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D E C I S I O N
of 26 February 2004

Case Number: T 0926/00 - 3.3.2

Application Number: 93923964.6

Publication Number: 0665753

IPC: A61K 31/70

Language of the proceedings: EN

Title of invention:
Fludarabine-5' monophosphate for the treatment of autoimmune diseases

Applicant:
Schering Aktiengesellschaft

Opponent:
-

Headword:
Treatment of autoimmune diseases/SCHERING

Relevant legal provisions:
EPC Art. 52(1), 54, 56, 123(2)

Keyword:
"Main request: novelty (yes) - use of fludarabine-5' monophosphate for the treatment of autoimmune diseases not directly and unambigously derivable from the cited state of the art; inventive step (no) - skilled person was provided with several hints and suggestions from the prior art pointing him in the direction of the claimed use: obvious to try"
"Second, third and fourth auxiliary requests - idem"
"First auxiliary request - contravention of Article 123(2) EPC"

Decisions cited:
T 0296/87, T 0666/89, T 0465/92, T 0511/92

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0926/00 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 332
of 26 February 2004

Appellant: SCHERING AKTIENGESELLSCHAFT
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 2 June 2000 refusing European application No. 93923964.6 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: G. F. E. Rampold
P. Mühlens

Summary of Facts and Submissions

I. This is an appeal against the decision of the examining division posted on 2 June 2000 to refuse European patent application No. 93 923 964.6 (the "application"), entitled "Fludarabine-5'-monophosphate for the treatment of autoimmune diseases".

The application was filed on 22 October 1993, claiming the priority of an earlier application in the United States on 23 October 1992, and was published under the PCT on 11 May 1994 as WO 94/09791. The decision under appeal is based on an amended set of 12 claims, filed on 6 September 1999 with the appellant's (applicant's) letter dated 1 September 1999. The independent claims are worded as follows:

"1. Use of an effective amount of fludarabine-5'-monophosphate for the production of a medicine for the treatment of an autoimmune disease.

4. Use of an effective amount of fludarabine-5'-monophosphate for the production of a medicine for the prevention of the symptoms of an autoimmune disease.

7. Use of an effective amount of fludarabine-5'-monophosphate for the production of a medicine for the amelioration of the symptoms of an autoimmune disease.

10. Use of an effective amount of fludarabine-5'-monophosphate for the production of a medicine for the prophylactical treatment of an autoimmune disease."

II. In the decision under appeal reference was made to the following six citations:

(1) David H. Boldt et al, "Effects on Human Peripheral Lymphocytes of *in vivo* Administration of 9-ß-D-Arabinofuranosyl-2-fluoroadenine-5'-monophosphate (NSC 312887), a New Purine Antimetabolite", CANCER RESEARCH, vol. 44, No. 10, 1984, pages 4661 to 4666;

(2) Carlos J. Carrera et al, "Potent Toxicity of 2-Chlorodeoxyadenosine toward Human Monocytes *in vitro* and *in vivo",* J. Clin. Invest. 1990, vol. 86, pages 1480 to 1488;

(3) The Merck Index, 11th Edition, 1989, item 4057;

(4) "Fludarabine and Psoriasis", The New England J. of Medicine, 1994, pages 1540 to 1541;

(5) Barbara S. Baker et al, "The Immunology of Psoriasis", British J. of Dermatology, 126, 1992, pages 1 to 9:

(6) Z. Ruszczak, "Immunsuppressiva zur Behandlung von Autoimmunkrankheiten der Haut und der Psoriasis", Der Hautarzt 28, 1977, pages 125 to 131.

III. The stated ground for the refusal was that the subject-matter of the claims did not involve an inventive step. The essence of the reasoning in the decision under appeal was as follows:

The examining division considered the teaching of citation (2) to be the closest state of the art. According to this prior art, the marked sensitivity of human monocyte function and survival to 2-chloro-2'-deoxyadnosine (hereinafter referred to as CldAdo) *in vitro*, together with the monocyte depletion in patients receiving CldAdo chemotherapy suggested that CldAdo and other 2'-deoxy-adenosine (hereinafter referred to as dAdo) analogues offered a novel therapeutic strategy for chronic inflammatory and autoimmune diseases.

Starting from citation (2) as the closest prior art, the examining division formulated the problem to be solved as *"providing a further treatment of autoimmune diseases, in particular rheumatoid arthritis"*. It considered the proposed solution to the problem posed, namely the administration of 9-ß-D-arabinofuranosyl-2-fluoroadenine-5'-monophosphate (hereinafter referred to as fludarabine-5'-monophosphate or FLP) to patients in need of it, to be obvious, in view of the teaching in citation (2) itself that the dAdo analogue FLP had been shown in the earlier citation (1) in a Phase I clinical trial to lower *in vivo* circulating OKM1 positive mononuclear cells, presumably monocytes.

In the opinion of the examining division, those skilled in the art would have found additional support for the usefulness of FLP in the treatment of autoimmune diseases in citation (1) because this citation already

taught that FLP or a related compound might be clinically useful as an immunosuppressive agent.

In the decision under appeal it was moreover mentioned that, according to the disclosure in citation (1), in particular T4 cells were sensitive to the cytotoxic effect of FLP and that, according to citation (5), therapy directed against T4 cells (such as anti-CD4 antibodies) was considered to be particularly effective in the treatment of the autoimmune disease psoriasis. Thus, in the opinion of the examining division, the combined teaching of (1) and (5) offered a further clear hint in the direction of the claimed invention.

Finally, the finding in citation (6) that purine antagonists were useful, amongst other kinds of immunosuppressive agents, in the therapy of dermatoses (autoimmune diseases of the skin) and psoriasis provided, in the judgment of the examining division, additional support for its objection of lack of inventiveness.

IV. During oral proceedings, held before the board on 26 February 2004, the appellant presented the claims 1 to 12 refused by the examining division as its main request (see I above) and filed four additional sets of claims forming its current first, second, third and fourth auxiliary requests.

The **first auxiliary request** consists of claims 1 to 12 of the main request with each independent claim being amended by the following addition indicated in bold italic letters below:

"1. Use of an effective amount of fludarabine-5'-monophosphate for the production of a medicine for the treatment of an autoimmune disease ***by at least partial elimination of B cells.***"

In the **second auxiliary request** the claimed therapeutic applications have been restricted in the independent claims to the treatment, prevention, amelioration or prophylaxis of the symptoms of **rheumatoid arthritis**; claim 1 reads as follows:

"1. Use of an effective amount of fludarabine-5'-monophosphate for the production of a medicine for the treatment of **rheumatoid arthritis**."

The independent claims in the **third auxiliary request** differ from those in the main request by the additional specification that FLP is applied in an amount in the range of 1 to 10 mg/kg/day; claim 1 reads as follows:

"1. Use of an effective amount of fludarabine-5'-monophosphate for the production of a medicine for the treatment of an autoimmune disease, wherein **the amount of fludarabine-5'-monophosphate is 1 to 10 mg/kg/day.**"

In the **fourth auxiliary request** the claimed therapeutic applications have been restricted in the independent claims to the treatment, prevention, amelioration or prophylaxis of the symptoms of rheumatoid arthritis and the claims contain the additional specification that FLP is applied in an amount in the range of 1 to 10 mg/kg/day; claim 1 reads as follows:

"1. Use of an effective amount of fludarabine-5'-monophosphate for the production of a medicine for the treatment of **rheumatoid arthritis**, wherein **the amount of fludarabine-5'-monophosphate is 1 to 10 mg/kg/day.**"

V. The appellant's arguments, submitted in writing and at the oral proceedings can be summarised as follows:

The subject-matter of the claimed invention was the use of the purine antimetabolite FLP in the treatment of autoimmune diseases, particularly rheumatoid arthritis. The invention was based on *in vitro* data showing that FLP was capable of selectively reducing the concentration of autoimmune-specific rheumatoid factor IgM-RF. In the present application, the efficacy of FLP against rheumatoid arthritis was also shown in an *in vivo* autoimmune model, the human type II collagen-induced arthritis in rats. A detailed inspection of the experimental data led to the conclusion that FLP surprisingly exhibited a strong and selective therapeutic activity for the treatment of autoimmune diseases.

Citation (2), which was considered by the examining division to represent the closest state of the art, included a series of experiments designed to test the toxicity of CldAdo toward human monocytes *in vitro* and *in vivo.* It was reported in (2) that monocytes exposed *in vitro* to CldAdo rapidly developed DNA strand breaks. Circulating monocytes were shown in (2) to disappear within one week in patients with cutaneous T cell lymphoma or with rheumatoid arthritis during continuous CldAdo infusion. The authors of (2) concluded from this

that CldAdo or other dAdo analogues offered a novel therapeutic strategy for chronic inflammatory and autoimmune diseases.

CldAdo showed significant differences in its chemical structure as compared to FLP. First, FLP was a purine antimetabolite having a phosphate moiety attached to the 5'-OH group of the sugar portion of the FLP molecule. The phosphate moiety was lacking in the CldAdo molecule, but was, in the appellant's opinion, crucial to the physiological properties of FLP, namely to its overall charge and its capability of penetrating the cell wall. Second, the sugar portion of the FLP molecule was a D-arabinofuranosyl group and as such different from the sugar portion of CldAdo which was a deoxyribofuranosyl group. Third, in contrast to the fluorine atom in position 2 of the adenine moiety of FLP, a chlorine atom was attached to the 2-position of the adenine moiety of CldAdo. These striking differences in their chemical structure resulted, according to the appellant, in different physiological properties and pharmacological activities of the two compounds in question.

Citation (2) disclosed that the dAdo analogue FLP had been shown in a Phase I clinical trial to lower circulating OKM1 positive mononuclear cells, presumably monocytes. This study, which was originally disclosed in citation (1), demonstrated that FLP caused marked and reversible lymphopenia and that, although all lymphocyte subclasses were affected, T-cells appeared to be more sensitive than B-cells. This result was in contrast to the findings in the present application

where B lymphocytes were shown to be more sensitive to the effects of FLP as compared to T lymphocytes.

In the appellant's opinion, the properties and capabilities of FLP reported in citation (1) did not in any way suggest to those skilled in the art the usefulness of this substance as a therapeutic agent for the treatment of autoimmune diseases. According to the appellant, it was moreover important to note that the period of about 8 years that had elapsed between the publication of the physiological and pharmacological properties of FLP reported in (1) and the priority date of the present application was a clear indication that the state of the art according to (1) did not point the skilled person in the direction of the claimed invention.

In this respect, the appellant essentially argued that the experimental data according to (1) had been obtained from peripheral lymphocyte populations of leukemia patients. It was evident that the lymphocyte population and also the population of the lymphocyte subclasses of such patients showed great deviations from the lymphocyte populations of patients suffering from autoimmune diseases. It was thus clearly inappropriate to simply apply the experimental data of (1), which reflect the cell status of leukemia patients, to the field of autoimmune diseases.

In Example 3 of the present application the effects of FLP on immunoglobulin accumulation, and in particular on the accumulation of IgM, IgG and the autoimmune specific IgM rheumatoid factor (IgM-RF) were compared favourably with those of CldAdo. In Figures 7A and 7B

it was shown that 5 µg/ml FLP were sufficient to block any measurable IgM accumulation, whereas 1 µg/ml FLP had only an intermediate effect on the IgM production. In contrast thereto, 1 µg/ml CldAdo was sufficient to block both IgM and IgG production. From Figure 7C it was derivable that the improved selectivity of FLP for IgM-RF compared with that of CldAdo permitted a more selective therapy of autoimmune diseases by avoiding undesired side-effects, such as a general deterioration of the immune system.

VI. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or on the basis of one of the auxiliary requests 1 to 4, filed in the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. The claimed invention in the present application is directed to a method of treating an autoimmune disease or preventing or ameliorating its symptoms; said method comprises administering to a patient in need of such treatment an effective amount of 9-ß-D-arabinofuranosyl-2-fluoroadenine-5'-monophosphate (hereinafter referred to as fludarabine-5'-monophosphate or FLP). In a preferred embodiment the disease is rheumatoid arthritis.

Closest state of the art

3. FLP is a synthetic, adenosine deaminase-resistant purine nucleoside antimetabolite which is described, *inter alia,* in citations (1) and (3). Its preclinical activity against a number of animal tumours, including L1210 and P388 lymphoid leukemias, CD8F1 mammary carcinoma, and the human LX1 lung tumour xenograft is well documented (see, *inter alia* (1), page 4664, left-hand column, end of first paragraph). Data from *in vitro* studies and preclinical animal toxicology trials indicate that FLP is lymphocytotoxic and that it causes profound myelosuppression and lymphopenia (see (1), page 4661, left-hand column, Abstract, first paragraph).

3.1 Included in citation (1) is a comprehensive study of the effects of FLP on peripheral lymphocytes of patients receiving the agent in a Phase I clinical trial. Eleven patients received 13 courses given by i. v. bolus daily for 5 days. Mononuclear cells were isolated, and lymphocyte subsets were quantified by immunofluorescence and flow cytometry 1 day before treatment and 4 hrs after the final infusion. FLP is shown in (1) to cause *in vivo* striking treatment-induced decreases in recoveries of total mononuclear cells, total T-cells, and the non-T-, non-B-cell subclass (the latter predominantly OKM1 positive cells). By contrast, there was no difference in mean pre- and post-treatment total B-cell recoveries. Considering individually the 13 treatment cycles in human subjects reported in (1), B-cell recoveries decreased during 6 cycles and actually increased during 6 cycles. These data are more direct evidence that, in general, B-cells may be more resistant to FLP than are T-cells (see (1),

especially page 4663, 2nd full paragraph, headed "Cell Recoveries and page 4664, Chart 5).

3.2 The above-mentioned results provide for FLP an initial assessment of the effects of an adenosine deaminase-resistant, adenine nucleotide analogue on lymphocyte subsets in humans. These results of *in vivo* investigations in (1) appear to be consistent with *in vitro* observations indicating that FLP is lymphocytotoxic and that it may express preferential cytotoxicity towards T-lymphocytes. The data obtained in (1) also indicate that the peripheral lymphocytopenia in the doses studied is reversible. The results and observations reported in (1) in their entirety imply in general that the synthetic haloadenine nucleotide analogue FLP or related compounds may be useful agents **for the treatment of lymphoid cancers, especially T-cell subtypes.** (cf. (1) especially page 4665, left-hand column, lines 20 to 28). As has been acknowledged in the introductory portion of the present application, FLP has already been shown to effect a dramatic **improvement in both complete and chronic lymphatic leukemia (B-CLL)** (see page 5, lines 9 to 11; M. J. Keating, 1990, Seminar in Oncology, 17(5):49, Suppl. 8).

3.3 The board agrees with the appellant's submission at the hearing that citation (1) should be considered as representing the closest prior art available in the proceedings because it is the only prepublished document before the board which relates to the adenosine deaminase-resistant purine antimetabolite **FLP** (fludarabine-5'-Monophysite) and also discloses **its pharmacological, physiological and therapeutic**

properties and its use in methods for **treatment of the human or animal body by therapy,** more specifically for the treatment of lymphoid cancers.

Problem and solution

4. In the light of this prior art, the problem to be solved by the claimed invention can be seen to be to find for FLP a further useful therapeutic application in addition to the one disclosed in (1).

It is generally recognised that finding a **useful new therapeutic application** for a known biologically active substance, already used in the state of the art for one or more therapeutic purposes, represents a desirable goal in the fields of medicine and pharmacology and a worthwhile technical problem which cannot be disregarded in assessing the inventive step of its solution as claimed. Moreover, as the tests for toxicity, mutagenicity, teratogenicity, metabolism and metabolites, mode of action, pharmacokinetic and pharmacodynamic properties, *etc.* of an entirely new pharmacologically active substance, designed for use in therapy, require more and more labourious, time consuming and expensive examinations, the person skilled in the art would be even more likely to try to find for a known therapeutically active substance, already successfully tested or used in the field of medicine, a further as yet unknown therapeutic effect or application.

4.1 According to claim 1 the problem is solved, in its broadest sense, by the proposed use of FLP as a medicament for the treatment of an autoimmune disease.

In view of the examples in the application, it is plausible that FLP shows suitable biological and pharmacological properties *in vitro* (Examples 2 to 4) and *in vivo* (Examples 1 and 5), making this substance useful in methods of treating autoimmune diseases, eg rheumatoid arthritis, or preventing or ameliorating its symptoms. The board is accordingly satisfied that the problem underlying the application is solved.

Novelty

5. Citation (2) states (see page 1480, left-hand column, 2nd paragraph) that "the marked sensitivity of human monocyte function and survival to CLAdo (2-chlorodeoxyadenosine) in vitro, together with the monocyte depletion in patients receiving CldAdo chemotherapy, suggests that CldAdo or other dAdo analogues (emphasis added) offer a novel therapeutic strategy for chronic inflammatory and autoimmune diseases characterised by inappropriate monocyte deployment or function". Citation (2) goes on to state (see page 1486, left-hand column, lines 4-8 from the bottom) that "recently, the dAdo analog 9-ß-D-arabinofuranosyl-2-fluoroadenine-5'-monophosphate (FLP, emphasis added) was shown in a Phase I clinical trial to lower circulating $OKM1^+$ mononuclear cells, presumably monocytes (emphasis added), in addition to lowering patient lymphocyte counts."

5.1 According to the consistent case law of the boards of appeal a prior art document anticipates the novelty of any claimed subject-matter derivable directly and unambiguously from that document, including any features implicit to a person skilled in the art in

what is expressly mentioned in the document (see decision T 511/92 unpublished in OJ EPO or T 465/92, OJ 1996, 32). Although the above-quoted statements in (2), in connection with the whole disclosure of this citation,

(i) suggest using CldAdo **or other dAdo analogues** for the treatment of **autoimmune diseases** characterised by **inappropriate monocyte deployment or function** and,

(ii) refer in this context to the capability of the **dAdo analogue FLP** to lower *in vivo* circulating OKM1 positive mononuclear cells, presumably **monocytes**,

the board concurs with the appellant's submission during the hearing that citation (2) does not, or at least not directly and unambiguously, disclose the claimed solution of the stated problem.

5.2 In the present case, in the board's judgment, it may be reasonable to assume that the skilled reader of the above-mentioned disclosures in citation (2) could readily have come to the idea of using FLP also in a method of treating autoimmune disease. However, this is a typical consideration or concept which is frequently relevant for assessing inventive step, namely, whether the notional addressee "would have tried, with reasonable expectation of success" to **bridge the technical gap** between a particular disclosure in the prior art and the subject-matter of a claim whose inventiveness is in question (ie in the present case the **gap** between the disclosures in (2) of the dAdo

analogues CldAdo and FLP and the effects of these two analogues on circulating monocytes *in vitro* and *in vivo* on the one hand, and the claimed use of FLP in the present application in a method of treating autoimmune disease characterised by inappropriate monocyte deployment or function, on the other). However, this "inventive-step concept" as such is fundamentally different from the "novelty concept" used at the EPO because in order to establish anticipation, there **cannot be a gap** of the above kind (see eg T 666/89, OJ EPO 1993,495). Accordingly, novelty over citation (2) is acknowledged. Novelty over the other documents on file is undisputed.

Inventive step

6. It therefore has to be established whether the proposed solution involves an inventive step.

6.1 As already mentioned in 2.1 above, FLP is a synthetic purine antimetabolite and belongs from a structural and biological point of view to the class of **purine antimetabolites,** more specifically to the class of **adenosine deaminase-resistant 2-haloadenine nucletoide analogues or congeners of 2'-deoxyadenosine (dAdo).** A skilled person, faced with the stated technical problem and seeking a solution to this problem would, in the board's judgment, primarily look in the state of the art for substances belonging to the same or a similar class of compounds and would be highly interested to learn about their biological, physiological and pharmacological properties reported in the prior art.

6.2 In the course of this search the person skilled in the art would immediately and inevitably come across the citation (2), since this document specifically relates to the purine antimetabolite 2-chlorodeoxyadenosine (CldAdo), **an adenosine deaminase-resistant 2-haloadenosine analogue or congener of dAdo,** and discloses in great detail the biological, physiological and pharmacological properties of this substance. Moreover, citation (2) contains at page 1486, left-hand column, lines 4 to 8 from the bottom, a cross-reference to FLP and citation (1).

6.3 The board is of the opinion that citation (2) and the other cited documents contain sufficient hints and indications likely to lead a person skilled in the art to the claimed subject-matter of the application.

6.3.1 Thus, citation (2) reports that **monocytes** exposed *in vitro* to CldAdo rapidly developed DNA strand breaks. Both the DNA damage and the toxicity of CldAdo were blocked by deoxycytidine, but not by inhibitors of poly(ADP-ribose)-polymerase. A partial decease in RNA synthesis and a gradual decline of cellular NAD were early biochemical events associated with monocyte DNA damage. Low CldAdo concentrations inhibited phagocytosis and reduced release of interleukin 6. Higher CldAdo concentrations led to a dose-and time-dependent monocyte viability (see page 1480, left-hand column, Abstract, first paragraph; page 1482, left-hand column to page 1484, left-hand column, end of fourth full paragraph).

6.3.2 Regarding the effects of CldAdo on **monocytes** *in vivo* it is reported in (2) that circulating monocytes disappeared within 1 week in patients with cutaneous T cell lymphoma or with **rheumatoid arthritis** during continuous CldAdo infusion (see page 1480, left-hand column, Abstract, second paragraph; page 1484, left-hand column, penultimate paragraph to right-hand column, second paragraph; Figure 6).

6.3.3 With regard to the proposed treatment of autoimmune diseases, the authors of (2) explain, *inter alia*, that cells of the mononuclear phagocyte system regulate both immunity and chronic inflammation, and hence represent a potential target for chemotherapeutic modulation. Derived from bone marrow myeloid precursors, **monocytes** give rise to a diverse array of tissue macrophages with specialised phagocytic and synthetic functions necessary for immune competence. Unlike lymphocytes, blood monocytes have little, if any, proliferative capacity. The recruitment and activation of **mononuclear phagocytes** contribute to the pathogenesis of **inflammatory arthritis and other autoimmune disorders** (see page 1480, right-hand column, first full paragraph). Phagocytosis, secretion of inflammatory mediators, and local tissue destruction are **mononuclear phagocyte** functions implicated in the pathogenesis of diverse syndromes such as immune cytopenias, rheumatoid arthritis, and sarcoidosis. Phagocytosis of immune complexes by monocyte-derived synoviocytes may foster inflammation and joint damage in **rheumatoid arthritis. Rheumatoid arthritis** is a disease in which **monocyte-derived** macrophages play a role in synovial inflammation and joint destruction. More recently, the levels of IL-6 in synovial fluid and serum from

rheumatoid arthritis patients have been found to correlate with certain indices of disease activity (see (2), the paragraph bridging the right-hand and left-hand columns on page 1486).

6.3.4 The results of the *in vitro* and *in vivo* investigations and tests performed in (2), seen in the context of the scientific background mentioned above, allow the authors of citation (2) to arrive at the conclusion that the *in vitro* and *in vivo* effects of CldAdo on **monocytes** described in (2) offer **a new approach** for the treatment of certain **chronic inflammatory and autoimmune diseases** (see page 1480, end of right-hand column). A similar conclusion is drawn elsewhere in citation (2), namely that the marked sensitivity of human monocyte function and survival to CldAdo *in vitro*, together with the monocyte depletion in patients receiving CldAdo chemotherapy, suggests that not only CldAdo, but also **other dAdo analogues** offer a novel therapeutic strategy **for chronic inflammatory and autoimmune diseases** characterised by inappropriate **monocyte** deployment or function (see page 1480, left-hand column, Abstract, 2nd paragraph).

6.3.5 However, in citation (2) a clear and unequivocal link is made between the effects of CldAdo and other dAdo analogues on circulating monocytes and the consequential use of such substances in the therapy of autoimmune diseases on the one hand, and the effects of the dAdo analogue FLP on monocytes and its use in the therapy of autoimmune diseases on the other. In the context of the reference in (2) to **CldAdo** and other **dAdo analogues** and their capability of reducing the absolute monocyte count, often to zero, and affecting

monocyte function and violability at concentrations below those that cause general myelosuppression, there is in citation (2) a clear cross-reference from CldAdo to the **dAdo analogue 9-ß-D-arabinofuranosyl-2-fluoroadenine-5'-monophosphate (FLP)** (which, incidentally, is the only dAdo analogue explicitly mentioned in (2)) and its capability of **lowering circulating OKM1 positive mononuclear cells, presumably monocytes**, in addition to lowering patient lymphocyte count (see page 1486, left-hand column, last full paragraph). These specific properties of FLP referred to in (2) are in full agreement with the *in vitro* and *in vivo* data on cell recoveries following the administration of FLP reported in (1) and the further suggestion in (1) that FLP or a related compound may serve as a clinically useful **immunosuppressive agent.**

6.3.6 From the foregoing it is clear that the above-mentioned, highly pertinent state of the art according to (2), alone or in combination with the prior art of (1), points the skilled person directly to the proposed solution of the problem underlying the application. Moreover, the additionally cited documents provide the skilled person with further useful guidance - should he need them - towards the claimed invention.

6.4 Thus, citation (1) discloses that administration of FLP to patients was followed by marked lymphocytopenia. The data in Chart 4 of (1) demonstrate that the major mature T-lymphocyte subsets T4 and T8 were both reduced substantially by FLP. However, **T4 cells were even more sensitive and their level fell to a greater degree,** resulting in a reversal of the circulating T4:T8 ratio

(see (1) page 4663, Chart 4; page 4664, right hand column).

6.4.1 Citation (5) discloses, *inter alia*, that activated CD4 T cells produce a variety of cytokines which may be involved in the initiation and maintenance of the psoriatic process, a well-known example of an autoimmune disease (see page 3, right-hand column, third paragraph, lines 10 to 13). The cited document goes on to state that future treatments for psoriasis could include anticytokine therapy but that it was unlikely that interfering with one cytokine within a very complex network would be very effective. However, in this context it is clearly suggested in (5) that therapy against **T4 cells** or their migration into the skin **is likely to be more fruitful** in the treatment of psoriasis (see page 7, left-hand column, lines 16 to 19 from the bottom).

6.4.2 There can be no serious doubt, in the board's view, that the above-mentioned combined teaching of the prior art of citations (1) and (5) provides a further clear suggestion in the direction of the claimed therapeutic application for FLP, even if in (5) it is stated that "all these therapies are non-specific and may interfere with normal immune defence mechanisms" (see page 7, left-hand column, lines 14 to 16 from the bottom). To solve the problem underlying the application, a person skilled in the art would, in the board's judgment, make use of the known prior art and look for any hint or suggestion on how to find a further useful therapeutic application for FLP. The combined teaching of (1) and (5) gives such a hint or suggestion that would not be overlooked or disregarded by the skilled practitioner.

6.5 Citation (6) suggests the use of **purine antagonists**, among other classes of known immunosupressive agents, for the treatment of autoimmune diseases of the skin in general and psoriasis in particular. With regard to the proposed use of purine antagonists in the therapy of autoimmune diseases in the cited state of the art, the appellant argued in its written submissions and orally at the hearing that the author of (6) himself had drawn attention in (6) to some of his own observations showing a reduced therapeutic efficacy of the immunosupressive purine antagonist Imurek® (Azathioprine, 6-(1-methyl-4-nitro-5-imidazolyl)mercaptopurine) against psoriatic conditions of the skin in comparison with the standard immunosupressive drug methothrexate (page 130, left-hand column, 2nd paragraph, lines 1 to 3). The appellant's conclusion was that the skilled person would not consider the use of purine antagonists, such as FLP, in the treatment of autoimmune diseases.

However, this argumentation entirely overlooks the fact that citation (6) itself gives clear information elsewhere in this document to contradict the appellant's above conclusion. Thus, it is pointed out in the statement at page 130, left-hand column, lines 6 to 8, that since 1972, ie long before the priority date of the present application, Imurek® has already **successfully been used** for the treatment of **particularly extended and serious cases of psoriasis resistant to other forms of therapy.**

6.6 To summarise, from the foregoing it is clear that in the present situation the notionally skilled person was provided with several hints and suggestions from the prior art pointing him in the direction of the claimed use. It was thus only necessary to confirm experimentally by a small number of routine tests that the expected result, namely the usefulness of FLP for the treatment of an autoimmune disease, was in fact obtained. However, the necessity of experimentally confirming a reasonably expected result cannot confer the required inventive step on an obvious solution of the problem to be solved.

The appellant essentially countered that a person skilled in the art would not have been led by the combined teaching of (1) and (2) and the other cited documents to consider using FLP as an agent for the treatment of autoimmune diseases because this person was not able to predict (in the strict scientific sense of this word) on the basis of the disclosures in the prior art that FLP would be effective in the treatment of such diseases. This opinion seems to imply that, since it was necessary to carry out some tests in order to know with certainty whether or not FLP would indeed be effective in the treatment of autoimmune diseases, the claimed use should have been regarded as unobvious because "obvious to try" is not the standard for assessing obviousness. This objection is unjustified since, in accordance with patent jurisprudence, an inventive step is not assessed from the view point of a highly specialised and outstanding scientist who, as is well-known, is extremely cautious with regard to unproven assumptions and, therefore, would be very reluctant to make a prediction in the absence of

sufficient proof, but rather from that of the notionally skilled person with his average ability and knowledge.

6.7 Contrary to the appellant's assertions, the fact that the experimental data of the *in vitro* and *in vivo* tests and examinations reported in (1) were obtained from leukemia patients would not have prevented those skilled in the art from using FLP for the successful treatment of patients suffering from autoimmune diseases. This is because citation (2) clearly suggests that adenosine deaminase-resistant dAdo analogues, such as CldAdo or FLP, offer an approach for the treatment of both categories of patients, that is to say patients with chronic lymphoid malignancies (leukemia) **and** patients suffering from chronic inflammatory and autoimmune diseases, such as rheumatoid arthritis (see 6.3.4 and 6.3.5 above).

6.8 Similarly, the structural differences between CldAdo and FLP would not have prevented those skilled in the art from using FLP for the treatment of patients suffering from autoimmune diseases because in the present case the skilled person was **not** led to the claimed use of FLP by a possible structural similarity between CldAdo and FLP (ie a structural similarity which is often used in chemistry and frequently carries conviction for the decision whether or not the claimed use of a chemical compound is based on an inventive step), but by the several **direct hints and suggestions** in the state of the art in the direction of the claims at issue.

6.9 From certain experimental data included in the application (see especially Example 3, Figures 7A, 7B, 7C) the appellant inferred that the selectivity of FLP for the autoimmune-specific IgM-RF compared favourably with that of CldAdo and concluded that the improved selectivity of FLP for IgM-RF might permit a more selective therapy of autoimmune diseases. If, as here, the aim was to find for a known physiologically and pharmacologically active substance already used in medicine a further useful therapeutic application (see 4 above), the first self-evident step - before any thought is given, say, to finding some other useful therapeutical applications for FLP - is to test the efficacy and usefulness of this substance (FLP) for that therapeutical application which would have immediately been envisaged by the skilled person in the light of the cited state of the art and which in the present case is, as shown above, straightforwardly obvious. Such tests are routine. According to the established case law of the boards of appeal (see eg T 296/87, OJ EPO 1990, 195), enhanced effects cannot be adduced as evidence of an inventive step if they emerge from obvious tests. Since, in the present case, the respective tests with FLP were obvious in view of the task at hand, the discovery of some slightly enhanced selectivity for IgM-RF exhibited by FLP as compared with CldAdo cannot be regarded as an indication of an inventive step. It follows that the discovery made within the framework of these tests that B lymphocytes were possibly more sensitive to the effects of FLP as compared to T lymphocytes cannot contribute to the acknowledgment of an inventive step either.

6.10 At the hearing before the board the appellant also argued in favour of inventive step that citation (1) had been published as early as October 1984 and that the "long period" of roughly eight years between the publication date of the citation deemed to be the closest prior art and the priority date of the present European patent application (23 October 1992) in this economically significant and frequently studied field should be considered as an indication of the presence of an inventive step. Viewed in isolation from the evolving state of the art, the period of eight years would possibly appear at first sight to be an indication in support of an inventive step. If, however, the particular therapeutic application proposed for FLP in the application under appeal is viewed against the background of the actual technical development in this field, one comes to the opposite conclusion.

6.11 The "allegedly long period of time" to be considered in the present case is clearly **not** the period that had elapsed between the publication of citation (1) and the priority date of the European patent application, but **only the period of two years** between the publication date of **citation (2)** (November 1990) and the priority date of the European patent application (23 October 1992). As explained in great detail above, the knowledge of the technical teaching of citation (2) gave the skilled person the relevant pointer in the direction of the claimed invention. Being misconceived both in its premise and detail, the appellant's argument concerning the age of citation (1) cannot succeed.

6.12 It follows from the foregoing that the subject-matter of claim 1 does not involve an inventive step, contrary to the requirements of Article 52(1) in conjunction with Article 56 EPC. Since a decision can only be taken on each request as a whole, there is no need to look into the patentability of any of the other claims.

First auxiliary request (see IV above)

7. The wording of the addition "by **at least partial** elimination of B cells [in the subject to be treated]" at the end of claim 1 and the other independent claims (see IV above) has to be interpreted as including the whole range from using FLP for the treatment of autoimmune diseases by **partial elimination** (regardless of the proportion of B cells actually eliminated) to using FLP for the treatment of autoimmune diseases by **total elimination** of the B cell population in the subject to be treated.

In the appellant's view, the basis for the above-mentioned amendment could be found at page 20, lines 2 to 4, of WO 94/09791 ("It was of interest to see that B lymphocytes were more sensitive to the drugs effects as compared to the T lymphocytes") and at page 23, lines 9 to 12 ("Cytofluorometric analysis of the B lymphocytes at the end of the 5 day culture period indicated that the drug had a significant effect on the CD20/CD5 positive B lymphocyte subpopulation").

7.1 However, neither the above-mentioned passages nor any other disclosure in the application as originally filed (WO 94/09791) provides a basis for a claim including the use of FLP for the treatment of autoimmune diseases

by **total elimination** of the B cell or B lymphocyte population in the subject to be treated. Accordingly, the amended claims of the first auxiliary request contravene Article 123(2) EPC. It follows that the first auxiliary request cannot be allowed.

Second auxiliary request (see IV above)

8. CldAdo is used in citation (2) specifically for the treatment of rheumatoid arthritis, a disease in which monocyte-derived macrophages play a role in synovial inflammation and joint destruction. The effects of CldAdo on circulating monocytes from a representative patient is shown in Figure 6 (see page 1485, top of left-hand column). This 63-year-old woman with seropositive **rheumatoid arthritis** received three treatments with CldAdo by continuous infusion for 5 days. As can be derived from the data in Figure 6, the blood monocyte count fell to zero during each infusion.

8.1 From the foregoing it follows that the reasons given above for the lack of an inventive step of the use of FLP for the treatment of an autoimmune disease in general according to the main request apply in the same manner for the use of FLP for the treatment of rheumatoid arthritis in accordance with the secondary auxiliary request. The second auxiliary request cannot therefore be allowed.

Third auxiliary request (see IV above)

9. Once the usefulness of FLP for the therapy of autoimmune diseases became obvious, determination of

the optimum dosage range required to achieve the desired therapeutic effect in the subject to be treated was then purely a matter of routine experimentation for the skilled practitioner.

9.1 The appellant's finding that FLP can be administered for the treatment of autoimmune diseases in an amount within the broad range of 1 to 10 mg/kg/day, which is generally lower than is typically administered for the treatment of leukemia, is not surprising. Those skilled in the art would be guided to such low doses by the disclosure of citation (2) where CldAdo was administered to a patient suffering from seropositive rheumatoid arthritis at a dose as low as 0.1 mg/kg/day (see page 1485, Figure 6).

9.2 Moreover, the dosage amount specified in claim 1, which may extend over the wide range from 1 to 10 mg/kg/day, cannot be considered as providing an unexpectedly advantageous specific teaching or instruction saving the skilled person the necessity to perform his own experiments; on the contrary, such a wide range would suggest that the experiments, albeit routine, could be extensive.

It follows that the subject-matter of claim 1 according to the appellant's third auxiliary request is not patentable (Article 52 in conjunction with Article 56 EPC) so that this request cannot be allowed either.

Fourth auxiliary request

10. As regards the restriction of claim 1 to the use of FLP for the treatment of rheumatoid arthritis, reference is

made to the observations in 8 and 8.1 above. As regards the additional specification in claim 1 that FLP is applied in an amount in the range of 1 to 10 mg/kg/day, reference is made to the observations in 9, 9.1 and 9.2 above.

10.1 With respect to auxiliary request 4 the board notes that the insertion of several straightforwardly obvious technical features into a claim which is in itself obvious cannot make an obvious teaching inventive. It follows that the amendments to claim 1 of the fourth auxiliary request cannot, either alone or in combination, support the presence of an inventive step.

11. In conclusion, neither the appellant's main request nor any of its auxiliary requests relates to a patentable invention. Thus, the appeal is clearly not allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Townend U. Oswald