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Language of the proceedings: EN

Title of invention:
FURTHER NOVEL FORMS OF INTERFERING RNA MOLECULES

Patent Proprietor:
Silence Therapeutics GmbH

Opponents:
ALCON LABORATORIES, INC.
Sirna Therapeutics
Grund, Martin, Dr.
Alnylam Pharmaceuticals Inc.

Headword:
Double stranded RNA modified 2'O-Methyl aligned phase shift pattern/SILENCE THERAPEUTICS

Relevant legal provisions:
EPC Art. 123(2), 84, 83, 56
RPBA Art. 12(4), 13(1)

Keyword:
Main Request - admissibility (yes);
Main Request - requirements of the EPC met (yes)

Decisions cited:

Catchword:

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Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 1094/10 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 11 February 2015

Appellant I: (Patent Proprietor)	Silence Therapeutics GmbH Robert-Rössle-Strasse 10 13125 Berlin (DE)
Representative:	Murphy, Joeeta Stratagem IPM Limited Meridian Court Comberton Road Toft Cambridge CB23 2RY (GB)
Appellant II: (Opponent 1)	ALCON LABORATORIES, INC. 6201 South Freeway Fort Worth TX 76134-2099 (US)
Representative:	Teipel, Stephan Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstrasse 2 80538 München (DE)
Respondent I: (Opponent 2)	Sirna Therapeutics 300 Third Street Cambridge, MA 02142 (US)
Representative:	Potter Clarkson LLP The Belgrave Centre Talbot Street Nottingham, NG1 5GG (GB)
Respondent II: (Opponent 3)	Grund, Martin, Dr. GRUND Intellectual Property Group Postfach 44 05 16 80754 München (DE)
Representative:	Grund, Martin Grund Intellectual Property Group Postfach 44 05 16 80754 München (DE)

Respondent III: (Opponent 4)	Alnylam Pharmaceuticals Inc. 300 Third street, Third Floor Cambridge MA 02142 (US)
Representative:	Vossius & Partner Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 15 March 2010 concerning maintenance of the European Patent No. 1527176 in amended form.**

Composition of the Board:

Chairman	M. Wieser
Members:	P. Julià
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 527 176, based on European patent application No. 03 784 183 and published as International patent application WO 2004/015107 ("*the application as filed*", hereinafter), was granted with 38 claims. Claim 1 read as follows:

"1. A ribonucleic acid comprising a double stranded structure, whereby the double stranded structure comprises a first strand and a second strand, whereby the first strand comprises a first stretch of contiguous nucleotides and whereby said first stretch is at least partially complementary to a target nucleic acid, and the second strand comprises a second stretch of contiguous nucleotides and whereby said second stretch is at least partially identical to the target nucleic acid,

characterised in

that said first stretch and said second stretch comprises a pattern consisting of a plurality of groups of modified nucleotides having a modification at the 2'-position whereby within the stretch each group of modified nucleotides is flanked on one or both sides by a flanking group of nucleotides whereby the flanking nucleotides forming the flanking group of nucleotides are either unmodified nucleotides or nucleotides having a modification different from the modification of the modified nucleotides."

II. Four oppositions were filed on the grounds of Articles 100(a),(b) and (c) EPC. The opposition division decided to maintain the patent on the basis of an Auxiliary Request 3. The Main Request (claims as granted) and

Auxiliary Request 1 were considered to contravene Article 54(3) EPC and Auxiliary Request 2 not to fulfil the requirements of Article 84 EPC. All auxiliary requests were filed at the oral proceedings before the opposition division on 14 October 2009.

Claim 1 of the Auxiliary Request 3 upheld by the opposition division read as follows:

"1. A ribonucleic acid comprising a double stranded structure, whereby the double stranded structure comprises a first strand and a second strand, whereby the first strand comprises a first stretch of contiguous nucleotides and whereby said first stretch is perfectly complementary to a target nucleic acid, and the second strand comprises a second stretch of contiguous nucleotides and whereby said second stretch is perfectly identical to the target nucleic acid,

characterised in

that said first strand and said second strand consists of a pattern consisting of a plurality of flanking groups of nucleotides and a plurality of groups of modified nucleotides having a modification at the 2'-position whereby within the strand each group of modified nucleotides is flanked on one or both sides by a flanking group of nucleotides
whereby the flanking nucleotides forming the flanking group of nucleotides are unmodified nucleotides
whereby each group of modified nucleotides consists of one nucleotide and
whereby each flanking group of nucleotides consists of one nucleotide,

with each group of modified nucleotides of the first strand being aligned with a flanking group of nucleotides on the second strand, whereby the most terminal 5' nucleotide of the first strand is a nucleotide of the group of modified nucleotides, and the most terminal 3' nucleotide of the second strand is a nucleotide of the flanking group of nucleotides,

wherein the first strand comprises eight to twelve, preferably nine to eleven, groups of modified nucleotides, and wherein the second strand comprises seven to eleven, preferably eight to ten, groups of modified nucleotides, wherein the length of the first stretch and of the second stretch is 15 to 23 bases and wherein the modification is 2'O-Methyl,

wherein the double stranded structure is blunt ended on both sides,

wherein the ribonucleic acid mediates RNA interference."

III. Notices of appeal were filed by the patentee and opponent 01 (appellants I and II, respectively).

With its statement of Grounds of Appeal, appellant I requested that the decision under appeal be set aside and that the patent be maintained as granted (Main Request). Appellant I filed new documentary evidence and new Auxiliary Requests 1 to 6. Except for minor changes, Auxiliary Request 6 was identical to Auxiliary Request 3 upheld by the opposition division.

With its statement of Grounds of Appeal, appellant II requested that the decision under appeal be set aside and that the patent be revoked.

IV. Submissions were filed by opponents 02 and 04 (respondents I and III) with the request to dismiss appellant I's appeal. No submissions were filed by opponent 03 (respondent II).

V. Appellants I and II replied to each other's statement of Grounds of Appeal.

VI. In a communication pursuant to Article 15(1) RPBA, annexed to the summons to oral proceedings, the board informed the parties of its preliminary opinion on the issues to be discussed at the upcoming oral proceedings.

VII. In reply to the board's communication, submissions were filed by appellant I and respondent III. Appellant I filed new Main and Auxiliary Requests 1 to 3 to replace all its previous requests on file. Except for minor changes, new Auxiliary Request 2 was identical to Auxiliary Request 3 upheld by the opposition division.

VIII. Appellant II and respondents I and II informed the board of their intention not to attend the upcoming oral proceedings.

IX. Oral proceedings took place on 11 February 2015 in the presence of appellant I and respondent III. At these proceedings, appellant I withdrew all previous requests and filed claims 1 - 12 of a new Main Request.

X. Claim 1 of the **Main Request** reads as claim 1 of the request upheld by the opposition division (cf. point II *supra*), except for the following amendments:

"1. A ribonucleic acid consisting of a double stranded structure, whereby the double stranded structure consists of a first strand and a second strand, whereby the first strand consists of a first stretch of contiguous nucleotides and whereby said first stretch is perfectly complementary to a target nucleic acid, and the second strand consists of a second stretch of contiguous nucleotides and whereby said second stretch is perfectly identical to the target nucleic acid,

characterised in ...

[as in claim 1 of the request upheld by the opposition division; cf. point II *supra*] ...

..., wherein the length of the first strand and of the second strand is 15 to 23 bases and wherein the modification is 2' O-Methyl,

wherein the ribonucleic acid is blunt ended on both sides, ...

[as in claim 1 of the request upheld by the opposition division; cf. point II *supra*]."

(underlining by the board, to show the differences between claim 1 of the Main Request and claim 1 of the request upheld by the opposition division).

Claims 2 to 4 were directed to preferred embodiments of claim 1. Claim 2 defined the double-stranded structure as having a length of 18 or 19 bases and, in claim 3, the length of the first and of the second strands was defined as being of 18 or 19 bases. Claims 5 to 7 were directed to uses of a ribonucleic acid according to any of claims 1 to 4 (target validation in claim 5 and

manufacture of a medicament in claims 6-7). Claims 8 and 9 were directed to a cell and to a non-human organism, respectively, containing a ribonucleic acid according to any of claims 1 to 4. Claims 10 and 11 were directed to a composition and to a pharmaceutical composition, respectively, containing a ribonucleic acid according to any of claims 1 to 4. Claim 12 was directed to an *in vitro* method for inhibiting the expression of a target gene.

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

D8: WO 02/16620 (publication date: 28 February 2002);

D9: WO 92/07065 (publication date: 30 April 1992);

D10: S.M. Elbashir et al., The EMBO Journal, Vol. 20, No. 23, 2001, pages 6877 to 6888;

D11: "Medicinal Chemistry of Antisense Oligonucleotides" by P.D. Cook, in "Antisense drug technology: Principles, strategies, and applications", ed. S.T. Crooke; Marcel Dekker, New York, 2001, Chapter 2, pages 29 to 56;

D12: S. Parrish et al., Molecular Cell, Vol. 6, November 2000, pages 1077 to 1087;

D13: WO 02/44321 (publication date: 6 June 2002).

XII. The submissions of appellant I (patentee), insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of the Main Request

The Main Request was based on the request upheld by the opposition division which had been on file from the beginning of the appeal proceedings. Amendments have only been introduced in reply to the objections raised by the board in its communication, in particular under Article 84 EPC, and to the objections raised at oral proceedings before the board. The amendments were a legitimate attempt to overcome these objections by simply limiting the breadth of the claims. They did not introduce new problems into the appeal proceedings.

Article 84 EPC

In a first step, claim 1 defined a "*pattern*" by reference to a plurality of flanking groups of nucleotides and a plurality of groups of modified nucleotides. In a subsequent step, the length of these groups was further defined. The terms "*flanking groups of nucleotides*" and "*groups of modified nucleotides*" were thus not open to interpretation, since they were defined as consisting of a single nucleotide. This definition excluded the presence of a group consisting of two continuous or adjacent modified or unmodified nucleotides. Thus, the reference to a group of modified nucleotides being flanked "*on one side*" by a flanking group of nucleotides applied only to the most terminal 5' and 3' nucleotides.

In accordance with the normal practice of the EPO, no objections could be raised against a functional feature (in claim 1, "*mediate RNA interference*") if tests for determining this feature were specified in the patent or known to a person skilled in the art. Moreover, there was no need to incorporate such tests into the claims. RNA interference was well-known in the art and

the patent referred to prior art from which appropriate tests could be immediately taken. The patent disclosed a comprehensible example in which RNA interference was measured (Example 1), and experimental procedures were also outlined in other examples of the patent.

Article 100(c) EPC; Article 123(2) EPC

The use in claim 1 of the indefinite article "*a*" instead of the definite article "*the*" when reference was made to the target nucleic acid was nothing but an evident error. As shown *inter alia* on page 10 of the patent with reference to Figure 1, the target sequence had to be, logically and compulsory, the same for both the first and second strands, otherwise no double stranded structure could be formed. In all examples of the patent, the same target sequence was addressed by both the first and second stretches.

The replacement in claim 1 of the term "*comprising*" by "*consists of*" was in line with established practice allowing the replacement of open language terms by closed language terms. All features defining the ribonucleic acid of claim 1 were disclosed by, and had a basis in, the application as filed.

Article 100(b) EPC; Article 83 EPC

The amendments introduced into the Main Request limited the scope of claim 1 to an embodiment which was already comprised within the scope of the claims of the request upheld by the opposition division and requests based thereupon. The objections raised for insufficiency of disclosure could have been raised at an earlier stage of the proceedings and thus, they should not be admitted into the proceedings at such a late stage. The

less so, because they were raised by a party that had not appealed the decision of the opposition division.

Ribonucleic acids of a short length were exemplified in the patent and they were shown to mediate RNA interference. A homolog stretch of 15 nucleotides was identified in Example 4 as being sufficient for gene silencing. Claim 1 did not require any specific efficiency or inhibition yield. Indeed, the efficiency depended on the properties of the group used to block the terminal 5' nucleotide of the ribonucleic acid. The bulkier the group, the less efficiency in mediating RNA interference. No evidence was on file showing that, for the specific ribonucleic acid claimed, RNA interference (RNAi) could not be achieved.

Article 100(a) EPC; Article 56 EPC

Several approaches for stabilizing RNA molecules were disclosed in the prior art but they were all different from the method disclosed in the patent, in that, for RNA antisense, the backbone of the nucleic acid was modified by phosphothioates and, for aptamers (gapmer technology), L-nucleotides were used instead of D-nucleotides. Since the mechanism and enzymes involved in RNAi were not characterized, a skilled person could not have expected that the stabilization strategies applied to other technologies would also have worked in RNAi. Thus, documents D9 and D11, concerned with ribozymes and antisense oligonucleotides, were not relevant.

The technical problem as formulated by the opposition division, namely the provision of a ribonucleic acid active in mediating RNAi and stable to degradation by nucleases, was solved by the claimed subject-matter

which was shown to be stable and active in a biochemical environment, such as a living cell. Moreover, it was not an arbitrary variation of modified RNA molecules known from the prior art.

Although document D8 suggested that the modification of pyrimidine bases could increase the stability of RNAi molecules, it did not provide any evidence for this suggestion. In any case, document D8 did not disclose a modification of the 2' position of the sugar moiety of nucleotides. Neither document D8 nor document D12 (both disclosing the modification of pyrimidines) would have led a skilled person to the specific modification pattern defined in claim 1.

In line with other prior art on file, document D13 disclosed that the modifications not affecting RNAi-mediating activity were limited to the overhang regions of the RNAi molecules. Thus, a skilled person was taught to modify the terminal nucleotides rather than nucleotides located in the middle of the RNAi-mediating molecule or nucleotides located at distinct positions throughout the entire RNAi molecule. The same teaching was derivable from document D10 which did not suggest any intermediate degree of modification. The suggestion to reduce the degree of modification as claimed could only have been made with hindsight knowledge of the invention. There was no hint in any of the prior art documents on file that would have led a skilled person to the specific pattern of modified and unmodified flanking nucleotides characterizing the claimed ribonucleic acid.

XIII. No submissions are on file from appellant II (opponent 01) as regards the Main Request. Appellant II's submissions concerning the request upheld by the

opposition division, made both in its Grounds of Appeal and in reply to appellant I's Grounds of Appeal (cf. points III and V *supra*), may be summarized, insofar as they are relevant to the Main Request, as follows:

Article 84 EPC

Claim 1 lacked clarity and conciseness. On the one hand, a pattern was defined as consisting of a plurality of flanking groups of nucleotides and a plurality of groups of modified nucleotides. On the other hand, each group of nucleotides was defined as consisting of only one nucleotide. The term "*group*", however, implied that there was more than one nucleotide. Claim 1 required the claimed ribonucleic acid to mediate RNA interference without indicating any specific test method. Since different methods for determining RNA interference led to different results, the scope of protection of claim 1 was unclear to a skilled person.

Article 100(c) EPC; Article 123(2) EPC

Claim 1 required the first stretch and the second stretch, respectively, to be perfectly complementary and perfectly identical to the same target nucleic acid. There was, however, no disclosure in the application as filed that both stretches referred to the same target nucleic acid. On pages 2-4 of the description as filed, the target nucleic acid was always defined by using the indefinite article "*a*".

The terms "*stretch*" and "*strand*" had a different meaning in the application as filed. There was no basis in the application as filed to support a replacement of one term by the other in claim 1. Likewise, the

replacement in claim 1 of the term "*comprising*" by "*consists of*" had no basis in the application as filed. Indeed, the specific combination of the numerous features of claim 1 was not directly and unambiguously derivable from the application as filed.

Article 100(b) EPC; Article 83 EPC

No objections were raised under this article in the statement of Grounds of Appeal. In reply to appellant I's Grounds of Appeal, the objections raised under this article were only directed against a Main Request then on file. When addressing the request upheld by the opposition division, reference to Article 83 EPC was made only in a general manner.

Article 100(a) EPC; Article 56 EPC

There was no reason for a skilled person, working in the field of RNA and facing the general problem of RNA stability, not to take into account teachings derived from other technical fields, such as antisense, ribosome or aptamer technology. Documents D9 and D11, concerned with ribozymes and antisense oligonucleotides, disclosed certain modifications at the 2'-O position to increase nuclease resistance and RNA stability. According to document D11, lack of activity of certain modified antisense oligonucleotides led to the development of gapmer technology. Several modification patterns were disclosed in document D9. Document D12 disclosed RNAi molecules with nucleotides modified at the 2'-position. Contrary to the modification of an entire strand, the presence of only certain modifications within a strand did not cause siRNA to lose its activity (Figure 5).

Claim 1 comprised ribonucleic acids with a pattern of alternating single modified and single unmodified nucleotides. However, since each modified nucleotide could be flanked "*on one or both sides*" by a flanking (unmodified) nucleotide, double-stranded structures with two modified nucleotides adjacent to each other were also contemplated. There was no evidence on file showing a special technical effect for any of the ribonucleic acids contemplated by claim 1 relative to other RNAi molecules known from the prior art.

The technical problem to be solved was thus the provision of an alternative modified double-stranded RNAi molecule. The ribonucleic acids of claim 1 merely represented arbitrary variants of known modified RNA molecules, such as those disclosed in documents D8, D10, D12 or D13, all concerning siRNA molecules with modified nucleotides. Document D10 taught that complete substitution of one or both siRNA strands by 2'-deoxy residues or 2'-O-Methyl residues abolished RNAi activity. It was thus obvious for a skilled person to reduce the degree of modification in both RNAi strands so as to retain RNAi activity and, at the same time, obtain stable ribonucleic acid molecules.

XIV. The submissions of respondent III (opponent 04), insofar as they are relevant to the present decision, may be summarized as follows:

Admissibility of the Main Request

The request, filed at the latest stage of appeal proceedings, intended to overcome objections that had been on file from the beginning of the proceedings. It could thus have been filed at an earlier stage of the proceedings.

Article 84 EPC

Claim 1 was ambiguous due to the combination of features requiring i) each group of modified nucleotides to be flanked "*on one or both sides*" by a flanking group of nucleotides, and ii) each group of modified nucleotides and each flanking group of nucleotides to consist of one single nucleotide. It was not clear whether the reference to "*one side*" applied only to the most 5' and 3' terminal nucleotides or whether double-stranded structures with two adjacent modified nucleotides adjacent were also contemplated.

Article 100(b) EPC; Article 83 EPC

According to claim 1, the length of the first strand and of the second strand of the ribonucleic acid could be as short as 15 bases. However, according to the patent, double-stranded ribonucleic acids had to be longer than 17 base pairs in order to have RNAi activity. Claim 1 comprised thus subject-matter that could not mediate RNA interference. This objection had originally been raised under Article 56 EPC against requests that did not require the claimed ribonucleic acid to mediate RNA interference, arguing that the technical problem was not solved over the whole scope of the claims. Since this requirement had been introduced into claim 1 of the Main Request, it was legitimate to raise this objection now under Article 83 EPC and no fresh case was created thereby.

Claim 1 required the claimed ribonucleic acid to be blunt ended on both sides and to have the most terminal 5' nucleotide modified. According to the patent, antisense strands could not be modified at the 5'-

terminal nucleotide, otherwise the ribonucleic acids could not mediate RNAi interference (Examples 6 and 8-10 of the patent). Thus, none of the ribonucleic acids having the structural features defined in claim 1 could fulfil the functional requirement defined in this claim. It was undue burden for a skilled person to identify and select ribonucleic acids mediating RNA interference among all possible ribonucleic acids having a short length (less than 18 bases) and a 5'-terminal modification which, in any case and according to the patent, had no RNAi activity at all. This objection could not have been raised at an earlier stage of the appeal proceedings because in none of the previous requests the claimed ribonucleic acids were required to be blunt ended on both sides and to have the most 5'-terminal modified.

XV. No submissions are on file from respondent I (opponent 02) as regards the Main Request. In respondent I's submissions made in reply to appellants' Grounds of Appeal (cf. points IV *supra*), an objection under Article 84 EPC was raised against a request which, except for minor changes, was identical to the request upheld by the opposition division (cf. page 3, point 3.6 of respondent I's letter of 10 December 2010). This objection, however, does not apply to the Main Request.

XVI. Appellant I (patentee) requested that the decision under appeal be set aside and the patent be maintained upon the basis of claims 1 - 12 of the Main Request submitted during the oral proceedings before the board on 11 February 2015.

XVII. Respondent III (opponent 04) requested to set aside the decision under appeal and to revoke the patent.

XVIII. Appellant II (opponent 01) and respondent I (opponent 02) requested, in writing, to set aside the decision under appeal and to revoke the patent.

XIX. There are no requests and no substantive submissions on file from respondent II (opponent 03).

Reasons for the Decision

Admissibility of the Main Request

1. The filing of the Main Request at oral proceedings before the board represents an amendment of appellant I's case which, according to Article 13(1) RPBA, may be admitted and considered only at the board's discretion. Article 114(2) EPC entitles the board to disregard facts or evidence which are not submitted in due time by the parties. In the present case, the following considerations are of relevance for the board to arrive at a decision:

1.1 The Main Request is based on the Auxiliary Request 3 upheld by the opposition division (cf. points II and X *supra*). Except for minor changes, the auxiliary request upheld by the opposition division had been on file from the beginning of the appeal proceedings (cf. point III *supra*) and it has never been withdrawn during these proceedings (cf. point VII *supra*).

1.2 The amendments introduced into the Main Request were made, firstly, in reply to the objections raised by the board in its communication pursuant to Article 15(1) RPBA, in particular under Article 84 EPC, and secondly, in reply to the objections raised at oral proceedings before the board, in particular under Articles 84 and

123(2) EPC. The amendments are simple, straightforward in nature and limit the claimed subject-matter to a particular embodiment exemplified in the patent. Thereby, they address, and attempt to overcome, most of the objections raised in the proceedings.

1.3 Although the amendments introduced into the Main Request raise new issues which, as such, were not addressed before in the proceedings, these issues are simple in nature, they could have been expected and do not render the case more complex (cf. points 12-13 *infra*).

2. Thus, the board, exercising the discretion conferred to it by Article 13(1) RPBA, decides to admit the Main Request into the appeal proceedings.

Article 84 EPC

3. Claim 1 is directed to a ribonucleic acid consisting of a double stranded structure which consists of a first and a second strand. These two strands are further defined as consisting of "*a pattern*" which itself is further characterized by the presence of several "*groups of modified nucleotides*" and "*flanking groups of nucleotides*". Although the term "*group*" may not be the most appropriate, in the context of claim 1 these "*groups*" of modified and of flanking nucleotides are explicitly defined as consisting of a single nucleotide only (cf. point X *supra*). No ambiguity or lack of clarity arises from these definitions.

4. It is also derivable from these definitions that the feature in claim 1 "*whereby within the strand each group of modified nucleotides is flanked on* ***one*** *or both* ***sides*** *by a flanking group of nucleotides*" (emphasis

added by the board), when relating to a flanking on one side, refers exclusively to the most terminal 5' and 3' nucleotides of these strands. These definitions exclude the presence of two modified nucleotides adjacent to each other. Two adjacent modified nucleotides would be a group of modified nucleotides consisting of two nucleotides, which is explicitly excluded by the wording of claim 1.

5. On page 2, paragraphs [0002] to [0007] of the patent, reference is made to a large number of prior art documents concerned with RNA interference (RNAi), double stranded RNA (dsRNA) and small interfering RNA (siRNA). Example 1 of the patent refers to commercial products and standard protocols used to perform RNAi experiments (cf. pages 11-13 of the patent). These experimental approaches are followed when performing the RNAi studies described in other examples of the patent (cf. Examples 2-13, pages 13-19 of the patent). Although the biological RNAi pathway and the enzymes involved therein were not fully characterized at the filing date of the patent (*infra*), the board has no doubts that tools and means were available for a skilled person to determine whether a ribonucleic acid consisting of a double stranded structure as defined in claim 1 mediates RNAi.

A certain variability in the results has to be accepted as being technically unavoidable in any experimental measure. This normal variability does not render a functional feature based on an experimental test method unclear or ambiguous. Based on the evidence on file and in the light of the prior art cited in the patent and the examples disclosed therein, the functional feature contained in claim 1, i.e. *"wherein the ribonucleic*

acid mediates RNA interference", does not introduce any unacceptable ambiguity.

6. Thus, the Main Request fulfils the requirements of Article 84 EPC.

Article 100(c) EPC; Article 123(2) EPC

7. The terms "*comprising*" and "*comprises*" have all been replaced in claim 1 by the terms "*consisting of*" and "*consists of*", respectively. The replacement limits the claimed subject-matter to a particular embodiment disclosed in the application as filed, namely to a most advantageous ribonucleic acid with the structural features exemplified in Example 11 of the application as filed.

According to Example 11, unexpectedly good results are obtained by ribonucleic acids consisting of a double-stranded structure with alternating modifications on both strands in an aligned phase shift pattern, wherein the most 5' terminal nucleotide of the antisense strand has a (2'-O-methyl) modification and the groups of modified nucleotides and of flanking nucleotides consist each of a single nucleotide. These ribonucleic acids, schematically shown in Figure 2B, show a significant improvement in stability and in down regulation of the protein expression encoded by the target nucleic acid.

In Example 11, these ribonucleic acids are the PTENA/PTENB V15 (21 nt, Figure 15B), Akt1A/Akt1B V5 (19 nt, Figure 16A) and the P110β V5 (19 nt, Figure 16C) molecules (cf. pages 42-45; in particular, the paragraph bridging pages 43-44, page 44, first full-paragraph, last sentence, and the sentence bridging

pages 44-45 to the end of the first paragraph on page 45 of the application as filed). All these RNA molecules have the structural features characterizing the ribonucleic acid of claim 1. The scope of this claim has been limited to these particular ribonucleic acids for which there is a clear and unambiguous basis in the application as filed.

8. The replacements discussed in point 7 above have the consequence that the term "*first and second strands*" is identical to "*first and second stretches*" and the term "*double-stranded structure*" to "*ribonucleic acid*". The replacement of the term "*stretch*" by "*strand*" in the last paragraph but one of claim 1 only renders this paragraph consistent with the amendments made in the preamble of this claim. There is thus no unallowable addition of subject-matter.

9. Likewise, the replacement of the indefinite article "*a*" by the definite article "*the*" in the last sentence of the preamble of claim 1 does not contravene Article 123(2) EPC. This replacement identifies the target nucleic acid as being the same for both the first and second stretches and, consequently, for both the first and second strands. The amendment merely limits the scope of claim 1 to the subject-matter exemplified in Example 11 of the application as filed by the PTENA/PTENB V15, Akt1A/Akt1B V5 and P110β V5 ribonucleic acids.

10. The Main Request fulfils thus the requirements of Article 123(2) EPC.

Article 100(b) EPC; Article 83 EPC

11. At oral proceedings before the board, respondent III raised two objections under Article 83 EPC (cf. point XIV *supra*).

The amendments introduced into claim 1 of the Main Request limit the claimed subject-matter to a particular embodiment already comprised within the scope of claim 1 of the request upheld by the opposition division (cf. points II and X *supra*). Thus, the objections applied also to the request upheld by the opposition division and, therefore, could have been raised earlier in the proceedings. These objections represent an amendment of respondent III's case, a non-appealing party to the present appeal proceedings, and according to Article 13(1) RPBA, may be admitted and considered at the board's discretion.

Although the embodiment now claimed in the Main Request was already comprised in the request upheld by the opposition division and in all requests based thereupon, the limitation to this embodiment makes evident the issues on which the objections are based. The objections are simple in nature and can be addressed in a straightforward manner. Their introduction into the proceedings is also fair and equitable in view of the late-filed submission of the Main Request.

The objections raised under Article 83 EPC are thus admitted into the proceedings (Article 13(1) RPBA).

12. As regards the first objection, respondent III argues that claim 1 comprises a group of ribonucleic acids which have a length shorter than 18 nucleotides and therefore, cannot fulfil the functional feature defined in claim 1 (cf. point XIV *supra*).

12.1 Claim 1 defines the length of the first and second strands as being "***15*** *to 23 bases*" (emphasis by the board) and thus, includes a group of ribonucleic acids with a length shorter than 18 nucleotides. Although the assays reported in Example 4 of the patent show that "*a homolog stretch of 15 nt between a target mRNA and RNai is sufficient for gene silencing*", all duplexes used therein have a length longer than 18 bases (cf. page 14, paragraphs [0071] to [0073] of the patent). In Example 3, the requirements concerning the duplex length of interfering RNA molecules for having *in vivo* RNAi activity are determined. It is repeatedly stated that "*the double strand duplex of the siRNA molecules has to be longer than 17 base pairs to show activity*", "*the shortest RNAi molecules successfully tested were 18 to 19 nucleotides or base pairs in length*", "*active siRNA duplexes should be at least 18 nt or longer*", "*the minimum requirement for optimum RNAi mediated interference is thus a duplex length of 18 or 19 nucleotides*" (cf. page 13, paragraph [0067] to page 14, paragraph [0070] of the patent). It is also stated in Example 3 that "*the duplex length itself, but not the base pairing of the antisense siRNA with the target mRNA seems to determine the minimum length of functional siRNAs*" (cf. page 13, line 58 to page 14, line 2 of the patent). Thus, the structural requirements defined in claim 1 embrace a group of short-length ribonucleic acids identified in the patent as not fulfilling the functional requirement defined in the claim.

12.2 However, claim 1 explicitly requires the claimed ribonucleic acids to mediate RNA interference. Thus, any ribonucleic acid not fulfilling this functional requirement is excluded from the scope of the claim.

Indeed, some ribonucleic acids fulfilling the structural requirements of claim 1 may be non-working embodiments of this claim. However, the patent informs a skilled person that short-length ribonucleic acids cannot fulfil the functional feature defined in claim 1 and the patent provides "*a large number of conceivable alternatives and ... contains sufficient information on the relevant criteria for finding appropriate alternatives over the claimed range with reasonable effort*" (cf. G 1/03, OJ EPO 2004, page 413, point 2.5.2 of the Reasons). Therefore, in the present case, the fact that claim 1 embraces some non-working embodiments is of no harm for the issue of Article 83 EPC.

13. As regards the second objection, respondent III argues that the claimed ribonucleic acids are required to have the most terminal 5' nucleotide of the first strand (2'-O-methyl) modified. A modification which is identified in the patent as preventing the modified ribonucleic acid to mediate RNA interference (cf. point XIV *supra*).

13.1 In Example 6 of the patent, it is stated that the modification by the presence of "*end protection groups on the 5' and 3' ends*" results in the inactivation of the ribonucleic acids (cf. page 15, paragraphs [0078] to [0081] of the patent). This teaching is confirmed in other examples of the patent, such as in Example 8 (cf. page 16, lines 3-8 of the patent).

13.2 However, according to Example 11, "*(i)n ... RNA interference activity assay an* ***unexpected*** *preference for molecules was observed which were modified at every second nucleotide beginning with the most 5' terminal nucleotide of the antisense strand (molecules* ***V15*** *and V12)*" (emphasis added by the board). It is further

stated that "*the data shown herein demonstrate that 2'-O-methyl modifications at particularly selected positions in the siRNA duplex can increase nuclease resistance and do not necessarily abolish RNAi completely*" (cf. page 17, paragraph [0098], in particular lines 33-43 of the patent). Similar results are also described in Example 11 for the modified siRNA Akt1 and P110β (molecule **V5**; cf. pages 17-18, paragraphs [0100] and [0101] of the patent). Molecules V15 and V5 fulfil all structural and functional requirements of the ribonucleic acids of claim 1 (cf. point 7 *supra*). For this particular group of ribonucleic acids with the pattern of alternating modifications defined in claim 1, the (2'-O-methyl) modification of the most terminal 5' nucleotide of the first strand does not result in an RNAi inactivation of the ribonucleic acids.

14. As the scope of the claims of the Main Request has been restricted to the specific embodiments of Example 11, the requirements of Article 83 EPC are fulfilled.

Article 100(a) EPC; Article 54 EPC

15. No objections in this respect have been raised at first instance proceedings with regard to the request upheld by the opposition division (cf. page 14 of the decision under appeal). No such objection has been raised by appellant II in its Grounds of Appeal or at any stage of the appeal proceedings. Thus, the Main Request fulfils the requirements of Article 54 EPC.

Article 100(a) EPC; Article 56 EPC

16. In the statement setting out its Grounds of Appeal, appellant II raised an objection under Article 56 EPC

against the request upheld by the opposition division (cf. pages 5-8, point 5 of appellant II's Grounds of Appeal). This objection was maintained, without any further elaboration, in the reply to appellant I's Grounds of Appeal (cf. page 17, point 7 of appellant II's letter dated 13 December 2010). None of the other parties in appeal proceedings (respondents I to III) filed any submissions concerning Article 56 EPC with regard to the request upheld by the opposition division or a requests based thereon.

17. In its submissions, appellant II referred to several documents in support of its arguments but it neither identified the closest prior art document nor formulated a problem solution approach as established in the case law (cf. "Case Law of the Boards of Appeal of the EPO", 7th edition 2013, I.D.2, page 165).

17.1 The documents cited by appellant II fall within two categories. A first group is concerned with inhibitory RNA (iRNA) or RNA interference (RNAi) with double-stranded RNA (dsRNA) (documents D8, D10, D12 and D13). A second group refers to related technologies, such as modified ribozymes, antisense and gapmer technology (documents D9 and D11). Since the patent is concerned with RNAi, the closest prior art document has to be selected from the documents of the first group.

Documents D8 and D13 refer to RNAi and to the requirements of dsRNA for having RNAi activity, such as a length of 15-25 base pairs, preferably 21 bp (cf. page 11, lines 29-30 and claims 29-30 of document D8; page 3, lines 18-27, page 4, lines 12-14 and claims 1-4 of document D13). While document D8 only refers to the presence of modified bases as conferring advantageous properties without further elaborating on this issue

(cf. page 12, lines 10-17 and claim 34 of document D8), document D13 provides more detailed information (cf. *inter alia*, page 5, lines 15-21, page 46, point 3.2.4 and claims 7-10 of document D13). The most detailed and systematic analyses of the structural dsRNA requirements ("*functional anatomy*") are provided by documents D10 and D12. Indeed, document D12 was identified by the opposition division as the closest prior art document (cf. page 16, point 8.3 of the decision under appeal). There is no reason for the board to deviate from this selection.

17.2 In Figure 5 of document D12, the effects of backbone modifications on the activity of the dsRNA are summarized. According thereto, modifications at the 2' O-position of the nucleotide sugar may have a significant influence on the activity of the dsRNA so that, depending on the type of modification and the (sense and/or antisense) strand modified, a substantial decrease, if not a complete loss, of activity may be obtained (cf. page 1081, Figure 5 of document D12). There is no reference in document D12 to the specific 2'O-methyl modification.

17.3 Starting from document D12, the objective technical problem to be solved has been formulated in the decision under appeal as the provision of synthetic interfering RNA molecules which are both stable and active in a biochemical environment such as in a living cell (cf. page 16, seventh paragraph of the decision under appeal). As far as these interfering RNA molecules are considered to be "*alternative*" molecules to other interfering RNA molecules disclosed in the prior art, all parties agree to this formulation of the technical problem.

17.4 Claim 1 is limited to a specific group of ribonucleic acids with a particular structure, namely a double-stranded structure with alternating modifications on both strands in an aligned phase shift pattern (cf. Figure 2B of the patent), wherein the most 5' terminal nucleotide of the antisense strand has a (2'-O-methyl) modification and the groups of modified nucleotides and of flanking nucleotides consist each of a single nucleotide. Examples for such structure are the ribonucleic acids V15 and V5 disclosed in Example 11 of the patent (cf. point 7 *supra*). Claim 1 excludes the presence of two adjacent modified groups within the (sense and antisense) strands of the claimed ribonucleic acids (cf. points 3-4 *supra*). The results shown in Example 11 for these specific ribonucleic acids demonstrate that the claimed subject-matter solves the technical problem and, in view of the functional feature of claim 1, this technical problem is solved over the whole breadth of the claim.

17.5 The board comes to the conclusion that the claimed ribonucleic acids are not derivable from the prior art in an obvious manner. There is nothing in this prior art leading a skilled person to these ribonucleic acids.

Document D10 states, *inter alia*, that "(d)*uplexes with blunted ends ... were sometimes functional and sometimes completely inactive*" (cf. page 6878, right-hand column, last full sentence) and that optimal results are obtained when using duplexes of 21 nucleotides with 3' overhanging ends of 2 nucleotides (cf. page 6877, left-hand column, abstract; page 6878, left-hand column, lines 6-4 from the bottom; page 6881, left-hand column, last sentence of first paragraph). The "*critical*" relevance of these overhangs is

emphasized in document D10 when discussing the prior art (cf. page 6884, left-hand column, first sentence of second full paragraph; page 6885, left-hand column, first sentence of first full paragraph and page 6885, right-hand column, last paragraph to page 6886, paragraph bridging left and right-hand columns). Document D10 further states that the "(s)*ubstitution of one or both siRNA strands by 2'-deoxy or 2'-O-methly oligonucleotides abolished RNAi, although multiple 2'-deoxynucleotide substitutions at the 3' end of siRNA were tolerated*" (cf. page 6877, left-hand column, abstract; paragraph bridging pages 6881 to 6882, page 6882, Figure 4), and concludes that "(m)*ore extensive 2' deoxy or 2'-O-methly modifications reduce the ability of siRNAs to mediate RNAi*" (cf. page 6885, left-hand column, last sentence of first full paragraph).

The same teaching is disclosed in document D13 which reports that, although no effects on siRNA activity have been found for a substitution of the 2 nucleotides of the 3' overhangs by 2'-deoxy nucleotides, the "(c)*omplete substitution of one or both siRNA strands by 2'-deoxy residues ... abolished RNAi, as did substitution by 2'-O-methly residues*" (cf. page 46, point 3.2.4). Indeed, document D13 further states that modifications, such as the replacement by nucleotide analogues, are preferably "*located at positions where the target-specific activity, e.g. the RNAi mediating activity is not substantially effected, e.g. in a region at the 5'-end and/or the 3'-end of the double-stranded RNA molecule*" (cf. page 5, lines 15-20). Contrary to that, the patent states that dsRNA's are usually inactivated by the presence of "*end protection groups on* [their] *5' and 3' ends*" (cf. point 13.1 *supra*).

In the light thereof, the board concludes that the presence of RNAi activity for ribonucleic acids having a structure as defined in claim 1, and exemplified by molecules V15 and V5, was completely unexpected (cf. point 13.2 *supra*) and thus, not obvious.

17.6 The same conclusion can also be drawn from teachings concerning other related technologies referred to by appellant II (cf. point 17.1 *supra*).

The relevance of certain (2'O-ribofuranosyl) modifications for increasing RNA nuclease resistance and for achieving other advantageous properties is explicitly acknowledged in document D11, a review document of antisense and gapmer technologies (cf. paragraph bridging pages 40-41). However, it is also acknowledged that "*oligomers uniformly modified ... were inactive or less active ... It is now well known that uniformly 2'-O-modified oligonucleotides do not support an RNase H mechanism*". Moreover, it is stated that "*(t)he lack of activity of 2'-O-modified oligonucleotides has led to the development of a chimeric oligonucleotide strategy (gapmer technology) ... This approach focuses on the design of high-binding, nuclease-resistant antisense oligonucleotides that are "gapped" with a contiguous sequence of 2'-deoxy phosphorothioates*". According to document D11, these modifications are preferably located in the flanking regions of the "gap" in order "*not only* [to] *provide nuclease resistance to exo- and endonucleases, but also not* [to] *compromise binding affinity and base-pair specificity*" (cf. paragraph bridging pages 47-48). This teaching will not lead a skilled person in an obvious way to ribonucleic acids having the specific structure defined in claim 1.

Apart from that, the board agrees with the opposition division that, notwithstanding the systematic analysis disclosed in documents D10 and D12, there was "*a lack of profound* [RNAi] *mechanistic understanding*" at the priority date of the patent, in particular of the enzymes involved in RNAi mechanism and post-transcriptional gene silencing (PTGS) as well as of the structural requirements which this mechanism and enzymes imposed on the associated siRNA (cf. *inter alia*, page 6877, right-hand column, last paragraph to page 6878, left-hand column, last paragraph but one of document D10; page 1077, right-hand column of document D12; page 17, second and third paragraph of the decision under appeal). Thus, a skilled person could not have expected that a successful RNA stabilization obtained in related techniques could warrant the same success in RNAi, certainly not in a straightforward manner.

18. Thus, the Main Request fulfils the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent with claims 1 - 12 of the Main Request received during oral proceedings of 11 February 2015 and a description to be adapted.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated