FACTS AND SUBMISSIONS

1 European Patent number EP-B-1616184 is based upon European Patent application number 04758356.2 having the date of filing of 26-03-2004 and claiming priority of 27-03-2003 and 04-11-2003. Mention of the grant of the patent was made in the European Patent Bulletin 2009/30 of 22-07-2009. The patent proprietors are Children's Hospital Medical Center and The Trustees of Columbia University (USA). They are represented by Stefan Weisgerber of Modiano Josif Pisanty & Staub Ltd (DE) and, under sub-authorisation, by Jane Evenson and David Miller of Mathys & Squire (UK).

2 With the letter received on 11-02-2010, an opposition was filed by Bioporto Diagnostics A/s, represented by Susanne Hoiberg and Pernille Winding Gojkovic of Hoiberg A/S (DK) (Opponent 1). A further notice of opposition was received on 22-04-2011. It was filed by Ute Kilger of Forrester and Boehmert (Opponent 2). The Opponents requested revocation of the patent in its entirety under Articles 100(a), (b), (c) EPC on grounds of lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC), insufficiency of disclosure (Article 83 EPC) and added subject-matter (Article 123(2) EPC). Both Opponents requested oral proceedings as an auxiliary measure (Article 116 EPC).

3 The Patentee filed reasoned arguments and a new Main Request with the letter received on 29-12-2010. The Patentee requested the maintenance of the patent on the basis of the new Main Request. Oral proceedings were requested as an auxiliary measure (Article 116 EPC).

4 Oral proceedings were scheduled with the summons of 09-05-2011 for 06-12-2011.

5 Opponent 1 replied to the summons with the letter dated 05-10-2011, Opponent 2 with the letter dated 06-10-2011. Both submitted further reasoned arguments.

6 The Patentee replied to the summons with the letter dated 06-10-2011. He filed Auxiliary Requests 1A to 1D and Auxiliary Requests 2-6 as well as evidence and reasoned arguments. These Auxiliary Requests are referred to as Auxiliary Requests 1-9 in this decision. The Patentee requested to maintain the patent on the basis of the Main Request or on one of the Auxiliary Requests.

7 During the oral proceedings on the 06-12-2011 the Patentee and both Opponents were present. The present decision is based on the Main Request and Auxiliary Request 1-9 filed in response to the summons to oral proceedings.

8 The Opponents supported the opposition by reference to documents D1-D20, the Patentee contributed documents D21-D23 (see Annex).

DECISION

- The opposition is admissible.
- Neither the Main Request nor Auxiliary Requests 1-9 fulfill the requirements of the EPC. The Opposition Division therefore decides to revoke the patent (Article 101 (3)(b) EPC).
- The decision is appealable.

REASONS FOR DECISION

1 **Admissibility of Opposition**

The opposition is admissible because the requirements of Articles 99(1) and 100 EPC as well as Rules 76(2)(c) and 3(1) EPC are fulfilled.

MAIN REQUEST

2 **Main Request: the independent claims**

The independent claims have the following features:

Claim 1 (features f1-7):

1. A method for the detection of a renal tubular cell injury, which is an ischemic renal injury, in a human patient, comprising the steps of :
2. 1) contacting a urine sample
3. obtained from a human patient
4. with an antibody for a biomarker consisting of NGAL,
5. appearing within the first 24 hours of the onset of the ischemic renal injury,
6. to allow formation of a complex of the antibody and the biomarker; and
7. 2) detecting the antibody-NGAL complex.

Claim 20 (features f1-6):

1. A method of identifying the extent of a renal tubular cell injury, which is an ischemic renal injury, caused by an event, comprising the steps of
2. 1) detecting in at least one urine sample
3. obtained from a human patient
4. the presence of a biomarker biomarker consisting of NGAL,
5. appearing within the first 24 hours of the onset of the ischemic renal injury, and
6. 2) determining the extent of the renal tubular cell injury based on the time for onset of the presence of NGAL in the urine sample, relative to the time of the event.

Claims 8 and 18 refer to the use of kits in a method according to claim 1. These claims therefore also comprise features 1-7 of claim 1.

3 **Main Request: Articles 100(c), 123, 84 EPC, Rule 80 EPC**

The Opponents had no objections under Articles 123 and 84 as well as Rule 80 EPC against the Main Request. The Opposition Division is of the opinion that Main Request fulfils the requirements of Articles 123 and 84 as well as Rule 80 EPC.

4 Main Request: Articles 100(b) and 83 EPC

The Opposition Division is of the opinion that the claims of the Main Request fulfill the requirements of Articles 100(b) & 83 EPC. The reasoning is as follows. All references relate to the patent as granted.

4.1 Article 83 EPC demands that the application must contain sufficient information to allow the person skilled in the art, using his common general knowledge, to perform the invention over the whole area claimed without undue burden and without needing inventive skill. A detailed description of at least one way of carrying out the invention must be given. Since the application is addressed to the person skilled in the art, it is neither necessary nor desirable that details of well-known ancillary features should be given, but the description must disclose any feature essential for carrying out the invention in sufficient detail to render it apparent to the skilled person how to put the invention into practice. An objection of lack of sufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts (EPO Guidelines C-II-4.9, D-V-4.3; T19/90).

4.2 The Opposition Division agrees with all parties that feature f5 of claim 1 (and claims 8, 18, 20) refers to an inherent property of the NGAL molecule present in a human patient. The Opposition Division also agrees with all parties that the claim provides no limitation with regard to the time of urine sampling after ischemic renal tubular cell injury, short "IRTCI".

4.3 The Opponents contest compliance of with Article 83 EPC (all claims), because given that NGAL is also present in the urine of subjects suffering from other diseases than IRTCI (cf. D5, D12), and in the urine of healthy subjects (cf. D2), its presence can not diagnose IRTCI.

The Opposition Division disagrees. In the technical context of the present patent, the skilled person is a medical practitioner. He is aware of the complexities of medicine. He understands that a final diagnosis is rarely based

on a single criteria / diagnostic result. Rather, findings need to be backed-up and complemented by further examination, and judged in view of the medical history of a subject. The skilled person therefore also knows that hardly any biomarker exists that is specific for a single pathology only. Consequently, when employing NGAL as biomarker for IRTCI any physician would understand that an obtained positive result would require further confirmation. In this respect, he knows about additional examinations, including further diagnostic tests, to exclude other possible pathologies, such as bladder cancer and other neoplasms (D5, D12), or other causes of RTCI, such as nephrotoxins (D4). Nevertheless, NGAL is of great value to the skilled person, because it allows him to guide and focus subsequent diagnostic steps, or confirm previous results obtained by other diagnostic means.

D2 teaches that NGAL is present in the urine collected over a period of 24 hours. The application found that NGAL is present in minimal amounts at least in the urine of healthy human subjects (par.94 & 95). In contrast, NGAL is significantly increased in urine of (human) patients suffering IRTCI compared to healthy subjects (examples 1-2, 5-6). Diagnosis is always based on comparison to a reference. Biomarker-based diagnosis is no exception to this. Hence, the skilled person, being aware of NGAL excretion in normal subjects, looks for the demonstrated differences in NGAL in sample *vs* control when carrying out the claimed method. Serial measurements are not required to detect such differences.

4.4 The Opponents take the view that detection of IRTCI requires indication of a NGAL threshold in all the claims (cf. D16).

The Opposition Division emphasises the fact that the absolute level of any biomarker detected is dependent on a variety of experimental parameters (sample size, sample treatment, assay set-up, type of assay components, etc) as well as patient characteristics (age, race and gender, spectrum of disease, body weight etc) (cf. D14: p.1754 col.1 par.2). Indication of specific NGAL threshold levels in a claim is therefore not desirable, unless all relevant parameters are indicated as well. For the same reason, comparing NGAL levels indicated in the patent as granted with NGAL levels published in other documents (eg D16: table 3) is not conclusive. The important fact a person skilled in the art can learn from the opposed patent is that urinary NGAL can be used to diagnose IRTCI at an early stage.

4.5 Opponent 2 is of the opinion that a diagnostic "decision" step is required for detection of IRTCI in all claims.
The Opposition Division disagrees. The skilled person understands that a method of diagnosis necessarily involves a step at which a decision for or against the presence of a disease is taken. Moreover, the opposed patent discloses a diagnostic "decision" step.

4.6 The Opponents hold the view that monitoring the effectiveness of IRTCI treatment with urinary NGAL (claim 5) is not enabled.
The Opposition Division disagrees. The patent demonstrates that NGAL increases in response to IRTCI, ie increased NGAL reflects tubular damage caused by IRI (ischemic renal injury). In the absence of any evidence to the contrary, it is reasonable to assume that NGAL levels would change depending on patient responsiveness to treatment (par.40). Regarding this issue D3 is not relevant, because it deals with NGAL expression during SV40 infection. Viral infection is not known to be linked to IRTCI.

4.7 Opponent 1 doubts that the skilled person is enabled to detect the extent of IRTCI with NGAL (claims 20-22).
The Opposition Division again disagrees. The patent sufficiently instructs the skilled person how to proceed for identifying the extent of injury (claims 20-22; par.37-40). Example 1 (figures 4-5) and examples 5-6 (figures 15-16, in particular figures 15B and 16B) illustrates how timing of NGAL appearance and excretion level change as function of severity of ischemia.

4.8 Opponent 1 alleges lack of enablement for claims 24-25, because damage to the kidney observed during transplantation / open heart surgery may be due to administered medication rather than IRI.
The Opposition Division disagrees. First, examples 5 & 6 demonstrate the claimed subject-matter. There exists no reason to believe that the investigators did not take the possible impact of administered medication into consideration and controlling for it when they had designed the clinical study. Second, while administration of nephrotoxins may result in RTCI, it is reasonable to assume that this depends on the dose regime. No data are available demonstrating that the dose regime typically applied before / during the treatments in question could be responsible for acute renal failure diagnosed in the present examples.

4.9 Conclusion: The Opposition Division takes the view that the objected lack of sufficiency of disclosure is neither based on serious doubts nor sufficiently substantiated by evidence. The subject-matter of the Main Request is enabled (Article 83 EPC) .

5 **Main Request - claim 1: Novelty (Articles 100(a) & 54 EPC)**

The Opposition Division is of the opinion that the claims of the Main Request fulfill the requirements of Article 54 EPC. The reasoning is as follows.

5.1 Article 54 EPC stipulates that a document takes away the novelty of any claimed subject-matter derivable directly and unambiguously from that document including any features implicit to a person skilled in the art in what is expressly mentioned in the document. Features may be implicit in the sense that, in carrying out the teaching of the prior document, the skilled person would inevitably arrive at a result falling within the terms of the claim. An implicit feature destroys novelty only where there is no reasonable doubt as to the practical effect of the prior teaching (EPO Guidelines C-III-9.2 & 9.6). In a method claim, the purpose of the method is a functional feature of the claim (EPO Guidelines C-III-4.12).

5.2 The Opposition Division agrees with all parties that feature f5 of claim 1 (and claims 8, 18, 20) is not limiting the claim because it refers to an inherent property of the NGAL molecule present in a human patient (see point 4.2).

5.3 The Opponents object to novelty of claim 1 in view of D1, D2, D5 and D13, arguing that each of these documents discloses all the features of claim 1. The Opposition Division disagrees:

5.3.1 D1 deals with NGAL analysis in a kidney tissue sample of a rat model of IRI (abstract). The document lacks f2-3 (see point 2). The fact that a smashed kidney contains urine does not qualify it as urine sample. Similarly, while a rat model is intended to simulate a human pathology, it is not a human patient.

5.3.2 D2 analyses NGAL in healthy subjects (abstract). It lacks f1 because it is silent with respect to IRI or IRTCI.

5.3.3 D5 detects NGAL in the urine of bladder cancer patients (abstract). The document does not disclose f1.

5.3.4 D13 discloses methods of diagnosing IRI by detecting KIM (kidney injury molecule) proteins. As none of the identified KIMs corresponds to NGAL, D13 lacks f4. While NGAL falls under the definition of a KIM (D13: p.6 ll.1-2), this is not relevant for novelty. A generic disclosure does not take away novelty of a specific example (EPO Guidelines C-IV-9.5).

5.4 Conclusion: Claim 1 of the Main Request is novel, because the subject-matter of the claim is not directly and unambiguously derivable from any prior art document (Article 54 EPC). Although no objections were raised against the other claims of the Main Request, the Opposition Division notes that they are novel for the same reasons as claim 1.

6 Main Request - claim 1: Articles 100(a) and 56 EPC

The Opposition Division agrees with the Opponents that claim 1 of the Main Request lacks an inventive step. The reasoning is as follows.

6.1 *The closest prior art*

The closest prior art is that which in one single reference discloses the combination of features which constitutes the most promising starting point for an obvious development leading to the invention. In selecting the closest prior art, the first consideration is that it should be directed to a similar purpose or effect as the invention or at least belong to the same or a closely related technical field as the claimed invention. In practice, the closest prior art is generally that which corresponds to a similar use and requires the minimum of structural and functional modifications to arrive at the claimed invention (EPO Guidelines C-IV-11.5.1).

6.1.1 The Opponents propose D1, D11, D15, D20, the Patentee D15 or D20, as closest prior art.
The Opposition Division identifies D15 as the closest prior art, because it is directed to a similar purpose and has the most features in common with claim 1. D15 discloses Cyr61 protein detected in urine as early biomarker for renal ischemic reperfusion injury. Mice and rats were subjected to bilateral ischemia. The authors screened a subtraction library to search for potential disease markers that would be induced rapidly after IRI. mRNA for Cyr61, a secreted growth factor-inducible immediate early gene, was markedly up-

regulated at two hours in the kidney but not other organs following renal ischemia. Cyr61 was synthesized in the proximal straight tubule. Induction of Cyr61 protein could be detected in the kidney within one hour, peaked at four to eight hours, and remained elevated for at least 24 hours following ischemia. Cyr61 protein was also detected in urine at three to six hours and peaked at six to nine hours after renal injury (abstract).

6.1.2 D1, D11 or D20 are considered to be less suitable as closest prior art:

1. D1 found that, in a rat model for IRI, NGAL is overexpressed in injured proximal tubuli in a kidney tissue sample. It is, however, directed to a different purpose than the patent as granted. It intends to characterise the processes involved in renal injury and repair, rather than to identify biomarkers for IRTCI (abstract).
2. D11 neither discloses NGAL nor is specifically directed to diagnosis of IRTCI. It relates to a variety of kidney diseases, and focuses on renal diabetes (summary of invention, examples).
3. D20 identifies urinal KIM-1 as novel biomarker for human ischemic renal proximal tubule injury. The authors investigated patients with ischemic acute tubular necrosis (ATN), which is a more advanced stage of IRTCI than that investigated in D15. The authors also note that the study does not permit to identify how early in the course of disease urinary KIM-1 can be detected (abstract; p.241 col.2). In contrast, the authors of D15 confirmed that Cyr61 is detectable in the urine at three to six hours after insult.

6.2 *The objective technical problem*

Establishing the objective technical problem is done by studying the patent, the closest prior art and the distinguishing feature(s) between the claimed invention and the closest prior art, followed by identifying the technical effect resulting from the distinguishing features, and finally formulating the technical problem (EPO Guidelines C-IV-11.5.2).

6.2.1 The Opposition Division establishes that the difference between claim 1 and closest prior art D15 is that NGAL instead of Cyr61 is used as early urinary IRTCI biomarker. No technical effect is associated with this difference. The objective problem underlying the present patent can thus be regarded as to provide an alternative urinary biomarker for IRTCI.

6.2.2 The Patentee defined the problem to be solved as to provide an early onset biomarker which appears as early as 2h after IRI. The Opposition Division observes that claim 1 does not indicate any time point at which NGAL is detected after IRTCI. Hence, such a feature should not be taken into account when formulating the objective technical problem based on the distinguishing features between the claimed invention and the closest prior art. The Opposition Division repeats in this context that f5 of claim 1 is not a distinguishing feature (see point 4.2).

6.3 *Obviousness of choosing NGAL as solution to the problem*

The term "obvious" means that which does not go beyond the normal progress of technology but merely follows plainly or logically from the prior art, i.e. something which does not involve the exercise of any skill or ability beyond that to be expected of the person skilled in the art (EPO Guidelines C-IV-11.4).

6.3.1 The Patentee takes the view that it is not obvious to choose NGAL as solution to the problem. The reasons are:

- The prior art discloses many other alternative biomarker candidates that could be selected instead of NGAL (cf. D21, D23).
- It is impossible to predict that NGAL is a urinary biomarker for IRTCI. Knowledge about NGAL is limited. Increased presence of NGAL in urine in diseases not related to IRTCI is irrelevant (cf. D5, D12). In general, the fact that a protein is up-regulated in renal tissue in response to injury allows no conclusion about its possible presence in the urine after injury (cf. D17, D23). Excretion is complex in healthy subjects and it is unforeseeable how it is impacted by disease. Even if a protein is secreted into the urine in response to injury, other requirements need to be fulfilled to qualify it as biomarker (eg stability, sustained presence).
- The prior art lacks any pointers to NGAL as solution of the problem.

6.3.2 The Opposition Division disagrees with the Patentee. The Opposition Division establishes that NGAL is known to have many of the properties that also qualify Cyr61 as biomarker for IRTCI. Both molecules were detected in differential expression analysis of a rat IRI model. Like Cyr61, NGAL is

overexpressed in the proximal tubules injured by IRI (D1). NGAL mRNA was more than 20-fold enhanced at 24h and 48h after IRI. Importantly, NGAL protein expression was up-regulated correspondingly after 24h and 48h. At least in healthy subjects NGAL is a secreted protein that finds its way into the urine, where it appears to be sufficiently stable to be detected (D2: abstract). The skilled person also learns from D1 that NGAL has potentially advantageous diagnostic properties over Cyr61. Cyr61 mRNA levels returned to normal within 24-72h. In contrast, NGAL mRNA levels stayed 20-fold up at least 48h, implying that increased NGAL protein levels may be longer detectable after IRI than those of Cyr61.

Further addressing the arguments of the Patentee, the Opposition Division equally establishes that the pathophysiological changes during IRTCI favor release of proteins located in the proximal renal tubule into the urine. The changes in acute tubular injury, which is either caused by ischemia or toxins, are reviewed in D17 (summarised in figure 1-14). Changes in ischemic renal injury are also reviewed in D6. According to the state of the art, tubular cells undergo morphological changes in response to an ischemic insult. First, there is a loss of cell polarity (D17 p.2 col.1, p.7). As a consequence, at least some of the molecules present in the disappearing apical brush border are released into the urine. The apical transport and transcellular re-absorption functions carried out by brush border cells are lost. Resulting ATP depletion is a hallmark of ischemia. Loss of cell polarity frequently results in tubular cell loss (exfoliation) and at least some of the those cells find their way into the urine (D17 p.2 col.2; D6: p.477 col.2, p.487 col.2 - p.488 col.1; D20: p.242 paragraph bridging col.1 & col.2). Second, cell death occurs in two forms: coagulative necrosis and apoptosis. As a consequence of the necrosis, cells may disintegrate. Apoptosis leads to cell fragmentation with at least some of the cells and remnants being shed into the urine (D17: p.4; D19: p.99 col.1). Apoptosis occurs already after short duration of ischemia (D17: p.8 col.1; D6: p.487 col.2 par.4).

The Opposition Division acknowledges that in healthy kidneys / renal tubules low-molecular weight proteins (LMWP) are typically excreted into the urine only in minimal amounts, the majority of protein being absorbed and eventually hydrolysed by proximal tubular cells via an endocytosis process (D22: p.2040 col.2; D23: par.19). NGAL is a LMWP (patent as granted par.49) and it is indeed present in urine of healthy subjects only in minimal amounts. But in IRTCI patients kidney / tubular cells are not healthy. They are damaged which can be expected to interfere with cell function and result in increased release of protein into urine, as explained above.

A further observation relates to the fact that NGAL levels in urine are significantly increased in bladder and breast cancer patients (D5, D12: abstracts). These diseases are not the result of IRI, or in any way related to disease of the kidney. Nevertheless, the skilled person learns from these findings that the healthy kidneys in these patients seem to be capable of secreting higher levels of the protein in the urine and this seems not to be compensated by increased re-absorption.

To summarise, the Opposition Division is of the opinion that there is already sufficient biomarker data for NGAL available to qualify it as promising alternative biomarker candidate to Cyr61. As NGAL is known to be present in the urine of heathy patients, it only remains to be demonstrated that it increases in urine after IRTCI. Common knowledge teaches the skilled person that IRTCI is expected to interfere with NGAL re-absorption and that damaged tubular cells, or molecules released therefrom, can be reasonably expected to find their way into urine.

6.3.3 Further addressing the arguments of the Patentee (see point 6.3.1), the Opposition Division observes that the prior art contains no information regarding NGAL that would dissuade the skilled person from choosing NGAL as alternative biomarker and from looking for changes in urine protein level in response to IRTCI. In other words, no prejudice or discouraging facts existed against choosing NGAL as alternative candidate urinary biomarker for diagnosing IRTCI. There is no doubt that many genes are up-regulated in response to IRI (D21: abstract). Few of the corresponding proteins, if up-regulated in response to IRI, will turn out to be good urinary biomarker for IRI. On the other hand, Cyr61 is by no means the only biomarker known to be present in urine. HGF, KIM-1, IL-18, pro-inflammatory cytokines and actin have all been found elevated in the urine due to ARF (D1: p.1608 col.2). HSP-72, another intracellular protein, is equally released from tubular cells following IRI (D19: p.99 col.1). The Opposition Division also notes that compared to many other up-regulated genes known in the art, characterisation and validation of NGAL as IRTCI biomarker is at an advanced stage. Its tissue localisation and changes in protein expression after IRI as well as its presence in the urine of healthy subjects (see point 6.3.2) favour it as IRTCI urinary biomarker candidate over other genes.

6.3.4 Finally, the Opposition Division establishes that at the filing date of the patent there was a great need for biomarkers for IRTCI. One of the major causes of acute renal failure (ARF) is IRTCI. Detection of IRTCI thus allows early diagnosis of ARF with the prospect of greater success in therapy. Potent biomarkers are also required for translation of an effective drug therapy for ARF from the laboratory bench to bedside (D15: abstract, introduction; D20: p. 237 col.2 par.1). The Opposition Division concludes that skilled person is highly motivated to find an alternative biomarker for IRTCI.

6.3.5 In summary, from the prior art it is known that NGAL - like Cyr61 - has many of the desirable properties of an IRTCI biomarker. While NGAL is detectable in the urine of healthy patients, knowledge of the pathophysiological changes in the renal tubules during IRTCI would lead the skilled person to expect that increases in NGAL expression in the proximal tubule due IRI would also be detectable in the urine. Verifying such presence, the skilled person would neither have to go against an established prejudice, nor enter unpredictable areas nor take incalculable risks. Instead the skilled person would have to carry out simple, straightforward routine experiments.
Consequently, the Opposition Division is of the opinion that the person skilled in the art would be instructed by D15 in combination with D1 to look for increased NGAL expression in the urine after IRTCI. He would do so with for the biomarker field reasonable expectation of success and without requiring any inventive skill. As a consequence, he would identify NGAL as IRTCI urinary biomarker.

6.4 Conclusion: Claim 1 is not inventive in view of the combination of D15 with D1 (Article 56 EPC).

AUXILIARY REQUESTS 1-6

7 **Auxiliary Requests 1-6 - claim 1: Articles 100(a) and 56 EPC**

Auxiliary Requests 1-6 share claim 1 with the Main Request. Consequently, claim 1 of these Auxiliary Requests lacks inventive step over D15 in combination with D1 (Article 56 EPC). The reasoning of point 6 applies.

AUXILIARY REQUESTS 7-8

8 Auxiliary Requests 7-8: the independent claims

Claim 1 of these Auxiliary Requests results from combining claims 1 and 5 of the Main Request to a method of detection of IRTCI employing urinary NGAL as biomarker and further monitoring effectiveness of treatment of IRTCI by analysing NGAL in post-treatment samples.

9 Auxiliary Request 7-8 - claim 1: Articles 100(a) and 56 EPC

9.1 The Opposition Division is of the opinion that a further step of monitoring the effectiveness of treatment does not render claim 1 of the Main Request inventive. Essentially, the reasoning of point 6 applies. As an increase in a diagnostic biomarker represents the presence of a pathology, its decrease is naturally expected to reflect improvement, due to healing and or treatment. Diagnostic biomarkers are commonly employed for monitoring treatment (D20: p.237 col.2 par.1 last sentence). Moreover, the Opposition Division observes that it is known from D1 that NGAL protein levels in tissue are elevated at the latest 24h after IRTCI and stay elevated at least up to 72h after injury. Such expression window is sufficiently long not only for diagnosing, but also for monitoring treatment of IRTCI.

9.2 Conclusion: Claim 1 of these Auxiliary Requests lacks inventive step over D15 in combination with D1 (Article 56 EPC).

AUXILIARY REQUEST 9

10 Auxiliary Request 9: the independent claim

Claim 1 of this Auxiliary Requests results from claim 20 of the Main Request being limited to surgical procedures (see point 2).

11 Auxiliary Request 9: Articles 100(a) and 56 EPC

11.1 The Opposition Division is of the opinion that employing NGAL to identify the extent of IRTCI is not inventive. Essentially, the reasoning of point 6 applies. As an increase in a diagnostic biomarker represents the presence of a pathology, the onset of increase of the biomarker (or its extent of increase) is naturally expected to reflect severity of disease. Moreover, surgical procedures such as kidney transplantation are a known common cause of IRI (D17: p.8 col.2 last paragraph).

11.2 Conclusion: Claim 1 of Auxiliary Request 9 lacks inventive step over D15 in combination with D1 as well (Article 56 EPC).