 or claim 2.

4.6 **Claim 14**

4.6.1 Claim 14 is directed to a pharmaceutical composition comprising a compound according to any one of claims 1 to 12 in combination with a pharmaceutically acceptable carrier, diluent or excipient.

4.6.2 Like claim 13, claim 14 defines subject matter not clearly and unambiguously derivable from the application as filed. Claim 14 derives from claim 18 as originally filed, which related to a compound according to any one of original claims 1 to 16. As claims 1 to 12 of the opposed patent do not correspond to any of claims 1 to 16 of the application as filed, claim 14 as granted has no basis in the application as originally filed and contravenes Article 123(2) EPC. As claim 14 relates to a composition comprising a compound according to claim 1 or claim 2, it likewise contravenes Article 76(1) EPC for the same reasons as claim 1 or claim 2.

4.7 **Claim 15**

4.7.1 Claim 15 relates to a method of preparing a pharmaceutical composition comprising the step of combining a compound according to any one of claims 1 to 12 with a pharmaceutically acceptable excipient, carrier or diluent

4.7.2 Claim 15 also defines subject matter not clearly and unambiguously derivable from the application as filed. Claim 15 derives from claim 19 as originally filed, which related to a compound according to any one of original claims 1 to 16. For the reasons set out above for claims 13 and 14, claim 15 likewise contravenes Articles 123(2) and 76(1) EPC.

4.8 **Description**

4.8.1 The description of the opposed patent extends beyond the content of the application as originally filed.

4.8.2 Page 3 line 12 to page 4 line 7 of the original description provided a counterpart to claim 1 as originally filed. During examination, that passage was amended in the same way as claim 1. This passage of the description is not clearly and unambiguously derivable from the application as originally filed for the reasons given above in the context of claim 1.

4.8.3 Referring to Formula (I), page 9 line 16 of the original description explained that "*Preferably, X and Y are independently selected from the group comprising F, H and OH*". This passage was amended to refer to X only. There is no basis in the application as filed for a compound of Formula (I) wherein, specifically, Y is F and X is F, H or OH. As stated in T296/96 and followed in many subsequent decisions, the content of a document is not to be viewed as a reservoir from which features pertaining to separate embodiments can be combined to artificially create new embodiments.

4.8.4 The above passages of the description cannot be clearly and unambiguously derived from the application as originally filed. The description therefore contravenes Article 123(2) EPC.

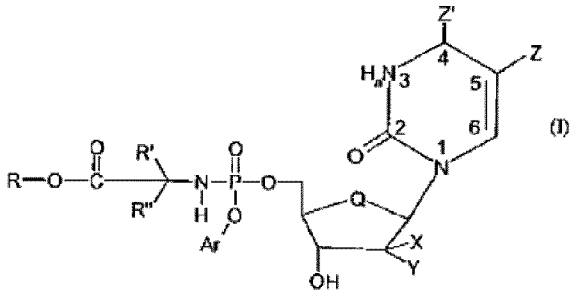
5 INSUFFICIENCY

5.1 Claims 1 to 11 do not meet the requirements of Article 83 EPC. Claims 13 to 15 do not meet the requirements of Article 83 EPC insofar as they are dependent on any one of claims 1 to 11.

5.2 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).

The Opposed Patent Lacks Teaching of any Exemplified Compound of Claim 1 except Compounds in Which Both Y is F and X is F

5.3 Claim 1 of the opposed patent is directed to a compound having the following general Formula I

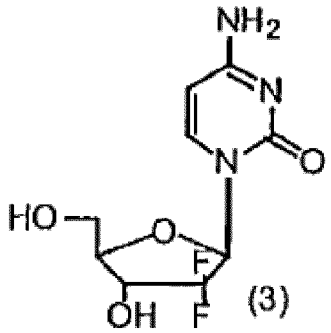


in which the moieties X and Y are defined thus:

"*X is independently selected from the group H, F, Cl, Br, I, OH and methyl (-CH_3);*
Y is F".

5.4 According to the Patentee, the compounds claimed in the opposed patent are characterised by having a particular substitution on the 2' position, corresponding to the moieties X and Y in Formula I. The representation of the positions of X and Y relative to the pentose ring in Formula I is somewhat unconventional. Nevertheless, the Patentee in D9, its letter to the Examining Division of 29 February 2016, stresses that the claimed compounds are distinguished from the cited art by virtue of requiring that Y is F (D9, page 2, paragraphs 5, 7 and 9). Thus according to the Patentee, the claimed compounds have 2'-fluoro in the "*down*" position and a group X in the "*up*" position on the pentose ring that forms part of the nucleoside moiety (D9, page 2, paragraphs 5, 7 and 9). Without necessarily agreeing that the stereochemistry of X and Y is clear in Formula I, the discussion which follows is directed at claims that are construed according to the Patentee's stated interpretation, i.e. compounds having a 2'-fluoro in the "*down*" position and a group X in the "*up*" position.

5.5 According to claim 1 as granted, X is "*independently selected from the group H, F, Cl, Br, I, OH and methyl (-CH_3)*". However, the only exemplified compounds are those in which X is fluoro, specifically those in which the nucleoside moiety is gemcitabine. As noted in paragraph [002] of the patent, this nucleoside analog has the structure



(3)

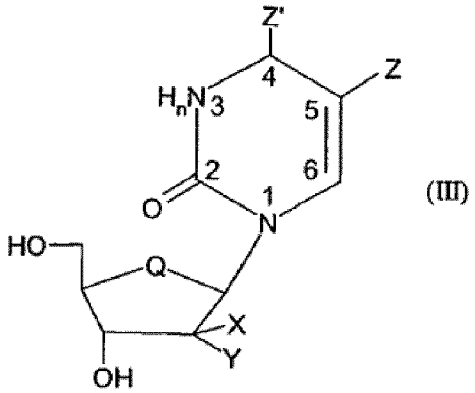
5.6 The patent does not exemplify any claimed compound in which X is other than F. In particular, the patent does not disclose any claimed compound in which Y = F and X = -CH_3.

The Opposed Patent does not Provide a General Scheme or Procedure that Enables the Skilled Person to Make a Compound of Claim 1 in which Y is F and X = CH_3

5.7 Sufficiency is assessed based on the content of the application as filed. In the following discussions, we will therefore refer to the text of the application as filed, published as WO 2005/012327. Page and line number references refer to WO 2005/012327.

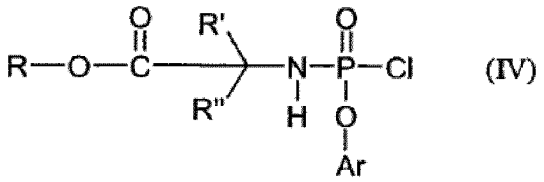
5.8 Sufficiency is judged on the basis of the content of the application as filed, taking into account common general knowledge at the relevant date. The patent has a filing date of 20 July 2004. If the Patentee wishes to rely on the priority date of 21 July 2003, then the disclosure is required to be an enabling disclosure at that date.

5.9 The description of how to prepare compounds according to claim 1 is given on page 16, line 28 to page 17, line 5. 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)*



(III)

with a compound of formula (IV)



(IV)

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

5.10 The skilled person is therefore required to use as the starting material a nucleoside analog of Formula III. The specification 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 $-CH_3$. As noted above, the only exemplified nucleoside analog in the specification is one in which Y is F and in which X is also F. This difluoro substituted compound, gemcitabine, is acknowledged in the specification to be a known, "*well established*" anti-cancer agent (see specification, page 1, lines 6 to 10).

5.11 According to the specification, if the skilled person wishes to prepare a compound of claim 1 in which Y = F and X = $-CH_3$, then the skilled person should use as a starting material a nucleoside analog of Formula III in which Y = F and X = $-CH_3$.

5.12 However, at the relevant date, such nucleoside analogs of Formula III were not known. Moreover, at the relevant date the skilled person would have had to engage in an extraordinary amount of experimentation to synthesise such a starting material.

5.13 As noted by the Boards of Appeal (Case Law of Boards of Appeal, 8th Ed., 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.

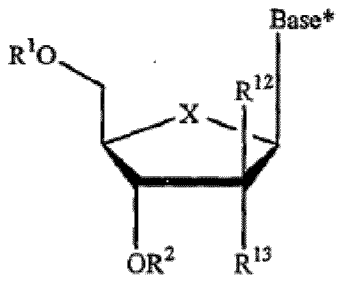
Information which could only be obtained after a comprehensive search was not to be regarded as part of the common general knowledge. This need for an enabling disclosure was also in conformity with the principle expressed in Article 83 EPC. The requirements as to the sufficiency of disclosure were, therefore, identical to these considerations of disclosure for the purposes of assessing novelty.

5.14 In the opposed patent, the starting material of Formula III in which Y = F and X = $-CH_3$ was not available to the skilled person at the relevant date. Such a compound was not known to the public. Neither was there any disclosure that would enable the skilled person, without undue burden, to synthesise such a compound of Formula III without undertaking a research programme.

5.15 Much of the evidence for this has already been 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 as 27 June 2003. 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.

5.16 Claim 1 of D1 is directed to:

"A compound of Formula (IX):



(IX)

or a pharmaceutically acceptable salt thereof, wherein:

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

X is O;

Base is a purine or pyrimidine base;*

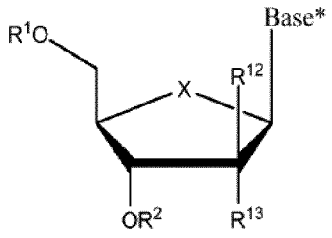
R^{12} is $C(Y^3)_3$;

Y^3 is H; and

R^{13} is fluoro".

Claim 1 of D34 is directed to:

"*A compound of Formula (IX):*



(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".

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.

5.17 The compounds claimed in D1, claim 1 and in D34, claim 1 are thus 2'-fluoro "*down*", 2'-methyl "*up*" 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 $-CH_3$. D1 does not contain any description of how to produce such 2'-fluoro "*down*" 2'-methyl "*up*" nucleosides. Nor does D34. The Patentee of D1 and D34 was therefore required to argue that at the relevant date (in the case of D1 and D34 this was 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 Division (OD) reviewed an extensive amount of evidence on this subject and concluded that the information was insufficient. For ease of reference, a copy of the OD Decision relating to D1 is attached as D2, and the separately-reasoned Decision relating to D34 is attached as D35.

5.18 The OD in D2 (Reasons 17.2) when considering the 2'-fluoro "*down*" 2'-methyl "*up*" 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 OD 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*".

5.19 The OD in D35 (Reasons 5.7, last 9 lines) when considering the 2'-fluoro "*down*" 2'-methyl "*up*" 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'CH_3(up) without extensive experimentation".*

5.20 It is clear from this that 2'-fluoro "*down*" 2'-methyl "*up*" nucleosides, such as compounds of Formula III in which Y = F and X = -CH_3, 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.

The Opposed Patent does not Teach What Starting Materials, Reagents or Chemical Reactions Could have been Used to Make a Compound of Formula III in Which Y = F and X = -CH_3

5.21 The opposed patent lacks any teaching regarding the starting materials, reagents or chemical reaction that a skilled person could have used as of 21 July 2003 (the priority date) or 20 July 2004 (the filing date) to make a compound of Formula III in which Y = F and X = -CH_3.

5.22 For example, such a compound of Formula III would have a 2'-fluoro "*down*" and 2'-methyl "*up*" substituent, but the opposed patent does not disclose what starting materials or reagents might be used to install such a substitution pattern on the sugar ring of a nucleoside. In particular, with regard to installing the 2'-fluoro "*down*" substituent, the opposed patent does not teach any fluorinated starting materials, fluorination reactions or the use of any fluorinating reagents. Nor does the opposed patent contain any guidance regarding what compound a skilled person could have fluorinated in order to make a 2'-fluoro 2'-methyl nucleoside.

Instead, the only fluorinated nucleoside is gemcitabine, which was publicly available. However, as of 21 July 2003 or 20 July 2004, 2'-fluoro-2'-methyl nucleosides were not available.

5.23 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'-fluoro "*down*" 2'-methyl "*up*" nucleoside. His statement is attached as D41A.

5.24 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 synthesizing 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 2'-fluoro "*down*" 2'-methyl "*up*" nucleoside given the lack of guidance in D1 and the available art.

5.25 Dr Marquez is now retired. Technical evidence in this opposition is therefore additionally provided by the declaration (D42A) 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' current 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.

5.26 In 2014 Prof Boons independently concluded in D43 (paragraphs 11.52-11.54) that in his opinion the synthesis of a 2'-fluoro-2'-methyl nucleoside in 2003 would have been a research project of significant complexity and uncertain outcome. He remains of this opinion (D42A, paragraph 5).

5.27 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).

5.28 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).

5.29 Prof Boons first notes that the opposed patent tells the skilled person nothing about how to prepare 2'-fluoro-2'-methyl 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'-fluoro-2'-methyl nucleoside (D42A, paragraph 10).

5.30 With respect to the task of synthesising a 2'-fluoro-2'-methyl 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).

5.31 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).

5.32 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).

5.33 While a number of fluorinating reagents had been disclosed in the art as of the relevant dates, the opposed patent fails to mention any of them. For example, nucleophilic fluorinating reagents such as hydrogen fluoride (HF), pyridine·HF, tetrabutylammonium hydrogen difluoride ($nBu_4N^+HF_2$), 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 (XFe_2), trifluoromethylhypofluorite (CF_3OF), and acyl and perfluoroacyl hypofluorites (RC(O)OF and $R_1C(O)OF$), 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 opposed patent 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 2'fluoro "*down*" 2'-methyl "*up*" nucleoside.

5.34 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 $-CH_3$, a skilled person as of the relevant dates would have had to determine whether to attempt to install the 2'-fluoro *"down"* 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).

5.35 Accordingly, the opposed patent 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 = $-CH_3$.

As of the relevant dates, Fluorination Chemistry is Unpredictable

5.36 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 = $-CH_3$ 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).

5.37 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 opposed patent 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).

5.38 The first published synthesis of a 2'-fluoro-2'-methyl 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.

5.39 They 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"*.

5.40 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 opposed patent.

5.41 The opposed patent 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'-hydroxy-2'-methyl substitution like the chemical intermediates reacted with DAST in D5. Rather, the opposed patent requires the skilled person to obtain the compound of Formula III from a commercial source (not possible for a 2'-fluoro-2'-methyl nucleoside as of 21 July 2003 or 20 July 2004) or to devise, without any guidance whatsoever, a method to produce such a 2'-fluoro-2'-methyl 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 2'-fluoro "*down*" 2'-methyl "*up*" nucleoside. In other words, a skilled person would not have known how to prepare starting material of Formula III in which Y = F and X = -CH_3.

5.42 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'-fluoro-2'-methyl nucleoside in 2003 or 2004, given the difficulties which they would have foreseen (which are discussed in D43).

5.43 Even if, *arguendo*, a skilled person as of the relevant dates had considered using DAST to try to make a 2'-fluoro "*down*" 2'-methyl "*up*" nucleoside of Formula III, 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.

5.44 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.

5.45 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 opposed patent 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 2'-fluoro "*down*" 2'-methyl "*up*" nucleoside of Formula III.

5.46 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 2'-fluoro "*down*" 2'-methyl "*up*" nucleoside of Formula III. Rather, it would have been

necessary to actually try such reactions to see if they gave the desired fluorinated products with the appropriate stereochemistry.

Given the Absence of any Teaching in the Opposed Patent, an Extraordinary Amount of Experimentation Would Have Been Required for a Skilled Person as of 21 July 2003 or 20 July 2004 to Make a Compound of Formula III in which Y = F and X = -CH_3

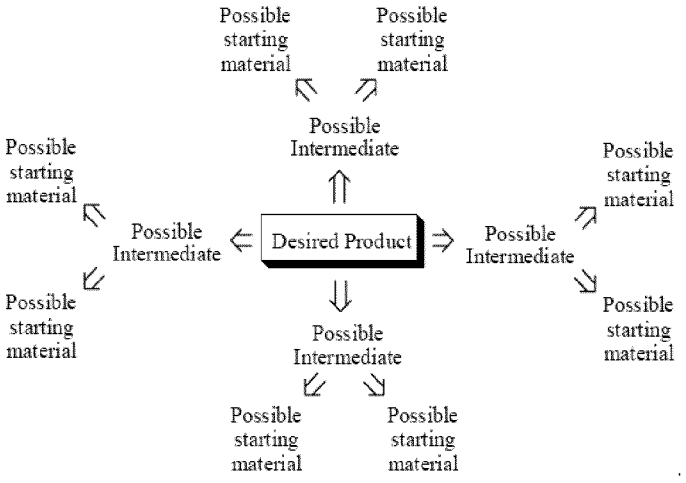
5.47 Using the disclosure of the opposed patent and in light of the art, an extensive amount of experimentation would have been required for a skilled person as of 21 July 2003 or 20 July 2004 to attempt to synthesise a 2'-fluoro "*down*" 2'-methyl "*up*" compound of Formula III. Given the absence of any teaching in the opposed patent, the skilled person would have had to design a synthesis *ab initio*, modifying the plan based on a substantial amount of work.

5.48 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 = -CH_3.

5.49 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 = -CH_3, the skilled person would determine 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'-fluoro *"down"*-2'-methyl *"up"* 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).

5.50 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. 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 might 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).

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



5.52 A skilled person as of the relevant dates might have considered multiple potential routes to making a compound of Formula III in which Y = F and X = -CH_3, and in particular to creating the 2'-fluoro-2'-methyl substitution on the sugar ring. The opposed patent provides no guidance as to which of these routes to try or how to carry out any of these methods.

5.53 Upon determining a reaction scheme (with no guidance from the opposed patent), 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).

5.54 The opposed patent 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. 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). Prof Boons concludes that the synthesis of a 2'-fluoro-2'-methyl nucleoside in 2003 or in 2004 would have been a research project of significant complexity and uncertain outcome (D42A, paragraph 11).

Contemporaneous Evidence of What a Skilled Team of People did

5.55 Evidence of the extensive experimentation that would be required when attempting to produce a compound of Formula III in which Y = F and X = $-CH_3$, i.e. a 2'-fluoro "*down*" 2'-methyl "*up*" nucleoside can be seen from the actions of Idenix Pharmaceuticals LLC ("*Idenix*") a Patentee of D1. This is contemporaneous evidence of what a skilled team of people actually did. Beginning in 2002, Idenix attempted to prepare a 2'-fluoro "*down*" 2'-methyl "*up*" 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 to try to identify a suitable procedure to make a 2'-fluoro "*down*" 2'-methyl "*up*" nucleoside.

5.56 It was only when information was available that derived from the authors of D5, that Idenix were able to produce a 2'-fluoro "*down*" 2'-methyl "*up*" nucleoside. This was more than two years after Idenix had begun the project to try to prepare such a compound.

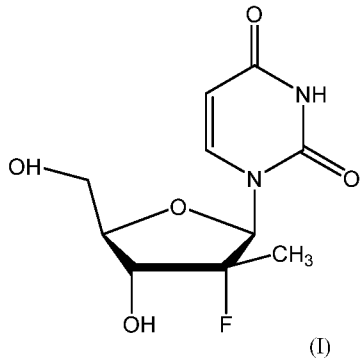
5.57 The validity of D1 has been considered in the UK High Court and Court of Appeal, resulting in the Decisions D10 and D11, respectively. The work carried out by Idenix between 2002 and early 2005 was reviewed by the court; several of the scientists involved in the project were cross-examined. Based on the witness statements and extensive documentary evidence, the Decision 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'-fluoro "*down*" and 2'-methyl "*up*" compound. These are also set out in Annex A to this Opposition Statement.

The Research Project to try to Make a 2'-F "*down*" 2'-Me "*up*" Nucleoside

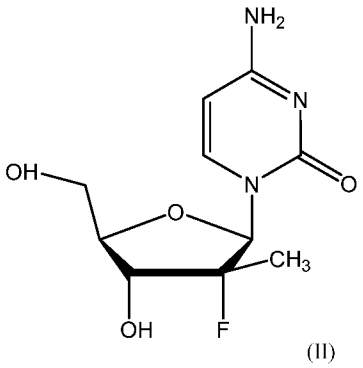
5.58 The team of skilled chemists working for Idenix, tried many different routes to make a 2'-F "*down*" 2'-Me "*up*" nucleoside. This involved extensive trial and error and many different synthesis routes over a period of years. This period spans from 2002 (before the priority date of the opposed patent) 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.

5.59 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'-F "*down*" 2'-

Me "*up*" nucleoside. The compounds that the project sought to make are 2'-fluoro-2'-methyl uridine nucleoside (I) and 2'-fluoro-2'-methyl cytidine nucleoside (II) whose structures are depicted in D25, paragraph 6 and reproduced below:



(I)



(II)

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, several of them being very skilled chemists indeed.

5.60 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). Professor Fleet is an eminent and experienced organic chemist; an expert in carbohydrate chemistry. 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 = $-CH_3$.

5.61 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); attending a training course in April 2003 on the subject matter of fluorination chemistry (D25, paragraph 120); 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).

5.62 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. In fact, Drs Gosselin and Imbach won an EPO Inventor of the Year award in 2012 for their work in the field of nucleosides. Clearly they are indeed skilled nucleoside chemists.

5.63 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)

5.64 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)

5.65 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)

5.66 Dr Coe then suggests some possible reagents, leaving groups and reaction conditions to make the target compound 9. Note also that Dr Coe warns against the use of DAST 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)

5.67 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.

5.68 Idenix also brought in additional chemists to work on the project to prepare a 2'-fluoro "*down*" 2'-methyl "*up*" nucleoside. D24 is the testimony of Dr Alastair Stewart 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 = $-CH_3$.

5.69 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 = CH_3) 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).

5.70 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, many of them very skilled chemists indeed. This team would at the very least have been aware of any relevant common general knowledge. Indeed, the depth of knowledge was clearly more than that of the average skilled person. 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 = $-CH_3$.

5.71 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'-fluoro "*down*" 2'-methyl "*up*" nucleoside. This demonstrates that the starting material

of Formula III of the opposed patent in which Y = F and X = -CH_3 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.

5.72 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 lactone to a dihydrofuranosyl sugar and condensation with a nucleobase)	**D21**, p. 1 (Scheme G1) (2004) **D22**, p. 2 (2004)

5.73 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) *see also* **D23**, p. 3 (numbered p. 2)
Diethylaminosulfur trifluoride (DAST)	**D23**, pp. 2, 3 (numbered pp. 1, 2)
$Et_3N{\cdot}3HF$	**D18**, p. 2 (numbered p. 11) **D17**, pp. 7, 8 (figs. a, 2)
Bu_4NHF_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 ($Bu_4NH_2F_3$)	**D17**, pp. 3, 6
Perfluoro-1-butanesulfonyl fluoride (PBSF)	**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_4NH_2F / $Fe(AcAc)_3$	**D18**, p. 2 (numbered p. 11) **D17**, p. 9 (fig. 3)

Conclusion

5.74 It is clear from the discussion that the skilled person at 21 July 2003 or at 20 July 2004 was presented with a research project if he wished to make a compound of claim 1 in which Y = F and X = $-CH_3$. The starting material,

a compound of Formula III in which Y = F and X = -CH_3, was not available to the skilled person. A skilled person who tried to make such a compound of Formula III would be required to undertake extensive experimentation, if indeed he would be able to succeed at all. This represented an undue burden. Since the skilled person would have been unable to find out from the patent or from common general knowledge how to obtain the required starting material, the patent does not provide a sufficient disclosure of compounds of claim 1 in which Y = F and X = CH_3.

5.75 It is also evident from the cited documents and from the discussion above that the difficulties facing the skilled person who in July 2003 or July 2004 wished to try to make the starting material of Formula III in which Y = F and X = -CH_3, were necessarily difficulties that the skilled person in July 2003 or July 2004 would have faced if he tried to make a corresponding compound of claim 1 via any alternative synthesis route that used a different starting material than Formula III (even though no such alternative route is contemplated or suggested in the patent). It is evident that it was the fluoro "*down*" methyl "*up*" substitution pattern at the 2' position of the nucleoside that was so difficult to create. This substitution pattern is present in the compounds of Formula I of claims 1 to 11 in which Y = F and X = CH_3. The substitution pattern at the 2' position is also the feature that the Patentee considers distinguishes the claimed compounds over the art (see D9). A skilled person in July 2003 or in July 2004 who tried to make a compound of Formula I of claim 1 having a fluoro "*down*" methyl "*up*" substitution pattern at the 2' position would be required to undertake extensive experimentation, if indeed he would be able to succeed at all. This represented an undue burden.

5.76 Accordingly, the subject matter of claims 1 to 11 do not meet the requirements of Article 83 EPC. Claims 13 to 15 also fail to meet the requirements of Article 83 EPC insofar as these claims depend on any one of claims 1 to 11.

6 THE CLAIMS LACK INVENTIVE STEP

6.1 Claims 1 to 12 lack inventive step over D36 (US 2003/0109697 A1).

6.2 The alleged invention relates to nucleotide derivatives and their use in the treatment of cancer (patent, paragraph [0001]). D36 corresponds to D1 cited during examination of the patent. D36 discloses that the compounds described in D36 are useful for treating cancer (D36, paragraph [0016]).

6.3 In response to an inventive step objection based on D36, the Patentee with its response letter filed the post-published paper D40. The Patentee asserted that this indicated that a surprising technical effect (an improved anti-cancer effect) had been achieved with compounds having a fluorinated pentose moiety. However

(i) The breadth of terms such as *"alkyl"* in claim 1 is such that it is not credible that any alleged technical effect is seen over the whole scope of the claim;

(ii) Evidence of a technical effect should be shown in comparison with the closest prior art, i.e. with D36, and not with a more distant compound. The information in D40 is not relevant.

(iii) Only three 2', 2'-difluoro compounds are exemplified in the patent. These compounds do not show an improvement over a compound of D36.

(iv) Compounds having a fluorinated pentose moiety have been shown to lack anti-cancer activity.

(v) D40 also shows that compounds of claim 1 in which R is isopropyl lack anti-cancer activity.

(i) The breadth of claim 1 is such that it is not credible that any alleged technical effect is seen over the whole scope of the claim.

6.4 As set out in T939/92 and followed in numerous subsequent decisions, the question as to whether or not a technical effect was achieved by all the chemical compounds covered by a claim might properly arise under

consideration of inventive step if this technical effect turned out to be the sole reason for the alleged inventiveness of these compounds. When only some but not substantially all claimed compounds exhibited a particular technical effect, the conclusion had to be that the invention as broadly defined in the independent claim was not a solution to the technical problem of achieving the given technical effect, with the consequence that the alleged technical effect of some of the claimed compounds was to be disregarded when determining the objective problem underlying the invention and thus when assessing inventive step (Case Law of the Boards of Appeal I.D.9.8.3, page 231).

6.5 The patent discloses three specific compounds that fall within the scope of claim 1: CPF-31, CPF-40 and CPF-41. As shown in paragraphs [0193], [0195] and [0197] of the patent, these three compounds are all similar in structure. Even if a technical effect were to be shown for these three specific compounds, the definitions used in claim 1 are broad and open ended such that it is not credible that all compounds within the scope of the claim show the technical effect on which inventive step was alleged to be based (improved anti-cancer activity). For example, R, R', R'' and Ar all use broad and open-ended terms such as *"alkyl"*, *"aryl"*, *"alkyl aryl"*, *"alkylene chain"*, *"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."* The optional substituents are not specified.

6.6 It is not credible that all such compounds show an anti-cancer effect, let alone is it credible that all such compounds show the technical effect alleged by the Patentee to be the basis for inventive step i.e. an improved anti-cancer effect.

(ii) The information contained in D40 is not a comparison with the closest prior art, D36.

6.7 D36 was cited during examination. In response the Patentee submitted a letter (D9) and a post-published paper D40. D40 was referred to in

examination as D5. The Patentee's letter and submission of D40 resulted in the Examination Division in its Communication of 20 June 2017 analysing inventive step as follows:

> *"D1 [D36] is considered to be the prior art closest to the subject matter of claims 1-15 and discloses nucleotide phosphoramidate derivatives as anticancer agents. No examples of 2'-F derivatives are given, however, in paragraph 109 the possibility of a 2'-F derivative is present.*
>
> *The subject matter of claims 1 to 15 differs from this known subject matter in that the claimed compounds can be seen as selections from various lists in D1 [D36]".*
>
> *"The technical effect of the above mentioned selection is that the compounds of the present application have an improved behaviour. One of the ProTides (see D5 [D40]) mentioned in the application as filed, CPF-31 (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 (D5). Data is present in the application as filed showing the anti-cancer activity of CPF-31, CPF-40 and CPF-41, (all falling within the present claims) thus demonstrating that a technical effect has been achieved".*

6.8 The objective technical problem (OTP) set out during examination was that the claimed compounds have an improved behaviour as anti-cancer agents. The allegation of improved behaviour was set out by the Patentee in comparison with gemcitabine. However, gemcitabine is not the closest prior art. It is not a compound of D36. It does not contain a phosphoramidate group, unlike the compounds of D36 which do contain a phosphoramidate group, as do the compounds of claim 1. The comparison showing alleged improved behaviour over gemcitabine is therefore not a comparison with the closest prior art.

6.9 It is well-established by the Boards of Appeal that alleged advantages to which the Patent Proprietor 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 (T 20/81). As stated in the Case Law of the Boards of Appeal (CLBA), 8th Edition,

> *"Some beneficial effects or advantageous properties, if appropriately demonstrated by means of truly comparable results, can in certain circumstances properly form a basis for the definition of the problem that the claimed invention sets out to solve and can, in principle, be regarded as an indication of inventive step. The only comparative tests suitable for this are, however, those which are concerned with the structurally closest state of the art to the invention, because it is only here that the factor of unexpectedness is to be sought".*
> (Emphasis added). [CLBA, I.D.4.2 page 175]

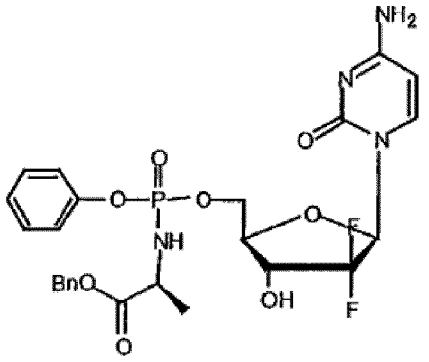
6.10 A comparison with gemcitabine is not therefore a comparison with the closest prior art and does not provide a technical effect on which any allegation of inventiveness may be based.

6.11 D36, for example, specifically discloses the compound of claim 12 of D36. This nucleotide phosphoramidate derivative of the closest prior art, D36, is thus a suitable compound against which to compare the claimed compounds when assessing whether improved behaviour is seen.

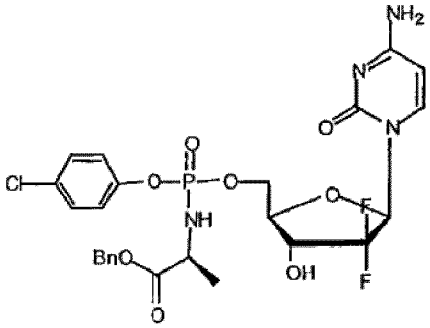
(iii) The three exemplified compounds of the patent do not show an improvement over the closest prior art.

6.12 The compound of claim 12 of D36 corresponds to Compound CPF 2 which was disclosed in the opposed patent as originally filed (page 27, line 10 to page 28, line 2) and is described in the opposed patent as an "*illustrative example*" (see page 14, lines 15 to 45 of the patent).

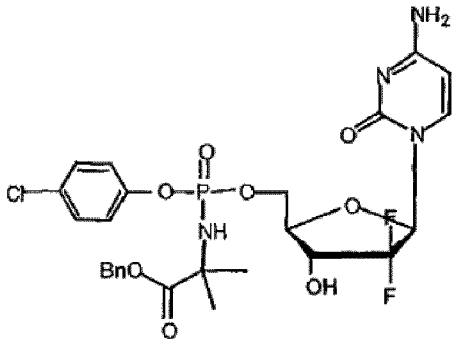
6.13 As was acknowledged during examination of the patent, the patent only discloses three specific compounds within the scope of claim 1 as granted: compounds CPF-31, CPF-40 and CPF-41.



CPF-31



CPF-40



CPF-41

6.14 The Table on pages 63 to 65 of the patent sets out experimental data reporting the activity of claimed compounds and comparative compounds with respect to human breast cancer cell line MDA MB231, human colon cancer cell line HT115 and human prostate cancer cell line PC-3 (see patent, paragraph [0297]). The activity is expressed as an EC50 in μM. The activity results of the compound of claim 12 of D36 (CPF-2) and

Compounds CPF31, CPF-40 and CPF-41 (within claim 1) are given below, taken from the Table in the opposed patent.

Compound	EC50/μM Breast MDA MB231	EC50/μM Colon HT115	EC50/μM 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

6.15 It will be seen from this that CPF 2, disclosed in D36, is more active than any of CPF-31, CPF-40 or CPF-41 against colon cancer. Even if the Patentee were to select one of the other cell lines as the cancer in which to measure the technical effect, it is clear that the alleged technical effect of improvement is not shown by all three exemplified compounds. There is no data to indicate an improvement that is shown by all three exemplified compounds over the closest prior art (CPF2), let alone any data to show an improvement across the whole scope of claim 1.

6.16 The subject matter of claim 1 does not therefore solve the problem of providing compounds with improved anticancer behaviour in comparison with the closest prior art. The objective technical problem is thus to provide alternative anticancer compounds. There is no purpose to the selection from the various lists of D36 and so there is no inventive step over the disclosure in D36 of nucleotide phosphoramidate derivatives.

(iv) Compounds having a fluorinated pentose moiety have been shown to lack anti-cancer activity.

6.17 The unjustified breadth of claim 1 can also be seen from additional documents such as D37. The Patentee in its letter of D9 (which led to the

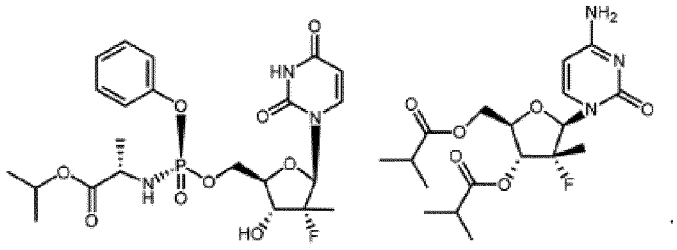
erroneous inventive step analysis of the Examination Report of 20 June 2017) stated:

> *"The present authors have shown that compounds having a fluorinated pentose moiety can be very potent anti-cancer agents, a result that could not have been predicted from D1 [D36]".* (Emphasis added). (D9, page 3, paragraph 3)

6.18 However, compounds having a fluorinated pentose moiety may fail to be very potent anti-cancer agents. Indeed, as shown by D37, compounds having a fluorinated pentose moiety may lack any activity as cancer agents.

6.19 The data in the patent to which the Patentee refers as showing the anti-cancer activity of the three exemplified compounds is set out in the Table in paragraph [0299]. These data are also set out in the Table above in paragraph 6.14 above. The exemplified compounds CPF-31, CPF-40 and CPF-41 are derivatives of gemcitabine, a 2' 2'-difluoro nucleoside. The Patentee's experimental data all relate to compounds having a fluorinated pentose moiety that is a 2'2'-difluoro moiety.

6.20 D37 is concerned with nucleotide inhibitors of hepatitis C virus (HCV NI). Specifically, D37 reports a study assessing *inter alia* the potential for clinical HCV NI to cause toxicity in various functional cell-based assays, including assays for cytotoxicity in multiple human cell lines and primary cells (D37, page 807, left-hand column, lines 6 to 9). The cell culture and cytotoxicity studies are described in D37, page 807, right-hand column, lines 10 ff. The cell lines tested included prostate metastatic carcinoma PC-3 (D37, page 807, right-hand column, line 13). The compounds tested in D37 are depicted in Figure 1 on page 807. The first two compounds in this Figure are sofosbuvir/GS-7977 and mericitabine/RG-7128 (nucleoside PSI-6130), whose structures are set out below:



Sofosbuvir/GS-7977 **Mericitabine/RG-7128 (nucleoside PSI-6130)**

6.21 As explained in D37, page 808, first full paragraph, in measuring the cytotoxic activity of the compounds, the cells were treated with the compound for five days. Cell viability was measured by the addition of viability reagents and the luminescence signal measured. The compound concentration that caused a fifty percent decrease in luminescent signal (CC_{50}) is a measure of toxicity. The results of cytotoxicity in human cell lines is given in Table 1 on page 809 of D37. The results for both "*sofosbuvir*" and "*PSI-6130*" show high CC_{50} values. For example, both compounds show a CC_{50} against prostate cells PC-3 of greater than 100.

6.22 The authors of D37 also comment:

> "*In this study we chose to measure the triphosphate concentration after 48-h incubations of compounds with PC-3 cells. As shown by the results in Table 3, sofosbuvir and PSI-6130 efficiently formed TP, illustrating that the lack of toxicity (CC_{50} <100 μM) (Table 1) was not due to poor intracellular activation*".

6.23 It is clear from D37 that sofosbuvir and PSI-6130 are not cytotoxic. The data provided by the Patentee only measures cytotoxic activity for three specific compounds, all of which include a nucleoside moiety having a 2',2'-difluoro pentose moiety, i.e. compounds of Formula I in which X and Y are both F. It is not plausible that compounds other than those having a 2',2'-difluoro pentose moiety solve the objective technical problem of providing alternative anti-cancer compounds, let alone that such

compounds solve any more onerous objective technical problem relating to any alleged improvement.

6.24 It is also instructive to consider documents submitted to the US PTO during prosecution and reissuance examination of the US patent corresponding to the opposed patent. We refer to D38 (Patentee's response to the US PTO of 22 December 2017) and D39 (Declaration by Hugh Griffith referred to in D38).

6.25 On page 2 of D38, in the section entitled "*Amendments to the claims*" it can be seen that the claims were limited to compounds having a 2',2'-difluoro pentose moiety, i.e. the claims were limited to each of X and Y being F (D38, page 2, lines 1 to 2).

6.26 The response explains the combination of properties that are required of a compound in order for it to achieve the required biological activity. The Patentee states:

> "*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 enzyme 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*". (D38 paragraph bridging pages 13 and 14)

6.27 The unpredictability of a compound's ability to be active against cancer is further explained in D39, which concludes:

> "*In collaboration with our academic partners approximately 4,500 phosphoramidate derivatives of nucleoside drugs have been designed and synthesised. For the majority of anti-cancer nucleoside drugs the phosphoramidate derivatives were less active than the parent nucleoside and/or did not retain activity in conditions associated with cell cancer resistance*". (D39, paragraph 20)

6.28 Accordingly, if the objective technical problem were to provide compounds with improved properties, the data in the patent show that

this problem has not been solved across the scope of the claims in comparison with a compound of D36 (the closest prior art). Moreover, D37, D38 and D39 show that it is not plausible that any anti-cancer activity is shown, let alone that any improved activity is shown for all compounds having a fluorinated pentose moiety in the nucleoside position.

(v) D40 shows that compounds of claim 1 in which R is isopropyl lack anti-cancer activity.

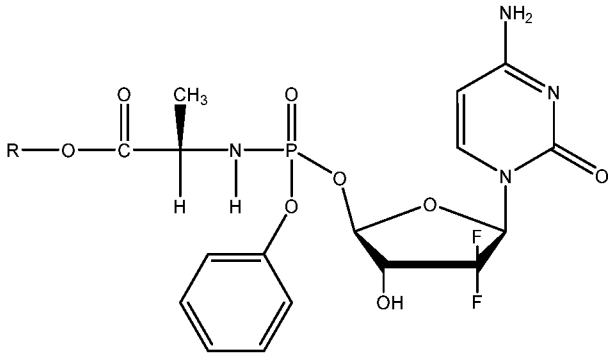
6.29 The unpredictability and lack of plausibility across the scope of the claims is even shown by those compounds of Formula I in which X and Y are both F i.e. compounds having a 2' 2'-difluoro pentose moiety. D40 shows that not even all compounds in which X and Y are both F have anti-cancer activity. The exact structure of the phosphoramidate is important. In a compound of claim 1, the value of e.g. R impacts significantly on anti-cancer activity.

6.30 Table 1 on page 1534 of D40 sets out the IC_{50} (μM) of selected compounds against four cancer lines: L1210 (leukaemia), CEM (human T lymphocyte), MP-2 (pancreatic) and BxPC-3 (gemcitabine-resistant pancreatic). Table 1 of D40 appears to include some of the data presented to the US PTO in D39. An extract from Table 1 of D40 is given below:

Entry	IC_{50} (μM)			
	L1210	CEM	MP-2	BxPC-3
6a	>5	>5	>5	>5
6f (CPF-31)	0.035 ± 0.02	0.1 ± 0.03	0.44 ± 0.06	0.15 ± 0.04
dFdC (gemcitabine)	0.013 ± 0.2	0.086 ± 0.003	1.04 ± 0.71	0.67 ± 0.34

6.31 The control compound is dFdC. This is 2', 2'-difluoro 2'-deoxycytidine, i.e. gemcitabine. This is acknowledged in the opposed patent, paragraph [0002] to be a well-established anti-cancer agent.

6.32 From Scheme 3 on page 1533 of D40, the structures of Compounds 6a and 6f can be seen to be



6a R = iso-propyl (i.e. alkyl)

6f R = benzyl (i.e. alkylaryl)

6.33 Both Compounds 6a and 6f are within the scope of at least claim 1. The only difference is the ester moiety corresponding to R in claim 1. The iso-propyl ester 6a has very much higher IC_{50} values than the benzyl ester compound 6f. Indeed, 6a has values higher than the "*well-established*" cancer agent gemcitabine.

6.34 Thus, based on the Patentee's own data, it is clear that the problem of providing alternative anti-cancer compounds is not solved across the whole scope of the claim. As the Patentee explained to the US PTO, the skilled person could not predict that any given compound would have the requisite combination of properties to show increased intracellular levels of active metabolite. Note in this respect that the claims of the corresponding US patent were limited to those in which the moiety R was selected from the group consisting of carbocyclic alkyl, aryl and alkyl aryl (D38, page 1, immediately below the structural formulae). Thus, to the extent that any claim covers compounds in which R is alkyl without limit to its size or cyclic nature, the claims include compounds that do not solve the problem of providing alternative anti-cancer compounds. This particularly applies to compounds in which R is isopropyl. Such subject matter lacks inventive step.

Summary

6.35 D36 is the closest prior art. The subject-matter of claims 1 to 15 differs in that the claimed compounds are selected from various lists in D36. The Objective Technical Problem set out during examination was that the claimed compounds have an improved behaviour as anti-cancer agents. However, it is not credible that this objective technical problem is solved across the whole scope of claim.

6.36 The claim includes broad and open ended terms such as *"alkyl"*. Moreover, any alleged improved behaviour should be seen in comparison with the closest prior art (D36). Only three compounds within claim 1 are exemplified in the patent. These do not show an improvement over the compound of claim 12 of D36.

6.37 The Patentee alleges that compounds having a fluorinated pentose moiety can be very potent anti-cancer agents. However, in D38 and D39 the Patentee indicated that anti-cancer activity is not predictable and that the majority of phosphoramidate derivatives were less active than the parent nucleoside and/or did not retain activity in conditions associated with cell cancer resistance.

6.38 D37 provides evidence of compounds having a fluorinated pentose moiety that lack activity as anti-cancer agents. D40 shows that the exact structure of the phosphoramidate is also important. The benzyl ester CPF-31 is active, whereas the corresponding isopropyl ester (compound 6a of D40) does not show activity. Both compounds are encompassed by claim 1.

6.39 If the objective technical problem from D36 is to identify compounds having an <u>improved</u> behaviour as anti-cancer agents, then this problem is not solved and in particular is not solved across the whole scope of the claim. The objective technical problem based on D36 is thus to provide <u>alternative</u> anti-cancer compounds. There is no purpose to the selection from the various lists of D36 and so there is no inventive step over the

disclosure in D36 of nucleotide phosphoramidate derivatives. Indeed, as the data in D40 show, claim 1 even encompasses compounds that do not solve the less onerous Objective Technical Problem of providing alternative anti-cancer compounds.

6.40 Claim 1 therefore lacks inventive step.

6.41 The same reasoning applies to each of dependent claims 2 to 12.

6.42 The same reasoning also applies to claim 13 (the medical use claim), claim 14 (to a pharmaceutical composition) and claim 15 (a method of preparing a pharmaceutical composition).

6.43 Claims 1 to 15 thus lack inventive step.

7 CONCLUSION

7.1 All claims of the opposed patent fail to meet the requirements of the EPC for one or more of the grounds provided by Article 100 EPC. The opposed patent should therefore be revoked in its entirety.

Europäisches Patentamt
European Patent Office
Office européen des brevets

Notice of opposition to a European patent

I. Patent opposed

Patent No.	EP2955190
Application No.	EP15154759.3
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	28 March 2018
Title of the invention	Chemical Compounds

II. Proprietor of the patent

first named in the patent specification	NuCana plc
Opponent's or representative's reference	Q40231EP

III. Opponent

Name	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City CA California 94404 United States of America
State of residence or of principal place of business	United States of America
Multiple opponents (see additional sheet)	☐

IV. Authorisation

1. Representative

	J A Kemp
Association No.:	811
Address of place of business	14 South Square Gray's Inn London Greater London WC1R 5JJ United Kingdom
Telephone/Fax	+44 20 3077 8600 / +44 20 7430 1000
E-mail:	mail@jakemp.com

Atea Pharmaceuticals, Inc.
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Multiple representatives (see additional sheet) ☐

Authorisation(s)

is/are enclosed ☐

has/have been registered under No. ☐

V. Opposition is filed against

the patent as a whole ☒

claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

- it is not new (Art. 52(1); Art. 54 EPC) ☐
- it does not involve an inventive step (Art. 52(1); Art. 56 EPC) ☒
- patentability is excluded on other grounds, namely articles ☐

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). ☒

(c) the subject-matter of the patent opposed extends beyond the content of the application/of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). ☒

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith on an attached document ☒

VIII. Other requests:

- Revocation of the patent in its entirety is requested. Oral proceedings are requested auxiliarily.

IX. Evidence presented

D01	Patent document	EP1523489 (B1) , 12.11.2014 original file name: D01 - EP 1523489 (B1).PDF attached as: Published-Evidence-1.PDF
D02	Other evidence	Opposition Division Decision original file name: D02 - Opposition Division Decision 18.04.2016.PDF attached as: Other-evidence-1.PDF
D03	Other evidence	Lal et al, Chem. Rev. 1996, 96, 1737-1755 original file name: D03 - Lal et al (1996).PDF attached as: Other-evidence-2.PDF
D04	Other evidence	Singh et al, Recent Advances in Nucleophilic Fluorination Reactions of Organic Compounds Using Deoxofluor and DAST, Synthesi original file name: D04 - Singh et al (2002).PDF attached as: Other-evidence-3.PDF
D05	Patent document	WO 2005/003147 (A2) , 13.11.2005 original file name: D05 - WO 2005_003147.PDF attached as: Published-Evidence-2.PDF
D06	Other evidence	Clark et al, J. Med. Chem. 2005, 48, 5504-5508 original file name: D06 - Clark et al (2005).PDF attached as: Other-evidence-4.PDF
D07	Other evidence	Clark et al, Bioorganic & Medicinal Chemistry Letters 16 (2006) 1712-1715 original file name: D07 - Clark et al (2006).PDF attached as: Other-evidence-5.PDF
D08	Other evidence	Clark et al, Synthesis, Journal of Carbohydrate Chemistry, 25:461-470, 2006 original file name: D08 - Clark et al Synthesis (2006).pdf attached as: Other-evidence-6.pdf
D09	Other evidence	Patentee Letter of 29 February 2016 to Examining Division original file name: D09 - Patentee letter of 29 February 2016 to Exam Division.PDF attached as: Other-evidence-7.PDF
D10	Other evidence	Idenix v Gilead UK High Court Judgement 1 December 2014 original file name: D10 - Idenix v Gilead UK Judgment - 01.12.14.PDF attached as: Other-evidence-8.PDF
D11	Other evidence	Idenix v Gilead UK Court of Appeal Judgement 8 November 2016 original file name: D11 - Idenix v Gilead UK Court of Appeal Judgement.pdf attached as: Other-evidence-9.pdf
D12	Other evidence	Email of 9 December 2018 - Dr J-F Griffon original file name: D12 - Email of 09.12.02 - Dr J-F Griffon.PDF attached as: Other-evidence-10.PDF
D13	Other evidence	Progress Report (Dec 2002) original file name: D13 - Progress Report (Dec 2002).PDF attached as: Other-evidence-11.PDF
D14	Other evidence	Email of 3 February 2003 - Dr J-F Griffon

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		original file name: D14 - Email of 03.02.03 - Dr J-F Griffon.PDF attached as: Other-evidence-12.PDF
D15	Other evidence	Email of 4 March 2003 - Dr J-F Griffon original file name: D15 - Email of 04.03.03 - Dr J-F Griffon.PDF attached as: Other-evidence-13.PDF
D16	Other evidence	Letter of 8 February 2003 from Dr Richard Storer of Idenix to Dr Paul Coe original file name: D16 - Letter of 08.02.03 (Dr Richard Storer).pdf attached as: Other-evidence-14.pdf
D17	Other evidence	Dr Coe's Letter replying to D16 original file name: D17 - Dr Coe_s Letter replying to D16.pdf attached as: Other-evidence-15.pdf
D18	Other evidence	Email of 03.06.03 - Dr J-F Griffon original file name: D18 - Email of 03.06.03 - Dr J-F Griffon.PDF attached as: Other-evidence-16.PDF
D19	Other evidence	Email of 28.08.03 - Dr J-F Griffon original file name: D19 - Email of 28.08.03 - Dr J-F Griffon.PDF attached as: Other-evidence-17.PDF
D20	Other evidence	Summary of Idenix Meeting (10.05.04) original file name: D20 - Summary of Idenix Meeting (10.05.04).PDF attached as: Other-evidence-18.PDF
D21	Other evidence	Report from meeting summarized in D20 original file name: D21 - Report from meeting summarized in D20.PDF attached as: Other-evidence-19.PDF
D22	Other evidence	Email of 11.11.04 (Dr Alastair Stewart) original file name: D22 - Email of 11.11.04 (Dr Alastair Stewart).PDF attached as: Other-evidence-20.PDF
D23	Other evidence	Email of 07.01.05 - (Dr Alastair Stewart) original file name: D23 - Email of 07.01.05 - (Dr Alastair Stewart).PDF attached as: Other-evidence-21.PDF
D24	Other evidence	Deposition of Dr Alastair Stewart (19.06.13) original file name: D24 - Deposition of Dr Alastair Stewart (19.06.13).PDF attached as: Other-evidence-22.PDF
D25	Other evidence	Substitute Declaration of Dr Griffon original file name: D25 - Substitute Declaration of Dr Griffon.pdf attached as: Other-evidence-23.pdf
D26	Other evidence	Notebook 1 original file name: D26 - Notebook 1.PDF attached as: Other-evidence-24.PDF
D27	Other evidence	Notebook 2 original file name: D27 - Notebook 2.PDF attached as: Other-evidence-25.PDF
D28	Other evidence	Summary of Results of Lit. Search of Dr Griffon original file name: D28 - Summary of Results of Lit. Search of Dr Griffon.PDF

		attached as: Other-evidence-26.PDF
D29	Other evidence	Report of Dr Griffon Meeting - 02.12.02 original file name: D29 - Report of Dr Griffon Meeting - 02.12.02.PDF attached as: Other-evidence-27.PDF
D30	Other evidence	Report of Dr Griffon Meeting - 03.12.02 original file name: D30 - Report of Dr Griffon Meeting - 03.12.02.PDF attached as: Other-evidence-28.PDF
D31	Other evidence	Resume of Dr Griffon original file name: D31 - Resume of Dr Griffon.PDF attached as: Other-evidence-29.PDF
D32	Other evidence	Transcript of English High Court Trial Day 4 pp.468-469 original file name: D32 - Transcript of English Trial Day 4 pp.468-469.PDF attached as: Other-evidence-30.PDF
D33	Other evidence	Transcript of English High Court Trial Day 2 pp.202-203 original file name: D33 - Transcript of English Trial Day 2 pp.202-203.PDF attached as: Other-evidence-31.PDF
D34	Patent document	EP2332952 (B1) , 29.04.2015 original file name: D34 - EP-B-2332952.PDF attached as: Published-Evidence-3.PDF
D35	Other evidence	Opposition Division Decision 26.04.18 original file name: D35 - Opposition Divison Decision 26.04.18.PDF attached as: Other-evidence-32.PDF
D36	Patent document	US2003/0109697 (A1) , 12.06.2003 original file name: D36 - US 2003 0109697 (A1).PDF attached as: Published-Evidence-4.PDF
D37	Other evidence	Feng J.Y. et al., Antimicrobial Agents and Chemotherapy, 2016, 60(2), 806-817 original file name: D37 - Feng - role of mitochondrial RNA polymerase....PDF attached as: Other-evidence-33.PDF
D38	Other evidence	US15279611 Response of 22 Dec 2017 to non-Final OA original file name: D38 - US15279611 Response of 22 Dec 2017 to non-Final OA.PDF attached as: Other-evidence-34.PDF
D39	Other evidence	Griffith declaration referred to in D38 original file name: D39 - Griffith declaration from US reissue.PDF attached as: Other-evidence-35.PDF
D40	Other evidence	Slusarczyk et al J Med Chem 2014 original file name: D40 - Slusarczyk et al J Med Chem 2014.PDF attached as: Other-evidence-36.PDF
D41A	Other evidence	Dr Marquez Declaration (26 Nov 2014) original file name: D41A - Dr Marquez Declaration (26 Nov 2014).PDF attached as: Other-evidence-37.PDF
D41B	Other evidence	CV of Victor Marquez - Oct14

		original file name: D41B - CV of Victor Marquez - Oct14.PDF attached as: Other-evidence-38.PDF
D42A	Other evidence	Professor Boons Declaration (24 Oct 2018) original file name: D42A - Prof. Boons Signed Declaration dated 24 Oct 2018.PDF attached as: Other-evidence-39.PDF
D42B	Other evidence	Professor Boons CV - Nov 2018 original file name: D42B - Updated Boons CV - Nov 2018.PDF attached as: Other-evidence-40.PDF
D43	Other evidence	Boons Expert Report (redacted) plus exhibits original file name: D43 - Boons Expert Report (redacted) plus exhibits.pdf attached as: Other-evidence-41.pdf

X. Payment

Method of payment: Debit from deposit account

The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated in the fees section below.

Currency: EUR

Deposit account number: 28050038

Account holder: J A Kemp

Refunds

Any refunds should be made to EPO deposit account: 28050038

Account holder: J A Kemp

Fees

	Factor applied	Fee schedule	Amount to be paid
010 Opposition fee	1	785.00	785.00
Total:		EUR	785.00

A Forms

	Details:	System file name:
A-1 Form for notice of opposition		ep-oppo.pdf

B Attached document files

		Original file name:	System file name:
B-1	1. Facts and arguments	Opposition Statement as filed 17 Dec 2018 Q40231EP JHS JZC.pdf	OPPO.pdf
B-2	1. Any annexes (other than citation) to an opposition letter - Cover Letter	File Opposition 17 Dec 2018 Q40231EP JHS JZC.PDF	OTHER-1.PDF
B-3	2. Any annexes (other than citation) to an opposition letter - Annex A - Summary of Attempts by Idenix to make 2'-F, 2'-Me Nucleoside	Annex A - Q40231EP.PDF	OTHER-2.PDF

C Attached evidence files

		Original file name:	System file name:
C-1	1. Patent document	D01 - EP 1523489 (B1).PDF	Published-Evidence-1.PDF
C-2	2. Patent document	D05 - WO 2005_003147.PDF	Published-Evidence-2.PDF
C-3	3. Patent document	D34 - EP-B-2332952.PDF	Published-Evidence-3.PDF

C-4	4. Patent document	D36 - US 2003 0109697 (A1).PDF	Published-Evidence-4.PDF
C-5	1. Other evidence	D02 - Opposition Division Decision 18.04.2016.PDF	Other-evidence-1.PDF
C-6	2. Other evidence	D03 - Lal et al (1996).PDF	Other-evidence-2.PDF
C-7	3. Other evidence	D04 - Singh et al (2002).PDF	Other-evidence-3.PDF
C-8	4. Other evidence	D06 - Clark et al (2005).PDF	Other-evidence-4.PDF
C-9	5. Other evidence	D07 - Clark et al (2006).PDF	Other-evidence-5.PDF
C-10	6. Other evidence	D08 - Clark et al Synthesis (2006).pdf	Other-evidence-6.pdf
C-11	7. Other evidence	D10 - Idenix v Gilead UK Judgment - 01.12.14.PDF	Other-evidence-8.PDF
C-12	8. Other evidence	D11 - Idenix v Gilead UK Court of Appeal Judgement.pdf	Other-evidence-9.pdf
C-13	9. Other evidence	D12 - Email of 09.12.02 - Dr J-F Griffon.PDF	Other-evidence-10.PDF
C-14	10. Other evidence	D13 - Progress Report (Dec 2002).PDF	Other-evidence-11.PDF
C-15	11. Other evidence	D14 - Email of 03.02.03 - Dr J-F Griffon.PDF	Other-evidence-12.PDF
C-16	12. Other evidence	D15 - Email of 04.03.03 - Dr J-F Griffon.PDF	Other-evidence-13.PDF
C-17	13. Other evidence	D16 - Letter of 08.02.03 (Dr Richard Storer).pdf	Other-evidence-14.pdf
C-18	14. Other evidence	D17 - Dr Coe_s Letter replying to D16.pdf	Other-evidence-15.pdf
C-19	15. Other evidence	D18 - Email of 03.06.03 - Dr J-F Griffon.PDF	Other-evidence-16.PDF
C-20	16. Other evidence	D19 - Email of 28.08.03 - Dr J-F Griffon.PDF	Other-evidence-17.PDF
C-21	17. Other evidence	D20 - Summary of Idenix Meeting (10.05.04).PDF	Other-evidence-18.PDF
C-22	18. Other evidence	D21 - Report from meeting summarized in D20.PDF	Other-evidence-19.PDF
C-23	19. Other evidence	D22 - Email of 11.11.04 (Dr Alastair Stewart).PDF	Other-evidence-20.PDF
C-24	20. Other evidence	D23 - Email of 07.01.05 - (Dr Alastair Stewart).PDF	Other-evidence-21.PDF
C-25	21. Other evidence	D24 - Deposition of Dr Alastair Stewart (19.06.13).PDF	Other-evidence-22.PDF

C-26	22. Other evidence	D25 - Substitute Declaration of Dr Griffon.pdf	Other-evidence-23.pdf
C-27	23. Other evidence	D26 - Notebook 1.PDF	Other-evidence-24.PDF
C-28	24. Other evidence	D27 - Notebook 2.PDF	Other-evidence-25.PDF
C-29	25. Other evidence	D28 - Summary of Results of Lit. Search of Dr Griffon.PDF	Other-evidence-26.PDF
C-30	26. Other evidence	D29 - Report of Dr Griffon Meeting - 02.12.02.PDF	Other-evidence-27.PDF
C-31	27. Other evidence	D30 - Report of Dr Griffon Meeting - 03.12.02.PDF	Other-evidence-28.PDF
C-32	28. Other evidence	D31 - Resume of Dr Griffon.PDF	Other-evidence-29.PDF
C-33	29. Other evidence	D32 - Transcript of English Trial Day 4 pp.468-469.PDF	Other-evidence-30.PDF
C-34	30. Other evidence	D33 - Transcript of English Trial Day 2 pp.202-203.PDF	Other-evidence-31.PDF
C-35	31. Other evidence	D35 - Opposition Divison Decision 26.04.18.PDF	Other-evidence-32.PDF
C-36	32. Other evidence	D37 - Feng - role of mitochondrial RNA polymerase....PDF	Other-evidence-33.PDF
C-37	33. Other evidence	D38 - US15279611 Response of 22 Dec 2017 to non-Final OA.PDF	Other-evidence-34.PDF
C-38	34. Other evidence	D39 - Griffith declaration from US reissue.PDF	Other-evidence-35.PDF
C-39	35. Other evidence	D40 - Slusarczyk et al J Med Chem 2014.PDF	Other-evidence-36.PDF
C-40	36. Other evidence	D41A - Dr Marquez Declaration (26 Nov 2014).PDF	Other-evidence-37.PDF
C-41	37. Other evidence	D41B - CV of Victor Marquez - Oct14.PDF	Other-evidence-38.PDF
C-42	38. Other evidence	D42A - Prof. Boons Signed Declaration dated 24 Oct 2018.PDF	Other-evidence-39.PDF
C-43	39. Other evidence	D42B - Updated Boons CV - Nov 2018.PDF	Other-evidence-40.PDF
C-44	40. Other evidence	D09 - Patentee letter of 29 February 2016 to Exam Division.PDF	Other-evidence-7.PDF
C-45	41. Other evidence	D43 - Boons Expert Report (redacted) plus exhibits.pdf	Other-evidence-41.pdf

Signature of opponent or representative

Place	**LONDON**
Date:	**17 December 2018**
Signed by:	**Jane Sexton 23466**
Association:	**J A Kemp**
Representative name:	**/Jane Sexton/**
Capacity:	**(Representative)**