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Datasheet for the decision
of 9 January 2014

Case Number: T 1492/09 - 3.3.04
Application Number: 00915762.9
Publication Number: 1165110
IPC: A61K38/00, C07K1/00, C07H21/04, C12P21/06, G01N33/566
Language of the proceedings: EN

Title of invention:
Antagonists of HMGI for treating inflammatory conditions

Patent Proprietor:
The Feinstein Institute for Medical Research

Opponent:
Alcedo Biotech GmbH

Headword:
Antagonists of HMGI for treating inflammatory conditions/
FEINSTEIN

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 104(1), 123(2), 123(3)
RPBA Art. 16

Keyword:
Main request - requirements of the EPC met (yes)
Apportionment of costs - (no)

Decisions cited:
G 0002/03

This datasheet is not part of the Decision.
It can be changed at any time and without notice.
Catchword:
Case Number: T 1492/09 - 3.3.04

DECISION of Technical Board of Appeal 3.3.04 of 9 January 2014

Appellant: Alcedo Biotech GmbH
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Decision under appeal: Decision of the Opposition Division of the European Patent Office posted on 8 June 2009 rejecting the opposition filed against European patent No. 1165110 pursuant to Article 101(2) EPC.

Composition of the Board:
Chairman: C. Rennie-Smith
Members: R. Morawetz
M. Montrone
Summary of Facts and Submissions

I. The appeal of the opponent (hereinafter "appellant") lies against the decision of the opposition division whereby the opposition to European patent No. EP 1 165 110 was rejected.

II. The patent at issue has the title "Antagonists of HMG1 for treating inflammatory conditions". It was granted on European application No. 00915762.9 which originated from international application PCT/US2000/003583 published as WO 2000/047104 (hereinafter "application as filed").

Independent claims 1, 5 and 10 as granted read as follows:

"1. An antagonist of HMG1 that inhibits HMG1-mediated activation of the inflammatory cytokine cascade for use as a pharmaceutical, wherein the antagonist is selected from the group consisting of an antibody that specifically binds to an HMG1 protein or fragment thereof and an HMG1 gene antisense sequence.

5. A pharmaceutical composition comprising:
(a) an antagonist of HMG1 that inhibits HMG1-mediated activation of the inflammatory cytokine cascade, wherein the antagonist is selected from the group consisting of an antibody that specifically binds to an HMG1 protein or fragment thereof and an HMG1 gene antisense sequence; and
(b) an antagonist of TNF, IL-1α, IL-1β, MIF or IL-6.

10. Use of an antagonist of HMG1 that inhibits HMG1-mediated activation of the inflammatory cytokine cascade, wherein the antagonist is selected from the
group consisting of an antibody that specifically binds to an HMG1 protein or fragment thereof and an HMG1 gene antisense sequence, for the manufacture of a medicament for the treatment of a condition characterized by activation of the inflammatory cytokine cascade, wherein said condition is selected from the group consisting of sepsis, acute pancreatitis, adult respiratory distress syndrome, reperfusion injury, cardiovascular disease, peritonitis, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, systemic lupus erythematosus, asthma, organ transplant rejection, graft-versus-host disease, cachexia, cystic fibrosis, psoriasis and multiple sclerosis."

III. The patent was opposed under Article 100(a) EPC 1973 on the grounds of lack of novelty (Article 54 EPC 1973) and inventive step (Article 56 EPC 1973) and under Article 100(b) EPC 1973.

IV. The opposition division held that the claims as granted fulfilled the requirements of the EPC and rejected the opposition.

V. With its statement of grounds of appeal the appellant filed new documents (D31) to (D36) and provided arguments why the claims as granted lacked novelty, inventive step and sufficiency of disclosure.

VI. The patent proprietor (hereafter "respondent") filed with its response to the grounds of appeal documents (D37) to (D42) and auxiliary requests 1 to 9 and provided arguments why the claims as granted fulfilled the requirements of the EPC. Auxiliary request 9 became during oral proceedings the main request (see section X below). Claims 1 and 5 of this request correspond to claims 1 and 5 as granted while claim 10 has been
amended by deletion of all conditions except sepsis.
Claims rendered redundant by the amendment of claim 10
have been deleted and the subsequent claims renumbered
accordingly. Claim 10 reads as follows (amendments with
respect to claim 10 as granted indicated by
strikethrough):

"10. Use of an antagonist of HMG1 that inhibits HMG1-
mediated activation of the inflammatory cytokine
cascade, wherein the antagonist is selected from the
group consisting of an antibody that specifically binds
to an HMG1 protein or fragment thereof and an HMG1 gene
antisense sequence, for the manufacture of a medicament
for the treatment of a condition characterized by
activation of the inflammatory cytokine cascade,
wherein said condition is selected from the group
consisting of sepsis, acute pancreatitis, adult
respiratory distress syndrome, reperfusion injury,
cardiocvascular disease, peritonitis, rheumatoid
arthritis, osteoarthritis, inflammatory bowel disease,
systemic lupus erythematosus, asthma, organ transplant
rejection, graft versus host disease, cachexia, cystic
fibrosis, psoriasis and multiple sclerosis."

VII. In a letter of 18 May 2012, the appellant's
representative announced that it no longer represented
the appellant and stated that further correspondence
should be sent to the appellant itself.

VIII. By a communication of 26 July 2013 the parties were
summoned to oral proceedings to be held on
9 January 2014.

IX. In a letter of 9 December 2013 the respondent informed
the board that it would attend the oral proceedings.
X. At the oral proceedings held on 9 January 2014 the appellant did not appear nor was it represented, despite having been duly summoned. Accordingly, the oral proceedings were held in the absence of the appellant (Article 15(3) RPBA). During the oral proceedings the respondent objected to the admission of documents (D28) to (D30) in the appeal proceedings. After discussion of the requirements of sufficiency of disclosure the respondent made pending auxiliary request 9 (see section VI above) the new main request and withdrew all other claim requests. At the end of the oral proceedings the respondent also requested an apportionment of costs.

XI. The following documents are referred to in this decision:

(D3) WO96/25493
(D5) Translation into English of document (D4)
(D20) Merenmies J. et al., JBC, vol. 266,
The submissions of the appellant - insofar as they are relevant to the main request - can be summarised as follows:

Claim interpretation - claim 1

The patent did not provide any definition of the term "specifically binds". Accordingly, the feature had to be given its broadest meaning and because of this, the anti-HMG1 antibody was any antibody which was binding to HMG1.

The feature that the antibody "inhibits HMG1-mediated activation of the inflammatory cytokine cascade" was not described in the patent. The same applied to the term "inflammatory cytokine cascade". Therefore both terms had to be given their normal meaning in the art. There was no normal meaning in the art of the term "HMG1-mediated activation of the inflammatory cytokine cascade". As a consequence, the term "an antibody that inhibits HMG1-mediated activation of the inflammatory cytokine cascade" had to be given its broadest meaning and any anti-HMG1 antibody was encompassed by the term.

Sufficiency of disclosure - claims 1, 5 and 10
Claim 1 consisted of two parts, the first part defining the antagonist such that it inhibited HMG1-mediated activation of the inflammatory cytokine cascade, the second part specifying the antagonist which was either an antibody that specifically bound to an HMG1 protein or fragment thereof, or an HMG1 antisense sequence. The antibody of claim 1, which was further specified as specifically binding to an HMG1 protein or a fragment thereof, was thus an antagonist of HMG1 that inhibited HMG1 mediated activation of the inflammatory cytokine cascade. This could mean that actually each and any such antibody specifically binding to HMG1 protein or fragment thereof inhibited HMG1-mediated activation. Alternatively, this wording could be interpreted such that the antibody specifically binding HMG1 protein had to meet the further requirement that it inhibited HMG1 mediated activation of the inflammatory cytokine cascade. Due to these possible two interpretations which could not be reconciled, a person skilled in the art was not clearly and unambiguously taught how to carry out the invention.

Additionally, there was no technical teaching on how to realise the feature that the antibody specifically binding to an HMG1 protein and the HMG1 antisense sequence met the further requirement that they inhibited HMG1-mediated activation of the inflammatory cytokine cascade. More specifically, the peptide against which the polyclonal antibodies were raised, i.e. the peptide having the amino acid sequence according to SEQ.ID.NO:4, was not part of that moiety of HMG1 which was interacting with RAGE, the receptor of HMG1.

Claim 5 was not in compliance with Article 83 EPC with
regard to the further feature of the claimed pharmaceutical composition referring to "an antagonist of TNF, IL-1a, IL-1 p, MIF or IL-6". The claim did not define the chemical nature of such kind of antagonist.

The patent provided experimental evidence related to LPS/endotoxin challenge. The skilled person would not have understood that the inhibition of HMG1 was also suitable for the treatment of diseases other than sepsis.

Novelty - claim 1

Document (D3) anticipated the subject-matter of claim 1 considering that actually each and any anti-HMG antibody or HMG1 gene antisense sequence was suitable to inhibit HMG1-mediated activation of the inflammatory cytokine cascade (see claim 7, page 3, lines 1 and 2, and page 4, lines 25 to 27).

Document (D5), which was the English translation of document (D4), disclosed in Figure 7 that the pro-inflammatory cytokine HMG1 was mediating the inflammatory cytokine cascade and produced various effects and that anti-HMG autoantibodies were useful in modifying these effects. An antagonist of HMG1 like the anti-HMG1 depicted in Figure 7 was suitable to inhibit the HMG1-mediated function, i.e. also the inflammatory cytokine cascade. This was explicitly mentioned in the second paragraph under heading (5) on page 16. When reading the passage under heading (5) of document (D5) a person skilled in the art immediately and unambiguously took therefrom the further feature that the disclosed antibody was actually intended as a medicament.
Document (D16) showed that the addition of an anti-HMG1 antibody resulted in inhibition of the differentiation process of murine erythroleukemia cells (see abstract, right column, lines 1 to 3). As the differentiation process was a prerequisite for the development of a respective malignancy and disease, respectively, document (D16) disclosed to a person skilled in the art a therapeutic use of an anti-HMG1 antibody.

Document (D20) disclosed, inter alia, the use of anti-HMG1 antibodies so as to inhibit the outgrowth of cytoplasmic processes in developing cells (see abstract, last sentence). Taking into account the fact that the outgrowth of cytoplasmic processes was an integral part of cell growth and cell spreading, particularly in connection with tumor cells such as neuroblastoma cells, inhibiting the outgrowth of such neuroblastoma cell by anti-HMG1 antibodies was a medical use of such antibodies.

Document (D36) disclosed the presence of anti-HMG1 and anti-HMG2 antibodies in the sera of ulcerative colitis (UC) patients (abstract and lines 6 to 8 from the bottom). The disclosure on page 139, right column, last paragraph was actually understood by a person skilled in the art to teach the therapeutic use of anti-HMG1 and anti-HMG2 antibodies for inflammatory diseases.

Inventive step - claim 1

Document (D10) disclosed that HMG1 bound in a dose-dependent manner to RAGE. Therefore, the person skilled in the art understood that HMG1 was a ligand to RAGE. The involvement of RAGE in the inflammatory cytokine cascade and thus in inflammatory diseases had been known prior to the priority date of the patent, see
documents (D11) or (D12). Insofar, from document (D10) in combination with either document (D11) or (D12), a person skilled in the art was aware that HMG1 through its binding to RAGE acted as a mediator to the inflammatory cytokine cascade.

In document (D5), the authors directly linked HMG1 and HMG2 to inflammation (see page 16, lines 3 to 5 of the third paragraph). Document (D5) also summarised the findings of auto-antibodies against HMG1 and inflammatory diseases like rheumatoid arthritis and Crohn’s disease. Furthermore, the author of document (D5) explained in connection with Fig. 7 of document (D5) the role of auto-antibodies against HMG1. A person skilled in the art obtained a clear impetus and incentive to carry out the kind of experiments described in the patent in dispute (see page 16, penultimate paragraph). Document (D13) had found an increased incidence of neutralising auto-antibodies against pro-inflammatory cytokine IL-1α in non-destructive chronic polyarthritis. Thus a person in the art concluded that these (auto)antibodies were beneficial. Starting from the problem to provide means for the treatment of inflammatory disease such as sepsis a person skilled in the art could and actually would have taken from the various documents of the prior art that HMG1 was involved in the pathomechanism and, accordingly, would have used a blocking antibody to HMG1 so as to interfere with the interaction of HMG1 in the pathomechanism.

There was evidence such as document (D34) that an anti-HMG1 antibody would not be suitable for the treatment of a tumor which, according to the patent, was regarded as a disease and condition, respectively, which was mediated by the inflammatory cytokine cascade.
Accordingly, the claimed invention could inherently not be practiced over the whole claimed range (see decision T 939/92).

An anti-HMGI antibody which was inhibiting the inflammatory cytokine cascade was not suitable for the treatment of a tumor (see document (D34)). Therefore, the patent was not in compliance with the requirement of decision T 1329/04 that the application had to make it plausible that the underlying problem was actually solved.

Inventive step - claim 5

It was obvious for the person skilled in the art to combine two types of antagonists so as to, potentially, have an increased efficacy (see document (D19)).

Inventive step - claim 10

The same arguments as presented in connection with claim 1 were, in principle, also applicable to the subject matter of claim 10.

XIII. The submissions of the respondent - insofar as they are relevant to the main request - can be summarised as follows:

Claim interpretation - claim 1

To the extent that the term "specifically binds" required interpretation, those skilled in the art would interpret it as requiring the antibody to discriminate between the target antigen and other, unrelated molecules, see also paragraph [0041] of the patent in suit.
Those skilled in the art would, at the priority date of the patent, have been perfectly capable of ascribing meanings to the terms "specifically binds" and "inhibits HMG1-mediated activation of the inflammatory cytokine cascade", see e.g. paragraph [0044] of the patent in suit and documents (D37) or (D38). Examples 3 and 8 of the patent indicated that TNFα release was stimulated by administration of recombinant HMG1, but inhibited if an HMG1 antagonist was also present. Thus those skilled in the art would have understood that the term excluded, for example, antibodies that bound to HMG1 but did not inhibit HMG1-mediated activation of the inflammatory cytokine cascade.

Sufficiency of disclosure - claims 1, 5 and 10

Those skilled in the art would have interpreted claim 1 as excluding HMG1 antagonists that did not meet the requirement of inhibiting "HMG1-mediated activation of the inflammatory cytokine cascade".

The examples of the patent disclosed how to generate antagonistic anti-HMG1 antibodies, an in vivo assay to test whether an HMG1 antagonist met the requirement to inhibit HMG1-mediated activation of the inflammatory cytokine cascade, and credible evidence that Gram-negative sepsis could be successfully treated by an HMG1 antagonist.

Paragraph [0012] of the patent disclosed various specific molecules that enabled the person skilled in the art to carry out the invention of claim 5. Those skilled in the art would have been aware (through common general knowledge) of suitable variants of the functionally-defined components of part (b) of the
composition of claim 5.

Example 8 of the patent provided credible evidence that Gram-negative sepsis could be successfully treated by an HMG1 antagonist.

Novelty - claim 1

Antibodies that bound to HMG1, but that did not possess the requisite inhibitory effect with respect to the inflammatory cytokine cascade, could not anticipate the subject-matter of claim 1. Moreover, due to the formats of the independent claims, prior art that failed to disclose a (specific) medical use of the antagonists defined in claim 1 was irrelevant.

Document (D3) related to the observation that genes for certain HMG proteins were associated with aberrant cell growth in multiple tumour types. Further, although document (D3) mentioned HMG1 and HMG2 as members of "the HMG gene family", it did not provide any evidence that the genes for either of HMG1 and HMG2 were associated with any tumours and was non-enabling with respect to antagonists of HMG1 that inhibited HMG1-mediated activation of the inflammatory cytokine cascade.

Document (D4) (and its translation into English, document (D5)) was a review article that summarised observations on autoantibodies identified in the sera of patients suffering from various inflammatory and autoimmune diseases. The autoantibodies that were the particular focus of the review were the perinuclear antineutrophilic cytoplasmic antibodies (P-ANCA) directed against HMG1 or HMG2. Document (D4) failed to disclose what effect HMG1 might have in relation to
inflammation. Document (D4) did not disclose any kind of antagonist of HMG1 that inhibited activation of the inflammatory cytokine cascade.

Documents (D16) and (D20) did not disclose any medical or therapeutic uses of anti-HMG1 antibodies, let alone antibodies that inhibited HMG-1 mediated activation of the inflammatory cytokine cascade.

Document (D36) reported observations on autoantibodies identified in the sera of patients suffering from ulcerative colitis (UC). Amongst the autoantibodies identified in UC patients where those binding to HMG1, or to HMG2. Document (D36) did not disclose any kind of antagonist of HMG1 that inhibited activation of the inflammatory cytokine cascade.

Inventive step - claim 1

The claimed invention provided agents and compositions that were useful in treating inflammatory disorders. Document (D5) mentioned autoantibodies to HMG1 and discussed what their relevance to inflammation might be. Document (D10) related to the interaction between amphoterin and RAGE, and in particular to the neurite outgrowth process that was mediated by that interaction. Document (D11) related to the interaction of RAGE with advanced glycosylation end products. Although document (D11) mentioned the interaction between amphoterin and RAGE, this was only for the purposes of drawing a comparison between the different effects produced when amphoterin (instead of an advanced glycation end product) bound to RAGE.

Document (D12) related to the interaction of RAGE with amyloid-β peptide. Document (D14) related to the incidence (and levels of) autoantibodies to TNFα in
both healthy subjects and patients with autoimmune diseases. None of documents (D5), (D10) to (D12), and (D14) represented the closest prior art as none of these documents disclosed the use of any agent or composition in the treatment of inflammatory disorders.

Document (D13) related to the incidence (and levels of) autoantibodies to IL-1α in both healthy subjects and patients with chronic arthritis. Document (D13) also disclosed that administration of anti-IL-1 antibodies was able to prevent both early and late stages of arthritis in mouse models. In the light of document (D13), the objective technical problem to be solved was the provision of a new medicament (agent or composition) that was useful in treating inflammatory disorders. The invention claimed in the patent represented an inventive solution to this problem as it involved the use of antagonists of HMG1. Prior to the disclosure of the patent, HMG1 was not recognised to play any role at all in the inflammatory cytokine cascade.

The apparent basis for the assertion that the claimed invention could not be practiced over the whole of the claimed scope (T 939/92) was document (D34), which the appellant alleged provided evidence that the antagonists defined in the claims of the patent would not be suitable for the treatment of a tumour. It was not understood why the appellant believed that the disclosure of document (D34) was in any way relevant to the issue of whether claim 1 solved the problem addressed across substantially the whole scope.

With respect to the appellant's allegations relating to T 1329/04, the objective problem addressed by the patent was the provision of an alternative agent or
composition that was useful in treating inflammatory disorders. The experimental results amply demonstrated that the problem of providing an alternative agent or composition that was useful in treating inflammatory disorders had been plausibly solved by the disclosure in the application.

Inventive step - claim 5

Document (D19) neither disclosed nor suggested any kind of antagonists of HMG1 and there was no disclosure or suggestion in the prior art of antagonists of HMG1 that inhibited activation of the inflammatory cytokine cascade.

Apportionment of costs

The appellant had not indicated that it would not attend the oral proceedings. In the jurisprudence it had been held that costs were awarded to the attending party when the other party did not attend the oral proceedings. This case concerned a commercially important patent and the respondent had to prepare for the oral proceedings in case the appellant attended. The costs sought to be apportioned were for one day's preparation for, and one day's attendance at the oral proceedings.

XIV. The appellant requested in writing that the decision under appeal be set aside and the patent be revoked. The respondent requested that the appeal be dismissed or a patent be granted on the basis of the main request filed during oral proceedings. It also requested an apportionment of costs.
Reasons for the Decision

Documents in the appeal proceedings

1. Documents (D28) to (D30) had not been admitted into the opposition proceedings by the opposition division (see decision under appeal, reasons, point 2.2). The appellant has not appealed against that particular decision. Since these documents were filed by the appellant (then opponent) and the respondent did not agree to their admission in the appeal proceedings these documents - and arguments based thereon - are not part of these proceedings.

2. Documents (D31) to (D41) were filed on appeal and as no objection to admissibility was raised by either party all these documents were admitted into the appeal proceedings by agreement of the parties.

Main (sole) request
Articles 123(2) and (3) and 84 EPC

3. The claims of the main request are identical to the claims as granted except for the restriction of claim 10 to the treatment of sepsis as the sole condition (see section VI above). In opposition proceedings, the appellant (then opponent) did not raise an objection under Article 100(c) EPC against the claims as granted. The board is satisfied that the amendment of claim 10 does not introduce new matter, does not extend the protection conferred and does not introduce any clarity problem. The amended claims are regarded as conforming to Articles 123(2)(3) and 84 EPC.
Claim interpretation - claim 1

4. The appellant submitted, that in the absence of a definition of the term "specifically binds" in the patent in suit, the antibody of claim 1 was any antibody that bound to HMG1. Likewise the feature that the antibody "inhibits HMG1-mediated activation of the inflammatory cytokine cascade" had to be given its broadest meaning. This meant that any anti-HMG1 antibody was encompassed by said term.

5. It is established jurisprudence of the Boards of Appeal that the skilled person when considering a claim should try to arrive at an interpretation of the claim which is technically sensible and takes into account the whole disclosure of the patent. In the absence of a definition of a particular term in the specification, terms should be given their normal meaning in the relevant art (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, sections II.A.6.1 and II.A.6.3.3).

6. The board notes that in paragraphs [0041] and [0044] of the patent in suit the specificity of the anti-HMG1 antibodies was assayed. The board is satisfied that in the light of this disclosure the person skilled in the art would interpret the term "specifically binds to an HMG1 protein" as requiring the antibody to discriminate between the target antigen HMG1 and other, unrelated molecules.

7. Examples 3 and 8 of the patent in suit show that administration of HMG1 induces TNFα release in murine macrophages in vitro and in rodents in vivo. At the priority date of the patent, the skilled person knew that TNFα in turn induces the production of multiple
proinflammatory cytokines (such as IL-1, IL-6 and INFγ) in immune cells, see e.g. Table 1 of document (D37).
The observation that one proinflammatory cytokine can induce the release of other proinflammatory cytokines was, at the priority date of the patent, commonly known as the cytokine cascade, see e.g. the first paragraph in the left hand column on page 91 of document (D38).

8. The board is thus satisfied that the skilled person would have been able to ascribe a specific meaning to the term in question. In the board's judgement those skilled in the art would have understood that the term excluded antibodies that bound to HMG1 but that did not inhibit HMG1-mediated activation of the inflammatory cytokine cascade (e.g. as determined by the measurement of TNFα release stimulated in murine macrophages by administration of recombinant HMG1).

Sufficiency of disclosure - claims 1, 5 and 10

9. In the decision under appeal the opposition division found, in connection with the main request then on file (claims as granted), that the invention as claimed in claims 1 to 27 was sufficiently disclosed (see reasons, point 2.4.3). Present claims 1 and 5 are identical to claims 1 and 5 as granted while claim 10 has been limited with respect to claim 10 as granted (see section VI above).

10. The appellant contested the opposition division's finding, arguing along several lines (see section XII above). The board is unable to accept any of these lines of arguments for the reasons set out below.

11. Firstly, the appellant asserted that claim 1 could be interpreted in two different ways which could not be
reconciled. This resulted in its view in a deficiency under Article 83 EPC.

12. The board considers that in view of the explicit wording of claim 1 those skilled in the art understand that the antibody specifically binding HMG1 protein has to meet the further requirement that it inhibits HMG1-mediated activation of the inflammatory cytokine cascade. Accordingly, the second interpretation of claim 1 as advocated by the appellant, namely that each and any antibody specifically binding to HMG1 protein or fragment thereof inhibits HMG1-mediated activation, contradicts the explicit wording of claim 1. Therefore appellant's first argument is not persuasive.

13. Additionally, the appellant submitted that there was no teaching on how to realise the feature that the antibody specifically binding to an HMG1 protein and the HMG1 gene antisense sequence met the further requirement that they inhibited HMG1-mediated activation of the inflammatory cytokine cascade. In particular, it was submitted that the polyclonal antibodies used in the patent had been raised against a peptide which was not part of that moiety of HMG1 which interacted with RAGE, the receptor of HMG1.

14. The board notes that the examples of the patent provide the following experimental information: HMG1 is a "late" mediator of endotoxemia (see example 1). Administration of recombinant HMG1 to cultures of human peripheral blood monocytes, or to test animals, elicits release of the proinflammatory cytokine TNF (see examples 3 and 8). Administration of recombinant HMG1 to test animals causes dose-dependent lethality (see example 6). HMG1-specific antibodies, which antibodies do not cross-react with other macrophage-derived
cytokines such as TNF and IL-1, confer protection against experimentally-induced endotoxemia in mice (see example 6). HMG1 is not detected in the sera of a number of healthy individuals, but is observed at high levels in sepsis patients, with the highest levels being observed in the patients with the worst prognosis (see example 7). Administration of recombinant HMG1 causes significant weight loss in mice. Example 4 of the patent in suit discloses how to generate polyclonal anti-HMG1 antibodies, while example 6 provides an in vivo assay to test whether an HMG1 antagonist meets the requirement to inhibit HMG1-mediated activation of the inflammatory cytokine cascade. In example 6, polyclonal antibodies against recombinant HMG1 were shown to be protective against LPS-induced lethality. Moreover, at the priority date of the patent in suit, the generation of monoclonal antibodies and antisense sequences belonged to the common general knowledge of the person skilled in the art.

15. The board is thus satisfied that the skilled person, on the basis of the guidance provided in the patent in suit together with the common general knowledge available to the skilled person at the priority date would have been in a position to prepare appropriate antagonists of HMG1, to test them and to select those which inhibit HMG1-mediated activation of the inflammatory cytokine cascade and, thus, that the skilled person could put the invention into practice over the whole scope of claim 1 without undue burden.

16. As regards claim 5, the board notes that the patent in suit discloses suitable antagonists (see paragraph [0011]) and that those skilled in the art would have been aware, through common general knowledge, of
suitable variants.

17. As regards the subject-matter of claim 10, the board notes that example 6 provides the results of a predictive lethal endotoxemia animal model of clinical sepsis. It is reported that the administration of anti-HMG1 antiserum was found to be protective against LPS-induced lethality in Balb/c mice. This is considered by the board to constitute credible evidence that Gram-negative sepsis can be successfully treated by HMG1 antagonists that inhibit HMG1-mediated activation of the inflammatory cytokine cascade.

18. For the above reasons the board considers that the requirements of Article 83 EPC are fulfilled.

**Novelty - claim 1**

19. In the decision under appeal (see reasons, point 2.3.3) the opposition division held that the subject-matter of claim 1 was novel vis-à-vis documents (D3), (D4), (D16) and (D20).

20. The appellant contested the opposition division's finding as regards documents (D3), (D4), (D16) and (D20) and cited one further document, document (D36), as anticipating the subject-matter of claim 1 (see section XII above). Having considered the arguments put forward by the appellant the board is not convinced that any of documents (D3), (D4), (D16), (D20) and (D36) anticipates the subject-matter of claim 1 for the reasons set out below.

21. According to established case law, for an invention to lack novelty, its subject-matter must be directly and unambiguously derivable from the prior art and all its
features must be known from the prior art (see Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, see section I.C.3). Independent claim 1 is drawn up in the form of a first medical use claim. As a consequence, prior art has to disclose a use of the antagonist defined in claim 1 in a medical method to anticipate the subject-matter of claim 1.

22. Document (D3) relates to the observation that genes for certain HMG proteins are associated with aberrant cell growth in multiple tumour types. Document (D3) mentions HMG1 and HMG2 as members of "the HMG gene family" and claims the therapeutic and diagnostic use of antibodies and antisense molecules directed against all HMG proteins and genes but does not provide any evidence that either HMG1 or HMG2 are associated with any tumours (see page 4, lines 18 to 24, page 34, lines 20 to 24; claim 7; examples).

23. Appellant's objection rests on the presumption that any anti-HMG1 antibody falls within the scope of claim 1. It has however been established (see point 8 above) that only antibodies that bind to HMG1 and inhibit HMG1-mediated activation of the inflammatory cytokine cascade fall within the scope of claim 1. As document (D3) fails to disclose such antibodies or their medical use it does not anticipate the subject-matter of claim 1.

24. Document (D4) (reference is made hereinafter to its translation into English, document (D5)), is a review article that summarises observations on autoantibodies identified in the sera of patients suffering from various inflammatory and autoimmune diseases. The autoantibodies that are the particular focus of the review are the perinuclear antineutrophilic cytoplasmic
antibodies (P-ANCA) directed against HMG1 or HMG2 (see page 1, 2nd paragraph, page 3, last paragraph, page 6, first paragraph, page 7, second and third paragraphs, page 11, first full paragraph). Document (D5) fails to disclose what effect HMG1 or anti-HMG1/HMG2 antibodies might have in relation to inflammation. Thus, document (D5) discloses with regard to HMG1/HMG2 (see in particular page 16, paragraphs 2 to 4) that: "Their role in the development process of cancer and inflammatory diseases is of interest, and particularly with regard to inflammatory diseases, there is potential for a deep relationship in terms of the process of treating wounds, including nerve regeneration, and in the interaction of cells and the extracellular matrix in local inflammations". Document (D5) concludes with stating that: "In the future, in addition to analyzing the dynamics of HMG1/HMG2 in neutrophils and cells of organs affected by inflammation, there should be clarification of how anti-HMG1/HMG2 antibodies are involved in the clinical condition of inflammatory diseases." Contrary to the assertion of the appellant, document (D5) does not disclose that anti-HMG autoantibodies are useful to inhibit the HMG1-mediated inflammatory cytokine cascade but acknowledges that the role of the anti-HMG1 antibodies is unclear. For these reasons, in the board's judgement, document (D5) does not anticipate the subject-matter of claim 1.

25. Document (D16) reports that HMG1 is essential for murine erythroleukemia (MEL) cell differentiation, and that the addition of an anti-HMG1 monoclonal antibody inhibits the differentiation process almost completely (see abstract, right column, lines 1 to 3). As for document (D3), appellant's objection rests on the presumption that any anti-HMG1 antibody falls within
the scope of claim 1. For the reasons set out above (see point 23) appellant's objection fails.

26. Document (D20) reports that amphoterin (a product of the HMG1 gene) is involved in the outgrowth of neurites, and that an antibody to HMG1 inhibits outgrowth of neurite-type cytoplasmic processes in in vitro cultures of N18 neuroblastoma cells (see abstract, last sentence). Again appellant's objection rests on the presumption that any anti-HMG1 antibody falls within the scope of claim 1 and again it fails (see point 23 above).

27. Document (D36) reports observations on autoantibodies identified in the sera of patients suffering from ulcerative colitis (UC). Amongst the autoantibodies identified in UC patients are those binding to HMG1, or to HMG2 (see abstract). According to document (D36) HMG1 and HMG2 act as transcription factors but the role of the antibodies against HMG1 and HMG2 is unclear. Document (D36) states in the second paragraph in the right hand column on page 139: "Upon stimulation and rupture of the cells, these antigens [HMG1 and HMG2] may be exposed to P-ANCA, leading to an immune interaction. Immune complex formation might sustain or even amplify an inflammatory process. Alternatively, the released antigens may be internalized into the surrounding inflammatory cells and reach the chromatin to activate the genes, which may amplify an inflammatory process. Further investigations are necessary to study the putative pathogenic roles of such antigens [HMG1 and HMG2] and autoantibodies."

Document (D36) thus speculates about a pro-inflammatory role of the autoantibodies but fails to disclose any kind of antagonist of HMG1 that inhibits HMG1-mediated activation of the inflammatory cytokine cascade.
Therefore document (D36) does not anticipate the subject-matter of claim 1.

28. The board concludes that the requirements of Article 54 EPC are fulfilled.

Inventive step

Closest prior art

29. In the decision under appeal the opposition division had come to the conclusion that document (D13) or document (D18) could be considered to represent the closest prior art for the patent; that the objective technical problem was the provision of a new medicament suitable for inhibiting the inflammatory cytokine cascade, and that the solution claimed in the patent was non-obvious because none of the cited documents disclosed or suggested HMG1 to be a proinflammatory cytokine (see reasons, point 2.3.6.1).

30. The appellant contested the choice of the closest prior art by the opposition division and formulated various inventive step objections based on documents (D4)/(D5), (D10), (D11), (D12) and (D14) (see section XII above).

31. For the assessment of inventive step the Boards of Appeal apply the "problem and solution approach" which, as a first step, requires the definition of the "closest prior art". The Boards have repeatedly pointed out that the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention (Case Law of the

32. From the patent as a whole (see in particular paragraphs [0001], [0009], and [0010]) it is understood that the purpose of the present invention is the treatment of inflammatory conditions.

33. Document (D4)/(D5) relates to autoantibodies against HMG1/HMG2. Document (D4)/(D5) states that the role of HMG1/HMG2 in the development of cancer and inflammatory diseases is of interest and that there should be clarification of how anti-HMG1/HMG2 antibodies are involved in the clinical condition of inflammatory diseases.

34. Document (D10) relates to the interaction between amphoterin and RAGE, and in particular to neurite formation by cortical neurons that is mediated by that interaction (see abstract and page 25760, right hand column, last paragraph).

35. Document (D11) relates to the interaction of RAGE with advanced glycosylation end products (AGEs, such as AGE-\(\beta_2M\)). Although document (D11) mentions the interaction between amphoterin and RAGE, this is only for the purposes of drawing a comparison between the different effects produced when amphoterin (instead of an AGE) binds to RAGE (see abstract and page 1092, right hand column, third paragraph).

36. Document (D12) relates to the interaction of RAGE with amyloid-\(\beta\) peptide (A\(\beta\)) and the inflammatory pathway triggered by this interaction.
37. Document (D14) relates to the incidence (and levels of) autoantibodies to TNFα in both healthy subjects and patients with autoimmune diseases.

38. None of documents (D4)/(D5), (D10), (D11), (D12) and (D14) discloses the use of any agent or composition in the treatment of inflammatory disorders. These documents are thus not directed to the same or a similar purpose as the claimed invention and do not qualify as closest prior art documents. Accordingly, appellant's arguments (see section XII above) based on these documents fail.

39. Document (D13) relates to the incidence of neutralizing autoantibodies to IL-1α in both healthy subjects and patients with chronic arthritis. Document (D13) also discloses that administration of anti-IL-1 antibodies was able to prevent both early and late stages of arthritis in mouse models (see the final sentence of the first paragraph on page 289 of D13) and thus qualifies as closest prior art.

Problem and its solution

40. In the light of document (D13), the objective technical problem to be solved is the provision of further means useful in treating inflammatory disorders. In view of the experimental results reported in the patent (see in particular examples 6 to 8) the board is satisfied that the subject-matter of claim 1 solves the problem.

41. The appellant submitted that claim 1 comprised a non-working embodiment, namely the treatment of a tumor, and that therefore the claimed invention could not be practiced over the whole claimed range and furthermore that it was not plausible that the underlying problem
was solved across the scope of the claim.

42. In the board's judgement appellant's objections have been (i) raised under the wrong provision of the EPC and are (ii) in any case inapplicable. Claim 1 is drawn up as a first medical use claim and the statement of purpose is an explicit feature of the claim which expresses an effect. Therefore any objection based on the assertion that the claim comprises non-working embodiments has to be raised in the context of Article 83 EPC, not Article 56 EPC (see decision G 02/03 of the Enlarged Board of Appeal, OJ EPO 2004, 448, reasons, point 2.5.2). The possibility that a tumour might not be treatable by an antagonist of HMG1 is of no consequence for present claim 1, which is directed to an antagonist of HMG1 that inhibits HMG1-mediated activation of the inflammatory cytokine cascade for use as a pharmaceutical. It has been established that the patent provides credible evidence that Gram-negative sepsis (a condition characterised by activation of the inflammatory cascade) can be successfully treated by HMG1 antagonists that inhibit HMG1-mediated activation of the inflammatory cytokine cascade (see point 17 above). According to established case law of the Boards of Appeal, the first to show a use of a substance or composition in a medical method should receive broad protection covering any use in a medical method, even if only one specific use is disclosed in the application (Case Law of the Boards of Appeal of the European Patent Office, 7th edition 2013, I.C.6.1.1). Therefore claim 1 fulfills the requirements of Article 83 EPC and appellant's objections fail.
Obviousness

43. Document (D13) is silent about HMG1 or its role in inflammatory disorders, accordingly the solution is not obvious from document (D13) alone.

44. Document (D4)/(D5) discloses the existence of autoantibodies against HMG1 but acknowledges that it is unclear how anti-HMG1 antibodies are involved in inflammatory diseases (see page 16, paragraphs 2 to 4). Document (D4)/(D5) neither discloses nor suggests that HMG1 is a proinflammatory cytokine. Accordingly the skilled person, when faced with the problem formulated above, would not derive any motivation from this document to provide an antagonist of HMG1.

45. Document (D14) does not overcome this deficiency. Although the authors of document (D14) identified an autoantibody to TNFα from one rheumatoid arthritis patient that neutralised certain effects of TNFα, they nevertheless state, in the last full sentence on page 520 of document (D14), that: "The biological relevance of autoantibodies to TNFα and other cytokines is unclear". None of the other documents on file identifies HMG1 as playing any role at all in the inflammatory cytokine cascade.

46. The board concludes that none of the cited documents provides any hint that would have motivated the skilled person to modify the teaching in the closest prior art document (D13) so as to arrive at the claimed invention in an obvious manner. The above considerations with respect to claim 1 also apply to the subject-matter of independent claims 5 and 10 and to all dependent claims. For these reasons the main request complies
with the requirement of Article 56 EPC.

Apportionment of costs

47. The respondent requested an apportionment of costs because the appellant did not attend the oral proceedings and had not indicated that it would not attend, so the respondent had been required to prepare for and attend the oral proceedings. The case law of the boards showed that such behaviour had been sanctioned by ordering the absent party to pay the attending party's costs of the oral proceedings. The board has some sympathy for the respondent. After the appellant's representative ceased to act as such, no response was received to any communication sent to the appellant company, including the summons to oral proceedings. Neither the respondent nor the board could know whether or not the appellant would attend the oral proceedings. There is no doubt that the appellant's silence was not just discourteous but caused unnecessary work.

48. In the event the appellant did not attend and the proceedings were probably shorter as a result. However, viewed objectively the respondent was obliged to attend the oral proceedings in the particular circumstances of the case, and would have been so obliged even if it had known in advance that the appellant would not attend. This was because the appellant had made a case in writing (in its statement of grounds of appeal) against the decision of the opposition division rejecting the opposition, the respondent's patent was thus under threat and the respondent could not know how the board might decide the case. An additional factor is that in the present case the board had issued a summons without a provisional opinion, although the board doubts that
any such opinion could have been so favourable to the respondent that it might then have decided to absent itself from the oral proceedings if it had known that the appellant would not attend. The respondent submitted that the patent was of commercial importance and that also suggests that the respondent might have attended even if the appellant had announced its absence in advance.

49. The respondent is correct that in other cases of unannounced absence, absent parties have been required to pay the costs of those parties who do attend. However, the distinction between such cases and the present case is that, generally speaking, in those other cases the attending parties would not have themselves attended had they known it would be unnecessary; on finding their adversaries are absent, they have been able to claim that they have wasted the time and cost of attendance. That is not the case here since, as mentioned above, the respondent had to attend in any event. The outcome of the oral proceedings demonstrates this - before the oral proceedings, the respondent's main request was to dismiss the appeal and thus to maintain the patent as granted. At the end of the oral proceedings, in the absence of the appellant and after discussion with only the board, it made its auxiliary request 9 its main request and withdrew all its other requests. That simply could not have been done in the respondent's absence. Thus the board took the view that an apportionment of costs would not have been equitable as required by Article 104(1) EPC.
Order

For these reasons it is decided that:

1. The request for apportionment of costs is dismissed.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of the main request filed during oral proceedings and a description and figures to be adapted thereto.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith

Decision electronically authenticated