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Datasheet for the decision of 22 February 2022

Case Number: T 1714/17 - 3.3.01

Application Number: 10182249.2

Publication Number: 2322155

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.

Opponents:
Glaxo Group Limited
Akebia Therapeutics, Inc.
Bayer Intellectual Property GmbH/Bayer Pharma Aktiengesellschaft/Bayer Animal Health GmbH

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
Amendments - added subject-matter (yes)

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Case Number: T 1714/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 22 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 2)	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 18 July 2017 revoking European patent No. 2322155 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. 2 322 155 (patent in suit) originates from European patent application No. 10 182 249.2, which is a divisional application of European patent application No. 04 754 383.0 (published as WO 2004/108121 A1).

II. Claim 1 of the patent in suit reads as follows:

> *1. A structural mimetic of 2-oxoglutarate that inhibits hypoxia inducible factor (HIF) prolyl hydroxylase for use in treating anemia in a subject having a percent transferrin saturation of less than 20%.*

III. The following abbreviations will be used below:

HIF - hypoxia inducible factor
TSAT - transferrin saturation

IV. Three notices of opposition were filed opposing the patent in suit under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was insufficiently disclosed, and extended beyond the content of the application as filed.

V. The patent proprietor requested the rejection of the oppositions (main request) and submitted a number of sets of amended claims as auxiliary requests.

VI. The decision under appeal is the opposition division's decision revoking the patent in suit announced on 29 May 2017 and posted on 18 July 2017.

VII. According to the decision under appeal:

(a) the claims as granted (main request) met the requirements of Articles 123(2) and 76(1) EPC

(b) the subject-matter of claim 1 as granted lacked novelty relative to the disclosure of document D6 (WO 03/053997 A2)

(c) claim 1 of auxiliary requests 1 and 7 did not meet the requirements of Article 123(2) EPC

(d) the subject-matter of claim 1 of each of auxiliary requests 2 to 6, 8 and 9 lacked novelty relative to the disclosure of document D6

VIII. The patent proprietor (appellant) filed an appeal against this decision.

IX. With its statement setting out the grounds of appeal, the appellant requested that the oppositions be rejected (main request) and re-filed the claims according to auxiliary requests 1 to 9 considered in the decision under appeal. The appellant also filed auxiliary requests 10 to 15.

X. With a submission dated 5 September 2018, the appellant filed additional sets of amended claims as auxiliary requests 16 to 23.

XI. In the course of the appeal proceedings, opponents 1 and 3 withdrew their oppositions and therefore ceased to be parties to the proceedings. Opponent 2 remained the sole respondent.

XII. Oral proceedings before the board were held on 22 February 2022.

XIII. The respondent argued that claim 1 of the main request and the auxiliary requests did not comply with Article 123(2) EPC.

The application as filed did not disclose the treatment of anemia in general but was restricted, for the most part, to anemia of chronic disease. A patient group having anemia and a TSAT below 20% was not originally disclosed. Structural mimetics of 2-oxoglutarate were not disclosed in connection with HIF prolyl hydroxylase inhibition or with TSAT levels.

XIV. The appellant's counter-arguments may be summarised as follows.

Technical pointers in the examples provided the core basis in the application as filed for the indication of anemia in general (i.e. as a genus) in claim 1 of the main request. Paragraph [0198] in example 1 and paragraph [0202] in example 2 concluded that the methods and compounds of the invention were useful to treat anemia in a subject, with anemia of chronic disease being mentioned as an example only.

According to the application as filed, structural mimetics of 2-oxoglutarate were preferred compounds of the invention. Based on the information provided in paragraphs [0082], [0121], [0122], [0157], [0158] and [0162], the skilled person would moreover recognise the link between HIF prolyl hydroxylase inhibition and 2-oxoglutarate mimetics.

Paragraph [0039] of the application provided a general disclosure of the patient sub-group having a TSAT level of less than 20% as a preferred feature. It was common general knowledge, and the skilled person would therefore be aware, that 20% TSAT was an important,

clinically relevant threshold for the initiation of therapies to increase erythropoiesis.

XV. The appellant (patent proprietor) requested that the decision under appeal be set aside and that the case be remitted to the opposition division for consideration of any remaining issues, in particular sufficiency of disclosure and inventive step, on the basis of:

- the claims as granted

or, in the alternative:

- the claims of one of auxiliary requests 1 to 15, all filed with the statement setting out the grounds of appeal, or one of auxiliary requests 16 to 23, all filed with the appellant's letter of 5 September 2018

The appellant requested that, in the further alternative, the opposition be rejected or the patent be maintained in amended form on the basis of the claims of one of auxiliary requests 1 to 23.

The appellant also requested that documents D161B and D171 to D191 (filed by the opponents with their replies to the appellant's grounds of appeal) not be admitted.

XVI. The respondent (opponent 2) requested that the appeal be dismissed and that:

- documents D161B and D182 to D186 be admitted
- auxiliary requests 10 to 23 not be admitted
- documents D192 to D195 and D197 to D206 (filed by the appellant) not be admitted

Furthermore, the respondent stated that it did not request remittal under Article 111 EPC and objected to the appellant's request for remittal.

Reasons for the Decision

1. Amendments - main request (Article 123(2) EPC)

1.1 The content of the parent application and the divisional application as filed (see point I. above) is identical, except that the divisional application as filed does not have any claims but instead includes 90 numbered "embodiments" corresponding to the 90 claims of the parent application.

1.2 It was not in dispute that this set of numbered embodiments in the application as filed does not provide a basis for the combination of technical features defined in claim 1 as granted. Thus, it had to be established whether the required combination of features was disclosed, directly and unambiguously, elsewhere in the original text.

1.3 The board considers that the application as filed does not provide a basis for a patient group having anemia in general in combination with a TSAT level of less than 20%.

1.3.1 The treatment of a patient group with low TSAT is disclosed in the application as filed in connection with the therapeutic indication of iron deficiency (see paragraphs [0038] and [0039]) and iron deficiency anemia (see paragraph [0040], mentioning a subject having a TSAT value of 10 to 15% or below 10%).

1.3.2 As set out in paragraphs [0003] and [0004] of the application as filed, anemia refers to any abnormality in hemoglobin or erythrocytes that leads to reduced oxygen levels in the blood. While it is mentioned in the description that iron deficiency anemia is the most

common form of anemia (see paragraph [0012]), this is still a specific form of anemia distinct from other forms, and the term does not cover anemia in general.

1.3.3 Paragraph [0039] relied on by the appellant relates to the treatment of iron deficiency rather than anemia. The pertinent passages in this paragraph read as follows:

> *"A subject of the invention could be a subject with any clinically accepted standard measurement of iron deficiency or of a risk of developing iron deficiency. For example, in certain embodiments, the subject has low serum ferritin levels (< 20 ng/ml), or reduced % transferrin saturation, e.g. less than 16% in adults. (...)*
>
> *Iron deficiency can be observed through onset of iron-restricted/iron-deficient erythropoiesis (impairment of hemoglobin synthesis that is observed typically when % transferrin saturation falls below 15 to 20%)."*

1.3.4 The appellant pointed out that the preceding paragraph [0038] disclosed iron deficiency associated with anemia. However, paragraph [0038] mentions various different kinds of iron deficiency:

> *"In further aspects, the iron deficiency is functional iron deficiency; is associated with anemia; is associated with a disorder selected from the group consisting of an inflammation, infection, immunodeficiency disorder, and neoplastic disorder; or is associated with a disorder selected from the group consisting of anemia of chronic disease, iron deficiency anemia (IDA), and microcytic anemia. "*

Even if the iron deficiency to be treated according to paragraph [0039] were iron deficiency associated with

anemia, the treatment of iron deficiency does not necessarily imply the treatment of anemia.

1.3.5 Since neither iron deficiency nor low TSAT levels are synonymous with anemia in general, iron deficiency being mentioned in paragraph [0039] in connection with low TSAT levels (e.g. lower than 16%) does not amount to a disclosure of anemia.

1.3.6 The two statements that:

- iron deficiency can be observed through the onset of iron-restricted/iron-deficient erythropoiesis, and
- iron-restricted/iron-deficient erythropoiesis is an impairment of hemoglobin synthesis observed *"typically"* when the TSAT level falls *"below 15 to 20%"*

establish a general technical background but do not directly and unambiguously disclose 20% as a diagnostic threshold criterion for identifying the patient group to be treated.

1.3.7 The appellant's argument that the person skilled in the art would in any case, in light of common general knowledge, be aware that 20% TSAT was an important, clinically relevant threshold for the initiation of therapies to increase erythropoiesis was based on known usage instructions for the treatment of anemia with commercially available erythropoietin (D16: Procrit® (epoetin alfa) for injection), in particular the following passage on page 4 of D16:

> *"Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% (...)".*

1.3.8 This argument cannot succeed. Document D16 relates to erythropoietin in the treatment of a patient group with a TSAT level of at least 20%, whereas the application as filed in paragraph [0039] discloses treatment with a different drug of a patient group having a TSAT level of less than 16%. It is not apparent how these pieces of information could be combined to make for a direct and unambiguous disclosure in the application as filed of the treatment of subjects with a TSAT value of less than 20%.

1.3.9 The only other passage in which a TSAT level of 20% is mentioned is in paragraph [0054]. This occurs in the context of a method for increasing transferrin saturation in a subject by administering a compound that stabilises HIFα. In one aspect, the TSAT "*is increased above a level selected from the group consisting of 10%, 15%, 20%, 30%, 40% and 50%*".

These options define a target value for TSAT to be reached by the treatment rather than a patient group with a starting value below a specified threshold. None of the options are presented as particularly preferred. Anemia is not mentioned or implied here as the therapeutic indication to be addressed.

1.3.10 The appellant argued that the application as filed also provided a general disclosure of "anemia" as the therapeutic indication which could be combined with all embodiments.

In this context, the appellant referred to paragraphs [0198] and [0202] in examples 1 and 2. The relevant passage in paragraph [0198] reads as follows:

> *"Further, the methods and compounds of the invention are useful to increase EPO production and, therefore, to treat anemia in a subject, for example, when the subject has a disorder associated*

with TNF-α, such as acute or chronic inflammation or other anemia of chronic disease".

The corresponding passage in paragraph [0202] only differs from this by referring to a disorder associated with IL-1β instead of with TNF-α.

1.3.11 The board considers that the cited passages in paragraphs [0198] and [0202] have to be evaluated in context and do not amount to a general disclosure of the treatment of anemia.

The experiments according to examples 1 and 2 were set up to test whether compounds according to the invention could overcome suppressive effects of TNF-α or IL-1β on erythropoietin (EPO) production in Hep3B cells.

Two compounds were tested: compound A ([(1-Chloro-4-hydroxy-isoquinoline-3-carbonyl)-amino]-acetic acid) and compound B ([(4-Hydroxy-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid), as disclosed in paragraph [0083] of the application.

In an additional experiment, Hep3B cells were treated with compound A or B in the absence of TNF-α or IL-1β. Regarding the results of this comparative test, examples 1 and 2 report that Hep3B cells treated with varying concentrations of either compound A or compound B according to the invention, in the absence of TNF-α or IL-1β, showed a dose-dependent increase in EPO production.

The conclusions drawn on the basis of these experiments are introduced, in both paragraphs [0198] and [0202], with the words "These results suggested that..." (see the application as filed, page 60, line 23 and page 61, line 31) in the sentence immediately preceding the one quoted in point 1.3.10 above. The quoted sentence starts with the word "Further, ..." since it presents

a further hypothesis suggested by the experimental results.

In these circumstances, rather than providing a general disclosure of the treatment of anemia, the statement in question is part of the test reports and merely reflects an assumption based on the test results.

Furthermore, it cannot necessarily be concluded that the specific mechanism mentioned (*"useful to increase EPO production"*) equals the treatment of anemia in general.

There is also no reference in the text linking the passage in examples 1 and 2 to the embodiment relating to the treatment of subjects having a low TSAT value.

1.3.12 The appellant also argued that example 20 in the application as filed provided data showing that the compounds of the invention were capable of increasing TSAT in anemic subjects. In this context, the appellant made reference to example 20, in paragraph [0276] (third sentence):

> *"Animals treated with compound A had increased transferrin saturation compared to non-treated non-anemic animals and to non-treated anemic animals. (See Figure 18B.) These results indicated that methods and compounds of the present invention are useful for increasing serum iron levels and percent transferrin saturation."*

1.3.13 This argument does not succeed because it relates to what might be inferred as obvious from the information provided in separate passages of the application rather than to showing a direct and unambiguous disclosure of the required combination of features.

1.3.14 In conclusion, there is no disclosure in the application as filed that establishes a link between a low TSAT level and the treatment of anemia (rather than iron deficiency and without limitation to iron deficiency anemia).

1.4 Furthermore, the application as filed does not specifically disclose a class of compounds defined as structural mimetics of 2-oxoglutarate which inhibit HIF prolyl hydroxylase. It also does not disclose such compounds for use in the treatment of subjects having anemia in general, let alone having anemia and a TSAT level of 20%.

1.4.1 As shown above (see point 1.3.11), the passage in paragraphs [0198] and [0202] of the application relied on by the appellant does not provide a general disclosure of the treatment of anemia. Other parts of the application refer to specific types of anemia only, such as anemia of chronic disease or iron deficiency anemia.

1.4.2 The application as filed refers to several alternative classes of compounds with different descriptions.

According to paragraph [0082], the compounds of the invention are defined as compounds that stabilise HIFα. The stabilisation occurs, for instance, through inhibition of HIF hydroxylase activity, preferably HIF prolyl hydroxylase activity.

Independently of this, paragraph [0082] also states that in various embodiments, a compound of the invention is selected from the group consisting of 2-oxoglutarate mimetics, iron chelators and proline analogues.

According to paragraph [0121], the "term 'prolyl hydroxylase inhibitor' [...] refers to any compound that reduces or otherwise modulates the activity of an enzyme that hydroxylates amino acid residues", and compounds "that can be used in the methods of the invention include, for example, iron chelators, 2-oxoglutarate mimetics, and modified amino acid, e.g. proline, analogs".

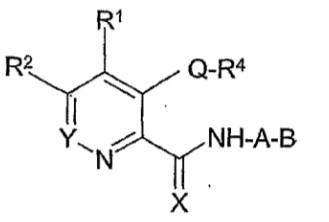
According to paragraph [0122], in particular embodiments, the invention provides for use of structural mimetics of 2-oxoglutarate. The passage goes on to state that PHIs (i.e. prolyl hydroxylase inhibitors) specifically contemplated for use in the methods of the invention are described in various literature references (given in the text).

According to paragraph [0157], in certain embodiments, a compound of the invention is a compound that inhibits HIF hydroxylase activity, preferably HIF prolyl hydroxylase activity.

According to paragraph [0158], "[i]n one aspect, a compound of the invention is any compound that inhibits or otherwise modulates the activity of a 2-oxoglutarate dioxygenase enzyme. 2-oxoglutarate dioxygenase enzymes include, but are not limited to, hydroxylase enzymes".

According to paragraph [0162], in some aspects, compounds of the invention include, for example, structural mimetics of 2-oxoglutarate.

According to paragraph [0163], in certain embodiments, compounds used in the methods of the invention are selected from a compound of the formula (I),



(I)

this being followed by a definition of the residues of the Markush formula (pages 39 to 49 of the application).

1.4.3 It appears from this that the compounds of the invention may be:

- compounds that stabilise HIFα
- compounds that inhibit HIF hydroxylase activity, preferably HIF prolyl hydroxylase activity
- compounds that inhibit or otherwise modulate the activity of a 2-oxoglutarate dioxygenase enzyme
- 2-oxoglutarate mimetics
- structural mimetics of 2-oxoglutarate
- compounds of formula (I)
- iron chelators
- proline analogues

1.4.4 As set out above (see point 1.4.2), these different descriptions of compounds by their structural or functional properties are juxtaposed in the application as filed, but the relationship and potential overlap between these definitions is not fully explained, nor is it self-explanatory in most instances. It is not possible to conclude that the compound classes and functionalities are synonymous or can be freely combined.

1.4.5 In particular, no specific disclosure of a class of compounds defined as structural mimetics of 2-oxoglutarate that inhibit HIF prolyl hydroxylase can

be derived from the language used in any of the cited passages.

1.4.6 This is also the case for the passages in paragraphs [0038] to [0040] and [0054] relating to the treatment of subjects with a low TSAT level. Both paragraphs [0038] and [0054] refer, instead, to a *"compound that stabilises HIFα"*, i.e. a rather general functional description of suitable compounds.

In any case, it cannot be directly and unambiguously derived from the information provided that the "compound that stabilises HIFα" mentioned in paragraphs [0038] and [0054] is, more specifically, a structural mimetic of 2-oxoglutarate that inhibits HIF prolyl hydroxylase (i.e. a compound as defined in granted claim 1), in particular because:

- according to paragraph [0082], compounds that inhibit HIF prolyl hydroxylase are only a subgroup of compounds that stabilise HIFα
- the application does not provide a definition of "structural mimetics of 2-oxoglutarate" and does not explain the relationship between these compounds and HIF prolyl hydroxylase inhibitors

1.5 For these reasons, the subject-matter of claim 1 of the main request extends beyond the content of the application as filed (Article 123(2) EPC).

2. Amendments - auxiliary requests

2.1 Claim 1 in all auxiliary requests relates to a structural mimetic of 2-oxoglutarate that inhibits HIF prolyl hydroxylase and the treatment of anemia in a subject having a TSAT level of less than 20% with additional limitations.

2.2 These further limiting technical features are:

(a) the additional purpose or effect of increasing serum iron (auxiliary requests 1, 7, 10, 13, 16, 17, 20 and 21)

(b) the additional purpose or effect of increasing transferrin saturation (auxiliary requests 11, 12, 14, 15, 18, 19, 22 and 23)

(c) the anemia to be treated is anemia of chronic disease (auxiliary requests 2, 6, 10, 12, 13, 15, 17, 19, 21 and 23)

(d) the structural mimetic of 2-oxoglutarate that inhibits HIF prolyl hydroxylase is a compound of formula (I) or its salt (auxiliary requests 3, 6 to 9, 13 to 15, 20 to 23)

(e) the subject to be treated is an adult with a TSAT value of less than 16% (auxiliary requests 4 and 8)

(f) the subject to be treated has iron-restricted or iron-deficient erythropoiesis (auxiliary requests 5 and 9)

(g) the subject is mammalian (auxiliary request 6)

2.3 These further limitations cannot change the outcome of the assessment of added subject-matter set out in section 1 above. At least one of the objections under Article 123(2) EPC established according to points 1.3 and 1.4 above also applies to claim 1 of each of the auxiliary requests.

2.4 The following observations may be added.

2.4.1 Where the subject is defined as an adult with a TSAT value of less than 16%, this patient group is still not disclosed in the application as filed together with anemia in general or with a structural mimetic of 2-oxoglutarate that inhibits HIF prolyl hydroxylase.

2.4.2 It cannot be inferred from the description "compound that stabilises HIFα" mentioned in the context of paragraphs [0038] and [0054] that the compound must be a compound of formula (I).

2.4.3 The treatment of anemia of chronic disease is not specifically disclosed with a patient group having a TSAT value less than 20%.

2.5 In conclusion, claim 1 in none of the auxiliary requests meets the requirements of Article 123(2) EPC.

3. Admittance of auxiliary requests and evidence

3.1 In view of the outcome in section 2, which is in favour of the respondent, a decision on the admittance of auxiliary requests 10 to 23 is not required.

3.2 Since documents D161B, D171 to D191, D192 to D195 or D197 to D206 were not pertinent to the issues in this decision, a ruling about their admittance is not required.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated