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Via EPO Online Filing

Dear Sirs

European Patent No. 1 831 699
Proprietor: Antibodyshop A/S
Opponent: Phadia AB
Our ref: OP004290EP1 MBE/BO

OPPOSITION

is hereby filed against the grant of a patent on European Patent Application No 05820913.1, patent No. 1 831 699, entitled "DETERMINATION OF NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (NGAL) AS A DIAGNOSTIC MARKER FOR RENAL DISORDERS" filed in the name of ANTIBODYSHOP A/S. Reference is also made to the enclosed Form 2300 "Notice of Opposition against a European Patent".

The opposition fee of EUR 705 is to be deducted from our account No. 28030014.

Facts and arguments, Rule 55(c) EPC

European Patent No. 1 831 699 (hereinafter referred to as "the opposed patent") is opposed in its entirety under Article 100(a), 100(b) and 100(c) EPC. It is hereby requested that the opposed patent be revoked in full.

1. Effective dates of the claims

The opposed patent was filed on 20 December 2005, claiming priority from US 60/637,503 filed on 20 December 2004 and from US 60/719,307 filed on 21 September 2005.

1.1. Claim 1

Claim 1 of the opposed patent recites the following features.

(1) *A method of diagnosing, monitoring or determining the likelihood of a renal disorder in a human being*

(2) *wherein said method discriminates between a renal disorder and a condition that is not affecting the kidney, said method comprising the steps of*

(3) *i) determining the concentration of human neutrophil gelatinase-associated lipocalin (NGAL) in a sample of bodily fluid from the human being,*

(4) *ii) comparing said concentration with a predetermined cut-off value,*

(5) *said cut-off value being 250 ng/mL or a higher value*

(6) *such as a value between 250 ng/mL and 525 ng/mL (non-limiting feature)*

(7) *chosen to exclude lower concentrations of NGAL associated with conditions that are not affecting the kidney, wherein a concentration above the cut-off value is indicative of a renal disorder.*

The earlier priority, US 60/637,503 (hereinafter referred to as "P1") filed on 20 December 2004 describes a method for diagnosing renal disorders in humans mentioning explicitly acute renal failure (ARF), acute tubular necrosis (ATN) and acute tubulo-interstitial nephropathy (ATIN). The method comprises measuring a concentration of human NGAL in a sample of bodily fluid, mentioning explicitly only urine, wherein a measured concentration of NGAL, which is higher than a defined cut-off value selected to exclude lower NGAL values characteristic of other disorders, is indicative of a renal disorder. It is stated that neutrophils should be removed from the urine sample prior to measuring the concentration of NGAL.

P1 discloses a cut-off value of 1000 ng/ml NGAL in urine. Values above this cut-off are disclosed as indicative of renal affection. The values of features (5) (250 ng/mL or a higher

value) and (6) (such as a value between 250 ng/mL and 525 ng/mL) are not disclosed in P1.

In P1, the value chosen to exclude lower concentrations of NGAL associated with conditions that are not affecting the kidney is 1000 ng/ml. However, the data presented in table 1 of P1 does not support that this cut-off value *discriminates between a renal disorder and a condition that is not affecting the kidney.* From table 1 it is evident that NGAL values from 11 patients were tested. Seven patients had an NGAL value of 1000 ng/ml or more. Of these, only three patients had renal affection (patient nos. 1, 2 and 5.) One patient (no. 7) had renal affection without a urinary NGAL concentration above 1000 ng/ml. Accordingly, the sensitivity of the test is only 75% and the positive predictive value of the test is only 42.8%.

Further, based on the disclosed diagnoses in table 1, it can be seen that five of eleven patients had some kind of inflammation, i.e. patient nos. 3, 4, 5, 6 and 7. Of these, four had urinary NGAL concentrations above 1000 ng/ml and three of these did not have a renal disorder. From the data given in table 1, the specificity of the test is only 42.8% and the negative predictive value is 75%. Specificity is the measure for the proportion of negatives which are correctly identified, e.g. the percentage of patients without a renal disorder (but perhaps another disorder such as inflammation) who are identified as not having renal disorder.

Obviously, a test with this low predictive value is useless as a diagnostic tool (supported also by the opposed patent, wherein it is stated that both the preferred positive and negative predictive value is to be 80% or more). The test must have a high specificity (~100%) in order to truly be able to "*discriminate between a renal disorder and a condition that is not affecting the kidney*", which is the object of the invention. Thus, from the data given in P1 it is clear that the cut-off value of 1000 ng/ml does not *discriminate between a renal disorder and a condition that apparently is not affecting the kidney*.

The only conclusion that may be drawn from the data given in P1 is that the combination of sepsis and ATN in patient 5 gives a concentration of NGAL in the urine, which is clearly higher than for the other diagnoses.

Accordingly, claim 1 of the opposed patent is not entitled to claim priority from P1.

The later filed priority, US 60/719,307 (hereinafter referred to as "P2") filed on 21 September 2005 discloses the same method as P1, but mentioning that the renal disorders ARF, ATN and ATIN may result from renal ischemic injury and that "renal disorders" include more than the disorders mentioned in P1.

Further, P2 discloses that the preferred human bodily fluid is urine, wherein neutrophils have been removed (P2, p.6, l. 25). The cut-off value disclosed in P2 for urine samples is 0.5 µg/ml to 10 µg/ml, such as 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9 and 10 µg/ml (P2, p.7, l. 18). The value and the range of features 5 and 6 of claim 1 of the opposed patent are thus not disclosed in P2.

Further, a cut-off level for NGAL concentration in plasma or serum is introduced. It is disclosed that this value should be between 300 ng/ml and 900 ng/ml, such as 350 or 400 or 500 or 600 or 700 or 800 or 900 ng/ml (P2, p. 7, ll. 23-24). Thus, the value and the range of NGAL concentrations in a bodily fluid (features 5 and 6 of claim 1) of the opposed patent are not disclosed in P2.

Notably, the new (compared to P1) cut-off values disclosed in P2 are based on the same data as disclosed in P1. As discussed above, these data do not support the cut-off value of 1000 ng/ml in urine (P1), and therefore the lower value disclosed in P2 lacks support to an even greater extend. The set of data presented in P1 and P2 reveals that the lower cut-off value disclosed in P2 (500 ng/ml NGAL in urine) gives additional false positive test results compared to the cut-off value disclosed in P1, which is causing the specificity of the urine test of P2 to fall to a value of only 28.5%.

Based on the above, it is clear that claim 1 of the opposed patent is not entitled to claim priority from P2.

For that reason, the claimed priority is invalid for claim 1. Since all of the claims 2-17 depend on claim 1, the effective date for all claims is the day of filing of the opposed patent, i.e. 20 December 2005.

It is further submitted that none of the priority documents comply with Art. 83 EPC as they do not disclose to the skilled person how to choose a suitable cut-off value. As stated

above, the data disclosed in P1 and P2 do not support the technical advantage of the inventions disclosed in those applications, even accepting a specificity of only 80%. Therefore, the skilled person cannot, without undue burden, choose a suitable cut-off value to use in the methods disclosed. Consequently, it is submitted that P1 and P2 are insufficient disclosures and that neither P1 nor P2 may serve the basis of priority for the invention claimed in the opposed patent.

1.2. Dependent claims

Without prejudice to the aforementioned, several of the features recited in the dependent claims 2-17 are, independently of the lack of priority of claim 1, not entitled to the claimed priority.

Claim 3 of the opposed patent reads:

> *"The method of claim 1, wherein the sample is a plasma or serum sample."*

The earlier priority document, P1, does not mention that the method may be performed on serum or plasma samples. Consequently, the effective date of this feature of claim 3 is 21 September 2005.

Claim 4 of the opposed patent reads:

> *"The method of any of the preceding claims, wherein the other condition is an inflammatory disorder and the cut-off value is chosen to exclude lower concentrations of NGAL associated with inflammatory disorders."*

Claim 5 of the opposed patent reads:

> *"The method of any of the preceding claims, wherein the method further discriminates between a renal disorder and an infective disorder and the cut-off value is chosen to exclude lower concentrations of NGAL associated with infective disorders."*

As explained above under claim 1, the data given in the two priority documents do not support that it is possible to choose a cut-off value that excludes lower concentrations of NGAL associated with inflammatory and/or infective disorders. In fact, the data provided in table 1 of these documents (and in the opposed patent, see section 4) suggest that the cut-off value of 1000 ng/ml NGAL in urine is diagnostic for inflammation with a sensitivity of 80% whereas the sensitivity for renal disorders applying this cut-off value is only 75%.

Consequently, the effective date of these features of claims 4 and 5 is 20 December 2005.

Claim 7 of the opposed patent reads:

> *The monitoring method of any of the preceding claims, comprising the further step of repeating steps i) and ii) one or more times.*

Claim 8 of the opposed patent reads:

> *"The monitoring method of any of the preceding claims, comprising the further step of repeating steps i) and ii) within 24 hours, e.g. within 12 hours, such as within 6 hours, e.g. within 3 hours."*

The feature of repeating steps i) and ii) was first introduced in P2 and thus, the effective date of this feature of claims 7 and 8 is 21 September 2005.

Claim 9 of the opposed patent reads:

> *The monitoring method of any of the preceding claims, comprising the further step of repeating steps i) and ii) after a treatment of the renal disorder has been initiated or completed.*

This feature is not mentioned in any of the priority documents. Hence, the effective date of this feature of claim 9 as such is 20 December 2005.

Claim 10 of the opposed patent reads:

> *"The method of any of the preceding claims, wherein the renal disorder is a post-ischemic renal injury."*

The earlier priority document, P1, does not mention that the renal disorder is a post-ischemic renal injury. Thus, the effective date of this feature of claim 10 is 21 September 2005.

Claim 13 of the opposed patent reads:

> *The method of any of the preceding claims, comprising the further step of comparing said concentration with a second cut-off value, said second cut-off value being chosen to exclude lower concentrations of NGAL not associated with a degree of renal disorder that requires treatment of the patient by dialysis, wherein a concentration above the cut-off value is indicative of a renal disorder requiring treatment by dialysis.*

Claim 14 of the opposed patent reads:

> *The method of claim 13, wherein said second cut-off value is between 1000 ng/mL and 3000 ng/mL, such as 1250 ng/mL, or 1500 ng/mL, or 1750 ng/mL, or 2000 ng/mL, or 2250 ng/mL, or 2500 ng/mL, or 2750 ng/mL.*

The features of these two claims are not disclosed in any of the priority documents. Consequently, the effective date of these features of claims 13 and 14 is 20 December 2005.

Claim 17 of the opposed patent reads:

> *The method of any of the preceding claims, wherein the bodily fluid is blood or plasma or serum.*

As mentioned above, the earlier priority document, P1, does not mention that the method may be performed on serum or plasma samples. Consequently, the effective date of this feature of claim 17 is 21 September 2005.

2. Documents cited herein

D1 WO 2004/088276 (Children's Hospital Medical Center)
Publication date: 14 October 2004

D4 US 2005/0272101 A1 (Children's Hospital Medical Center)
Publication date: 8 December 2005

D5 Xu et al, "Serum measurements of human neutrophil lipocalin (HNL) discriminate between acute bacterial and viral infections" Scand J Clin Lab Invest, 1995, Vol. 55: 125-131. Publication date: April 1995

D10 Mishra J et al, "Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury" J Am Soc Nephrol 14:2534-2543. Published in 2003.

D11 Mori et al, "Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury" J Clin Invest 2005 Mar;115(3):610-621. Published March 2005.

D12 Mishra et al, "Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker or acute renal injury after cardiac surgery". Lancet 65:1231-1238. Published 2 April 2005.

D13 Bangert et al, "Urinary Ngal Is Dramatically Increased In Acute Renal Failure". Submitted abstract of 18th annual ESICM Congress. Published 25-28 September 2005.

D14 L. O. Uttenthal, "NGAL: a marker molecule for the distressed kidney?" Published in CLI Nov 2005.

D15 WO 2010/058378 (Phadia AB)
Publication date: 27 May 2010

D16 NGAL Elisa Kit (Kit 036). Inlay, downloaded on 10 August 2010 from http://www.bioporto.com/products/bioporto_diagnostics/ngal_elisa_kits/ngal_elisa_kit__1

D17 M. Bennett et al, "Urine NGAL Predicts Severity of Acute Kidney Injury After Cardiac Surgery: A Prospective Study", Clin J Am Soc Nephrol 3: 665-673, 2008

D18 The assay was presented for the first time at the 18th annual ESICM Congress in Amsterdam on 25-28 September 2005 as evidenced by the message to Copenhagen stock exchange of 22 September 2005.

D19 Translation of D18

3. The subject matter of the patent extends beyond the subject matter of the application as filed (Art. 100 (c))

Claim 1 discloses that a cut-off value of 250 ng/mL or a higher value (feature 5) such as a value between 250 ng/mL and 525 ng/mL (feature 6) is to be used as the predetermined cut-off value for comparison (feature 4) with the concentration of human neutrophil gelatinase-associated lipocalin (NGAL) that has been determined in a sample of bodily fluid from the human being (feature 3).

However, the application as filed does not support the use of this range of predetermined cut-off values in diagnosis when performed on bodyfluid samples in general, but only discloses such use in association with diagnosis performed on samples of urine, plasma or serum.

Thus, claim 1 of the opposed patent extends beyond the application as filed and contravenes Art 100(c) EPC.

4. Insufficiency of disclosure (Article 83 EPC)

4.1. The examples do not support the alleged invention

The description of the opposed patent does not disclose the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

Allegedly, the method of the invention is a method for

"*Diagnosing, monitoring or determining the likelihood of a renal disorder in a human being wherein said method discriminates between a renal disorder and a condition that is not affecting the kidney, said method comprising the steps of*

i) determining the concentration of human neutrophil gelatinase-associated lipocalin (NGAL) in a sample of bodily fluid from the human being,

ii) comparing said concentration with a predetermined cut-off value, said cut-off value being 250 ng/mL or a higher value, such as a value between 250 ng/mL and 525 ng/mL, chosen to exclude lower concentrations of NGAL associated with conditions that are not affecting the kidney, wherein a concentration above the cut-off value is indicative of a renal disorder."

Accordingly, the method of the opposed patent claims that it discriminates between renal disorders and conditions not affecting the kidney and associated with lower (higher than normal) concentrations of NGAL by comparing the measured concentration with a predetermined cut-off value of *250 ng/mL or a higher value* (*such as a value of between 250 and 525 ng/ml)*. Conditions not affecting the kidney and associated with lower (higher than normal) concentrations of NGAL are e.g. infective or inflammatory states or carcinomas that do not give rise to renal injury.

On page 5, paragraph 15 it is stated that:

> *"Accordingly, the present invention relates to measurement of NGAL in a sample of bodily fluid, preferably human urine from which any neutrophils have been removed, as a diagnostic marker of renal disorders, especially those due to renal ischemia or nephrotoxic agents. In the present invention, for the concentration of NGAL to be specifically indicative of renal disorder, it must exceed a cut-off value set to exclude those lower concentrations of NGAL that may result from infective or inflammatory states or carcinomas that do not give rise to renal injury."* (My emphasis)

Further, in paragraph 16 (page 5) it is stated that:

> *"The method of the present invention in one embodiment comprises the steps of measuring the concentration of human NGAL in a sample of urine, preferably centrifuged to remove any neutrophils, from the individual to be diagnosed, and comparing the measured concentration with a selected cut-off value determined to exceed those urinary concentrations found in humans that have no renal disorder, but may either be apparently healthy or have other disorders including inflammatory conditions, bacterial infections or carcinomas. If the measured NGAL concentration exceeds the cut-off level, this is an indication that the human has suffered renal injury and may develop or has developed ARN, ATN or ATIN."*

In paragraph 17 (p.5), various different cut-off values that allegedly enable the above mentioned discrimination are proposed. However, the skilled person looking at the disclosures of Table 1 and example 5 will soon realise that none of these cut-off values are able to make such discrimination between a condition causing a renal disorder and a condition not causing renal disorder such as "*infective or inflammatory states or carcinomas*" as stated in paragraph 15.

Table 1 discloses data obtained from eleven unselected patients admitted to intensive care. Urine and serum NGAL levels and precise diagnoses are disclosed. From this table it is evident that only four patients (nos. 1, 2, 5 and 7) had some kind of renal affection or renal disease. The other seven patients suffered from various inflammations or other disorders. However, a total of nine patients had urinary NGAL levels above 900 ng/ml. Five patients with an NGAL concentration in urine above 950 mg/ml had a condition that was not affecting the kidneys, but had another disorder including inflammatory and bacterial infections (such as pneumonia, peritonitis and septic shock). Accordingly, the skilled person looking at these data will realise that a cut-off value of 250 ng/ml or a *value between 250 and 525 ng/ml* does not help him to discriminate *between a condition causing a renal disorder and a condition not causing renal disorder.* This is further clear from the following paragraph:

Example 5 (data of Table 1) of the opposed patent states that (see p. 10, para. 36):

> *"Patient nos. 3 and 4, who at the time of sampling had no clinical diagnosis of renal disorder and whose p-creatinine was at that time within the normal range, had levels of urinary NGAL that were higher than that of patient no. 2, who was receiving hemodialysis for anuria after rupture of an aortic aneurysm. The two patients (nos. 3 and 4) may have developed renal ischemic injury because of their severe infections, the rise in urinary NGAL preceding any rise in p-creatinine, as was also observed in patient no. 5, who was clinically diagnosed as having ATN."* (My emphasis).

In other words, patients 3 and 4 (of Table 1) had severe infections, but did not have a renal disorder. These patients had urinary NGAL values of 3800 ng/ml and 2700 ng/ml, respectively. It is speculated in the specification that these patients may develop renal disorders, but it is not confirmed. Rather, it is confirmed that the patients were suffering from infections and that the patients had very high concentrations of NGAL in the urine. Further, patients 6 and 8 also presented urinary NGAL values of 1000 ng/ml or higher without having a renal disorder, but a disorder not affecting the kidneys of these patients (septic shock and acute respiratory distress syndrome, respectively). These data do not support that a cut-off value of 250 ng/ml such as a value between 250 and 525 ng/ml can discriminate between disorders causing renal affection and disorders such as inflammation or infections that do not give rise to renal affection.

Nevertheless, the specification and claims instruct the skilled person to choose a cut-off value of between 250 and 525 ng/ml in order to perform the invention in a particularly preferred way.

Thus, the description and table 1 of the opposed patent do not teach the skilled person how to choose a cut-off value that will allow discrimination between a renal disorder and a condition that is not affecting the kidney. The skilled person would be in doubt as to which cut-off value to use based on the contradictory disclosures of the opposed patent.

Accordingly, the disclosure of the opposed patent does not enable the skilled person clearly and without undue burden to choose a cut-off value that discriminates between a renal disorder and a disorder not affecting the kidneys.

The skilled person wishing to understand the rationale of the disclosed cut-off values may turn to Table 2 of the opposed patent to see whether data from this table together with the

information given in example 6 are more informative on a cut-off value that allows for the discrimination of disorders affecting the kidney from disorders not affecting the kidney, such disorders allegedly associated with lower NGAL values.

Firstly, it is noted that the table does not provide the exact diagnoses of the patients. The opponent submits that patients with an unknown diagnosis (either with or without renal affection), i.e. patients not diagnosed with sepsis or cancer, cannot reasonably be said to suffer from conditions not affecting the kidney and associated with lower, *but higher than normal*, concentrations of NGAL. Accordingly, these patients do not suffer from a condition to be excluded according to the object of the invention. Thus, these patients are to be regarded as "normal" patients and are thus to be disregarded when evaluating the method according to claim 1 and the data presented in table 2. That is when evaluating the ability of the method with respect to excluding lower concentrations of NGAL associated with inflammation, infection or carcinomas. Thus, these patients are to be disregarded.

It is noted that 27 patients were diagnosed with sepsis and that only 9 of these were diagnosed to be without renal affection. According to the opposed patent, the NGAL concentration in urine and/or plasma from these patients should be a lower value than the cut-off value of claim 1 in order for the method to be discriminative as claimed in claim 1 of the opposed patent. Interestingly, of these 9 patients 4 had plasma levels of NGAL of above 250 ng/ml, and 2 had urinary levels of NGAL of above 250 ng/ml. Accordingly, the specificity^{sepsis} of the test was 77.8% in urine and 55.6% in plasma revealing that the method is not able to discriminate these patients from patients that do have renal affection. In other words, patients suffering from sepsis but not renal disorder were misdiagnosed as having renal affection.

From this calculation, it is clear that claims 4 and 5 are insufficiently disclosed, and accordingly that claim 1 is insufficiently disclosed.

It is recalled that the specificity is the ability of the test to correctly exclude those lower concentrations of NGAL that may result from infective or inflammatory states or carcinomas that do not give rise to renal injury, i.e. the object of the invention, as stated e.g. in paragraph 15, p. 5:

> *"[...] for the concentration of NGAL to be specifically indicative of renal disorder, it must exceed a cut-off value set to exclude those lower concentrations of NGAL that may result from infective or inflammatory states or carcinomas that do not give rise to renal injury."*

The table further discloses that 15 patients had a cancer diagnosis and that 4 of the cancer patients did not have renal affection (patient nos. 20, 65, 80,100). All of these patients presented serum NGAL values above 250 ng/ml and 3 of the patients presented urinary NGAL values above 250 ng/ml. Accordingly, the specificity$^{\text{cancerous disease}}$ was as low as 25 % in urine and 0% in plasma revealing that the method is completely unable to discriminate these patients from patients that do have renal affection.

From this calculation, it is clear that claim 6 is insufficiently disclosed, and accordingly that claim 1 is insufficiently disclosed.

Taken together, it is evident that 12 patients had a diagnosis of sepsis and/or cancer without having renal affection (i.e. patient nos. 3, 20, 47, 59, 65, 69, 80, 82, 83, 88, 100 and 108). Of these 12 patients, 7 had plasma levels of NGAL of above 250 ng/ml, and 4 had urinary levels of NGAL of above 250 ng/ml. Accordingly, the specificity$^{\text{sepsis and/or cancerous disease}}$ of the test was 66.7 % in urine and 41.7% in plasma.

The proprietor emphasises in the submission of 7 April 2008 to the EPO that it is a distinguishing feature of the opposed patent…

> *"…that it is possible to discriminate between conditions that are not affecting the kidney, and conditions that are affecting the kidney, if the NGAL concentration in a body fluid is above the cut-off value 250 ng/ml."*

The proprietor further argues (in the submission to EPO of 7 April 2008) that this cut-off value is established based on the work disclosed in Table 2 and example 6 and that the data presented herein "*clearly shows that there is a significant correlation between renal affections and NGAL level*". However, the method of the claimed invention is not a method of merely diagnosing renal affection, but for *discriminating* between renal disorders and disorders that are not affecting the kidney, and wherein a cut-off value is chosen to exclude lower concentrations of NGAL associated with conditions that are not affecting the kidney. The disclosure of Table 2 does not confirm that such discrimination be made.

It is submitted that the data from patients with an unknown diagnosis are to be ignored when evaluating the method according to claim 1. However, even if included, the skilled person will appreciate that 9 out of 25 patients from table 2 diagnosed to be without renal affection had a plasma NGAL level of above 250 ng/ml and thus would be diagnosed as false positives (having a disorder not affecting the kidneys, but diagnosed as suffering from renal disorder). For urine samples, 5 out of 25 patients would be false positives. Accordingly, at a cut-off level of 250 ng/ml, the specificity of the plasma and urine samples is only 64% and 80%, respectively, revealing that the method is not able to discriminate these patients from patients that do have renal affection.

Based on the above, the opponent submits that the description and examples of the opposed patent do not substantiate that the NGAL values associated with disorders not affecting the kidneys are lower than the suggested cut-off values to exclude these disorders. Thus, the skilled person is not provided with information to choose a cut-off value that allows the kind of discrimination disclosed in claim 1. Accordingly, the description of the opposed patent does not disclose the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

4.2. Different methods for determining the NGAL concentration give different results

The specification of the opposed patent does not provide the skilled person with a reliable method for measuring NGAL concentrations.

Feature 5 of claim 1 requires that a cut-off value is set as a concentration of 250 ng/ml or higher. Feature 7 requires that this cut-off is “chosen to exclude lower concentrations of NGAL associated with conditions that are not affecting the kidney”.

Although the specific cut-off value to be used when actually performing the method is not given in claim 1 (as claim 1 only recites that it should be 250 ng/ml or higher and chosen to exclude concentrations associated with conditions not affecting the kidney), it is obvious that the cut-off value must be an absolute concentration of NGAL in the bodily fluid when the method is actually implemented in a routine assay. Otherwise, the person working the

invention would have to establish the cut-off value each and every time the method is performed, which would clearly be an undue burden.

The specification of the opposed patent suggests four different assays for measuring NGAL concentrations. These are disclosed in examples 1-4.

Examples 1-3 teach a dipstick test, a lateral flow device and a minicolumn test, respectively. These assays are all based on a capture antibody that binds NGAL and this complex is then detected by a suitable colouring agent. No specific protocols are given on how to adapt these assays so as to be able to measure absolute concentrations of NGAL in an accurate and reliable way, and no references are given to direct the reader of the specification to any such protocol or any further information at all. Therefore, examples 1-3 do not provide the skilled person with an assay for determining absolute concentrations of NGAL.

Example 4 discloses a sandwich ELISA in more detail. It is essentially this assay that is used in the further examples (see page 7, lines 46-49). The assay of example 4 is also essentially the same as the assay sold by BioPorto Diagnostics A/S under the name “NGAL ELISA Kit (KIT 036)” (D16).

The assay of example 4 provides results that are interpreted as absolute concentrations in examples 5 and 6 of the opposed patent. The assay is, however, not calibrated against any other quantitative assay for measuring NGAL concentrations. Therefore, it is not shown in the specification of the opposed patent that the concentrations shown in Tables 1 and 2 are truly absolute concentrations or that they are values related to the concentration in some assay-specific way.

Claim 1 of the opposed patent is not restricted to determination of NGAL concentrations with any specific method. The opponent submits that alternative assays for measuring NGAL concentrations give different results for the same NGAL concentrations. All four assays discussed in the opposed patent are based on anti-NGAL antibodies that should bind to NGAL, where after bound NGAL is detected and correlated to a concentration of NGAL in the sample. Obviously, such antibody-based assays are highly dependent on the specific antibody or antibodies used, such as their binding characteristics for NGAL, and the assay

results may vary substantially depending on the antibody or antibodies used and other assay-specific conditions.

That different assays give different results is clear from D15 and D17. In example 1 of D15, three different methods for determining NGAL concentrations are compared; one polyclonal-based RIA, one polyclonal-monoclonal ELISA and one monoclonal-monoclonal ELISA. The assay disclosed in example 4 of the opposed patent is a sandwich ELISA using two monoclonal anti-NGAL antibodies, 211-1 as capture antibody and 211-2 as detection antibody. Thus, it is of the same type as the monoclonal-monoclonal ELISA assay discussed in D15.

In paragraph [0067] of D15, the following relationships between the concentration values from the respective methods are given:

HNL(RIA) = 0.6553+0.5358* monoclonal-monoclonal ELISA (HNL = NGAL)

polyclonal-monoclonal ELISA = 0.0370 + 0.1135* monoclonal-monoclonal ELISA

polyclonal-monoclonal ELISA = -0.002192+0.2002*NGAL(RIA)

As evidenced by D15, the NGAL concentration values obtained by a certain method need not be the same as the values obtained by another method. On the contrary, they are very likely to differ substantially.

This is further evidenced by D17. In D17, the authors compare a standardised clinical platform (ARCHITECT analyzer from Abbott Laboratories) with the research-based ELISA kit of D16, see D17 “Materials and Methods” page 666. The relation between NGAL concentrations obtained on the ARCHITECT platform is related to the concentrations obtained by the kit of D16 according to the following formula (see Figure 1).

NGAL(ARCHITECT) = -3.5 + 1.59*NGAL(D16)

In his submission of 7 April 2008, the proprietor defines the objective technical problem as being: “how to establish a diagnostic method that allows for discrimination between condi-

tions that are affecting the kidney, and conditions that are not affecting the kidney". The solution is the establishment of a cut-off value of 250 ng/ml.

However, if a method for measuring the NGAL concentrations in samples of bodily fluids other than the ELISA disclosed in example 4 of the opposed patent is used, this cut-off would be substantially different. For instance, if the NGAL(RIA) method discussed in D15 is used, and if the re-calculation factors of D15 apply to the data of the opposed patent, the cut-off would be about 0.6553+0.5358*250 = 135 ng/ml. If the polyclonal-monoclonal ELISA is used, the cut-off would be 0.0370 + 0.1135*250 = 28 ng/ml. If the ARCHITECT platform is used, the cut-off would be -3.5 + 1.59*250 = 394 ng/ml. Although it may be argued that the recalculation factors of D15 and D17 cannot be directly transferred to the data presented in the opposed patent, it is submitted that D15 and D17 substantiate that different methods for determination of NGAL give different results.

Consequently, the cut-off value defined in claim 1 may be a totally different value if an alternative method for determining NGAL concentrations is used. If there are different measuring methods that yield different results, this amounts to an undue burden for the skilled person to work the invention (cf. T225/93). Also for this reason, claim 1 is insufficiently disclosed.

5. Lack of novelty (Article 54 EPC)

5.1. Claim 1

Claim 1 of the opposed patent recites the following features.

(1) *A method of diagnosing, monitoring or determining the likelihood of a renal disorder in a human being*

(2) *wherein said method discriminates between a renal disorder and a condition that is not affecting the kidney, said method comprising the steps of*

(3) *i) determining the concentration of human neutrophil gelatinase-associated lipocalin (NGAL) in a sample of bodily fluid from the human being,*

(4) *ii) comparing said concentration with a predetermined cut-off value,*

(5) *said cut-off value being 250 ng/mL or a higher value*

(6) *such as a value between 250 ng/mL and 525 ng/mL (not limiting feature)*

(7) *chosen to exclude lower concentrations of NGAL associated with conditions that are not affecting the kidney, wherein a concentration above the cut-off value is indicative of a renal disorder.*

5.1.1. Claim 1 lacks novelty over D1

Feature 1 of claim 1 is found in D1, e.g. in claim 1 and in paragraph 40:

> *"The method of the invention can be used to detect the onset of renal tubular cell injury, and to monitor the treatment thereof [….]. The renal tubular cell injury can be an ischemic renal injury, a nephrotoxic renal injury, or other injury that affects the tubular cells of the kidney."*

Thus, D1 discloses a method of diagnosing, monitoring or determining the likelihood of a renal disorder in a human being.

Feature 2 of claim 1 is found in D1, e.g. in the above-cited paragraph. It is implicit that a method of detecting the *onset* of a renal disorder is also a method of detecting whether there has not been onset of a renal disorder, and thus, the method is discriminating between a renal disorder and a condition that is not affecting the kidney.

Hence, the method of D1 discriminates between a renal disorder and a condition that is not affecting the kidney.

Feature 3 of claim 1 is found in D1, e.g. in paragraph 99:

> *"Urinary NGAL was quantified by Western blot and ELISA and found to be elevated in five of these fifteen patients."*

Thus, the method of D1 determines the concentration of NGAL in a sample of bodily fluid from the human being.

Features 4, 5, 6 and 7 of claim 1 are found in D1, e.g. in paragraph 98, example 5:

> *"Also, urine from patients with urinary tract infections and kidney transplant rejection (two neutrophil-related disorders) contained only minimal quantities of NGAL (not shown), easily distinguishable from the significantly greater quantities in cadaveric kidney transplants (greater than 100 ng/ml). These data demonstrate that NGAL is a novel early urinary biomarker for acute renal injury following kidney transplantation."* (My emphasis)

From this paragraph, it is evident that D1 discloses a comparison of the NGAL concentration with a predetermined value associated with renal disorder, the cut-off value disclosed in D1 being 100 ng/ml or a greater value and chosen to exclude lower concentrations of NGAL associated with conditions that are not affecting the kidneys (such as urinary tract infections), wherein a concentration above the cut-off value is indicative of a renal disorder. The cut-off value of 250 ng/ml or above of the opposed patent is not explicitly mentioned. However, as 250 ng/ml or above comprise only values confined by values *greater than 100 ng/ml,* features 4, 5, 6 and 7 of claim 1 cannot confer novelty in view of D1.

Example 6 of D1 discloses that NGAL concentrations increase within hours following acute renal failure (see paragraph 99):

> *"...patients who subsequently developed acute renal failure displayed a greater than 10-fold increase in the 2 hour value for urinary NGAL (75+10 ng/mg creatinine), and a greater than 20-fold increase in the 4 hour value for urinary NGAL (120+12 ng/mg creatinine)."*

The above-disclosed NGAL values are relative to serum creatinine values. However, it is clear from the above that NGAL concentrations are markedly increased due to acute renal failure.

Based on the above, the opponent submits that claim 1 of the opposed patent is not novel in view of D1.

5.1.2. Claim 1 lacks novelty over D1 as a selection invention

As a precaution and without prejudice to the aforementioned, it is submitted that claim 1 of the opposed patent is also not novel if it is regarded as a selection invention where the cut-off value is selected from the range mentioned in D1.

The cut-off value of the opposed patent is chosen within the range of 250 ng/ml and higher values, whereas D1 discloses a range of 100 ng/ml and higher values.

According to established case law of the boards of appeal (T 198/84 and T 279/89), a selection of a sub-range of numerical values from a broader range confers novelty if (and only if) each of the following criteria is satisfied:

(a) the selected sub-range is narrow;
(b) the selected sub-range is sufficiently far removed from the known range illustrated by means of examples;
(c) the selected area is not an arbitrary specimen from the prior art, i.e. not a mere embodiment of the prior description, but another invention (purposive selection).

The opponent submits that the selected range of claim 1 of the opposed patent, i.e. from 250 ng/ml or a higher value (feature 5), is not a narrow range compared to the range disclosed in D1. Both ranges are open-ended ("*or a higher value*") and consequently, the range of feature 5 cannot be regarded as a "narrow" range. Although the range of feature (6) may be argued as a "narrow" range, feature 6 is not presently limiting claim 1 and may be disregarded in this respect.

Further, obviously, the open-ended range of feature (5) is not sufficiently far removed from the range of D1.

Likewise, the range of feature (6) is not sufficiently far removed from the known range of above 100 ng/ml. Armed with the general knowledge (it is submitted that at least the NGAL levels of "healthy" patients are within the common general knowledge of the skilled person) that e.g. "normal" levels of NGAL are in the range of 100ng/ml (evidenced e.g. by D5, page 129, HNL=NGAL) and that infectious conditions commonly result in levels of NGAL of above 250 ng/ml (evidenced e.g. by D5, page 127), the skilled person would seriously contemplate performing the disclosure of D1 within the range of feature 6 of the opposed patent.

Finally, it is submitted that the selected range of cut-off values of features 5 and 6 of the opposed patent does not constitute a purposive selection. The proprietor has argued that

the cut-off value is chosen to exclude lower values of NGAL associated with conditions that are not affecting the kidney, and where a concentration above the cut-off value is indicative of a renal disorder. As has been thoroughly argued above, the opponent submits that this purpose is not obtained in the range specified by feature 6 because the urinary and blood NGAL concentrations of several disorders not associated with renal affection (e.g. cancer and inflammation, see tables 1 and 2 of opposed patent) are not lower than the selected range of cut-off values (see also D5, page 127). Thus, it has not been made plausible that the ranges of cut-off values (250 ng/ml or greater, such as a value between 250 ng/mL and 525 ng/mL) define a technical area, within which the cut-off values exhibit superior properties and outside which ranges, these properties would be inferior, whereby a new teaching would be given. As no improvement can be seen by this selection of ranges, this means that the selected ranges (250 ng/ml or greater such as a value between 250 ng/mL and 525 ng/mL) must be regarded as having the same properties and capabilities as the whole range (100 ng/ml or greater) and that only an arbitrary specimen from the prior art has been selected.

Thus, as a selection invention, claim 1 is also not novel in view of D1.

5.1.3. Claim 1 lacks novelty over D12

D12 was published 2 April 2005. As the effective date of claim 1 of the opposed patent is 20 December 2005, D12 is a relevant document for the assessment of novelty.

The opponent submits that the opposed patent is not novel in view of D12.

Feature 1 of claim 1 is found in D12, e.g. on p. 1236, right column:

> *"This study design allowed us to determine the precise timing of NGAL appearance in the urine and serum after cardiopulmonary bypass. Our results indicate that NGAL is not only a powerful immediate early biomarker for acute renal injury, but is also a valid discriminatory marker for the entire duration of the study."*

Thus, D12 discloses a method of diagnosing, monitoring or determining the likelihood of a renal disorder in a human being (the data obtained from patients submitted to a children's hospital).

Feature 2 of claim 1 is found in D12, e.g. on p. 1235, left column:

> *"In the 51 [children] who never developed acute renal injury, a small increase in urinary NGAL was noted at 2 h and 4 h after cardiopulmonary bypass. Children who subsequently developed acute renal injury displayed a remarkable increase in urinary NGAL at all timepoints."*

Accordingly, the method of D12 discriminates between a disorder not affecting the kidneys (such as cardiopulmonary disorder or surgery) and a disorder affecting the kidney (such as acute renal injury).

Feature 3 of claim 1 is found in D12, e.g. on p. 1236, right column:

> *"Second, we established and validated an ELISA procedure for NGAL in human urine and serum (….). Standard curves were straight in the 1-1000 µg/L range, which covers the entire spectrum of NGAL concentrations detected in our study."*

Accordingly, the method of D12 discloses a determination of concentrations of human NGAL in a sample of bodily fluid from the human being.

Feature 4 of claim 1 is found in D12, e.g. on p. 1235, left column:

> *"A scatterplot of the first available postoperative urine NGAL measurements showed that all children who subsequently developed acted renal injury had a concentration of urinary NGAL above an arbitrary cut-off value of 50 µg/L (…)."*

Thus, D12 discloses a comparison of said concentration with a predetermined cut-off value above 50 µg/L. As the cut-off value of the opposed patent is above 50 ng/ml, it is submitted that D12 discloses the features 5 and 6 implicitly, i.e. that the cut-off value may be 250 ng/ml (same as 250 µg/L) or a higher value, such as a value between 250 ng/ml and 525 ng/ml.

Feature 7 of claim 1 is found in D12, e.g. on p. 1237, left column:

> *"Our results showing a small transient increase in urine and serum NGAL in children who did not develop acute renal failure accord with previous observations that cardiopulmonary bypass surgery leads to release of NGAL into the circulation, probably secondary to inflammatory activation of leucocytes initiated by the extracorporeal circuit."*

And, further on p. 1235, left column:

> *"In the 51 [children] who never developed acute renal injury, a small increase in urinary NGAL was noted at 2 h and 4 h after cardiopulmonary bypass. Children who subsequently developed acute renal injury displayed a remarkable increase in urinary NGAL at all timepoints."*

Accordingly, D12 discloses that the cut-off value should exclude lower concentrations of NGAL associated with conditions, which are not affecting the kidney, and above which cut-off value, the concentration is indicative of a renal disorder.

Accordingly, D12 discloses all the features of claim 1 and thus, claim 1 is not novel in view of D12.

5.1.4. Claim 1 lacks novelty over D12 as selection invention

As a precaution and without prejudice to the aforementioned, it is submitted that claim 1 of the opposed patent is also not novel in view of D12 if the opposed patent is regarded as a selection invention where the cut-off value is selected from the range mentioned in D12, i.e. in the range of 50 ng/ml or greater values. The cut-off value of the opposed patent is chosen within the range of 250 ng/ml and higher values.

The opponent submits that the selected range of claim 1 of the opposed patent, i.e. 250 ng/ml or a higher value (feature 5), is not a narrow range compared to the range disclosed in D12. Both ranges are open-ended ("*or a higher value*") and consequently, the range of feature 5 cannot be regarded as a "narrow" range. Although the range of feature (6) may be argued as a "narrow" range, feature 6 is not presently limiting claim 1 and may be disregarded in this respect.

Further, obviously, the open-ended range of feature (5) is not sufficiently far removed from the range of D12.

Likewise, the range of feature (6) is not sufficiently far removed from the known range of above 50 ng/ml. Armed with the general knowledge (it is submitted that at least the NGAL levels of "healthy" patients are within the common general knowledge of the skilled person) that e.g. "normal" levels of NGAL are in the range of 100ng/ml (evidenced e.g. by D5, page

129, HNL=NGAL) and that infectious conditions commonly result in levels of NGAL of above 250 ng/ml (evidenced e.g. by D5, page 127), the skilled person would seriously contemplate performing the disclosure of D12 within the range of feature 6 of the opposed patent.

Finally, it is submitted that the selected range of cut-off values of features 5 and 6 of the opposed patent does not constitute a purposive selection. The proprietor has argued that the cut-off value is chosen to exclude lower values of NGAL associated with conditions, which are not affecting the kidney, and where a concentration above the cut-off value is indicative of a renal disorder. As has been thoroughly argued above, the opponent submits that this purpose is not obtained in the range specified by feature 6 because the urinary and blood NGAL concentrations of several disorders not associated with renal affection (e.g. cancer and inflammation, see tables 1 and 2 of opposed patent) are not lower than the selected range of cut-off values (see also D5, page 127). Thus, it has not been made plausible that the ranges of cut-off values (250 ng/ml or greater, such as a value between 250 ng/mL and 525 ng/mL) define a technical area, within which the cut-off values exhibit superior properties and outside which ranges, these properties would be inferior, whereby a new teaching would be given. As no improvement can be seen by this selection of ranges, this means that the selected ranges (250 ng/ml or greater such as a value between 250 ng/mL and 525 ng/mL) must be regarded as having the same properties and capabilities as the whole range (100 ng/ml or greater) and that only an arbitrary specimen from the prior art has been selected.

Thus, as a selection invention, claim 1 is also not novel in view of D12.

6. Lack of inventive step (Article 56 EPC)

For the avoidance of doubt, the opponent maintains that claim 1 is not novel. However, should the Opposition Division find the above observations not to be persuasive, further arguments are provided below with respect to lack of inventive step of the claims.

D1 is related to the same technical field as the invention and further addresses the technical problem of the opposed patent, i.e. to provide methods allowing discrimination of renal

disorder and disorder not affecting the kidney. Further D1 provides essentially all the features of claim 1 of the opposed patent.

D1 may consequently be seen as constituting the closest prior art.

The difference (if any) between the opposed patent and D1 may (without prejudice to the arguments presented in section 5.1.1 and 5.1.2) be seen as the selection of a higher cut-off value than the value disclosed in D1.

The technical effect of this difference is that a lower proportion of diagnostic assays will result in false positive results (i.e. a lower proportion of conditions that are not affecting the kidney will be incorrectly diagnosed), and thus, that a higher specificity of the test is obtained. This will be at the expense of the sensitivity of the test because a higher proportion of patients with a condition that is affecting the kidneys will be incorrectly diagnosed as negative, i.e. false negative.

The proprietor suggest that the objective technical problem is *"how to establish a diagnostic method that allows for the discrimination of disorder that are affecting the kidney and disorder that are not affecting the kidney"* (see submission from the proprietor of 7/4-2008). However, as evidenced above in section 4, this problem is not solved by the claimed invention and consequently, cannot be said to be the objective technical problem.

The objective technical problem of the invention is therefore "how to provide a cut-off value of NGAL alternative to the cut-off value of 100 ng/ml, which alternative cut-off value results in a higher specificity, i.e. a lower proportion of diagnostic assays resulting in false positives positive results."

The disclosures of each of D4, D10, D11, D13 and D14 are all in the technical field of the invention and its technical problem and the skilled person would consult these teachings in order to try to solve the objective technical problem of the opposed patent. D4, D10, D11, D13 and D14 disclose collectively that disorders affecting the kidney result in elevated levels of NGAL in body-fluids. This teaching may even be said to constitute the general knowledge of the skilled person.

D4 discloses in [0078] that *"A small transient increase in urine and serum NGAL in patients who did not develop ARF was consistent with previous observations that cardiopulmonary bypass surgery leads to release of NGAL into the circulation, probably secondary to inflammatory activation of leukocytes initiated by the extracorporeal circuit"*. Further, D4 discloses in [0058] that *"Ngal is a sensitive non-invasive biomarker for renal tubular cell injuries, including renal ischaemia and nephrotoximia"*.

D10 discloses *"that NGAL represents a novel, sensitive, non-invasive urinary biomarker for renal ischemia."* And further*, "that urinary NGAL was evident even after very mild subclinical renal ischemia" (*see "Discussion" section).

Specifically D11 states that urinary NGAL levels rise to 557 ng/ml following acute tubular necrosis and further that "*NGAL expression [correlate] with acute kidney damage, implicating the kidney as the major source of serum and urinary NGAL"* (see results section, page 611).

D13 is an abstract from the 18th ESICM Congress in Amsterdam held on 25-28 September 2005 by i.a. Dr. Uttenthal, who is one of the inventors of the opposed patent. As evidenced by D18, the assay was presented both professionally and commercially at this conference. D13 concludes that "*increased NGAL in serum and urine is not a reflection of neutrofilia, nor is it just an acute phase reactant, as shown by the absence of correlation with CPR*", and further that "*The results suggest that NGAL produced in organ damage spills over into the blood and is excreted in the urine, but renal NGAL in acute tubular necrosis also passes directly into the urine to produce dramatically elevated levels before plasma creatinine has been affected. Highly elevated levels of NGAL may be an effective marker for acute renal injury*" (see D13 conclusion section).

D14 is an article by Dr. Uttenthal. D14 discloses that NGAL is raised in patients suffering from inflammation, infections, neoplastic conditions and renal disorders. Further, it is stated that NGAL may serve as an early marker for ischaemic renal injury. It is stated that: *"It is therefore apparent that a large variety of renal disorders are associated with raised plasma and urinary levels of NGAL. While plasma and urinary NGAL levels are closely correlated in acute conditions, it is to be expected that urinary NGAL levels will be particularly high after ischaemic renal injury severe enough to result in acute renal failure, acute tubular necrosis*

or acute tubulo-interstitial nephropathy. However, the use of urinary NGAL as a potential marker for these conditions is subject to the proviso that the presence of concurrent conditions tat are independently associated with raised NGAL levels are taken into account." (see the section "NGAL and the kidney").

As acknowledged in section [0005] of the specification of the opposed patent, the skilled person knows that diseases resulting in activation of neutrophils result in elevated levels of NGAL, but only resulting in slightly elevated levels NGAL. As disclosed in D5 on page 128, the optimal cut-off level for detection of bacterial infection is 155 ng/ml, and "normal" levels are in the range of 38 – 190 ng/ml. However, given the variation of NGAL levels in patients with bacterial infections, the skilled person would obviously appreciate that cut-off levels excluding samples from patients with bacterial infections as well as "healthy" patients must be above these values, e.g. in the range comprised by claim 1.

Accordingly, the skilled person trying to solve the objective technical problem would appreciate that 1) highly elevated levels of NGAL would correlate with renal disease such as kidney damage, and that 2) NGAL levels in the range of 38 – 190 ng/ml are expected following most diseases not affecting the kidney ("healthy patients"), and that 3) NGAL levels increase due to infectious disease and consequently that around 3-400 ng/ml NGAL are expected following some diseases not affecting the kidney (bacterial infection, see D5 page 127).

Therefore, the skilled person would easily recognise that the cut-off value should be raised from the cut-off value of 100 ng/ml proposed in D1 and at least above the "normal" values disclosed in D5 in order to provide a cut-off value of NGAL alternative to the cut-off value of 100 ng/ml, which alternative cut-off value results in a lower proportion of diagnostic assays resulting in false positive results (i.e. a lower proportion of conditions that are not affecting the kidney will be incorrectly diagnosed). The skilled person would even be expected to suggest a cut-off value of above 3-400 ng/ml.

Consequently, the skilled person would without inventive effort appreciate that the cut-off level should be higher than 100 ng/ml, such as higher than 250 ng/ml as claimed in the opposed patent.

Consequently, feature 5 cannot contribute to inventive step.

Further, the skilled person would also appreciate that the cut-off value should not be raised infinitely in order to provide a cut-off value of NGAL alternative to the cut-off value of 100 ng/ml, which alternative cut-off value does not result in an unacceptably high proportion of diagnostic assays causing false negatives (i.e. a higher proportion of conditions that are affecting the kidney will be incorrectly diagnosed).

Consequently, the introduction of a preferred upper limit of cut-off values of feature 6 cannot contribute to inventive step.

Although none of D4, D10, D11, D13 or D14 mention a cut-off value of specifically 250 ng/ml or a cut-off value of between 250 ng/mL and 525 ng/mL, it is submitted that these numbers are arbitrarily selected features that are not supported by the data submitted in the application as filed.

In any event, should it be re-alleged by the proprietor that the cut-off value of specifically 250 ng/ml (or between 250 ng/mL and 525 ng/mL) is supported by the experimental data submitted in the application as filed, it is submitted that conducting experiments such as the ones conducted by the proprietor in order to identify a suitable cut-off value, is a mere routine for the skilled person, and, as such, does not seem to provide unexpected results.

On the contrary, the skilled person would expect to be able to identify suitable cut-off values following the experiments that the proprietor has submitted. Thus, the skilled person trying to solve the objective technical problem would arrive at the present invention as a matter of routine based on D1 and his common general knowledge and/or any one of D4, D10, D11, D13 and D14.

Consequently, claim 1 of the opposed patent lacks an inventive step in view of D1 in combination with common general knowledge and/or in combination with any of D4, D10, D11, D13 and D14.

7. Dependent claims

None of the dependent claims introduce features and/or limitations that remedy the lack of sufficient disclosure of the opposed patent. Likewise, none of the dependent claims introduce features and/or limitations that remedy the lack of novelty and/or inventive step.

Particularly, it is noted that **claims 2 and 3** (and claims 16 and 17) of the opposed patent cannot contribute novelty over D1 and D12 and cannot be considered relevant for the assessment of inventive step.

Further, it is noted that **claims 4-6** cannot be considered to contribute to an inventive step as the skilled person would appreciate that the disorders to be excluded, i.e. inflammatory, infective and cancerous disorders, all result in NGAL levels that are increased, but not elevated to the levels associated with renal injury. This is particularly evidenced by D14, and particularly the last statement on page 1:

> *"However, the use of urinary NGAL as a potential marker for these conditions is subject to the proviso that the presence of concurrent conditions that are independently associated with raised NGAL levels are taken into account".*

According to the preceding paragraphs of D14, the *"concurrent conditions that are independently associated with raised NGAL levels"* are inflammatory, infective and cancerous disorders.

Claims 7-9 relate to the repeated monitoring of the NGAL levels in the test samples. This feature cannot contribute to inventive step as it is obvious for the skilled person that repeated monitoring of the early progression of NGAL levels would provide a more useful diagnostic tool than a single measurement. This is also reflected in D14 where it is stated (page 2, section *"NGAL as potential diagnostic marker"*, last sentence) that:

> *"It is to be expected that serial rather than isolated single measurements of NGAL, whether in urine or plasma, will provide the most useful data from patients with concurrent pathologies".*

Claim 10 discloses that the renal disorder is a post-ischemic renal injury. **Claim 11** discloses that the renal disorder is a disorder that may cause acute renal failure, acute tubular necrosis or acute tubulo-interstitial nephropathy. **Claim 12** discloses that the renal disorder is caused by a nephrotoxic agent. However, D11 (abstract) discloses that NGAL accumulates in blood and urine of humans after nephrotoxic and ischemic injury, rendering these features obvious.

Claims 13 and 14 are insufficiently disclosed. Reference is made to the arguments put forward under section 4.

Claim 15 cannot contribute to inventive step as this feature is common general knowledge of the skilled person.

8. Conclusion

In conclusion and based on the above, the opponent requests that the opposed patent be revoked in full for all designated contracting states. In the event that the Opposition Division is minded to maintain the patent in any form, the opponent requests oral proceedings (Art. 116 EPC).

Yours faithfully
Chas. Hude A/S

Mikkel Bender
Representative of the Opponent