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Datasheet for the decision of 6 March 2018

Case Number: T 0867/13 - 3.3.04

Application Number: 01951000.7

Publication Number: 1301201

IPC: A61K38/47, A61P21/00

Language of the proceedings: EN

Title of invention:
Treatment of glycogen storage disease type II

Patent Proprietor:
Duke University

Opponent:
ZyStor Therapeutics, Inc.

Headword:
Pompe disease/DUKE UNIVERSITY

Relevant legal provisions:
EPC Art. 56

Keyword:
Main (sole) request - inventive step (no)

This datasheet is not part of the Decision.
It can be changed at any time and without notice.

Decisions cited:
T 0455/91, T 0939/92, T 0207/94, T 1102/00, T 0247/11

Catchword:

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Case Number: T 0867/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 6 March 2018

Appellant: (Patent Proprietor)	Duke University Durham, North Carolina 27710 (US)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Respondent: (Opponent)	ZyStor Therapeutics , Inc. 10437 Innovation Drive, Suite 100 Milwaukee, WI 53226-4838 (US)
Representative:	Lock, Graham James Fry Heath & Spence LLP Unit A, Faraday Court Faraday Road Crawley, West Sussex RH10 9PU (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 1 February 2013 revoking European patent No. 1301201 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	R. Morawetz
	P. de Heij

Summary of Facts and Submissions

I. The appeal by the patent proprietor (hereinafter "appellant") lies against the decision of the opposition division revoking European patent No. 1 301 201 entitled "*Treatment of glycogen storage disease type II*".

II. The patent had been opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Article 100(b) and (c) EPC. The opposition division had decided that the subject-matter of claim 1 of the main request before it lacked novelty and that the subject-matter of claim 1 of auxiliary requests 1 and 2 lacked inventive step.

III. With its statement of grounds of appeal the appellant filed a sole claim request which was the same as auxiliary request 1 underlying the decision under appeal. The request comprised one independent and 8 dependent claims.

Independent claim 1 of the sole claim request reads:

"1. Use of human acid α-glucosidase produced in Chinese hamster ovary cell culture for the manufacture of a medicament for the treatment of glycogen storage disease type II in a human, or the treatment of cardiomyopathy associated with glycogen storage disease type II in a human."

IV. In its reply to the statement of grounds of appeal the opponent (hereinafter "respondent") maintained its objections under Article 56 EPC.

V. The board summoned the parties to oral proceedings and sent a communication pursuant to Article 15(1) RPBA.

VI. The oral proceedings were held on 6 March 2018. At the end of them, the chair announced the board's decision.

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

D1 Fuller M. et al., Eur. J. Biochem. (1995), vol. 234, pages 903 to 909

D2 Van Hove J.L.K. et al., PNAS (1996), vol. 93, pages 65 to 70

D3 Kikuchi T. et al., J. Clin. Invest. (1998), vol. 101, pages 827 to 833

D8 Declaration of Dr R. Cummings, 29 November 2010

D10 de Barsy T. et al., Birth Defects Org. Ser. (1973), vol. IX, pages 184 to 190

D25 US 6,537,785 (25 March 2003)

D27 Zhao K.-W. and E.F. Neufeld, Protein Expression and Purification (2000), vol. 19, pages 202 to 211

D45 Declaration of Dr D. Koeberl, 9 October 2012

D60a McVie-Wylie A. et al., abstract (2003)

D67 Pharming press release, 15 March 2000, pages 1 and 2

D73 Declaration by B.J. Byrne, 16 November 2012

D73d Bijvoet A.G.A. et al., Human Molecular Genetics (1998), vol. 7, pages 1815 to 1824

D73f Y.-T. Chen and A. Amalfitano, Molecular Medicine Today (June 2000), vol. 6, pages 245 to 251

D95 PR Newswire, 7 August 2001, press release

D96 PR Newswire, 10 December 2001, press release

D97 EP 1 224 266 B1 (12 September 2007)

D98 Declaration of Dr Y.-T. Chen, 6 June 2013

D99 Second declaration of Dr R. Cummings, 9 June 2013

D100 Second declaration of Dr D. Koeberl, 9 June 2013

D103 McVie-Wylie A. et al., Molecular Genetics and Metabolism (2008), vol. 94, pages 448 to 455

VIII. The arguments of the appellant, submitted in writing and during the oral proceedings, may be summarised as follows:

Sole claim request

Inventive step (Article 56 EPC) - claim 1

Closest prior art

Document D67 was the closest prior art. It disclosed the results of a phase II clinical study with recombinant human acid α-glucosidase (rhGAA) produced in the milk of transgenic rabbits. The skilled person would conclude from document D67 that rabbit-milk-produced rhGAA "*was a technically feasible enzyme replacement therapy* [ERT] *for GSD-II* [glycogen storage disease type II]".

Technical problem and its solution

That the claimed treatment was an improvement over the treatment disclosed in document D67 could be inferred from paragraphs [0008], [0009], [0013] and [0043] of the patent. The results obtained with rhGAA derived from Chinese hamster ovary (CHO) cells were better than those obtained in document D67 with rabbit-milk-produced rhGAA, as evidenced by patient 3.

Documents D60a and D103 provided evidence that CHO-cell-derived rhGAA was better than rabbit-milk-produced rhGAA in effecting glycogen clearance.

The problem to be solved could thus be formulated as the provision of an improved treatment for human GSD-II or its associated cardiomyopathy.

Obviousness

Even if the problem was formulated as the provision of an alternative treatment for GSD-II, the claimed solution was inventive.

Deviation from using rabbit-milk-produced GAA

The skilled person had no reason to deviate from the teaching of document D67, which was the first report of a successful treatment of GSD-II in humans by ERT.

The skilled person had in particular no reason to switch to CHO-cell-derived rhGAA, for which no data on efficacy in humans was yet available (see document D73f, page 249, right-hand column, third paragraph) and for which the production costs were higher than for milk-derived rhGAA (see document D73d, page 1820, right-hand column).

Reasonable expectation of success

Furthermore, the skilled person had no reasonable expectation that CHO-cell-produced rhGAA could be successfully used for the treatment of GSD-II in humans in view of the teachings of documents D73f, D73d, D10, D27, D25, D95, D96 and D97 and expert declarations D8, D45, D98, D99 and D100, for the following reasons.

The teaching of document D73f

Document D73f did not carry much evidential weight since it was the opinion of the inventor himself, which could not be considered to be objective evidence in the scientific evaluation underlying the reasonable-expectation-of-success analysis (see decision T 207/94, Reasons, point 31).

The document could not add to any reasonable expectation of success as it merely summarised the information that was already known to the public and contributed nothing new to that analysis.

The statement in document D73f that "*the pre-clinical data suggests that enzyme replacement therapy will be successful*" could not give the skilled person any reasonable expectation of success, because the prior art, in the absence of this statement, did not give any either.

Document D73f pointed out several reasons to doubt that CHO-cell-produced rhGAA could successfully treat GSD-II (see paragraph bridging pages 247 and 248 and table on page 250).

Search for alternative therapies after the publication of document D73f

Even after the publication of document D73f, experts in the field continued to disagree about which GAA enzyme could be a successful treatment for GSD-II, as shown by Genzyme's continued pursuit of all potential treatment options for GSD-II (see documents D95 and D96) and by documents D25 and D97. Document D25 (see column 3, lines 41 to 43) and document D97 (see paragraph [0009])

showed that experts had no expectation that CHO-cell-produced rhGAA would result in a therapy for GSD-II. The doubts of these experts at the time had to translate into doubts of the notional skilled person.

The experts' disagreement at the time of the invention was reflected in the disagreement between the appellant's and the respondent's experts today.

Identity of rabbit-milk-derived and CHO-cell-derived rhGAA and hGAA extracted from placenta

Milk-derived and CHO-cell-derived rhGAA and hGAA extracted from placenta looked alike (see document D73d, page 1818, left-hand column, second paragraph, to right-hand column, second paragraph) but from document D10 (see abstract) it was known that hGAA purified from human placenta did not lead to a clinical improvement.

Glycosylation/phosphorylation

Document D27 showed that CHO cells did not properly add the mannose-6-phosphate (M-6-P) targeting signal to recombinant lysosomal enzymes (see end of abstract).

First declarations of Drs Cummings (D8) and Koeberl (D45)

Dr Cummings and Dr Koeberl had analysed the prior art relating to CHO-cell-produced rhGAA and had come to the conclusion that, based on the available scientific evidence, the skilled person could have no reasonable expectation that CHO-cell-produced rhGAA would be a successful treatment for GSD-II.

According to Dr Cummings there were doubts, of which the skilled person would be aware, that CHO-cell-produced rhGAA would be a successful treatment, i.e. doubts relating to general clearance mechanisms; doubts relating to the distribution of the enzyme to the target cells; doubts relating to the introduction of a protein with "non-human" glycosylation into humans, including immunogenicity and clearance concerns; doubts relating to the inefficiency of CHO cells in proper phosphorylation; and doubts relating to the inefficient uptake of the enzyme by target cells (see declaration D8, paragraphs 11 to 36).

According to Dr Cummings the work of another expert in the field, the author of document D25, showed that experts in this field had no expectation that CHO-cell-produced rhGAA would result in a therapy for GSD-II disease (see declaration D8, paragraph 25).

Dr Cummings concluded that the experimental results disclosed in documents D1 to D3 would not have given the skilled person the requisite reasonable expectation of success.

Dr Koeberl also concluded that the skilled person could have no reasonable expectation of success based on the available scientific evidence.

Second declarations of Drs Cummings (D99) and Koeberl (D100)

In their second declarations, Dr Cummings and Dr Koeberl explained that none of the concerns of the skilled person were lessened by the publication of document D67. Because of the requirements of the cells targeted by this treatment and the significant

differences between GAA enzymes produced by different animals, the skilled person understood that any information gained from the study of transgenic-rabbit-produced rhGAA was unique to that enzyme and could not be applied to CHO-cell-produced rhGAA.

Cerezyme™

The opposition division had been wrong to assess the prior art Cerezyme therapy, an ERT for Gaucher disease, in that the therapeutic target of Cerezyme – highly vascularised tissue, e.g. liver – was completely different from the target tissue of GSD-II, muscle cells.

Cell/animal experiment vs therapy in humans

The prior art cell and animal experiments could not be correlated to any expectation in humans (see declaration D8). Even after the priority date the person skilled in the art was well aware of a lack of correlation; see document D60a, "*Conclusions*", points 4 and 5.

In summary, the only conclusion that could be drawn was that the skilled person hoped that the CHO-cell-produced rhGAA would be a successful treatment, but hope did not amount to the requisite reasonable expectation of success (see decision T 296/93, Reasons, point 7.4.4).

IX. The arguments of the respondent, submitted in writing and during the oral proceedings, may be summarised as follows:

Sole claim request

Inventive step (Article 56 EPC) - claim 1

Closest prior art

Document D67 disclosed an effective treatment for GSD-II in humans with rabbit-milk-derived rhGAA and was the closest prior art.

Technical problem and its solution

There was not sufficient evidence to prove that, in the context of human treatment, CHO-cell-derived rhGAA was better than rabbit-milk-derived rhGAA.

It could not be derived from paragraph [0013] of the patent that the assumed difference in glycosylation of CHO-cell-derived rhGAA was the cause of success of the treatment in patient 3. The patent did not provide sufficient information to draw any conclusions with regard to glycosylation of CHO-cell-derived rhGAA.

Documents D60a and D103 compared the effects of CHO-cell-derived rhGAA and rabbit-milk-derived rhGAA in mice, not in humans, and did not plausibly establish any improvement in the case of human treatment.

The problem to be solved could thus not be formulated as the provision of an improved treatment but was the provision of an alternative treatment for human GSD-II or its associated cardiomyopathy.

Obviousness

The notional person skilled in the art was interested in providing alternatives. The skilled person would have been motivated to use CHO-cell-derived rhGAA instead of rabbit-milk-derived rhGAA in view of the teaching of document D73f, which said that it was possibly superior to the milk-derived enzyme (see page 247, right-hand column, first full paragraph).

Deviation from using rabbit-milk-produced GAA

The recombinant production of proteins in CHO cells was well established and widely used and not necessarily more expensive than production in rabbit milk (see document D73d, page 1820, right-hand column, lines 10 to 6 from the bottom).

Reasonable expectation of success

There was no information on file, in particular not in documents D73f, D73d, D10, D27, D25, D95, D96 or D97 or expert declarations D8, D45, D98, D99 or D100, on the basis of which it could be concluded that the skilled person would have had reason to think that there was no reasonable expectation of success (see also decision T 2506/12, Reasons, points 3.11 and 3.12). No doubts about or negative reappraisal of the pre-clinical data had been published in the peer-reviewed scientific literature.

The teaching of document D73f

Document D73f was not authored by Dr Chen alone; it was jointly authored by Drs Chen and Amalfitano, the latter also being an expert in Pompe disease, but not an inventor. There was no justification for asserting that Dr Chen had abandoned academic rigour simply on the basis that he was an inventor on a patent application.

Document D73f was significant not only because it added technical data to the primary literature, but also because it had been published immediately prior to the priority date and clearly expressed the joint opinion of two experts in the field that CHO-cell-derived rhGAA would be successful.

Indeed, document D73f went further than e.g. document D3 in suggesting that the CHO-cell-derived enzyme may be clinically superior to the milk-derived enzyme (see page 247, right-hand column, first complete paragraph).

According to document D73f, the pre-clinical data suggested that ERT would be successful, and the meaning of that statement was clear. It meant that at least two experts (the authors of document D73f) considered the pre-clinical data to suggest that ERT would be successful. Moreover, the interpretative statements assessing the significance of the pre-clinical data in the primary literature were uniformly positive, and quite consistent with this view.

Document D73f had to be read in the light of the teaching of document D67. Thus, the person skilled in the art was already aware that rabbit-milk-derived rhGAA was therapeutically active in humans. When read in the light of document D67, document D73f would have

led the skilled person to expect that CHO-cell-derived rhGAA would perform at least as well as, and quite possibly better than, rabbit-milk-derived rhGAA in human therapy.

Document D73f provided no disincentives or counter-teaching to discourage the skilled person. At the priority date of the patent, clinical trials with CHO-cell-produced rhGAA were ongoing. To the extent that document D73f referred to problems, these would arise only if the treatment was successful; see page 248, left-hand column, first paragraph, and page 249, right-hand column, third paragraph.

The "*outstanding questions*" listed in document D73f did not raise doubts as to the prospects of success with CHO-cell-produced rhGAA. In fact, such questions implied that some benefit was assumed.

Search for alternative therapies after the publication of document D73f

Genzyme's pursuit of alternative therapies for GSD-II (see documents D95 and D96) was a common business strategy and did not imply a rejection (or the failure) of the CHO-cell-based rhGAA technology.

Identity of rabbit-milk- and CHO-cell-derived rhGAA and hGAA extracted from placenta

The passage referred to in document D97, paragraph [0009], merely confirmed what was known at the priority date. Document D97 did not establish a prejudice against the use of CHO-cell-derived rhGAA in the

treatment of GSD-II. It merely represented efforts to exploit the M-6-P receptor-mediated uptake pathway for GAA by hyper-phosphorylating the enzyme.

Document D73d addressed glycosylation in general (see Fig. 6) but not M-6-P specifically. Document D73d did not imply that placenta-derived hGAA was equivalent to CHO-cell-derived rhGAA. That the placental hGAA was not functional was known (see document D10) and by the priority date it was also known why (see document D1, page 903, right-hand column).

Glycosylation/phosphorylation

Of all the documents relied on by the appellant as providing a disincentive, only document D27 had been published before the priority date. The findings relied on by the appellant as providing a disincentive were specific to one particular enzyme, α-L-iduronidase (see page 210, right-hand column, second paragraph). Any concerns document D27 might have raised had been superseded by positive teachings as regards CHO-cell-derived rhGAA that reinforced the reasonable expectation of success of the skilled person.

First declarations of Drs Cummings (D8) and Koeberl (D45)

The skilled person would have dismissed the concerns and doubts raised in declaration D8, which were not substantiated by the primary scientific literature. The positive assessment of the prospects for human therapy with CHO-cell-derived rhGAA in document D73f rendered the evidence referred to in declaration D8 irrelevant.

None of the "*concerns*" raised in declaration D8 were relevant to the legal test of whether the notional skilled person would reasonably expect CHO-cell-produced rhGAA to be useful in the treatment of Pompe disease. Rather, they merely related to technical uncertainties, which were inherent when *in vitro* or animal experiments were extrapolated to human therapy.

The general clearance mechanism was acknowledged in declaration D8 as being of concern to any potential therapeutic. The skilled person knew that an enzyme had a half-life *in vivo* and knew too how to deal with potential downsides from clearance.

Distribution to target cells was specifically addressed in the animal models described in documents D2 and D3, where the enzyme was in fact shown to reach the target cells, including skeletal muscle and heart, after intravenous injection. The fact that similar data was not available for humans did not prejudice a reasonable expectation of success.

Documents D2 and D3 showed that immunological clearance mechanisms arising from non-native glycosylation did not necessarily preclude therapeutic action by CHO-cell-derived rhGAA.

At the relevant date it was known that M-6-P was needed for efficient enzyme uptake via the M-6-P receptor (see document D1, page 903, right-hand column, first full paragraph) and the CHO-cell-derived enzyme was known at the priority date to be appropriately phosphorylated such that uptake via the M-6-P receptor could take place; see document D1 (page 908, paragraph bridging

columns), document D2 (page 69, right-hand column, last paragraph) and document D3 (page 831, right-hand column, first and second paragraphs).

The efficient uptake of the CHO-cell-produced enzyme by target cells was specifically addressed in document D2 (see abstract), and document D3 suggested that a relatively low dosing regimen would be effective in humans (see page 832, left-hand column, last sentence of second paragraph).

Document D73f, published shortly before the priority date of the patent, summarised the pre-clinical studies with CHO-cell-produced rhGAA and clearly suggested that it was a viable alternative to rabbit-milk-derived rhGAA.

The probative value of declaration D45 was compromised by inaccurate statements of fact.

Second declarations of Drs Cummings (D99) and Koeberl (D100)

The points made by Drs Cummings and Koeberl in declarations D99 and D100 respectively, in relation to document D73f, failed to take into account the fact that document D73f had to be read in the context of the state of the art at the priority date, which included the teachings of document D67. Thus the skilled person was already aware that rabbit-milk-derived rhGAA was therapeutically active in humans.

Qualification of Drs Cummings, Koeberl and Chen to give an opinion on legal questions

Drs Cummings, Koeberl and Chen were not qualified to give an opinion on the application and proper outcome of the legal test involved in establishing whether a notionally skilled person would have had a reasonable expectation of success (see decision T 926/00, Reasons, point 6.6).

Inconsistent treatment of Dr Chen's evidence

The appellant's position was inconsistent in, on the one hand, relying on evidence from Dr Chen (declaration D98) while, on the other hand, asserting that Dr Chen's status as an inventor invalidated his objectivity. No weight should be attached to Dr Chen's declaration. Moreover, it was inappropriate to adduce expert witness evidence from Dr Chen in relation to a simple matter of semantics. The assertion that the scientific community reacted with astonishment was not corroborated by any evidence.

Cerezyme™

The opposition division's reference to Cerezyme™ was in the context of other successful therapies based on the use of CHO cells as a source for a therapeutic protein and established that there could have been no generally applicable technical prejudice against the use of CHO cells in the production of pharmaceutical products.

Cell/animal experiment vs therapy in humans

The appellant relied on document D60a to support the contention that there was a lack of correlation between cell and animal experiments and humans. However, that information had not been available to the person skilled in the art at the priority date and could not have influenced the expectations of the skilled person at that date.

X. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the sole claim request filed with the statement of grounds of appeal.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

Introduction

2. The invention concerns the treatment of glycogen storage disease type II (hereinafter "GSD-II"), which is also known as Pompe disease or acid maltase deficiency (hereinafter "AMD"). GSD-II is an autosomal recessive genetic disorder and is heterogenous in nature, with various molecular defects in the lysosomal acid α-glucosidase (hereinafter "GAA") gene, resulting in a partial or complete deficiency in GAA activity. The enzyme defect results in lysosomal glycogen accumulation in almost all tissues of the body, with cardiac and skeletal muscle the most seriously affected. The disease can manifest itself in

early- and late-onset forms. The most severe phenotype is the infantile-onset form of GSD-II, originally described by J.C. Pompe. Infants suffering from Pompe disease generally die from cardiorespiratory failure before the age of one year. Juvenile and adult forms ofGSD-II are correlated with higher residual levels of GAA (see also document D73f, page 245, left-hand column, first paragraph, to right-hand column, first paragraph).

Sole claim request

Inventive step (Article 56 EPC) - claim 1

3. This decision deals with the issue of whether the claimed subject-matter involves an inventive step, all other issues having been decided in the appellant's favour in the decision under appeal.

Closest prior art

4. The opposition division held that the subject-matter of claim 1 lacked inventive step, regardless of whether document D67 or document D73f was taken as the closest prior art (see decision under appeal, points 3.5.1 to 3.5.37).

5. On appeal, both parties agreed that document D67 was the closest prior art. The board sees no reason to differ.

6. Document D67 reports that a phase II clinical trial in infantile Pompe patients with recombinant human acid α-glucosidase (rhGAA) produced in the milk of transgenic rabbits "*has finalised with positive results*" (see page 1, first paragraph). The objective of the clinical

study was to obtain data on the safety and efficacy of rhGAA (see page 2, second paragraph). After 36 weeks of the study, the four infantile patients had reached the age range of 12 to 17 months, "*which is well beyond the mean age of survival in untreated infantile Pompe patients*" (see page 1, second paragraph).

Muscle biopsies demonstrated that the recombinant enzyme was taken up by the main target tissue, skeletal muscle, reaching normal levels of GAA activity, which were comparable to those in healthy individuals. Moreover, the enzyme was shown to be active in the skeletal muscle tissue since, on histological evaluation, lysosomal glycogen storage decreased and muscle regeneration was observed (*ibid.*).

According to document D67, the most prominent effect of the treatment was seen in the heart, with reduced symptoms of cardiac instability in all patients (see page 1, third paragraph). Under the heading "*Clinical breakthrough*" document D67 reports that "*one of the infants in the trial can even walk now without help of its parents*" (see page 2, fourth paragraph).

The board agrees with the appellant that the skilled person would conclude from document D67 that enzyme replacement therapy (ERT) with rabbit-milk-derived rhGAA was a technically feasible treatment for GSD-II in humans.

Technical problem and its solution

7. The subject-matter of claim 1 differs from the disclosure of document D67 in that the human rhGAA used for the treatment of GSD-II is produced in Chinese hamster ovary (CHO) cells.

8. According to the appellant, the technical effect associated with this difference is an improved treatment for GSD-II, as is derivable from paragraphs [0008], [0009], [0013] and [0043] of the patent and further supported by documents D60a and D103.

8.1 According to paragraph [0008] of the patent the infants treated "*demonstrated improvement of cardiac status, pulmonary function, and neurodevelopment, as well as reduction of glycogen levels in tissues*", while paragraph [0009] of the patent explains that the results seen in patient 3 were better than those seen in patients 1 and 2, because the latter developed anti-GAA antibodies. Paragraph [0043] of the patent then reports that one patient, patient 3, "*has been walking independently since 12 months of age*".

8.2 However, document D67 also reports an improvement in cardiac status, respiratory function and decrease in lysosomal glycogen storage in skeletal muscle tissue of the patients (see point 6). Moreover, one of the infantile patients treated with transgenic rabbit-milk-produced rhGAA could walk without help (see point 6).

Thus, no improvement over the treatment known from document D67 can be derived from paragraphs [0008], [0009] and [0043] of the patent.

8.3 Paragraph [0013] of the patent discloses that CHO-cell-derived rhGAA is preferred and further that it "*is assumed that the glycosylation differs from that of GAA that is produced in transgenic mouse and rabbit milk* (...)". In the board's judgement, it does not follow directly and unambiguously from this statement that the assumed difference in glycosylation leads to an improved treatment if CHO-cell-derived rhGAA is used rather than transgenic rabbit-milk-produced rhGAA.

8.4 Documents D60a and D103 - both published after the priority date - relate to effects seen in Pompe mice (document D60a; see left-hand column, second paragraph under the heading "*Results*", and right-hand column, first paragraph under the heading "*Conclusions*") and GAA knockout mice (see document D103, page 452, right-hand column, fourth and fifth paragraphs, and Figures 3 and 4). However, these results obtained in mice do not establish that CHO-cell-derived rhGAA is better than rabbit-milk-derived rhGAA at effecting glycogen clearance in humans. Moreover, the alleged effect - an improved treatment for GSD-II - could only be taken into account when determining the problem underlying the invention for the purpose of assessing inventive step, if it can be deduced by the skilled person from the patent considered in relation to the closest prior art (see also Case Law of the Boards of Appeal, 8th edition 2016, I.D.4.4.2 and I.D.4.4.6). In the present case, no improvement over the treatment known from document D67 is derivable from the patent (see points 8.1 to 8.3).

8.5 In the board's judgement, the subject-matter of claim 1 can thus not be considered to provide an improved treatment over the treatment disclosed in document D67.

9. Therefore, starting from the closest prior art document, D67, the objective technical problem to be solved is the same as formulated by the opposition division, namely the provision of an alternative treatment for human GSD-II or its associated cardiomyopathy (see decision under appeal, Reasons, point 3.5.12).

Obviousness

10. The opposition division held that the claimed solution was obvious in light of the teachings of the available prior art documents, in particular document D73f (see decision under appeal, Reasons, points 3.5.18 to 3.5.30).

11. To determine whether the claimed invention, starting from the closest prior art and the objective technical problem, would have been obvious to the skilled person, the boards of appeal apply the "could-would approach". When considering whether or not claimed subject-matter constitutes an obvious solution to an objective technical problem, the question to be answered is whether or not the skilled person, in the expectation of solving the problem, would have modified the teaching in the closest prior art document in the light of other teachings in the prior art so as to arrive at the claimed invention (see Case Law of the Boards of Appeal, 8th edition 2016, I.D.5.). Accordingly, what the skilled person, starting from the closest prior art and faced with the objective technical problem, would or would not do depends not solely on the disclosure of the closest prior art document, but also on the state of the art in the relevant technical field (see also decision T 939/92, OJ EPO 1996, 309, Reasons, point 2.4.3).

Furthermore, in accordance with the case law of the boards of appeal, a course of action can be considered obvious within the meaning of Article 56 EPC if the skilled person would have carried it out in expectation of some improvement or advantage. In other words, obviousness is not only present when the results are clearly predictable but also when there is a reasonable expectation of success (see Case Law of the Boards of Appeal, 8th edition 2016, I.D.7.1).

12. The appellant submitted that, in view of the disclosure of document D67, which reported a successful treatment for a lethal disease for the first time, the skilled person was not motivated to look for an alternative treatment, i.e. the skilled would not have been motivated to modify the treatment disclosed in document D67.

13. However, it is established case law that it is the normal task of a skilled person working in a certain field not to remain inactive but to seek alternatives, to be constantly occupied with the elimination of deficiencies, with the overcoming of drawbacks and with the achievement of improvements of known devices and/or products (cf. *inter alia*, decisions T 247/11 of 24 February 2017; Reasons, point 25; T 1102/00 of 1 June 2004, Reasons, point 14; T 455/91, OJ EPO 1995, 684, Reasons, point 5.1.3.2). In the board's view, it is not conceivable that in the case of the treatment of a potentially lethal disease the motivation of the skilled person to search for further - or alternative - treatments stops, solely because one treatment exists - even if it is perceived as satisfactory at the time. Indeed, when document D67 was published, alternative treatments were already pursued in clinical trials (see

below, point 14) and there is no evidence that these were stopped in view of the success reported in document D67.

14. As to teachings in the prior art (see point 11) other than the teaching in document D67, at the priority date of the patent, the skilled person was aware of the teaching of document D73f, a review article entitled "*Towards a molecular therapy for glycogen storage disease type II (Pompe disease)*". This document discloses that ERT and gene therapy are being pursued for the treatment of GSD-II (see page 246, right-hand column, second paragraph). The document also reports that rhGAA has been produced "*in its precursor form in Chinese hamster ovary (CHO) cell lines and in transgenic mouse and rabbit milk*" (see page 247, left-hand column, third paragraph).

As regards the CHO-cell-derived rhGAA, document D73f then summarises the pre-clinical results disclosed in references 19, 20 and 25, which are documents D2, D1 and D3 respectively in these appeal proceedings (see references on pages 250 and 251 of document D73f).

Thus, document D73f reports with regard to those documents that "*[i]ncubation of the precursor form of rhGAA with primary fibroblasts derived from patients with infantile-onset GSD-II resulted in the uptake of the enzyme and normalization of GAA activity and glycogen levels in the fibroblasts. This uptake is inhibited by M-6-P, suggesting mediation of uptake by M-6-P receptors. Injection of purified rhGAA into guinea pigs resulted in increased GAA activity levels in liver, heart and skeletal muscle*" (see page 247, left-hand column, third paragraph).

Document D73f further reports that *in vivo* efficacy has been studied in Japanese quail with acid maltase deficiency (AMD quail). AMD quail "*cannot fly, lift their wings or right themselves from the supine position*", but intravenous treatment with rhGAA "*resulted in the ability of the quail to both right themselves and flap their wings*". Moreover, GAA activity had increased in most tissues examined and glycogen levels and histopathology had been restored to normal levels in the heart and liver (see page 247, left-hand column, fifth paragraph).

Document D73f then notes that "*[s]imilarly, rhGAA purified from the milk of transgenic mice and rabbits has been shown to correct GAA deficiency and reduce glycogen storage in heart and skeletal muscle of GSD-II knockout mice. The dose of the milk enzyme required to correct the enzyme deficiency as well as the glycogen storage in the mouse model was larger than the dose of the CHO-derived enzyme that had been used in the quail model. The duration of the treatment required to see a therapeutic effect with the milk enzyme was also longer than with the CHO enzyme. Furthermore, no clinical improvement was seen in the mouse model following treatment with the milk-derived enzyme*" (see page 247, right-hand column, second paragraph).

Furthermore document D73f reports that "*the observation that rhGAA improves muscle strength (in the quail model) and histopathology and biochemical parameters (in both quail and mouse models) suggests that rhGAA is a promising enzyme replacement therapy for human GSD-II. Based on these results, two clinical trials using different enzyme sources have recently been initiated to investigate the potential of rhGAA to safely treat GSD-II patients. A phase II study is being conducted in*

the Netherlands (...) *using GAA purified from the milk of transgenic rabbits and a Phase I/II study using rhGAA purified from CHO cells is being conducted in the USA* (...)" (see page 247, right-hand column, third paragraph).

Document D73f adds that, although no efficacy data is yet available for the two ongoing clinical trials of rhGAA replacement therapy, "*pre-clinical data suggest that enzyme replacement therapy will be successful*" (see page 249, right-hand column, third paragraph).

14.1 The board considers that the evidential value of document D73f is not lessened because it is authored by the inventor of the patent, as it is co-authored by another expert in Pompe disease who is not an inventor on the patent. Moreover, document D73f is a scientific article, published in an academic journal. In the board's opinion, it is therefore not conceivable that the authors of document D73f were not objective in their assessment of the pre-clinical data in the primary literature they reviewed merely because one of the authors was also an inventor on what, at the time, was a patent application.

14.2 While document D73f summarises the information that was already known in the prior art, in the board's opinion, it does indeed also add to this information by expressing the joint opinion of two experts on the significance of the pre-clinical data in the primary literature, i.e. it gives the clear statement that these data "*suggest that enzyme replacement therapy will be successful*".

14.3 In the board's opinion, the skilled person also understands that, to the extent document D73f refers to problems, these might arise – i.e. will not necessarily arise in all patients – only if the treatment is successful. Indeed, document D73f states that "*[a] successful treatment might unmask the underlying neurologic problem. Furthermore, immune responses could limit the efficacy*" (see page 249, right-hand column, third paragraph; emphasis added by the board).

As can also be taken from document D73f, an immune response was more likely to develop in infantile patients carrying a null mutation, but not in juvenile and adult patients with residual enzyme activity which might render them immunologically tolerant (see page 248, left-hand column, first paragraph), which thus suggests successful therapy at least in the latter patient groups.

14.4 In the board's opinion, the skilled person would have perceived the "*outstanding questions*" formulated with regard to ERT in document D73f in the table on page 250 to be rather academic ones and the answers to them not crucial to the success of the therapy. They would therefore not have led to any concerns as regards the suitability of CHO-cell-derived rhGAA because (i) the mechanism underlying an effective therapy does not have to be known for there to be a reasonable expectation of success, (ii) the prevention of further damage would in itself be considered an improvement, and (iii) neurological and immunological issues would arise only if the treatment was successful (see also point 14.3).

14.5 In the board's judgement, the teaching of document D73f would therefore motivate the skilled person to choose CHO-cell-derived rhGAA as an alternative for the

treatment of GSD-II in humans in that it indicates that it may be clinically superior to the milk-derived enzyme on at least three accounts (see page 247, right-hand column, second paragraph) and given the background that milk-derived rhGAA was already known at the priority date to be effective in human GSD-II therapy (see document D67 and point 6 above).

14.6 Based on the pre-clinical work summarised in document D73f, which established that CHO-cell-derived rhGAA targets muscle and heart cells and enters the correct cell compartment, reducing glycogen storage there, i.e. having a direct effect on the cause of GSD-II, the board considers that the skilled person also had a reasonable expectation that enzyme replacement therapy based on CHO-cell-derived rhGAA would be efficacious in treating GSD-II or its associated cardiomyopathy in humans.

14.7 In the board's opinion, the skilled person would have been further motivated by the disclosure of document D67 in this regard since, at the priority date of the patent, the skilled person was aware from document D67 that one of the two clinical trials mentioned in document D73f, namely the clinical trial with rabbit-milk-derived rhGAA, had been completed and had indeed been successful (see document D67 and point 6 above). In other words, the pre-clinical data obtained in *in vitro* and in animal models with rabbit-milk-derived rhGAA had indeed translated into successful enzyme replacement therapy for GSD-II in human infants - as predicted in document D73f.

14.8 In the board's opinion, the "*potentially cheaper production in milk of transgenic animals*" (see document D73d, page 1820, right-hand column, lines 10 to 6 from

the bottom) would not have deterred the skilled person from pursuing CHO-cell-derived rhGAA for the treatment of GSD-II, not least because it was perceived to be better than milk-derived rhGAA (see point 14 above). Moreover, the board notes that - according to the appellant's expert - CHO cells "*are easier and less expensive to work with than rabbits*" (see declaration D99, paragraph 33).

15. The board is not persuaded by any of the appellant's other lines of argument, based on documents D73f, D73d, D10, D27, D25 and D95 to D97 and expert declarations D8, D45, D99 and D100, to the effect that, on the priority date, the skilled person had doubts about the suitability of CHO-cell-derived rhGAA for the treatment of GSD-II, as will be explained in the following.

15.1 In the board's opinion, the observation that hGAA isolated from placenta and CHO-cell-derived rhGAA have a similar glycosylation pattern but that hGAA extracted from placenta is not functional (see document D73d, page 1818, left-hand column, second paragraph, to right-hand column, second paragraph) would not have raised any doubts as to the expectation of success. At the priority date the skilled person not only knew that hGAA extracted from placenta was not functional (see document D10, abstract) but also that this was due to a lack of M-6-P groups (see document D1, page 903, right-hand column, and document D73f, page 246, right-hand column, first paragraph). Importantly, he also knew that the CHO-cell-derived rhGAA was appropriately phosphorylated such that uptake via the M-6-P receptor could take place; see document D1 (page 908, paragraph bridging columns), document D2 (see page 69, right-hand column), document D3 (see page 831, right-hand column)

and document D73f (page 247, left-hand column, second full paragraph).

15.2 The finding that one particular enzyme, α-L-iduronidase, is not properly glycosylated (see document D27, page 210, right-hand column, second paragraph) would not have influenced the skilled person's expectation as regards therapy with CHO-cell-derived rhGAA, since it is established in documents D1 to D3 (see preceding point) that CHO-cell-derived rhGAA is indeed appropriately phosphorylated such that uptake via the M-6-P receptor can take place.

15.3 In the board's opinion, the pursuit of alternative treatments for GSD-II after the priority date, as apparent from documents D95 and D96, cannot be taken to imply a rejection or the failure of the CHO-cell-based rhGAA technology and certainly not at the priority date. Indeed, at the relevant date, CHO-cell-based rhGAA was also being pursued, even in clinical trials (see document D73f, page 247, right-hand column, second full paragraph).

15.4 The board considers that the passages relied on by the appellant from document D25 (see column 3, lines 12 to 47) and document D97 (paragraph [0009]) are unsuitable to establish that the "*experts in this field at the time of the invention had no expectation that CHO produced GAA would result in a therapy for GSD-II disease*" as they merely confirm what was already known at the priority date of the patent, namely that lysosomal enzymes require adequate amounts of M-6-P to bind to M-6-P receptors to be transported to the lysosome. However, the cited passages neither address

CHO-cell-derived rhGAA specifically nor question the results obtained in documents D1 to D3 and summarised in document D73f.

The board notes in this context that the statement (see declaration D8, paragraph 25) that document D25 concluded that "*the CHO-produced enzyme would be inefficiently targeted to affected cells and (...) of limited effectiveness in the treatment of [GSD-II] (id. at col. 3, lns 41-43*" is incorrect because document D25 does not address CHO-cell-derived rhGAA in column 3, lines 41 to 43, but hGAA extracted from placenta, which was well known at the priority date of the patent in suit not to be efficiently internalised by cells due to a lack of M-6-P (see point 15.1 above).

15.5 Moreover, the board notes that, at the priority date, the skilled person was not aware of the phosphorylation results reported in document D25 (see column 20, lines 44 to 47) and document D97 (see example 27 and Table 1). The appellant's argument that these documents showed "*the real world disbelief*" in the invention and that the doubts of the experts must translate into doubts of the notional skilled person thus also fails.

15.6 Finally, the board notes that the results reported in document D60a were also only available after the priority date and could therefore not have possibly influenced the skilled person's expectation of success at the relevant date.

15.7 To summarise, none of documents D10, D25, D27, D60a, D73d, D73f, D95, D96 and D97 establishes that, at the priority date, the skilled person would have had any reason to think that CHO-cell-produced rhGAA could not be used successfully for the treatment of GSD-II. Thus,

the positive expectations the skilled person had based on the disclosure of document D67 in combination with the teaching of document D73f would not have been lessened by the teaching of any of these documents.

16. As regards the various further doubts formulated by the appellant's expert Dr Cummings (see declaration D8, paragraphs 6 to 44), the board considers that the notional skilled person, aware of the teaching of documents D1 to D3, had in fact no reason to doubt that CHO-cell-produced rhGAA reaches the target cells (muscle and heart), is internalised by the target cells and delivered to its final site of action within the lysosomes of those cells and is functional there. The reasons for this are as follows.

16.1 That recombinant production in CHO cells yields rhGAA which is properly glycosylated to allow M-6-P receptor-mediated endocytosis of such rhGAA is shown in documents D1 to D3 (see point 15.1 above). Document D2 (see abstract and page 68, left-hand column, last paragraph) discloses that CHO-cell-derived rhGAA is "*efficiently taken up by fibroblasts from Pompe patients*" such that intracellular levels reach intracellular levels seen in normal fibroblasts, restoring normal levels of GAA and glycogen. Moreover, CHO-cell-derived rhGAA is also shown to be "*endocytosed efficiently by cultured muscle cells of an infantile GSD-II patient*" and to clear the stored lysosomal glycogen (see document D1, page 907, paragraph bridging left- and right-hand columns).

16.2 The distribution of CHO-cell-derived rhGAA to target cells was specifically addressed in the animal models described in documents D2 (see abstract) and D3 (see abstract), where the enzyme was in fact shown to reach

the target cells, including in the skeletal muscle and heart, after intravenous injection.

16.3 Moreover, the board finds no support in the prior art for the assertions that, at the priority date, "*it was therefore widely believed that CHO cells were not suitable for the production of GAA for the treatment of GSD-II*" (see declaration D8, paragraph 13) and "*the prevailing belief was that an enzyme produced in CHO culture either would not reach, or would not be taken up by, the target cells in sufficient quantities to produce a therapeutic effect*" (see declaration D8, paragraph 14 to 29). On the contrary, a group of experts, the authors of documents D1 (see page 908, right-hand column, last sentence), D2 (page 69, right-hand column, last paragraph) and D3 (see end of abstract), all considered CHO-cell-derived rhGAA to be a promising candidate for the treatment of GSD-II in humans, as did the authors of document D73f (page 247, right-hand column, second paragraph, and page 249, right-hand column, third paragraph). Moreover, this positive assessment was not contradicted by any negative reappraisal of the pre-clinical data in the peer-reviewed scientific literature.

16.4 Of course, to establish that CHO-cell-derived rhGAA reaches the target cells *in vivo* too required clinical studies in humans. Such clinical trials were indeed ongoing at the priority date, and in the board's opinion the skilled person had every reason to be optimistic about their outcome. Firstly, the skilled person was aware that rhGAA from a different non-human source, namely the rabbit-milk-derived rhGAA, had been shown to reach the target cells *in vivo* in humans (see document D67 and point 6). Secondly, several CHO-cell-derived recombinant proteins, including a lysosomal

protein, Cerezyme™, had been successfully used in human therapy before (see declaration D73, paragraphs 37 and 38), indicating that there could have been no generally applicable technical prejudice against the use of CHO cells in the production of pharmaceutical products for human use.

16.5 In the board's opinion, declaration D45 by Dr Koeberl does not help the appellant's case either because, by basing its analysis on the statement that "*in the specific case of enzyme replacement therapy ("ERT") for GSD-II, human clinical trials had universally failed for more than 30 years*" (see paragraph 5), it ignores the successful treatment of GSD-II with rabbit-milk-derived rhGAA reported in document D67.

16.6 In the board's opinion, the renewed assertion in Dr Cummings' second declaration, D99, that "*CHO cells were thought to be an extremely unlikely source for a replacement enzyme to treat GSD-II*" (see paragraph 18) carries no weight as the only literature referred to in support was post-published (document D25 and document D60a), and the assertion is contradicted by the uniformly positive assessment of the suitability of CHO-cell-derived rhGAA for ERT for GSD-II in the published scientific literature (see points 14 to 14.5).

16.7 Since document D73f is read by the skilled person with the knowledge of document D67 (see point 14.7 above), the assertion that a person skilled in the art would not conclude from either document D67 or document D73f, when considered alone, that CHO-cell-produced rhGAA would be likely to prove a successful treatment for GSD-II therefore misses the point (see declaration D99,

paragraphs 30 to 40, and declaration D100, paragraphs 10 to 21).

16.8 The board agrees with the respondent that the appellant's position is inconsistent in relying on evidence from Dr Chen (in the case of declaration D98) while asserting that Dr Chen's status as an inventor invalidates his objectivity as an author of a peer-reviewed article (in the case of document D73f).

16.9 In any case, declaration D98 does not help the appellant's case because the attempt to reinterpret the clear statement in D73f that "*the pre-clinical data suggest that enzyme replacement therapy will be successful*" to mean "*the very limited preclinical data in AMD quail did, in fact, "suggest" the hope that the therapy would succeed, and that is why human clinical trials were undertaken*" (see paragraph 22) fails because the meaning of the statement in D73f is clear and in line with teachings in the prior art. Thus, the pre-clinical data presented in the primary literature was also regarded as positive by the authors in each of documents D1 (see page 908, right-hand column, last sentence), D2 (page 69, right-hand column, last paragraph), D3 (see end of abstract) and D73d (see page 1820, right-hand column).

The assertion that the scientific community reacted "*with astonishment to the ability of CHO-produced GAA to provide an effective treatment of the disease*" (declaration D98, paragraph 24) is not corroborated by any objective evidence and thus is not persuasive.

17. The board concludes that the prior art motivated the skilled person to use CHO-cell-derived rhGAA for the manufacture of a medicament for the treatment of human GSD-II or its associated cardiomyopathy and that, based on a scientific evaluation of the facts available (see decision T 207/94, OJ EPO 1999, 273, Reasons, point 31), the skilled person also had a reasonable expectation of success. Therefore, the subject-matter of claim 1 is considered to be obvious and thus to fail to meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

P. Cremona G. Alt

Decision electronically authenticated