

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: Christopher Verni
Sarepta Therapeutics, Inc.
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Date of mailing
(day/month/year)

09 AUG 2019

Applicant's or agent's file reference
8163.52.WO00

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US19/33768

International filing date (day/month/year)

23 May 2019 (23.05.2019)

Priority date (day/month/year)

29 May 2018 (29.05.2018)

International Patent Classification (IPC) or both national classification and IPC

IPC - A61K 31/5375; A61P 13/02 (2019.01)

CPC - A61K 31/5375; A61P 13/02

Applicant

Sarepta Therapeutics, Inc.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US
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Date of completion of this opinion

25 July 2019 (25.07.2019)

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**WRITTEN OPINION OF THE
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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(b)).
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☒ the entire international application.

☐ claims Nos. 13, 16, 21-27

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 13, 16, 21-27 are so unclear that no meaningful opinion could be formed (*specify*):

Claims Nos. 13, 16, and 21-27 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4 (a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 13, 16, 21-27

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	----Please See Below----	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	----Please See Below----	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	----Please See Below----	YES
	Claims	NONE	NO

2. Citations and explanations:

----Continued from Box No. V: 1. Statement----

Novelty (N): YES: Claims 1-9, 10/1-3, 10/7-8, 11/1-3, 11/7-8, 12/11/1-3, 12/11/7-8, 14/1-3, 14/7-8, 15/14/1-3, 15/14/7-8, 17/10/1-3, 17/10/7-8, 18/10/1-3, 18/10/7-8, 19/10/1-3, 19/10/7-8, 20/17/10/1-3, 20/17/10/7-8

Inventive step (IS): YES: Claims 1-9, 10/1-3, 10/7-8, 11/1-3, 11/7-8, 12/11/1-3, 12/11/7-8, 14/1-3, 14/7-8, 15/14/1-3, 15/14/7-8, 17/10/1-3, 17/10/7-8, 18/10/1-3, 18/10/7-8, 19/10/1-3, 19/10/7-8, 20/17/10/1-3, 20/17/10/7-8

Industrial applicability (IA): YES: Claims 1-9, 10/1-3, 10/7-8, 11/1-3, 11/7-8, 12/11/1-3, 12/11/7-8, 14/1-3, 14/7-8, 15/14/1-3, 15/14/7-8, 17/10/1-3, 17/10/7-8, 18/10/1-3, 18/10/7-8, 19/10/1-3, 19/10/7-8, 20/17/10/1-3, 20/17/10/7-8

----Box No. V: 2. Citations and Explanations----

Claims 1-3, 7-8, 10/1-3, 10/7-8, 11/1-3, 11/7-8, 12/11/1-3, 12/11/7-8, 14/1-3, 14/7-8, 15/14/1-3, 15/14/7-8, 17/10/1-3, 17/10/7-8, 18/10/1-3, 18/10/7-8, 19/10/1-3, 19/10/7-8, 20/17/10/1-3 and 20/17/10/7-8 meet the criteria set out in PCT Article 33(2)-(3).

Claim 1 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an antisense oligomer conjugate of Formula I, as shown, or a pharmaceutically acceptable salt thereof, wherein: each Nu is a nucleobase which taken together form a targeting sequence; and T is a moiety selected from three moieties, as shown; R1 is C1-C6 alkyl, wherein the targeting sequence is complementary to an exon 52 annealing site in the dystrophin pre-mRNA designated as H52A(-01+24).

US 2012/0289457 A1 (HANSON) discloses an antisense oligomer conjugate of Formula I, as shown (formula in figure 1C in which W is O, Y is O, Pi is a base-pairing moiety, the morpholino oligomer containing 8-25 nucleotide bases, i.e., where Pi is a nucleotide base and x is 6 to 23, excluding 5' and 3' bases shown separately in figure 1C, X is N(CH₃)₂, each linkage in the oligomer is -N(CH₃)₂, and the carrier peptide comprises the oligo arginine sequence (R)₆G, the terminal amino acid is capped with an acetyl, and further, the peptide AcR₆G, i.e., in which the terminal arginine is capped with acetyl moiety, was conjugated with the morpholino oligomer PMO having unprotected 3'-H, and which is binding mouse exon 23, i.e., where the conjugation proceeds between unprotected glycine residue of the peptide AcR₆G and unprotected 3'-H of the PMO, thus producing the oligomer, as shown; figure 1C; paragraphs [0174]-[0177], [0185], [0251], [0350], [0121], [0124], [0477]) wherein: each Nu is a nucleobase which taken together form a targeting sequence (Pi is a base-pairing moiety, the morpholino oligomer containing 8-25 nucleotide bases, i.e., where Pi is a nucleotide base and x is 6 to 23; paragraph [0350]); and T is the first moiety, as shown (formula in figure 1C, comprising the terminal oligoethylene glycol moiety attached to the Piperazinyl ring through the phosphate residue, where W is O, Y is O and X is N(CH₃)₂, each linkage in the oligomer is -N(CH₃)₂; figure 1C; paragraphs [0174]-[0177], [0185]); R1 is not chosen (the first formula does not comprise R1); wherein the targeting sequence is complementary to the dystrophin pre-mRNA (an antisense oligomer capable of producing exon skipping in the dystrophin protein having a sequence selected from SEQID NOs: 22 to 35, to restore partial activity of the dystrophin protein, the oligomer targets a splice site of a pre-mRNA; paragraphs [0320], [0369]). However, Hanson does not disclose wherein the targeting sequence is complementary to an exon 52 annealing site in the dystrophin pre-mRNA designated as H52A -01+24, i.e., covers the positions -1 to 24 of the dystrophin exon 52.

WO 2017/049407 A1 (UNIVERSITE LAVAL) (hereinafter "Laval") discloses sequence comprising an exon 52 annealing site in the dystrophin designated as H52A -01+24 (sequence ID 54, 168 bp). However, Laval does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

US 2008/0249052 A1 to Duan, et al (hereinafter "Duan") discloses sequence comprising an exon 52 annealing site in the dystrophin designated as H52A -01+24 (sequence ID 40, 321 bp). However, Duan does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

The publication entitled "RP43-026J01, complete sequence" by Berg, et al (hereinafter "Berg") discloses sequence comprising an exon 52 annealing site in the dystrophin designated as H52A -01+24 (sequence; page 1-43). However, Berg does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

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In case the space in any of the preceding boxes is not sufficient.

Continuation of:

-Continued from Box V: Citations and Explanations-

The publication entitled "Rational Design of Antisense Oligomers to Induce Dystrophin Exon Skipping" by Mitrpant, et al (hereinafter "Mitrpant") discloses wherein the targeting sequence is complementary to an exon 52 annealing site in the dystrophin (a single oligonucleotide H52A +12+41, was found to efficiently remove human exon 52 from the mature dystrophin transcript; page 1422, second column, third paragraph). However, Mitrpant does not disclose wherein the targeting sequence is designated as H52A -01+24, i.e., covers the positions -1 to 24 of the dystrophin exon 52.

The publication entitled "A dystrophic Duchenne mouse model for testing human antisense oligonucleotides" by Veltrop, et al (hereinafter "Veltrop") discloses wherein the targeting sequence is complementary to an exon 52 in the dystrophin (two Transcription Activator-like Effector Nucleases TALENs sets were built with a recognition sequences close to the intron 51-exon 52 and exon 52-intron 52 boundary to facilitate the targeting of exon 52, where the oligonucleotides are not complementary to the positions -01+24 of the exon 52, as shown in supplementary figure S1; page 7, second paragraph; supplementary figure S1). However, Veltrop does not disclose wherein the targeting sequence is designated as H52A -01+24, i.e., covers the positions -1 to 24 of the dystrophin exon 52.

Thus, the prior art does not teach or fairly suggest an antisense oligomer conjugate of Formula I, as shown, or a pharmaceutically acceptable salt thereof, wherein: each Nu is a nucleobase which taken together form a targeting sequence; and T is a moiety selected from three moieties, as shown; R1 is C1-C6 alkyl, wherein the targeting sequence is complementary to an exon 52 annealing site in the dystrophin pre-mRNA designated as H52A(-01+24), and sufficient motivation, based upon the previous disclosures of the Hanson, Laval, Duan, Berg, Mitrpant and Veltrop references, does not exist to have determined and implemented the antisense oligomer conjugate as described in claim 1 of the instant PCT application.

Claims 2-3, 10/1-3, 11/1-3, 12/11/1-3, 14/1-3, 15/14/1-3, 17/10/1-3, 18/10/1-3, 19/10/1-3 and 20/ 17/10/1-3 meet the criteria set out in PCT Article 33(2)-(3) because they depend on positive claim 1.

Claim 4 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an antisense oligomer of Formula V, as shown, or a pharmaceutically acceptable salt thereof, wherein: each Nu is a nucleobase which taken together form a targeting sequence; and T is a moiety selected from three moieties, as shown; R1 is C1-C6 alkyl; R2 is selected from H or acetyl, wherein the targeting sequence is complementary to an exon 52 annealing site in the dystrophin pre-mRNA designated as H52A(-01+24).

US 2014/0330006 A1 (Sarepta Therapeutics, Inc) (hereinafter "Sarepta") discloses an antisense oligomer similar to the oligomer of Formula V, as shown (final compound on figure 4, where X is X1, which is N(CH3)2; figure 4; paragraphs [0038], [0040]), wherein: each Nu is a nucleobase which taken together form a targeting sequence (base is in the final compound on figure 4, and further, the base pairing moiety is a purine or pyrimidine found in native DNA or RNA and includes A, G, C, T, or U; figure 4; paragraph [0692]) and T is the first moiety, as shown (the 3' end of the oligonucleotide comprises the moiety shown; figure 4). In the first embodiment Sarepta does not disclose wherein the length of the oligonucleotide is as shown, and further does not disclose wherein the targeting sequence is complementary to an exon 52 annealing site in the dystrophin pre-mRNA designated as H52A -01+24, i.e., covers the positions -1 to 24 of the dystrophin exon 52. However, in a separate embodiment Sarepta discloses wherein the length of the oligonucleotide is as shown (general Formula I, where n is an integer from 1 to 50; paragraphs [0011], [0013]). Thus, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the oligomer, as previously disclosed by Sarepta in the first embodiment, in order to have provided for wherein the length of the oligonucleotide is as shown, as previously disclosed by Sarepta in the second embodiment (paragraphs [0011], [0013]), for improving the effectiveness of the compound in treatment of viral infections (paragraph [0723]). Further, provided that in both embodiments discloses the compounds of similar structures (figure 4; paragraphs [0011], [0013]), where the compounds are designed for treatment of viral infections (paragraph [0723]), the modification to Sarepta's oligomer, of providing for wherein the length of the oligonucleotide is as shown, would provide the benefit of improving the effectiveness of the compound in treatment of viral infections (paragraph [0723]).

Laval discloses sequence comprising an exon 52 annealing site in the dystrophin designated as H52A -01+24 (sequence ID 54, 168 bp). However, Laval does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

Duan discloses sequence comprising an exon 52 annealing site in the dystrophin designated as H52A -01+24 (sequence ID 40, 321 bp). However, Duan does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

Berg discloses sequence comprising an exon 52 annealing site in the dystrophin designated as H52A -01+24 (sequence; page 1-43). However, Berg does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

Mitrpant discloses wherein the targeting sequence is complementary to an exon 52 annealing site in the dystrophin (a single oligonucleotide H52A +12+41, was found to efficiently remove human exon 52 from the mature dystrophin transcript; page 1422, second column, third paragraph). However, Mitrpant does not disclose wherein the targeting sequence is designated as H52A -01+24, i.e., covers the positions -1 to 24 of the dystrophin exon 52.

Veltrop discloses wherein the targeting sequence is complementary to an exon 52 in the dystrophin (two Transcription Activator-like Effector Nucleases TALENs sets were built with a recognition sequences close to the intron 51-exon 52 and exon 52-intron 52 boundary to facilitate the targeting of exon 52, where the oligonucleotides are not complementary to the positions -01+24 of the exon 52, as shown in supplementary figure S1; page 7, second paragraph; supplementary figure S1). However, Veltrop does not disclose wherein the targeting sequence is designated as H52A -01+24, i.e., covers the positions -1 to 24 of the dystrophin exon 52.

-Continued Within the Next Supplemental Box-

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In case the space in any of the preceding boxes is not sufficient.

Continuation of:

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Thus, the prior art does not teach or fairly suggest an antisense oligomer of Formula V, as shown, or a pharmaceutically acceptable salt thereof, wherein: each Nu is a nucleobase which taken together form a targeting sequence; and T is a moiety selected from three moieties, as shown; R1 is C1-C6 alkyl; R2 is selected from H or acetyl, wherein the targeting sequence is complementary to an exon 52 annealing site in the dystrophin pre-mRNA designated as H52A(-01+24), and sufficient motivation, based upon the previous disclosures of the Sarepta, Laval, Duan, Berg, Mitrpant and Veltrop references, does not exist to have determined and implemented the antisense oligomer as described in claim 4 of the instant PCT application.

Claims 5-6 meet the criteria set out in PCT Article 33(2)-(3) because they depend on positive claim 4.

Claim 7 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an antisense oligomer conjugate of Formula IV, as shown, or a pharmaceutically acceptable salt thereof.

Hanson discloses an antisense oligomer conjugate of formula similar to the Formula IV, as shown (formula in figure 1C in which W is O, Y is O, Pi is a base-pairing moiety, the morpholino oligomer containing 8-25 nucleotide bases, i.e., where Pi is a nucleotide base and x is 6 to 23, excluding 5' and 3' bases shown separately in figure 1C, X is N(CH₃)₂, each linkage in the oligomer is -N(CH₃)₂, and the carrier peptide comprises the oligo arginine sequence (R)₆G, the terminal amino acid is capped with an acetyl, and further, the peptide AcR₆G, i.e., in which the terminal arginine is capped with acetyl moiety, was conjugated with the morpholino oligomer PMO having unprotected 3'-H, and which is binding mouse exon 23, i.e., where the conjugation proceeds between unprotected glycine residue of the peptide AcR₆G and unprotected 3'-H of the PMO, thus producing the oligomer, as shown; figure 1C; paragraphs [0174]-[0177], [0185], [0251], [0350], [0121], [0124], [0477]). However, Hanson does not disclose the oligonucleotide having sequence CTGTTCCAAATCCTGCATTGTTGCC.

Laval discloses a sequence comprising subsequence CTGTTCCAAATCCTGCATTGTTGCC (sequence ID 54, 168 bp). However, Laval does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

Duan discloses a sequence comprising subsequence CTGTTCCAAATCCTGCATTGTTGCC (sequence ID 40, 321 bp). However, Duan does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

Berg discloses a sequence comprising subsequence CTGTTCCAAATCCTGCATTGTTGCC (sequence; page 1-43). However, Berg does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

Mitrpant discloses wherein the targeting sequence is complementary to an exon 52 annealing site in the dystrophin (a single oligonucleotide H52A +12+41, was found to efficiently remove human exon 52 from the mature dystrophin transcript; page 1422, second column, third paragraph). However, Mitrpant does not disclose wherein the targeting sequence is CTGTTCCAAATCCTGCATTGTTGCC.

Veltrop discloses wherein the targeting sequence is complementary to an exon 52 in the dystrophin (two Transcription Activator-like Effector Nucleases TALENs sets were built with a recognition sequences close to the intron 51-exon 52 and exon 52-intron 52 boundary to facilitate the targeting of exon 52, where the oligonucleotides are not complementary to the positions -01+24 of the exon 52, as shown in supplementary figure S1; page 7, second paragraph; supplementary figure S1). However, Veltrop does not disclose wherein the targeting sequence CTGTTCCAAATCCTGCATTGTTGCC.

US 2016/0201089 A1 (DUKE UNIVERSITY) (hereinafter "Duke") discloses wherein the targeting sequence is complementary to an exon 52 in the dystrophin (sequence 247Dys-E52-R in table 5 on page 33, is a reverse primer binding in exon 52; paragraph [0348]). However, Duke does not disclose wherein the targeting sequence CTGTTCCAAATCCTGCATTGTTGCC.

Thus, the prior art does not teach or fairly suggest an antisense oligomer conjugate of Formula IV, as shown, or a pharmaceutically acceptable salt thereof, and sufficient motivation, based upon the previous disclosures of the Hanson, Laval, Duan, Berg, Mitrpant, Veltrop, and Duke references, does not exist to have determined and implemented the antisense oligomer as described in claim 7 of the instant PCT application.

Claims 8, 10/7-8, 11/7-8, 12/11/7-8, 14/7-8, 15/14/7-8, 17/10/7-8, 18/10/7-8, 19/10/7-8 and 20/ 17/10/7-8 meet the criteria set out in PCT Article 33(2)-(3) because they depend on claim 7.

Claim 9 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest an antisense oligomer of Formula VIIA, as shown, or a pharmaceutically acceptable salt thereof.

Sarepta discloses an antisense oligomer similar to the oligomer of Formula VIIA, as shown (final compound on figure 4, where X is X1, which is N(CH₃)₂, the base pairing moiety is a purine or pyrimidine found in native DNA or RNA and includes A, G, C, T, or U; figure 4; paragraphs [0038], [0040], [0692]). However, Sarepta does not disclose the oligonucleotide having sequence CTGTTCCAAATCCTGCATTGTTGCC.

Laval discloses a sequence comprising subsequence CTGTTCCAAATCCTGCATTGTTGCC (sequence ID 54, 168 bp). However, Laval does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

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Duan discloses a sequence comprising subsequence CTGTTCCAAATCCTGCATTGTTGCC (sequence ID 40, 321 bp). However, Duan does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

Berg discloses a sequence comprising subsequence CTGTTCCAAATCCTGCATTGTTGCC (sequence; page 1-43). However, Berg does not disclose a motivation to select the 25 bases long fragment of the sequence from the entire sequence.

Mitrpant discloses wherein the targeting sequence is complementary to an exon 52 annealing site in the dystrophin (a single oligonucleotide H52A +12+41, was found to efficiently remove human exon 52 from the mature dystrophin transcript; page 1422, second column, third paragraph). However, Mitrpant does not disclose wherein the targeting sequence is CTGTTCCAAATCCTGCATTGTTGCC.

Veltrop discloses wherein the targeting sequence is complementary to an exon 52 in the dystrophin (two Transcription Activator-like Effector Nucleases TALENs sets were built with a recognition sequences close to the intron 51-exon 52 and exon 52-intron 52 boundary to facilitate the targeting of exon 52, where the oligonucleotides are not complementary to the positions -01+24 of the exon 52, as shown in supplementary figure S1; page 7, second paragraph; supplementary figure S1). However, Veltrop does not disclose wherein the targeting sequence CTGTTCCAAATCCTGCATTGTTGCC.

Thus, the prior art does not teach or fairly suggest an antisense oligomer conjugate of Formula IV, as shown, or a pharmaceutically acceptable salt thereof, and sufficient motivation, based upon the previous disclosures of the Sarepta, Laval, Duan, Berg, Mitrpant, Veltrop, and Duke references, does not exist to have determined and implemented the antisense oligomer as described in claim 9 of the instant PCT application.

Claims 1-9, 10/1-3, 10/7-8, 11/1-3, 11/7-8, 12/11/1-3, 12/11/7-8, 14/1-3, 14/7-8, 15/14/1-3, 15/14/7-8, 17/10/1-3, 17/10/7-8, 18/10/1-3, 18/10/7-8, 19/10/1-3, 19/10/7-8, 20/17/10/1-3 and 20/17/10/7-8 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.