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**Datasheet for the decision  
of 2 July 2015**

**Case Number:** T 1350/11 - 3.3.04  
**Application Number:** 02733789.8  
**Publication Number:** 1357942  
**IPC:** A61K39/395, A61K39/00,  
A61P37/00  
**Language of the proceedings:** EN

**Title of invention:**

Methods and compositions for treatment of immune dysfunction disorders

**Applicant:**

The Lauridsen Group Incorporated

**Headword:**

Orally administered immunoglobulins for the treatment of immune disorders/LAURIDSEN

**Relevant legal provisions:**

EPC Art. 83  
EPC R. 115(2)  
RPBA Art. 13(1), 13(3), 15(3)

**Keyword:**

Sufficiency of disclosure - of all requests (no)

**Decisions cited:**

T 0609/02

**Catchword:**



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Case Number: T 1350/11 - 3.3.04

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.04**  
**of 2 July 2015**

**Appellant:** The Lauridsen Group Incorporated  
(Applicant) 2325 North Loop Drive,  
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**Representative:** Webber, Philip Michael  
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**Decision under appeal:** **Decision of the Examining Division of the  
European Patent Office posted on 2 November 2010  
refusing European patent application No.  
02733789.8 pursuant to Article 97(2) EPC.**

**Composition of the Board:**

**Chairwoman** G. Alt  
**Members:** M. Montrone  
M. Blasi

## Summary of Facts and Submissions

- I. The appeal was lodged by the applicant (hereinafter "appellant") against the decision of the examining division to refuse European patent application No. 02733789. The application was filed as an international application, published as WO 02/078742 (hereafter "the application") and has the title "*Methods and compositions for treatment of immune dysfunction disorders*".
- II. In its decision the examining division dealt with a main and three auxiliary requests. It took the view that the subject-matter of claim 1 of the main and second auxiliary request infringed Article 123(2) EPC and that the subject-matter of claims 1 to 4 of the first and third auxiliary request lacked an inventive step (Article 56 EPC).
- III. With the statement of grounds of appeal, the appellant submitted a main request and eleven auxiliary requests. The first, seventh, eighth and eleventh auxiliary request corresponded to the requests dealt with in the decision under appeal.
- IV. The appellant was informed about the board's preliminary view on the pending requests in a communication pursuant to Article 15(1) RPBA. The board observed *inter alia* that the data of example 5 did not appear to show that the oral delivery of a cross-species derived immunoglobulin concentrate lowered TNF- $\alpha$  levels. Nor did the application seem to disclose any such effect on serum IgG levels. It therefore appeared doubtful that the requirements of Article 83 EPC were fulfilled (see point 19 of the communication).

V. In reply to the board's communication the appellant submitted with its letter dated 19 June 2015, *inter alia*, a new main request, 15 auxiliary requests and documents D19 to D23. It moreover withdrew its request for oral proceedings and announced that it would not attend should the board maintain the date fixed for oral proceedings.

VI. Claim 1 of the main request reads:

"1. An immunoglobulin concentrate derived from the blood of a non-human animal for use in a method of treating chronic immune stimulation, Crohn's disease, rheumatoid arthritis, ulcerative colitis or severe malabsorption associated with AIDS in a human wherein the immunoglobulin concentrate is for oral administration and wherein the immunoglobulin concentrate lowers serum IgG and TNF- $\alpha$  levels and wherein this lowering is not specific to particular antibodies in the immunoglobulin concentrate".

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request except that the reference to "chronic immune stimulation" has been deleted.

Claim 1 of auxiliary request 2 is identical to claim 1 of the main request except that "derived from the blood of a non-human animal" has been replaced with "derived from pig, bovine, ovine, poultry, equine or goat plasma".

Claim 1 of auxiliary request 3 is identical to claim 1 of the main request except that "derived from the blood of a non-human animal" has been replaced with "derived from pig, bovine, ovine, poultry, equine or goat plasma" and that the feature "wherein the

immunoglobulin concentrate contains an effective amount of IgG" has been added.

Claim 1 of auxiliary request 4 reads:

"1. An immunoglobulin concentrate derived from pig, bovine, ovine, poultry, equine or goat plasma wherein the immunoglobulin concentrate contains an effective amount of IgG for use in a method of treating Crohn's disease in a human wherein the immunoglobulin concentrate is for oral administration."

Claim 1 of auxiliary request 5 is identical to claim 1 of auxiliary request 4 except that the feature "and wherein the immunoglobulin concentrate lowers serum IgG and TNF- $\alpha$  levels and wherein this lowering is not specific to particular antibodies in the immunoglobulin concentrate" has been added.

Claim 1 of auxiliary request 6 is identical to claim 1 of auxiliary request 4 except that "contains an effective amount of IgG" has been replaced with "contains more than 50% IgG".

Claim 1 of auxiliary request 7 is identical to claim 1 of auxiliary request 4 except that "contains an effective amount of IgG" has been replaced with "contains more than 50% IgG" and that the feature "and wherein the immunoglobulin concentrate lowers serum IgG and TNF- $\alpha$  levels and wherein this lowering is not specific to particular antibodies in the immunoglobulin concentrate" has been added.

Claim 1 of auxiliary request 8 is identical to claim 1 of auxiliary request 4 except that "the immunoglobulin concentrate contains an effective amount of IgG" has

been replaced with "the immunoglobulin concentrate is in the form of a spray-dried powder containing 35-50% IgG".

Claim 1 of auxiliary request 9 is identical to claim 1 of auxiliary request 4 except that "the immunoglobulin concentrate contains an effective amount of IgG" has been replaced with "wherein the immunoglobulin concentrate is in the form of a spray-dried powder containing 35-50% IgG" and that the feature "and wherein the immunoglobulin concentrate lowers serum IgG and TNF- $\alpha$  levels and wherein this lowering is not specific to particular antibodies in the immunoglobulin concentrate" has been added.

Claim 1 of auxiliary request 10 reads:

"1. An immunoglobulin concentrate derived from pig, bovine, ovine, poultry, equine or goat plasma wherein the immunoglobulin concentrate contains an effective amount of IgG for use in a method of treating Irritable Bowel Disease (IBD) in a human wherein the immunoglobulin concentrate is for oral administration and wherein the immunoglobulin concentrate lowers serum IgG and TNF- $\alpha$  levels and wherein this lowering is not specific to particular antibodies in the immunoglobulin concentrate."

Claim 1 of auxiliary request 11 is identical to claim 1 of auxiliary request 10 except that "contains an effective amount of IgG" has been replaced with "contains more than 50% IgG".

Claim 1 of auxiliary request 12 is identical to claim 1 of auxiliary request 10 except that "the immunoglobulin concentrate contains an effective amount of IgG" has

been replaced with "the immunoglobulin concentrate is in the form of a spray-dried powder containing 35-50% IgG".

Claim 1 of auxiliary request 13 is identical to claim 1 of auxiliary request 10 except that the reference to Irritable Bowel Disease (IBD) has been replaced with "autoimmune disorders".

Claim 1 of auxiliary request 14 is identical to claim 1 of auxiliary request 10 except that the reference to Irritable Bowel Disease (IBD) has been replaced with "autoimmune disorders" and that "contains an effective amount of IgG" has been replaced with "contains more than 50% IgG".

Claim 1 of auxiliary request 15 is identical to claim 1 of auxiliary request 10 except that the reference to Irritable Bowel Disease (IBD) has been replaced with "autoimmune disorders" and that "the immunoglobulin concentrate contains an effective amount of IgG" has been replaced with "the immunoglobulin concentrate is in the form of a spray-dried powder containing 35-50% IgG".

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

D3: WO 98/14209

D9: Elliot et al., Arthritis & Rheumatism, 36,  
1681-1690 (1993)

D12: Davidson, Exp. Opin. Invest. Drugs, 7, 1115-1120,  
(1998)

D18: Moreto et al., Poster W1801, 1-12, (2010)

D19: Declaration by Dr Weaver of 21 February 2015

D20: Shafran et al., scientific article in preparation  
for publication

D21: Asmuth et al., AIDS, 27, 2207-2217, (2013)

D22: Wilson et al., Clin. Med. Insights:  
Gastroenterology, 6, 49-60, (2013)

D23: Hilal et al., Open J. Gastroenterology, 4,  
321-328, (2014)

VIII. Oral proceedings before the board were held on 2 July 2015 in the absence of the appellant. At the end of the oral proceedings the chairwoman announced the board's decision.

IX. The appellant's arguments submitted in writing may be summarised as follows:

*Admission of the main request, auxiliary requests 1 to 15 and of documents D19 to D23, all filed with the letter dated 19 June 2015*

The main request, auxiliary requests 1 to 15 and documents D19 to D23 should be admitted into the proceedings.



*Sufficiency of disclosure (Article 83 EPC)*

*Main request and auxiliary requests 1 to 15*

The involvement of tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) in inflammatory diseases and specifically in the diseases referred to in the claims and an improvement of these diseases by blocking or reducing TNF- $\alpha$  was commonly known from the prior art before the relevant date of the application (e.g. from documents D3, D9, D12 and page 10, lines 7 to 13 of the application).

The invention underlying the application was based on the finding that the oral administration of an immunoglobulin (Ig) concentrate from a cross-species source lowered circulating immune parameters, especially immunoglobulin G (IgG) and TNF- $\alpha$ , and thereby reduced the activity of the immune system. This amounted to the elucidation of a new mechanism of action that led to the use of orally administered immunoglobulins for the treatment of a wide variety of diseases characterised by either a chronic stimulation of the immune system (i.e. rheumatoid arthritis or Crohn's disease) or by malabsorption processes in the intestine (i.e. ulcerative colitis and AIDS).

Examples 2 and 3 of the application disclosed a lowering effect of an orally fed Ig concentrate on the IgG blood level of pigs.

Example 5 of the application disclosed *in vitro* data of two experiments. The first experiment disclosed isolated macrophages derived from mice that were either orally pre-treated or non-treated with plasma proteins derived from a cross-species source. These macrophages produced less TNF- $\alpha$  if unstimulated or stimulated by

endotoxin (LPS) than macrophages that were derived from the non-treated mice (see table 1, page 37). A second experiment analysed the production of TNF- $\alpha$  of macrophages that were derived from mice artificially pre-stimulated with LPS before they received Ig concentrate or plasma proteins both derived from a cross-species source. The data did not consistently show a TNF- $\alpha$  reduction of macrophages isolated from Ig concentrate or plasma protein-treated mice versus untreated mice (see table 4, page 38). However, the data disclosed *in toto* in the application supported the finding that the oral administration of immunoglobulins did indeed result in a reduction of TNF- $\alpha$ . This rendered credible the suitability of an orally administered immunoglobulin concentrate to treat the diseases as claimed.

Under these circumstances and in accordance with the case law, in particular decision T 609/02, the consideration of evidence from post-published documents D18 to D23 was admissible to back up the findings of the application.

- X. The appellant requested in writing that a European patent be granted on the basis of either the main request or one of the first to fifteenth auxiliary requests, all filed with the letter dated 19 June 2015.

The appellant further requested that, if these requests were not admitted, a patent be granted on the basis of either the main or one of auxiliary requests 1 to 11, all filed with the statement of grounds of appeal.

Lastly, the appellant requested that in the event that the board "*has any other objections to the grant of the application on the basis of one of the above claims Requests [sic]*", that the board contacts the appellant "*in writing or by telephone*".

### **Reasons for the Decision**

1. Even though the appellant withdrew its request for oral proceedings with the letter dated 19 June 2015, the board considered oral proceedings to be expedient in accordance with Article 116(1) EPC and maintained the date as scheduled.

As announced, the appellant did not attend the oral proceedings. Therefore, these took place in accordance with Rule 115(2) EPC and Article 15(3) RPBA and the appellant was treated as relying on its written case.

*Admission of the main request and auxiliary requests  
1 to 15 and documents D19 to D23, all filed with the letter  
dated 19 June 2015*

2. The appellant requested as its main procedural request that a patent be granted on the basis of the claims of the main request or, alternatively, on the basis of the claims of one of auxiliary requests 1 to 15.

As its auxiliary procedural request, the appellant requested that, if the above indicated requests were not admitted, a patent be granted on the basis of either the main request or one of auxiliary requests 1 to 11 as filed with the statement of grounds of appeal.

- 2.1 In view of Articles 12 and 13 RPBA the admission of the claim requests filed with the letter dated 19 June 2015 lies in the discretion of the board. Taking, in the present case, account of the criteria mentioned in Article 13(1) and (3) RPBA, in particular, the aspects of complexity and procedural economy, the board decided to admit these claim requests.
- 2.2 Hence, the appellant's auxiliary procedural request (see point 2 above) is moot and consequently the main request and the auxiliary requests 1 to 11 filed with the statement of grounds of appeal need not to be considered in the present proceedings.
- 2.3 Documents D19 to D23 were admitted for the same reasons as the claim requests (see point 2.1 above).

*Sufficiency of disclosure (Article 83 EPC)*

*Main request - claim 1*

3. Claim 1 relates to a second medical use in the form of a purpose-limited product claim pursuant to Article 54(5) EPC.
4. For the requirement of sufficiency of disclosure to be fulfilled the European patent application "*shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art*" (Article 83 EPC).
5. It is established case law in relation to claims directed to a medical use that, unless this is already known to the skilled person at the priority date, the

application must disclose the suitability of the product to be manufactured for the claimed medical use. The skilled person may also use common general knowledge to supplement the information presented in the application (see Case Law of the Boards of Appeal of the EPO, 7th edition 2013, section II.C.3.1, second paragraph and section II.C.6.2, first and second paragraphs).

- 5.1 Regarding the quality of evidence to demonstrate the suitability of a product for a claimed medical use, the Boards of Appeal have held that there is no mandatory requirement for clinical studies or studies carried out in animal models. The application must however contain some information - experimental tests carried out *in vitro* may for example be sufficient - showing that the product has a direct effect on the underlying metabolic mechanism specifically involved in the disease. This mechanism may either be disclosed in the application or known from the prior art (see decision T 609/02, point 9 of the reasons).
  
6. The product according to claim 1 is an immunoglobulin (Ig) concentrate derived from the serum of a non-human animal and it is for oral administration in humans. Further according to claim 1 this Ig concentrate is useful for the treatment of "chronic immune stimulation, Crohn's disease, rheumatoid arthritis, ulcerative colitis or a severe malabsorption associated with AIDS" and the claim also recites the mechanism by which this is achieved, namely "by specifically lowering the serum levels of IgG and TNF- $\alpha$ ".
  - 6.1 It was known at the priority date of the application that the diseases referred to in claim 1 are

characterised by a dysfunction of the immune system or a chronic inflammation (see for example page 5, lines 18 and 19; page 10, lines 4 to 28 of the application) and that they are associated with elevated serum levels of immunoglobulin G (IgG) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ).

Regarding TNF- $\alpha$ , it was also known from the prior art that reducing or inhibiting its activity resulted in the amelioration of a chronic immune stimulation, Crohn's disease, rheumatoid arthritis (RA) and ulcerative colitis (see documents D9, abstract and D12, abstract). It had also been proposed to slow down HIV replication by the use of an anti-TNF- $\alpha$  antibody (see document D3, page 11, lines 21 to 24).

7. Hence, for that the requirements of Article 83 EPC be considered as fulfilled with regard to the claimed invention there should, in view of the case law outlined in point 5.1 above, be evidence that an orally administered Ig concentrate as defined in the claim has a lowering effect on the serum levels of IgG and TNF- $\alpha$ , this being the critical mechanism on which the claimed treatment relies.
8. The appellant argued that there is such evidence in the application, in examples 2 and 3 for the reduction of IgG and in example 5 for the reduction of TNF- $\alpha$ .
9. Concerning evidence for a reduction of TNF- $\alpha$ , experiment II of example 5 discloses the use of an orally administered serum-derived Ig concentrate from one species, *i.e.* either cattle or pig, to another one, *i.e.* mice (see page 35, lines 3 to 5, line 13).

9.1 The mice are in a first step "all challenged with endotoxin on d 1 in an attempt to prime the immune system in all animals. Previous reports have found that priming macrophages will reduce immunological responsiveness upon subsequent challenge" (see page 35, lines 24 to 27).

After the endotoxin challenge the mice are *inter alia* orally fed with an Ig concentrate of either 2.5%, 0.5% or with a control diet that does not contain the Ig concentrate (see page 31, lines 15 to 26; page 34, lines 10 to 13).

Macrophages are then isolated from the mice and these are subsequently exposed to endotoxin ("stimulated") or not ("unstimulated").

Lastly, the amount of TNF- $\alpha$  produced by the macrophages is determined and compared to that produced by cells derived from the control mice.

9.2 In the absence of an explanation of the purpose underlying the set-up of this experiment and in view of the disclosure in the general part of the application, the board assumes that the endotoxin-stimulated macrophages are meant to reflect the disease state whereas those which are not stimulated are meant to reflect the normal, healthy state.

9.3 As to the results of the experiment, table 4 discloses that unstimulated macrophages isolated from mice fed with 0.5% Ig concentrate produce significantly less TNF- $\alpha$  (20 pg/ml) than unstimulated macrophages from mice that were fed the control diet (128 pg/ml). There is however no significant reduction of TNF- $\alpha$  when cells

from mice fed with the higher 2.5% Ig concentrate are considered (107 pg/ml versus 128 pg/ml).

- 9.4 The results for the endotoxin-stimulated macrophages show that the levels of TNF- $\alpha$  (308 or 325 pg/ml) nearly correspond to the level measured for the control cells (296 pg/ml), irrespective of whether the mice were fed with 0.5% or 2.5% Ig concentrate.
- 9.5 In the board's view, the data of table 4 for unstimulated macrophages are at odds with the expectations of the skilled person because they demonstrate a significant reduction of TNF- $\alpha$  in relation to the lower, but not the higher Ig concentration. The data for the stimulated macrophages are at odds with the general teaching of the application that orally delivered Ig concentrates cause a reduction of TNF- $\alpha$  in the context of diseases that are associated with elevated TNF- $\alpha$  levels. In fact these data appear to show the opposite, *i.e.* no TNF- $\alpha$  reduction after the oral administration of the Ig concentrate under conditions which are meant to mimick a disease state.
- 9.6 Experiment I of example 5 discloses the use of orally administered serum proteins, but not of an Ig concentrate (see table 1, page 37). However, Ig concentrates contain only a sub-fraction of all serum proteins. Since, in the board's view, it is not excluded that an effect achieved by the total serum protein fraction is due to or influenced by constituents in the fraction which are absent from the Ig concentrate, the data of experiment I of example 5 cannot be considered to reflect the situation for an Ig concentrate.



10. Concerning the evidence for a reduction of the serum IgG level, examples 2 and 3 of the application assess the influence of orally fed Ig concentrate on different blood parameters of weaning pigs, including IgG (see table 4 on page 22 for example 2 and table 9 on page 26 for example 3). It is however not disclosed from which species the Ig concentrate is derived, *i.e.* whether the administration takes place under cross-species conditions as claimed - or not. Moreover, both examples relate to healthy pigs.
11. In view of the observations in points 9 and 10 above, the board cannot come to the conclusion that the evidence referred to by the appellant, examples 2, 3 and 5 of the application, shows that an Ig concentrate as defined in the claim, through oral administration, has a lowering effect on the serum levels of IgG and TNF- $\alpha$ . Such evidence is also not available from the prior art and it has not been argued that it was.
12. Thus, at the priority date of the application there was no evidence available demonstrating the suitability of the product and route of administration as referred to in claim 1 for the treatment of any of the disorders recited in that claim.
13. Since the requirement of sufficiency of disclosure has to be fulfilled at the priority date of an application (or, as the case may be, the filing date), it has been established by the case law that under these circumstances evidence published after that date cannot be relied on to demonstrate the suitability of a

claimed product for a medical use (see Case Law of the Boards of Appeal of the EPO, 7th edition 2013, section II.C.6.2, third paragraph). Hence, in the present case, the teaching of documents D18 to D23 cannot be taken into account.

14. Even if it were, it appears to the board that it would not support the argument that the Ig concentrate of claim 1 is in fact suitable to achieve the therapeutic effect ascribed to it.

Slide 5 of document D18 demonstrates only an insignificant reduction of the TNF- $\alpha$  expression in the intestine of mice fed with porcine Ig concentrate when compared to control mice.

The experiments in documents D20 to D23 (see documents D20, page 5, second paragraph, page 27, line 1; D21, page 2208, column 2, second paragraph; D22, page 51, column 1, first paragraph; D23, page 322, third paragraph) were carried out with a specific serum-derived bovine immunoglobulin/protein isolate (SBI, EnteraGam<sup>TM</sup>) which contains >50% IgG, about 1% IgA and about 5% IgM and other proteins and peptides (see point 10 of document D19). An Ig concentrate of this particular composition is not disclosed in the application. Explicitly, the application discloses Ig concentrates containing about 35-50% IgG (see page 8, lines 1 and 2), *i.e.* a concentration below that of the IgGs in EnteraGam<sup>TM</sup> and without specifying the content of IgM and IgA. In view of the specific composition of EnteraGam<sup>TM</sup> it appears therefore doubtful whether predictions could be made on the basis of any effect achieved by this product towards Ig concentrates in accordance with the application.

15. Therefore, the board concludes that the application does not disclose the invention as defined in claim 1 in a manner sufficiently clear and complete for it to be carried out by the skilled person. Accordingly, the main request fails to meet the requirements of Article 83 EPC.

*Auxiliary requests 1 to 15 - claim 1*

16. Claim 1 of auxiliary requests 1 to 15 relates, as claim 1 of the main request, to a second medical use in the form of a purpose-limited product claim pursuant to Article 54(5) EPC. Compared to the main request the amendments of claim 1 of the auxiliary requests essentially concern a reduction in the number of disorders referred to (auxiliary requests 1 and 4 to 9) or the recitation of a further disorder (auxiliary requests 10 to 15), or the further definition of the Ig concentrate in terms of the source (auxiliary requests 2 to 15), or the amount of IgG in the Ig concentrate (auxiliary requests 3 to 15), or the form in which IgG is applied (auxiliary requests 8, 9 and 12), or lastly, the deletion of the two functional features at the end of the claim (auxiliary requests 4, 6 and 8).
17. These amendments do not change the essence of the invention as defined in claim 1 of the main request, *i.e.* the oral administration of an immunoglobulin concentrate derived from the blood of a non-human animal to human patients suffering from inflammatory diseases or diseases associated with immune dysfunction.

18. Therefore, the reasoning in points 5 to 14 above applies *mutatis mutandis* to the respective claims 1 of auxiliary requests 1 to 15. Hence, none of these requests is allowable since they do not fulfil the requirements of Article 83 EPC.

*Request for contact in writing or by telephone*

19. The appellant requested in its letter dated 19 June 2015 to be contacted in writing or by telephone "*In the event that the Board has any other objections to the grant of a the application on the basis of one of the above claims Requests*". In the circumstances of the case this request applies to the main request and auxiliary requests 1 to 15 admitted into the proceedings and dealt with in substance in this decision (see section IX and point 2 above).
20. In relation to this request the board notes, firstly, that while there is a right to oral proceedings pursuant to Article 116 EPC, there is no right to an informal telephone conversation with a member of the board or the issuance of a communication concerning possible further objections, especially if such objections could be dealt with during the scheduled oral proceedings. Secondly, the board decided that the concerned claim requests failed to meet the requirements of Article 83 EPC, *i.e.* they were not allowed for a reason that was well-known to the appellant (see section IV and points 17 and 20 above). Hence, there were no "*any other objections*" - in the sense of "*new objections relevant for the decision*" - about which the appellant could have been informed.

**Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated