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Datasheet for the decision of 21 October 2021

Case Number: T 1724/19 - 3.3.04

Application Number: 12761825.4

Publication Number: 2694092

IPC: A61K38/18, A61P3/00

Language of the proceedings: EN

Title of invention:
Method of treating or ameliorating metabolic disorders using growth differentiation factor 15 (GDF-15)

Patent Proprietor:
Amgen Inc.

Opponents:
NGM Biopharmaceuticals, Inc.
Merck Sharp & Dohme Corp.

Headword:
GDF-15 and metabolic disorders/AMGEN

Relevant legal provisions:
EPC Art. 54, 56
RPBA 2020 Art. 13(2)

Keyword:
Novelty - (yes)
Inventive step - (no)
Auxiliary request 2 filed during oral proceedings - exceptional circumstances (no)
Filing of new document after summons - exceptional circumstances (yes)

Decisions cited:
T 0431/03, T 2221/10, T 0197/10

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Case Number: T 1724/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 21 October 2021

Appellant: (Patent Proprietor)	Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320-1799 (US)
Representative:	Grünecker Patent- und Rechtsanwälte PartG mbB Leopoldstraße 4 80802 München (DE)
Appellants: (Opponents)	NGM Biopharmaceuticals, Inc. 333 Oyster Point Blvd. S. San Francisco, CA 94080 (US) Merck Sharp & Dohme Corp Whitehouse Station, NJ (US)
Representative:	Jones Day Rechtsanwälte, Attorneys-at-Law, Patentanwälte Prinzregentenstraße 11 80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 6 May 2019 concerning maintenance of the European Patent No. 2694092 in amended form**

Composition of the Board:

Chairwoman	M. Blasi
Members:	O. Lechner
	D. Luis Alves

Summary of Facts and Submissions

I. Both the patent proprietor (appellant I; hereinafter "patent proprietor") and the joint opponents (appellants II; hereinafter "opponents") filed an appeal against the decision of the opposition division that European patent No. 2 694 092 having the title "*Method of treating or ameliorating metabolic disorders using growth differentiation factor 15 (GDF-15)*" in the version of auxiliary request 1, and the invention to which it related, met the requirements of the EPC.

II. The patent is based on European patent application No. 12 761 825.4, which was filed as an international application published as WO 2012/138919.

III. The opponents had requested the revocation of the patent, invoking lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) under Article 100(a) EPC, as well as raising further objections under Article 100(b) and (c) EPC as grounds for opposition.

IV. The decision under appeal dealt with an amended main request and one auxiliary request. The opposition division decided that the main request complied with the requirements of Article 123(2) EPC but failed to comply with the requirements of Article 83 EPC, and auxiliary request 1 was held to comply with the requirements of the EPC. Documents D31, D34 and D35 were admitted into the opposition proceedings by the opposition division, while document D32 was not.

V. With the statement of grounds of appeal the opponents provided arguments concerning the admission of

documents D32 and D33, and raised objections concerning an extension of protection (Article 123(3) EPC), sufficiency of disclosure (Article 83 EPC), clarity (Article 84 EPC), novelty (Article 54 EPC) and inventive step (Article 56 EPC).

VI. With the statement of grounds of appeal the patent proprietor resubmitted the main request and auxiliary request 1 as dealt with in the decision under appeal, and explained why, in its view, the main request met the requirements of Article 83 EPC.

VII. By letter dated 30 January 2020, the patent proprietor replied to the objections raised in the opponents' statement of grounds of appeal.

VIII. By letter dated 14 February 2020, the opponents replied to the patent proprietor's statement of grounds of appeal.

IX. The board issued a summons for oral proceedings to be held in view of corresponding requests of the parties.

X. By letter dated 23 November 2020, the opponents provided arguments relating to novelty, inventive step and Article 123(2) and (3) EPC.

XI. The board issued a communication providing the board's preliminary assessment of relevant issues pursuant to Article 15(1) RPBA 2020.

XII. By letter dated 27 August 2021 the opponents made further submissions, *inter alia*, on claim construction.

XIII. By letter dated 20 September 2021, the patent proprietor filed the set of claims of auxiliary request 2 and document A50.

XIV. By letter dated 8 October 2021, the opponents argued against the admittance of auxiliary request 2 and document A50 under Article 13(2) RPBA 2020 and raised objections under Article 84, as well as Article 123(2) and (3) EPC against this request.

XV. Oral proceedings took place as scheduled in the presence of both parties.

During the oral proceedings, the patent proprietor replaced auxiliary request 2 with a new auxiliary request 2.

Claim 1 of the main request reads as follows:

"1. A human GDF15 polypeptide for use in the treatment of a metabolic disorder,
a) wherein the metabolic disorder is type 2 diabetes,
b) wherein the metabolic disorder is dyslipidemia,
c) wherein the metabolic disorder is diabetic nephropathy, or
d) wherein the metabolic disorder comprises a condition in which a subject has a fasting blood glucose level of greater than or equal to 100 mg/dL."

Claim 1 of auxiliary request 1 reads as follows (amendments with regard to the main request underlined by the board):

"1. A human GDF15 polypeptide for use in the treatment of a metabolic disorder,
a) wherein the metabolic disorder is type 2 diabetes,

b) wherein the metabolic disorder is dyslipidemia,
c) wherein the metabolic disorder is diabetic nephropathy, or
d) wherein the metabolic disorder comprises a condition in which a subject has a fasting blood glucose level of greater than or equal to 100 mg/dL,
wherein the human GDF15 polypeptide comprises an amino acid sequence that is at least 85 percent identical to a GDF15 polypeptide of any of SEQ ID NOs: 2, 6 or 10."

Claim 1 of auxiliary request 2 reads as follows (amendments with regard to the main request underlined and crossed out by the board):

"1. A human GDF15 polypeptide for use in the treatment of a metabolic disorder,
a) wherein the metabolic disorder is type 2 diabetes,
~~b) wherein the metabolic disorder is dyslipidemia,~~
be) wherein the metabolic disorder is diabetic nephropathy.
~~d) wherein the metabolic disorder comprises a condition in which a subject has a fasting blood glucose level of greater than or equal to 100 mg/dL,"~~

XVI. At the end of the oral proceedings, the Chair announced the board's decision.

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

D1 : Johnen H. *et al.*, Tumor-induced anorexia and weight loss are mediated by the TGF-beta superfamily cytokine MIC-1, Nat Med (2007), 13(11):1333-1340

D11: Golay A., Link between obesity and type 2 diabetes, Best Practice & Research Clinical Endocrinology & Metabolism (2005), 19(4): 649-663

D20: Web extract from www.diabetesselfmanagement.com/diabetes-resources/definitions/prediabetes/[20/09/2017]

D21: Web extract from www.who.int/mediacentre/news/releases/2004/pr81/en/[20/09/2017]

D22: Hossain P. *et al.*; N Engl J Med (2007), 356(3): 213-215

D27: Diabetes mellitus type 2 - Wikipedia, https://en.wikipedia.org/wiki/Diabetes_mellitus type_2, 19.03.2018

D31: WO 2005/099746 Al

D34: Position Statement: Standards of Medical Care in Diabetes-2011, American Diabetes Association, Diabetes Care (2011), 34(Suppl 1): S11-S61

D35: Principles and Practice of Endocrinology and Metabolism, 2nd edition (1995), Editor: K.L. Becker, Part IX: Disorders of fuel metabolism, Chapter 125: Obesity, pages 1155-1164; Chapter 137: Diet and exercise in diabetes, pages 1231-1235; and Chapter 144: Diabetic nephropathy, pages 1283-1297

A47: Declaration Prof. Samuel Breit, 16 November 2018

A48: Decision of the opposition division for application EP 05 729 508.1, patent number EP B 1 734 986, 27 February 2018

A50: Hayes V.M. *et al.*, Macrophage Inhibitory Cytokine-1 H6D Polymorphism, Prostate Cancer Risk, and Survival, Cancer Epidemiology Biomarkers Prev (2006); 15(6):1223-1225

XVIII. The patent proprietor's submissions relevant to the present decision can be summarised as follows:

Admittance of document A50 - Article 13(2) RPBA 2020

Document A50 should be admitted into the proceedings. It had been filed in response to the board's preliminary opinion on how the term "human GDF15" had to be construed. The document illustrated that it was clear from scientific literature that variants of (human) GDF15 were also referred to as "(human) GDF15".

Main request

Claim construction

"Human GDF15" in claim 1 included variants, mutants and fragments as defined in the description.
It was not common practice to assume that the designation "human GDF15" was limited exclusively to the full-length human protein. All of the definitions provided in the description in paragraphs [0008], [0023] to [0028], or [0038] could not be ignored when construing the claims and were perfectly consistent with the typical understanding in the art (see Case Law of the Boards of Appeal, 9th edition 2019 ("CLBA"), II.A.6.1 and 6.3.1).

As evidenced by documents D31, A48 and A50, the term "human GDF15" not only denoted full-length wild-type

sequences but also "typical variants, mutants, fragments, etc.".

The clarity of "human" in claim 1 could not be the subject of appeal.
According to the opponents' own interpretation of "human GDF15" in the notice of opposition, the term was not restricted to one specific protein only. This was also evident from the wording of claims 1 and 4, which related to a "human GDF15 polypeptide" (see CLBA, II.A.6.3.3 and decision T 1018/02).

Novelty - Article 54 EPC

Neither document D1 or D31 nor any other of the prior-art documents cited by the opponents provided a clear and unambiguous disclosure of the embodiment of claim 1(d). Obese patients did not automatically have an increased fasting blood glucose level within the specified range and - *vice versa* - patients with an increased fasting blood glucose level did not necessarily suffer from obesity.
The ob/ob mouse model in document D1 was only used for obesity, not for diabetes or prediabetes. Consequently, the subject-matter of claim 1 was anticipated neither by the teaching in document D1 nor by the teaching in document D31.

Inventive step - Article 56 EPC

Document D1 represented the closest prior art.

Claim 1 differed from the disclosure of document D1 in that it was directed to the use of GDF15 for treating a) type 2 diabetes, b) dyslipidaemia, c) diabetic nephropathy and d) metabolic disorders which comprise a

condition in which a subject has a fasting blood glucose level of greater than or equal to 100 mg/dL. The objective technical problem was to find another beneficial therapeutic use of GDF15/MIC-1.

Example 5 and Figure 4B of the patent depicted the results of an experiment in which reasonable amounts of GDF15 had been administered to the hyperglycemic ob/ob mice. The results showed that murine GDF15 improved hyperglycemia independently of changes in food intake and body weight. Example 6 as well as Figures 5A and 5D showed that the efficacy of murine GDF15 was more robust in a high-fat diet-induced obesity (DIO) model than in normal chow-fed animals.

The tests in the xenograft tumour model of document D1 were neither designed nor intended for the study of metabolic disorders now claimed. The data in document D1 (see Figures 3 and 4 and supplementary Table 1 as well as the sentence bridging pages 1334 and 1335) suffered from two experimental deficiencies that made them unsuitable for comparison with the data in the patent. Firstly, GDF15 expression was analysed in cancer patients with anorexia who were at the terminal stage, at which the body had no normal metabolism anymore. Secondly, Figure 1a of document D1 showed that a weight-reducing effect of GDF15 could only be observed for serum GDF15 levels of >8500 pg/ml. Thus, very high concentrations of GDF15 were necessary to induce weight loss and these high concentrations were not used in any medication. The effects observed in document D1 could only be attributed to a reduced food intake, as evidenced by the pair-fed data (see page 1334, right-hand column, last paragraph, and supplementary Figures 3 and 4). In addition, the data in supplementary Table 1 were based on animals at the

terminal disease stage having already lost 18% of their body weight and had not been collected in a proper diabetes model. They were thus meaningless for non-tumour mice.
D1 mentioned the treatment of obesity (see, e.g., abstract and discussion) but did not mention diabetes once. In the absence of any link between GDF15 and the conditions of the present claims, there was no motivation to use GDF15 in the treatment of the metabolic disorders currently claimed.

Examples 15 to 17 and Figure 14 in the patent disclosed the usefulness of GDF15 as an active agent in the treatment of diabetic dyslipidaemia. An appropriate animal model for dyslipidaemia, however, was not derivable from document D1 and nor did the findings on the tumour model allow for any conclusions with regard to dyslipidaemia.

The conditions of the patent were entirely different from those of document D1: the patent used an obese mouse model, the mice were not starved and the patent showed that the effect of GDF15 on glucose was 3 to 4 times higher than that observed when food intake was reduced.
To arrive at the claimed subject-matter starting from document D1 required hindsight.

The behaviour of GDF15 was unpredictable in any disease. Faced with the problem of finding another beneficial therapeutic use of GDF15/MIC-1, the skilled person could have investigated in many different directions. There was no pointer and no motivation to investigate in the direction of diabetes or any of the other claimed conditions. The experiments performed in document D1 on brain neuronal tissue (see Figure 4)

motivated the skilled person to investigate whether GDF15 had different effects compared to leptin.

Documents D34 and D35, which reflected the common general knowledge, mentioned weight loss and discussed diabetes type 2 as well as dyslipidaemia. However, these documents also explained that not all obese patients were diabetic and nor were all diabetic patients suffering from obesity (see document D35, page 1161, column 1 in D35). A similar disclosure could be found for dyslipidaemia in document D34, according to which weight loss was useful (for some of the patients) if indicated (see D34, page S29, middle column 2), i.e. there were also patients suffering from dyslipidaemia who were not obese, and *vice versa*.

The real teaching of document D34 and D35 was that obesity had follow-up complications and that obese patients might be treated by a diet or should lose weight in order to avoid risks or complications (which might be diabetes, dyslipidaemia, etc.). However, such diet/weight-loss treatment constituted a treatment for obesity and its complications rather than the treatment of patients suffering from type 2 diabetes, dyslipidaemia or hyper-glucose levels as cited in claim 1.
For the skilled person seeking to establish a medication against type 2 diabetes, dyslipidaemia or high blood glucose levels, the medicament needed to be effective in reducing the primary parameters of these diseases (glucose, triglycerides, etc., - see patent proprietor's letter of 30 January 2020, page 20, penultimate paragraph) rather than contributing to an indirect potential improvement of the pre-conditions of obese patients (such as by the induction of weight loss).

Auxiliary request 1

Inventive step - Article 56 EPC

The inventive-step arguments put forward in the context of the main request also applied to auxiliary request 1.

Auxiliary request 2

Admittance - Article 13(2) RPBA 2020

Auxiliary request 2 should be admitted into the appeal proceedings. The set of claims of this request was filed during the oral proceedings as a reaction to the board's unanticipated negative finding on inventive step concerning the treatment of b) dyslipidaemia and d) metabolic disorders comprising a condition in which a subject has a fasting blood glucose level of greater than or equal to 100 mg/dL.

XIX. The opponents' submissions relevant to the present decision can be summarised as follows:

Admittance of document A50 - Article 13(2) RPBA 2020

Document A50 should not be admitted into the proceedings. It was late-filed under Article 13(2) RPBA 2020 and was not relevant for the discussion on claim construction.

Main request

Claim construction

Claim 1 related only to native human GDF15. Given a very high degree of homology with other species, "human GDF15" could only be understood as native human GDF15. Under Article 84 EPC, the claims defined the protection sought and it was settled case law that an interpretation pursuant to Article 69 EPC was reserved for national courts. The following decisions were cited: T 1279/04, T 2017/07, T 1208/97, T 881/01, T 197/10, T 2563/11 as well as T 1018/02.
However, since national courts were instructed by law to construe the claims in the light of the description, there was an "*imminent danger*" that the claims would be construed differently, i.e. much more broadly, by those courts. Legal certainty had to be established by securing the correct interpretation through the introduction into the claims of amino acid sequences of human GDF15 disclosed in the application. Claim 4 was in line with the skilled person's understanding of claim 1.

Novelty - Article 54 EPC

Claim 1(d) recited a metabolic disorder comprising "a condition in which a subject has a fasting blood glucose level of greater than or equal to 100 mg/dL". This could be any metabolic disorder where the indicated fasting blood glucose level was reached at a specific time. Therefore, part (d) of claim 1 did not refer only to prediabetes, as assumed by the opposition division, but to other disorders too, e.g. those comprising prediabetes as a comorbidity. Clearly, the subject having a metabolic disorder could be obese,

since it was well-known that obesity was associated with diabetes or prediabetes, i.e. having the indicated blood glucose levels, as also evidenced by documents D11, D20 to D22, D27 or D34. Claim 1(d) did not meet the requirements of novelty in view of a disclosure of the treatment of obesity with GDF15.

Document D1 stated that Mic-1 (= GDF15) can be used for treating obesity (see Abstract and last sentence of Discussion section) and disclosed the treatment of an obese mouse (ob/ob model) - which was also a model for diabetes and thus related to an elevated blood glucose parameter according to claim 1(d) - using recombinant GDF15 to induce weight loss (see D1, page 1334, right-hand column). Accordingly, the subject-matter of claim 1(d) lacked novelty over D1.

Document D31 related to the administration of GDF15 as a pharmaceutical composition for use in the modulation (including decreasing) of appetite and body weight (see page 1, "Field of the Invention"; page 2, lines 27 to 30; and page 8, lines 12 to 13). Claims 9 and 12 of document D31 disclosed the use of GDF15 for decreasing appetite and/or body weight in obese subjects. Accordingly, the subject-matter of claim 1(d) also lacked novelty over document D31.

Inventive step - Article 56 EPC

Closest prior-art document D1 identified GDF15 as a central regulator of metabolism using different animal models, including GDF15-expressing tumour cells-xenografted mice, ob/ob mice or normal Balb/c mice. GDF15 administration resulted in a reduced food intake and influenced, as evidenced in supplementary Table 1, different biochemical parameters such as glucose,

glucagon, triglycerides etc., the body fat composition and especially total white fat (see Figure 1e). It was known that white fat was responsible for metabolite derangement and linked to diabetes. This effect of GDF15 was independent of the mouse model analysed. The observation of weight loss in the xenograft model was confirmed in normal (Balb/c) mice, and obese and diabetic ob/ob mice, all of which had been administered subcutaneously human GDF15, as well as in transgenic mice that overexpressed GDF15 from their birth onwards. The effects in mice were in line with observations in humans.

The reported changes in free fatty acids, triglycerides, etc. (see paragraph bridging pages 1334 and 1335) were also consistent with the observed loss of lean and fat mass by these mice. The observed effects in the xenotransplant-mouse model were due to the GDF15 expression, given that mice with control tumours continued to gain weight (see page 1333, right-hand column, last full sentence). Further evidence that the observed effects were due to GDF15 was that specific anti-GDF15 antibodies were able to reverse these effects.

The objective technical problem resided in the provision of further therapeutic uses for GDF15.

Based on the observed reduction in glucagon and glucose levels and the concomitant increase in insulin levels, the skilled person had been motivated to use GDF15 in the treatment of diabetes, metabolic disorders comprising increased fasting blood glucose, and conditions resulting therefrom such as nephropathy. Based on the observed effects on blood fat content, the skilled person would have treated conditions

characterised by an increase in blood fat content such as dyslipidaemia. Actually, there was not merely a motivation but, rather, a one-way-street situation resulting also in a reasonable expectation of success, and the skilled person had no other choice.

The patent proprietor's allegation that the tested xenografted mice were at a terminal stage was unproven. Since the claims failed to mention a specific GDF15 dose, the high-GDF15 dose argument also fell short. The data in the patent, which were actually obtained using the same animal models, merely confirmed the observations made in document D1. The data reported in Example 5 and Figure 4 of the patent, i.e. a weight-loss-independent effect on glucose levels, did not change anything and did not open up any new therapeutic application. In any case, there were no equivalent experimental results in the patent concerning other blood parameters such as fat. Moreover, it was known and also reported in document D1 that there were fluctuations in pair-feeding studies. It was established case law that the provision of an additional effect, even if surprising, could not render obvious subject-matter inventive (see T 1028/05, Reasons 2.3.5., and T 1031/00).

Contrary to the patent proprietor's statements, the skilled person knew, as evidenced, e.g., by documents D11, D20, and D22, that obesity and type 2 diabetes or prediabetes were closely related, i.e. having blood glucose values in excess of 100 mg/dl. As evidenced by documents D11, D34 and D35, it was also common general knowledge that most patients with NIDDM are overweight (see documents D11 or D35, page 1161, column 1), that weight loss is an established treatment for type 2 diabetes (i.e. feature a) of claim 1) and associated

disorders such as diabetic nephropathy (i.e. feature c) of claim 1) and fasting blood glucose level of greater than or equal to 100 mg/dl (i.e. feature d) of claim 1) and for the treatment of dyslipidaemia (i.e. feature b) of claim 1).

Thus, in view of the disclosure of the closest prior art document D1 and the common general knowledge of the person skilled in the art, represented, e.g., by documents D11, D20, D22, D34 and D35, the subject-matter of claim 1a) to d) did not involve an inventive step.

Auxiliary request 1

Inventive step - Article 56 EPC

The subject-matter of claims of auxiliary request 1 lacked an inventive step for the same reasons as provided for the claims of the main request.

Auxiliary request 2

Admittance - Article 13(2) RPBA 2020

Auxiliary request 2 should not be admitted into the appeal proceedings. No cogent reasons had been presented for the timing of filing (Article 13(2) RPBA 2020). Inventive step of each of the claimed conditions a) to d) had already been addressed from the very beginning, in the notice of opposition, in points 6., 6.4.1. and 6.4.2. of the statement of grounds of appeal as well as in the letter of 23 November 2020. The patent proprietor could not argue to have been taken by surprise. It was the patent

proprietor's deliberate decision not to file an appropriate auxiliary request.

XX. The requests of the parties were as follows:

The patent proprietor requested:

- that the patent be maintained in amended form on the basis of the main request in the version of 17 January 2019, i.e. the patent as granted with deletions in paragraphs [0025] and [0027] of the description; or,
- alternatively, on the basis of auxiliary request 1 as considered allowable by the opposition division, implying that the opponents' appeal be dismissed; or,
- further alternatively, on the basis of the set of claims of auxiliary request 2 filed at the oral proceedings before the board.

The opponents requested that the decision under appeal be set aside and the patent be revoked in its entirety.

Reasons for the Decision

1. The appeals are admissible.

Admittance of document A50 - Article 13(2) RPBA 2020

2. The patent proprietor filed document A50 with its letter of 20 September 2021 to support the argument that human GDF-15/MIC-1 encompassed the "typical variants, mutants, fragments etc.". Document A50 allegedly showed "*that a skilled person also refers to*

a polymorphism/mutant (H6D variant) as 'MIC-1' (now GDF-15)" and that "[t]*hese terms denote not only full-length wild-type sequences but also the typical variants thereof.*"

The board considers the filing of newly cited document A50 to be an amendment of the patent proprietor's appeal case within the meaning of Article 13(2) RPBA 2020, thus giving the board discretion as to its admission. The document was submitted in written proceedings in response to the board's claim construction, which differed from that proposed by the parties and that adopted by the opposition division in the decision under appeal (set out in points 12 to 14 of the communication under Article 15(1) RPBA 2020).

Document A50 discloses naturally occurring polymorphic variants of human GDF15 and was filed by the patent proprietor in support of its arguments concerning how the person skilled in the art would construe the term "(a) human GDF15 (polypeptide)" of claim 1. The patent proprietor's position as to how this term was to be understood was already derivable from the statement of grounds of appeal (see point 2 thereof) and the filing of document A50, and the related submission served as further support of this understanding.

Consequently, document A50 and the related submissions in the letter of 20 September 2021 did not raise new issues and nor did they add any further complexity to the case. Considering that document A50 and the related submissions had been presented about one month before the oral proceedings and, in the absence of any indication to the contrary, the board considered that the opponents had sufficient time to prepare for this

further detail. In view of the above considerations, the board decided to admit document A50 - and the associated submissions - into the appeal proceedings in accordance with Article 13(2) RPBA 2020.

Main request

Claim construction

3. Claim 1 of the main request reads:

"1. A human GDF15 polypeptide for use in the treatment of a metabolic disorder, [...]."

The claim is identical to claim 1 as granted.

The claim is drafted in the format pursuant to Article 54(5) EPC and is therefore a purpose-limited product claim. It concerns the second medical use of a compound for the treatment of metabolic disorders as further specified in the claim as alternatives a), b), c) or d).

4. The terms "human GDF15" and "a human GDF15 polypeptide" clearly and unambiguously refer to clearly-characterised, naturally occurring protein. This is also supported by the explanations in the "Background of the Invention" section in the patent in suit, which reflects the skilled person's knowledge at the filing date. In view of the clear meaning of the term in the background art, it is not necessary for the skilled person to consult the description on how "[a] human GDF15 (polypeptide)" is to be interpreted.

5. With reference to paragraphs [0008], [0023] to [0028] and [0038] of the patent as well as, e.g., the

definition contained in document D31, both the patent proprietor and the opponents argued that the term "human GDF-15/MIC-1" encompassed the "typical variants, mutants, fragments etc.".

However, according to general principles of established case law the description cannot be used to interpret a term of a claim in a different way if this term as used in the claim has a clear technical meaning. In the case of a discrepancy between the claim and the description, the unambiguous claim wording must be interpreted as it would be understood by the person skilled in the art without the help of the description (see Case Law of the Boards of Appeal 9th edition 2019, "CLBA", II.A.6.3.1, especially decisions T 431/03, Reasons 2.2.2, T 2221/10, Reasons 33, and T 197/10, Reasons 2.3). The argument that the claims had to be read in the context of the specific definitions provided in the description of a patent document thus fails.

6. Accordingly, the board construes claim 1 as being directed to the use of a naturally occurring "human GDF15 (polypeptide)" expressed in humans (see paragraph [0023] of the patent) for the indicated therapeutic uses. The term includes naturally occurring polymorphic forms of this protein as found in the human population (see, e.g., document A50). However, "human GDF15 (polypeptide)" cannot be interpreted, as suggested by the patent proprietor, to also encompass, for instance, variants with (unlimited) modifications in the polypeptide's amino acid sequence or GDF15 proteins from non-human species, as suggested in paragraphs [0023] or [0025] of the patent.

7. Interpretations provided by an opposition division in the context of the proceedings relating to document D31, e.g. proceedings involving European patent 1 734 986 (document A48 in the present proceedings), are not considered to be of relevance for the present case as the board has to take its own decision.

Novelty

8. According to established case law of the boards of appeal, a prior-art document anticipates the novelty of claimed subject-matter if the latter is directly and unambiguously derivable from that document, including any features that are implicit for a person skilled in the art. However, an alleged disclosure can only be considered implicit if it is immediately apparent to the skilled person that nothing other than the alleged implicit feature forms part of the subject-matter disclosed (see also CLBA I.C.4.3.).

9. The board concurs with the patent proprietor in its argument that neither document D1 or D31 nor any of documents D11, D20 to D22, D27 or D34 provides a direct and unambiguous disclosure, be it explicit or implicit, that obese patients are characterised by having a fasting blood glucose level of greater than or equal to 100 mg/dL. Consequently, the teaching of documents D1 and D31 cannot anticipate the subject-matter of claim 1(d) and the claimed subject-matter is novel within the meaning of Article 54 EPC.

Inventive step - Article 56 EPC

Closest prior art

10. Document D1 was taken to represent the closest prior art.

11. D1 reports that MIC-1/GDF15 is a newly defined central regulator of appetite and weight and is a potential target for the treatment of both cancer related anorexia and weight loss, as well as obesity (see abstract and discussion). The experiments were carried out on a) Balb/c nude mice xenografted with GFD15-expressing tumour cells (see page 1339, left-hand column, last paragraph), b) "*massively obese ob/ob mice*" (see page 1334, left-hand column paragraph 2), c) normal Balb/c mice (see page 1334, right-hand column, line 13) and d) C57/BL6 transgenic mice that overexpress GDF15 (see page 1336, right-hand column, last paragraph).

Figure 1a reports that GDF15 serum concentrations of >8500 pg/ml led to a reduction in weight gain; Figures 1b and 1c show that the weight-lowering effect of GDF15 can be reversed by inhibition with anti-GDF15 antibodies in a dose-dependent manner.

Figure 1d and 1f show that GDF15 leads to a reduction in food intake and also in lean as well as fat mass. These effects were reversible by neutralisation with anti-GDF15 antibodies (see Figures 1g and 1h).

Figure 1e discloses the GDF15-mediated reduction in total white fat. GDF15-induced weight loss in xenografted mice is described as being due to a reduced food intake and as leading to a substantial reduction

in serum concentrations of free fatty acids, triglycerides, glucose, glucagon, leptin and insulin-like growth factor-1 (see paragraph bridging pages 1334 and 1335; supplementary Table 1), which is described as being consistent with the reduction of lean and fat mass.

Difference, its technical effect and objective technical problem

12. Claim 1 differs from the disclosure of the closest prior art in that it claims the use of GDF15 for treating a) type 2 diabetes, b) dyslipidaemia, c) diabetic nephropathy and d) metabolic disorders comprising a condition in which a subject has a fasting blood glucose level of greater than or equal to 100 mg/dL.

13. The patent does not directly show treatment of one of these conditions. However, Example 4 discloses that GDF15 reduces food intake, body-weight gain, blood insulin, glucose and lipid levels in obese and diabetic ob/ob mice (see also Figure 3). Example 5 shows that GDF15 improves hyperglycaemia in ob/ob mice independently of reduction in food intake and without body-weight gain (see also Figure 4).

Examples 6 to 8 and 11 report similar results as well as reduction in fat mass in a diet-induced obesity (DIO) mouse model (reported to be a rodent model for examining efficacy of diabetic therapies). Examples 9 to 10 report that GDF15 prevents worsening of insulin sensitivity and glucose tolerance in KK-Ay mice (obese-diabetic rodent model). Improvements in glucosuria and proteinuria are also observed in these mice.

14. The board concurs with the opposition division (point 4.5 of the reasons) and the parties that, starting from the teaching of document Dl as the closest prior art, the objective technical problem to be solved can be defined as the provision of particular further therapeutic uses for GDF15.

Obviousness

15. The board agrees with the patent proprietor that, faced with the problem of identifying potential further therapeutic uses for GDF15, the person skilled in the art would first of all have looked for effects of this protein on primary parameters characterising a given disease and only in a second step for indirect potential improvements.

16. Following this approach and considering the results provided in supplementary Table 1 of document D1, which show a GDF15-dependent reduction in free fatty acids and triglycerides, the person skilled in the art would have used GDF15 for treating conditions characterised by elevated levels of these parameters.

Document D34 (see page S22, right-hand column, page S29, middle column; page S30, left-hand column) recommends for the treatment of dyslipidaemia e.g. lifestyle modifications including weight loss and increased physical activity to improve the lipid profiles in patients with diabetes.

Document D35 (see page 1161, left-hand and right-hand columns, page 1163, "*CONCLUSION*", page 1232, left-hand column, second full paragraph) reports that weight gain may precede and precipitate NIDDM (i.e. diabetes type 2), may coincide with its development, or may aggravate

existing diabetes. Weight loss in most obese diabetic patients improves the metabolic aspects of the diabetic state. With attainment and maintenance of normal or near-normal body weight, all metabolic functions may be restored to normal, and all evidence of NIDDM may disappear. Even modest degrees of weight loss, e.g. as little as a 10% reduction in weight, appear to improve glycemic control and to reduce blood pressure and plasma triglycerides. Weight reduction is also reported to restore plasma triglycerides to normal or near-normal levels.

Thus, the person skilled in the art would have arrived at dyslipidaemia (claim 1b)).

17. Elevated glucose and glucagon levels were known to be key parameters in (type 2) diabetes (see, e.g., document D27, "Pathophysiology" and "Diagnosis" or D34, Table 2 on page S13). Based on the statistically significant decreased glucose and glucagon levels observed in mice xenotransplanted with GDF15-expressing tumours (see document D1 supplementary Table 1 and page 1335, left-hand column, paragraph 1), the person skilled in the art would have been prompted to use GDF15 in the treatment of type 2 diabetes (claim 1a)) and other metabolic disorders comprising a condition in which a subject has a fasting blood glucose level of greater than or equal to 100 mg/dL (claim 1d)).

18. The opposition division held in its decision (see point 4.5) that the effects reported in document D1 reflected the metabolic disturbance associated with tumour-associated anorexia. Such negative effects did not provide for a reasonable expectation that GDF15 would have beneficial effects in the defined metabolic disorders.

19. The board does not agree with the opposition division. Indeed, the data provided in supplementary Table 1 compare different metabolic parameters in animals xenografted either with MIC-1 (GDF15) expressing tumour cells ("MIC-1 tumour") or xenografted with the same tumour cells which do not express GDF15 (i.e. "control tumour"). Thus, the observed statistically significant decrease in free fatty acids, triglycerides, glucose and IGF-1 can be attributed to the action of GDF15.

Moreover, the weight loss and/or reduction in body fat mass observed in the GDF15-expressing tumour-cells xenografted mice could also be observed in i) transgenic mice overexpressing GDF15 (see page 1136, paragraph bridging the two columns and Figure 3), last paragraph) and ii) massively obese ob/ob mice (see supplementary Figure 3) and iii) normal Balb/c mice (see supplementary Figures 2 and 4). The reversibility of these GDF15-effects by anti-GDF15 antibodies was also shown for Balb/c mice (see Figures 1g and 1h).

Thus, the skilled person had a reasonable expectation that the changes in the biochemical parameters listed in supplementary Table 1 would also translate to other non-tumour mice with increased GDF15 levels.

20. The observed reduction in total (white) fat mass can be considered as a further pointer to use GDF15 in the treatment of type 2 diabetes (claim 1a), dyslipidaemia (claim 1b) and conditions characterised by elevated blood glucose concentrations as defined in claim 1d. As pointed out by the opponents, it was common general knowledge that weight loss is an established treatment for type 2 diabetes and associated disorders and for dyslipidaemia (see D34, page S22, right-hand column,

page S29, middle column; page S30, left-hand column; D35, page 1161, left and right-hand columns, page 1163, "*CONCLUSION*", page 1232, left-hand column, second full paragraph).

21. The fact that not all obese patients are diabetic and nor are all diabetic patients suffering from obesity as well as similar disclosures regarding dyslipidaemia are of no relevance since the claimed therapeutic use is not limited to the sub-population of non-obese patients. It was known that the majority of patients with type 2 diabetes are overweight (see document D11, page 650, paragraph 2; document D22, page 213, right-hand column, penultimate paragraph; document D35, page 1161, left-hand column, paragraph 1).

22. In view of the above considerations, the board concludes that the subject-matter of claim 1 does not involve an inventive step within the meaning of Article 56 EPC.

Auxiliary request 1

Inventive step - Article 56 EPC

23. The subject-matter of claim 1 of auxiliary request 1 differs from claim 1 of the main request only by the addition of the definition "wherein the human GDF15 polypeptide comprises an amino acid sequence that is at least 85 percent identical to a GDF15 polypeptide of any of SEQ ID NOs:2, 6 or 10". This amendment has no effect on the board's considerations as set out in connection with inventive step for the main request, which thus also apply in full to claim 1 of auxiliary request 1. The board therefore concludes that the subject-matter of claim 1 of auxiliary request 1 also

does not involve an inventive step within the meaning of Article 56 EPC, for the same reasons as provided for the main request (see points 15. to 22. above).

Auxiliary request 2

Admittance - Article 13(2) RPBA 2020

24. The set of claims of auxiliary request 2 differs from the set of claims of the main request in that in claim 1 the conditions to be treated have been limited to type 2 diabetes and diabetic nephropathy.

25. The submission of this set of claims at the oral proceedings before the board represented an amendment to the patent proprietor's case, the admission of which into the appeal proceedings was at the board's discretion pursuant to Article 13(2) RPBA 2020.

26. The patent proprietor justified the late filing by arguing that the negative finding of the board on inventive step of the subject-matter of the main request had come as a surprise.

The board agrees with the opponents that inventive-step objections under Article 56 EPC had been raised in the appeal proceedings against all of the individual conditions a) to d) of claim 1 of the main request from the outset - see the opponents' statement of grounds of appeal, in particular points 6, 6.4.1 and 6.4.2. While the opponents grouped the four alternatives in their argumentation ("*treatment of type 2 diabetes and associated disorders on the one hand (i.e. diabetic nephropathy and part (d)) and dyslipidemia on the other*", see point 6.4.1), the opponents' submissions leave no doubt that all of the four alternatives were

objected to for lack of inventive step, albeit based in part on similar lines of argumentation.

In the board's communication issued under Article 15(1) RPBA 2020 dated 18 December 2020, the board had indicated that the matter of whether the treatment of the conditions according to claim 1 was obvious would be addressed during the oral proceedings.

It was, therefore, a possible scenario that one or several alternatives could be found not to involve an inventive step at the oral proceedings. The patent proprietor's justification that it had been taken by surprise at the oral proceedings was therefore not convincing. No exceptional circumstances were presented and nor was it apparent to the board why this claim request, presented at the latest possible stage of the appeal proceedings, should be admitted.

Thus, the board decided not to admit auxiliary request 2 into the proceedings pursuant to Article 13(2) RPBA 2020.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

I. Aperribay M. Blasi

Decision electronically authenticated