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Datasheet for the decision of 25 February 2022

Case Number: T 0126/17 - 3.3.01

Application Number: 04754383.0

Publication Number: 1633333

IPC: A61K31/00, A61K31/395, A61K31/165, A61P7/06

Language of the proceedings: EN

Title of invention:
USE OF HIF ALPHA STABILIZERS FOR ENHANCING ERYTHROPOIESIS

Patent Proprietor:
Fibrogen, Inc.

Opponent:
Akebia Therapeutics, Inc.

Relevant legal provisions:
EPC Art. 54, 56, 100(b)
RPBA Art. 13(2)

Keyword:
Grounds for opposition - insufficiency of disclosure (no)
Novelty - (yes)
Inventive step - (yes) - auxiliary request

Decisions cited:
T 0914/18, T 0995/18, T 0544/12, G 0001/03

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Case Number: T 0126/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 25 February 2022

Appellant: (Patent Proprietor)	Fibrogen, Inc. 409 Illinois Street San Francisco, CA 94158 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Opponent)	Akebia Therapeutics, Inc. 245 First Street, Suite 1100 Cambridge MA 02142 (US)
Representative:	Jones Day Rechtsanwälte, Attorneys-at-Law, Patentanwälte Prinzregentenstrasse 11 80538 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 13 January 2017 revoking European patent No. 1633333 pursuant to Article 101(3)(b) EPC.**

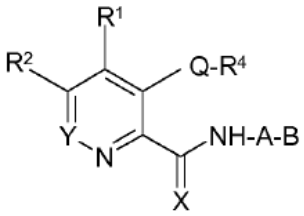
Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 633 333 (patent in suit) was granted with a set of thirty claims. The independent claims (claims 1, 6, 12 and 15) read as follows:

1. A compound of formula (I) that stabilizes HIFα for use in treating anemia of chronic disease in a subject:



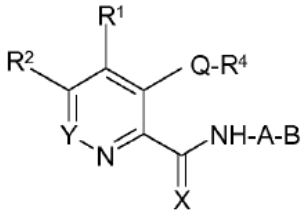
(I)

wherein

[there follows a definition of the substituents A, B, Q, R^1, R^2, R^4, Y, and X of formula (I), see page 42, line 41 to page 47, line 36 in claim 1 of the patent in suit]*;*

or a physiologically active salt derived therefrom; wherein the subject has a percent transferrin saturation of less than 20%.

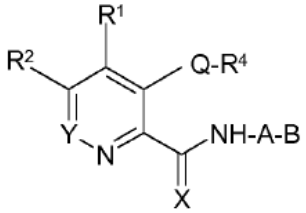
6. A compound of formula (I) that stabilizes HIFα for use in treating anemia that is refractory to treatment with exogenously administered erythropoietin (EPO) in a subject:



(I)

wherein A, B, Q, R^1, R^2, R^4, Y, and X are as defined in claim 1.

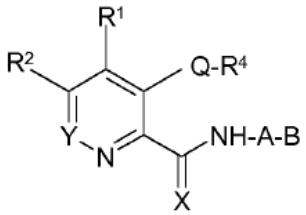
12. A compound of formula (I) that stabilizes HIFα for use in treating or preventing microcytosis in microcytic anemia in a subject:



(I)

wherein A, B, Q, R^1, R^2, R^4, Y, and X are as defined in claim 1.

15. A compound of formula (I) that stabilizes HIFα for use in treating iron deficiency in a subject:



(I)

wherein A, B, Q, R^1, R^2, R^4, Y, and X are as defined in claim 1.

II. "HIFα" mentioned in the claims is the alpha subunit of hypoxia inducible factor ("HIF") (see paragraphs [0023] and [0025] of the patent in suit). In addition, the following abbreviations are used below:

ACD : anemia of chronic disease
TSAT: transferrin saturation
EPO : erythropoietin
rEPO: recombinant human erythropoietin

III. The patent in suit originates from European patent application No. 04 754 383.0 (published as WO 2004/108121 A1) and claims priority from five US applications, the earliest being US 60/476,704 P of 6 June 2003). Three divisional applications were filed: European patent applications Nos. 10 182 213.8

(published as EP2322153), 10 182 249.2 (published as EP2322155) and 14 178 232.6 (published as EP2826471 and numbered D91 in these proceedings).

IV. The patent in suit was opposed under Article 100(a), (b) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

V. The documents cited in the proceedings before the opposition division included the following:

D3: WO 03/053997 A2 (3 July 2003)

D5: J.R. Wingard, G.D. Demetri (editors): Clinical Applications of Cytokines and Growth Factors, ISBN 0-7923-8486-5 (1999), 187-197

D14: Procrit® (Epoetin alfa) FOR INJECTION package insert (2000, revised: 12/2009)

D22: Clinical Nephrology, 43(4), 256-259 (1995)

D23: WO 03/049686 A2

D46: Bioorganic & Medicinal Chemistry Letters 16, 5616-5620 (2006)

D47: Poster presentation at the Keystone Conference "Molecular, Cellular, Physiological and Pathogenic Responses to Hypoxia" in Vancouver, British Columbia, 15-20 January, 2008

D48: Declaration of J. Patrick Elsevier (January 2016)

D49: Joint Status Report filed in the United States District Court for the Northern District of California (23 December 2015)

D50: Test results for compound classes tested by the appellant (patent proprietor)

D53: Declaration of Trevor J. Franklin (8 February 2016) with Annex 3: Inhibition results for 39 compounds

D74: Annals of Internal Medicine, 111(12), 992-1000 (1989)

D91: EP 2 826 471 A1

E2: Declaration of Lynda Szczech (6 October 2016)

E2-Annex 6: Clin J Am Soc Nephrol 11, 982-991 (2016) and supplementary data

E2-Annex 7: Am J Kidney Dis, 67(6), 912-924 (2016)

VI. The patent proprietor requested that the opposition be rejected, and submitted six sets of claims as auxiliary requests 1 to 6.

VII. In a letter dated 29 September 2016, the patent proprietor made the following statement (highlighting by the patent proprietor):

> *"(...) Nevertheless, the claims are clearly novel and inventive starting from the filing date of 4th June 2004. To save the opposition division from preparing for a lengthy discussion of priority at the oral proceedings, and to expedite this matter and for the convenience of the opposition division,* ***the patentee hereby withdraws its five claims to priority in respect of this patent****, in accordance with T 1136/03 and Guidelines F-VI, 3.5, E-VII, 6.2. This withdrawal does* ***not*** *constitute an admission on the patentee's part that patentee is not in fact entitled to earlier priority dates, nor does this decision made for convenience apply to any other patents or applications belonging to the patentee. To be clear, this withdrawal does* ***not*** *apply to the patent's divisional applications i.e. granted patents EP2322155, EP2322153, or pending*

application no. 14178232.6 (Guideline A-IV, 1.2.2)."

VIII. In response, the opponent observed that this request was ambiguous, and expressed doubt that it should be taken into account. If, on the other hand, the priority claims were validly withdrawn, then the patent's divisional applications would be prior art against the patent (see the opponent's letter of 7 October 2016, sections 3.1 and 4.2).

IX. The decision under appeal is the opposition division's decision revoking the patent in suit, announced on 9 December 2016 and posted on 13 January 2017.

X. The decision under appeal addressed the following points:

(a) the subject-matter of independent claims 1, 6, 12 and 15 as granted did not go beyond the content of the application as filed (Article 100(c) EPC);

(b) the claimed subject-matter met the requirement of sufficiency of disclosure (Article 100(b) EPC);

(c) the effective date of the patent was the filing date (4 June 2004);

(d) the disclosure of document D3, which related to the same compounds, anticipated the subject-matter of claims 1 and 15 (Articles 100(a), 52(1) and 54 EPC);

(e) starting from the disclosure of D3, the subject-matter of claims 6 and 12 did not involve an inventive step (Articles 100(a), 52(1) and 56 EPC);

(f) the three divisional applications EP2322153, EP2322155 and D91 (EP2826471) were state of the art within the meaning of Article 54(3) EPC and, since their technical content was identical to that of

the patent in suit, they anticipated the subject-matter of all the independent claims;

(g) the objections regarding lack of novelty and inventive step were equally valid for the auxiliary requests, as each of these requests contained three of the independent claims of the main request in unamended form.

XI. The patent proprietor (appellant) filed an appeal against this decision, maintained its main request and auxiliary requests 1 to 6, and filed further sets of claims as auxiliary requests 7 to 22. In its statement setting out the grounds of appeal (see points 7.21 and 7.22), the appellant also indicated its willingness to delete in its requests any claims found unallowable during the appeal proceedings. Requests with such deletions were envisaged as further auxiliary requests.

XII. In its reply to the appellant's statement setting out the grounds of appeal, the opponent (respondent) *inter alia* submitted that the claims of the main request and of all the auxiliary requests failed to comply with Articles 100(c)/123(2) EPC (see page 3 of the reply).

XIII. In a communication under Article 15(1) RPBA dated 7 April 2020, which accompanied a summons to oral proceedings, the board observed that the respondent had not substantiated its objection of added subject-matter under Articles 100(c)/123(2) EPC in respect of, *inter alia*, the main request (see point 1.2 of the board's communication).

XIV. In a letter dated 27 May 2020, the respondent maintained that stating that the claims violated Article 123(2) EPC constituted a clear reference to the

grounds and substantiation filed during first-instance proceedings (see section 5 of the respondent's letter).

XV. The following documents submitted in the course of the appeal proceedings remain relevant to the present decision:

D94a: Wick et al: Clinical Aspects and Laboratory - Iron Metabolism, Anemias - Novel concepts in the anemias of malignancies and renal and rheumatoid diseases, 23-35, 93-110, 5th edn., Springer, Vienna 2003

D105: Williams: Hematology, 6th edn. (2001), Chapter 41, pp. 481-487

D107: Seminars in Dialysis 30(1), 29-31 (2017)

Document D105 was filed by the appellant with a letter dated 5 March 2018. Documents D94a and D107 were filed by the respondent with a letter dated 24 July 2018. No objection was raised against the admittance of these documents.

XVI. Oral proceedings before the board were held, after postponement, on 24 and 25 February 2022.

The parties were heard on the issues of sufficiency of disclosure, the effect of the appellant's statements in the letter of 29 September 2016 (see point VII. above), and novelty and inventive step of the independent claims of the main request in respect of the disclosure of the intermediate document D3.

The appellant stated that it did not intend to rely on its right to priority in respect of any independent claim, with the exception of claim 6.

In a first approach, inventive step was discussed on the assumption that the subject-matter of the

independent claims, including claim 6, did not enjoy any of the priorities.

After deliberating on each issue, the board advised the parties of its opinion regarding each of the independent claims of the main request. This amounted to the conclusion that the grounds for opposition under Article 100(a) and (b) EPC as discussed in the appeal proceedings did not prejudice maintenance of independent claims 1, 6 and 15 as granted, but that the subject-matter of independent claim 12 as granted did not involve an inventive step.

In order to address this remaining objection, the patent proprietor filed an amended set of claims as "auxiliary request A".

The claims of auxiliary request A are identical to the claims as granted except that independent claim 12 and its dependent claims 13 and 14 were deleted and the subsequent claims and claim dependencies were adapted accordingly, i.e. claims 15 to 30 as granted became claims 12 to 27 of auxiliary request A.

Finally, the issues of admittance of auxiliary request A and admittance of the respondent's objections under Articles 100(c)/123(2) EPC were addressed.

XVII. The respondent's arguments may be summarised as follows:

Inventive step - claim 12 as granted

Starting from the technical teaching of document D3, the subject-matter of claim 12 as granted did not involve an inventive step.

This claim related to treating microcytic anemia by treating microcytosis. Starting from the teaching of document D3 in paragraph [0064], the objective

technical problem was to provide a way of treating microcytic anemia.

Paragraph [0064] of document D3 provided a clear pointer to treating microcytic anemia with compounds of formula (I). This must by definition involve treating microcytosis, the characterising symptom of microcytic anemia, which meant increasing the size of red blood cells being produced.

Contrary to the appellant's view, increasing the number of microcytes (rather than increasing cell size) could not be considered a treatment of microcytic anemia. Also, the skilled person would have had no reason to believe that the treatment according to D3 might worsen microcytosis (as argued by the appellant).

Admittance of auxiliary request A

That one of the independent claims of the main request, in this case claim 12, might be found obvious by the board could not be regarded as an unexpected development that warranted the filing of a new auxiliary request under Article 13(2) RPBA. The fact that none of the existing auxiliary requests 11 to 22 contained a claim corresponding to claim 12 as granted showed that this contingency had, in fact, been previously considered by the appellant. The appellant could, and should, therefore, have filed auxiliary request A at an earlier time. Moreover, the request was *prima facie* not allowable under Article 123(2) EPC.

Admittance of the respondent's objections in respect of added subject-matter

It was clear from the respondent's written submissions that it relied on the same reasoning as in the proceedings before the opposition division for substantiating the ground of opposition under Articles

100(c)/123(2) EPC. There could be no doubt that this reasoning applied equally to auxiliary request A, which was identical to the main request except for the deletion of certain claims. Article 13 RPBA did not apply, because the previously-known substantiation did not constitute an amendment to the respondent's case.

Sufficiency of disclosure

The compounds referred to in the claims were defined by a structural definition (formula (I)) in combination with a functional definition, namely the additional requirements of HIFα stabilisation and specified therapeutic effects.

It was implausible that substantially all compounds covered by the structural definition of formula (I) would also meet the functional requirements of the claims.

Indeed, document D50 provided evidence, in the form of the appellant's own screening data, that a large number of compounds of formula (I) were in fact inactive. Reference was also made to documents D46 to D49.

Also, no clear link or correlation between HIFα stabilisation and increased levels of endogenous erythropoietin and serum iron had been established.

While formula (I) encompassed an extremely large number of compounds, the patent in suit did not provide a commensurately broad range of examples. Indeed, only single data points were exemplified on the basis of the three structurally similar compounds A, B and C identified in the patent. The experimental results obtained with these compounds could not reasonably be extrapolated across the scope of formula (I).

Document D107 showed (in Table 2) that roxadustat, a compound of formula (I) which differed from the

contested patent's "compound B" only by a methyl group, did not increase serum iron in human subjects. This was relevant because the therapeutic uses of all the independent claims were based on the effect of increasing serum iron. This post-published finding illustrated the difficulty of predicting activity from the compounds' structural features. It also cast doubt on the suitability of the animal models employed according to the examples of the patent in suit, and the conclusiveness of the data obtained on that basis.

On the whole, the patent did not provide sufficient guidance, such as a selection rule or a reliable standard test, to distinguish working from non-working embodiments.

To carry out the invention, the skilled person would have to test any conceivable compound of formula (I) for HIFα stabilisation and also for the therapeutic indications defined in the claims and their underlying effects, such as induction of EPO, increase of serum iron and cytokine suppression. The extensive screening tests and *in vivo* tests necessary to identify working embodiments by trial-and-error experimentation placed an undue burden on the skilled person. In this context, reference was made to principles established in the case law of the Boards of Appeal, in particular decision T 544/12.

Novelty over the disclosure of D3

Claims 1 and 12 of auxiliary request A (corresponding to claims 1 and 15 as granted) lacked novelty over the disclosure of document D3.

Novelty - claim 1 - auxiliary request A

When characterising anemia of chronic disease (ACD), the patent in suit (paragraphs [0002], [0023], [0061]

and [0088]) referred to essentially the same underlying disease conditions as D3 (paragraphs [0004], [0018] and [0044]). The therapeutic indication and patient group in claim 1 were anticipated in particular by paragraph [0072] of D3. This passage referred to rheumatoid arthritis, known to cause ACD (see D94a, paragraph bridging pages 108 and 109). While it was conceded that subjects having ACD did not inevitably have TSAT levels below 20%, it was known that ACD in inflammations (which included rheumatic diseases) was associated with low TSAT levels (see D94a, paragraph bridging pages 28 and 29). In any case, the patient group characterised by a TSAT level of less than 20% was chosen arbitrarily and this threshold was not linked to any particular technical effect in comparison with the treatment according to D3, which also covered such patients.

Novelty - claim 12 - auxiliary request A

The therapeutic indication of claim 12 (i.e. treating iron deficiency) was anticipated by paragraphs [0018] and [0072] and claim 24 of D3 relating to the enhancement of iron transport, uptake and utilisation, and by example 3 and Figures 4C and 4D of D3.

Withdrawal of claims to priority

The opposition division had been correct in deciding that the withdrawal of the priority rights by the appellant was unconditional and therefore valid.
The appellant itself had provided the legal basis by citing the Guidelines for Examination and relevant case law in its letter of 29 September 2016.

Inventive step

Starting from the technical teaching of document D3, the subject-matter of none of the independent claims in auxiliary request A involved an inventive step.

Inventive step - claim 1 - auxiliary request A

The inventive-step assessment was based on the assumption that the subject-matter of claim 1 differed from the disclosure of D3 by the group of subjects to be treated, i.e. those having ACD and a TSAT value of less than 20%. The objective technical problem was to provide an alternative group of subjects treatable by the compounds of formula (I).

It was common in anemia patients as targeted by D3 (e.g. those with rheumatoid arthritis and other diseases that could lead to ACD) to have reduced TSAT levels (see D94a, pages 28 and 108). The treatment for increasing endogenous EPO according to D3 was applicable to patients with any level of transferrin saturation. The technical effect underlying the treatment according to claim 1 of auxiliary request A was identical to the known technical effect. Selecting subjects with a TSAT of less than 20% was therefore an arbitrary and obvious selection which did not provide a contribution over the prior art.

The known guidelines for the administration of rEPO would not have played a role in the skilled person's expectation of success, because D3 related to different active agents (small-molecule compounds of formula (I)) and furthermore taught that these agents, apart from increasing endogenous EPO, also provided favourable effects on iron metabolism.

Inventive step - claim 6 - auxiliary request A

The subject-matter of claim 6 differed from the disclosure of D3 by defining the anemia to be treated as refractory to treatment with exogenously administered erythropoietin. Starting from the teaching of document D3, the objective technical problem was to provide an alternative subgroup of anemia patients treatable by compounds of formula (I). D3 taught that the methods and compounds of D3 provided additional benefits not addressed by the then-current anemia therapeutics such as rEPO (see D3, paragraphs [0008] and [0072]). This meant that they could be used when rEPO (i.e. exogenously administered EPO) did not work.

Anemia refractory to treatment with exogenously administered EPO was iron deficiency anemia. Microcytic and sideroblastic anemia mentioned in paragraphs [0064] and [0072] of D3 arose from iron deficiency and could therefore be expected to be refractory to treatment with exogenously administered EPO. With the information provided in D3, the person skilled in the art was thus in a "try-and-see" situation with regard to treating refractory anemia as defined in claim 6.

Inventive step - claim 12 - auxiliary request A

The subject-matter of claim 12 differed from the disclosure of D3 by defining the therapeutic indication as treating iron deficiency as such. The objective technical problem to be solved was the treatment of a further condition.

The solution defined in claim 12 would have been obvious with knowledge of D3 and in the light of common general knowledge. D3 taught the treatment of anemias associated with defects in iron transport, processing or utilisation (claim 24 and paragraphs [0018], [0044] and [0072]), and thus also associated with iron

deficiency. In the examples, D3 taught that an increase in haemoglobin production was maintained over an extended period of time. The skilled person would have inferred from this that iron was made available, which was required in the production of haemoglobin. The skilled person would simply have followed the teaching of D3 and would have tested for further parameters relating to iron deficiency.

It was known that microcytic anemia and sideroblastic anemia mentioned in D3 (paragraphs [0064] and [0072]) were anemias that resulted from iron deficiency. In this context, document D5 (see page 194), which represented common general knowledge, taught that the same cytokines which had an effect on EPO production and responsiveness to EPO in ACD were also believed to affect iron metabolism.

XVIII. The appellant's arguments may be summarised as follows:

Inventive step - claim 12 as granted

Starting from the teaching of document D3, especially in paragraph [0064] mentioning microcytic anemia as a condition to be treated, the objective technical problem underlying claim 12 was to provide a new and improved way of treating microcytic anemia.

The technical effect provided by claim 12 was treating microcytosis in microcytic anemia (as supported by the experimental data provided in example 20 of the patent in suit).

D3 did not provide technical data or other indications suggesting that compounds of formula (I) increased the size of red blood cells being produced, i.e. that they reduced microcytosis. Instead, D3 focused in its teaching on the aim of increasing the level of endogenous erythropoietin (EPO) to stimulate the

production of red blood cells, i.e. increase their number. EPO was, moreover, known to worsen microcytosis, as it decreased serum iron. The skilled person would have been aware of this fact. In this regard, reference was made to document D22.

Thus, while mentioning microcytic anemia, D3 did not teach treating microcytosis. There were other ways of treating microcytic anemia, e.g. increasing the number of red blood cells produced, that were in conformity with the general teaching of D3.

Admittance of auxiliary request A

Auxiliary request A overcame the remaining objection regarding lack of inventive step of claim 12 as granted by deleting this claim and all its dependent claims. This amendment did not give rise to new issues with regard to the remaining claims. Hence the filing of auxiliary request A did not constitute an amendment to the appellant's appeal case within the meaning of Article 13(2) RPBA. Reference was made in this regard to the case law of the Boards of Appeal, e.g. as set out in T 914/18. *Prima facie* allowability under Article 123(2) EPC, while disputed by the respondent, was not a requirement for admittance under Article 13(2) RPBA.

Admittance of the respondent's objections in respect of added subject-matter

The ground relating to added subject-matter had been raised, but the respondent had not substantiated it in the written appeal proceedings, even after the board, in its communication under Article 15(1) RPBA, had pointed out the lack of substantiation. It would be unacceptable for the appellant to be required to

respond to this issue for the first time during oral proceedings before the board of appeal.

Sufficiency of disclosure

Contrary to the respondent's argument, the patent in suit did provide the necessary guidance for carrying out the claimed invention, by describing a specific class of compounds and providing simple assays to use to confirm their usefulness in the invention.
In addition, the patent contained experimental data showing the effects of the compounds in *in vitro* and *in vivo* examples, including data from human tests in example 21.

Compounds of formula (I) and their synthesis were well-known from published prior art referenced in the patent in suit (see paragraphs [0138] to [0142]).
The patent also identified exemplary compounds.

The compounds were also known for their activity in stabilising HIFα and could be screened for activity by following the teaching of the patent in suit and of referenced prior-art documents (D3 and D23, both documents cited in paragraph [0129] of the patent in suit):

Example 9 of D3 taught an *in vitro* assay for inhibition of HIF prolyl hydroxylase, corresponding to stabilisation of HIFα. Example 1 of D23 taught an *in vitro* assay for HIFα-stabilising activity.

The patent in suit itself (see paragraph [0146] and examples 1 and 2) taught that the stabilising effect of the claimed compounds on HIFα could be shown directly or indirectly, e.g. indirectly by a cell-based assay of EPO induction. Erythropoietin determined according to the protocol of examples 1 and 2 was

an HIF-responsive target protein in the sense of paragraph [0146].

Testing compounds for HIFα-stabilising or EPO-inducing activity, including at a number of different concentrations, was straightforward routine practice that did not amount to an undue burden. The appellant itself had tested numerous compounds and had found consistently good activity, as shown, *inter alia*, in D50.

It was for the respondent, in its role as the opponent, to establish insufficiency. The respondent had not shown that substantial parts of formula (I) did not work. Indeed, the respondent had failed to demonstrate that any compounds of formula (I) were incapable of stabilising HIFα. If the appellant's screening data provided in D50 suggested that certain of these compounds were less active than others, that did not prove they were inactive, as alleged by the respondent. In particular, it was wrong to conclude that a compound was inactive based on an IC_{50} value above 200 µM. This was merely an arbitrary threshold the appellant had chosen for identifying the most promising compounds. In any case, the less active compounds were far outnumbered by the majority of more active compounds.

If there were inactive compounds within the scope of formula (I) (something the respondent had not actually shown), these could be identified and avoided without undue burden by applying the methods taught in the patent. *In vivo* testing was not even necessary to identify suitable compounds, since it had been demonstrated in example 15 of the patent that structurally different compounds were capable of treating the same disorders by virtue of their ability to stabilise HIFα.

The therapeutic uses of claims 1, 6 and 12 of auxiliary request A were rendered credible by experimental data provided in the patent and the application as filed (for claim 1: examples 1, 2, 17 and 20 and Figures 18A, 18B; for claim 6: examples 2 and 20; for claim 12: examples 19 and 20 and Figures 18A, 18B could be mentioned). The therapeutic indication according to claim 1 was also supported by the post-published findings in E2-Annex 6.

Contrary to the respondent's argument made in the context of assessing document D107, the patent in suit did not teach that all the therapeutic uses named in the independent claims were based on increasing the level of serum iron, nor was this effect reflected in the technical features of these claims.

Furthermore, serum iron status had not been the targeted end point in the clinical trial described in document D107. Indeed, the interpretation of the results for serum iron shown in Table 2 of D107 was less straightforward than suggested by the respondent.

This was illustrated by further post-published findings: E2-Annex 7 was a publication discussing the results of a clinical trial in which roxadustat was used in a comparator study with rEPO in dialysis-dependent kidney disease patients. Table 4 in Annex 7 showed that serum iron increased in patients treated with roxadustat, but decreased in patients receiving rEPO. The findings reported in E2-Annex 6 confirmed that roxadustat was capable of treating iron-deplete patients with a TSAT of less than 20%.

Novelty over the disclosure of D3

Novelty - claim 1 - auxiliary request A

The term "anemia of chronic disease", abbreviated as ACD, had a specific meaning in the art, as illustrated by document D105 (page 484: "Differential Diagnosis"). While document D3 mentioned the treatment of anemia, including anemia associated with certain conditions that might be regarded as chronic (e.g. cancer or autoimmune diseases), it did not unambiguously disclose ACD, nor did it disclose a subgroup of ACD patients having transferrin saturation levels below 20%.
D3 did not disclose actual efficacy of compounds of formula (I) in the treatment of rheumatoid arthritis or an associated anemia either. Hence the subject-matter of claim 1 was novel over the disclosure of document D3. The threshold of 20% TSAT was relevant in the field of erythropoiesis-stimulating agents as it defined an iron-deplete patient group.

Novelty - claim 12 - auxiliary request A

The subject-matter of claim 12 was also novel. Document D3 did not mention the treatment of iron deficiency and did not disclose increasing serum iron, which was critical for treating iron deficiency. The statement in paragraph [0072] of D3 asserting effects on enzymes and proteins involved in iron uptake, transport and processing was not supported by experimental data, and in any case did not directly and unambiguously relate to a treatment of iron deficiency. It would also have been impossible for the skilled person to conclude on the basis of the data presented in Example 3 of D3 (relating to an increase in haemoglobin maintained over a longer period of time) that the compounds of formula (I) were capable of treating iron deficiency. In fact, it was accepted

knowledge that treatment with EPO, the established erythropoiesis-stimulating agent, could cause or worsen iron deficiency (see the recommendations in D14, page 16 and D94A, page 110, table 30, which were based on seminal studies such as reported in D74, see in particular page 996, right-hand column, fourth paragraph). D3 itself envisaged iron supplementation (paragraph [0018]).

Withdrawal of claims to priority

In the proceedings before the opposition division, the respondent had repeatedly argued that the independent claims as granted were not entitled to priority, while the appellant had argued that these claims were in any event novel and inventive from the filing date of the patent in suit. To simplify proceedings, the appellant had attempted with its letter of 29 September 2016 to avoid any further discussion of priority, while maintaining that the priority claims were in any event valid. The opposition division had been wrong to conclude that the divisional applications could be considered novelty-destroying prior art against the patent. In fact, the appellant's letter had to be understood in the context of the proceedings, and the stated withdrawal did not constitute an admission that the patent was not entitled to the priorities.

Inventive step

Inventive step - claim 1 - auxiliary request A

Starting from the technical teaching of document D3, the objective technical problem to be solved was to provide an alternative use for the compounds of D3.

The ability of the compounds of claim 1 to provide positive therapeutic benefits in ACD regardless of iron depletion status was backed up by experimental data in

the patent in suit and had subsequently been confirmed by clinical trial. Effective treatment of the claimed group of subjects would not have been expected on the basis of the rather unspecific information provided in D3, and in the light of the commonly-known clinical guidelines for the established treatment using exogenous EPO as an erythropoiesis-stimulating agent (D14, requiring that TSAT should be at a level of at least 20% prior to initiation of therapy).

Inventive step - claim 6 - auxiliary request A

The objective technical problem in relation to claim 6 was to provide a new use for the compounds of D3.

Paragraph [0008] of D3 cited by the respondent mentioned "deficiencies in current production and use of recombinant EPO". This could not be interpreted, without hindsight, to mean conditions refractory to treatment with rEPO.

The experimental data presented in D3 went no further than supporting efficacy in aspects that corresponded to the efficacy of EPO. The usefulness of the compounds in treating anemia refractory to treatment with exogenously administered EPO could not have been derived from this data.

The statements made in paragraphs [0064] and [0072] did not amount to an incentive for the skilled person to try treating anemia that was refractory to treatment with exogenously administered EPO. The respondent's argument relying on the mention of microcytic or sideroblastic anemia in D3 was weak: in fact, outside the section on technical background, D3 did not mention any type of anemia in which all patients had iron deficiency.

As far as the argument relying on sideroblastic anemia was concerned, the respondent had never presented this in writing and had not provided any evidence that this disorder involved iron deficiency or that it was refractory to treatment with exogenously administered EPO.

Inventive step - claim 12 - auxiliary request A

Starting from the technical teaching of document D3, the objective technical problem was to identify a new condition that could be treated with the compounds of D3.

While mentioning that some positive effects on iron metabolism might be expected, the disclosure of D3 lacked any indication that the compounds could treat iron deficiency. The reported rise in haemoglobin and haematocrit was not necessarily indicative of that.

On the other hand, it was well known that exogenously administered EPO could cause and worsen iron deficiency. This would have given rise to a similar expectation for EPO generated by the administration of a compound of formula (I). A mere verbal statement (in paragraph [0072] of D3) mentioning a potential for positive effects on iron metabolism would not have completely reversed this expectation.
The reference, in this context, to a possible increase in ceruloplasmin was not conclusive in this regard.
The mere mention that certain disorders such as microcytic anemia and sideroblastic anemia might also be treated did not translate into a motivation or expectation of success with respect to the treatment of iron deficiency.

XIX. The appellant requested that the decision under appeal be set aside and that the opposition be rejected;

or, in the alternative, that the patent be maintained in amended form on the basis of the claims according to auxiliary request A, filed during the oral proceedings on 25 February 2022;

or in the further alternative, that the patent be maintained in amended form on the basis of the claims according to

- one of auxiliary requests 1 to 4, filed on 4 January 2016; or
- one of auxiliary requests 5 and 6, filed on 7 October 2016; or
- one of auxiliary requests 7 to 22, filed with the statement setting out the grounds of appeal.

The appellant also requested that the respondent's objection under Articles 123(2)/100(c) EPC against auxiliary request A not be admitted.

XX. The respondent requested that the appeal be dismissed.

It also requested that auxiliary request A not be admitted.

Reasons for the Decision

1. Technical background

1.1 The patent in suit (see paragraph [0001]) relates to compounds for regulating or enhancing erythropoiesis (red blood cell production) and iron metabolism, and for treating or preventing iron deficiency and anemia of chronic disease.

1.2 The treatment envisaged in the patent involves administering a compound which induces erythropoiesis by stabilising HIFα (see paragraph [0014] and points 1.7 to 1.11 below). The active compound as defined in the claims is a small-molecule organic compound according to formula (I) (see paragraph [0136] and claim 1 of the patent in suit). Further downstream effects of HIFα stabilisation relate to iron metabolism.

Anemia of chronic disease, iron deficiency and transferrin saturation (TSAT)

1.3 Anemia is a class of conditions with variable causes in which the blood has a reduced ability to carry oxygen due to a lower-than-normal number of red blood cells (erythrocytes) or a reduction in the amount of haemoglobin.

1.4 Most patients suffering from chronic infections, chronic inflammations or various malignancies develop a mild to moderate anemia, which is designated anemia of chronic disease (ACD). ACD is associated with increased production of inflammatory cytokines, which reduce the production of erythropoietin (EPO, a naturally-occurring hormone that stimulates erythropoiesis, see point 1.7 below) and impair its

action. In ACD, numerous physiological deficiencies are observed that contribute to ineffective or impaired erythropoiesis, including in particular reduced EPO production and iron deficiencies. Microcytic anemia (characterised by abnormally small blood cells) may also develop (see patent in suit, paragraphs [0003] to [0005], and D105, page 481, first paragraph).

1.5 Two categories of iron deficiencies are distinguished: the deficiency may be absolute (inadequate iron stores in the body) or functional (impaired ability to access and utilise iron stores) (see patent in suit, paragraphs [0008] and [0009]). Iron deficiency of any kind can lead to iron-restricted erythropoiesis (see patent in suit, paragraph [0010]).

1.6 Transferrin is a carrier protein which binds most of the iron present in serum. It contains two binding sites for iron. Transferrin saturation (TSAT) is the percentage occupation of the available iron-binding sites. Low TSAT levels reflect low iron availability (see paragraph [0011] of the patent in suit).

Erythropoietin (EPO) and hypoxia inducible factor (HIF)

1.7 EPO is a naturally-occurring hormone that stimulates erythropoiesis, i.e. the production of red blood cells, which carry oxygen (bound to haemoglobin) through the body. EPO is normally secreted by the kidneys, and endogenous EPO is increased under conditions of oxygen deprivation (hypoxia) (see D3, paragraph [0003]).

1.8 Treatment with exogenous EPO, in particular recombinant human EPO (rEPO), as an erythropoiesis-stimulating agent was known as a therapy for anemia, including anemia of chronic disease (see application as filed, paragraph [0127], and D3, paragraphs [0007] and

[0008]). However, resistance to EPO had also been observed in ACD patients. This was attributed to increased levels of inflammatory cytokines (see patent in suit, paragraph [0005], D105, page 481, first paragraph, D5: page 194, and point 1.4 above).

1.9 HIFα is the alpha subunit of hypoxia inducible factor (HIF), which is a factor involved in a number of physiological processes, including erythropoiesis.

As set out in the application as filed (see paragraphs [0130] and [0131]), the genomic response to conditions of hypoxia involves changes in gene expression and cell physiology to counteract the effects of oxygen deprivation.

HIF is a transcription factor composed of an oxygen-regulated alpha subunit (HIFα) and a constitutively expressed beta subunit (HIFβ). In environments with adequate levels of oxygen, HIFα is destabilised due to hydroxylation of specific proline residues by HIF-specific proline hydroxylases (HIF-PHs). However, in hypoxic environments, HIF-PHs cannot hydroxylate HIFα, and active HIF complexes form. These active HIF complexes translocate to the nucleus, and activate gene transcription.

1.10 According to the patent in suit, the compounds of the invention pharmaceutically mimic hypoxia by stabilising HIFα. This induces endogenous EPO production. Further mechanisms involved also enhance iron uptake, transport and utilisation (see paragraphs [0014], [0016] and [0112]; see also D3, paragraph [0014]).

1.11 Thus the patent sets out a concept of addressing anemic disorders not by administering exogenous EPO but by administering a small molecule (the compound of

formula (I)) that induces endogenous EPO production by stabilising HIFα. Additional effects mentioned relate to iron metabolism.

Main request

2. Inventive step - claim 12 as granted

Subject-matter of claim 12

2.1 Claim 12 as granted relates to a compound of formula (I) that stabilises HIFα for use in treating or preventing microcytosis in microcytic anemia in a subject.

2.2 Microcytosis is the disorder of having abnormally small red blood cells (microcytes), as reflected, for instance, in decreased mean corpuscular volume. Microcytic anemia is any form of anemia involving microcytosis (see paragraphs [0010], [0239] and [0246] of the patent in suit).

2.3 Experimental data in relation to this therapeutic indication were provided in example 20 of the patent in suit (see paragraphs [0232], [0239], [0241] and [0246]).

Starting point in the prior art

2.4 As set out above (see point XVI.), it was common ground that inventive step should be assessed starting from the technical teaching of document D3, presumed to form part of the state of the art under Article 56 EPC.

2.5 Like the patent in suit, D3 relates to compounds of formula (I) that stabilise HIFα. It was not in dispute that formula (I) in D3 is identical to formula (I) in the patent in suit.

2.6 D3 aims to increase endogenous erythropoietin (EPO) levels to prevent or treat EPO-associated disorders by stabilising HIFα. Compounds to be administered in order to achieve this purpose may be compounds of formula (I). The disorders which may be treated include conditions associated with anemia. These, in turn, include abnormal haemoglobin and/or erythrocytes (i.e. red blood cells), such as found in, *inter alia*, microcytic anemia (see D3, claim 11, paragraphs [0026] and [0064]).

Technical problem and solution

2.7 The subject-matter of claim 12 as granted differs from the disclosure of D3 in that the specific indication of microcytosis in microcytic anemia is to be treated.

2.8 The technical effect attained is the treatment of microcytosis in microcytic anemia.

2.9 Claim 12 is drafted in the format according to Article 54(5) EPC, and the medical use stated in the claim is considered a limiting technical feature. Thus the technical effect is achieved across the claimed scope.

2.10 Starting from the technical teaching of document D3, the objective technical problem solved by the subject-matter of claim 12 as granted is to provide a further medical use of a compound of formula (I).

Obviousness of the solution

2.11 The passage in paragraph [0064] of D3 contains an explicit pointer, as it mentions that disorders associated with anemia including

> *"abnormal hemoglobin and/or erythrocytes, such as found in disorders such as microcytic anemia, hypochromic anemia, aplastic anemia, etc."*

are among the EPO-associated conditions which can be prevented or treated by the methods and compounds of D3.

2.12 It is not further specified here that microcytosis in microcytic anemia, in particular, will be addressed. The statement does suggest, however, that the compounds of D3 may have a benefit in microcytic anemia by preventing or mitigating abnormalities in haemoglobin and/or erythrocytes. The cited passage therefore encourages the person skilled in the art to investigate and observe the effects of compounds of formula (I) on such abnormalities. As indicated by the label of "microcytic" anemia, these abnormalities prominently include microcytosis. The person skilled in the art following this teaching and investigating the effects of compounds (I) on microcytic anemia, e.g. in a suitable animal model, would thus verify that there is an effect on microcytosis, and arrive at the claimed subject-matter without exercising inventive skill.

2.13 The appellant argued that the general teaching of document D3, and common general knowledge as represented by D22, nevertheless taught away from the subject-matter of claim 12.

2.14 This argument does not succeed, for the following reasons:

2.14.1 In the board's opinion, the explicit pointer in paragraph [0064] has more weight than indirect inferences that the skilled person might, or might not, have drawn on the basis of the general teaching in D3. While its main focus is on increasing the level of endogenous EPO, and thereby increasing the number of red blood cells produced, D3 also teaches that the compounds of formula (I) may have an impact on various aspects of iron metabolism (see D3, paragraph [0072]).

The overall teaching in D3 does not give rise to an expectation that no improvement in microcytosis could be achieved in the disorders mentioned in paragraph [0064].

2.14.2 The appellant also referred to document D22 as proof of the skilled person's alleged common general knowledge that EPO (whether recombinant or endogenous) would have been expected to worsen microcytosis.

D22 is a scientific journal article reporting the results of a study of the *"effects of recombinant human erythropoietin on mean corpuscular volume in patients with the anemia of chronic renal failure".*

As a specialised journal article, D22 does not, however, qualify as evidence of common general knowledge. D3 itself does not discuss the issue.

2.15 For these reasons, the subject-matter of claim 12 as granted does not involve an inventive step within the meaning of Article 56 EPC.

Auxiliary request A

3. Admittance of auxiliary request A

3.1 Auxiliary request A was filed during the oral proceedings before the board, after an exhaustive debate on all the substantive issues (sufficiency of disclosure, novelty and inventive step) in relation to the independent claims of the main request, and after the board had advised the parties of its conclusions regarding each of these claims (see also minutes of the oral proceedings and point XVI. above). In summary, the board considered that the grounds for opposition under Article 100(a) and (b) EPC did not prejudice maintenance of independent claims 1, 6 and 15 as granted, but that the subject-matter of independent

claim 12 as granted did not involve an inventive step (Articles 100(a), 52(1) and 56 EPC).

3.2 The set of claims according to auxiliary request A differs from the claims as granted by the deletion of claim 12 and its dependent claims 13 and 14. The subsequent claims and claim dependencies were adapted accordingly (see point XVI. above).

3.3 This results in the deletion of an alternative within the set of claims of the main request. This deletion merely sets aside the objection of lack of inventive step against claim 12 as granted, without changing the focus, or the factual and legal framework, of the proceedings. The issues, submissions and conclusions with regard to the remaining claims, which had always been in the focus as well, are unaffected. These claims were already part of the appellant's case and the subject of the proceedings under Article 12(1) and (2) RPBA 2007 (corresponding to Article 12(1) and (3) RPBA 2020).

3.4 The amendment is thus comparable to the withdrawal of certain objections or lines of attack by an opponent, which has also never been regarded as a change of case (see T 914/18, Reasons, 4.1 and T 995/18, Reasons, 2).

3.5 Under these circumstances, Article 13 RPBA does not apply.

3.6 The board also observes that, with a main request including four independent claims, and a case involving various grounds and objections as well as a large number of citations, it would not have been proportionate to expect the appellant to file a large number of claim sets containing any possible permutation of the independent claims in anticipation of potential future developments, nor would this have

served procedural efficiency. In view of this situation, the appellant mentioned in its statement of grounds of appeal (point 7.12) that it would, as further auxiliary requests, delete any claims that were found unallowable, and also requested at the outset of the oral proceedings to be given the opportunity to delete claims found unallowable by the board.

3.7 As a result of these considerations, the board saw no reason to hold auxiliary request A inadmissible.

4. Admittance of the respondent's objections in respect of added subject-matter

4.1 In its reply to the appellant's grounds of appeal, the respondent submitted that the claims of the main request and all the auxiliary requests failed to comply with Articles 100(c)/123(2) EPC (see respondent's letter of 9 October 2017, page 3).

4.2 However, this ground was not substantiated as far as the claims of the main request (i.e. the claims of the patent as granted) were concerned:

4.2.1 The mere statement that the claims violated Articles 100(c)/123(2) EPC does not provide any information as to the underlying reasoning.

4.2.2 In its letter of 9 October 2017, the respondent did not explain, either, why it believed that the decision under appeal was wrong on the issue of added subject-matter. The arguments provided with regard to auxiliary requests 7 to 10 on pages 35 and 36 of the respondent's letter only relate to the addition of the feature "increasing serum iron" to the claims of these requests. This passage does not shed any light on the respondent's reasoning in respect of the claims as granted.

4.2.3 The respondent also referred to its remarks regarding the issue of novelty in point 1.1 on page 16 of its letter of 9 October 2017:

> *"As a sidenote in this regard, the Respondent maintains its objection under Article 123(2) EPC against present claim 1, in particular with feature 3. Since the same legal standard is to be applied for the disclosure of the contested patent and D91, claim 1 either violates Art. 123(2) EPC or is anticipated by D91."*

However, nothing more can be learned from this passage than that an unspecified objection under Article 123(2) EPC is maintained. No reference is made to any specific passage of the respondent's submissions in the proceedings before the opposition division.

4.3 In view of these circumstances, the board considers that the respondent, in the written appeal proceedings, never actually defined its objections under Articles 100(c)/123(2) EPC against the claims of the patent as granted.

4.4 Auxiliary request A contains only claims which were already present in the set of claims of the patent as granted (see point XVI. above).

4.5 Under Article 12(2) RPBA 2007, the respondent should have specified all its objections against these claims at the outset of the appeal proceedings, rather than wait until the oral proceedings before the board to confront the opposing party and the board with a new discussion. There are no exceptional circumstances in this case which prevented the appellant from doing so.

4.6 For these reasons, and in accordance with the provisions of Article 13(2) RPBA, the board did not

admit the respondent's objections regarding added subject-matter.

5. Sufficiency of disclosure

5.1 Sufficiency of disclosure must be satisfied at the effective date of the patent, on the basis of the information provided in the patent application as filed together with the common general knowledge then available to the person skilled in the art.

Issues in relation to the current claims

5.2 The claims under consideration are drafted in the format according to Article 54(5) EPC. The medical use stated in each claim is considered a technical feature of the claim. For the requirement of sufficiency of disclosure to be met, the therapeutic efficacy of the compounds in respect of the stated medical uses has to be credible.

5.3 Formula (I) defines a group of substances by the structural definition of a Markush formula.
The claims in auxiliary request A combine this definition with functional features, namely (i) HIFα-stabilising activity (as a limiting feature further defining the compounds) and (ii) the respective therapeutic indications.

5.4 The respondent contended that since formula (I) was excessively broad, identifying those compounds of formula (I) that also met all the functional requirements defined in the claims imposed an undue burden on the person skilled in the art. Also, the efficacy of the compounds of formula (I) in the therapeutic indications at issue was not credible, or at least not across the scope claimed.

5.5 The board has the following considerations with regard to the issues to be resolved.

5.6 The functional requirements in the claims relate to two aspects:

- The first aspect is the definition of the compounds as compounds of formula (I) with HIFα-stabilising activity.
- The second aspect is the suitability of these compounds for the therapeutic uses recited in the claims.

5.7 The following relevant criteria in relation to these aspects apply and can be taken from Boards of Appeal case law:

First aspect

- The definition of a group of compounds in a claim by both structural and functional features is generally acceptable under Article 83 EPC as long as the skilled person is able to identify, without undue burden, those compounds defined by the structural features in the claim which also meet the claimed functional requirements (see T 544/12, Reasons 4.2).
- In the present case, this means that the person skilled in the art must, in a first step, be able to identify compounds as defined in the claims (i.e. compounds of formula (I) with HIFα-stabilising activity) without undue burden.

Second aspect

- In situations with a large number of conceivable alternatives, the inclusion of non-working embodiments is of no harm, as long as it is possible to find working embodiments (i.e. carry

out the invention) over the claimed range of these alternatives with reasonable effort (see G 1/03, Reasons 2.5.2).

- In the present case, this means that the person skilled in the art must, in a second step, be able to find working embodiments for the therapeutic uses with reasonable effort, over the range of compounds as defined in the claims (i.e. compounds of formula (I) with HIFα-stabilising activity).

Availability of compounds of formula (I)

5.8 It was not in dispute that compounds of formula (I) and their synthesis are described in the prior art. Relevant documents are referenced in the patent in suit and the corresponding passages of the application as filed (see the publications cited in paragraphs [0165] to [0169] and documents D3 and D23 cited in paragraph [0156] of the application).

Step 1: Identification of compounds that stabilise HIFα

5.9 The board also considers, firstly, that the person skilled in the art is provided with sufficient guidance to identify HIFα-stabilising compounds by routine screening and, secondly, that the respondent failed to establish that there would nevertheless be an undue burden because a large proportion of compounds of formula (I) lack the required HIFα-stabilising activity, for the following reasons.

5.10 Screening for HIFα-stabilising activity

5.10.1 The application as filed provides some guidance on direct and indirect measurement of the ability of a compound to stabilise HIFα, or inhibit HIF hydroxylase activity, and also cites relevant references in the prior art (see paragraphs [0173] to [0175] of the

application as filed, corresponding to paragraphs [0146] to [0148] of the patent in suit).
Paragraph [0173] states that:

> *"Measuring and comparing levels of HIF and/or HIF-responsive target proteins in the absence and presence of the compound will identify compounds that stabilise HIFα and/or activate HIF."*

Accordingly, examples 1 and 2 of the application use an indirect method measuring EPO induction in a cell-based assay (EPO being an HIF-responsive target protein).

5.10.2 Documents D3 and D23 are specifically cited as disclosing compounds that stabilise HIFα (see paragraph [0156] of the application as filed). Example 9 of D3 teaches an *in vitro* assay for HIF prolyl hydroxylase inhibition activity (corresponding to stabilisation of HIFα, see also example 10 of D23), and example 1 of D23 teaches an *in vitro* assay for HIFα-stabilising activity.

5.10.3 All these indications provide orientation to the person skilled in the art in implementing screening for HIFα-stabilising activity. The screening methods themselves use conventional techniques and there is no reason to assume that performing these tests would be unduly difficult.

5.11 "Inactive" compounds

5.11.1 Document D50 shows screening data determined by the appellant and covers structurally diverse compounds including more than 1000 compounds conforming to formula (I). The respondent contended that D50 provided evidence of inactive compounds.

5.11.2 The board considers that the appellant's screening data presented in D50 does not demonstrate that a large proportion, or specific segments, of compounds of formula (I) lack HIFα-stabilising activity:

A considerable proportion of the tested compounds of formula (I), of varied structural classes, were found to be in the "more active" range (see D53, paragraphs 19 to 25; "Annex 2" discussed in D53 is identical to D50).

Indeed, the respondent did not show that the less active compounds identified in D50 (i.e. those with an IC_{50} higher than 200 µM) are inactive. In the present context, IC_{50} is the concentration at which a compound causes 50% inhibition of HIF prolyl hydroxylase. The threshold value of IC_{50} at 200 µM was used by the appellant in its drug development research to identify particularly promising compounds, but cannot be interpreted as a cutoff for activity. This is demonstrated by Annex 3 of document D53, which shows that 39 compounds with an IC_{50} value higher than 200 µM still provided inhibitory activity.

All in all, it would thus appear that the success rate in identifying compounds of formula (I) with HIFα-stabilising activity would be high.

5.11.3 The respondent's further argument that the compounds tested according to D50 only cover limited areas of formula (I), with a strong focus on isoquinolines, is by itself not sufficient to raise serious doubts about the properties of other structural subgroups of formula (I).

5.11.4 In its written submissions, the respondent also made mention of documents D48, D49 and the corresponding arguments provided in its submissions at first instance (see reply to the grounds of appeal, page 32, and

letter of 24 July 2018, page 16). Like D50, D49 (109 pages) and the accompanying declaration D48 (223 pages including annexes) concern evidence that was originally produced in the course of litigation relating to a different patent (EP1463823) that encompassed different definitions of the active compound. D49 does not reproduce actual data sets or identify the structures of any compounds tested. In its appeal submissions, the respondent did not develop any reasoning in relation to D48/D49 or explain which passages it deemed to have specific relevance to the current case going beyond the line of argument based on D50, nor did the respondent rely on D48 and D49 at the oral proceedings before the board. Under these circumstances, the board considers that it has not been provided with a sufficient basis for taking these documents into account.

5.11.5 In the same context, the respondent also referred to document D46 in its written submissions. As correctly pointed out by the appellant, D46 lacks relevance because the compounds it discloses, with hydrogen at the position corresponding to QR^4, do not conform to formula (I).

5.12 To summarise the board's conclusions, compounds of formula (I) can be synthesised, and they can be screened for HIFα-stabilising activity without undue burden. As far as the definition of the compounds as HIFα-stabilising compounds of formula (I) is concerned, the respondent's arguments for insufficiency are, therefore, not convincing.

Step 2: Suitability for the therapeutic indications specified in the claims

5.13 Correlation of HIFα stabilisation with EPO induction

5.13.1 Referring to the data shown in D50 for EPO induction, the respondent pointed out several instances (namely compounds 159, 176, 180, 183 and 185) where the IC_{50} value for HIFα stabilisation was favourable but *in vivo* data did not confirm induction of EPO. According to the respondent, this showed that EPO induction was not reliably correlated to HIFα stabilisation.

5.13.2 However, these are single data points. D50 shows that, in the large majority of cases where *in vivo* EPO induction was determined, the compounds were indeed found to be active. (This also includes compound 159, which showed ">1 fold induction" in comparison with the EPO level observed with the control vehicle.) In each case, the test was only performed with one particular dosage (20 mg/kg or 60 mg/kg, respectively). It cannot be inferred from this that there would be no activity at higher dosages. For these reasons, the board finds the respondent's argument against the mechanism postulated in the application not persuasive.

5.13.3 Presumably, the skilled person seeking to carry out the claimed subject-matter would in any case perform confirmatory *in vitro* and/or *in vivo* screening for (preferably high) EPO-inducing activity, but this would not be an undue burden going beyond routine activity in pharmaceutical development.

5.13.4 In its written submissions, the respondent also referred to document D47, and its earlier allegation, made in the proceedings before the opposition division, that D47, a poster presentation by the patentee, confirmed that not all HIF prolyl hydroxylase

inhibitors increased endogenous EPO or stimulated erythropoiesis (see respondent's reply to the grounds of appeal, section II on page 32, and letter dated 23 May 2016, page 5, second paragraph). However, the respondent failed to substantiate this objection in its appeal submissions, or to address the appellant's counter-arguments (see appellant's letter dated 5 March 2018, page 18, arguing that all the components tested in D47 did indeed induce EPO). A mere reference to an unsubstantiated allegation made at first instance is not enough for the board to find any merit in the respondent's objection.

5.13.5 To summarise, the respondent did not show that the claimed compounds systematically (as opposed to occasional failures) lack activity in inducing endogenous EPO production, or that it would be an undue burden on the skilled person to screen for such activity.

5.14 Claim 1: Treatment of anemia of chronic disease in a subject with a TSAT of less than 20%

5.14.1 As already mentioned (see point 1.4 above), ACD is associated with increased production of inflammatory cytokines. These include tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). These inflammatory cytokines are known to adversely affect EPO production and EPO responsiveness, thereby blocking erythropoiesis in patients with ACD (see application as filed, paragraph [0006]).

Examples 1 and 2 of the application show in an *in vitro* model that compounds A and B (both representative of compounds defined in claim 1, see paragraphs [0083], [0122], [0169] and [0170]) overcame the suppressive effect of TNF-α and IL-1β on EPO production. This

supports the alleged benefit of the claimed compounds in the treatment of ACD.

5.14.2 Example 20 used an animal (rat) model of ACD to show that treatment with compound A stimulated erythropoiesis (as indicated by increased reticulocyte count) and favourably affected various parameters relevant to the treatment of anemia (increase in haematocrit levels (Figures 8 and 13), haemoglobin levels (Figures 9 and 14), red blood cell count, mean corpuscular volume and mean corpuscular haemoglobin levels). Compound A also had the effect of increasing serum iron levels and transferrin saturation in both anemic and non-anemic (control) animals (Figures 18A and 18B, paragraph [0276]), and of increasing intestinal expression of proteins involved with iron transport and absorption in the intestine (while untreated anemic animals showed reduced expression levels). While the respondent remarked that the rats according to Figure 18B did not have baseline TSAT levels of less than 20%, the results observed nevertheless demonstrate an increase in TSAT.

These data indicate that iron status may also be improved (see also example 17 as discussed in point 5.16.1 below), which supports the alleged benefit of the claimed compounds in treating iron-deplete subjects with a TSAT level of less than 20%. This benefit was also confirmed in later clinical trials (see, for instance, Annex 6 of Declaration E2, discussed in point 5.18.3 below).

5.14.3 Based on these results, the therapeutic indication of treating ACD in iron-deplete subjects having a TSAT of less than 20% appears credible.

5.15 Claim 6: Treatment of anemia refractory to treatment with exogenous erythropoietin

5.15.1 In many patients with anemia, the condition is refractory to treatment with exogenous erythropoietin. In such cases, rEPO treatment cannot overcome inhibition of erythropoiesis caused by inflammatory cytokines.

5.15.2 The experimental results presented in examples 1, 2 and 20 (discussed above in the context of claim 1) also render the therapeutic indication of claim 6 credible.

5.16 Claim 12: Treatment of iron deficiency

5.16.1 The experimental data presented in the examples of the application as filed suggest that the claimed compounds may be capable of treating both absolute and functional iron deficiency:

Example 17 (relating to an investigation of the expression of genes encoding iron-processing proteins in mice) and example 20 (series 2) demonstrate the ability of representative compounds to increase factors involved in iron uptake from the gut, such as NRAMP2 and sproutin (see paragraphs [0252], [0277] and [0278]). This may increase iron supply to the body.

Example 17 also demonstrates the ability of compound A to decrease hepcidin expression (see paragraphs [0249] and [0250] with Table 4). Decreased hepcidin expression is associated with increased iron release from stores in the body and increased intestinal iron absorption.

Increased iron utilisation was confirmed in a human study on healthy volunteers described in example 21, where compound A was found to increase soluble transferrin receptor and decrease serum ferritin levels (see paragraphs [0283] and [0284]).

5.16.2 Considering the data supplied in the application as filed, the therapeutic indication of treating iron deficiency is therefore rendered credible.

5.17 HIFα-stabilising activity as the basis for efficacy

5.17.1 The respondent argued that the compounds exemplified in the application were few and structurally similar, and that the experimental results observed with these similar compounds could not plausibly be extrapolated across the scope of formula (I).

5.17.2 It is however plausible, on the basis of the technical background set out in section 1 above, that similar results would be obtained with compounds that stabilise HIFα, with regard to downstream effects of HIF. Apart from their structural definition, this HIFα-stabilising effect is a mandatory functional feature and common property of the claimed compounds.

5.17.3 This concept is also supported by the results reported in example 15 ("Enhanced expression of erythropoiesis genes *in vitro*"), which investigates the effects of compounds B and D, two structurally unrelated compounds that stabilise HIFα (as taught in the application). Compound B is a compound of formula (I), while compound D is a substituted propionamide of formula (III) (see paragraphs [0015], [0082], [0083], [0170] and [0172] of the application as filed; see also paragraph [0156] of the application referencing D23; and D23, Fig 1A independently confirming the HIFα-stabilising activity of compound D (identical to compound C in D23)). According to example 15, both compounds were found to induce ceruloplasmin, a factor involved in iron metabolism. Since the compounds are structurally unrelated, the effect may reasonably be attributed to their HIFα-stabilising activity. The

respondent did not establish that any other mechanism might be responsible.

5.17.4 Thus the respondent's argument does not succeed, since the alleged therapeutic benefits are not based on formula (I) alone but are plausibly attributed to the compounds' shared HIFα-stabilising activity.

5.17.5 On the basis of the available data as set out in points 5.14 to 5.16 above, it is therefore credible that compounds which satisfy the structural and functional definition given in the claims (i.e. compounds of formula (I) that stabilise HIFα) will achieve the respective therapeutic effects.

5.18 Disclosure of document D107

5.18.1 Post-published document D107 relates to epoetin-alfa (rEPO) therapy and functional iron deficiency in chronic or end-stage renal disease.

D107 reports that it had been observed, in such cases, that serum ferritin levels often decreased markedly after initiation of epoetin-alfa (rEPO) therapy and the release of stored iron did not keep up with the demand for haemoglobin synthesis imposed by rEPO. Supplemental, in particular intravenous, iron therapy was required to maintain TSAT above 20%.

The occurrence of functional iron deficiency by dysregulation of iron metabolism was attributed to elevated hepcidin levels. HIF, e.g. when stabilised by HIF prolyl hydroxylase inhibitors, could bring down hepcidin levels. Roxadustat, which is a compound of formula (I) that stabilises HIFα by inhibiting HIF prolyl hydroxylase, had been shown to decrease hepcidin in clinical trials.

D107 *inter alia* discusses a post-published clinical study (reference (14) in D107) in which human patients with end-stage renal disease received roxadustat and were randomised to receive either intravenous iron, oral iron or no iron supplementation. This study included dialysis patients with a mean TSAT of 18.8% and a mean ferritin level of 159 mg/ml at baseline, of whom only 32% could be considered iron replete at baseline. The primary endpoint in this study was the maximal change in haemoglobin from baseline. D107 concludes that roxadustat increased haemoglobin regardless of iron depletion status or supplementation regimen. While a greater haemoglobin change from baseline was maintained in the group receiving iron supplementation versus the group receiving no iron, oral iron supplementation was as effective as IV supplementation.

5.18.2 Relying on data shown in Table 2 in document D107, the respondent argued that roxadustat did not increase serum iron and TSAT in patients who did not receive iron supplementation. This was relevant because the therapeutic uses of all the independent claims were based on the effect of increasing serum iron. D107 showed that roxadustat treatment required concomitant oral iron supplementation. Since roxadustat differed from "compound B" of the patent in suit only by a methyl group, this post-published finding illustrated the difficulty of predicting activity from the compounds' structural features, and/or cast doubt on the suitability of the animal models employed according to the examples of the patent in suit, and the conclusiveness of the data obtained on that basis.

5.18.3 The board is not convinced by this line of argument, for the following reasons:

The study described in D107 focuses on anemia (in end-stage renal disease) and change in haemoglobin as the primary endpoint. Clinical factors that may have affected serum iron levels or TSAT are not discussed.

On the other hand, reports about further clinical trials carried out by the appellant suggest favourable effects of roxadustat on iron availability:

Annex 7 of Declaration E2 (cited by the appellant and identical to reference (15) in D107) discusses the results of another clinical trial in which roxadustat was used in a comparator study with rEPO in dialysis-dependent kidney disease patients. The primary endpoint was, again, haemoglobin level response. Table 4 of Annex 7 shows an increase in serum iron for patients treated with roxadustat, as opposed to a decrease in patients treated with rEPO, and a larger decline in TSAT in patients treated with rEPO than in those treated with roxadustat. The authors of Annex 7 conclude that these data are consistent with roxadustat's expected positive impact on iron availability (see E2-Annex 7, table 4 and page 920, right-hand column, lines 17 to 22). No distinction is made, though, between patients who received oral iron supplementation and patients who did not receive a supplement.

Annex 6 of Declaration E2 (cited by the appellant and identical to reference (16) in D107) relates to another clinical trial with roxadustat for the treatment of anemia in patients with chronic kidney disease.
At baseline, only 52.4% of patients were iron replete (ferritin > 100 ng/ml and TSAT > 20%), and 53 of 145 patients (37%) were receiving oral iron or began oral iron during the treatment phase. Although TSAT and

ferritin declined during the initial weeks of treatment, they stabilised thereafter. Mean reticulocyte haemoglobin content levels were maintained despite robust erythropoiesis, which, according to the authors, indicated the absence of functional iron deficiency during roxadustat treatment. The iron used in erythropoiesis in these patients could have come from mobilisation of internal stores as well as from oral supplementation, but the latter was given to only 37% of patients. Haemoglobin response to roxadustat in patients who were not iron replete and not on oral iron at baseline was as good as in those who were iron replete and on oral iron (see E2-Annex 6: abstract, page 984, paragraph bridging columns; paragraph bridging pages 988 and 989).

Thus, contrary to the respondent's view, the available information does not warrant the conclusion that treatment with roxadustat requires oral iron supplementation - which, in any case, is not excluded by the wording of the current claims. Moreover, the teaching of Annex 6 further confirms the credibility of the therapeutic indication defined in claim 1, as roxadustat was capable of treating iron-deplete patients with a TSAT of less than 20%.

Nor did the appellant claim that the therapeutic uses of all the independent claims were based on the effect of increasing serum iron, and it is not self-evident that this should be the case.

5.18.4 In conclusion, it was not established that roxadustat would fail to achieve the therapeutic effects indicated in the claims. Even less was it established that larger groups of the compounds defined in the claims would not work.

The size of the structural class (formula (I)) is not decisive

5.19 Contrary to the respondent's view, the person skilled in the art seeking to implement the claimed subject-matter would have no reason to test all the compounds of formula (I) in multiple series of tests for all the functional features mentioned in the claims, because this is not a prerequisite to carrying out the invention:

5.19.1 Only those compounds of formula (I) with HIFα-stabilising activity fall within the scope of the claims, and these are reasonable candidates for the claimed therapeutic indications (see section 5.17 above).

5.19.2 In order to carry out the claimed subject-matter, the skilled person is also not obliged to identify all compounds of formula (I) that stabilise HIFα, and among them, all the compounds which are suitable for the therapeutic indications.

5.19.3 To satisfy the criterion of sufficiency of disclosure, the skilled person merely has to be able to identify further suitable compounds, across the claimed scope, in addition to those disclosed in the application (see point 5.7, second aspect, above).

5.20 Screening for HIFα-stabilising activity, among one or more chosen subgroups of formula (I), does not represent an undue burden as it relies on conventional tests and there is no evidence of a large proportion of failures (see points 5.9 to 5.12 above). Since, for these reasons, the situation in the present case is not one of mere trial-and-error experimentation on a host of alternatives without any guidance, it differs from

the situation addressed in decision T 0544/12 invoked by the respondent.

5.21 After the simple and rapid preselection of a pool of likely candidates provided by the functional test for HIFα stabilisation, the person skilled in the art has the usual methodology of pharmaceutical development (including further screening such as EPO induction assays) at their disposal to sort out occasional failures and identify particularly useful compounds. This exercise may be repeated, if desired, with further pools of HIFα-stabilising candidates of formula (I). While such a procedure may be work-intensive, it does not go beyond routine work in pharmaceutical development and does not constitute an undue burden.

5.22 It has not been established that this should not be possible across the scope of compounds of formula (I) that stabilise HIFα (see points 5.13.5, 5.17.2 to 5.17.5 and 5.18.4 above).

5.23 For the reasons set out above, claims 1, 6 and 12 of auxiliary request A meet the requirement of sufficiency of disclosure (Article 100(b) EPC, Article 83 EPC).

6. Novelty over the disclosure of D3

6.1 Document D3 relates to methods for increasing endogenous EPO in a subject and teaches that this can be achieved by the administration of compounds that stabilise HIFα. Preferred compounds are compounds of formula (I). It was not in dispute that formula (I) in D3 (see paragraphs [0026] and [0077]) is identical to formula (I) according to the patent in suit.

6.2 In a claim directed to a second medical use of a compound and drafted in a format conforming to Article 54(5) EPC (as is the case for the present

independent claims), the therapeutic indication is a technical feature of the claim, to be taken into account in assessing patentability. In order to anticipate the claimed subject-matter, an item of prior art must disclose the therapeutic efficacy of the compound addressed in the claim with regard to this therapeutic indication.

6.3 Novelty - claim 1 - auxiliary request A

6.3.1 Document D3 includes background information on possible causes of anemia (see paragraphs [0004] and [0044]) and mentions that anemia arising in various contexts, including in association with certain diseases which may be considered chronic, may be prevented or treated by the methods of the invention (D3, paragraphs [0017] and [0018]). However, D3 does not use the terms "anemia of chronic disease" or "ACD".

6.3.2 As pointed out by the appellant, "anemia of chronic disease" has a specific meaning in the art, and anemia in patients with chronic diseases (as mentioned in D3) is not necessarily anemia of chronic disease. This is illustrated by document D105, a textbook of haematology, which states (see D105, page 484, under the heading "Differential Diagnosis"):

> *"Most patients with chronic infections, inflammations, or neoplastic disorders are anemic, but such anemias should be designated anemias of chronic disease only if the anemia is moderate, the cellular pattern in the marrow is nearly normal, the serum iron and iron-binding capacity are low, the iron content of the marrow macrophages is normal or increased, and the serum ferritin is elevated."*

6.3.3 Even if the diseases or conditions mentioned in D3 are the same as those mentioned in the patent in suit in connection with ACD, the board considers that the disclosure of D3 is different, as it does not specifically mention ACD. The text of the patent in suit itself cannot be used to re-interpret D3 since it is not prior art and does not reflect the skilled person's considerations. The chronic diseases mentioned in D3 may be associated with ACD but also with anemias not qualifying as ACD, as this is not ruled out in the text of D3. This also applies to rheumatoid arthritis mentioned in paragraphs [0044] and [0072] of D3, and is not ruled out by the passage in D94a (paragraph bridging pages 108 and 109) cited by the respondent.

6.3.4 In summary, D3 does not provide direct and unambiguous disclosure of anemia of chronic disease and its treatment.

6.3.5 Furthermore, D3 does not disclose that subjects having a TSAT level of less than 20% are to be treated. This is neither implicit (inherent to patients having anemia) nor derivable from any statement in D3. The threshold of 20% is not arbitrary since clinically a TSAT below 20% is used to identify patients at risk for iron-restricted erythropoiesis (see also section 8.9 below).

6.3.6 For these reasons, the subject-matter of claim 1 of auxiliary request A is novel over the disclosure in D3 (Articles 52(1) and 54 EPC).

6.4 Novelty - claim 12 - auxiliary request A

6.4.1 According to claim 12, the compound of formula (I) that stabilises HIFα is the active agent that treats iron deficiency. As mentioned above (see point 1.5), iron deficiency may fall into two categories, absolute and

functional iron deficiency. Claim 12 does not specify a category.

6.4.2 Document D3 does not contain an explicit reference to treating iron deficiency (whether functional or absolute) with compounds of formula (I).

6.4.3 What is mentioned, apart from the main focus in D3 on promoting endogenous EPO production, is the general possibility of treating anemias associated with defects in iron transport, processing or utilisation (see D3, claim 24 and paragraph [0018]). It is furthermore mentioned that "the invention contemplates increasing iron transport, processing and utilization" and that the methods in D3 may increase the levels of enzymes and proteins involved in these processes (see D3, paragraph [0072]). Such enzymes and proteins may include transferrin, transferrin receptor and ceruloplasmin. It is postulated that this may result in improving the transport and utilisation of iron, as a benefit in addition to inducing EPO, in the treatment of anemic disorders such as rheumatoid arthritis and sideroblastic anemia.

6.4.4 However, the patients in that context are not identified as having iron deficiency, the methods of D3 are not presented as an effective treatment for iron deficiency, and D3 lacks data showing the effect of the treatment on iron deficiency - in other words, the condition mentioned in point 6.2 above is not met.

6.4.5 Example 3 in D3 relates to an animal study in healthy rats examining the effect of administering a compound conforming to formula (I) ("compound C" in D3). The parameters determined were erythropoietin levels, haemoglobin and haematocrit. It is not apparent why this experimental setup, with subjects not described as having iron deficiency and with these specific test

parameters, would reflect a possible impact of the treatment on iron deficiency.

6.4.6 According to the respondent, the fact that the observed increase in haemoglobin and haematocrit was sustained over a certain period of time (20 days, as shown in Figures 4C and 4D of D3) was indicative of a positive effect on serum iron levels. However, this remains an unsubstantiated allegation. Even with the respondent's rationale that increased haemoglobin is a downstream effect of increased serum iron, it is not self-evident that the only possible explanation of the effects observed would be an increase in serum iron, and D3 itself does not draw this specific conclusion.

6.4.7 The general teaching in D3, which proposes additional iron supplementation (see paragraph [0018]), does not suggest, either, that compounds of formula (I) treat iron deficiency.

6.4.8 The board considers, therefore, that the above-cited passages in D3 do not amount to a direct and unambiguous disclosure of the treatment of iron deficiency.

6.4.9 For these reasons, the subject-matter of claim 12 of auxiliary request A is novel over the disclosure of D3 (Articles 52(1) and 54 EPC).

7. Withdrawal of claims to priority

7.1 This issue had to be resolved as a preliminary issue to an objection of lack of novelty in relation to document D91, a divisional application of the patent in suit.

7.2 Document D3, which was cited by the respondent against both novelty and inventive step, is an intermediate

document published before the filing date, but after the earliest priority date, of the patent in suit.

7.3 In the proceedings before the opposition division, the appellant did not invoke priority but argued that the claims of the main request were, in any event, novel and inventive over D3 from the filing date of the patent in suit. The appellant's letter of 29 September 2016 stating that it "withdrew" all claims to priority in respect of the patent in suit was an attempt to avoid a discussion of priority deemed unnecessary by the appellant (as stated in the letter itself, see point VII. above).

7.4 The opposition division considered the withdrawal to be unconditional and valid. According to the decision under appeal, the legal consequence of the withdrawal was that the effective date of the patent in suit was the filing date, i.e. 4 June 2004. The opposition division furthermore held that the patent's three divisional applications (EP2322153, EP2322155 and D91 = EP2826471) still enjoyed the claimed priorities and thus represented prior art under Article 54(3) EPC.

7.5 The board comes to a different conclusion:

7.5.1 The decision under appeal does not deal with the limiting statements in the appellant’s letter, and gives no reasons either why the withdrawal was considered to be "unconditional".

7.5.2 Whereas the verb "withdraw" employed in the letter of 29 September 2016 implies the retraction by the appellant of its claims to priority, the letter as a whole conveys the more limited intention to avoid, for convenience, a discussion considered irrelevant in the opposition case under consideration. The letter also states that *"This withdrawal does not constitute an*

admission on the patentee's part that patentee is not in fact entitled to earlier priority dates (...)".

7.5.3 Thus the statements in the appellant's letter, when considered in context and as a whole, are at least ambiguous and cannot be understood as an unconditional withdrawal.

7.5.4 In the interest of legal certainty, procedural declarations have to be unambiguous (see J 11/94, OJ EPO 1995, 596; J 27/94, OJ EPO 1995, 831; T 3043/19, Reasons 4).

7.5.5 As the appellant's statement was not unambiguous, the "withdrawal" of the appellant's claims to priority has no legal effect in the present proceedings.

7.5.6 As a consequence, there is no basis for the respondent's argument that the divisional applications should be considered prior art for assessing novelty.

7.5.7 It is not necessary, therefore, to address the further questions of whether it is at all possible for a patent proprietor to surrender claims to priority in the course of opposition proceedings, and whether in such a case the divisional applications derived from the patent in suit would retain the priorities and represent prior art under Article 54(3) EPC.

8. Inventive step - claim 1 - auxiliary request A

Technical background

8.1 Anemia of chronic disease (ACD) is a well-known form of anemia associated with chronic diseases such as chronic infections, neoplastic disorders and chronic inflammatory disorders (see also points 1.4 and 6.3.2 above, and D105, page 484). A subgroup of patients suffering from ACD are also iron deplete, which is

reflected in a low transferrin saturation (in particular TSAT less than 20%).

Starting point in the prior art

8.2 As set out above (see point XVI.), it was common ground that inventive step should be assessed starting from the technical teaching of document D3, on the assumption, in the respondent's favour, that the subject-matter of the independent claims did not enjoy any of the priorities and that document D3 formed part of the state of the art for assessing inventive step.

Technical problem and solution

8.3 The claimed subject-matter differs from the disclosure in D3 by the therapeutic indication, which is the treatment of ACD in a subject having a TSAT of less than 20%.

8.4 The technical effect achieved by the claimed subject-matter is efficacy in the treatment of ACD in a subject having a TSAT of less than 20%.

8.5 Claim 1 is drafted in the format according to Article 54(5) EPC, and the medical use stated in the claim is considered a limiting technical feature. Thus the technical effect is achieved across the scope of the claim.

8.6 The objective technical problem is, accordingly, to provide a further medical use for compounds of formula (I) that stabilise HIFα.

Obviousness of the solution

8.7 Document D3 teaches that the inventive compounds work by increasing endogenous EPO. While D3 does not refer specifically to the treatment of ACD, it does refer, in a broader sense, to anemias occurring in association

with chronic diseases as possible therapeutic indications to be treated (see points 6.3.1 to 6.3.3 above).

The treatment of ACD was a known application of exogenously administered EPO.

On this basis, the person skilled in the art would have considered also using the compounds of D3, based on their effect of increasing endogenous EPO, in the treatment of ACD.

The question to be answered is, therefore, whether in this context it would have been obvious to treat patients with a TSAT level of less than 20%.

8.8 The board agrees with the appellant's position that the person skilled in the art seeking to solve the objective technical problem would have been well aware of established medical guidelines regarding the administration of exogenous EPO (such as reflected in D14) and would have taken these into account, since both the administration of exogenous EPO and the induction of endogenous EPO will have the same effect of increasing EPO.

8.9 It was well known at the filing date that, in accordance with medical guidelines, EPO should not be administered to iron-deficient patients with a TSAT level of less than 20%, because this was not safe until the iron deficiency had first been treated by iron supplementation.

8.9.1 In evidence of this common general knowledge, the appellant referred to document D14, an extract from the package insert for Procrit® (epoetin alfa for injection, i.e. rEPO containing the identical amino acid sequence of isolated natural EPO).

8.9.2 As this document is a version revised in December 2009, it could have been published only after the filing date of the application. Because an earlier, pre-published version with the same relevant content exists, the respondent agreed that D14 could serve as evidence of prior common general knowledge about treatment with rEPO.

8.9.3 It was known that iron deficiency (characterised *inter alia* by low TSAT) could be the cause of non-responsiveness to EPO treatment. TSAT should be increased to, and maintained at, a level which could adequately support erythropoiesis stimulated by rEPO (see D14, page 16; see also points 1.6 and 6.3.5 above).

8.9.4 In the section "Indications and Usage" on page 4, D14 states:

> *"Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL."*

Thus it was known that initiation of EPO treatment was not recommended for TSAT levels under 20%.

8.10 In the light of this, the definition of the patient group with a TSAT level of less than 20% in claim 1 is not arbitrary, but represents a clinically relevant threshold for safe treatment with EPO.

8.11 The respondent argued that, nevertheless, document D3 taught not only that the inventive compounds increased endogenous EPO, but also that they increased enzymes and proteins involved in iron transport, processing and utilisation. Based on the second effect, the person

skilled in the art would have found it obvious also to treat subjects with TSAT levels under 20%.

8.12 This argument does not succeed, for the following reasons.

8.12.1 As far as effects on iron transport, processing and utilisation are concerned, the statements in D3 remain on a fairly general level. D3 does not teach specific effects of the compounds in connection with iron repletion or transferrin saturation (TSAT). Indeed, D3 does not mention TSAT at any point as a parameter or as a criterion defining a patient group.

8.12.2 The experimental data provided in D3 relate to the effect of increasing endogenous EPO. This is also the case for Examples 3 (dose response) and 4 (treatment of anemia induced by cisplatin) cited by the respondent.

These examples relate to *in vivo* experiments in rats. The blood samples obtained after administration of a compound of formula (I) (in comparison with a control) were processed for EPO level, reticulocyte count, haemoglobin and haematocrit, as shown in Figures 4 and 5 of D3. These parameters do not directly reflect TSAT levels or iron repletion and do not provide any teaching regarding subjects with a low TSAT level.

8.12.3 In sum, the teaching in D3 about the further potential effects of the compounds on iron metabolism is not specific enough to provide an actual incentive for the skilled person to disregard the caution warranted by common general knowledge about the patient group with a TSAT level lower than 20%. In other words, based on the information in D3 and in the light of common general knowledge, it would not have been obvious to try and treat this patient group.

8.13 As a consequence, the subject-matter of claim 1 of auxiliary request A involves an inventive step within the meaning of Article 56 EPC.

9. Inventive step - claim 6 - auxiliary request A

Starting point in the prior art

9.1 As set out in points XVI. and 8.2 above, it was common ground that inventive step was to be assessed starting from the technical teaching of document D3.

Objective technical problem and solution

9.2 The claimed subject-matter differs from the disclosure in D3 by specifying that the anemia to be treated is refractory to treatment with exogenously administered EPO.

9.3 The technical effect achieved by the claimed subject-matter is effectiveness in the treatment of anemia refractory to treatment with exogenously administered EPO.

9.4 Claim 6 is drafted in the format according to Article 54(5) EPC. The medical use is considered a limiting technical feature of the claim. Thus the technical effect is achieved across the scope of the claim.

9.5 The objective technical problem solved by claim 6 is to provide a further medical use for compounds of formula (I) that stabilise HIFα.

Obviousness of the solution

9.6 Document D3 does not contain a technical teaching that refers explicitly to the treatment of anemia refractory to treatment with exogenously administered EPO.

9.7 There is also no pointer in D3 towards targeting such conditions:

9.7.1 The statement in paragraph [0008] that there remains a need for new treatment methods and compounds in view of "deficiencies in current production and use of recombinant EPO" is much less specific and does not define an objective to address refractory anemia. Likewise, the statement in the final sentence of paragraph [0072] that the methods according to D3 may provide benefits not addressed by current anemia therapeutics such as rEPO does not relate specifically to anemia refractory to treatment with exogenously administered EPO.

9.7.2 Since D3 teaches that compounds of formula (I) treat anemia by increasing endogenous EPO (see D3, paragraph [0002], examples 1 and 2), the claimed compounds would not have been readily expected to treat a specific form of anemia that does not respond adequately to EPO.

9.7.3 The respondent also referred to the mention of microcytic anemia and sideroblastic anemia in paragraphs [0064] and [0072] of D3 as conditions that might be treated. According to the respondent, both conditions involve iron deficiency and are, therefore, refractory to treatment with exogenously administered EPO.

9.7.4 For background on microcytic anemia, the respondent relied on the following statement in D5 (page 194):

> *"In severe and chronic cases of ACD, the persistently low percent transferrin saturation results in impaired iron delivery to the developing erythroid marrow. This, in turn, leads to the production of microcytic red cells and increased erythrocyte zinc protoporphyrin levels."*

9.7.5 The complete passage in D5 from which this is taken does not relate to microcytic anemia but to ACD, which according to this passage may involve low iron levels and may also involve the production of microcytic cells. The board considers that this falls short of providing an unbroken logical chain showing that microcytic anemia invariably involves iron deficiency to a degree that makes it refractory to treatment with exogenously administered EPO.

9.7.6 As far as sideroblastic anemia is concerned, the respondent's allegation (made for the first time at the oral proceedings before the board) that this was a condition arising from iron deficiency and refractory to treatment with exogenously administered EPO remains unsubstantiated.

9.8 For these reasons, the subject-matter of claim 6 of auxiliary request A involves an inventive step within the meaning of Article 56 EPC.

10. Inventive step - claim 12 - auxiliary request A

10.1 Claim 12 of auxiliary request A is identical to claim 15 as granted.

Starting point in the prior art

10.2 As already mentioned (see points XVI. and 8.2 above), it was common ground that inventive step was to be assessed starting from the technical teaching of document D3.

Technical problem and solution

10.3 As set out above in the section on novelty, the technical difference between the claimed subject-matter

and the disclosure of D3 is the medical condition to be treated, namely iron deficiency.

10.4 Accordingly, the technical effect achieved by the claimed subject-matter is effectiveness in the treatment of iron deficiency.

10.5 Claim 12 is drafted in the format according to Article 54(5) EPC. The medical use stated in the claim is considered a limiting technical feature of the claim. Thus the technical effect is achieved across the scope of the claim.

10.6 The objective technical problem solved by claim 12 is to provide a further medical use for compounds of formula (I) that stabilise HIFα.

Obviousness of the solution

10.7 The teaching in D3 focuses on the compounds' activity in increasing endogenous EPO production. The references in D3 to facilitating iron uptake, transport and processing (see D3, paragraphs [0018] and [0072]) relate to potential additional benefits of the treatment. Rather than suggest treatment of iron deficiency in a patient as a specific application, the pertinent comments in D3 remain on a more general, speculative level, do not indicate the expected magnitude of effects and are not accompanied by any data to show that the compounds have these effects to a degree that would be effective in the treatment of iron deficiency.

10.8 On the other hand, it was well known that the administration of exogenous EPO could cause or worsen iron deficiency, and supplementary iron therapy might be necessary in order to ensure effective erythropoiesis (D14, page 16; D74 [reference (5)

in D14], page 996, right-hand column, lines 25 to 38). Since D3 teaches that administering HIFα-stabilising compounds of formula (I) likewise has the effect of increasing EPO, the person skilled in the art would not have had the expectation that such treatment could at the same time improve iron deficiency.

10.9 The conditions of microcytic anemia and sideroblastic anemia are merely mentioned in D3 as possible treatment targets (paragraphs [0064] and [0072]), but this does not provide a straightforward association with the treatment of iron deficiency (see also points 9.7.3 to 9.7.6 above). With regard to the further remark in paragraph [0072] that the treatment may increase enzymes such as ceruloplasmin, the respondent did not substantiate its allegation, made for the first time at the oral proceedings before the board and contested by the appellant, that this was a clear pointer to the treatment of iron deficiency.

10.10 All in all, document D3 would not have provided an incentive or expectation of success to the skilled person regarding the treatment of iron deficiency with the claimed compounds.

10.11 As a consequence, the subject-matter of claim 12 of auxiliary request A involves an inventive step within the meaning of Article 56 EPC.

11. Conclusion

For the reasons set out above, the subject-matter of the claims according to auxiliary request A meets the requirements of the EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent with the following claims and a description to be adapted thereto:

   Claims 1 to 27 of auxiliary request A filed during the oral proceedings on 25 February 2022.

The Registrar: On behalf of the Chair
(according to Art.8(3) RPBA):

M. Schalow L. Bühler

Decision electronically authenticated