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Datasheet for the decision of 13 July 2018

Case Number: T 2115/13 - 3.3.02

Application Number: 06825554.6

Publication Number: 1934174

IPC: C07D205/04, C07D205/06, C07D401/06, C07D401/12, C07D401/14, C07D403/04, C07D403/06, C07D403/12, C07D405/12, C07D409/06, C07D409/12, C07D413/12, C07D413/14, C07D417/12, C07D471/04

Language of the proceedings: EN

Title of invention:
AZETIDINES AS MEK INHIBITORS FOR THE TREATMENT OF PROLIFERATIVE DISEASES

Patent Proprietor:
Exelixis, Inc.

Opponent:
EIP Limited

Headword:
Azetidines/EXELIXIS

Relevant legal provisions:
RPBA Art. 12(4), 13(1), 13(3)
EPC Art. 111(1), 54, 56, 83, 57, 123(2), 100(a), 100(b), 100(c)

Keyword:

Decisions cited:

Catchword:

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Case Number: T 2115/13 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 13 July 2018

Appellant: (Opponent)	EIP Limited Fairfax House 15 Fulwood Place London WC1V 6HU (GB)
Representative:	Sharples, Andrew John EIP Fairfax House 15 Fulwood Place London WC1V 6HU (GB)
Respondent: (Patent Proprietor)	Exelixis, Inc. 210 East Grand Avenue South San Francisco, CA 94080 (US)
Representative:	Cohausz & Florack Patent- & Rechtsanwälte Partnerschaftsgesellschaft mbB Postfach 10 18 30 40009 Düsseldorf (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 5 August 2013 rejecting the opposition filed against European patent No. 1934174 pursuant to Article 101(2) EPC**

Composition of the Board:

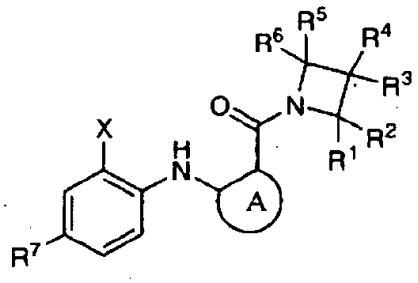
Chairman	M. O. Müller
Members:	J. Molina de Alba
	L. Bühler

Summary of Facts and Submissions

I. The present appeal by the opponent (appellant) lies from the decision of the opposition division to reject the opposition filed against European patent No. 1 934 174.

II. The patent had been granted with 43 claims. Granted independent claims 1, 38, 39, 40 and 42 read as follows:

"1. A compound of formula I:



I

or a single stereoisomer or mixture of stereoisomers thereof and optionally as a pharmaceutically acceptable salt or solvate, thereof, wherein A, X, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as defined in Group A, Group B, Group C, or Group D:

Group A:

A is arylene optionally substituted with one, two, three or four groups selected from R^{10}, R^{12}, R^{14}, and R^{16} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, amino,

alkylamino, dialkylamino, haloalkyl, $-NHS(0)_2R^8$, $-CN$, $-C(0)R^8$, $-C(0)0R^8$, $-C(0)NR^8R^{8'}$ and $-NR^8C(0)R^{8'}$;
X is alkyl, halo, haloalkyl, or haloalkoxy;
R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(0)_2R^8$, $-CN$, $-S(0)_mR^8$, $-S(0)_2NR^8R^{8'}$, $-C(0)R^8$, $-C(0)0R^8$, $-C(0)NR^8R^{8'}$, $-NR^8C(0)0R^{8'}$, $-NR^8C(0)NR^{8'}R^{8''}$, $-NR^8C(0)OR^{8'}$, $-NR^8C(0)R^{8'}$, $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}0(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl; where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(0)_2R^9$, $-CN$, $-S(0)_mR^9$, $-C(O)R^8$, $-C(0)0R^8$, $-C(0)NR^8R^{8'}$, $-NR^8C(0)NR^{8'}R^{8''}$, $-NR^8C(0)0R^{8'}$ and $-NR^8C(0)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);
m is 0, 1, or 2;
R^7 is hydrogen, halo or alkyl;
R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl; where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and

heterocycloalkyl are independently optionally substituted with one, two, three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, alkoxycarbonyl, alkenyloxycarbonyl, optionally substituted cycloalkyl, optionally substituted cycloalkyloxycarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted aryloxycarbonyl, optionally substituted arylalkyl, optionally substituted arylalkyloxy, optionally substituted arylalkyloxycarbonyl, nitro, cyano, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, $-S(0)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{34}S0_2R^{34a}$ (where R^{34} is hydrogen or alkyl and R^{34a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl), $-S0_2NR^{35}R^{35a}$ (where R^{35} is hydrogen or alkyl and R^{35a} is alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl), $-NR^{32}C(0)R^{32a}$ (where R^{32} is hydrogen or alkyl and R^{32a} is alkyl, alkenyl, alkoxy, or cycloalkyl), $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(0)NR^{33}R^{33a}$ (where R^{33} is hydrogen or alkyl and R^{33a} is alkyl, alkenyl, alkynyl, or cycloalkyl); and R^9 is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl; where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally susbstituted with one, two, three, four, or five groups selected from halo, hydroxy, alkyl,

haloalkyl, haloalkoxy, amino, alkylamino, and dialkylamino;
R^{25} and R^{25b} are independently hydrogen, alkyl, alkenyl, optionally sbustituted cycloalkyl, or optionally substituted aryl; and
R^{25a} is hydrogen, alkyl, or alkenyl;

Group B:

A is heteroarylene optionally substituted with one, two, three, or four groups selected from R^{10}, R^{12}, R^{14}, R^{16} and R^{19} where R^{10}, R^{12}, R^{14} and R^{16} are independently hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, cyano, amino, alkylamino, dialkylamino, haloalkyl, alkylsulfonylamino, alkyl carbonyl, alkenylcarbonyl, alkoxycarbonyl, alkenyloxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, or alkylcarbonylamino; where R^{19} is hydrogen, alkyl, or alkenyl; and where each alkyl and alkenyl, either alone or as part of another group within R^{10}, R^{12}, R^{14}, R^{16} and R^{19}, is independently optionally substituted with halo, hydroxy, or alkoxy;
X is alkyl, halo, haloalkyl, or haloalkoxy;
R^{1}, R^{2}, R^{3}, R^{4}, R^{5} and R^{6} are independently hydrogen, halo, nitro, $-NR^{8}R^{8'}$, $-OR^{8}$, $-NHS(0)_2R^{8}$, $-CN$, $-S(0)_mR^{8}$, $-S(0)_2NR^{8}R^{8'}$, $-C(0)R^{8}$, $-C(0)0R^{8}$, $-C(0)NR^{8}R^{8'}$, $-NR^{8}C(0)0R^{8'}$, $-NR^{8}C(0)NR^{8'}R^{8''}$, $-NR^{8}C(0)\ OR^{8'}$, $-NR^{8}C(0)R^{8'}$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected

from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(0)_2R^9$, $-CN$, $-S(0)_mR^9$, $-C(O)R^8$, $-C(0)0R^8$, $-C(O)NR^8R^{8'}$, $-NR^8C(0)NR^{8'}R^{8''}$, $-NR^8C(0)0R^{8'}$ and $-NR^8C(0)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 1 or 2;

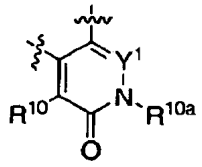
R^7 is hydrogen, halo or alkyl; and

R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substi tuted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(0)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(0)_2R^{36a}$ (where R^{36} is hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{37}C(0)R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl,

optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, $-NHC(0)R^{32}$ (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(0)NHR^{33}$ (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl):

Group C:

A is



where R^{10} is hydrogen, alkyl, alkenyl, alkynyl, halo, haloalkoxy, hydroxy, alkoxy, amino, alkylamino, di alkylamino, haloalkyl, $-NHS(0)R^{8}$, $-CN$, $-C(0)R^{8}$, $-C(0)0R^{8}$, $-C(0-NR^{8}R^{8'}$ and $-NR^{8}C(0)R^{8'}$;
R^{10a} is hydrogen, alkyl, or alkenyl;
Y^{1} is =CH- or =N-;
X is alkyl, halo, haloalkyl, or haloalkoxy;
R^{1}, R^{2}, R^{3}, R^{4}, R^{5} and R^{6} are independently hydrogen, halo, nitro, $-NR^{8}R^{8'}$, $-OR^{8}$, $-NHS(0)R^{8}$, $-CN$, $-S(0)_{m}R^{8}$, $-S(0)_{2}NR^{8}R^{8'}$, $-C(0)R^{8}$, $-C(0)0R^{8}$, $-C(0)NR^{8}R^{8'}$, $-NR^{8}C(0)0R^{8'}$, $-NR^{8}C(0)NR^{8'}R^{8''}$, $-NR^{8}C(0)OR^{8'}$, $-NR^{8}C(0)R^{8'}$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl,

heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(0)_2R^9$, $-CN$, $-S(0)_mR^9$, $-C(O)R^8$, $-C(0)0R^8$, $-C(0)NR^8R^{8'}$, $-NR^8C(0)NR^{8'}R^{8''}$, $-NR^8C(0)0R^{8'}$ and $-NR^8C(0)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 0, 1, or 2;

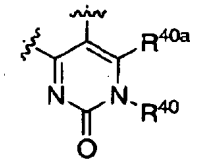
R^7 is hydrogen, halo or alkyl; and

R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substituted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(0)_nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(0)_2R^{36a}$ (where R^{36} is hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted

heterocycloalkyl, or optionally substituted heteroaryl), $-S(0)_2NR^{37}R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substitut ed cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, $-NHC(0)R^{32}$ (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(0)NHR^{33}$ (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl); or

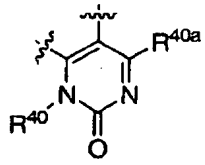
Group D:

A is



(b)

or



(c)

R^{40} and R^{40a} are independently hydrogen or alkyl;
X is alkyl, halo, haloalkyl, or haloalkoxy;

R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(0)_2R^8$, -CN, $-S(0)_mR^8$, $-S(0)_2NR^8R^{8'}$, $-C(0)R^8$, $-C(0)0R^8$, $-C(0)NR^8R^{8'}$, $-NR^8C(0)0R^{8'}$, $-NR^8C(0)NR^{8'}R^{8''}$, $-NR^8C(0)OR^{8'}$, $-NR^8C(0)R^{8'}$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(0)_2R^9$, -CN, $-S(0)_mR^9$, $-C(O)R^8$, $-C(0)0R^8$, $-C(0)NR^8R^{8'}$, $-NR^8C(0)NR^{8'}R^{8''}$, $-NR^8C(0)0R^{8'}$ and $-NR^8C(0)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH);

m is 1 or 2;

R^7 is hydrogen, halo or alkyl; and

R^8, $R^{8'}$ and $R^{8''}$ are independently selected from hydrogen, hydroxy, optionally substituted alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, where the alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two three, four, or five groups independently selected from alkyl, halo, hydroxy, hydroxyalkyl, optionally substi tuted alkoxy, alkoxyalkyl, haloalkyl, carboxy, carboxy ester, nitro, cyano, $-S(0)nR^{31}$ (where n is 0, 1, or 2 and R^{31} is optionally substituted alkyl,

optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-NR^{36}S(0)_2R^{36a}$ (where R^{36} is hydrogen, alkyl, or alkenyl and R^{36a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), $-S(0)_2NR^{37}R^{37a}$ (where R^{37} is hydrogen, alkyl, or alkenyl and R^{37a} is alkyl, alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, or optionally substituted heteroaryl), optionally substitut ed cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted aryloxy, optionally substituted arylalkyloxy, optionally substituted heteroaryl, $-NHC(0)R^{32}$ (where R^{32} is alkyl, alkenyl, alkoxy, or cycloalkyl) and $-NR^{30}R^{30'}$ (where R^{30} and $R^{30'}$ are independently hydrogen, alkyl, or hydroxyalkyl), and $-C(0)NHR^{33}$ (where R^{33} is alkyl, alkenyl, alkynyl, or cycloalkyl)."

"38. A pharmaceutical composition comprising a compound of claim 1 or a single stereoisomer or mixture of stereoisomers thereof, optionally as a pharmaceutically acceptable salt or solvate therof, and a pharmaceutically acceptable carrier, excipient, or diluent."

"39. An in vitro method of inhibiting MEK in a cell, said method comprising contacting said cell with a compound of claim 1 or a single stereoisomer or mixture of stereoisomers thereof, optionally as a pharmaceutically acceptable salt or solvate thereof,

and optionally a pharmaceutically acceptable carrier, excipient, or diluent."

"40. A compound, or single stereoisomer or mixture of stereoisomers thereof, optionally as a pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1 to 37 for use in medicine."

"42. A compound, or single stereoisomer or mixture of stereoisomers thereof, optionally as a pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1 to 37 for use in the treatment of cancer."

In addition, dependent claims 41 and 43 had the following wording:

"41. The compound, or single stereoisomer or mixture of stereoisomers thereof, optionally as a pharmaceutically acceptable salt or solvate thereof, of Claim 40 where the use is treatment of a proliferative disease."

"43. The compound, or single stereoisomer or mixture of stereoisomers thereof of claim 42, where the cancer is melanoma, colon cancer, rectal cancer, pancreatic cancer, breast cancer, non-small cell lung cancer, small cell lung cancer, papillary and anaplastic thyroid cancer, endometrial cancer, or ovarian cancer."

III. The following documents are referred to in the present decision:

(2) WO 2004/113347

(3) WO 99/01421

(4) WO 2005/051301

(5) WO 2005/023759

(10) WO 2005/051906

(11) WO 03/077914

(12) WO 03/077855

(13) WO 2005/051302

(14) WO 2004/000846

(15) WO 2005/009975

(16) US 60/724,578 (priority application of the patent in suit filed on 7 October 2005)

(17) US 60/802,840 (priority application of the patent in suit filed on 23 May 2006)

(20) WO 2006/061712

(21) K.D. Rice et al., ACS Med. Chem. Lett., 2012, 3, 416-421

(21a) Supporting information for the publication in document (21), filed by the respondent on 2 July 2018

(24) Dr Lamb's declaration dated 16 May 2013

(25) Dr Buckwalter's declaration dated 17 June 2013

(26a) Dr Stent's declaration dated 23 April 2014

(26b) K. Dodgson's declaration dated 12 May 2014

(27) Dr Lamb's declaration dated 24 September 2014

(28) Dr Buckwalter's declaration dated 29 August 2014

(29) Dr Malek's declaration dated 27 August 2014

(30) Kinase tree chart filed by the respondent on 25 September 2014

(32) Comparative data filed by the appellant with the statement of grounds of appeal

(34) Dr Lamb's declaration dated 1 July 2018

(35) Dr Malek's declaration dated 1 July 2018

(35a) Compendium of figures filed by the respondent on 2 July 2018

(35b) Legends to the figures in document (35a)

IV. In the decision under appeal, the opposition division considered that the patent as granted did not add subject-matter, that its underlying invention was sufficiently disclosed, and that the claimed subject-matter was novel, inventive and industrially applicable.

V. With its statement of grounds of appeal dated 4 October 2013 the appellant filed *inter alia* documents (16), (17), (21) and (32). With a letter dated 4 June 2018 it filed documents (26a) and (26b).

VI. With a letter dated 25 September 2014 the respondent (patent proprietor) replied to the statement of grounds of appeal and filed 10 sets of claims as auxiliary requests 1 to 10. In addition, it filed *inter alia* documents (27) to (30).

VII. In its preliminary opinion of 23 February 2018, annexed to the summons to oral proceedings, the board *inter alia* concurred with the respondent that the objections of lack of novelty based on documents (11) and (14) had not been substantiated in the statement of grounds of appeal and that the disclosures of documents (4), (5), (10) and (13) did not anticipate the compounds in granted claim 1. The board was also inclined to uphold the opposition division's decision that the invention underlying the granted claims was sufficiently disclosed, that granted claim 1 did not add subject-matter and that the compounds in granted claim 1 were industrially applicable.

VIII. In preparation for oral proceedings, the respondent filed letters on 11 May 2018, 2 July 2018, 9 July 2018 and 10 July 2018. With its letter of 11 May 2018 it filed new auxiliary requests 2 and 3 and five additional sets of claims as auxiliary requests 11 to 15. On 2 July 2018 it filed *inter alia* documents (21a), (34), (35), (35a) and (35b).

IX. The appellant filed letters in preparation for oral proceedings on 12 June 2018 and 4 July 2018.

X. Oral proceedings were held before the board on 12 and 13 July 2018.

XI. The appellant's arguments where relevant to the present decision may be summarised as follows:

Admission of document (32)

Document (32) had been filed with the statement of grounds of appeal. The data on compounds A to P had been obtained by repeating the tests filed in opposition proceedings, the credibility of which had been questioned by the respondent. The new tests on compounds U to Z and AA to AV contained cyclic structures. They were a reaction to the opposition division's opinion that open chains were not suitable for comparison and to the tests filed by the respondent shortly before the oral proceedings in opposition.

As the data in document (32) had been filed at the first possible occasion in response to the evidence required by the opposition division and that filed by the respondent, they should be admitted.

Admission of documents (16) and (17)

Documents (16) and (17) had been filed with the grounds of appeal to rebut the opposition division's view in its decision that the invention was sufficiently disclosed. They reinforced an attack previously made and their content was highly relevant, since they contained examples (compounds 21, 22 and 25 in table 2 of both documents) demonstrating that compounds encompassed by granted claim 1 did not exhibit sufficient MEK inhibition for practical use. Moreover, the documents were the priority applications of the patent, and the respondent had to be well acquainted with their content.

Admission of documents (21) and (21a)

Document (21) had to be admitted because it was a publication from the respondent, filed with the statement of grounds of appeal, which merely reinforced an attack already made before the opposition division. The document was highly relevant because it demonstrated (see right column, second full paragraph, on page 417) that the compounds in granted claim 1 missing a hydroxyl group at the 3-position of the azetidine ring did not solve the problem of providing improved MEK inhibitors.

By contrast, document (21a) should not be admitted because it had been filed too shortly before the oral proceedings in appeal to allow the appellant to prepare a full reply. In any case, if document (21) were not admitted, document (21a) should not be admitted either.

Admission of documents (26a) and (26b)

Documents (26a) and (26b) had been filed at the respondent's request in the appellant's letter of 2 April 2014 and in response to its criticisms on the data presented in document (32). The documents were self-evident and did not require substantiation. Furthermore, the respondent had had four years to study their content.

Admission of the written submissions filed on and after 12 June 2018

The submissions in the letters dated 12 June 2018 and 4 July 2018 were a reply to the respondent's assumption in its letter of 11 May 2018 that the appellant had accepted the inconsistencies in the experimental data

of document (32) pointed out by the respondent in its letter of 25 September 2014 and in declaration (29).

In the letter dated 12 June 2018 the appellant rebutted the respondent's criticisms, explaining that it was common general knowledge that IMAP and Alphascreen tests showed highly variable results when the activity of the tested compound was very low. Further, in the letter dated 4 July 2018, the appellant had questioned neither the respondent's honesty nor the validity of the respondent's data; its only intention had been to maintain that its own data were as valid as the respondent's. So the appellant's submissions should be admitted.

On the respondent's submissions of 2 July 2018, which included documents (34) and (35) and some accompanying exhibits, they were not a reply to the letter of 12 June 2018; they contained criticisms that should have been filed longer than 10 days before oral proceedings, and the time for preparing a response to the extensive evidence filed with documents (34) and (35) was insufficient. Hence, the respondent's submissions filed after 12 June 2018 should not be admitted.

Added subject-matter

The deletion in granted claim 1 of the substituents $-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(NO_2))$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$ and $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, which were present in the definition of R^1 to R^6 in groups B, C and D in claim 1 as filed (see pages 277, 278, and 280), created a new subset of compounds and added subject-matter.

Novelty

The compounds in granted claim 1 were not novel because they resulted from a single selection among the compounds disclosed in documents (4), (5), (10), (11), (13) and (14):

Compound 6 in figure 1 of document (4) was a generic structure with substituents corresponding to X, R^7 and A in group C of granted claim 1. In addition, the group $-C(O)NR^3R^4$ could be -C(O)(azetidine) by selecting the choice in paragraph [0076] that R^3 and R^4 formed a 4- to 10-membered ring together with the atom to which they were attached.

Similarly, compound 112 on page 25 of document (5) had substituents corresponding to X, R^7 and A in group B of claim 1, and its group -C(O)NR'R" could be -C(O)(azetidine) by selecting the choice in the last paragraph on page 4 that R' and R" formed a 4- to 10-membered ring together with the atom to which they were attached.

Any of the formulae 7, 25, 37, 77, 83, 96 and 102 in document (10) (see figures 1, 3, 6, 19, 20, 22 and 23, respectively) also had substituents corresponding to X, R^7 and A in group B of claim 1, and their group $-C(O)NR^3R^4$ could be -C(O)(azetidine) by selecting the choice in paragraph [0016] that R^3 and R^4 formed a 4- to 10-membered ring together with the atom to which they were attached. The choice of the compounds having the group $-C(O)NR^3R^4$ in the mentioned figures did not represent a selection because each of the reaction sequences in figures 1, 3, 6, 19, 20, 22 and 23 ended up with only two products, and compounds 7, 25, 37, 77,

83, 96 and 102 were one of those two products. As the choice of one out of two possibilities was not narrow, it was not a selection.

As in the case of document (10), compounds 5, 9, 20, 24, 36 and 40 in document (13) (see figures 1, 2, 4, 5, 7 and 8, respectively) had substituents corresponding to X, R^7 and A in group B of claim 1, and their group $-C(O)NR^3R^4$ could be -C(O)(azetidine) by selecting the choice in paragraph [0013] that R^3 and R^4 formed a 4- to 10-membered ring together with the atom to which they were attached. Here, too, the choice of compounds having the group $-C(O)NR^3R^4$ in figures 1, 2, 4, 5, 7 and 8 was not a selection because it constituted a choice between only two possibilities.

Inventive step

Document (3) was the closest prior art for the compounds in group A of granted claim 1, and any of documents (12) and (15) for the compounds in group B. Alternatively, document (2) was the closest prior art for the compounds in group B (see statement of grounds of appeal, sections 8.2.2., 8.3.1, 8.4.1 and 8.5.3).

Starting from document (3), the compounds in group A represented a selection where the substituent Z in formula (I) of document (3) had been chosen to be -C(O)(azetidine). The closest compounds in document (3) were the ones in examples 95, 100, 103, 130 and 134. The compounds in group A differed from those compounds in that they contained an azetidine ring instead of a ring with an additional carbon atom. The technical problem to be solved was the provision of alternative MEK inhibitors, because an improvement of MEK inhibition had not been shown across the whole breadth

of group A. The reasons for this were that it was inherently implausible that all the compounds in group A exhibited improved activity, that the respondent had failed to provide sufficient data in this respect, and that the teaching in document (21) and the data in documents (32) and (16) proved that lack of improvement. Thus, considering that the skilled person would have been motivated to prepare alternative compounds having rings with one carbon atom fewer, the compounds in group A of granted claim 1 were obvious.

Starting from document (12), the substituent W in formula (I) represented *inter alia* $-C(O)NR^3R^4$ or -C(O)(heterocyclyl), both of which encompassed -C(O)(azetidinyl). Admittedly, the definition of "heterocyclyl" in paragraph 2 on page 13 of document (12) did not mention 4-membered rings. However, this was an obvious mistake in view of the citation of "azetidinyl" in the same paragraph and of the compound in example 6, which contained an azetidinyl ring. Hence, the compounds in group B were a selection among those in document (12). The technical problem to be solved was again the provision of alternative MEK inhibitors, because an improvement across the whole breadth of group B had not been demonstrated. The compounds in group B were an obvious solution because they were encompassed by formula (I) in document (12). Moreover, the combination of document (12) with its closely related document (11), especially with the compounds in example 39, would also have rendered the compounds in group B obvious.

Starting from document (15), the closest embodiments were compounds 55 and 59 on page 38. The compounds in group B differed from them in that they had an azetidine ring instead of a pyrrolidine ring, and the

problem to be solved was once again the provision of alternative MEK inhibitors. As argued starting from document (3), the replacement of a nitrogenated 5-membered ring (pyrrolidine) by its analogue with one carbon atom fewer (azetidine) was intrinsically obvious and could not involve an inventive step. The same conclusion was reached from the combination of document (15) with document (11), both of which dealt with MEK inhibitors having closely related structures. Document (15) could also be read in conjunction with document (12), such that the teaching in document (12) that W was -C(O)(azetidine) could be applied to the compounds in document (15), in particular to compounds 55 and 59 on page 38. This would have led the skilled person to the compounds in group B in an obvious manner. Moreover, in view of the general structure of MEK inhibitors known from documents (3) to (5) and (10) to (15), the skilled person would have concluded that the important site of modification for providing alternatives was the position at which the claimed compounds contained the azetidine ring. Lastly, the replacement of a 5-membered ring by a 4-membered ring was obvious from document (2), which showed that testing 4-, 5-, and 6-membered ring analogues was a common strategy in the art.

With regard to document (2), it dealt with p38 MAP kinase inhibitors, a group of compounds suitable for the treatment of proliferative diseases. Thus, the document was a promising starting point for solving the technical problem of providing compounds suitable for the treatment of proliferative diseases. The closest compounds in document (2) were the ones in examples 33, 69 and 71. The compounds in group B differed from them by the substituent on the nitrogen atom of the heteroarylene group (N-aryl in document (2) vs. N-alkyl

in group B). As the exchange of an alkyl group for an aryl group in a substituted ring was obvious, the compounds in group B lacked an inventive step. This was even clearer in the light of document (14), which disclosed p38 MAP kinase inhibitors having an alkyl group on the nitrogen atom of the heteroarylene ring.

Sufficiency of disclosure

The patent lacked sufficiency of disclosure in two respects: the skilled person was not able to prepare all the compounds in granted claim 1, and many of those compounds did not show any practical MEK inhibition.

On the feasibility of the compounds in granted claim 1, formula (I) was defined in such broad terms that it encompassed a limitless number of compounds, many of which could not be synthesised at all for reasons such as steric hindrance or electronic effects; the reduced number of compounds that had been illustrated in the patent was not sufficient for the skilled person to carry out the invention across the whole breadth of granted claim 1.

On the presence of practical MEK inhibition, an effect had been shown only for compounds where X and R^7 were halogen, although X and R^7 in granted claim 1 had a much broader meaning. Similarly, with respect to group B, the only heteroarylenes tested were benzimidazoles. Thus, considering that the effect of a modification on the chemical structure of MEK inhibitors could not be predicted, it could not be expected that sufficient MEK inhibition would be found for all the compounds encompassed by granted claim 1, especially for those structurally far away from the tested compounds. In fact, document (16) showed that compounds 21, 22 and

25, which fell within the scope of granted claim 1, had an IC_{50} of more than 10µm. This meant that they were insufficiently active, since compounds having an IC_{50} beyond the low micromolar range had no practical use. This was also the case for compounds B, U, W and Y in document (32).

Industrial applicability

As discussed in the context of lack of sufficiency of disclosure, granted claim 1 encompassed compounds with no practical activity. Those compounds were not industrially applicable.

XII. The respondent's arguments where relevant to the present decision may be summarised as follows:

Admission of document (32)

Document (32) should not be admitted because it contained not only a repetition of the examples filed in opposition proceedings but also new examples that could and should have been filed before. The examples filed in opposition proceedings were intended for comparison with compounds in document (15), while the new examples aimed at a comparison with compounds in document (12). The admission of those new examples would create a fresh case in appeal.

Moreover, the document was *prima facie* not relevant because its data were inconclusive; they contradicted the data on compounds A to P presented in opposition proceedings, and the ranking order of the compounds according to their results with the IMAP and the Alphascreen tests was inconsistent.

Admission of documents (16) and (17)

Documents (16) and (17) had been publicly available at the filing date of the notice of opposition. So, filing them for the first time in appeal was too late. Furthermore, the documents did not *prima facie* prejudice the maintenance of the patent.

Admission of documents (21) and (21a)

The respondent would not object to the admission of document (21) if document (21a) were admitted too.

Document (21a) had to be admitted as a reply to the doubts raised by the appellant on the validity of the respondent's biological assays filed in appeal. The document detailed the biological assays underlying the data presented in document (21), which had been carried out following the same method as in the patent and documents (24), (25), (27) and (28). Thus, document (21a) showed that the respondent's assays fulfilled the high standards required for peer-reviewed publication in renowned international journals.

Admission of documents (26a) and (26b)

Documents (26a) and (26b) should not be admitted because the appellant had explained their content for the first time in its letter of 12 June 2018, while the respondent's objection regarding the lack of detail of the tests in document (32) had been raised in 2014. This late substantiation had not allowed the respondent to prepare sufficiently for oral proceedings.

Admission of the written submissions filed on and after 12 June 2018

The content of the appellant's letter of 12 June 2018 should not be admitted because it was late-filed and contained unfounded allegations and criticisms as to declaration (29) that should have been filed earlier. The time remaining until the oral proceedings was not enough to react to this letter.

Should the appellant's submissions nevertheless be admitted, then the respondent's letters of 2 July 2018 and 10 July 2018 in reply to those submissions had to be admitted too. In any case, even if the appellant's submissions of 12 June 2018 were not admitted, the respondent's arguments defending the honesty and best practice of its scientists should be admitted so that no doubts remained.

Added subject-matter

The deletion of some substituents in the definition of R^1 to R^6 in groups B, C and D of original claim 1 did not add subject-matter because it restricted the scope of claim 1 without singling out individual compounds or creating a new subset.

Novelty - Articles 100(a) and 54 EPC

Starting from documents (4), (5), (10) and (13), multiple selections had to be made in order to arrive at the compounds in granted claim 1; it was at least necessary to choose the compounds having the group $-C(O)NR_xR_y$ and then to select that NR_xR_y be azetidin-1-yl.

This was also the case for the figures in documents (10) and (13) cited by the appellant. Each of these figures disclosed three or more products according to their inventions, and only one of those products had the group $-C(O)NR_xR_y$. This was apparent in document (10) from figures 1, 3, 6, 19, 20, 22 and 23, their corresponding figure captions in paragraphs [0035], [0037], [0040], [0053], [0054] and [0056], and the definition of W in claim 6. The same was true of document (13) (see figures 1, 2, 4, 5, 7 and 8, figure captions in paragraphs [0032], [0033], [0035], [0036], [0038] and [0039], and the definition of W in claim 17).

Inventive step - Articles 100(a) and 56 EPC

Starting from document (3), the compounds in group A represented a selection which solved the problem of providing improved MEK inhibitors. This was supported by the evidence filed in Annex II of document (24) and confirmed by document (21) and by the appellant's data in document (32), which demonstrated that replacement of a piperazine or pyrrolidine ring by an azeditine ring resulted in higher MEK inhibition. With respect to the obviousness of the claimed compounds, the skilled person would not have focused on the compounds in examples 95, 100, 103, 130 and 134 of document (3) because they were not among the most active ones. Nevertheless, even starting from those compounds, the skilled person would not have arrived at the compounds of group A, firstly because a modification of the compounds in document (3) at the Z position was not the only option, but also because, even modifying the Z position, it was still necessary to select the group $-C(O)NR^6R^7$ among other alternatives and then to choose the option that NR^6R^7 formed a ring of 3 to 10 members

(see page 9, lines 24-32). Moreover, the choice of NR^6R^7 being azeditine was neither disclosed nor suggested in document (3). As to the appellant's argument that document (16) proved that not all the compounds in group A solved the problem posed, the fact that compounds 21, 22 and 25 in document (16) had an IC_{50} of higher than 10 µM did not demonstrate that no improvement had been achieved.

Starting from document (12), the compounds in group B differed in that they had an azetidinyl ring while the compounds of document (12) had a 5- to 7-membered ring or a fused ring. This was clear from the definitions of group W and the terms "heteroaryl" and "heterocyclyl" in document (12) (see pages 7, 12 and 13, respectively). The inconsistency noted by the appellant, that the compound in example 6 of document (12) had an azetidine ring, could not be used to amend the general definition of W, which excluded 4-membered rings. Based on this difference, the technical problem to be solved was the provision of improved MEK inhibitors. However, even if the problem had to be reformulated as the provision of alternative MEK inhibitors, it had been solved in a non-obvious manner: the data in documents (24), (25), (28) and (32) confirmed that the compounds in group B were MEK inhibitors; document (12) did not teach unfused azetidine rings; and the preferred meaning of group W was $-C(O)OR^3$ or $-C(O)NR^4OR^3$ rather than $-C(O)NR^3R^4$ or -C(O)(heterocyclyl) (see claims 3 and 9 to 12 and examples). Thus, it was not obvious to modify the group W in formula (I) of document (12) to be $-C(O)NR^3R^4$ or -C(O)(heterocyclyl), let alone that NR^3R^4 or heterocyclyl be azetidin-1-yl. The same was concluded from reading document (12) in combination with document (11). The definition of W on page 7 of document (11)

was the same as in document (12), with the exception that R^3 and R^4 could form a **4-** to 10-membered ring with the atom to which they were attached (see paragraph 2 on page 6). However, the skilled person would have realised that the only examples in document (11) where W was $-C(O)NR^3R^4$ with NR^3R^4 being a heterocycle - examples 11pp, 11qq and 11ss - had low activity (see example 39 and the passage bridging pages 37 and 38). So there was no motivation to select the group $-C(O)NR^3R^4$ with NR^3R^4 being a heterocycle or -C(O)(heterocyclyl), let alone the specific group azetidin-1-yl, which was neither disclosed nor suggested.

Starting from document (15), the compounds in group B were alternative MEK inhibitors because they were not encompassed by formula (I). Document (15) did not contain any suggestion to modify W and to select it to be -C(O)(azetidine). Regarding compounds 55 and 59 on page 38, they were specific examples and the skilled person had no motivation to modify them, even less to replace their pyrrolidine rings with an azetidine ring, not only because azetidine was in no way suggested, but also because, in view of the examples, acyclic substituents were clearly preferred. Similarly, the combination of document (15) with document (12) suggested 5- to 7-membered heterocyclyl rings and therefore taught away from azeditine. The unlikely combination with document (11) could not render the claimed compounds obvious either, for the reasons set out in the discussion starting from document (12). Lastly, a combination with document (2) was not realistic because the latter dealt with a completely different receptor (p38 MAP kinases). In addition, document (2) did not represent the common general

knowledge for modifying ring structures, since it was merely a patent application.

With regard to document (2) and its combination with document (14), neither of those documents was relevant to the issue of inventive step because they dealt with inhibitors of p38 MAP kinases, a kinase family other than MEK which used a different signalling pathway (see document (30)). Furthermore, documents (2) and (14) stated that their p38 MAP kinase inhibitors were selective (see document (2): page 6, lines 16-18; document (14): page 6, lines 13-15, and page 27, lines 19-22). Hence, the skilled person would never have considered that p38 MAP kinase inhibitors would also be MEK inhibitors. For that reason, documents (2) and (14) taught away from the compounds of the invention. The appellant's formulation of the technical problem as the provision of alternative compounds for the treatment of proliferative diseases was not permissible because the effect discussed in the patent was the treatment of proliferative diseases by MEK inhibition; at the filing date, many different proliferative diseases were known and it could not be expected that a class of compounds effective against a specific proliferative disease would be effective for proliferative diseases in general.

Sufficiency of disclosure - Articles 100(b) and 83 EPC

The respondent had not met its burden of proving that the invention was not sufficiently disclosed.

On the issue of whether the skilled person was able to synthesise the compounds in granted claim 1, the patent disclosed a large number of examples, schemes and references (see paragraphs [0210] to [0242]) and

specific synthetic examples (see paragraphs [0243] to [0455]) falling into each of groups A, B, C and D in granted claim 1. In addition, the claimed compounds represented a selection within the broader disclosures in documents (3), (4) or (5), which had been considered by the appellant in its discussion of novelty or inventive step as being enabling, even if they contained only few examples. Lastly, paragraph [0063] of the patent excluded compounds that were neither sterically practical nor synthetically feasible.

With respect to the presence of MEK inhibition across the whole breadth of granted claim 1, all the experimental results on file showed that the claimed compounds were MEK inhibitors. The appellant provided neither a definition of what was to be understood by insufficient activity nor any proof that compounds with a high IC_{50} had no practical utility. In addition, low activities could be improved with targeting technologies or formulations. Regarding the use of MEK inhibitors in the claimed therapeutic treatments, it was an established principle that MEK was one of the proliferators implicated in cancer, so that MEK inhibitors were cancer drugs.

Industrial applicability - Articles 100(a) and 57 EPC

The claimed compounds were MEK inhibitors, as explained in the discussion of sufficiency of disclosure. Therefore they were industrially applicable for the treatment of proliferative diseases.

XIII. The final requests of the parties were as follows:

- The appellant requested that the decision under appeal be set aside and that European patent No. 1 934 174 be revoked.

- The respondent requested that the appeal be dismissed (main request), or alternatively that the patent be maintained in amended form on the basis of the claims of one of auxiliary request 1, filed with the letter dated 25 September 2014, or auxiliary requests 2 and 3, filed with the letter dated 11 May 2018, or auxiliary requests 4 to 10, filed with the letter dated 25 September 2014, or auxiliary requests 11 to 15, filed with the letter dated 11 May 2018.

XIV. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of document (32)

Document (32) was filed with the statement of grounds of appeal and contains two types of comparative test: a repetition of the tests filed by the appellant with the notice of opposition (compounds A to P) and tests in which azetidine compounds are compared with their pyrrolidine, piperidine and piperazine analogues (compounds U to AV).

The repetition of examples A to P was intended to rectify an error committed by the appellant which led the opposition division to disregard the assays as valid comparative examples (see minutes of oral proceedings, paragraph 14; and decision, paragraph 15.2.7). The tests with comparative ring structures U to AV were filed as a reaction to the opposition division's view that open substituents were not suitable for comparison with azetidine rings and in reply to the data in documents (24) and (25), filed by the respondent respectively two months and one month before oral proceedings.

The tests in document (32) thus constitute a reaction to the opposition division's decision and the respondent's data in documents (24) and (25), and they were filed on the earliest possible occasion, i.e. with the statement of grounds of appeal. Consequently, the board admitted document (32) under Article 12(4) RPBA.

3. Admission of documents (16) and (17)

Documents (16) and (17) were filed with the grounds of appeal in order to reinforce the appellant's argument of lack of sufficiency set out in opposition proceedings that not all the claimed compounds had a practical therapeutic activity. More specifically, the appellant argued that compounds 21, 22 and 25 in table 2 of both documents fell within the scope of granted claim 1 and that their reported level of MEK inhibition was nevertheless low. In addition, the documents are the priority applications of the patent.

Thus, taking into consideration that the documents were filed on the first possible occasion after the decision was issued, that they do not introduce a new attack but

merely reinforce an argument that was rejected by the opposition division, and that the respondent was familiar with their content, the board admitted documents (16) and (17) under Article 12(4) RPBA.

4. Admission of documents (21) and (21a)

Document (21) was filed with the grounds of appeal to show that an improvement of MEK inhibition had not been made credible across the whole breadth of granted claim 1, such that its subject-matter was not inventive (see grounds of appeal, point 8.1.11). The filing of document (21) thus merely reinforces an attack already made before the opposition division. It is furthermore a publication from the respondent itself and contains information on the development of a compound arising from the teaching of the patent. So the respondent was familiar with this document. Therefore, the board admitted document (21) under Article 12(4) RPBA.

Document (21a) was filed by the respondent on 2 July 2018 in reaction to the criticisms against the biological assays in documents (24), (25), (27) and (28), raised by the appellant in its letter of 12 June 2018. The document on page 22 discloses the protocol of how the biological assays underlying document (21) had been carried out. As that protocol is essentially the same underlying the assays in documents (24), (25), (27) and (28), document (21a) supports the respondent's argument that its assays meet the standards required for publication in renowned international journals. Accordingly, the board admitted document (21a) under Article 13(1) RPBA.

5. Admission of documents (26a) and (26b)

Document (26a) discloses the synthesis and characterisation of the compounds tested in document (32). Document (26b) discloses the details of the biological tests carried out with those compounds. Both documents were filed on 4 June 2014 in response to the respondent's letter of 2 April 2014 (see page 1, paragraph 2), which requested this information, and after the board referred to this specific point in its communication dated 10 April 2014. In addition, the documents are relatively short, do not present particular difficulties, and were even commented on in the respondent's reply to the grounds of appeal (see point IV.4.7 in the letter of 25 September 2014). Hence, the board admitted the documents under Article 13(1) RPBA.

On this issue, the respondent argued that substantiation based on documents (26a) and (26b) had been provided for the first time one month before oral proceedings, thus creating a fresh case at a late stage of the appeal proceedings. For this reason, the documents should not be admitted.

The board disagrees, because documents (26a) and (26b) are self-explanatory, especially in view of point 23 in document (26b), which addresses the respondent's criticisms against the tests in document (32).

6. Admission of the written submissions filed on and after 12 June 2018

6.1 On 12 June 2018, i.e. one month before oral proceedings before the board, the appellant filed a letter dealing with several issues. On the one hand, it contained

allegations against the respondent's honesty and new arguments which questioned the validity of the respondent's experimental evidence. On the other hand, it contained arguments defending the correctness of the biological tests in document (32) against the doubts raised by the respondent in its letter of 25 September 2014 and in declaration (29) filed therewith.

The letter of 12 June 2018, especially its allegations and the criticisms of the respondent's assays, triggered a reply by the respondent on 2 July 2018. This included the filing of declaration (34) with its accompanying exhibits A to C, declaration (35) with its accompanying exhibits A and B, and documents (35a) and (35b). The respondent likewise requested an adjournment of the oral proceedings to have sufficient time to prepare its full reply.

The appellant filed a further reply on 4 July 2018, and the respondent did so on 9 July 2018 and 10 July 2018.

6.2 In the board's view, the appellant's attacks on the respondent's biological assays, including its attacks on the respondent's honesty, are new issues that were raised late in the proceedings. The remaining part of the appellant's letter of 12 June 2018, i.e. its arguments defending the correctness of the biological tests in document (32), constitute a response to the respondent's letter dated 25 September 2014. Waiting almost four years for such a response is not acceptable. So this part of the appellant's letter is equally unjustifiably late.

In addition, admission of the appellant's late submissions of 12 June and 4 July 2018 would have

required admission of the respondent's replies and supporting evidence. This would clearly have added complexity to the proceedings at a very late stage. For instance, it would have been necessary to discuss in depth the principles underlying the IMAP and Alphascreen tests, the limits of their applicability in connection with the evidence on file, and the statistical assessment of their results. In fact, had the board admitted the appellant's late submissions, the oral proceedings would have had to be adjourned to give the respondent sufficient time to react.

6.3 As regards the late filing of arguments defending the correctness of the biological tests in document (32), the appellant argued that its letter of 12 June 2018 was also a reply to the respondent's letter of 11 May 2018, and thus was not late. It specifically referred to the assumption in the respondent's letter that the appellant had accepted that there were inconsistencies in its own experimental data of document (32) (see second paragraph on page 5 of the respondent's letter of 11 May 2018).

The board acknowledges that, in its letter of 11 May 2018, the respondent did indeed observe that the appellant had not reacted to the arguments and data filed with the letter of 25 September 2014 and that it concluded therefrom that the appellant had accepted these arguments and data and thus admitted that its own data contained inconsistencies. The board fails to see however how this can justify the appellant's late submission of 12 June 2018. There is in particular no reason apparent to the board, and none was given by the appellant, why it waited almost four years to react to these arguments and data. Hence, the appellant's reaction in the form of its letter of 12 June 2018 was

too late. This lateness is not justified by the fact that another event, i.e. the respondent's letter dated 11 May 2018, allegedly triggered this reaction.

The same arguments apply to the appellant's further submission of 4 July 2018.

6.4 Following from the above, the board decided not to admit the appellant's arguments and evidence filed on and after 12 June 2018 and, for the same reasons, the respondent's replies to those submissions (Article 13(1) and (3) RPBA).

The board nevertheless made two exceptions: Firstly, the admission of document (21a), treated separately in point 4 above. Secondly, the admission of the argument that it is common general knowledge that at low activity ranges the results obtained with the IMAP and Alphascreen tests are highly variable. This argument was admitted because both parties agreed on the existence of that common general knowledge and its admission did not raise any complex new issues.

7. Admission of charts 1 to 14 and 23 to 25

The appellant did not object to the presentation of these charts during the oral proceedings. The board therefore decided to admit these charts into the proceedings (Article 13(1) and (3) RPBA).

8. Request for adjournment

In reaction to the appellant's submission of 12 June 2018, the respondent requested that the oral proceedings be adjourned. As set out above (point 6.4), apart from the non-contentious issue of the variation

of data at low activity ranges, the board did not admit this submission into the proceedings. It therefore saw no need to adjourn the oral proceedings and rejected the respondent's request for adjournment.

9. Remittal

The respondent requested that the case be remitted to the opposition division if any of documents (16), (17), (21) and (32) were admitted. The appellant was against a remittal because it would have delayed a settlement of the case to a date certainly after the expiry of the patent.

Article 111 EPC does not give the parties an absolute right to have every point decided by two instances. Thus, taking into consideration that, apart from some additional evidence in the discussion of inventive step and sufficiency of disclosure, the case remained within the same lines of argument as before the opposition division and that a remittal would have unduly delayed a final settlement of the case, the board decided not to remit the case (Article 111(1) EPC).

10. Added subject-matter

The definition of substituents R^1 to R^6 in groups B, C and D of claim 1 as filed was the following (emphasis added by the board):

"R^1, R^2, R^3, R^4, R^5 and R^6 are independently hydrogen, halo, nitro, $-NR^8R^{8'}$, $-OR^8$, $-NHS(0)_2R^8$, $-CN$, $-S(0)_mR^8$, $-S(0)_2NR^8R^{8'}$, $-C(0)R^8$, $-C(0)0R^8$, $-C(0)NR^8R^{8'}$, $-NR^8C(0)0R^{8'}$, $-NR^8C(0)NR^{8'}R^{8''}$, $-NR^8C(0)\ OR^{8'}$, $-NR^8C(0)R^{8'}$, **$-CH_2N(R^{25})(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(NR^{25a}R^{25b})$, $-CH_2NR^{25}C(=NH)(N(R^{25a})(N0_2))$,**

$-CH_2NR^{25}C(=NH)(N(R^{25a})(CN))$, $-CH_2NR^{25}C(=NH)(R^{25})$, $-CH_2NR^{25}C(NR^{25a}R^{25b})=CH(NO_2)$, alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, or heterocycloalkyl, where the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, and heterocycloalkyl are independently optionally substituted with one, two, three, four, five, six or seven groups independently selected from halo, alkyl, haloalkyl, nitro, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, $-OR^8$, $-NR^8R^{8'}$, $-NR^8S(0)_2R^9$, -CN, $-S(0)_mR^9$, $-C(O)R^8$, $-C(0)0R^8$, $-C(0)NR^8R^{8'}$, $-NR^8C(0)NR^{8'}R^{8''}$, $-NR^8C(0)0R^{8'}$ and $-NR^8C(0)R^{8'}$; or one of R^1 and R^2 together with the carbon to which they are attached, R^3 and R^4 together with the carbon to which they are attached, and R^5 and R^6 together with the carbon to which they are attached form C(O) or C(=NOH)".

In granted claim 1, this definition remains the same with the exception that the substituents written in bold have been deleted. It is therefore apparent from the length of the list of possible substituents R^1 to R^6 in both the original claim and the granted claim that the scope of the latter has been only slightly narrowed and that, contrary to the appellant's argument, this narrowing neither singles out compounds or groups of compounds nor provides information that was not present in claim 1 as filed.

In consequence, the board agrees with the opposition division and the respondent that the patent does not add subject-matter (Articles 100(c) and 123(2) EPC).

11. Novelty

In section 7 of the statement of grounds of appeal, the appellant raised objections as to novelty based on documents (4), (5), (10), (11), (13) and (14). However, the objections based on documents (11) and (14) were not substantiated, either in the statement of grounds of appeal or in the subsequent written and oral proceedings. Accordingly, the objections raised vis-à-vis these documents have been disregarded.

In its objections of lack of novelty, the appellant started from compounds in the prior art having the generic group $-C(O)NR_xR_y$ and stated that, starting from those compounds, only one selection was needed to arrive at the compounds in granted claim 1, namely the choice that R_x and R_y together with the nitrogen to which they were attached formed a 4- to 10-membered ring. This would, in the appellant's opinion, unambiguously disclose the group -C(O)(azetidin-1-yl).

The board cannot accept this argument, at least because the choice of the embodiments comprising the group $-C(O)NR_xR_y$ from which the appellant starts already requires a selection. So, a minimum of two selections would be needed to arrive at the claimed compounds. In the following, this is analysed for each individual document.

11.1 Figures 1 to 34 in document (4) disclose a long list of compounds according to its invention (see paragraph [0034] and figure captions in paragraphs [0035] to [0068]). Focusing on the generic compounds 6, 26, 57 and 64 in the respective figures 1, 6, 15 and 19 as the starting materials bearing the group $-C(O)NR^3R^4$ already represents a selection. Thus, the combination of these

compounds with the embodiment in paragraph [0076] that R^3 and R^4 form a 4- to 10-membered ring together with the atom to which they are attached constitutes a double selection. For this reason alone, and independently of whether or not further selections are needed to arrive at the compounds in granted claim 1, document (4) does not anticipate said compounds.

11.2 In document (5), compound 112 in scheme 1 (see page 25) bears the group -C(O)NR'R". The choice of this compound among all other compounds according to the invention disclosed in schemes 1 to 9 (see pages 25 to 33) represents a first selection. This choice, combined with the embodiment in the last paragraph on page 4, that R' and R" form a 4- to 10-membered ring together with the atom to which they are attached, again involves a double selection.

11.3 In its discussion of document (10), the appellant cited compounds 7, 25, 37, 77, 83, 96 and 102 in figures 1, 3, 6, 19, 20, 22 and 23, respectively, as the starting compounds bearing the group $-C(O)NR^3R^4$. According to the appellant, each of these compounds was a choice between two possibilities depicted at the end of each synthesis scheme in the corresponding figures. As that choice was not narrow (1 out of 2), the appellant considered that it could not be seen as a selection.

The board disagrees, firstly because a choice between two compounds does indeed represent a selection, but also because, as noted by the respondent, figures 1, 3, 6, 19, 20, 22 and 23 do not contain only two compounds according to the invention of document (10) but at least three of them. This is apparent from paragraphs [0035], [0037], [0040], [0053], [0054] and [0056] and from the preferred definition of the group W in claim

6, which includes not only the groups $-C(O)NHR^3$ and $-C(O)NHOR^3$ but also $-C(O)OR^3$. Therefore, the selection in each of figures 1, 3, 6, 19, 20, 22 and 23 of the compound having the group $-C(O)NR^3R^4$ was made among at least three compounds. As a result, the combination of the compounds selected from figures 1, 3, 6, 19, 20, 22 and 23 with the embodiment in paragraph [0016] whereby R^3 and R^4 form a 4- to 10-membered ring together with the atom to which they are attached involves a double selection.

11.4 The case of document (13) is analogous to that of document (10); the choice of the compounds 5, 9, 20, 24, 36 and 40 in figures 1, 2, 4, 5, 7 and 8 represents a first selection among at least three possible options (see figure captions in paragraphs [0032], [0033], [0035], [0036], [0038] and [0039] and the definition of W in claim 17). This first selection combined with the embodiment in paragraph [0013] whereby R^3 and R^4 form a 4- to 10-membered ring together with the atom to which they are attached constitutes a double selection.

11.5 The board therefore concludes that the compounds in granted claim 1 are novel (Articles 100(a) and 54 EPC).

12. Inventive step

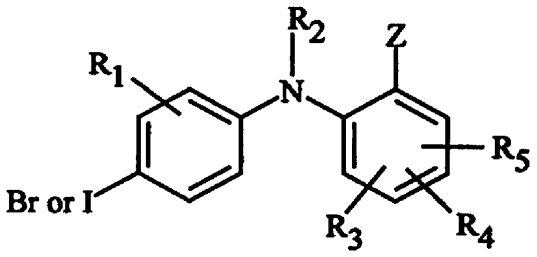
12.1 The patent relates to a family of azetidine compounds and to their use as MEK inhibitors for the treatment of proliferative diseases. Granted claim 1 discloses four groups of compounds as groups A, B, C and D.

The parties and the opposition division cited three documents which disclose MEK inhibitors with a chemical structure closely related to the ones in granted claim 1 as the closest prior art: document (3) for group A

and documents (12) and (15) for group B. The appellant considered that document (2) was also a promising starting point. Starting from these documents, the appellant argued that the subject-matter of claim 1, in as far as groups of compounds A and B were concerned, lacked an inventive step.

12.2 Starting from document (3)

12.2.1 Document (3) is directed to the preparation of MEK inhibitors of the following formula (I):



The parties did not dispute that the compounds in group A of granted claim 1 constituted a selection among the MEK inhibitors in document (3). This was apparent from the definition of group Z in document (3) (see page 4 or claim 1) as *inter alia* $-CONR_6R_7$, wherein R_6 and R_7 together with the nitrogen to which they are attached complete a 3- to 10-membered ring. The azetidine group required for group A of claim 1 is a 4-membered ring and thus constitutes an undisclosed selection out of the range of 3- to 10-membered rings. Document (3) discloses specific heterocyclic amides only in examples 95, 100, 103, 130 and 134, where the heterocycle is pyrrolidine or piperazine, rather than azetidine.

12.2.2 Starting from document (3), the respondent formulated the technical problem to be solved as the preparation of **improved** MEK inhibitors.

Annex II of document (24) provides comparative examples *in vitro* and *in cell*, which show that three compounds according to group A are considerably better MEK inhibitors than their analogues where the azetidine ring has been replaced by a pyrrolidine or a piperidine ring. These results are confirmed by the appellant's data in section 2 of document (32), where the IC_{50} value in the Alphascreen test on the azeditine derivative AK (IC_{50}= 228) is much lower than that of its piperidine analogue AJ (IC_{50}= 30117). Similarly, the azetidine compound AM is a better MEK inhibitor (IC_{50}= 649) than its pyrrolidine analogue AF (IC_{50}= 38326) or its piperidine analogue AN (IC_{50}= 195345). This is likewise the case for the azetidine AS (IC_{50}= 37) compared with the pyrrolidines AH (IC_{50}= 10982) and AU (IC_{50}= 866) and the piperidines AG (IC_{50}= 21404) and AQ (IC_{50}= 28421). The same trend is also observed in document (21), which states in the right column on page 417 that "*Increasing the ring size of the carboxamide to pyrrolidine or piperidine analogues resulted in a dramatic loss of activity*".

Accordingly, the board is satisfied that the evidence in documents (24) and (32) and the teaching in document (21) credibly show that the selection of the compounds of group A out of the broader family of MEK inhibitors disclosed in document (3) does indeed result in an improvement in MEK inhibiting activity.

12.2.3 In this context, the appellant contended that the evidence provided by the respondent was too narrow to justify the breadth of group A in granted claim 1.

However, as discussed above, the evidence on file demonstrates improved MEK inhibition for the claimed

compounds. Thus, in the absence of evidence which could raise doubts that not substantially all compounds in group A will have improved MEK inhibiting properties, the board cannot accept the appellant's argument that an improvement across the whole breadth of group A would be inherently implausible.

In addition, the appellant set out two further arguments based on documents (16) and (21):

- Document (16) showed in table 2 that compounds 21, 22 and 25 had an IC_{50} classified as E, which meant that their MEK inhibiting activity was of IC_{50}> 10µM (see paragraph [0111]). As those three compounds were encompassed by group A and their high IC_{50} values were an indication that they lacked practical activity, the technical problem was not solved across the whole breadth of group A.

- Similarly, document (21) stressed (see right column on page 417) the importance of having a hydroxyl group at the 3-position of the azetidine ring. So, the absence of such a hydroxyl group in many of the compounds in group A would imply a lack of improvement across the whole breadth of claim 1.

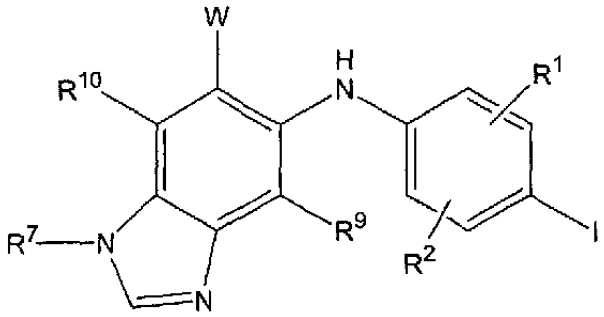
These arguments did not convince the board, firstly because the appellant did not provide any evidence proving that there is an established IC_{50} threshold beyond which a compound would not be considered to be a MEK inhibitor, and secondly because the problem to be solved is an improvement of the MEK inhibiting activity, and neither of documents (16) and (21) shows that their less active compounds - i.e. compounds 21, 22 and 25 in document (16), and compounds without a hydroxyl group at the 3-position of the azetidine ring

in document (21) - are not better MEK inhibitors than their analogues in document (3).

12.2.4 Turning to the issue of obviousness, the board holds that, even starting from examples 95, 100, 103, 130 and 134 in document (3), the skilled person had to make several choices in order to arrive at the claimed compounds. Firstly, they had to decide to modify the compounds of document (3) at the Z-position and to choose the group $-C(O)NR^6R^7$ among other alternatives. Then they had to select the option that in $-C(O)NR^6R^7$ the group NR^6R^7 forms a ring of 3 to 10 members (see page 9, lines 24-32). And then they still had to select the undisclosed possibility of the 3- to 10-membered ring being azetidin-1-yl. In the board's opinion, the skilled person had no motivation to make all these selections with the expectation of obtaining better MEK inhibitors. The compounds in group A of granted claim 1 are therefore inventive, starting from document (3).

12.3 Starting from document (12)

12.3.1 The MEK inhibitors disclosed in document (12) have the following generic formula (I):



The appellant and the opposition division considered that the compounds in group B of granted claim 1 were encompassed by this general formula (I). So the

compounds in group B were a selection among those disclosed in document (12).

The board disagrees. As noted by the respondent, formula (I) above does not encompass the compounds in group B because document (12) (see the passage bridging pages 7 and 8) does not include the possibility of W being -C(O)(azetidin-1-yl), with the azetidin-1-yl ring not being fused to another ring. The reasons for this are the following:

According to document (12), W is "*selected from heteroaryl, heterocyclyl, -C(O)OR^3, -C(O)NR^{3}R^4, -C(O)NR^{4}OR^3, -C(O)R^{4}OR^3, -C(O)(C$_3$-C$_{10}$ cycloalkyl), -C(O)(C$_1$-C$_{10}$ alkyl), -C(O)(aryl), -C(O)(heteroaryl) and -C(O)(heterocyclyl), each of which is optionally substituted...*". From this definition, the only residues that might mean -C(O)(azetidin-1-yl) are **-C(O)(heterocyclyl)** or **-C(O)NR^{3}R^4**.

With regard to the residue -C(O)(heterocyclyl), "heterocyclyl" in the sense of document (12) means (see page 13, paragraph 2): "*one or more carbocyclic ring systems of 5-, 6-, or 7-membered rings which includes fused ring systems of 4-10 atoms containing at least one and up to four heteroatoms...*", wherein "*A fused system can be a heterocycle fused to an aromatic group. Preferred heterocycles include...azetidinyl...*". Hence, the heterocycles in document (12) are restricted to **heterocycles of 5 to 7 ring members**, or to **fused ring systems of 4 to 10 atoms**. This definition excludes non-fused ring systems having four members, such as azetidinyl. In this context, the mention of azetidinyl in the citation above is understood as referring to the fused ring systems of 4 to 10 atoms.

On this issue, the appellant argued that the compound in example 6 of document (12) contained a non-fused azetidinyl substituent, so that "heterocyclyl" in document (12) meant in fact 4- to 7-membered rings rather than 5- to 7-membered rings. The board however cannot infer from this inconsistency in a single example that the general definition of the term "heterocyclyl" on page 13 of document (12) may be construed as desired by the appellant. At most, it could be considered that the meaning of the term "heterocyclyl" in document (12) is uncertain and therefore that it does not unambiguously encompass non-fused azetidinyl.

With regard to the residue $-C(O)NR^3R^4$, paragraph 2 on page 6 of document (12) states that R^3 and R^4 can be taken together with the atom to which they are attached to form a 4- to 10-membered carbocyclic, heteroaryl or heterocyclic ring. However, 4-membered rings in this context refer to carbocyclic rings only. This transpires from the definition of "heteroaryl" and "heterocyclyl" as rings with 5 to 7 members (see paragraph 3 on page 12 and paragraph 2 on page 13, respectively), while "carbocycles" may have from 3 to 10 carbon atoms (see paragraph 4 on page 12).

In conclusion, the board holds that the compounds in group B of granted claim 1 are not encompassed by formula (I) in document (12). As a result, the claimed compounds differ from those in document (12) in that the substituent of the claimed compound called W in document (12) is -C(O)(non-fused azetidin-1-yl).

12.3.2 In accordance with the passages in paragraphs [0001] and [0011] and the biochemical examples in the patent, the board considers that the technical problem solved

by this difference is the provision of **alternative** MEK inhibitors.

The experimental evidence on file supports the fact that the solution proposed in granted claim 1, in particular the compounds of group B, effectively solve this technical problem. The compounds disclosed in Annex 1 of document (24) are in accordance with granted claim 1 (including some of group B) and exhibit MEK inhibition *in vitro* and *in cell* at nanomolar concentrations. Documents (25) and (28) show the MEK inhibiting activity of other compounds belonging to group B (see table on page 2 of document (25) and compounds (R) and (BC) in document (28)). Likewise, the appellant's data in document (32) demonstrate that compounds belonging to group B exhibit MEK inhibition to a certain extent (see compounds B, D, F, J, P, U, W, Y, AA, AC and AE). In this context, the fact that the activity of compound M in document (32) was insufficient to be calculated by the IMAP or Alphascreen methods does not preclude the above conclusion, because the impossibility of measuring MEK activity could be due to the reduced solubility of the compound in the testing medium, rather than to a real lack of activity.

Hence, the board is satisfied that the compounds of group B are MEK inhibitors.

The appellant further pointed to document (21), which is a publication arising from the results of the development of some of the compounds in granted claim 1. According to the appellant, this document made clear on page 417 (see right column, second full paragraph) that the presence of a hydroxyl group at the 3-position of the azetidine ring was essential for the compounds

in granted claim 1 to exhibit MEK inhibition. In particular, the appellant mentioned the following passage: "*The hydroxyl group at the 3-position of the azeditine was important for biochemical potency, and deletion in the case of 6 was poorly tolerated*". Thus, as not all the compounds in granted claim 1 contained this feature, the problem of providing MEK inhibitors was not solved across the whole breadth of granted claim 1.

On this point, the board notes that document (21) does indeed underline the importance of having a hydroxyl group at the 3-position of the azetidine ring. However, it does not state that compounds missing such a hydroxyl group fail to show MEK inhibition. In fact, compound 6 referred to in the cited passage as an example of a compound without a 3-hydroxyl group on the azetidine ring is shown in table 1 of document (21) to have considerable MEK inhibiting activity. The appellant's argument is therefore not convincing.

12.3.3 The next step then is to investigate whether or not the compounds in granted claim 1 were an obvious solution to the skilled person faced with the problem of providing alternative MEK inhibitors.

In this respect, it has already been discussed that document (12) neither discloses nor suggests that substituent W be -C(O)(azetidin-1-yl): on the one hand because it focuses on W being $-C(O)OR^3$ or $-C(O)NR^4OR^3$ (see claims 3-12 and all examples) rather than $-C(O)NR^3R^4$ or -C(O)(heterocyclyl) - the latter groups are merely mentioned within a list of nine other generic groups, never as preferred options (see page 7, last paragraph, and claims 1 and 2); on the other hand because, even considering the groups $-C(O)NR^3R^4$ or

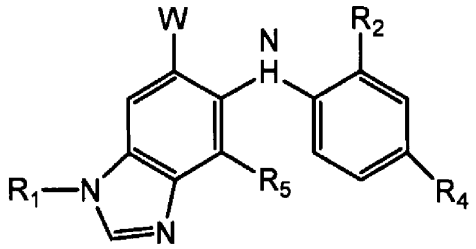
-C(O)(heterocyclyl) as possible options for W, document (12) does not suggest stand-alone, 4-membered heterocyclic rings, let alone the specific 4-membered heterocyclic group azetidin-1-yl. As a result, starting from document (12), the skilled person would not have arrived at the compounds of group B in granted claim 1.

12.3.4 The appellant argued that the teaching of document (12) could be combined with that of document (11) because they were closely related, both of them concerning the provision of MEK inhibitors and disclosing compounds of a similar structure. Thus, as document (11) defined compounds in which the group W was a cyclic amide (see examples on pages 96 and 97), the skilled person would also have used cyclic amides, such as -C(O)(azetidin-1-yl), as group W in document (12).

The board rejects this argument because, even if the skilled person combined documents (12) and (11) and contemplated the use of cyclic amides - which, as noted by the respondent, are a clear minority among the examples in document (11) - it is not apparent why they would think of using the specific 4-membered cyclic amide -C(O)(azetidin-1-yl), knowing that the cyclic amides in document (11) have 5- or 6-membered rings and that the document does not suggest the use of 4-membered rings, let alone of azetidine. Hence, the combination of documents (12) and (11) does not render the compounds in group B obvious either.

12.4 Starting from document (15)

12.4.1 Similarly to document (12), document (15) discloses MEK inhibitors of the following generic formula (I):



In this case it is even clearer than in document (12) that group W, defined on page 2 of document (15), cannot be -C(O)(azetidin-1-yl). The closest possibility would be the double selection whereby W was -C(O)Q and Q was optionally substituted $-NH_2$, $-NH[(CH_2)_kCH_3]$ or $-NH[O(CH_2)_kCH_3]$. However, still in that case, document (15) does not foresee the option of W being -C(O)(azetidin-1-yl).

12.4.2 Based on this difference and on the effect shown in documents (24), (25), (28) and (32), the problem may be formulated once again as the provision of **alternative** MEK inhibitors.

12.4.3 Considering that neither document (15) nor its combination with other cited documents suggests the possibility of the substituent W being -C(O)(azetidin-1-yl), the compounds of group B in granted claim 1 are inventive.

12.4.4 The appellant contended that the skilled person would have been motivated to modify the cyclic amides 55 and 59 on page 38 of document (15) or even the open amide 44 on page 34 in order to obtain alternative MEK inhibitors. In this connection, it submitted that the preparation of analogues with 4-, 5- and 6-membered rings was a common strategy for modifying cyclic amides, as illustrated in document (2) (see scheme 6 on page 45). This would have led the skilled person to the

compounds in granted claim 1 in an obvious manner. Also, the combination of document (15) with (11) or (12) rendered the claimed compounds obvious.

The board disagrees. Firstly because document (2) is a patent application dealing with the inhibition of receptors other than MEK and is not a document representative of the common general knowledge; so its scheme 6 cannot represent what the skilled person would consider to be a general strategy for the modification of amides, let alone for obtaining MEK inhibitors alternative to the ones in document (15). Secondly because, as discussed above, neither of documents (11) and (12) suggests the preparation of compounds with the group -C(O)(azetidin-1-yl).

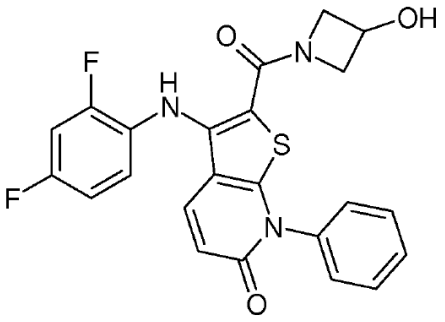
12.5 Starting from document (2)

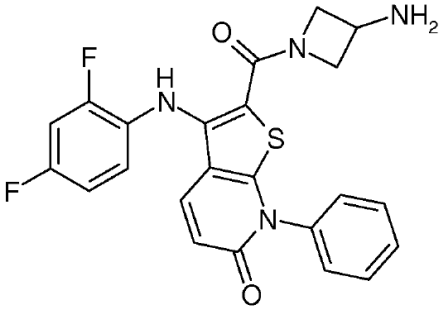
12.5.1 Document (2) discloses thienopyridone derivatives as inhibitors of p38 MAP kinases for the treatment of immune or inflammatory disorders.

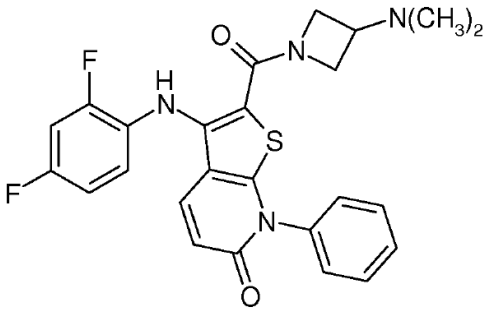
The board agrees with the respondent that document (2) is not a suitable starting point for arriving at the compounds in granted claim 1, because p38 MAP kinase belongs to a different subfamily of mitogen-activated protein kinase than MEK (MAPK/ERK kinase). Thus, even if the skilled person started from document (2), it is not apparent how they would modify the compounds in it to prepare MEK inhibitors. In this respect, the board also agrees with the respondent that different proliferative diseases were known at the filing date and that a class of compounds effective against one of those diseases could not be expected to be effective against proliferative diseases associated with

different signal transduction pathways, especially taking into consideration the statement in document (2) that p38 MAP kinase inhibitors are selective (see lines 16-18 on page 6 of document (2)). Hence, the compounds in granted claim 1 are not obvious starting from document (2).

12.5.2 In this respect, the appellant referred to compounds 33, 69 and 71 in document (2), which have the following formulae, respectively,







and noted that the compounds in group B differed from them in the nature of the substituent on the heteroarylene group (see section 8.5 of the statement of grounds of appeal). It then contended that, because the inhibition of both MEK and p38 MAP kinases was useful for the treatment of proliferative disorders, the problem to be solved could be defined as the provision of compounds for the treatment of proliferative disorders. In the appellant's view, this

broader formulation of the problem was allowable because granted claim 1 defined only compounds and therefore their effect was not limiting. Following this reasoning, the appellant concluded that in the light of document (14), which also dealt with p38 MAP kinase inhibitors, the skilled person would have modified the compounds in document (2) so as to arrive at those in group B.

12.5.3 The board cannot accept that application of the problem-solution approach, because it overlooks the fact that the patent is not directed to the treatment of proliferative diseases in general but to those proliferative diseases that may be treated by MEK inhibition. Therefore, it is not apparent how the skilled person would modify the p38 MAP kinase inhibitors in document (2) to provide MEK inhibitors, or why they would combine the teaching of document (2) with a document dealing with p38 MAP kinase inhibitors, such as document (14), in order to produce MEK inhibitors.

12.6 In conclusion, the board considers the compounds in granted claim 1 to be inventive. As a direct consequence, the compositions, methods and therapeutic uses defined in granted claims 38 to 43 are inventive too (Articles 100(a) and 56 EPC).

13. Sufficiency of disclosure

In its analysis of sufficiency of disclosure, the appellant raised two issues. On the one hand, it disputed the skilled person's ability to prepare the broad range of compounds encompassed by granted claim 1. On the other hand, it questioned whether all the claimed compounds exhibited the practical MEK

inhibition required for carrying out the invention underlying granted claims 38 to 43.

13.1 With respect to the feasibility of the compounds in granted claim 1, the board observes that the documents cited by the appellant in the context of the discussion of novelty and inventive step, in particular the schemes and examples in documents (2) to (5) and (10) to (15), disclose a broad range of compounds closely related to those in granted claim 1 and that they provide synthetic schemes and concrete preparation examples. Furthermore, the patent discloses 40 specific synthesis examples. Accordingly, the skilled person has extensive knowledge of how to prepare the compounds in granted claim 1, and their preparation does not entail an undue burden.

In addition, as preparing a pharmaceutical composition from a known active ingredient is a matter of routine and falls within the competence of the skilled person, the preparation of a pharmaceutical composition as in granted claim 38, which is characterised by the fact that it contains a compound from granted claim 1, does not involve an undue burden either.

13.2 On the question of whether the patent makes plausible that the claimed compounds are suitable for carrying out the inventions underlying granted claims 39 to 43, two facts need to be taken into consideration:

i) Document (3) discloses a generic formula of MEK inhibitors which encompasses the compounds in group A of granted claim 1. The document contains examples of MEK inhibitors, and its sufficiency has not been disputed by the appellant. It is then credible that the compounds in granted claim 1 are

MEK inhibitors, a fact that has been confirmed by the evidence filed during the appeal proceedings, in particular by documents (21), (24), (25), (28) and (32).

ii) The parties have not disputed that the inhibition of MEK is generally known as being directly linked to the inhibition of proliferative diseases, such as cancer. The appellant raised the concern that compounds with very low MEK inhibition might not achieve a therapeutic effect. However, it did not provide evidence that there is a threshold of minimum MEK inhibition in order for a compound to be suitable for medical purposes and that compounds encompassed by granted claim 1 are below that threshold. In this respect, the fact that some of the compounds in granted claim 1 have been shown in documents (16) and (32) to exhibit high IC_{50} values is not sufficient to prove that they are not suitable for treating proliferative diseases.

In consequence, the invention underlying claims 39 to 43 is sufficiently disclosed.

13.3 Following from the above, the board holds that the invention underlying the subject-matter claimed in the patent as granted is sufficiently disclosed (Articles 100(b) and 83 EPC).

14. Industrial applicability

As explained above, it has been made credible that the compounds in granted claim 1 may be used for the treatment of proliferative diseases. Therefore, the invention underlying the patent is susceptible of industrial application (Articles 100(a) and 57 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated