Certificate of Hand Delivery
I hereby certify that this correspondence is being filed with the United States Patent and Trademark Office to the Commissioner for Patents via hand delivery to the Office of Legal Administration, Room MDW 7B85, 600 Dulany Street (Madison Building), Alexandria, VA 22314, **Attention: Mary Till** on this 14 day of November 2016.

Signature of person delivering: Steven P. O'Connor

Typed or printed name of person: STEVEN P. O'CONNOR 41,225

Docket No.: AVN-008CN25
(Patent)

RECEIVED

NOV 14 2016

PATENT EXTENSION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Donald WILTON *et al.*

Patent No.: 9,018,368 B2

Issued: April 28, 2015

For: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

Approved Product:
EXONDYS 51™ (eteplirsen)
NDA No.: 206488

U.S.F.D.A. Approval Date:
September 19, 2016

Assignee:
University of Western Australia

05/30/2017 SMOHAMM2 00000004 14316603
01 FC:1457 1120.00 DA

Exhibit N

Mail Stop HATCH-WAXMAN PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATION

I, AMY E. MANDRAGOURAS, ESQ., do hereby certify that this accompanying application for extension of term of U.S. Patent No. 9,018,368 B2 under 35 U.S.C. §156 including its attachments and supporting papers is being submitted as one original and two (2) copies thereof, pursuant to 37 C.F.R. §1.740(b).

Dated: November 11, 2016

Respectfully submitted,

By: _____
Amy E. Mandragouras, Esq.
Registration No.: 36,207
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4626
(617) 742-4214 (Fax)
Attorney/Agent For Applicants

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Signature of person delivering: Steven P. O'Connor

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Docket No.: AVN-008CN25
(Patent)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Donald Wilton *et al.*

Patent No.: 9,018,368 B2

Issued: April 28, 2015

For: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

NDA No.: 206488

Assignee: University of Western Australia

U.S. F.D.A. Approval Date: September 19, 2016

Mail Stop HATCH-WAXMAN PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Dear Sir:

The University of Western Australia hereby requests an extension of the patent term of the above-identified patent under 35 U.S.C. §156. The instant request for patent term extension is timely because it is being submitted within the sixty-day period beginning on the date the product received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use. 35 U.S.C. §156(d)(1). Applicants represent that The University of Western Australia is empowered to request the instant patent term extension because The University of Western Australia is the sole owner of the instant patent, as evidenced by the assignment recorded at: Reel 035009 and Frame 0811 on February

23, 2015 from inventors Stephen Donald Wilton, Sue Fletcher, and Graham McClorey to The University of Western Australia.

I, Amy E. Mandragouras, represent that I am a registered practitioner appointed by the patent owner of record, The University of Western Australia, and am filing this Application for Extension of Patent Term on behalf thereof. A Power of Attorney, authorizing me to act on behalf of The University of Western Australia is attached hereto as Exhibit A.

Sarepta Therapeutics, Inc. and Sarepta International CV (collectively, "Sarepta") are the exclusive licensees of U.S. Patent No. 9,018,368 by virtue of an Amended and Restated Exclusive License Agreement effective as of November 24, 2008 and restated as of April 10, 2013. Sarepta was the marketing applicant of the approved product, EXONDYS 51™ (eteplirsen) injection, before the Food and Drug Administration. Applicants submit that there has been an agency relationship between The University of Western Australia and Sarepta during the regulatory review period of EXONDYS 51™ (eteplirsen) injection. To show that The University of Western Australia is authorized to rely upon the activities of Sarepta before the Food and Drug Administration, a copy of a letter from Sarepta specifically authorizing The University of Western Australia to rely upon such activities and file this Extension of Patent Term based on the regulatory review period of EXONDYS 51™ (eteplirsen) injection is attached as Exhibit B. 37 C.F.R. § 1.730 and M.P.E.P. 2752.

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

(1) The approved product, EXONDYS 51™ (eteplirsen) injection, is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass.

The chemical names of eteplirsen include:

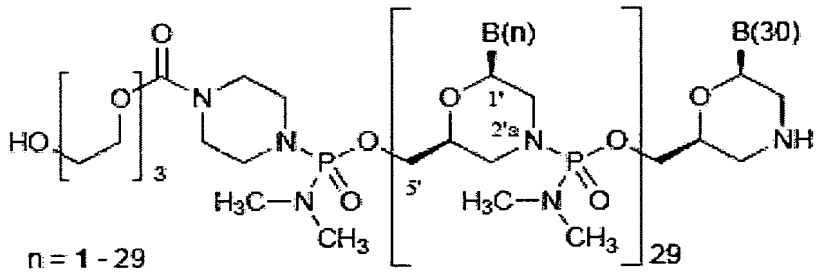
RNA, [*P*-deoxy-*P*-(dimethylamino)](2',3'-dideoxy-2',3'-imino-2',3'-seco)(2'a→5')(C-m5U-C-C-A-A-C-A-m5U-C-A-A-G-G-A-A-G-A-m5U-G-G-C-A-m5U-m5U-m5U-C-m5U-A-G), 5'-[*P*-[4-[[2-[2-(2-hydroxyethoxy)ethoxy]ethoxy]carbonyl]-1-piperazinyl]-*N*,*N*-dimethylphosphonamidate]

and

P,2',3'-trideoxy-*P*-(dimethylamino)-5'-*O*-{*P*-[4-(10-hydroxy-2,5,8- trioxadecanoyl)piperazin-1-yl]-*N*,*N*-dimethylphosphonamidoyl}-2',3'-imino-2',3'- secocytidylyl-(2'a→5')-*P*,3'-dideoxy-*P*-(dimethylamino)-2',3'-imino-2',3'-secothymidylyl- (2'a→5')-*P*,2',3'-trideoxy-*P*-(dimethylamino)-2',3'-imino-2',3'-secocytidylyl-(2'a→5')- *P*,2',3'-trideoxy-*P*-(dimethylamino)-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,2',3'- trideoxy-*P*-(dimethylamino)-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-(dimethylamino)-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,3'-dideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secoguanylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-(dimethylamino)-2',3'-imino-2',3'-secoguanylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secoguanylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,3'-dideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-(dimethylamino)-2',3'-imino-2',3'-secoguanylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-

2',3'-imino-2',3'-secoguanylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secoadenylyl-(2'a→5')-*P*,3'-dideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,3'-dideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,3'-dideoxy-*P*-(dimethylamino)-2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*- (dimethylamino)-2',3'-imino-2',3'-secocytidylyl-(2'a→5')-*P*,3'-dideoxy-*P*-(dimethylamino)- 2',3'-imino-2',3'-secothymidylyl-(2'a→5')-*P*,2',3'-trideoxy-*P*-(dimethylamino)-2',3'-imino- 2',3'-secoadenylyl-(2'a→5')-2',3'-dideoxy-2',3'-imino-2',3'-secoguanosine.

The chemical structure of eteplirsen is:



(2) The approved product, EXONDYS 51™ (eteplirsen), was subject to regulatory review under the Federal Food, Drug, and Cosmetic Act (FDCA), Section 505(b).

(3) The approved product, EXONDYS 51™ (eteplirsen), received permission for commercial marketing or use under Section 505(b) of the Federal Food, Drug and Cosmetic Act (FDCA) on September 19, 2016. A copy of the Approval Letter from the Food and Drug Administration is attached as Exhibit C.

(4) The active ingredient in EXONDYS 51™ is eteplirsen, which on information and belief, has not been approved for commercial marketing or use under Section 505 of the Federal

Food, Drug, and Cosmetic Act prior to the approval of NDA 206488 for EXONDYS 51™ by the Food and Drug Administration on September 19, 2016. A copy of the package insert describing the approved product is attached as Exhibit D.

(5) This application for extension of patent term under 35 U.S.C. §156 is being submitted within the sixty-day period pursuant to 37 C.F.R. 1.720(f), said period will expire on November 17, 2016, if September 19, 2016, is day one (1) of the sixty (60) day period.

(6) The complete identification of the patent for which a term extension is being sought is as follows:

Inventors:	Stephen Donald Wilton; Sue Fletcher; Graham McClorey
Patent No.:	9,018,368
Issue Date:	April 28, 2015
Expiration Date:	June 28, 2025 (subject to a terminal disclaimer over U.S. Patent Nos: 7,807,816, 7,960,541, and 8,486,907)

(7) A true and complete copy of the patent for which an extension is being sought is attached as Exhibit E.

(8) No reexamination certificate or certificate of correction has been issued on this patent. A copy of the terminal disclaimer filed on February 26, 2015 over U.S. Patent Nos. 7,807,816, 7,960,541, and 8,486,907 is attached as Exhibit F. A copy of the maintenance fee statement indicating payment of the four-year maintenance fee is due by April 29, 2019 is attached as Exhibit G.

(9) Claims 1 and 2 of U.S. Patent No. 9,018,368 claim the active ingredient of the approved product, which is EXONDYS 51™. A complete claim chart that lists each applicable claim of U.S. Patent No. 9,018,368 and demonstrates the manner in which each applicable claim reads on the approved product is attached as Exhibit H.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human services to determine the applicable regulatory review period are as follows:

Investigational New Drug Application (IND 77,429) for EXONDYS 51™ was submitted on August 2, 2007 and became effective on June 25, 2010. A copy of the IND submission letter and a copy of the letter from the Food and Drug administration establishing the effective date of the IND are attached as Exhibits I and J, respectively.

New Drug Application (NDA 206488) for EXONDYS 51™ was submitted to FDA on a rolling basis, and the submission of the NDA was completed on June 26, 2015. A copy of the NDA submission letter and a copy of the letter from the Food and Drug Administration confirming the completion of the application and submission of the NDA on this date are attached as Exhibits K and L, respectively.

New Drug Application (NDA 206488) for EXONDYS 51™ was approved on September 19, 2016. A copy of the Approval Letter from the Food and Drug Administration is attached as Exhibit C.

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

(11) A brief description of the significant activities undertaken by the marketing applicant, Sarepta Therapeutics, Inc., during the applicable regulatory review period with respect to EXONDYS 51™ and the dates applicable to these significant activities are set forth in a chronology of events at Exhibit M.

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

(12)(i) U.S. Patent No. 9,018,368 is eligible for extension of the patent term under 35 U.S.C. §156 because it satisfies all of its requirements for such extension. For the convenience of the Patent and Trademark Office, the requirements for extension of a patent under 35 U.S.C. §156 are presented in a format which follows Section 156 of Title 35 of the United States Code.

(a) 35 U.S.C. §156 - U.S. Patent No. 9,018,368 claims the product EXONDYS 51™.

(b) 35 U.S.C. §156(a)(1) - U.S. Patent No. 9,018,368 has not expired before submission of the instant application.

(c) 35 U.S.C. §156(a)(2) – The term of U.S. Patent No. 9,018,368 has never been extended under 35 U.S.C. §156(e)(1).

(d) 35 U.S.C. §156(a)(3) – The application for extension is submitted by the owner of record of the patent in accordance with the requirements of paragraph (1) through (4) of 35 U.S.C. §156(d) and the rules of the Patent and Trademark Office.

(e) 35 U.S.C. §156(a)(4) – The product EXONDYS 51™ has been subject to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. §156(a)(5)(A) – The permission for the commercial marketing or use of the product EXONDYS 51™ after the regulatory review period is the first permitted commercial marketing or use of the product EXONDYS 51™ under the provision of the Federal Food, drug, and Cosmetic Act (i.e., Section 505) under which such regulatory review period occurred.

(g) 35 U.S.C. §156(c)(4) – No other patent has been extended under 35 U.S.C. §156(e)(i) for the same regulatory review period for any product, including the product EXONDYS 51™. Applicants draw the Office's attention to the "Notice Regarding Multiple Applications" herein below.

(12)(ii) The length of the extension of patent term of U.S. Patent No. 9,018,368 claimed by Applicants is that period authorized by 35 U.S.C. §156(c), which has been calculated to be 481 days. The length of the extension was determined pursuant to Section 1.775 of Title 37 of the Code of Federal regulations as follows:

(a) The length of the regulatory review period under 37 C.F.R. 1.775(c) is calculated as beginning on June 25, 2010 and ending on September 19, 2016, which is a total of 2,279 days, which is the sum of (1) and (2) below:

(1) The number of days in the "Testing Phase" under 35 U.S.C. §156(g)(1)(B)(i), which is calculated to be 1,827 days, which is the period beginning on the date an exemption under subsection (i) of Section 505 of the Federal Food, drug, and Cosmetic Act became effective for the approval of EXONDYS 51™, which is June 25, 2010, and ending on the date an application was initially submitted for the product EXONDYS 51™ under such section, which is June 26, 2015; and

(2) The number of days in the "Approval Phase" under 35 U.S.C. 156(g)(1)(B)(ii), which is calculated to be 452 days, which is the number of days in the period beginning on the date the application was initially submitted for the approved product EXONDYS 51™ under subsection (b) of Section 505 of the Federal Food, Drug, and Cosmetic Act, which is June 26, 2015, and ending on the date such application was approved under such section, which is September 19, 2016.

(b) The term of the patent as extended is determined by:

(1) Subtracting from the length of the regulatory review period under 37 C.F.R. §1.775(c) calculated according to sub-paragraph (12)(ii)(a) above (2,279 days), the sum of the periods (A) to (C) below, which is calculated to be 1,798 days, to arrive at a period of 481 days:

(A) The number of days in the regulatory review period which were on and before the date on which the patent issued (April 28, 2015), which is calculated to be 1,769 days; and

(B) The number of days in the regulatory review period during which applicant did not act with due diligence, which is zero (0) days; and

(C) One-half the number of days remaining in the regulatory review period determined by sub-paragraph (12)(ii)(a)(1) (i.e., the Testing Phase) after that period is reduced in accordance with the determinations of sub-paragraphs (12)(ii)(b)(1)(A) and (12)(ii)(b)(1)(B) immediately above ignoring any half-days (one-half of 58 (i.e., 1,827 days-1,769 days)), which is 29 days.

(c) The number of days as determined in sub-paragraph (12)(ii)(b) (481 days) when added to the expiration date of the original term of U.S. Patent No. 9,018,368 (June 28, 2025) would result in the date of October 22, 2026.

(d) Adding fourteen (14) years to the date of approval of the application under subsection (b) of Section 505 of the Federal Food, Drug, and Cosmetic Act (September 19, 2016) is determined to be September 19, 2030.

(e) Comparing the date for the end of the period obtained pursuant to sub-paragraph (12)(ii)(c), which is October 22, 2026, with the date for the end of the period obtained pursuant to sub-paragraph (12)(ii)(d), which is September 19, 2030, the earlier of October 22, 2026 is selected.

(f) Because U.S. Patent No. 9,018,368 was issued after September 24, 1984, the dates under sub-paragraphs (12)(f)(1) and (12)(f)(2) are determined:

(1) the date obtained by adding five (5) years to the original expiration date of U.S. Patent No. 9,018,368 as shortened by any terminal disclaimer, which is June 28, 2030; and

(2) the date obtained in sub-paragraph (12)(ii)(e), which is October 22, 2026.

(g) Comparing the date determined under sub-paragraph (12)(ii)(f)(1) and (12)(ii)(f)(2) and selecting the earlier date results in a selection of October 22, 2026.

(h) In summary, Applicants' calculation of the extension of the patent term under 35 U.S.C. 156 for U.S. Patent No. 9,018,368 results in a period of extension of 481 days, thereby extending the patent term from June 28, 2025 to October 22, 2026.

(13) Applicants acknowledge a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

Notice Regarding Multiple Applications

Applicants are contemporaneously filing an application for term extension on one additional patent that it owns (U.S. Patent No. 7,807,816; Reissue Application No. 15/349,535) based on the same regulatory review period for EXONDYS 51™. Applicants will make an election of only one patent in accordance with 37 C.F.R. §1.785(b) upon receipt of notice of final determination in these applications from the U.S. Patent and Trademark Office.

(14) The Commissioner is hereby authorized by this paper to charge the required fee of $1,120.00 under 37 C.F.R. 1.20(j)(1) or any additional amount due or credit any overpayment to Deposit Account 12-0080.

(15) All correspondence and inquiries may be directed to the undersigned, whose address, telephone number, and fax number are as follows:

Amy E. Mandragouras, Esq.

NELSON MULLINS RILEY & SCARBOROUGH LLP

One Post Office Square

Boston, Massachusetts 02109-2127

Phone: 617-217-4626

Fax: 617-742-4214

Customer Number 123147

[REMAINDER OF PAGE INTENTIONALLY LEFT BLANK]

(16) Applicants hereby certify that the instant application for extension of patent term under 35 U.S.C. §156 including all exhibits and supporting papers is being submitted as one original and two (2) additional copies thereof at Exhibit N pursuant to 37 C.F.R. §1.740(b).

Dated: November 11, 2016

Respectfully submitted,

By: _____

Amy E. Mandragouras, Esq.
Registration No.: 36,207
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4626
(617) 742-4214 (Fax)
Attorney/Agent For Applicants

EXHIBIT A

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

Exhibit A

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	14/316,603
Filing Date	June 26, 2014
First Named Inventor	Stephen Donald WILTON
Title	ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF
Art Unit	1674
Examiner Name	K. Chong
Attorney Docket Number	AVN-008CN25

SIGNATURE of Applicant or Patent Practitioner

Signature	/Amy E. Mandragouras, Esq./	Date (Optional)	February 23, 2015
Name	Amy E. Mandragouras, Esq.	Registration Number	36,207
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: February 23, 2015 Electronic Signature for Amy E. Mandragouras, Esq.: /Amy E. Mandragouras, Esq./

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

[X] I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 123147

OR

[ ] I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

[X] The address associated with the above-mentioned Customer Number

OR

[ ] The address associated with Customer Number:

OR

Firm or Individual Name	Amy E. Mandragouras, Esq. NELSON MULLINS RILEY & SCARBOROUGH LLP				
Address	One Post Office Square				
City	Boston	State	MA	Zip	02109-2127
Country	US				
Telephone	(800) 237-2000	Email	ipboston.docketing@nelsonmullins.com		

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

The University of Western Australia

[ ] Inventor or Joint Inventor (title not required below)

[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

[X] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Simon Handford	Date (Optional)	16/May/14
Name	Simon J. Handford		
Title	Associate Director, Research Development and Innovation		

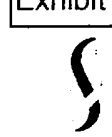
NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

[ ] Total of 1 forms are submitted.

EXHIBIT B

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

Exhibit B



SAREPTA

November 10, 2016

Via First Class Mail

The University of Western Australia
35 Stirling Highway
Crawley, WA 6009
Australia

Attn: Director, Office of Industry and Innovation

Re: U.S. Patent No. 7,807,816 B2 Issued: October 5, 2010
U.S. Patent No. 9,018,368 B2 Issued: April 28, 2015
Inventor(s): Stephen Donald Wilton et al.
Assignee: The University of Western Australia
Titled: Antisense Oligonucleotides for Inducing Exon Skipping and Methods of Use Thereof

Dear Sir:

As you know, Sarepta Therapeutics, Inc. ("Sarepta") received approval of its NDA for EXONDYS 51™ (eteplirsen) on September 19, 2016 from the U.S. Department of Health and Human Services, Food and Drug Administration ("FDA"). In addition, The University of Western Australia ("UWA") will timely file an Application for Patent Term Extension Under 35 U.S.C. §156 in the United States Patent and Trademark Office in connection with the above-identified patents.

This letter serves to acknowledge the "agency relationship" (as defined in section 2752 of the Manual of Patent Examining Procedure) between UWA as the owner of the above-identified patents and Sarepta as the marketing applicant before the FDA during the regulatory review period. This letter further specifically authorizes UWA as the applicant for Patent Term Extension to rely on the activities of Sarepta as the marketing applicant before the FDA.

If you have any questions, please do not hesitate to contact me.

Very Truly Yours,

[Signature Page Follows]

SAREPTA

Sarepta Therapeutics, Inc.

By: _____
Name: David Tyronne Howton, Jr.
Title: Senior Vice President, General Counsel and Corporate Secretary

Sarepta International C.V.,
by ST International Holdings, Inc., its general partner

By: _____
Name: Heidy Abreu King-Jones
Title: Vice President
Date: November 10, 2016
Location: Bermuda

cc: Amy E, Mandragouras, Esq.
Erika L. Wallace, Ph.D.

[Sarepta Letter of Authorization to UWA]

SAREPTA

Sarepta Therapeutics, Inc.	Sarepta International C.V., by ST International Holdings, Inc., its general partner
By: _____ Name: David Tyronne Howton, Jr. Title: Senior Vice President, General Counsel and Corporate Secretary	By: _____ Name: Heidy Abreu King-Jones Title: Vice President Date: November 10, 2016 Location: Bermuda

cc: Amy E. Mandragouras, Esq.
Erika L. Wallace, Ph.D.

[Sarepta Letter of Authorization to UWA]

EXHIBIT C

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

Exhibit C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206488

ACCELERATED APPROVAL

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Sr. Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) dated June 26, 2015, received June 26, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exondys 51 (eteplirsen) Injection, 50 mg per mL.

We acknowledge receipt of your major amendment dated January 8, 2016, which extended the goal date by three months.

This new drug application provides for the use of Exondys 51 (eteplirsen) Injection, 50 mg per mL, for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on March 28, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 206488.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

In addition, we refer to your June 10, 2016, submission in which you commit to implement the carton container label revisions requested in our June 6, 2016, correspondence. Specifically, you agree to remove the reference to the compendial grades from the carton labels at the time of next printing, but no later than 120 days post-approval, and to notify us of this change via submission of a "Changes Being Effected" supplemental application.

PRODUCT QUALITY

Based on evaluation of the stability data provided, an expiration dating period of 18 months is established for eteplirsen injection when stored refrigerated (5°C).

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number: PRV NDA 206488. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher:

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of

times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
  - the estimated demand in the U.S. for the product, and
  - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf1 (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated August 4, 2016. This requirement, along with required completion dates as agreed upon on September 16, 2016, is listed below.

3095-1 In order to verify the clinical benefit of eteplirsen, conduct a 2-year randomized, double-blind, controlled trial of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Patients should be randomized to the approved dosage of eteplirsen (30 mg/kg weekly) or to a dosage that provides significantly higher exposure, e.g., 30 mg/kg daily. The primary endpoint will be the North Star Ambulatory Assessment.

Draft Protocol Submission:	10/2016
Final Protocol Submission:	04/2017
Trial Completion:	11/2020
Final Report Submission:	05/2021

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the trial.

Submit clinical protocol to your IND 077429 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s).**"

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity or an unexpected serious risk of immunogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3095-2 A two-year carcinogenicity study of intravenously administered eteplirsen in rat.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2016
Final Protocol Submission:	03/2017
Study Completion:	04/2020
Final Report Submission:	06/2020

3095-3 A 26-week carcinogenicity study of eteplirsen, administered by a clinically relevant route, in an appropriate transgenic mouse model.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2016
Final Protocol Submission:	01/2017
Study Completion:	05/2018
Final Report Submission:	06/2018

You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on these protocols prior to beginning the studies.

3095-4 A study to evaluate:

1. patient immune responses, including IgM and IgG isotypes, to eteplirsen, its induced dystrophin protein, and full length dystrophin;
2. the impact of immune responses on product PK and clinical efficacy and safety.

The assays for antibodies to eteplirsen, the induced dystrophin, and full length dystrophin should be performed with sampling times optimized to detect early, peak, and late antibody responses, and should be fully validated.

3. for subjects whose serum screens positive for antibodies, the samples should be tested for neutralizing activity, to product activity, and/or product uptake. Antibody titer and persistence should be monitored throughout the duration of the study.
4. in patients who seroconvert, antibody levels should be monitored until they return to baseline.
5. for patients developing hypersensitivity responses, assays to evaluate IgE responses including skin testing or RAST assays should be developed and employed.

Until these assays have been fully validated and reviewed by FDA, sufficient samples should be banked and stored under appropriate conditions so as to allow for re-testing if deemed necessary.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2017
Final Protocol Submission:	08/2017
Study Completion:	12/2017
Final Report Submission:	02/2018

Additional guidance for immunogenicity assay development, though more specific for therapeutic protein products, may be found in the draft guidance: "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products

http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf. You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocols prior to initiation of the studies.

Submit the protocols to your IND 077429, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3095-5 Conduct a 2-year controlled trial in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 or 53 skipping with a phosphorodiamidate morpholino oligomer (PMO) designed to bind to a regulatory site governing splicing of the corresponding exon. The trial should include at least two well-separated doses of each PMO, with the high dose designed to provide the greatest dystrophin response possible, based upon preliminary dose-finding, with an expectation of acceptable tolerability. The primary objective of this study will be to evaluate the effect of the two PMO doses (combined-active group) compared to control on the North Star Ambulatory Assessment. The secondary objective will be to evaluate dystrophin levels as percent of normal by Western blot, with tissue to be obtained by needle biopsy.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 12/2016
Final Protocol Submission: 04/2017
Trial Completion: 04/2021
Final Report Submission: 10/2021

A double-blind, placebo-controlled trial design should be used, if feasible, as this would be most informative. If it is not feasible to include a placebo group, an untreated concurrent control group may be considered, with appropriate care to reduce bias in outcome assessments given the lack of randomization and blinding. You should allow sufficient time for the Agency to review, provide feedback, and come to concurrence on the protocol prior to initiation of the trial.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3095-6 Evaluate possible reasons for the upward trend in assay results from drug product stability studies. Initial investigations are expected to focus on any potential degradants that could co-elute with the main peak, re-authentication of the concentration of the reference standard solution, and quality attributes of the IP-HPLC reagents. Identify any other potential causes for the upward trend observed in the drug product stability.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2016
Study Completion: 06/2017
Final Report Submission: 08/2017

If you believe proposed changes to your manufacturing and control procedures are warranted based on the data derived from this study, we request that you submit the final report for this study as a supplement to your approved NDA.

3095-7 Revalidate the suitability in-process (b) (4) used during drug product manufacture with respect to the accuracy of the method and the robustness of the method in terms of (b) (4). Explore additional possible root causes for the bias in the in-process (b) (4) results and the release (b) (4) results that were observed at lot release.

The timetable you submitted on September 16, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2016
Study Completion: 06/2017
Final Report Submission: 08/2017

If you believe proposed changes to your manufacturing and control procedures are warranted based on the data derived from this study, we request that you submit the final report for this study as a supplement to your approved NDA.

Submit clinical protocols to your IND 077429 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has also contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic

License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET WOODCOCK
09/19/2016

EXHIBIT D

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

Exhibit D

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXONDYS 51™ safely and effectively. See full prescribing information for EXONDYS 51.

EXONDYS 51 (eteplirsen) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

EXONDYS 51 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 *[see Clinical Studies (14)]*. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- 30 milligrams per kilogram of body weight once weekly (2.1)
- Administer as an intravenous infusion over 35 to 60 minutes (2.1, 2.3)
- Dilution required prior to administration (2.2)

DOSAGE FORMS AND STRENGTHS

Injection:
- 100 mg/2 mL (50 mg/mL) in single-dose vial (3)
- 500 mg/10 mL (50 mg/mL) in single-dose vial (3)

CONTRAINDICATIONS

None (4)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥35% and higher than placebo) were balance disorder and vomiting (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

Revised: 09/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 *[see Clinical Studies (14)]*. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of EXONDYS 51 is 30 milligrams per kilogram administered once weekly as a 35 to 60 minute intravenous infusion.

If a dose of EXONDYS 51 is missed, it may be administered as soon as possible after the scheduled time.

2.2 Preparation Instructions

EXONDYS 51 is supplied in single-dose vials as a preservative-free concentrated solution that requires dilution prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use aseptic technique.

a. Calculate the total dose of EXONDYS 51 to be administered based on the patient's weight and the recommended dose of 30 milligrams per kilogram. Determine the volume of EXONDYS 51 needed and the correct number of vials to supply the full calculated dose.

b. Allow vials to warm to room temperature. Mix the contents of each vial by gently inverting 2 or 3 times. Do not shake.

c. Visually inspect each vial of EXONDYS 51. EXONDYS 51 is a clear, colorless solution that may have some opalescence. Do not use if the solution in the vials is discolored or particulate matter is present.

d. With a syringe fitted with a 21-gauge or smaller non-coring needle, withdraw the calculated volume of EXONDYS 51 from the appropriate number of vials.

e. Dilute the withdrawn EXONDYS 51 in 0.9% Sodium Chloride Injection, USP, to make a total volume of 100-150 mL. Visually inspect the diluted solution for particulates.

f. EXONDYS 51 contains no preservatives and should be administered immediately after dilution. Complete infusion of diluted EXONDYS 51 solution within 4 hours of dilution. If immediate use is not possible, the diluted solution may be stored for up to

24 hours at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard unused EXONDYS 51.

2.3 Administration Instructions

Application of a topical anesthetic cream to the infusion site prior to administration of EXONDYS 51 may be considered.

EXONDYS 51 is administered via intravenous infusion. Flush the intravenous access line with 0.9% Sodium Chloride Injection, USP, prior to and after infusion.

Infuse the diluted EXONDYS 51 solution over 35 to 60 minutes. Do not mix other medications with EXONDYS 51 or infuse other medications concomitantly via the same intravenous access line.

3 DOSAGE FORMS AND STRENGTHS

EXONDYS 51 is a clear and colorless solution that may have some opalescence, and is available as follows:

- Injection: 100 mg/2 mL (50 mg/mL) solution in a single-dose vial
- Injection: 500 mg/10 mL (50 mg/mL) solution in a single-dose vial

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the EXONDYS 51 clinical development program, 107 patients received at least one intravenous dose of EXONDYS 51, ranging between 0.5 mg/kg (0.017 times the recommended dosage) and 50 mg/kg (1.7 times the recommended dosage). All patients were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 4 to 19 years. Most (89%) patients were Caucasian.

EXONDYS 51 was studied in a double-blind, placebo-controlled study for 24 weeks (Study 1), followed by an open label extension (Study 2). In Study 1, 12 patients were randomized to receive weekly intravenous infusions of EXONDYS 51 (n=8) or placebo (n=4) for 24 weeks. All 12 patients continued in Study 2 and received open-label EXONDYS 51 weekly for up to 208 weeks.

In Study 1, 4 patients received placebo, 4 patients received EXONDYS 51 30 mg/kg, and 4 patients received EXONDYS 51 50 mg/kg (1.7 times the recommended dosage). In Study 2, 6

patients received EXONDYS 51 30 mg/kg/week and 6 patients received EXONDYS 51 50 mg/kg/week *[see Clinical Studies (14)]*.

Adverse reactions that occurred in 2 or more patients who received EXONDYS 51 and were more frequent than in the placebo group in Study 1 are presented in Table 1 (the 30 and 50 mg/kg groups are pooled). Because of the small numbers of patients, these represent crude frequencies that may not reflect the frequencies observed in practice. The 50 mg/kg once weekly dosing regimen of EXONDYS 51 is not recommended *[see Dosage and Administration (2.1)]*.

The most common adverse reactions were balance disorder and vomiting.

Table 1. Adverse Reactions in DMD Patients Treated with 30 or 50 mg/kg/week[1] EXONDYS 51 with Incidence at Least 25% More than Placebo (Study 1)

Adverse Reactions	EXONDYS 51 (N=8) %	Placebo (N=4) %
Balance disorder	38	0
Vomiting	38	0
Contact dermatitis	25	0

[1] 50 mg/kg/week = 1.7 times the recommended dosage

In the 88 patients who received ≥30 mg/kg/week of EXONDYS 51 for up to 208 weeks in clinical studies, the following events were reported in ≥10% of patients and occurred more frequently than on the same dose in Study 1: vomiting, contusion, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection.

There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of EXONDYS 51 infusion.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human or animal data available to assess the use of EXONDYS 51 during pregnancy. In the U.S. general population, major birth defects occur in 2 to 4% and miscarriage occurs in 15 to 20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There are no human or animal data to assess the effect of EXONDYS 51 on milk production, the presence of eteplirsen in milk, or the effects of EXONDYS 51 on the breastfed infant.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EXONDYS 51 and any potential adverse effects on the breastfed infant from EXONDYS 51 or from the underlying maternal condition.

8.4 Pediatric Use

EXONDYS 51 is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, including pediatric patients *[see Clinical Studies (14)]*.

Intravenous administration of eteplirsen (0, 100, 300, or 900 mg/kg) to juvenile male rats once weekly for 10 weeks beginning on postnatal day 14 resulted in renal tubular necrosis at the highest dose tested and decreased bone densitometry parameters (mineral density, mineral content, area) at all doses. The kidney findings were associated with clinical pathology changes (increased serum urea nitrogen and creatinine, decreased urine creatinine clearance). No effects were observed on the male reproductive system, neurobehavioral development, or immune function. An overall no-effect dose was not identified. Plasma eteplirsen exposure (AUC) at the lowest dose tested (100 mg/kg) was similar to that in humans at the recommended human dose (30 mg/kg).

8.5 Geriatric Use

DMD is largely a disease of children and young adults; therefore, there is no geriatric experience with EXONDYS 51.

8.6 Patients with Renal or Hepatic Impairment

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

10 OVERDOSAGE

There is no experience with overdose of EXONDYS 51.

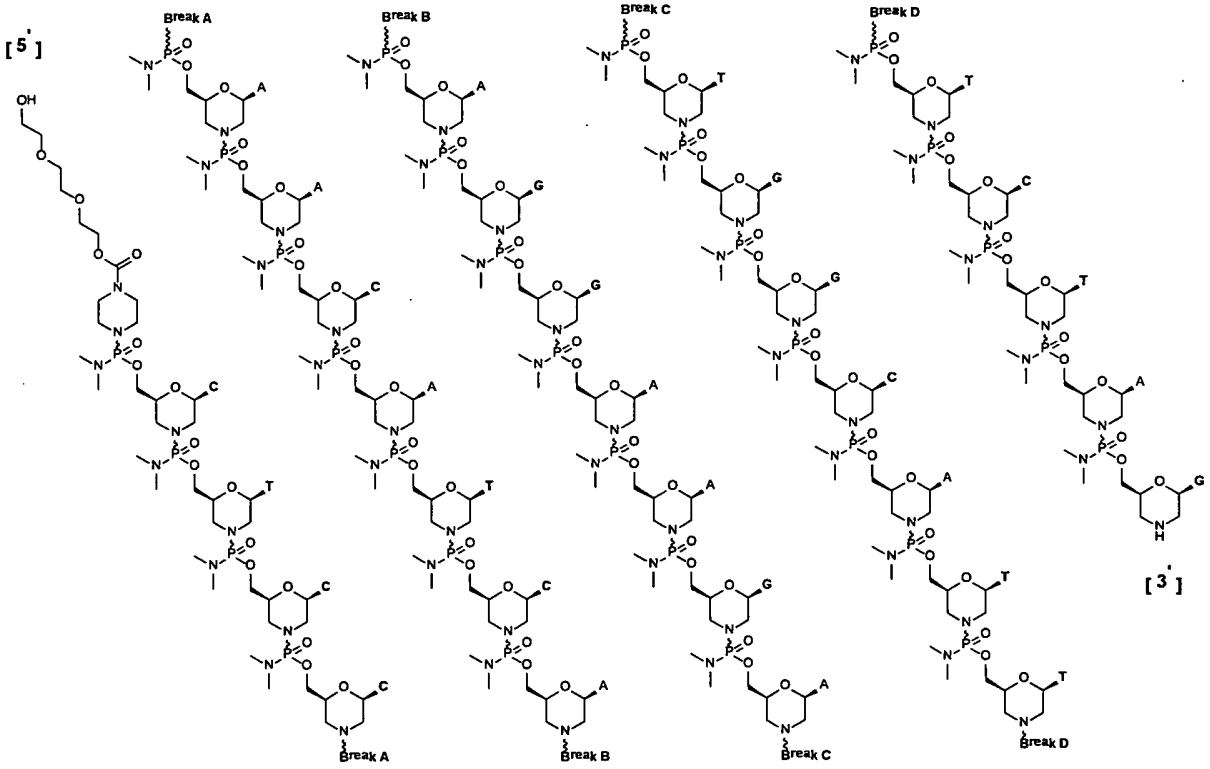
11 DESCRIPTION

EXONDYS 51 (eteplirsen) injection is a sterile, aqueous, preservative-free, concentrated solution for dilution prior to intravenous administration. EXONDYS 51 is clear and colorless, and may have some opalescence. EXONDYS 51 is supplied in single dose vials containing 100 mg or 500 mg eteplirsen (50 mg/mL). EXONDYS 51 is formulated as an isotonic, phosphate buffered saline solution with an osmolality of 260 to 320 mOsm and a pH of 7.5. Each milliliter of EXONDYS 51 contains 50 mg eteplirsen; 0.2 mg potassium chloride, 0.2 mg potassium phosphate monobasic, 8 mg sodium chloride, and 1.14 mg sodium phosphate dibasic, anhydrous, in water for injection. The product may contain hydrochloric acid or sodium hydroxide to adjust pH.

Eteplirsen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings

found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Eteplirsen contains 30 linked subunits. The molecular formula of eteplirsen is $C_{364}H_{569}N_{177}O_{122}P_{30}$ and the molecular weight is 10305.7 daltons.

The structure and base sequence of eteplirsen are:



The sequence of bases from the 5' end to the 3' end is:
CTCCAACATCAAGGAAGATGGCATTTCTAG

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eteplirsen is designed to bind to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein, which was evaluated in Study 2 and Study 3 [*see Clinical studies (14)*].

12.2 Pharmacodynamics

All EXONDYS 51-treated patients evaluated (n=36) were found to produce messenger ribonucleic acid (mRNA) for a truncated dystrophin protein by reverse transcription polymerase chain reaction.

In Study 2, the average dystrophin protein level in muscle tissue after 180 weeks of treatment with EXONDYS 51 was 0.93% of normal (i.e., 0.93% of the dystrophin level in healthy subjects). Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, the average dystrophin protein level was 0.16% of normal before treatment, and 0.44% of normal after 48 weeks of treatment with EXONDYS 51 *[see Clinical studies (14)]*. The median increase in truncated dystrophin in Study 3 was 0.1% *[see Clinical Studies (14)]*.

12.3 Pharmacokinetics

Following single or multiple intravenous infusions of EXONDYS 51 in male pediatric DMD patients, plasma concentration-time profiles of eteplirsen were generally similar and showed multi-phasic decline. The majority of drug elimination occurred within 24 hours. Approximate dose-proportionality and linearity in PK properties were observed following multiple-dose studies (0.5 mg/kg/week [0.017 times the recommended dosage] to 50 mg/kg/week [1.7 times the recommended dosage]). There was no significant drug accumulation following weekly dosing across this dose range. The inter-subject variability for eteplirsen C_{max} and AUC range from 20 to 55%.

Following single or multiple intravenous infusions of EXONDYS 51, the peak plasma concentrations (C_{max}) of eteplirsen occurred near the end of infusion (i.e., 1.1 to 1.2 hours across a dose range of 0.5 mg/kg/week to 50 mg/kg/week).

Distribution

In vitro investigation suggested that plasma protein binding of eteplirsen in human ranges between 6 to 17%. The mean apparent volume of distribution (Vss) of eteplirsen was 600 mL/kg following weekly intravenous infusion of EXONDYS 51 at 30 mg/kg.

Twenty-four hours after the end of the infusion, mean concentrations of eteplirsen were 0.07% of C_{max}. Accumulation of eteplirsen during once weekly dosing has not been observed.

Elimination

The total clearance of eteplirsen was 339 mL/hr/kg following 12 weeks of therapy with 30 mg/kg/week.

Metabolism

Eteplirsen did not appear to be metabolized by hepatic microsomes of any species tested, including humans.

Excretion

Renal clearance of eteplirsen accounts for approximately two-thirds of the administered dose within 24 hours of intravenous administration. Elimination half-life ($t_{1/2}$) of eteplirsen was 3 to 4 hours.

Specific Populations

Age:

The pharmacokinetics of eteplirsen have been evaluated in male pediatric DMD patients. There is no experience with the use of EXONDYS 51 in patients 65 years of age or older.

Sex:

Sex effects have not been evaluated; EXONDYS 51 has not been studied in female patients.

Race:

Potential impact of race is not known because 89% of the patients in studies were Caucasians.

Renal or Hepatic Impairment:

EXONDYS 51 has not been studied in patients with renal or hepatic impairment.

Drug Interaction Studies

In vitro data showed that eteplirsen did not significantly inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Eteplirsen did not induce CYP2B6 or CYP3A4, and induction of CYP1A2 was substantially less than the prototypical inducer, omeprazole. Eteplirsen was not a substrate nor did it have any major inhibitory potential for any of the key human transporters tested (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, MRP2 and BSEP). Based on *in vitro* data on plasma protein binding, CYP or drug transporter interactions, and microsomal metabolism, eteplirsen is expected to have a low potential for drug-drug interactions in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with eteplirsen.

Mutagenesis

Eteplirsen was negative in *in vitro* (bacterial reverse mutation and chromosomal aberration in CHO cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Impairment of Fertility

Fertility studies in animals were not conducted with eteplirsen. No effects on the male reproductive system were observed following intravenous administration of eteplirsen (0, 5, 40, or 320 mg/kg) to male monkeys once weekly for 39 weeks. Plasma eteplirsen exposure (AUC)

in monkeys at the highest dose tested was 20 times that in humans at recommended human dose (30 mg/kg).

14 CLINICAL STUDIES

EXONDYS 51 was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

In Study 1, patients were randomized to receive weekly infusions of EXONDYS 51 (30 mg/kg, n=4); EXONDYS 51 (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters, and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between patients treated with EXONDYS 51 and those treated with placebo.

All 12 patients who participated in Study 1 continued treatment with open-label EXONDYS 51 weekly for an additional 4 years in Study 2. The 4 patients who had been randomized to placebo were re-randomized 1:1 to EXONDYS 30 or 50 mg/kg/week such that there were 6 patients on each dose. Patients who participated in Study 2 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 2 had a muscle biopsy after 180 weeks of treatment with EXONDYS 51, which was analyzed for dystrophin protein level by Western blot. Study 2 failed to provide evidence of a clinical benefit of EXONDYS 51 compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with EXONDYS 51 was 0.93% of the dystrophin level in healthy subjects. Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1.

In Study 3, 13 patients were treated with open-label EXONDYS 51 (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months. Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with EXONDYS 51 ($p < 0.05$). The median increase after 48 weeks was 0.1%.

Individual patient dystrophin levels from Study 3 are shown in Table 2.

Table 2. Western Blot Results: EXONDYS 51-Treated (Week 48) vs Pre-treatment Baseline (% Normal Dystrophin) (Study 301)

Patient Number	Baseline % normal dystrophin	Week 48 % normal dystrophin	Change from Baseline % normal dystrophin

1	0.13	0.26	0.13
2	0.35	0.36	0.01
3	0.06	0.37	0.31
4	0.04	0.10	0.06
5	0.17	1.02	0.85
6	0.37	0.30	-0.07
7	0.17	0.42	0.25
8	0.24	1.57	1.33
9	0.11	0.12	0.01
10	0.05	0.47	0.43
11	0.02	0.09	0.07
12	0.18	0.21	0.03
Mean	0.16	0.44	0.28; p=0.008

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EXONDYS 51 injection is supplied in single-dose vials. The solution is clear and colorless, and may have some opalescence.

- Single-dose vials containing 100 mg/2 mL (50 mg/mL) eteplirsen NDC 60923-363-02
- Single-dose vials containing 500 mg/10 mL (50 mg/mL) eteplirsen NDC 60923-284-10

16.2 Storage and Handling

Store EXONDYS 51 at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light and store EXONDYS 51 in the original carton until ready for use.

Manufactured for:
Sarepta Therapeutics, Inc.
Cambridge, MA 02142 USA

EXHIBIT E

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

Exhibit E

US009018368B2

(12) **United States Patent**
Wilton et al.

(10) **Patent No.: US 9,018,368 B2**
(45) **Date of Patent: *Apr. 28, 2015**

(54) **ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF**

(71) Applicant: **The University of Western Australia**, Crawley (AU)

(72) Inventors: **Stephen Donald Wilton**, Applecross (AU); **Sue Fletcher**, Bayswater (AU); **Graham McClorey**, Bayswater (AU)

(73) Assignee: **The University of Western Australia**, Crawley (AU)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/316,603**

(22) Filed: **Jun. 26, 2014**

(65) **Prior Publication Data**

US 2014/0309283 A1 Oct. 16, 2014

Related U.S. Application Data

(63) Continuation of application No. 13/741,150, filed on Jan. 14, 2013, which is a continuation of application No. 13/168,857, filed on Jun. 24, 2011, now abandoned, which is a continuation of application No. 12/837,359, filed on Jul. 15, 2010, now Pat. No. 8,232,384, which is a continuation of application No. 11/570,691, filed as application No. PCT/AU2005/000943 on Jun. 28, 2005, now Pat. No. 7,807,816.

(30) **Foreign Application Priority Data**

Jun. 28, 2004 (AU) 2004903474

(51) **Int. Cl.**
C07H 21/04 (2006.01)
C12N 15/113 (2010.01)

(52) **U.S. Cl.**
CPC ***C12N 15/113*** (2013.01); *C12N 2310/11* (2013.01); *C12N 2310/3519* (2013.01); *C12N 2320/33* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,458,066	A	7/1984	Caruthers et al.
5,034,506	A	7/1991	Summerton et al.
5,138,045	A	8/1992	Cook et al.
5,142,047	A	8/1992	Summerton et al.
5,149,797	A	9/1992	Pederson et al.
5,166,315	A	11/1992	Summerton et al.
5,185,444	A	2/1993	Summerton et al.
5,190,931	A	3/1993	Inouye
5,217,866	A	6/1993	Summerton et al.
5,506,337	A	4/1996	Summerton et al.
5,521,063	A	5/1996	Summerton et al.
5,627,274	A	5/1997	Kole et al.
5,665,593	A	9/1997	Kole et al.
5,698,685	A	12/1997	Summerton et al.
5,869,252	A	2/1999	Bouma et al.
5,892,023	A	4/1999	Pirotzky et al.
5,916,808	A	6/1999	Kole et al.
5,976,879	A	11/1999	Kole et al.
6,153,436	A	11/2000	Hermonat et al.
6,210,892	B1	4/2001	Bennett et al.
6,312,900	B1	11/2001	Dean et al.
6,391,636	B1	5/2002	Monia
6,653,466	B2	11/2003	Matsuo
6,653,467	B1	11/2003	Matsuo et al.
6,656,732	B1	12/2003	Bennett et al.
6,727,355	B2	4/2004	Matsuo et al.
6,784,291	B2	8/2004	Iversen et al.
6,806,084	B1	10/2004	Debs et al.
7,001,761	B2	2/2006	Xiao
7,070,807	B2	7/2006	Mixson
7,163,695	B2	1/2007	Mixson
7,250,289	B2	7/2007	Zhou
7,314,750	B2	1/2008	Zhou
7,468,418	B2	12/2008	Iversen et al.
7,534,879	B2	5/2009	van Deutekom
7,655,785	B1	2/2010	Bentwich
7,655,788	B2	2/2010	Khvorova et al.
7,807,816	B2	10/2010	Wilton et al.
7,902,160	B2	3/2011	Matsuo et al.
7,960,541	B2	6/2011	Wilton et al.
7,973,015	B2	7/2011	van Ommen et al.
8,084,601	B2	12/2011	Popplewell et al.

(Continued)

FOREIGN PATENT DOCUMENTS

AU	780517	11/2001
AU	2003284638 A1	6/2004

(Continued)

OTHER PUBLICATIONS

Summerton et al. (Biochemica et Biophysica Acta 1489 , 1999, 141-158).*

Iversen et al. (Clinical Cancer Research, Jul. 2003, vol. 9, 2510-2519).*

Gebski, Bianca L. et al., "Morpholino antisense oligonucleotide induced dystrophin exon 23 skipping in mdx mouse muscle," Human Molecular Genetics, vol. 12(15):1801-1811 (2003).

Heasman, Janet, "Morpholino Oligos: Making Sense of Antisense?" Developmental Biology, vol. 243:209-214 (2002).

(Continued)

Primary Examiner — Kimberly Chong

(74) *Attorney, Agent, or Firm* — Nelson Mullins Riley & Scarborough LLP; Amy E. Mandragouras, Esq.; Erika L. Wallace

(57) **ABSTRACT**

An antisense molecule capable of binding to a selected target site to induce exon skipping in the dystrophin gene, as set forth in SEQ ID NO: 1 to 202.

2 Claims, 22 Drawing Sheets

(56) **References Cited**

U.S. PATENT DOCUMENTS

8,232,384	B2	7/2012	Wilton et al.	
8,324,371	B2	12/2012	Popplewell et al.	
8,361,979	B2	1/2013	Aartsma-Rus et al.	
8,450,474	B2	5/2013	Wilton et al.	
8,455,634	B2	6/2013	Wilton et al.	
8,455,635	B2	6/2013	Wilton et al.	
8,455,636	B2	6/2013	Wilton et al.	
8,461,325	B2	6/2013	Popplewell et al.	
8,476,423	B2	7/2013	Wilton et al.	
8,486,907	B2	7/2013	Wilton et al.	
8,501,703	B2	8/2013	Bennett et al.	
8,501,704	B2	8/2013	Mourich et al.	
8,524,676	B2	9/2013	Stein et al.	
8,524,880	B2	9/2013	Wilton et al.	
8,536,147	B2	9/2013	Weller et al.	
8,552,172	B2	10/2013	Popplewell et al.	
8,592,386	B2	11/2013	Mourich et al.	
8,618,270	B2	12/2013	Iversen et al.	
8,624,019	B2	1/2014	Matsuo et al.	
8,637,483	B2	1/2014	Wilton et al.	
8,697,858	B2	4/2014	Iversen	
8,741,863	B2	6/2014	Moulton et al.	
8,759,307	B2	6/2014	Stein et al.	
8,759,507	B2	6/2014	Van Deutekom	
8,779,128	B2	7/2014	Hanson et al.	
8,785,407	B2	7/2014	Stein et al.	
8,785,410	B2	7/2014	Iversen et al.	
8,835,402	B2	9/2014	Kole et al.	
8,865,883	B2	10/2014	Sazani et al.	
8,871,918	B2	10/2014	Sazani et al.	
8,877,725	B2	11/2014	Iversen et al.	
8,895,722	B2	11/2014	Iversen et al.	
8,906,872	B2	12/2014	Iversen et al.	
2001/0056077	A1	12/2001	Matsuo	
2002/0049173	A1	4/2002	Bennett et al.	
2002/0055481	A1	5/2002	Matsuo et al.	
2002/0110819	A1	8/2002	Weller et al.	
2002/0156235	A1	10/2002	Manoharan et al.	
2003/0166588	A1 *	9/2003	Iversen et al.	514/44
2003/0224353	A1	12/2003	Stein et al.	
2003/0235845	A1	12/2003	van Ommen et al.	
2004/0248833	A1	12/2004	Emanuele et al.	
2004/0254137	A1	12/2004	Ackermann et al.	
2005/0026164	A1	2/2005	Zhou	
2005/0048495	A1 *	3/2005	Baker et al.	435/6
2005/0153935	A1	7/2005	Iversen et al.	
2006/0099616	A1	5/2006	van Ommen et al.	
2006/0147952	A1	7/2006	van Ommen et al.	
2006/0148740	A1	7/2006	Platenburg	
2006/0287268	A1	12/2006	Iversen et al.	
2007/0037165	A1	2/2007	Venter et al.	
2007/0082861	A1	4/2007	Matsuo et al.	
2008/0194463	A1	8/2008	Weller et al.	
2008/0200409	A1	8/2008	Wilson et al.	
2008/0209581	A1	8/2008	van Ommen et al.	
2009/0076246	A1	3/2009	van Deutekom	
2009/0082547	A1	3/2009	Iversen et al.	
2009/0088562	A1	4/2009	Weller et al.	
2009/0099066	A1	4/2009	Moulton et al.	
2009/0228998	A1	9/2009	van Ommen et al.	
2009/0269755	A1	10/2009	Aartsma-Rus et al.	
2009/0312532	A1	12/2009	Van Deutekom et al.	
2010/0016215	A1	1/2010	Moulton et al.	
2010/0130591	A1	5/2010	Sazani et al.	
2010/0168212	A1	7/2010	Popplewell et al.	
2011/0015253	A1	1/2011	Wilton et al.	
2011/0015258	A1	1/2011	Wilton et al.	
2011/0046203	A1	2/2011	Wilton et al.	
2011/0046360	A1	2/2011	Matsuo et al.	
2011/0110960	A1	5/2011	Platenburg	
2011/0263682	A1	10/2011	De Kimpe et al.	
2011/0263686	A1	10/2011	Wilton et al.	
2011/0281787	A1	11/2011	Lu et al.	
2011/0294753	A1	12/2011	De Kimpe et al.	
2011/0312086	A1	12/2011	Van Deutekom	
2012/0022134	A1	1/2012	De Kimpe et al.	
2012/0022144	A1	1/2012	Wilton et al.	
2012/0022145	A1	1/2012	Wilton et al.	
2012/0029057	A1	2/2012	Wilton et al.	
2012/0029058	A1	2/2012	Wilton et al.	
2012/0029059	A1	2/2012	Wilton et al.	
2012/0029060	A1	2/2012	Wilton et al.	
2012/0041050	A1	2/2012	Wilton et al.	
2012/0046342	A1	2/2012	Van Deutekom et al.	
2012/0059042	A1	3/2012	Platenburg et al.	
2012/0065244	A1	3/2012	Popplewell et al.	
2012/0108652	A1	5/2012	Popplewell et al.	
2012/0108653	A1	5/2012	Popplewell et al.	
2012/0115150	A1	5/2012	Bozzoni et al.	
2012/0122801	A1	5/2012	Platenburg	
2012/0149756	A1	6/2012	Schumperli et al.	
2012/0172415	A1	7/2012	Voit et al.	
2012/0202752	A1	8/2012	Lu	
2013/0072671	A1	3/2013	Van Deutekom	
2013/0090465	A1	4/2013	Matsuo et al.	
2013/0197220	A1	8/2013	Ueda	
2013/0211062	A1	8/2013	Watanabe et al.	
2013/0289096	A1	10/2013	Popplewell et al.	
2013/0302806	A1	11/2013	Van Deutekom	
2014/0057964	A1	2/2014	Popplewell et al.	
2014/0080896	A1	3/2014	Nelson et al.	
2014/0113955	A1	4/2014	De Kimpe et al.	
2014/0128592	A1	5/2014	De Kimpe et al.	
2014/0213635	A1	7/2014	Van Deutekom	
2014/0221458	A1	8/2014	De Kimpe et al.	
2014/0275212	A1	9/2014	van Deutekom	
2014/0296323	A1	10/2014	Leumann et al.	
2014/0316123	A1	10/2014	Matsuo et al.	
2014/0343266	A1	11/2014	Watanabe et al.	
2014/0350076	A1	11/2014	van Deutekom	
2014/0357698	A1	12/2014	Van Deutekom et al.	
2014/0357855	A1	12/2014	Van Deutekom et al.	

FOREIGN PATENT DOCUMENTS

CA	2507125	A1	6/2004
EP	1054058	A1	11/2000
EP	1160318	A2	12/2001
EP	1160318	B1	12/2001
EP	1191097	A1	3/2002
EP	1191098	A2	3/2002
EP	1191098	B9	3/2002
EP	1495769	A1	1/2005
EP	1495769	B1	1/2005
EP	1544297	A2	6/2005
EP	1544297	B1	6/2005
EP	1568769	A1	8/2005
EP	1606407	B1	12/2005
EP	1619249	A1	1/2006
EP	1619249	B1	1/2006
EP	1766010	B1	3/2007
EP	1857548	A1	11/2007
EP	2119783	A1	11/2009
EP	2135948	A2	12/2009
EP	2206781	A2	7/2010
EP	2258863	A1	12/2010
EP	2284264	A1	2/2011
EP	2374885	A2	10/2011
EP	2386636	A2	11/2011
EP	2392660	A2	12/2011
EP	2488165	B1	8/2012
EP	2530153	A1	12/2012
EP	2530154	A1	12/2012
EP	2530155	A1	12/2012
EP	2530156	A1	12/2012
EP	2581448	A1	4/2013
EP	2594640	A1	5/2013
EP	2594641	A1	5/2013
EP	2594642	A1	5/2013
EP	2602322	A1	6/2013
EP	2607484	A1	6/2013
EP	2612917	A1	7/2013
EP	2614827	A2	7/2013
EP	2623507	A1	8/2013

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

EP	2636740	A1	9/2013
EP	2636741	A1	9/2013
EP	2636742	A1	9/2013
EP	2435582	B1	10/2013
EP	2435583	B1	7/2014
EP	2135948	B1	9/2014
EP	2799548	A1	11/2014
EP	2801618	A1	11/2014
JP	2000-325085	A	11/2000
JP	2002-10790		1/2002
JP	2002-529499	A	9/2002
JP	2002-325582		11/2002
JP	2002-340857		11/2002
JP	2004-509622	A	4/2004
JP	2008-507577	A	3/2008
JP	2010-268815		12/2010
JP	2011-101655	A	5/2011
JP	4777777		7/2011
JP	2011-200235	A	10/2011
JP	04846965	B2	12/2011
JP	5138722		11/2012
JP	05138722	B2	2/2013
JP	5378423		10/2013
JP	2014-54250		3/2014
JP	2014-111638	A	6/2014
JP	2014-138589	A	7/2014
WO	93/20227	A1	10/1993
WO	94/02595	A1	2/1994
WO	94/26887	A1	11/1994
WO	96/10391	A1	4/1996
WO	96/10392	A1	4/1996
WO	97/30067	A1	8/1997
WO	97/34638	A1	9/1997
WO	00/15780	A1	3/2000
WO	00/44897	A1	8/2000
WO	0078341	A1	12/2000
WO	01/49775	A2	7/2001
WO	01/72765	A1	10/2001
WO	01/83740	A2	11/2001
WO	02/18656	A2	3/2002
WO	02/24906	A1	3/2002
WO	0229406	A1	4/2002
WO	03/053341	A2	7/2003
WO	2004/048570	A1	6/2004
WO	2004/083432	A1	9/2004
WO	2004/083446	A2	9/2004
WO	2004083432	A1	9/2004
WO	2006/000057	A1	1/2006
WO	2006/021724	A2	3/2006
WO	2006/112705	A2	10/2006
WO	2007/058894	A2	5/2007
WO	2007/133812	A2	11/2007
WO	2007/135105	A1	11/2007
WO	2008/036127	A2	3/2008
WO	2009/054725	A2	4/2009
WO	2009/101399	A1	8/2009
WO	2009/139630	A2	11/2009
WO	2010/048586	A1	4/2010
WO	2010/050801	A1	5/2010
WO	2010/050802	A2	5/2010
WO	2010/115993	A1	10/2010
WO	2010/123369	A1	10/2010
WO	2010/136415	A1	12/2010
WO	2010/136417	A1	12/2010
WO	2010/150231	A1	12/2010
WO	2011/024077	A2	3/2011
WO	2011/045747	A1	4/2011
WO	2011/057350	A1	5/2011
WO	2011/143008	A1	11/2011
WO	2012/001941	A1	1/2012
WO	2012/029986	A1	3/2012
WO	2012/043730	A1	4/2012
WO	2012/109296	A1	8/2012
WO	2012/150960	A1	11/2012
WO	2013/033407	A2	3/2013
WO	2013/053928	A1	4/2013
WO	2013/100190	A1	7/2013
WO	2013/112053	A1	8/2013
WO	2014/007620	A2	1/2014

OTHER PUBLICATIONS

Summerton, James et al., "Morpholino and Phosphorothioate Antisense Oligomers Compared in Cell-Free adn In-Cell Systems," Antisense & Nucleic Acid Drug Development, vol. 7:63-70 (1997).

Aartsma-Rus, Annemieki et al., "Antisense-Induced Multiexon Skipping for Duchenne Muscular Dystrophy Makes More Sense," Am. J. Hum. Genet., vol. 74:83-92 (2004).

Aartsma-Rus, Annemieki et al., "Targeted exon skipping as a potential gene correction therapy for Duchenne muscular dystrophy," Neuromuscular Disorders, vol. 12:S71-S77 (2002).

Aartsma-Rus, Annemieki et al., "Therapeutic antisense-induced exon skipping in cultured muscle cells from six different DMD patients," Human Molecular Genetics, vol. 12(8):907-914 (2003).

Abbs, Stephen et al., "A convenient multiplex PCR system for the detection of dystrophin gene deletions: a comparative analysis with cDNA hybridisation shows mistypings by both methods," J. Med. Genet., vol. 28:304-311 (1991).

Agrawal, Sudhir et al., "Oligodeoxynucleoside phosphoramidates and phosphorothioates as inhibitors of human immunodeficiency virus," Proc. Natl. Acad. Sci. USA, vol. 85:7079-7083 (1988).

Akhtar, Saghir et al., "Cellular uptake and intracellular fate of antisense oligonucleotides," Trends in Cell Biology, vol. 2:139-144 (1992).

Akhtar, Saghir, (ed.), Delivery Strategies for Antisense Oligonucleotide Therapeutics, CDC Press, Boca Raton, Florida (1995).

Anderson, W. French, "Human Gene Therapy," Science, vol. 256:808-813 (1992).

Arechavala-Gomeza, V. et al., "Comparative Analysis of Antisense Oligonucleotide Sequences for Targeted Skipping of Exon 51 During Dystrophin Pre-mRNA Splicing in Human Muscle," Human Gene Therapy, vol. 18:798-810 (2007).

Arora, Vikram et al., "c-Myc Antisense Limits Rat Liver Regeneration and Indicates Role for c-Myc in Regulating Cytochrome P-450 3A Activity," The Journal of Pharmacology and Experimental Therapeutics, vol. 292(3):921-928 (2000).

Asvadi, Parisa et al., "Expression and functional analysis of recombinant scFv and diabody fragments with specificity for human RhD," Journal of Molecular Recognition, vol. 15:321-330 (2002).

Berge, Stephen M. et al., "Pharmaceutical Salts," Journal of Pharmaceutical Sciences, vol. 66(1):1-19 (1977).

Brown, Susan C. et al., "Dystrophic phenotype induced in vitro by antibody blockade of muscle alpha-dystroglycan-laminin interaction," Journal of Cell Science, vol. 112:209-216 (1999).

Cirak, Sebahattin et al., "Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study," Lancet, vol. 378(9791):595-605 (2011).

Collins, C.A. et al., "Duchenne's muscular dystrophy: animal models used to investigate pathogenesis and develop therapeutic strategies," Int. J. Exp. Pathol., vol. 84(4):165-172 (2003).

De Angelis, Fernanda Gabriella et al., "Chimeric snRNA molecules carrying antisense sequences against the splice junctions of exon 51 of the dystrophic pre-mRNA induce exon skipping and restoration of a dystrophin synthesis in 48-50 DMD cells," PNAS, vol. 99(14):9456-9461 (2002).

Dellorusso, Christiana et al., "Functional correction of adult mdx mouse muscle using gutted adenoviral vectors expressing full-length dystrophin," PNAS, vol. 99(20):12979-12984 (2002).

Dirksen, Wessel P. et al., "Mapping the SF2/ASF Binding Sites in the Bovine Growth Hormone Exonic Splicing Enhancer," The Journal of Biological Chemistry, vol. 275(37):29170-29177 (2000).

Dominski, Zbigniew et al., "Identification and Characterization by Antisense Oligonucleotides of Exon and Intron Sequences Required for Splicing," Molecular and Cellular Biology, vol. 14(11):7445-7454 (1994).

(56) **References Cited**

OTHER PUBLICATIONS

Dominski, Zbigniew et al., "Restoration of correct splicing in thalassemic pre-mRNA by antisense oligonucleotides," Proc. Natl. Acad. Sci. USA, vol. 90:8673-8677 (1993).

Dunckley, Matthew G. et al., "Modification of splicing in the dystrophin gene in cultured Mdx muscle cells by antisense oligoribonucleotides," Human Molecular Genetics, vol. 5(1):1083-1090 (1995).

Dunckley, Matthew G. et al., "Modulation of Splicing in the DMD Gene by Antisense Oligoribonucleotides," Nucleosides & Nucleotides, vol. 16(7-9):1665-1668 (1997).

Elayadi, Anissa N. et al., "Application of PNA and LNA oligomers to chemotherapy," Current Opinion in Investigational Drugs, vol. 2(4):558-561 (2001).

Errington, Stephen J. et al., "Target selection for antisense oligonucleotide induced exon skipping in the dystrophin gene," The Journal of Gene Medicine, vol. 5:518-527 (2003).

Fall, Abbie M. et al., "Induction of revertant fibres in the mdx mouse using antisense oligonucleotides," Genetics Vaccines and Therapy, vol. 4:3, doi:10.1186/1479-0556-4-3, 12 pages (2006).

Fletcher, Susan et al., "Dystrophin expression in the mdx mouse after localised and systemic administration of a morpholino antisense oligonucleotide," J. Gene Med., vol. 8:207-216 (2006).

Fletcher, Susan et al., "Gene therapy and molecular approaches to the treatment of hereditary muscular disorders," Curr. Opin. Neurol., vol. 13:553-560 (2000).

Fletcher, Sue et al., "Targeted Exon Skipping to Address 'Leaky' Mutations in the Dystrophin Gene," Molecular Therapy-Nucleic Acids, vol. 1, e48, doi:10.1038/mtna.2012.40, 11 pages (2012).

Friedmann, Theodore, "Progress Toward Human Gene Therapy," Science, vol. 244(4910):1275-1281 (1989).

Gennaro, Alfonso, R., (ed.), Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing, Co., Eastern PA (1990).

Giles, Richard V. et al., "Antisense Morpholino Oligonucleotide Analog Induces Missplicing of C-myc mRNA," Antisense & Nucleic Acid Drug Development, vol. 9:213-220 (1999).

Harel-Bellan, Annick et al., "Specific Inhibition of c-myc Protein Biosynthesis Using an Antisense Synthetic Deoxy-Oligonucleotide in Human T Lymphocytes," The Journal of Immunology, vol. 140(7):2431-2435 (1988).

Hudziak, Robert M. et al., "Resistance of Morpholino Phosphorodiamidate Oligomers to Enzymatic Degradation," Antisense & Nucleic Acid Drug Development, vol. 6:267-272 (1996).

Hussey, Nicole D. et al., "Analysis of five Duchenne muscular dystrophy exons and gender determination using conventional duplex polymerase chain reaction on single cells," Molecular Human Reproduction, vol. 5(11):1089-1094 (1999).

Jones, Simon S. et al., "The Protection of Uracil and Guanine Residues in Oligonucleotide Synthesis," Tetrahedron Letters, vol. 22(47):4755-4758 (1981).

Karras, James G. et al., "Deletion of Individual Exons and Induction of Soluble Murine Interleukin-5 Receptor-alpha Chain Expression through Antisense Oligonucleotide-Mediated Redirection of Pre-mRNA splicing," Molecular Pharmacology, vol. 58:380-387 (2000).

Kaye, Ed, "Results of the Eteplirsen Phase 2b and Phase 2b Extension Study in Duchenne Muscular Dystrophy," 8th Annual Meeting of the Oligonucleotide Therapeutics Society, Session 9: Advances in Oligonucleotide Clinical Development II, p. 48 (2012).

Kinali, Maria et al., "Local restoration of dystrophin expression with the morpholino oligomer AVI-4658 in Duchenne muscular dystrophy: a single-blind, placebo-controlled, dose-escalation, proof-of-concept study," Lancet Neurol., vol. 8:918-928 (2009).

Larsen, H. Jakob et al., "Antisense properties of peptide nucleic acid," Biochimica et Biophysica Acta, vol. 1489:159-166 (1999).

Liu, Hong-Xiang et al., "Identification of functional exonic splicing enhancer motifs recognized by individual SR proteins," Genes & Development, vol. 12:1998-2012 (1998).

Lu, Qi Long et al., "Functional amounts of dystrophin produced by skipping the mutated exon in the mdx dystrophic mouse," Nature Medicine, vol. 9(8):1009-1014 (2003).

Lu, Q.L. et al., "Massive Idiosyncratic Exon Skipping Corrects the Nonsense Mutation in Dystrophic Mouse Muscle and Produces Functional Revertant Fibers by Clonal Expansion," The Journal of Cell Biology, vol. 148(5):985-995 (2000).

Lu, Qi-long et al., "What Can We Learn From Clinical Trials of Exon Skipping for DMD?" Molecular Therapy—Nucleic Acids, vol. 3:e152, doi:10.1038/mtna.2014.6, 4 pages (2014).

Mann, Christopher J. et al., "Antisense-induced exon skipping and synthesis of dystrophin in the mdx mouse," PNAS, vol. 98(1):42-47 (2001).

Mann, Christopher J. et al., "Improved antisense oligonucleotide induced exon skipping in the mdx mouse model of muscular dystrophy," The Journal of Gene Medicine, vol. 4:644-654 (2002).

Matsuo, Masafumi, "Duchenne and Becker Muscular Dystrophy: From Gene Diagnosis to Molecular Therapy," IUBMB Life, vol. 53:147-152 (2002).

Matsuo, Masafumi, "Duchenne/Becker muscular dystrophy: from molecular diagnosis to gene therapy," Brain & Development, vol. 18:167-172 (1996).

Matsuo, Masafumi et al., "Exon Skipping during Splicing of Dystrophin mRNA Precursor due to an Intraexon Deletion in the Dystrophin Gene of Duchenne Muscular Dystrophy Kobe," J. Clin. Invest, vol. 87:2127-2131 (1991).

Matsuo, Masafumi et al., "Treatment of Duchenne Muscular Dystrophy with Oligonucleotides against an Exonic Splicing Enhancer Sequence," Basic Appl. Myol., vol. 13(6):281-285 (2003).

Matteucci, Mark, "Structural modifications toward improved antisense oligonucleotides," Perspectives in Drug Discovery and Design, vol. 4:1-16 (1996).

McClorey, G. et al., "Antisense oligonucleotide-induced exon skipping restores dystrophin expresion in vitro in a canine model of DMD," Gene Therapy, vol. 13:1373-1381 (2006).

McClorey, G. et al., "Induced dystrophin exon skipping in human muscle explants," Neuromuscular Disorders, vol. 16:583-590 (2006).

McClorey, Graham et al., "Splicing intervention for Duchenne muscular dystrophy," Current Opinion in PHarmacology, vol. 5:529-534 (2005).

Mitrpant, Chalermchai et al., "Rational Design of Antisense Oligomers to Induce Dystrophin Exon Skipping," Molecular Therapy, vol. 17(8):1418-1426 (2009).

Monaco, Anthony P. et al., "An Explanation for the Phenotypic Differences between Patients Bearing Partial Deletions of the DMD Locus," Genomics, vol. 2:90-95 (1988).

Nelson, David L. et al., "Nucleotides and Nucleic Acids," Lehninger Principles of Biochemistry, 3rd Edition, Chapter 10, pp. 325-328 and glossary p. G-11, Worth Publishers, New York (2000).

Pramono, Zacharias Aloysius Dwi et al., "Induction of Exon Skipping of the Dystrophin Transcript in Lymphoblastoid Cells by Transfecting an Antisense Oligodeoxynucleotide Complementary to an Exon Recognition Sequence," Biochemical and Biophysical Research Communicaitons, vol. 226:445-449 (1996).

Reese, Colin B. et al., "Reaction Between 1-Arenesulphonyl-3-Nitro-1,2,4-Triazoles and Nucleoside Base Residues. Elucidation of the Nature of Side-Reactions During Oligonucleotide Synthesis," Tetrahedron Letters, vol. 21:2265-2268 (1980).

Reese, Colin B. et al., "The Protection of Thymine and Guanine Residues in Oligodeoxyribonucleotide Synthesis," J. Chem. Soc. Perkin Trans. 1, pp. 1263-1271 (1984).

Roberts, Roland G. et al., "Exon Structure of the Human Dystrophin Gene," Genomics, vol. 16:536-538 (1993).

Rosso, Mario G. et al., "An *Arabidopsis thaliana* T-DNA mutagenized population (GABI-Kat) for flanking sequence tag-based reverse genetics," Plant Molecular Biology, vol. 53:247-259 (2003).

Shapiro, Marvin B. et al., "RNA splice junctions of different classes of eukaryotes: sequence statistics and functional implications in gene expression," Nucleic Acids Research, vol. 15(17):7155-7174 (1987).

(56) **References Cited**

OTHER PUBLICATIONS

Sherratt, Tim G. et al., "Exon Skipping and Translation in Patients with Frameshift Deletions in the Dystrophin Gene," Am. J. Hum. Genet., vol. 53:1007-1015 (1993).

Shiga, Nobuyuki et al., "Disruption of the Splicing Enhancer Sequence within Exon 27 on the Dystrophin Gene by a Nonsense Mutation Induced Partial Skipping of the Exon and Is Responsible for Becker Muscular Dystrophy," J. Clin. Invest., vol. 100:2204-2210 (1997).

Sierakowska, Halina et al., "Repair of thalassemic human beta-globin mRNA in mammalian cells by antisense oligonucleotides," Proc. Natl. Acad. Sci. USA, vol. 93:12840-12844 (1996).

Stein, David et al., "A Specificity Comparison of Four Antisense Types: Morpholino, 2'-O-Methyl RNA, DNA, and PHosphorothioate DNA," Antisense & Nucleic Acid Drug Development, vol. 7:151-157 (1997).

Summerton, James et al., "Morpholino Antisense Oligomers: Design, Preparation, and Properties," Antisense & Nucleic Acid Drug Development, vol. 7:187-195 (1997).

Takeshima, Yasuhiro et al., "Modulation of in Vitro Splicing of the Upstream Intron by Modifying an Intra-Exon Sequence Which Is Deleted from the Dystrophin Gene in Dystrophin Kobe," J. Clin. Invest., vol. 95:515-520 (1995).

Tanaka, Kenji et al., "Polypurine Sequences within a Downstream Exon Function as a Splicing Enhancer," Molecular and Cellular Biology, vol. 14(2):1347-1354 (1994).

Than H, Le Htiet et al., "Characterization of Revertant Muscle Fibers in Duchenne Muscular Dystrophy, Using Exon-Specific Monoclonal Antibodies against Dystrophin," Am. J. Hum. Genet., vol. 56:725-731 (1995).

Van Deutekom, Judith C. T. et al., "Advances in Duchenne Muscular Dystrophy Gene Therapy," Nature Reviews Genetics, vol. 4(10):774-783 (2003).

Van Deutekom, Judith C. T. et al., "Antisense-induced exon skipping restores dystrophin expression in DMD patient derived muscle cells," Human Molecular Genetics, vol. 10(15):1547-1554 (2001).

Volloch, Vladimir et al., "Inhibition of Pre-mRNA Splicing by Antisense RNA in Vitro: Effect of RNA Containing Sequences Complementary to Exons," Biochemical and Biophysical Research Communications, vol. 179 (3):1593-1599 (1991).

Wahlestedt, Claes et al., "Potent and nontoxic antisense oligonucleotides containing locked nucleic acids," PNAS, vol. 97(10):5633-5638 (2000).

Watakabe, Akiya et al., "The role of exon sequences in splice site selection," Genes & Development, vol. 7:407-418 (1993).

Wilton, Stephen D. et al., "Antisense oligonucleotides in the treatment of Duchenne muscular dystrophy: where are we now?" Neuromuscular Disorders, vol. 15:399-402 (2005).

Wilton, Stephen D. et al., "Specific removal of the nonsense mutation from the mdx dystrophin mRNA using antisense oligonucleotides," Neuromuscular Disorders, vol. 9:330-338 (1999).

Wu, Bo et al., "Targeted Skipping of Human Dystrophin Exons in Transgenic Mouse Model Systemically for Antisense Drug Development," PLoS One, vol. 6(5):e19906, 11 pages (2011).

AVI BioPharma, Inc., "Exon 51 Sequence of Dystrophin," Document D19 as filed in Opposition of European Patent EP1619249, filed Jun. 23, 2009, 7 pages.

European Search Report for Application No. 10004274.6, 12 pages, dated Jan. 2, 2013.

European Search Report for Application No. 12162995.0, 11 pages, dated Jan. 15, 2013.

International Search Report for Application No. PCT/US01/14410, 5 pages, dated Mar. 6, 2002.

International Search Report for Application No. PCT/AU2005/000943, 5 pages, dated Oct. 20, 2005.

International Preliminary Report on Patentability for Application No. PCT/AU2005/000943, 8 pages, dated Dec. 28, 2006.

Partial European Search Report for Application No. 10004274.6, 6 pages, dated Oct. 2, 2012.

Partial European Search Report for Application No. 12162995.0, 6 pages, dated Oct. 2, 2012.

Patentee's Response to European Patent Application No. 05076770.6, dated Jul. 28, 2006, 4 pages.

U.S. Patent Application Publication No. 2002/0049173 ("Bennett et al.") (Exhibit No. 1081 filed in interferences 106008, 106007 on Dec. 23, 2014).

U.S. Patent No. 5,190,931 ("the '931 Patent") (Exhibit No. 1069 filed in interferences 106008, 106007 on Dec. 23, 2014).

U.S. Patent No. 7,001,761 (the "Xiao" Patent) (Exhibit No. 1070 filed in interferences 106008, 106007 on Dec. 23, 2014).

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Statement Concerning Subsequent Settlement Discussion, 3 pages, Patent Interference Nos. 106,007 and 106,008, dated Dec. 30, 2014.

USPTO Written Description Training Materials, Revised Mar. 25, 2008, Example 12 (Exhibit No. 1068 filed in interferences 106008, 106007 on Dec. 23, 2014).

Van Deutekom et al., Antisense-induced exon skipping restores dystrophin expression in DMD patient derived muscle cells, 10:15 Human Molecular Genetics 1547-1554 (2001) (Exhibit No. 1084 filed in interferences 106008, 106007 on Dec. 23, 2014).

Van Deutekom, Judith C. et al., "Local Dystrophin Restoration with Antisense Oligonucleotide PRO051," The New England Journal of Medicine, vol. 357:2677-2686 (2007).

Van Ommen 2002 PCT (WO 02/24906 AI) (Exhibit No. 1071 filed in interferences 106008, 106007 on Dec. 23, 2014).

Van Vliet, Laura et al., "Assessment of the Feasibility of Exon 45-55 Multiexon Skipping for Duchenne Muscular Dystrophy", BMC Medical Genetics, vol. 9(1):105 (2008).

Wang, Chen-Yen et al., "pH-sensitive immunoliposomes mediate target-cell-specific delivery and controlled expression of a foreign gene in mouse," Proc. Natl. Acad. Sci. USA, vol. 84:7851-7855 (1987).

Wilton, Steve D. et al., "Antisense Oligonucleotide-induced Exon Skipping Across the Human Dystrophin Gene Transcript," Molecular Therapy, vol. 15(7):1288-1296 (2007).

Wolff, Jon A. et al., "Direct Gene Transfer into Mouse Muscle in Vivo," Science, vol. 247:1465-1468 (1990).

Written Opinion for Application No. PCT/AU2010/001520, 6 pages, dated Jan. 21, 2011.

Written Opinion for Application No. PCT/AU2010/001520, 7 pages, dated Oct. 13, 2011.

Wu, B. et al., "Dose-dependent restoration of dystrophin expression in cardiac muscle of dystrophic mice by systemically delivered morpholino," Gene Therapy, vol. 17:132-140 (2010).

Wu, Bo et al., "Effective rescue of dystrophin improves cardiac function in dystrophin-deficient mice by a modified morpholino oligomer," PNAS, vol. 105(39):14814-14819 (2008).

Wu, George Y. et al., "Receptor-mediated Gene Delivery and Expression in Vivo," The Journal of Biological Chemistry, vol. 263(29):14621-14624 (1988).

Wu, George Y. et al., "Receptor-mediated in Vitro Gene Transformation by a Soluble DNA Carrier System," The Journal of Biological Chemistry, vol. 262(10):4429-4432 (1987).

Yin, HaiFang et al., "Cell-penetrating peptide-conjugated antisense oligonucleotides restore systemic muscle and cardiac dystrophin expression and function," Human Molecular Genetics, vol. 17(24):3909-3918 (2008).

Popplewell, Linda J. et al., "Comparative analysis of antisense oligonucleotide sequences targeting exon 53 of the human DMD gene: Implications for future clinical trials," Neuromuscular Disorders, 9 pages (2010) (Exhibit No. 2031 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Prosensa, "GSK and Prosensa Announce Primary Endpoint Not Met in Phase III Study of Drisapersen in Patients With Duchenne Muscular Dystrophy," press release, 4 pages, dated Sep. 20, 2013 (Exhibit No. 2039 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Sarepta, "AVI BioPharma Initiates Dosing in Phase 2 Study of Eteplirsen in Duchenne Muscular Dystrophy Patients," press release, 4 pages, dated Aug. 15, 2011 (Exhibit No. 2082 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

(56) **References Cited**

OTHER PUBLICATIONS

Sarepta, "Sarepta Therapeutics Announces Eteplirsen Demonstrates Continued Stability on Walking Test through 120 Weeks in Phase Iib Study in Duchenne Muscular Dystrophy," press release, 3 pages, dated Jan. 15, 2014 (Exhibit No. 2034 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Sarepta, "Sarepta Therapeutics Reports Long-Term Outcomes through 144 Weeks from Phase IIb Study of Eteplirsen in Duchenne Muscular Dystrophy," press release, http://investorrelations.sarepta.com/phoenix.zhtml?c=64231&p=irol-newsArticle&id=1946426, 8 pages, dated Jul. 10, 2014.

Shimizu, Miho et al., "Oligo(2'-O-methyl)ribonucleotides Effective probes for duplex DNA," FEBS Letters, vol. 302 (2):155-158 (1992) (Exhibit No. 1035 filed in interferences 106008, 106007 on Nov. 18, 2014).

Sontheimer, Erik J. et al., "Metal ion catalysis during splicing of premessenger RNA," Nature, vol. 388:801-805 (1997) (Exhibit No. 1036 filed in interferences 106008, 106007 on Nov. 18, 2014).

Sontheimer, Erik J. et al., "The U5 and U6 Small Nuclear RNAs as Active Site Components of the Spliceosome," Science, vol. 262:1989-1997 (1993) (Exhibit No. 1058 filed in interferences 106008, 106007 on Nov. 18, 2014).

Stein, CA, "Delivery of antisense oligonucleotides to cells: a consideration of some of the barriers," Monographic supplement series: Oligos & Peptides—Chimica Oggi—Chemistry Today, vol. 32(2):4-7 (2014) (Exhibit No. 2022 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Stein, Cy A. et al., "Therapeutic Oligonucleotides: The Road Not Taken," Clin. Cancer Res., vol. 17(20):6369-6372 (2011) (Exhibit No. 2026 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Summerton, James, "Morpholino antisense oligomers: the case for an Rnase H-independent structural type," Biochimica et Biophysica Acta, vol. 1489:141-158 (1999) (Exhibit No. 1038 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

'T Hoen, Peter A.C. et al., "Generation and Characterization of Transgenic Mice with the Full-length Human DMD Gene," The Journal of Biological Chemistry, vol. 283(9):5899-5907 (2008) Exhibit No. 2030 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Tian, Xiaobing et al., "Imaging Oncogene Expression," Ann. N.Y. Acad. Sci., vol. 1002:165-188 (2003) (Exhibit No. 2029 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Verma, Sandeep et al., "Modified Oligonucleotides: Synthesis and Strategy for Users," Annu. Rev. Biochem., vol. 67:99-134 (1998) (Exhibit No. 1040 filed in interferences 106008, 106007 on Nov. 18, 2014).

Voit, Thomas et al., "Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (Demand II): an exploratory randomised, placebo-controlled phase 2 study," Lancet Neurol., vol. 13:987-996 (2014) (Exhibit No. 2037 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Wijnaendts, L.C.D. et al., "Prognostic importance of DNA flow cytometric variables in rhabdomyosarcomas," J. Clin. Pathol., vol. 46:948-952 (1993) (Exhibit No. 1041 filed in interferences 106008, 106007 on Nov. 18, 2014).

Wong, Marisa L. et al., "Real-time PCR for mRNA quantitation," BioTechniques, vol. 39:75-85 (2005) (Exhibit No. 1066 filed in interferences 106008, 106007 on Nov. 18, 2014).

European Response, Application No. 10004274.6, 7 pages, dated Nov. 5, 2013 (Exhibit No. 1060 filed in interferences 106008, 106007 on Nov. 18, 2014).

European Response, Application No. 12198517.0, 7 pages, dated Oct. 21, 2014 (Exhibit No. 2084 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

European Response, Application No. 13160338.3, 4 pages, dated Jun. 26, 2014 (Exhibit No. 2085 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Annotated Claims, Patent Interference No. 106,007, 15 pages, dated Aug. 15, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Annotated Claims, Patent Interference No. 106,008, 14 pages, dated Aug. 21, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Annotated Claims, Patent Interference No. 106,013, 14 pages, dated Oct. 27, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Clean Claims and Sequences, 5 pages, dated Jul. 31, 2014 (Exhibit No. 2045 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Clean Claims and Sequences, 5 pages, dated Aug. 5, 2014 (Exhibit No. 2047 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Clean Claims and Sequences, 5 pages, dated Oct. 15, 2014 (Exhibit No. 2050 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Clean Involved Claims and Sequences, Patent Interference No. 106,007, 8 pages, dated Aug. 1, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Clean Involved Claims and Sequences, Patent Interference No. 106,008, 8 pages, dated Aug. 7, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Clean Involved Claims and Sequences, Patent Interference No. 106,013, 7 pages, dated Oct. 14, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Corrected Notice of Related Proceedings, Patent Interference No. 106,007, 3 pages, dated Aug. 1, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Declaration of Interference, Patent Interference No. 106,007, 7 pages, dated Jul. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Declaration of Interference, Patent Interference No. 106,013, 8 pages, dated Sep. 29, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Declaration of Interference, Patent Interference No. 106,008, 7 pages, dated Jul. 24, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL List of Proposed Motions, Patent Interference No. 106,008, 8 pages, dated Sep. 10, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA List of Proposed Motions, Patent Interference No. 106,008, 6 pages, dated Sep. 10, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL List of Proposed Motions, Patent Interference No. 106,007, 6 pages, dated Sep. 10, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA List of Proposed Motions, Patent Interference No. 106,007, 7 pages, dated Sep. 10, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Miscellaneous Motion 1, 5 pages, Patent Interference No. 106,008, dated Oct. 17, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Notice of Related Proceedings, Patent Interference No. 106,007, 3 pages, dated Jul. 31, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Notice of Related Proceedings, Patent Interference No. 106,007, 3 pages, dated Aug. 1, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Notice of Related Proceedings, Patent Interference No. 106,008, 3 pages, dated Aug. 5, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Notice of Related Proceedings, Patent Interference No. 106,008, 5 pages, dated Aug. 7, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Notice of Related Proceedings, Patent Interference No. 106,013, 3 pages, dated Oct. 14, 2014.

(56) **References Cited**

OTHER PUBLICATIONS

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Notice of Related Proceedings, Patent Interference No. 106,013, 3 pages, dated Oct. 15, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Order—Authorizing Motions, Patent Interference No. 106,007, 6 pages, dated Sep. 23, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Order—Authorizing Motions, Patent Interference No. 106,008, 6 pages, dated Sep. 23, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Order—Authorizing Motions, Patent Interference No. 106,007, 3 pages, dated Sep. 26, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Redeclaration, Patent Interference No. 106,008, 2 pages, dated Sep. 23, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Declaration of Erik Sontheimer, Patent Interference Nos. 106,007 and 106,008, 112 pages, dated Nov. 17, 2014 (Exhibit No. 1012 filed in interferences 106008, 106007 on Nov. 18, 2014).
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Declaration of Matthew J.A. Wood, Patent Interference Nos. 106,007, 106,008 and 106,113, 184 pages, dated Sep. 19, 2014 (Exhibit No. 2081 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
Declaration of Judith van Deutekom, pp. 45, Exhibit No. 1125 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Deposition Transcript of Erik J. Sontheimer, Ph.D. of Jan. 21, 2015 (99 pages), Exhibit No. 1215 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Deposition Transcript of Matthew J. A. Wood, M.D. , D. Phil., Jan. 22, 2015, including Errata Sheet, pp. 198, Exhibit No. 1007 filed in Interference 106,013 on Feb. 17, 2015.
Deposition Transcript of Matthew J. A. Wood, M.D., D. Phil., pp. 196, Exhibit No. 1122 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Desalting of Oligonucleotides, pp. 2, Exhibit No. 1132 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Doyle et al. (2001) "Inhibition of Gene Expression Inside Cells by Peptide Nucleic Acids: Effect of mRNA Target Sequence, Mismatched Bases, and PNA Length," Biochemistry 40:53-64, (Exhibit No. 2123 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Dr. Wood Errata Sheet—Jan. 22, 2015, pp. 2, Exhibit No. 1227 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Email from Danny Huntington to Interference Trial Section, dated Sep. 21, 2014, pp. 2, Exhibit No. 3001 filed in Interference 106,007, 106,008, and 106,013 on Sep. 26, 2014.
Email From Sharon Crane to Interference Trial Section, dated Nov. 14, 2014, pp. 2, Exhibit No. 3002 filed in Interference 106,007, 106,008, and 106,013 on dated Nov. 14, 2014.
Errata sheet for the Jan. 22, 2015 deposition of Matthew J. A. Wood, M.D., D. Phil., 8 pages, (Exhibit No. 2128 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Exon 51 Internal Sequence Schematic, pp. 1, Exhibit No. 1224 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Exon 53 Internal Sequence Schematic, pp. 1, Exhibit No. 1225 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Fairclough et al., "Therapy for Duchenne muscular dystrophy: renewed optimism from genetic approaches," Nature Reviews, vol. 14, pp. 373-378 (Jun. 2013), Exhibit No. 1112 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Federal Register, vol. 58, No. 183, pp. 49432-49434, Sep. 23, 1993 (6 pages); [Cited as: 58 FR 49432-01, 1993 WL 371451 (F.R.)], Exhibit No. 1221 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Federal Register, vol. 69, No. 155, pp. 49960-50020 dated Aug. 12, 2004 (62 pages), Exhibit No. 1220 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
File Excerpts from Prosecution History of U.S. Appl. No. 13/270,992 (UWA's U.S. Patent No. 8,486,907), pp. 111, Exhibit No. 1006 filed in Interference 106,013 on Feb. 17, 2015.
File Excerpts from U.S. Appl. No. 11/233,495: Response to Non-Final Office Action, filed Jul. 26, 2011 (14 pages), Exhibit No. 1222 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
File Excerpts from U.S. Appl. No. 13/270,992 (UWA's U.S. Patent No. 8,486,907): NFOA, dated Jul. 30, 2012; Applicant-Initiated Interview Summary, dated Nov. 8, 2012; Amendment, as filed Jan. 30, 2013; NOA, dated Apr. 4, 2013, Exhibit No. 1118 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Flanagan et al., "A cytosine analog that confers enhanced potency to antisense of oligonucleotides," Proc. Nat'l Acad. Sci. USA, vol. 96, pp. 3513-3518 (Mar. 1999), Exhibit No. 1211 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Flanigan et al. (2003) "Rapid Direct Sequence Analysis of the Dystrophin Gene," Am. J. Hum. Genet. 72:931-939, dated Feb. 17, 2015 (Exhibit No. 2120 filed in interference 1006,007 and 106,008 on Feb. 17, 2015.
Generic Method for Average Mass Determination Using LC-UV-MS in the Negative Mode, pp. 15, Exhibit No. 1145 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Generic UPLC Purity Method for Oligonucleotides (19- to 25-mers), pp. 18, Exhibit No. 1156 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
GlaxoSmithKline Press Release, Issued in London, UK, dated Jun. 27, 2013 (5; pages), Exhibit No. 1202 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Gordon et al., "Kinetic Characterization of the Second Step of Group II Intron Splicing: Role of Metal Ions and the Cleavage Site 2'-OH in Catalysis," Biochemistry, vol. 39, pp. 12939-12952 (2000), Exhibit No. 1188 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Hammond et al., "Genetic therapies for RNA mis-splicing diseases," Cell, vol. 27, No. 5, pp. 196-205 (May 2011), Exhibit No. 1113 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Hammond et al., "PRO-051, an antisense oligonucleotide for the potential treatment of Duchenne muscular dystrophy," Curr. Opinion Mol. Therap., vol. 12, No. 4, pp. 478-486 (2010), Exhibit No. 1121 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
Harding, P.L. et al., "The Influence of Antisense Oligonucleotide Length on Dystrophin Exon Skipping," Molecular Therapy, vol. 15(1):157-166 (2007).
Havenga et al., "Exploiting the Natural Diversity in Adenovirus Tropism for Therapy and Prevention of Disease," J. Virol., vol. 76, No. 9, pp. 4612-4620 (May 2002), Exhibit No. 1123 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
Interim Guidance on Patent Subject Matter Eligibility (the December Guidance, 16 pages,(Exhibit No. 2119 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
International Patent Application No. PCT/AU2000/00693 ("Wraight"), published as WO 00/78341 on Dec. 28, 2000, 201 pages, (Exhibit No. 2125 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Invitation to pay fees issued by the International Search Authority in International Patent Application No. PCT/US2014/029689 dated Jul. 29, 2014.
Lab-on-a-Chip Data, pp. 28, Exhibit No. 1185 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Laboratory Notebook Entry (Exon 51 Experiments): RT-PCR Analysis of 8036 Cells, pp. 2, Exhibit No. 1179 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Laboratory Notebook Entry (Exon 51 Experiments): RT-PCR Analysis of KM155.C25 Cells, pp. 2, Exhibit No. 1178 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Laboratory Notebook Entry (Exon 51 Experiments): Transfection of 8036 Cells, pp. 1, Exhibit No. 1172 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Laboratory Notebook Entry (Exon 51 Experiments): Transfection of KM155.C25 Cells, pp. 1, Exhibit No. 1171 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.

(56) **References Cited**

OTHER PUBLICATIONS

Laboratory Notebook Entry (Exon 53 Experiments): RT-PCR Analysis of KM155.C25 Cells, pp. 2, Exhibit No. 1180 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Laboratory Notebook Entry (Exon 53 Experiments): RT-PCR Analysis of R1809 Cells, pp. 2, Exhibit No. 1181 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Laboratory Notebook Entry (Exon 53 Experiments): Transfection of KM155.C25 Cells, pp. 1, Exhibit No. 1173 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Laboratory Notebook Entry (Exon 53 Experiments): Transfection of R1809 Cells, pp. 1, Exhibit No. 1174 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Laboratory Notebook Entry: General RNA recovery, pp. 2, Exhibit No. 1176 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Laboratory Notebook Entry: Lab-on-a-Chip Analysis, pp. 3, Exhibit No. 1184 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Larsen et al., "Antisense properties of peptide nucleic acid," Biochim. Et Biophys. Acta, vol. 1489, pp. 159-166 (1999), Exhibit No. 1190 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
List of Publications for Matthew J. A. Wood, M.D., D. Phil., 11 pages, (Exhibit No. 2124 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Lu et al, Massive Idiosyncratic Exon Skipping Corrects the Nonsense Mutation in Dystrophic Mouse Muscle and Produces Functional Revertant Fibers by Clonal Expansion, 98:1 The Journal of Cell Biology, 985-995, Mar. 6, 2000 ("Lu et al."), Exhibit No. 1082 filed in interferences 106,007 and 106,008 on Dec. 23, 2014.
Lyophilisation of Oligonucleotides, pp. 2, Exhibit No. 1133 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Matthews et al., "Expanded Sequence Dependence of Thermodynamic Parameters Improves Prediction of RNA Secondary Structure," J. Mol. Biol., vol. 288, pp. 911-940 (1999), Exhibit No. 1212 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Morcos, Paul A., "Gene switching: analyzing a broad range of mutations using steric block antisense oligonucleotides," Methods in Enzymology, vol. 313:174-189 (1999).
Oberbauer, "Renal uptake of an 18-mer phosphorothioate oligonucleotide," Kidney Int'l, vol. 48, pp. 1226-1232 (1995), Exhibit No. 1191 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Oligonucleotide Cleavage and Deprotection Laboratory Notebook Entry, pp. 1, Exhibit No. 1138 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
"Efficacy Study of AVI-4658 to Induce Dystrophin Expression in Selected Duchenne Muscular Dystrophy Patients" ClinicalTrials.gov dated Jan. 22, 2013.
3rd Declaration of Erik J. Sontheimer, Ph.D. ("3rd S. Decl."), Pages 123, Exhibit No. 1186 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
King et al., "A Dictionary of Genetics," Oxford University Press, 4th Ed. (1990), Exhibit No. 1189 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
A Comparative Study on AONs between 20 and 50 Nucleotides Designed to Induce the Skipping of Exon 53 from the Dystrophin Pre-mRNA, pp. 6, Exhibit No. 1128 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
A Comparative Study on AONs Between 20 and 50 Nucleotides Designed to Induce the Skipping of Exon 51 from the Dystrophin Pre-mRNA, pp. 6, Exhibit No. 1127 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Analysis of Second PCR Product by Gel Electrophoresis, pp. 1, Exhibit No. 1182 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1958 Mass Spectrometry Data, pp. 7, Exhibit No. 1146 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1958 UPLC Data, pp. 2, Exhibit No. 1157 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1959 Mass Spectrometry Data, pp. 5, Exhibit No. 1147 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1959 UPLC Data, pp. 2, Exhibit No. 1158 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1960 Mass Spectrometry Data, pp. 8, Exhibit No. 1148 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1960 UPLC Data, pp. 2, Exhibit No. 1159 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1961 Mass Spectrometry Data, pp. 5, Exhibit No. 1149 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1961 UPLC Data, pp. 2, Exhibit No. 1160 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1962 Mass Spectrometry Data, pp. 7, Exhibit No. 1150 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1962 UPLC Data, pp. 2, Exhibit No. 1161 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1963 Mass Spectrometry Data, pp. 10, Exhibit No. 1151 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1963 UPLC Data, pp. 2, Exhibit No. 1162 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1964 Mass Spectrometry Data, pp. 13, Exhibit No. 1152 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1964 UPLC Data, pp. 2, Exhibit No. 1163 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1965 Mass Spectrometry Data, pp. 9, Exhibit No. 1153 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1965 UPLC Data, pp. 2, Exhibit No. 1164 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1966 Mass Spectrometry Data, pp. 8, Exhibit No. 1154 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1966 UPLC Data, pp. 2, Exhibit No. 1165 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1967 Mass Spectrometry Data, pp. 7, Exhibit No. 1155 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS1967 UPLC Data, pp. 2, Exhibit No. 1166 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS229 (h53AON1) HPLC Chromatograph pp. 2, Exhibit No. 1140 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS229 (h53AON1) HPLC Method Report, pp. 3, Exhibit No. 1139 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS229 (h53AON1) Mass Spectrometry Data, pp. 3, Exhibit No. 1142 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS229 (h53AON1) Synthesis Laboratory Notebook Entry, pp. 1, Exhibit No. 1137 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS229L (h53AON229L) Certificate of Analysis, pp. 1, Exhibit No. 1129 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
AON PS43 (h51AON1) Certificate of Analysis, pp. 2, Exhibit No. 1134 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS43 (h51AON1) HPLC Chromatogram, pp. 1, Exhibit No. 1131 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
AON PS43 (h51AON1) HPLC Method Report, pp. 4, Exhibit No. 1130 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
AON PS43 (h51AON1) Mass Spectrometry Data, pp. 3, Exhibit No. 1135 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AON PS43 (h51AON1) UPLC-UV Data, pp. 2, Exhibit No. 1136 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
AONs PS1958, PS1959, PS1960, PS1961, PS1962, PS1963, PS1964, PS1965, PS1966, and PS1967 HPLC Method Report, pp. 3, Exhibit No. 1143 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Bestas et al., "Design and Application of Bispecific Splice Switching Oligonucleotides," Nuc. Acid Therap., vol. 24, No. 1, pp. 13-24 (2014), Exhibit No. 1120 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Claim Chart U.S. Appl. No. 11/233,495, pp. 57, Exhibit No. 1216 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Claim Chart U.S. Appl. No. 13/550,210, pp. 45, Exhibit No. 1217 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Claim Comparison Chart—Claims 11 and 29 in U.S. Appl. No. 13/550,210, pp. 1, Exhibit No. 1226 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.

(56) **References Cited**

OTHER PUBLICATIONS

Claim Comparison Chart U.S. Appl. No. 13/550,210 vs U.S. Appl. No. 11/233,495, pp. 18, Exhibit No. 1218 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Claim Comparison Chart U.S. Appl. No. 13/550,210 vs U.S. Appl. No. 12/198,007, pp. 1, Exhibit No. 1219 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Confirmation of Dystrophin Exon 48 to 50 Deletion in Cell Line 8036 Laboratory Notebook Entry, pp. 3, Exhibit No. 1167 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Confirmation of Dystrophin Exon 52 Deletion in Cell Line R1809 Laboratory; Notebook Entry, pp. 3, Exhibit No. 1168 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Corrected Priority Statement filed by UWA in Int. No. 106,008 (as PN 219),pp. 5, Exhibit No. 1002 filed in Interference 106,013 on Feb. 17, 2015.
Cortes et al., "Mutations in the conserved loop of human U5 snRNA generate use of novel cryptic 5' splice sites in vivo," EMBO J., vol. 12, No. 13, pp. 5181-5189 (1993), Exhibit No. 1187 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Curriculum Vitae of Judith van Deutekom, pp. 6Exhibit No. 1126 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Decision on Appeal, Ex Parte Martin Gleave and Hideaki Miyake, Appeal No. 2005-2447, U.S. Appl. No. 09/619,908 (Jan. 31, 2006) (2009 WL 6927761 (Bd.Pat.App.& Interf.), pp. 12, Exhibit No. 1207 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Decision on Request for ReHearing, Ex Parte Roderick John Scott, Appeal No. 2008-004077, U.S. Appl. No. 10/058,825 (Jan. 6, 2010) (2010 WL 191079 (Bd.Pat.App. & Interf.),pp. 21, Exhibit No. 1208 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
PD-10 Desalting Columns, pp. 12, Exhibit No. 1141 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Pramono, "Induction of Exon Skipping of the Dystrophin Transcript in Lymphoblastoid Cells by Transfecting an Antisense Oligodeoxynucleotide Complementary to an Exon Recognition Sequence," Biochem. and Biophy. Res. Comm., vol. 226, pp. 445-449 (1996), Exhibit No. 1192 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Proliferation and Differentiation of Myoblast Cultures, pp. 3, Exhibit No. 1169 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Prosensa Press Release, dated Oct. 10, 2014 (2 pages), Exhibit No. 1203 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Raz et al. v. *Davis et al.*, Board of Patent Appeals and Inteferences, Patent and Trademark Office, Int. No. 105,712, Tech. Ctr. 1600, Sep. 29, 2011 (24 pages) (2011 WL 4568986 (Bd.Pat.App. & Intern, Exhibit No. 1209 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Rhodes et al., "BioMarin Bulks Up," BioCentury, pp. 6-8 (Dec. 2014), Exhibit No. 1193 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
RNA Isolation Using RNA-BEE, pp. 1, Exhibit No. 1175 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Roest et al., "Application of in Vitro Myo-Differentiation of Non-Muscle Cells to Enhance Gene Expression and Facilitate Analysis of Muscle Proteins," Neuromuscul. Disord., vol. 6, No. 3, pp. 195-202 (May 1996), Exhibit No. 1124 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Sarepta Therapeutics Press Release, dated Jan. 12, 2015, Exhibit No. 1119 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Sarepta, "Sarepta Therapeutics Reports Long-Term Outcomes through 144 Weeks from Phase IIb Study of Eteplirsen in Duchenne Muscular Dystrophy," press release, http://investorrelations.sarepta.com/phoenix.zhtml?c=64231& p=irol-newsArticle&id=1946426, 8 pages, dated Jul. 10, 2014.
Second Written Opinion for Application No. PCT/AU2010/001520, 7 pages, dated Oct. 13, 2011.
Semi Quantitative Lab-on-Chip Analysis of Second PCR Product, pp. 1, Exhibit No. 1183 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Sequence Listing—U.S. Appl. No. 13/550,210, as filed Jul. 16, 2012 (9 pages), Exhibit No. 1205 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Shabanpoor et al., "Bi-specific splice-switching PMO oligonucleotides conjugated via a single peptide active in a mouse model of Duchenne muscular dystrophy," Nucleic Acids Res., pp. 1-11 (Dec. 2014), Exhibit No. 1114 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Siemens Healthcare Diagnostics, Inc. v. *Enzo Life Sciences, Inc.*, 2013 WL 4411227, 11 [Parallel cite: U.S.D.C., D. Mass., Civil No. 10-40124-FDS], Decided Aug. 14, 2013 (12 pages); [Cited as: 2013 WL 4411227], Exhibit No. 1210 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Sontheimer et al., "Metal ion catalysis during group II intron self-splicing: parallels with the spliceosome," Genes & Development, vol. 13, pp. 1729-1741 (1999), Exhibit No. 1195 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Sontheimer et al., "Three Novel Functional Variants of Human U5 Small Nuclear RNA," vol. 12, No. 2, pp. 734-746 (Feb. 1992), Exhibit No. 1194 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Standard Operating Procedure FPLC Desalting, pp. 3, Exhibit No. 1144 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Summary of Professional Experience (Dr. Erik J. Sontheimer), pp. 4, Exhibit No. 1223 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Suter et al., Double-target antisense U7 snRNAs promote efficient skipping of an aberrant exon in three human ?—thalassemic mutations, 8:13 Human Molecular Genetics 2415-2423 (1999)(Exhibit No. 1083 filed in interference 106,007 on Dec. 23, 2014.
Table 1: Primer and Product Details for Exon 51 and 53 Reports on AONs of 20 to 50 Nucleotides dd Jan. 7, 2015, pp. 2, Exhibit No. 1177 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
Takeshima et al., "Oligonucleotides against a splicing enhancer sequence led to dystrophin production in muscle cells from a Duchenne muscular dystrophy patient," Brain & Dev., vol. 23, pp. 788-790 (2001), Exhibit No. 1196 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
The Regents of the University of California v. *Dako North America, Inc.*, U.S.D.C., N.D. California, No. C05-03955 MHP, Apr. 22, 2009 (2009 WL 1083446 (N.D.Cal.), Exhibit No. 1206 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
Transcript of Dec. 12, 2014 Teleconference with Administrative Patent Judge Schafer (rough draft) (previously filed in Int. No. 106,008 as Ex. 2114), pp. 23 Exhibit No. 1001 filed in Interference 106,013 on Feb. 17, 2015.
Transcript of the Jan. 21, 2015 deposition of Erik Sontheimer, Ph.D., Patent Interference Nos. 106,007 and 106,008, 98 pages, dated Jan. 21, 2015 (Exhibit No. 2122 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
Transfection of AON, pp. 1, Exhibit No. 1170 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.
U.S. Food and Drug Administration Statement, dated Dec. 30, 2014 (2 pages), Exhibit No. 1204 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden List of Exhibits, 18 pages, Patent Interference No. 106,007, (Doc 391), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden List of Exhibits, 18 pages, Patent Interference No. 106,008, (Doc 398), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden List of Exhibits, 3 pages, Patent Interference No. 106,013, (Doc 147), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden Opposition 1 (35 U. S.C. § 112(a)), 83 pages, Patent Interference No. 106,008, (Doc 400), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden Opposition 1 (35 U. S.C. § 112(a)), 93 pages, Patent Interference No. 106,007, (Doc 392), dated Feb. 17, 2015.

(56) **References Cited**

OTHER PUBLICATIONS

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden Opposition 1 (Standing Order ¶ 203.1 and 37 C.F.R. § 41.202(a) and (e)), 20 pages, Patent Interference No. 106,013, (Doc 148), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden Opposition 2 (Indefiniteness), 31 pages, Patent Interference No. 106,007, (Doc 396), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden Opposition 2 (Indefiniteness), 32 pages, Patent Interference No. 106,008, (Doc 401), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden Opposition 3 (35 U. S.C. §135(b)), 44 pages, Patent Interference No. 106,008, (Doc 397), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden Opposition 3 (Standing Order § 203.1 and 37 C.F.R. § 41.202(a) and (e)), 20 pages, Patent Interference No. 106,007, (Doc 389), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden Responsive Motion 4 (To Add Two New Claims), 57 pages, Patent Interference No. 106,008, (Doc 245), dated Dec. 23, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academisch Ziekenhuis Leiden Responsive Motion 4 (To Add Two New Claims), 65 pages, Patent Interference No. 106,007, (Doc 241), dated Dec. 23, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academish Ziekenhuis Leiden Supplemental Notice of Real Party in Interest, pp. 3, DOC 149, Patent Interference No. 106,013 dated Feb. 23, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academish Ziekenhuis Leiden Supplemental Notice of Real Party in Interest, pp. 3, Doc 413, Patent Interference No. 106,0007 dated Feb. 23, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Academish Ziekenhuis Leiden Supplemental Notice of Real Party in Interest, pp. 3, Doc 421, Patent Interference No. 106,0008 dated Feb. 23, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Amendment and Response, U.S. Appl. No. 11/233,495, filed Jan. 22, 2014, 8 pages, (Exhibit No. 2117 filed in interferences 106,007 and 106, 008, on Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Exhibit List, 10 pages, Patent Interference No. 106,007 dated Dec. 23, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Exhibit List, 10 pages, Patent Interference No. 106,008, dated Dec. 23, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Responsive Motion, 57 pages, Patent Interference No. 106,008, dated Dec. 23, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Responsive Motion, 65 pages, Patent Interference No. 106,007 dated Dec. 23, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Joint Stipulation regarding Time Periods 2, 3 and 4, 3 pages, Patent Interference No. 106,013, (Doc 135), dated Jan. 25, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Joint Stipulation regarding Time Periods 3-4, 4 pages, Patent Interference No. 106,007, (Doc 243), dated Jan. 29, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Joint Stipulation regarding Time Periods 3-4, 4 pages, Patent Interference No. 106,008, (Doc 247), dated Jan. 29, 2015.
Heemskerk, Hans et al., "In Vivo Comparison of 2'-O-Methyl phhosphorothioate and Morpholino Antisense Oligonucleotides for Duchenne Muscular Dystrophy Exon Skipping," Journal of Gene Medicine, John Wiley & Sons, Inc, vol. 11(3):257-266 (2009).
US Application for Letters Patent for U.S. Appl. No. 11/233,495 as-filed and preliminary amendment, 77 pages, dated Sep. 21, 2005 (Exhibit No. 2095 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
Preliminary Amendment for U.S. Appl. No. 12/198,007, 3 pages, dated Nov. 7, 2008 (Exhibit No. 2067 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Preliminary Amendment and application as-filed for U.S. Appl. No. 12/976,381, 68 pages, dated Dec. 22, 2010).
Preliminary Amendment for U.S. Appl. No. 12/976,381, 4 pages, dated Dec. 22, 2010 (Exhibit No. 2066 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US application as-filed and Preliminary Amendment for U.S. Appl. No. 13/550,210, 59 pages dated Jul. 16, 2012 (Exhibit No. 2087 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Preliminary Remarks for U.S. Appl. No. 14/198,992, 1 page, dated Mar. 6, 2014 (Exhibit No. 2097 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Proposed Terminal Disclaimer for U.S. Appl. No. 12/860,078, 2 pages, dated Oct. 17, 2014 (Exhibit No. 2001 filed in interferences 106008 on Oct. 17, 2014).
US Remarks for U.S. Appl. No. 14/248,279, 2 pages, dated Aug. 27, 2014 (Exhibit No. 2110 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Response and amendments for U.S. Appl. No. 13/550,210, 12 pages, dated Jan. 21, 2014 (Exhibit No. 2063 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US claim amendments for U.S. Appl. No. 13/550,210, 3 pages, dated May 12, 2014 (Exhibit No. 2078 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
U.S. Appl. No. 13/550,210, 12 pages; excerpts of prosecution history including: Response and Amendment dated May 12, 2014; Response to Non-Final Office Action dated Jan. 21, 2014; Second Preliminary Amendment dated Jan. 3, 2013 (Exhibit No. 2055 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Revised Figure 4H, U.S. Appl. No. 13/271,080, 1 page (Exhibit No. 1050 filed in interferences 106008, 106007 on Nov. 18, 2014).
US Second Preliminary Amendment for U.S. Appl. No. 13/550,210, 5 pages, dated Jan. 3, 2013.
US Terminal Disclaimer for U.S. Appl. No. 14/248,279, 1 page, dated Aug. 7, 2014 (Exhibit No. 2109 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Terminal Disclaimer for U.S. Appl. No. 14/198,992, 1 page, dated Jul. 15, 2014 (Exhibit No. 2096 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Track One Request, Application as-filed, and Application Data Sheet for U.S. Appl. No. 14/248,279, 68 pages, dated Apr. 8, 2014 (Exhibit No. 2108 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Transmittal, application as-filed, and Preliminary Amendment for U.S. Appl. No. 11/570,691, 102 pages, dated Dec. 15, 2006 (Exhibit No. 2103 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Transmittal, application as-filed, and Preliminary Amendment for U.S. Appl. No. 13/271,080, 115 pages, dated Oct. 11, 2011 (Exhibit No. 2111 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Updated Filing Receipt for U.S. Appl. No. 13/550,210, 3 pages, dated Dec. 11, 2012 (Exhibit No. 2044 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Transmittal, application as-filed, and Preliminary Amendment for U.S. Appl. No. 13/270,992, 101 pages, dated Oct. 11, 2011 (Exhibit No. 2098 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
US Application as-filed for U.S. Appl. No. 14/198,992, 52 pages, dated Mar. 6, 2014 (Exhibit No. 2086 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
PCT Application as-filed for application No. PCT/NL03/00214, 64 pages, dated Sep. 21, 2005 (Exhibit No. 2042 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).
University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Exhibit List, 7 pages, Patent Interference Nos. 106,007 and 106,008, dated Dec. 12, 2014.

(56) **References Cited**

OTHER PUBLICATIONS

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Miscellaneous Order under 37 CFR 41.104(a), 4 pages, Patent Interference Nos. 106,007 and 106,008, dated Dec. 15, 2014.

UWA submission of teleconference transcript, 28 pages, dated Dec. 12, 2014 (Exhibit No. 2114 filed in interferences 106008 and 106007 on Dec. 12, 2014).

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Miscellaneous motion 1, 5 pages, Patent Interference No. 106,008, dated Oct. 17, 2014.

U.S. Appl. No. 12/198,007 as-filed, 104 pages, dated Aug. 25, 2008 (Exhibit No. 2092 filed in interferences 106008, 106013, and 106007 on Nov. 18, 2014).

Aartsma-Rus, Annemieke et al., "194th ENMC international workshop. 3rd ENMC workshop on exon skipping: Towards clinical application of antisense-mediated exon skipping for Duchenne muscular dystrophy Dec. 8-10, 2012, Naarden, The Netherlands," Neuromuscular Disorders, vol. 23:934-944 (2013).

Aartsma-Rus, Annemieke et al., "Functional Analysis of 114 Exon-Internal AONs for Targeted DMD Exon Skipping: Indication for Steric Hindrance of SR Protein Binding Sites," Oligonucleotides, vol. 15:284-297 (2005) (Exhibit No. 2016 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Aartsma-Rus, Annemieke et al., "Guidelines for Antisense Oligonucleotide Design and Insight Into Splice-modulating Mechanisms," Molecular Therapy, vol. 17(3):548-553 (2009) (Exhibit No. 2014 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Agrawal, Sudhir et al., "GEM 91—An Antisense Oligonucleotide Phosphorothioate as a Therapeutic Agent for AIDS," Antisense Research and Development, vol. 2:261-266 (1992).

Alignments of Dystrophin mRNA and Oligonucleotides, 6 pages, submitted to the Patent Trial and Appeal Board in interference No. 106008, dated Nov. 18, 2014 (Exhibit No. 1054 filed in interferences 106008, 106007 on Nov. 18, 2014).

Anthony, Karen et al., "Dystrophin quantification: Biological and Translational Research Implications," Neurology, vol. 83:1-8 (2014) (Exhibit No. 2028 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Australian Application No. 2004903474, 36 pages, dated Jul. 22, 2005 (Exhibit No. 1004 filed in interferences 106008, 106007 on Nov. 18, 2014).

Bellare, Priya et al., "A role for ubiquitin in the spliceosome assembly pathway," Nature Structural & Molecular Biology, vol. 15(5):444-451 (2008) (Exhibit No. 1057 filed in interferences 106008, 106007 on Nov. 18, 2014).

Bellare, Priya et al., "Ubiquitin binding by a variant Jab1/MPN domain in the essential pre-mRNA splicing factor Prp8p," RNA, vol. 12:292-302 (2006) (Exhibit No. 1056 filed in interferences 106008,106007 on Nov. 18, 2014).

Bennett, C. Frank et al., "RNA Targeting Therapeutics: Molecular Mechanisms of Antisense Oligonucleotides as a Therapeutic Platform," Annu. Rev. Pharmacol. Toxicol., vol. 50:259-293 (2010) (Exhibit No. 1025 filed in interferences 106008, 106007 on Nov. 18, 2014).

Braasch, Dwaine A. et al., "Locked nucleic acid (LNA): fine-tuning the recognition of DNA and RNA," Chemistry & Biology, vol. 8:1-7 (2001) (Exhibit No. 2009 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Braasch, Dwaine A. et al., "Novel Antisense and Peptide Nucleic Acid Strategies for Controlling Gene Expression," Biochemistry, vol. 41(14):4503-4510 (2002) (Exhibit No. 2006 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Bremmer-Bout, Mattie et al., "Targeted Exon Skipping in Transgenic hDMD Mice: A Model for Direct Preclinical Screening of Human-Specific Antisense Oligonucleotides," Molecular Therapy, vol. 10(2):232-240 (2004) (Exhibit No. 2024 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Claim Chart, U.S. Patent No. 7,807,816, 14 pages (Exhibit No. 1063 filed in interferences 106008, 106007 on Nov. 18, 2014).

Claim Chart, U.S. Patent No. 7,960,541, 17 pages (Exhibit No. 1064 filed in interferences 106008, 106007 on Nov. 18, 2014).

Claim Chart, U.S. Patent No. 8,455,636, 32 pages (Exhibit No. 1062 filed in interferences 106008, 106007 on Nov. 18, 2014).

Corey, David R. et al., Morpholino antisense oligonucleotides: tools for investigating vertebrate development, Genome Biology, vol. 2(5):1015.1-1015.3 (2001) (Exhibit No. 1026 filed in interferences 106008, 106007 on Nov. 18, 2014).

Crooke, Stanley T., Antisense Drug Technology, Principles, Strategies, and Applications, Marcel Dekker, Inc., New York, Chapters 15 and 16, pp. 375-389, 391-469 (2001) (Exhibit No. 2075 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Curriculum Vitae, Erik Joseph Sontheimer, 18 pages, dated Sep. 29, 2014 (Exhibit No. 1013 filed in interferences 106008, 106007 on Nov. 18, 2014).

CV, Professor Matthew J.A. Wood, 3 pages (Exhibit No. 2003 filed in interferences 106008, 106007 on Nov. 18, 2014).

Davis, Richard J. et al., "Fusion of PAX7 to FKHR by the Variant t(1;13)(p36;q14) Translocation in Alveolar Rhabdomyosarcoma," Cancer Research, vol. 54:2869-2872 (1994) (Exhibit No. 1027 filed in interferences 106008, 106007 on Nov. 18, 2014).

Douglas, Andrew G.L. et al., "Splicing therapy for neuromuscular disease," Molecular and Cellular Neuroscience, vol. 56:169-185 (2013) (Exhibit No. 2005 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Eckstein, F., "Nucleoside Phosphorothioates," Ann. Rev. Biochem., vol. 54:367-402 (1985) (Exhibit No. 1028 filed in interferences 106008, 106007 on Nov. 18, 2014).

Flanigan, Kevin M. et al., "Pharmacokinetics and safety of single doses of drisapersen in non-ambulant subjects with Duchenne muscular dystrophy: Results of a double-blind randomized clinical trial," Neuromuscular Disorders, vol. 24:16-24 (2014) (Exhibit No. 2038 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Fragall, Clayton T. et al., "Mismatched single stranded antisense oligonucleotides can induce efficient dystrophin splice switching," BMC Medical Genetics, vol. 12:141, 8 pages (2011) (Exhibit No. 2019 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Frazier, Kendall S. et al., "Species-specific Inflammatory Responses as a Primary Component for the Development of Glomerular Lesions in Mice and Monkeys Following Chronic Administration of a Second-generation Antisense Oligonucleotide," Toxicologica Pathology, 13 pages (2013).

GlaxoSmithKline, "GSK and Prosensa announce start of Phase III study of investigational Duchenne Muscular Dystrophy medication," press release, 6 pages, dated Jan. 19, 2011 (Exhibit No. 2060 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

GlaxoSmithKline, Prosensa regains rights to drisapersen from GSK and retains rights to all other programmes for the treatment of Duchenne muscular dystrophy (DMD), press release, 4 pages, dated Jan. 13, 2014.

Goemans, Nathalie M. et al., "Systemic Administration of PRO051 in Duchenne's Muscular Dystrophy," The New England Journal of Medicine, vol. 364:1513-1522 (2011) (Exhibit No. 2036 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Gordon, Peter M. et al., "Metal ion catalysis during the exon-ligation step of nuclear pre-mRNA splicing: Extending the parallels between the spliceosome and group II introns," RNA, vol. 6:199-205 (2000) (Exhibit No. 1055 filed in interferences 106008, 106007 on Nov. 18, 2014).

Hammond, Suzan M. et al., "Correlating in Vitro Splice Switching Activity With Systemic in Vivo Delivery Using Novel ZEN-modified Oligonucleotides," Molecular Therapy—Nucleic Acids, vol. 3:1, 11 pages (2014) (Exhibit No. 2011 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Harding, PL et al., "The Influence of Antisense Oligonucleotide Length on Dystrophin Exon Skipping," Molecular Therapy, vol. 15(1):157-166 (2007) (Exhibit No. 1030 filed in interferences 106008, 106007 on Nov. 18, 2014).

Heemskerk, Hans A. et al., "In vivo comparison of 2'-O-methyl phosphorothioate and morpholino antisense oligonucleotides for Duchenne muscular dystrophy exon skipping," The Journal of Gene

(56) **References Cited**

OTHER PUBLICATIONS

Medicine, vol. 11:257-266 (2009) (Exhibit No. 2020 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Heid, Christian A. et al., "Real Time Quantitative PCR," Genome Research, vol. 6:986-994 (1996) (Exhibit No. 1061 filed in interferences 106008, 106007 on Nov. 18, 2014).

Herschlag, Daniel et al., "Contributions of 2'Hydroxyl Groups of the RNA Substrate to Binding and Catalysis by the Tetrahymena Ribozyme: An Energetic Picture of an Active Site Composed of RNA," Biochemistry, vol. 32:8299-8311 (1993) (Exhibit No. 1031 filed in interferences 106008, 106007 on Nov. 18, 2014).

Hudziak, Robert M. et al., "Antiproliferative Effects of Steric Blocking Phosphorodiamidate Morpholino Antisense Agents Directed against c-myc," Antisense & Nucleic Acid Drug Development, vol. 10:163-176 (2000) (Exhibit No. 1026 filed in interferences 106008, 106007 on Nov. 18, 2014).

ISIS Pharmaceuticals website, 2 pages, http://www.isispharm.com/Pipeline/Therapeutic-Areas/Other.htm (2014) (Exhibit No. 2021 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Iversen, Patrick L. et al., "Efficacy of Antisense Morpholino Oligomer Targeted to c-myc in Prostate Cancer Xenograft Murine Model and a Phase I Safety Study in Humans," Clinical Cancer Research, vol. 9:2510-2519 (2003).

Jarver, Peter et al., "A Chemical View of Oligonucleotides for Exon Skipping and Related Drug Applications," Nucleic Acid Therapeutics, vol. 24(1):37-47 (2014) (Exhibit No. 2061 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Jason, Tracey L.H. et al., "Toxicology of antisense therapeutics," Toxicology and Applied Pharmacology, vol. 201:66-83 (2004) (Exhibit No. 2027 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Karlen, Yann et al., "Statistical significance of quantitative PCR," BMC Bioinformatics, 8:131, 16 pages (2007) (Exhibit No. 1033 filed in interferences 106008, 106007 on Nov. 18, 2014).

Koenig, M. et al., "The Complete Sequence of Dystrophin Predicts a Rod-Shaped Cytoskeleton Protein," Cell, vol. 53:219-228 (1988) (Exhibit No. 1010 filed in interferences 106008, 106007 on Nov. 18, 2014).

Koenig, M. et al., "The Molecular Basis for Duchenne versus Becker Muscular Dystrophy: Correlation of Severity with Type of Deletion," Am. J. Hum. Genet, vol. 45:498-506 (1989) (Exhibit No. 1011 filed in interferences 106008, 106007 on Nov. 18, 2014).

Koshkin, Alexei A. et al., "LNA (Locked Nucleic Acids): Synthesis of the Adenine, Cytosine, Guanine, 5-Methylcytosine, Thymine and Uracil Bicyclonucleoside Monomers, Oligomerisation, and Unprecedented Nucleic Acid Recognition," Tetrahedron, vol. 54:3607-3630 (1998) (Exhibit No. 2007 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

McCarville, M. Beth et al., "Rhabdomyosarcoma in Pediatric Patients: The Good, the Bad, and the Unusual," AJR, vol. 176:1563-1569 (2001) (Exhibit No. 1034 filed in interferences 106008, 106007 on Nov. 18, 2014).

Mendell, Jerry R. et al., "Eteplirsen for the Treatment of Duchenne Muscular Dystrophy," Ann. Neurol., vol. 74:637-647 (2013) (Exhibit No. 2058 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Mendell, Jerry R. et al., "Eteplirsen in Duchenne Muscular Dystrophy (DMD): 144 Week Update on Six-Minute Walk Test (6MWT) and Safety," slideshow, presented at the 19th International Congress of the World Muscle Society, 17 pages (2014) (Exhibit No. 2059 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Muntoni, Francesco et al., "128th ENMC International Workshop on 'Preclinical optimization and Phase I/II Clinical Trials Using Antisense Oligonucleotides in Duchenne Muscular Dystrophy' Oct. 22-24, 2004, Naarden, The Netherlands," Neuromuscular Disorders, vol. 15:450-457 (2005) (Exhibit No. 2025 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Muntoni, Francesco et al., "149th ENMC International Workshop and 1st TREAT-NMD Workshop on: 'Planning Phase I/II Clinical trials using Systemically Delivered Antisense Oligonucleotides in Duchenne Muscular Dystrophy,'" Neuromuscular Disorders, vol. 18:268-275 (2008).

Oligonucleotide diagrams, 5 pages (Exhibit No. 1053 filed in interferences 106008, 106007 on Nov. 18, 2014).

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Exhibit list, 7 pages, Patent Interference No. 106,007, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL List of Exhibits, 9 pages, Patent Interference No. 106,007, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Motion 1 (for Judgement Under 35 U.S.C., section 112(a)), 40 pages, Patent Interference No. 106,007, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Motion 3, 36 pages, Patent Interference No. 106,007, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Notice of Filing Priority Statement, 2 pages, Patent Interference No. 106,007, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Motion 1 (For Judgement that UWA's Claims are Unpatentable), 69 pages, Patent Interference No. 106,007, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Motion 2 (For Judgement Under 35 U.S.C. section 112(b)), 34 pages, Patent Interference No. 106,007, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Motion 2 (To Deny UWA the Benefit of AU 2004903474), 23 pages, Patent Interference No. 106,007, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Motion 3 (For Judgement of Unpatentability based on Myriad), 19 pages, Patent Interference No. 106,007, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Order—Miscelaneous, 2 pages, Patent Interference Nos. 106,007, 106,008, 106,013, dated Nov. 14, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Motion 1 (To Maintain Interference between UWA U.S. Patent No. 8,486,907 and AZL U.S. Appl. No. 14/198,992), 45 pages, Patent Interference No. 106,013, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Exhibit list, 7 pages, Patent Interference No. 106,013, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Exhibit List as of Nov. 18, 2014, 7 pages, Patent Interference No. 106,008, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, Notice of Filing Priority Statement, 2 pages, Patent Interference No. 106,008, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Motion 3 (For Judgment of Unpatentability based on Myriad) 20 pages, Patent Interference No. 106,008, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Motion 1 (For judgment under 35 U.S.C. section 112(a)), 38 pages, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Motion 2 (To Deny UWA the Benefit of AU 2004903474), 24 pages, Patent Interference No. 106,008, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, List of Exhibits, as of Nov. 18, 2014, 9 pages, Patent Interference No. 106,008, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, AZL Motion 1 (For Judgment that UWA's Claims are Unpatentable Under 35 U.S.C. sections 102 and 103, 69 pages, Patent Interference No. 106,008, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Motion 2 (For Judgment Under 35 U.S.C. section 112(b)), 32 pages, Patent Interference No. 106,008, dated Nov. 18, 2014.

University of Western Australia v. *Academisch Ziekenhuis Leiden*, UWA Motion 3 (For judgment that Claims 11-12, 14-15, and 17-29 of U.S. Appl. No. 13/550,210 are barred under 35 U.S.C. section 135(b)), 25 pages, Patent Interference No. 106,008, dated Nov. 18, 2014.

(56) **References Cited**

OTHER PUBLICATIONS

Patrick O. Brown and Tidear D. Shalon v. *Stephen P.A. Fodor, Dennis W. Solas and William J. Dower*: Interference Merits Panel, Interference No. 104,358, 24 pages, dated Aug. 9, 1999 (Exhibit No. 2113 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Abandonment for U.S. Appl. No. 13/902,376, 1 page, dated Jun. 12, 2014 (Exhibit No. 1047 filed in interferences 106008, 106007 on Nov. 18, 2014).

US Amendment for U.S. Appl. No. 11/233,495, 15 pages, dated Apr. 1, 2009 (Exhibit No. 2071 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Amendment for U.S. Appl. No. 11/233,495, 19 pages, dated Sep. 16, 2009 (Exhibit No. 2072 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Amendment for U.S. Appl. No. 11/233,495, 19 pages, dated Oct. 31, 2007 (Exhibit No. 2070 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Amendment for U.S. Appl. No. 11/570,691, 9 pages, dated Jun. 15, 2010 (Exhibit No. 1043 filed in interferences 106008, 106007 on Nov. 18, 2014).

US Amendment for U.S. Appl. No. 13/271,080, 30 pages, dated Jan. 30, 2013 (Exhibit No. 1049 filed in interferences 106008, 106007 on Nov. 18, 2014).

US Amendment for U.S. Appl. No. 13/902,376, 36 pages, dated Mar. 21, 2014 (Exhibit No. 1046 filed in interferences 106008, 106007 on Nov. 18, 2014).

US Amendment After Non-Final Action for U.S. Appl. No. 11/233,495, 31 pages, dated Jun. 24, 2010 (Exhibit No. 2073 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Amendments to the Claims for U.S. Appl. No. 11/233,495, 4 pages, dated May 8, 2014 (Exhibit No. 2077 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Amendment in Response to Advisory Action for U.S. Appl. No. 11/233,495, 23 pages, dated Mar. 14, 2011 (Exhibit No. 2074 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Response to Office Action and Amendments to the Claims for U.S. Appl. No. 13/550,210, 10 pages, dated May 12, 2014 (Exhibit No. 2064 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Amendments to the Claims for U.S. Appl. No. 14/198,992, 3 pages, dated Jul. 16, 2014 (Exhibit No. 2079 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Applicant-Initiated Interview Summary and Notice of Allowance for U.S. Appl. No. 13/550,210, 9 pages dated May 19, 2014 (Exhibit No. 2076 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Application as-filed, Application Data Sheet, and Preliminary Amendment for U.S. Appl. No. 12/837,359, 101 pages, dated Jul. 15, 2010 (Exhibit No. 2100 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Application as-filed and Claims for U.S. Appl. No. 11/233,495, 78 pages, dated Sep. 21, 2005 (Exhibit No. 2068 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Claims for U.S. Appl. No. 12/976,381, 1 page, dated Dec. 22, 2010 (Exhibit No. 2065 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Declaration of Richard K. Bestwick, for U.S. Appl. No. 11/570,691, 5 pages, dated Jun. 15, 2010 (Exhibit No. 1044 filed in interferences 106008, 106007 on Nov. 18, 2014).

US E-mail from Patent Trial and Appeal Board to Danny Huntington, 2 pages, dated Oct. 9, 2014 (Exhibit No. 2002 filed in interferences 106008 on Oct. 17, 2014).

U.S. Appl. No. 11/233,495, 74 pages; excerpts of prosecution history for including: US Supplemental Amendment and Response dated May 8, 2014; Second Supplemental Response dated Jul. 5, 2013; Supplemental Amendment dated Jun. 26, 2013; Amendment after Non-final Action dated Nov. 1, 2010; Amendment under 35 USC 1.114 dated Sep. 16, 2009 (Exhibit No. 2054 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Second Preliminary Amendment filed in U.S. Appl. No. 13/550,210, 5 pages, dated Jan. 3, 2013 (Exhibit No. 2062 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

U.S. Appl. No. 14/198,992, 17 pages; excerpts of prosecution history including: Supplemental Amendment dated Jul. 16, 2014; Response to Non-Final Office Action dated Jul. 14, 2014 (Exhibit No. 2056 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

U.S. Appl. No. 14/248,279, 29 pages; excerpts of prosecution history including: Amendment under 37 CFR 1.312 dated Sep. 19, 2014; Amendment in Response to Final Office Action dated Aug. 7, 2014; Declaration under 37 CFR 1.132 dated May 26, 2014; Declaration under 37 CFR 1.132 dated May 27, 2014; Response dated Jun. 3, 2014 (Exhibit No. 2057 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Amendment under 37 CFR 1.312 for U.S. Appl. No. 14/248,279, 5 pages, dated Sep. 19, 2014 (Exhibit No. 2053 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Non-Final Office Action for U.S. Appl. No. 11/570,691, 16 pages, dated Mar. 15, 2010 (Exhibit No. 1042 filed in interferences 106008, 106007 on Nov. 18, 2014).

US Office Action for U.S. Appl. No. 13/271,080, 25 pages, dated Jul. 30, 2012 (Exhibit No. 1048 filed in interferences 106008, 106007 on Nov. 18, 2014).

US Office Action for U.S. Appl. No. 13/550,210, 12 pages, dated Sep. 27, 2013 (Exhibit No. 2080 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

US Office Action for U.S. Appl. No. 13/902,376, 7 pages, dated Jan. 7, 2014 (Exhibit No. 1045 filed in interferences 106008, 106007 on Nov. 18, 2014).

US Preliminary Amendment for U.S. Appl. No. 11/233,495, 10 pages, dated Sep. 21, 2005 (Exhibit No. 2069 filed in interferences 106008, 106013, 106007 on Nov. 18, 2014).

Wang et al., "In Vitro evaluation of novel antisense oligonucleotides is predictive of in vivo exon skipping activity for Duchenne muscular dystrophy," J. Gene Medicine, vol. 12, pp. 354-364 (Mar. 2010), Exhibit No. 1115 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.

Watanabe et al., "Plasma Protein Binding of an Antisense Oligonucleotide Targeting Human ICAM-1 (ISIS 2302)," Oligonucleotides, vol. 16, pp. 169-180 (2006), Exhibit No. 1197 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.

Wilton et al. (2007) "Antisense Oligonucleotide-induced Exon Skipping Across the Human Dystrophin Gene Transcript," Molecular Therapy 15(7):1288-1296, 10 pages, (Exhibit No. 2121 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.

WO 2004/083432 (the published AZL PCT Application, "Van Ommen"), pp. 71, Exhibit No. 1003 filed in Interference 106,013 on Feb. 17, 2015.

Wood, "Toward an Oligonucleotide Therapy for Duchenne Muscular Dystrophy: A Complex Development Challenge," Science Translational Medicine, vol. 2, No. 25, pp. 1-6 (Mar. 2010), Exhibit No. 1116 filed in interferences 106,007 and 106,008 on Feb. 17, 2015, Doc 335.

Wyatt et al. "Site-specific cross-linking of mammalian U5 snRNP to the 5' splice site before the first step of pre-mRNA splicing," Genes & Development, vol. 6, pp. 2542-2553 (1992), Exhibit No. 1198 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.

Yin et al., "A fusion peptide directs enhanced systemic dystrophin exon skipping and functional restoration in dystrophin-deficient mdx mice," Human Mol. Gen., vol. 18, No. 22, pp. 4405-4414 (2009), Exhibit No. 1200 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.

Yin et al., "Cell Penetrating peptide-conjugated antisense cardiac dystrophin expression and function," Human Mol. Gen., vol. 17, No. 24, pp. 3909-3918 (2008), Exhibit No. 1199 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.

Yin et al., "Functional Rescue of Dystrophin-deficient mdx Mice by a Chimeric Peptide-PMO," Mol. Therapy, vol. 18, No. 10, pp. 1822-1829 (Oct. 2010), Exhibit No. 1117 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.

Yokota et al., "Efficacy of Systematic Morpholino Exon-Skipping in Duchenne Dystrophy Dogs," American Neurological Assoc., vol. 65, No. 6, pp. 667-676 (Jun. 2009), Exhibit No. 1214 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.

(56) **References Cited**

OTHER PUBLICATIONS

"Eteplirsen—Inhibitor of Dystrophin Expression—Treatment of Duchenne Muscular Dystrophy", Drugs of the Future, vol. 38(1):13-17 (2013).
2nd Expert Declaration of Dr. Erik Sontheimer ("2nd S Decl.") (Exhibit No. 1067 filed in interferences 106008, 106007 on Dec. 23, 2014).
Aartsma-Rus, Annemieke et al., "Antisense-induced exon skipping for duplications in Duchenne muscular dystrophy," BMC Medical Genetics, vol. 8:43, doi:10.1186/1471-2350-8-43, 9 pages (2007).
Abes, S. et al., "Efficient Splicing Correction by PNA Conjugation to an R6-Pentratin Delivery Peptide", Nucleic Acids Research vol. 35(13):4495-4502 (2007).
Alter, Julia et al., "Systemic delivery of morpholino oligonucleotide restores dystrophin expression bodywide and improves dystrophic pathology," Nature Medicine, vol. 12(2):175-177 (2006).
AZL's U.S. Appl. No. 14/295,311 and claims, as-filed Jun. 3, 2014 ("the '311 Application") (Exhibit No. 1077 filed in interferences 106008, 106007 on Dec. 23, 2014).
Beaucage, S.L. et al., "Deoxynucleoside Phosphoramidites—A New Class of Key Intermediates for Deoxypolynucleotide Synthesis," Tetrahedron Letters, vol. 22(20):1859-1862 (1981).
Canonico, A.E. et al., "Expression of a CMV Promoter Drive Human alpha-1 Antitrypsin Gene in Cultured Lung Endothelial Cells and in the Lungs of Rabbits," Clinical Research, vol. 39(2):219A (1991).
Doran, Philip et al., "Proteomic profiling of antisense-induced exon skipping reveals reversal of pathobiochemical abnormalities in dystrophic mdx diaphragm," Proteomics, vol. 9:671-685, DOI 10.1002/pmic.200800441 (2009).
European Office Action for Application No. 09752572.9, 5 pages, dated Feb. 29, 2012.
File Excerpt from AZL U.S. Appl. No. 11/233,495: Amendment After Non-Final Office Action, as-filed Nov. 1, 2010 (Exhibit No. 1085 filed in interferences 106008, 106007 on Dec. 23, 2014).
File Excerpt from AZL U.S. Appl. No. 11/233,495: Claims examined in Non-Final Office Action, dated Dec. 1, 2008 (Exhibit No. 1079 filed in interferences 106008, 106007 on Dec. 23, 2014).
File Excerpt from AZL U.S. Appl. No. 11/233,495: Final Office Action dated Aug. 31, 2010 (Exhibit No. 1086 filed in interferences 106008, 106007 on Dec. 23, 2014).
File Excerpt from U.S. Appl. No. 11/233,495: Non-Final Office Action dated Dec. 1, 2008 and Final Office Action dated Jun. 25, 2009 (Exhibit No. 1078 filed in interferences 106008, 106007 on Dec. 23, 2014).
File Excerpt from U.S. Appl. No. 12/198,007: AZL's Preliminary Amendment and Response, as-filed Nov. 7, 2008 (Exhibit No. 1075 filed in interferences 106008, 106007 on Dec. 23, 2014).
File Excerpt from U.S. Appl. No. 12/976,381: AZL's First Preliminary Amendment, as-filed Dec. 22, 2010 (Exhibit No. 1076 filed in interferences 106008, 106007 on Dec. 23, 2014).
Fletcher, Sue et al., "Dystrophin Isoforms Induction in Vivo by Antisense-mediated Alternative Splicing," Molecular Therapy, vol. 18(6):1218-1223 (2010).
Foster, Helen et al., "Genetic Therapeutic Approaches for Duchenne Muscular Dystrophy," Human Gene Therapy, vol. 23:676-687 (2012).
Fraley, Robert et al., "New generation of liposomes: the engineering of an efficient vehicle for intracellular delivery of nucleic acids," Trends Biochem., vol. 6:77-80 (1981).
Goyenvalle, Aurelie et al., "Prevention of Dystrophic Pathology in Severely Affected Dystrophin/Utrophin-deficient Mice by Morpholino-oligomer-mediated Exon-skipping," Molecular Therapy, vol. 18(1):198-205 (2010).
International Preliminary Report on Patentability and Written Opinion for Application No. PCT/US2009/061960, 8 pages, dated Apr. 26, 2011.
International Search Report and Written Opinion of the International Searching Authority issued in International Patent Application No. PCT/US2013/077216 dated dated Mar. 27, 2014.
International Search Report and Written Opinion of the International Searching Authority issued in International Patent Application No. PCT/US2014/029610 dated Sep. 18, 2014.
International Search Report and Written Opinion of the International Searching Authority issued in International Patent Application No. PCT/US2014/029689 dated Oct. 21, 2014.
International Search Report and Written Opinion of the International Searching Authority issued in International Patent Application No. PCT/US2014/029766 dated Oct. 21, 2014.
International Search Report for Application No. PCT/US2009/061960, 5 pages, dated Apr. 6, 2010.
Jearawiriyapaisarn, Natee et al., "Long-term improvement in mdx cardiomyopathy after therapy with peptide-conjugated morpholino oligomers," Cardiovascular Research, vol. 85:444-453 (2010).
Jearawiriyapaisarn, Natee et al., "Sustained Dystrophin Expression Induced by Peptide-conjugated Morpholino Oligomers in the Muscles of mdx Mice," Mol. Ther, vol. 16(9):1624-1629 (2008).
Kurreck J., "Antisense Technologies: Improvement Through Novel Chemical Modifications", European Journal of Biochemistry, vol. 270(8):1628-1644 (2003).
Mannino, Raphael J. et al., "Liposome Mediated Gene Transfer," BioTechniques, vol. 6(7):682-690 (1988).
Marshall, N.B. et al., "Arginine-rich cell-penetrating peptides facilitate delivery of antisense oligomers into murine leukocytes and alter pre-mRNA splicing," Journal of Immunological Methods, vol. 325:114-126 (2007).
Mendell, Jerry R. et al., "Gene therapy for muscular dystrophy: Lessons learned and path forward," Neuroscience Letters, vol. 527:90-99 (2012).
Moulton, H.M., "Compound and Method for Treating Myotonic Dystrophy," U.S. Appl. No. 12/493,140, 82 pages, filed Jun. 26, 2009.
Moulton, Hong M. et al., "Morpholinos and their peptide conjugates: Therapeutic promise and challenge for Duchenne muscular dystrophy," Biochimica et Biophysica Acta, vol. 1798:2296-2303 (2010).
Muntoni, Francesco et al., "149the ENMC International Workshop and 1st TREAT-NMD Workshop on: 'Planning Phase I/II Clinical trials using Systemically Delivered Antisense Oligonucleotides in Duchenne Muscular Dystrophy,'" Neuromuscular Disorders, vol. 18:268-275 (2008).
Popplewell, Linda J. et al., "Comparative analysis of antisense oligonucleotide sequences targeting exon 53 of the human DMD gene: Implications for future clinical trials," Neuromuscular Disorders, vol. 20(2):102-110 (2010).
Popplewell, Linda J. et al., "Design of Antisense Oligonucleotides for Exon Skipping of the Human Dystrophin Gene," Human Gene Therapy, vol. 19(4):407, Poster Presentation No. P-35 (2008).
Popplewell, Linda J. et al., "Design of phosphorodiamidate morpholino oligomers (PMOs) for the induction of exon skipping of the human DMD gene," Human Gene Therapy, vol. 19(10):1174, Poster Presentation No. P 203 (2008).
Popplewell, Linda J. et al., "Design of Phosphorodiamidate Morpholino Oligomers (PMOs) for the Induction of Exon Skipping of the Human DMD Gene," Molecular Therapy, vol. 17(3):554-561 (2009).
Popplewell, Linda J. et al., "Targeted Skipping of Exon 53 of the Human DMD Gene Recommendation of the Highly Efficient Antisense Oligonucleotide for Clinical Trial," Human Gene Therapy, vol. 17(3):399, Poster Presentation No. P 10 (2009).
Reexamination Certificate—U.S. Appl. No. 90/011,320, issued Mar. 27, 2012 (Exhibit No. 1072 filed in interferences 106008, 106007 on Dec. 23, 2014).
Scully, Michele et al., "Reviews of Phase II and Phase III Clinical Trials for Duchenne Muscular Dystrophy", Expert Opinion on Orphan Drugs, vol. 1(1):33-46 (2013).
Sequence of Exon 46 of Dystrophin Gene, 1 page, 2014.
Sequence of Exon 51 of Dystrophin Gene, 1 page, 2014.
Stanton, Robert et al., "Chemical Modification Study of Antisense Gapmers", Nucleic Acid Therapeutics, pp. 344-359 (2012).
Supplementary European Search Report for Application No. 10829367.1, 8 pages, dated May 22, 2013.
Suter et al., Double-target antisense U7 snRNAs promote efficient skipping of an aberrant exon in three human /3-thalassemic muta-

(56) **References Cited**

OTHER PUBLICATIONS

tions, 8:13 Human Molecular Genetics 2415-2423 (1999) (Exhibit No. 1083 filed in interferences 106008, 106007 on Dec. 23, 2014).
U.S. Appl. No. 12/198,007, as-filed Aug. 25, 2008 ("The '007 Application") (Exhibit No. 1073 filed in interferences 106008, 106007 on Dec. 23, 2014).
U.S. Appl. No. 12/976,381, as-filed Dec. 22, 2010 ("The '381 Application") (Exhibit No. 1074 filed in interferences 106008, 106007 on Dec. 23, 2014).
U.S. Patent Application Publication No. 2001/0056077 ("Matsuo") (Exhibit No. 1080 filed in interferences 106008, 106007 on Dec. 23, 2014).
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Joint Stipulation regarding Time Periods 3-4, 4 pages, Patent Interference No. 106,013, (Doc 243), dated Jan. 29, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Second Declaration of Matthew J. A. Wood, M.D., D. Phil., Patent Interference Nos. 106,007 and 106,008, 78 pages, dated Feb. 17, 2015 (Exhibit No. 2116 filed in interferences 106,007 and 106,008,on Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Statement Concerning Settlement Discussions, 3 pages, Patent Interference No. 106,007, (Doc 242), dated Dec. 30, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Statement Concerning Settlement Discussions, 3 pages, Patent Interference No. 106,008, (Doc 246), dated Dec. 30, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Statement Concerning Settlement Discussions, 3 pages, Patent Interference No. 106,013, (Doc 136), dated Dec. 30, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Statement Concerning Subsequent Settlement Discussion, 3 pages, Patent Interference No. 106,008, dated Dec. 30, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, Statement Concerning Subsequent Settlement Discussion, 3 pages, Patent Interference No. 106,013, dated Dec. 30, 2014.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, University of Western Australia Opposition 1 (Regarding Patentability Under 35 U.S.C. § 102/103), 38 pages, Patent Interference No. 106,007, (Doc 393), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, University of Western Australia Opposition 1 (Regarding Patentability Under 35 U.S.C. § 102/103), 39 pages, Patent Interference No. 106,008, (Doc 402), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, University of Western Australia Opposition 2 (To Retain UWA's Benefit of AU 2004903474), 31 pages, Patent Interference No. 106,008, (Doc 403), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, University of Western Australia Opposition 2 (To Retain UWA's Benefit of AU 2004903474), 37 pages, Patent Interference No. 106,007, (Doc 394), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, University of Western Australia Opposition 3 (Regarding Patentability Under 35 U.S.C. § 101), 22 pages, Patent Interference No. 106,007, (Doc 395), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, University of Western Australia Opposition 3 (Regarding Patentability Under 35 U.S.C. § 101), 22 pages, Patent Interference No. 106,008, (Doc 404), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, University of Western Australia Opposition 4 (To deny entry of AZL's Proposed New Claims 104 and 105), 36 pages, Patent Interference No. 106,007, (Doc 397), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, University of Western Australia Opposition 4 (To deny entry of AZL's Proposed New Claims 30 and 31), 36 pages, Patent Interference No. 106,008, (Doc 405), dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, University of Western Australia, Exhibit List as of Feb. 17, 2015, 8 pages, Patent Interference No. 106,007, (Doc No. 398) dated Feb. 17, 2015.
University of Western Australia v. *Academisch Ziekenhuis Leiden*, University of Western Australia, Exhibit List as of Feb. 17, 2015, 8 pages, Patent Interference No. 106,008, (Doc No. 406) dated Feb. 17, 2015.
U.S. Patent No. 8,450,474 (Wilton et al.), pp. 95, Exhibit No. 1087 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,455,634 (Wilton et al.) pp. 95, Exhibit No. 1088 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,455,635 (Wilton et al.), pp. 96, Exhibit No. 1089 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,476,423 (Wilton et al.), pp. 15, Exhibit No. 1111 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,501,703 (Bennett et al.), pp. 16, Exhibit No. 1090 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,501,704 (Mourich et al.), pp. 39, Exhibit No. 1091 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,524,676 (Stein et al.), pp. 28, Exhibit No. 1092 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,524,880 (Wilton et al.), pp. 89, Exhibit No. 1093 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,536,147 (Weller et al.), pp. 95, Exhibit No. 1094 filed in interferences 106,007 and 106,008 on Feb. 17, 2015,Doc 251.
U.S. Patent No. 8,592,386 (Mourich et al.), pp. 46, Exhibit No. 1095 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,618,270 (Iversen et al.), pp. 28, Exhibit No. 1096 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,637,483 (Wilton et al.), pp. 28, Exhibit No. 1097 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,697,858 (Iversen), pp. 95, Exhibit No. 1098 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,703,735 (Iversen et al.)pp. 73, Exhibit No. 1099 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,741,863 (Moulton et al.), pp. 68, Exhibit No. 1100 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,759,307 (Stein et al.), pp. 35, Exhibit No. 1101 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,779,128 (Hanson et al.), pp. 104, Exhibit No. 1102 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,785,407 (Stein et al.), pp. 35, Exhibit No. 1103 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,785,410 (Iversen et al.), pp. 20, Exhibit No. 1104 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,835,402 (Kole et al.), pp. 27, Exhibit No. 1105 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,865,883 (Sazani et al.), pp. 199, Exhibit No. 1106 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,871,918 (Sazani et al.), pp. 195, Exhibit No. 1107 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,877,725 (Iversen et al.), pp. 34, Exhibit No. 1108 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,895,722 (Iversen et al.), pp. 29, Exhibit No. 1109 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
U.S. Patent No. 8,906,872 (Iversen et al.), pp. 69, Exhibit No. 1110 filed in interferences 106,007 and 106,008 on Feb. 13, 2015.
USPTO "2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving . . . Natural Products" ("the March Guidance"), 19 pages, (Exhibit No. 2118 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
UWA Clean Claims and Sequence, as filed in Interference No. 106,007 on Aug. 1, 2014 (Paper 12), 8 pages, (Exhibit No. 2126 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.
UWA Clean Claims and Sequence, as filed in Interference No. 106,007 on Aug. 7, 2014 (Paper 12), 8 pages, (Exhibit No. 2127 filed in interferences 106,007 and 106,008 on Feb. 17, 2015.

(56) **References Cited**

OTHER PUBLICATIONS

UWA Motion 1 (For Judgment Under 35 § 112(a)) from Int. No. 106,007 (PN 210), pp. 40, Exhibit No. 1005 filed in Interference 106,013 on Feb. 17, 2015.

UWA Motion 1 (For Judgment Under 35 § 112(a)) from Int. No. 106,008 (PN 213), pp. 38, Exhibit No. 1004 filed in Interference 106,013 on Feb. 17, 2015.

van Deutekom et al., "Local Dystrophin Restoration with Antisense Oligonucleotide PRO051," N. Engl. J. Med., vol. 357, No. 26, pp. 2677-2686 (Dec. 2007), Exhibit No. 1213 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.

Wahlestedt et al., "Potent and nontoxic antisense oligonucleotides containing locked nucleid acids," PNAS, vol. 97, No. 10, pp. 5633-5638 (May 2000), Exhibit No. 1201 filed in Interferences 106,007 and 106,008 on Feb. 17, 2015.

GlaxoSmithKline, Prosensa regains rights to drisapersen from GSK and retains rights to all other programmes for the treatment of Duchenne muscular dystrophy (DMD), (Exhibit 2040 in Interferences 106007, 106008, and 106013 on Nov. 18, 2014) press release, 4 pages, dated Jan. 13, 2014.

Standard Operating Procedure FPLC Desalting, pp. 6, Exhibit No. 1144 filed in Interferences 106,007 and 106,008 on Feb. 16, 2015.

* cited by examiner

FIGURE 1

bp
Acceptor
ESE
Donor
ucaugcacugagugaccucuuucucgcagGCGCUAGCUGGAGGCA////CCGUGCAGACUGACGgucucau
SEQ ID NO:213
SEQ ID NO:214

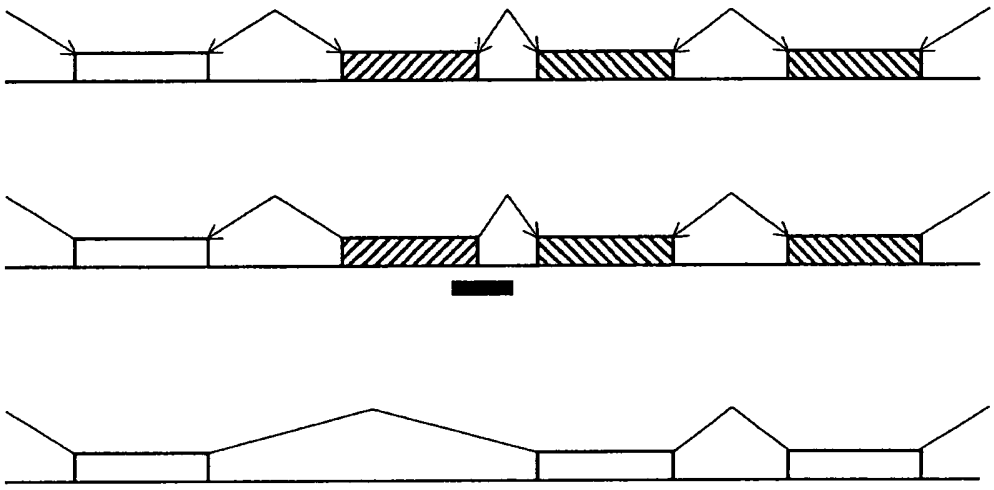


FIGURE 2

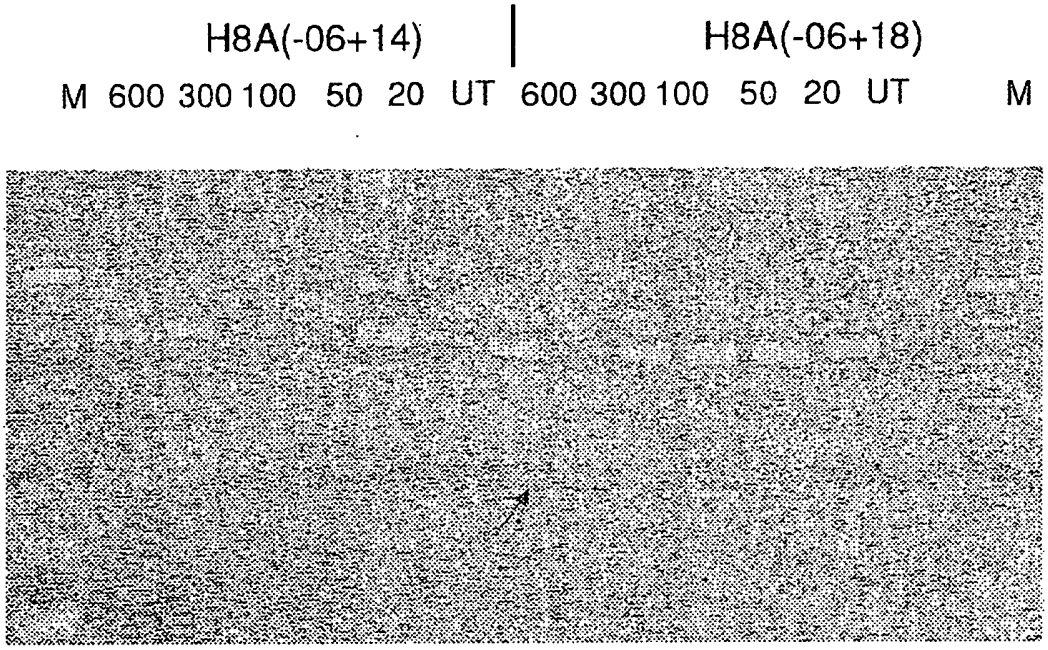


FIGURE 3

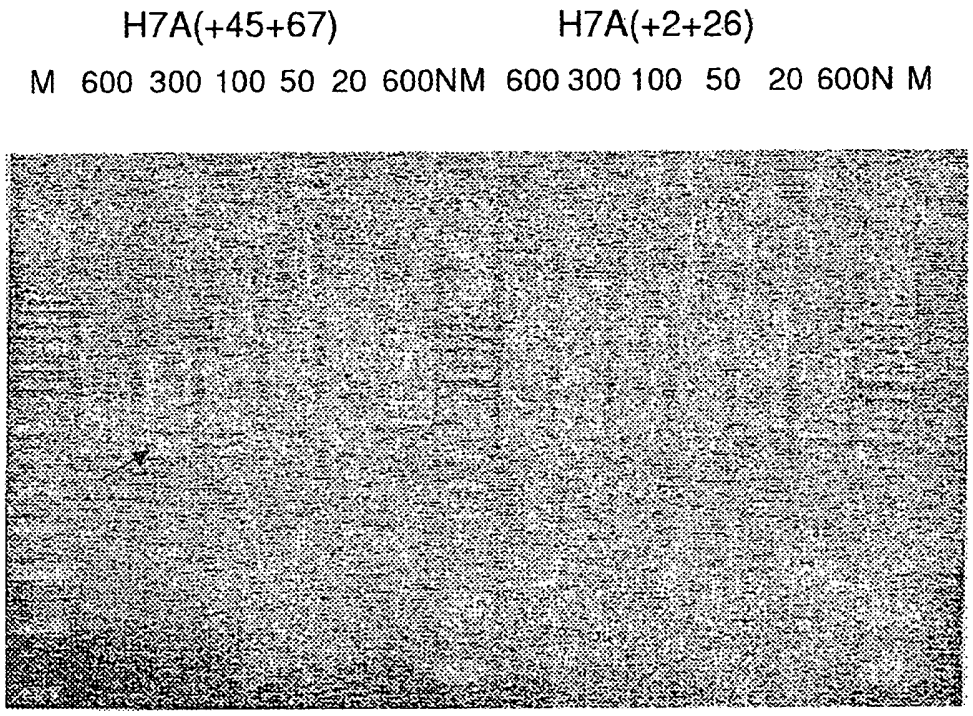

H7A(+45+67)
H7A(+2+26)
M 600 300 100 50 20 600NM 600 300 100 50 20 600N M

FIGURE 4

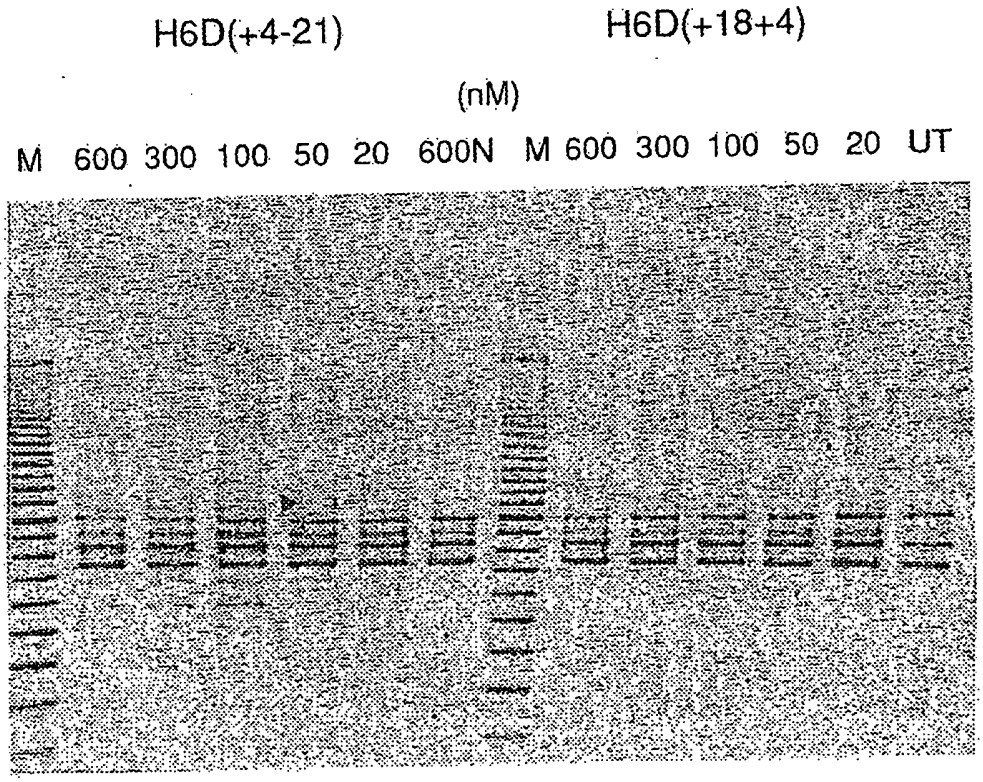


FIGURE 5

6A(+69+91)

M 600 300 200 100 50 20 UT

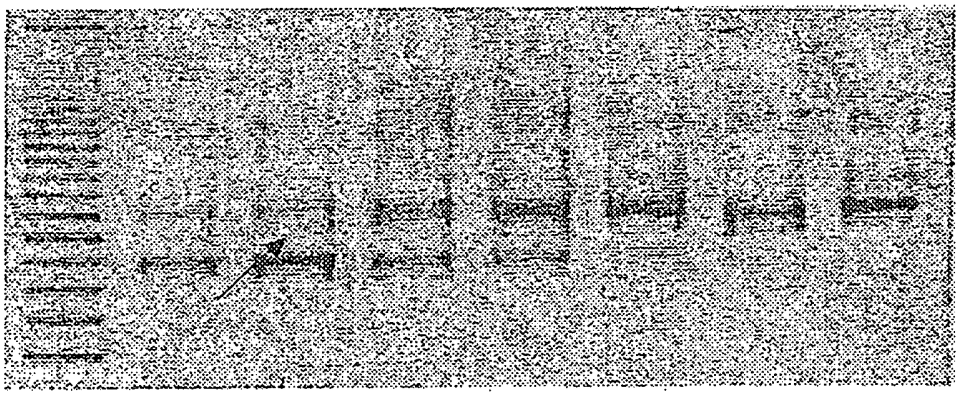


FIGURE 6

H4A(+13+32)

M 600 300 100 50 20 UT Neg M

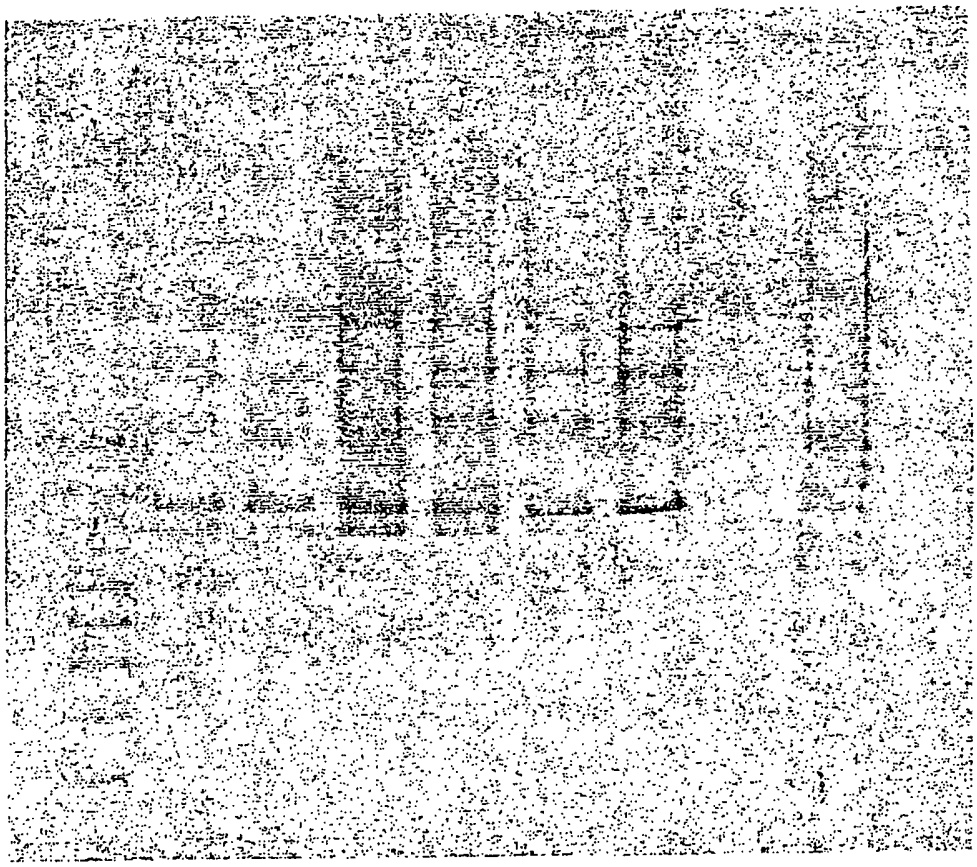


FIGURE 7

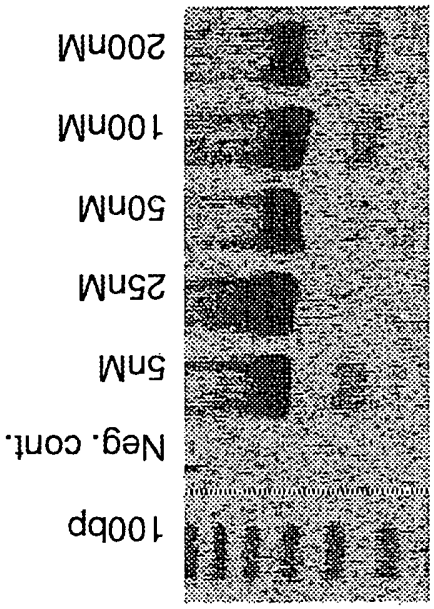


FIGURE 8B

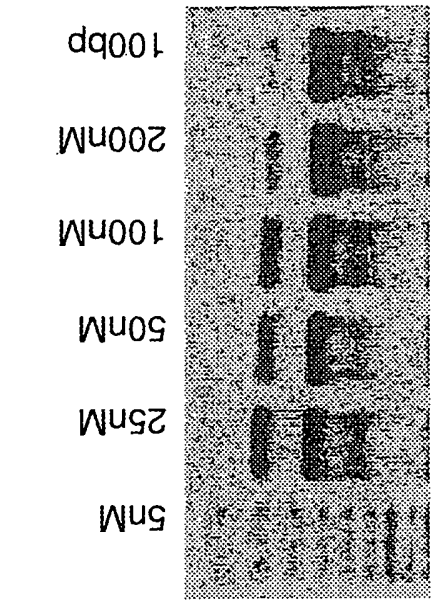
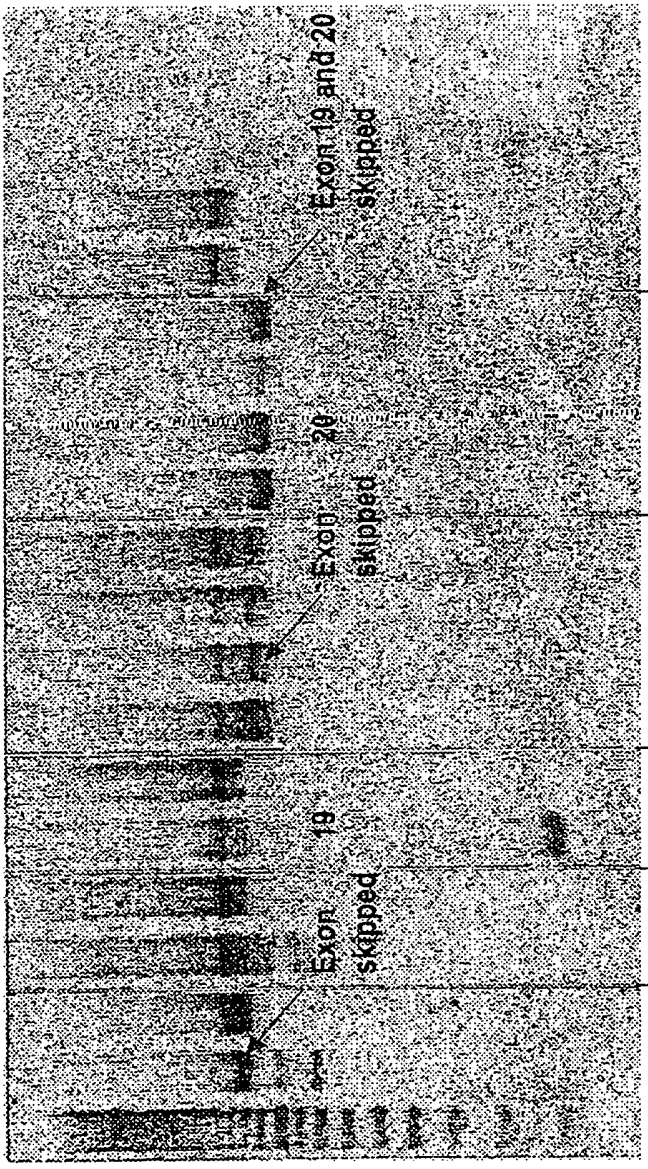


FIGURE 8A

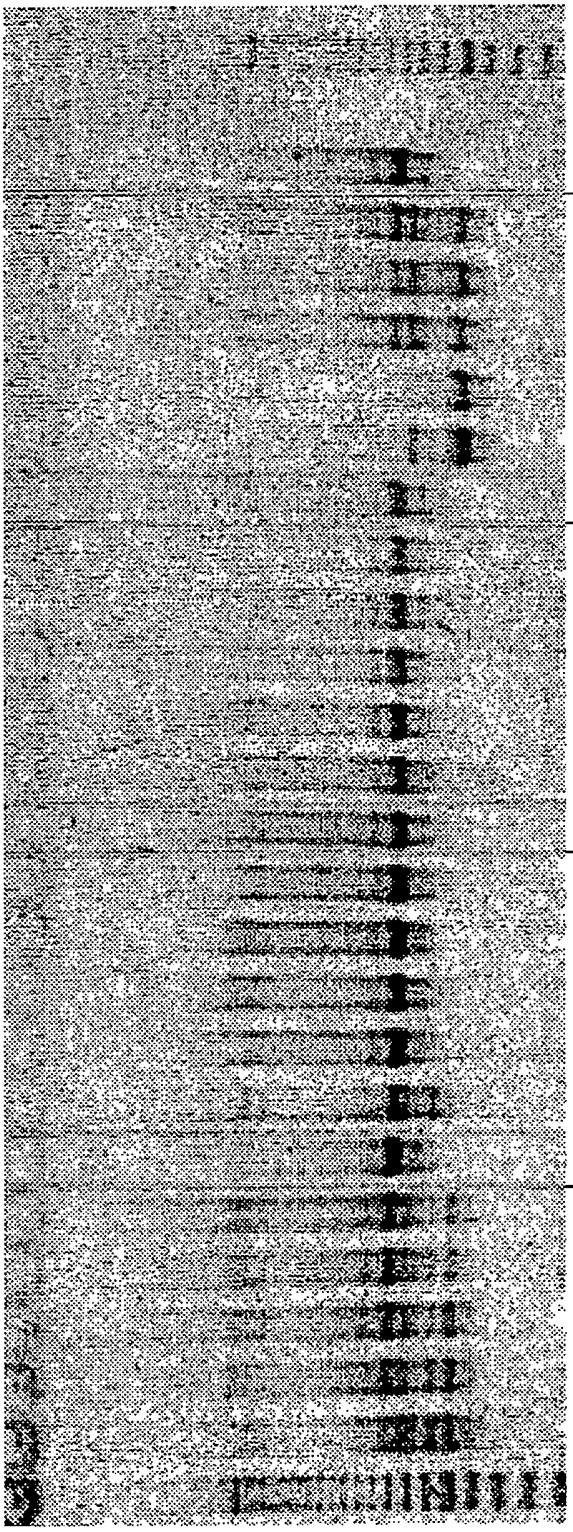
FIGURE 9A

FIGURE 9B



100bp	600	100	HM19A(+35+36)	600	100	H20A(+44+71)	600	100	H20A(+149+170)	600	300	100	50	20/20 cocktail H20A(+44+71) H20A(+149+170)	600	300	100	50	19/20/20 cocktail HM19A(+35+36) H20A(+44+71) H20A(+ 49+170)	L2K	UT

FIGURE 10



Weasel19/20/20 H19A(+35+53)-aa-H20A(+44+63)-aa-H20A(+149+168)

Weasel19/20 H19A(+35+53)-aa-H20A(+44+63)

Weasel19/20 H19A(+35+53)-aa-H20A(+149+168)

19/20/20 cocktail HM19A(+35+36) H20A(+44+71) H20A(+149+170)

FIGURE 11

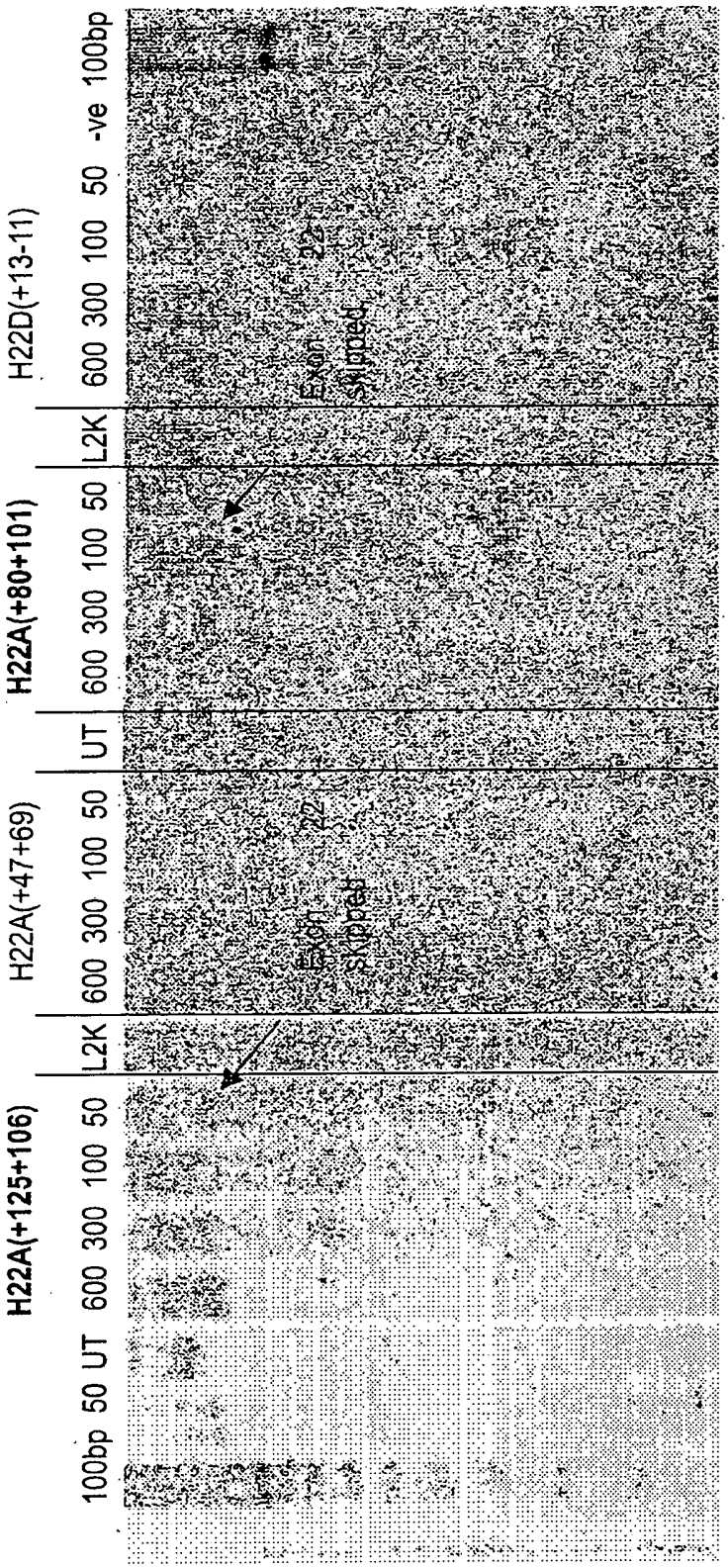

H22A(+125+106)
H22A(+47+69)
H22A(+80+101)
H22D(+13-11)
100bp 50 UT 600 300 100 50 L2K 600 300 100 50 UT 600 300 100 50 L2K 600 300 100 50 -ve 100bp
Exon 22 skipped
Exon 22

FIGURE 12

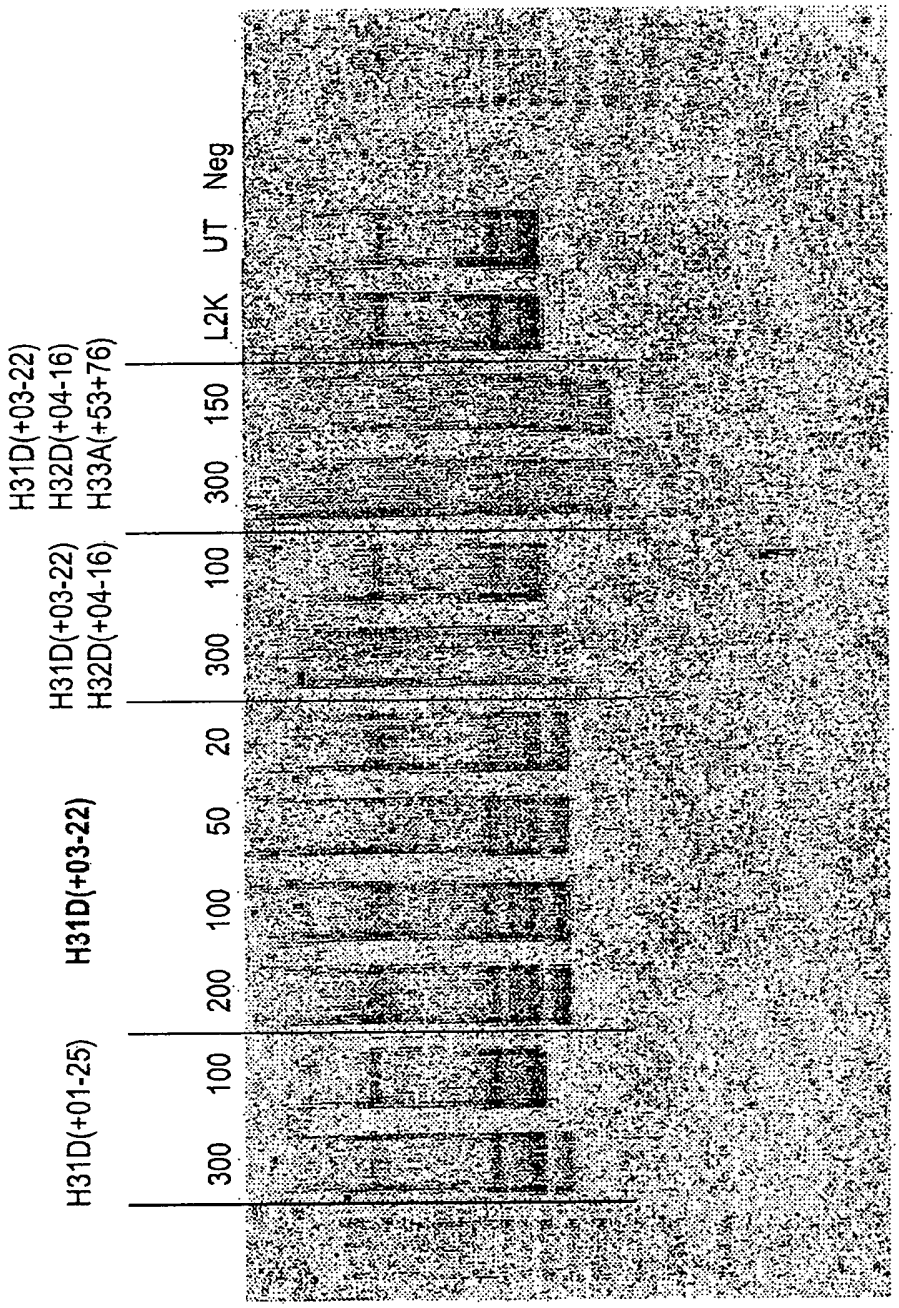

H31D(+01-25)
300
100
H31D(+03-22)
200
100
50
20
H31D(+03-22)
H32D(+04-16)
300
100
H31D(+03-22)
H32D(+04-16)
H33A(+53+76)
300
150
L2K
UT
Neg

FIGURE 13

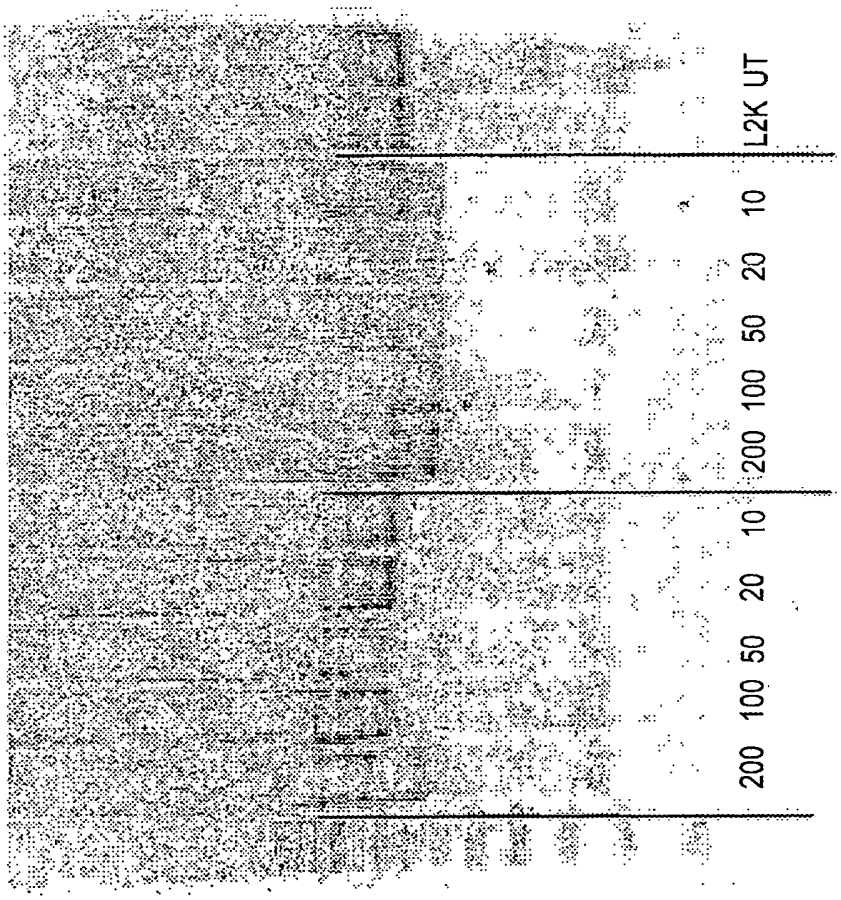


FIGURE 14

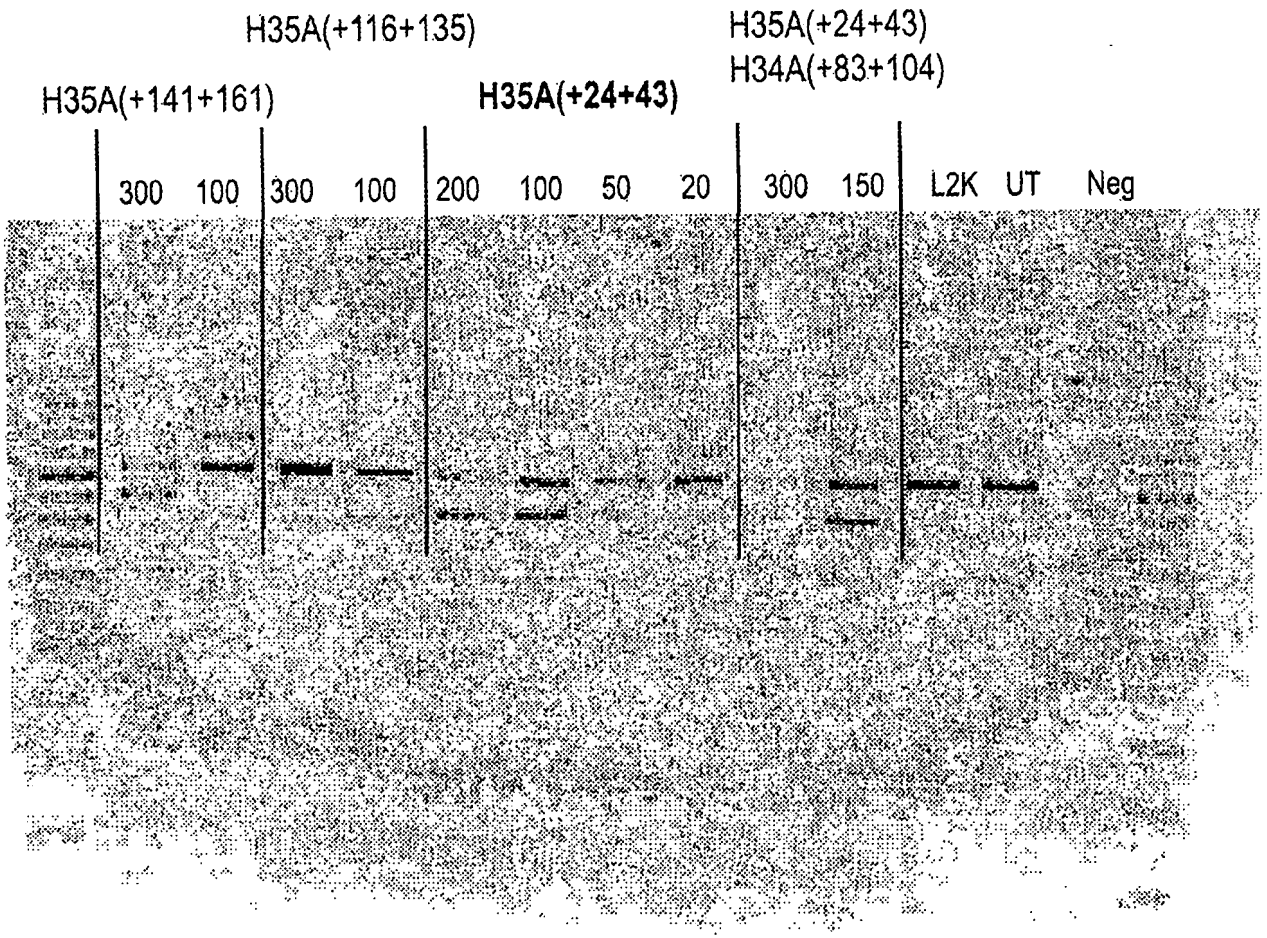

H35A(+116+135)
H35A(+24+43)
H34A(+83+104)
H35A(+141+161)
H35A(+24+43)
300 100 300 100 200 100 50 20 300 150 L2K UT Neg

FIGURE 15

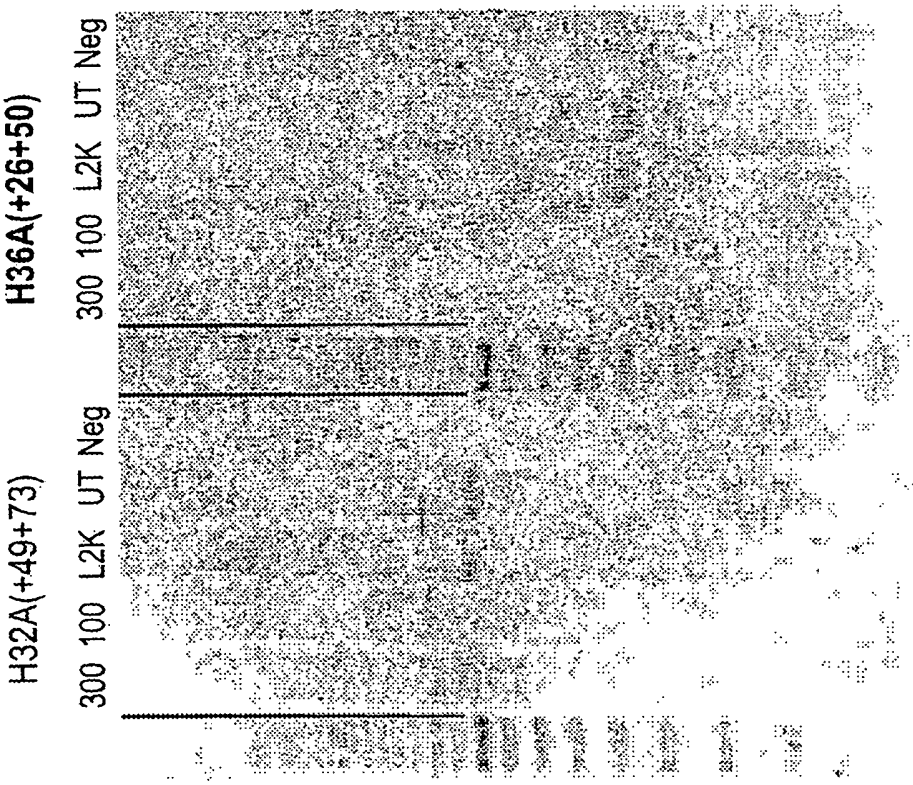


FIGURE 16

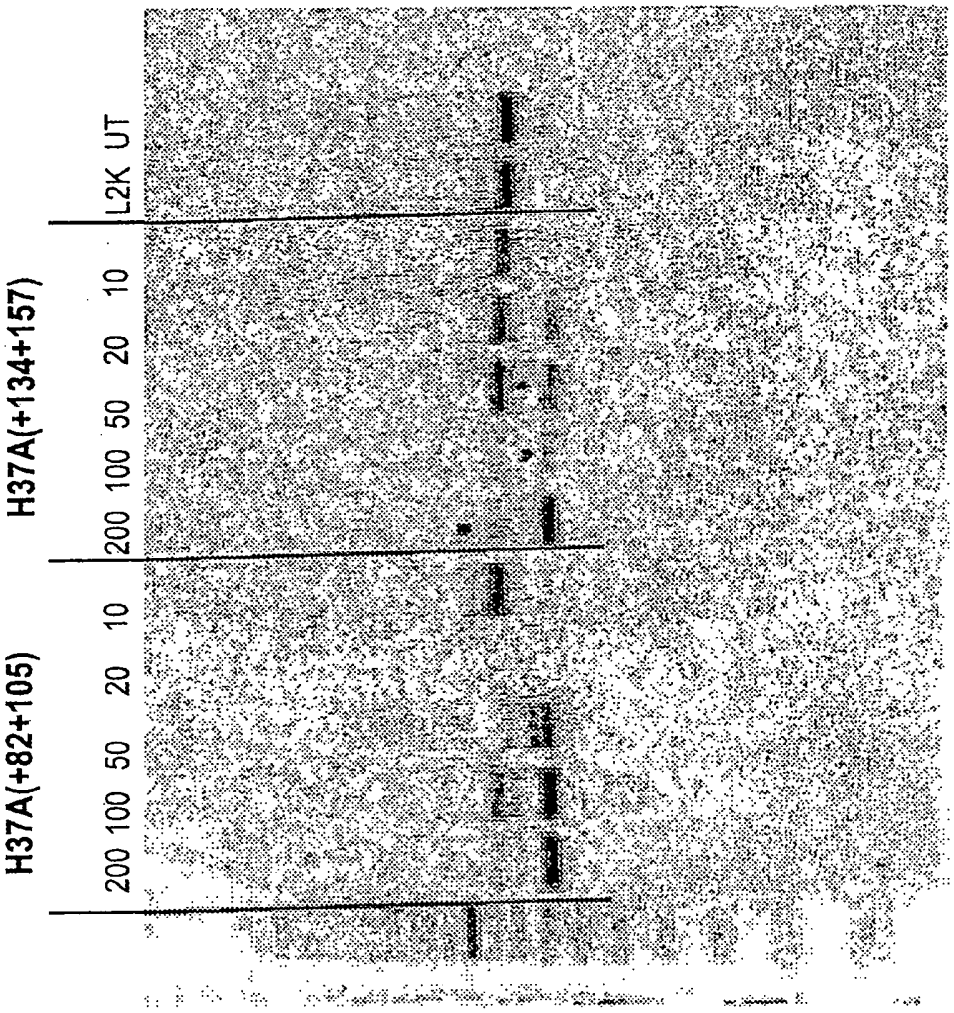


FIGURE 17

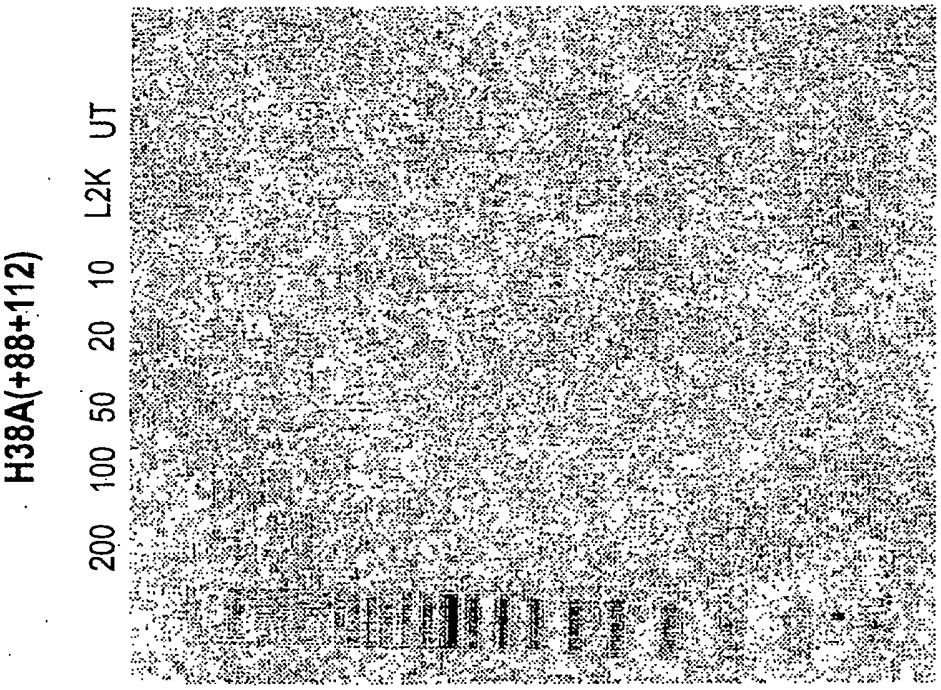


FIGURE 18

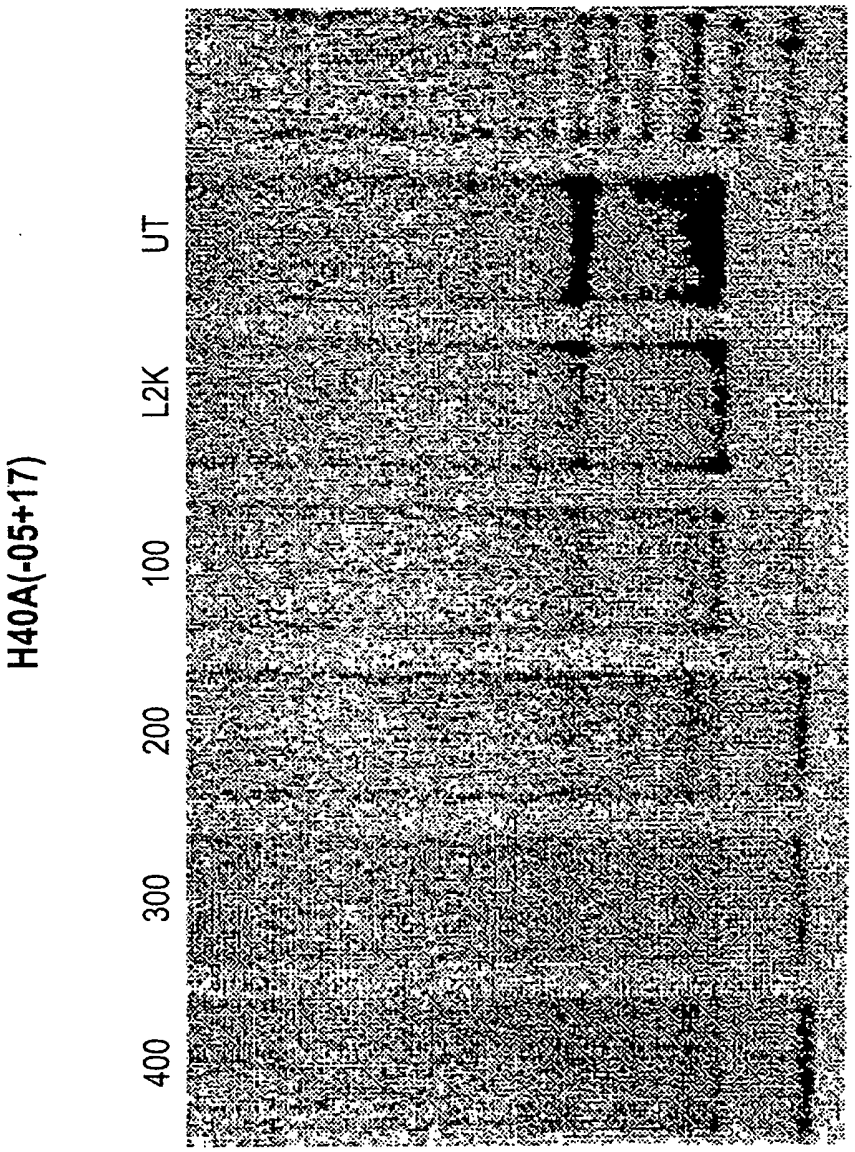


FIGURE 19

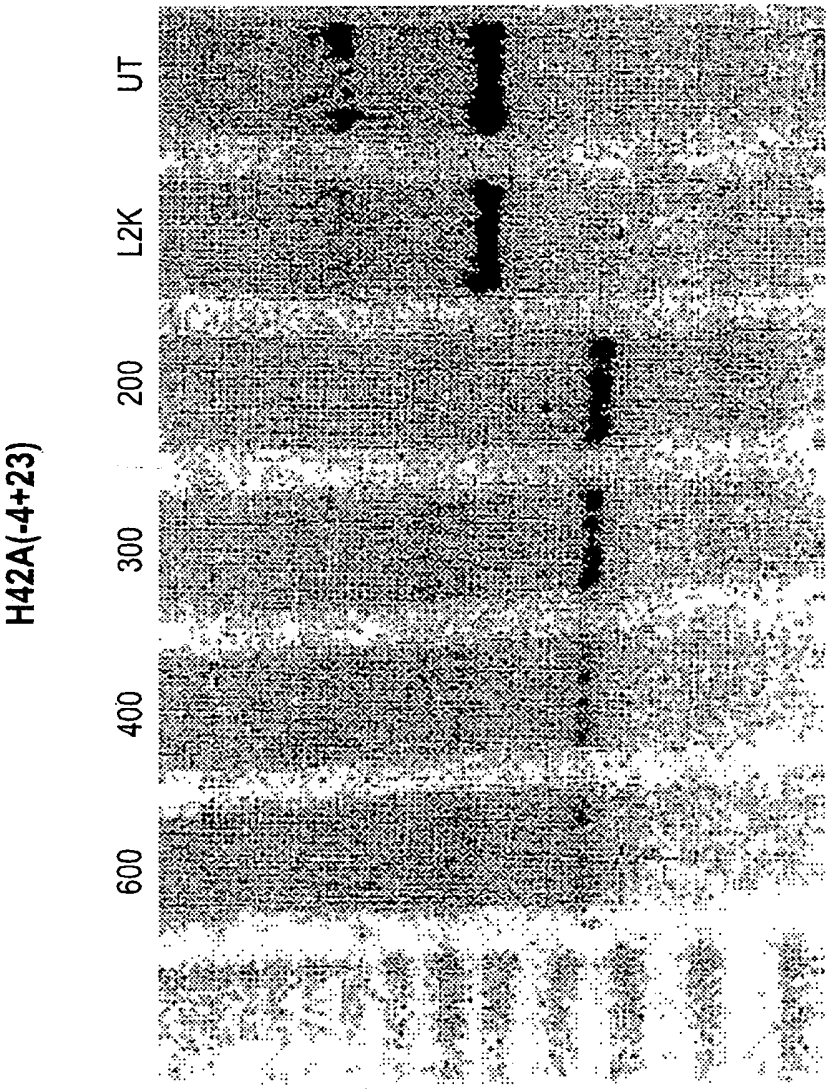


FIGURE 20

H46A(+86+115)

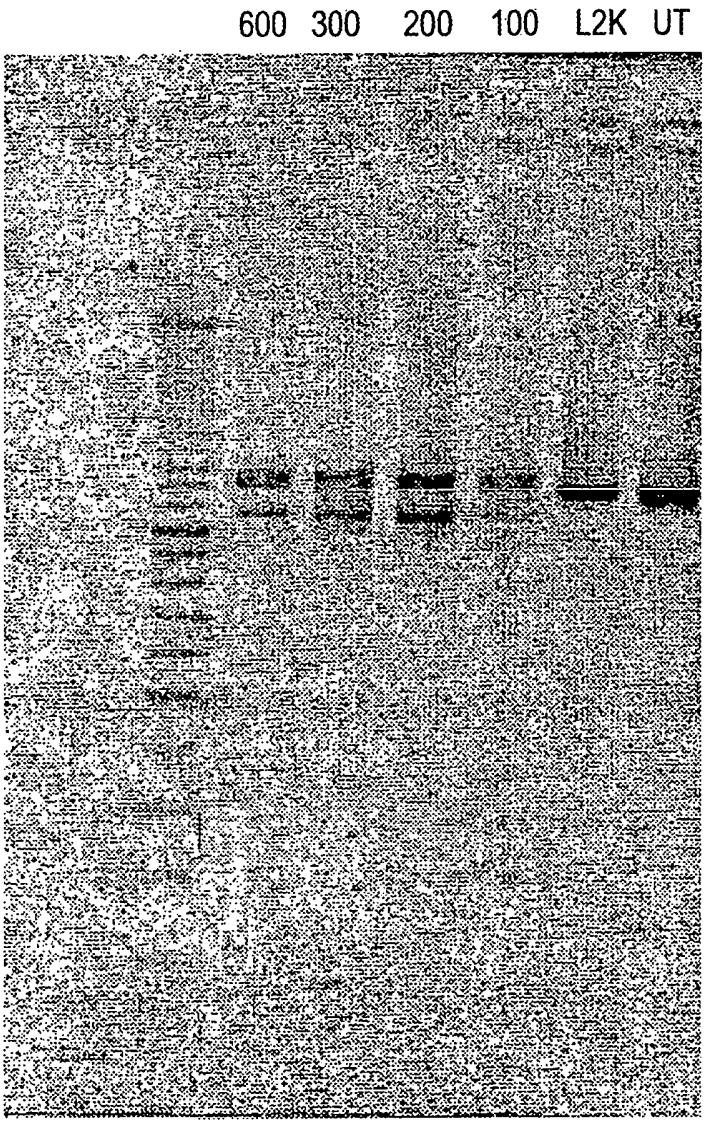


FIGURE 21

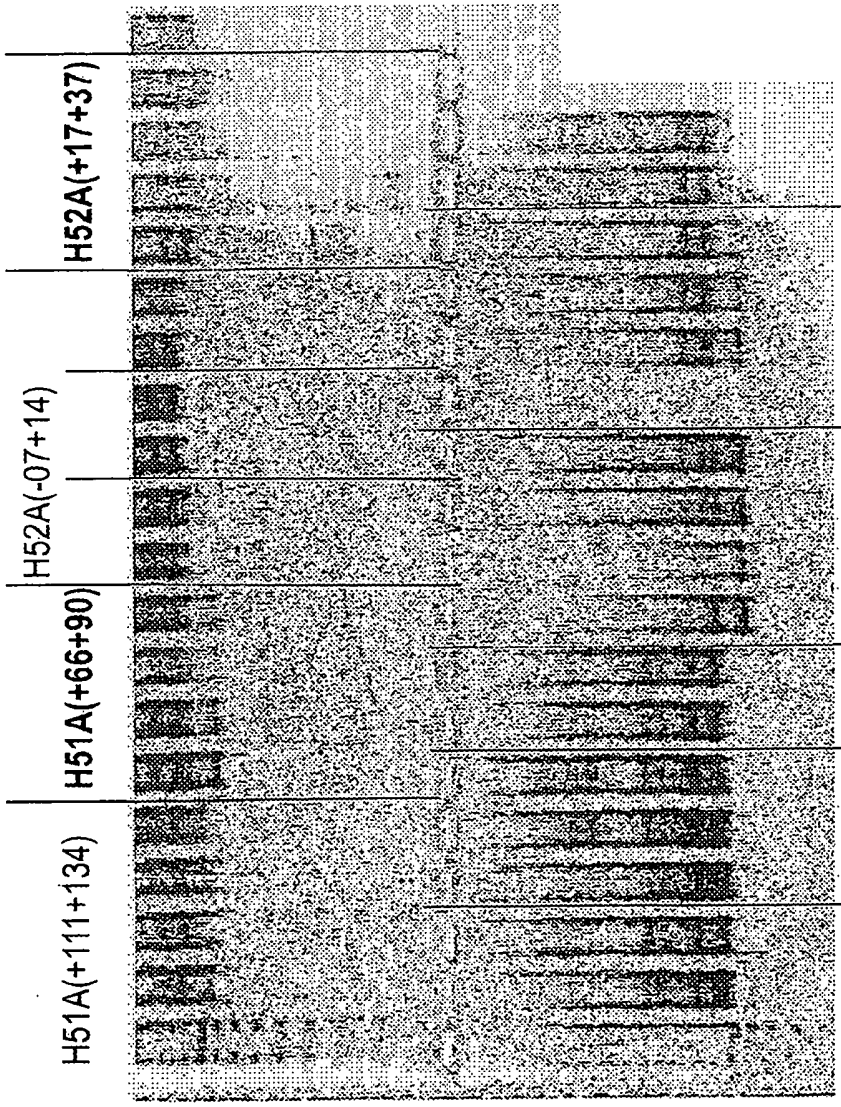

H52A(+17+37)
H52A(-07+14)
H51A(+66+90)
H51A(+111+134)
Cocktail
H53D(+23+47)
(+150+175)(+14-07)
H53D(+39+69)
H52A(+93+112)
H52D(+05-15)

FIGURE 22

ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 13/741,150, filed Jan. 14, 2013, now pending, which application is a continuation of U.S. patent application Ser. No. 13/168,857, filed Jun. 24, 2011, abandoned, which application is a continuation of U.S. patent application Ser. No. 12/837,359, filed Jul. 15, 2010, now issued as U.S. Pat. No. 8,232,384, which application is a continuation of U.S. patent application Ser. No. 11/570,691, filed Jan. 15, 2008, now issued as U.S. Pat. No. 7,807,816, which application is a 35 U.S.C. §371 National Phase Application of PCT/AU2005/000943, filed Jun. 28, 2005, which claims priority to Australian Patent Application No. 2004903474, filed Jun. 28, 2004; which applications are each incorporated herein by reference in their entireties.

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with the application is provided in text format in liew of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is SequenceListing.txt. The text file is 61 Kilobytes, was created on Jun. 26, 2014 and is being submitted electronically via EFS-Web.

FIELD OF THE INVENTION

The present invention relates to novel antisense compounds and compositions suitable for facilitating exon skipping. It also provides methods for inducing exon skipping using the novel antisense compounds as well as therapeutic compositions adapted for use in the methods of the invention.

BACKGROUND ART

Significant effort is currently being expended researching methods for suppressing or compensating for disease-causing mutations in genes. Antisense technologies are being developed using a range of chemistries to affect gene expression at a variety of different levels (transcription, splicing, stability, translation). Much of that research has focused on the use of antisense compounds to correct or compensate for abnormal or disease-associated genes in a myriad of different conditions.

Antisense molecules are able to inhibit gene expression with exquisite specificity and because of this many research efforts concerning oligonucleotides as modulators of gene expression have focused on inhibiting the expression of targeted genes such as oncogenes or viral genes. The antisense oligonucleotides are directed either against RNA (sense strand) or against DNA where they form triplex structures inhibiting transcription by RNA polymerase II. To achieve a desired effect in specific gene down-regulation, the oligonucleotides must either promote the decay of the targeted mRNA or block translation of that mRNA, thereby effectively preventing de novo synthesis of the undesirable target protein.

Such techniques are not useful where the object is to up-regulate production of the native protein or compensate for mutations which induce premature termination of translation

such as nonsense or frame-shifting mutations. Furthermore, in cases where a normally functional protein is prematurely terminated because of mutations therein, a means for restoring some functional protein production through antisense technology has been shown to be possible through intervention during the splicing processes (Sierakowska H, et al., (1996) *Proc Natl Acad Sci USA* 93, 12840-12844; Wilton S D, et al., (1999) *Neuromusc Disorders* 9, 330-338; van Deutekom J C et al., (2001) *Human Mol Genet* 10, 1547-1554). In these cases, the defective gene transcript should not be subjected to targeted degradation so the antisense oligonucleotide chemistry should not promote target mRNA decay.

In a variety of genetic diseases, the effects of mutations on the eventual expression of a gene can be modulated through a process of targeted exon skipping during the splicing process. The splicing process is directed by complex multi-particle machinery that brings adjacent exon-intron junctions in pre-mRNA into close proximity and performs cleavage of phosphodiester bonds at the ends of the introns with their subsequent reformation between exons that are to be spliced together. This complex and highly precise process is mediated by sequence motifs in the pre-mRNA that are relatively short semi-conserved RNA segments to which bind the various nuclear splicing factors that are then involved in the splicing reactions. By changing the way the splicing machinery reads or recognises the motifs involved in pre-mRNA processing, it is possible to create differentially spliced mRNA molecules. It has now been recognised that the majority of human genes are alternatively spliced during normal gene expression, although the mechanisms invoked have not been identified. Using antisense oligonucleotides, it has been shown that errors and deficiencies in a coded mRNA could be bypassed or removed from the mature gene transcripts.

In nature, the extent of genetic deletion or exon skipping in the splicing process is not fully understood, although many instances have been documented to occur, generally at very low levels (Sherrat T G, et al., (1993) *Am J Hum Genet* 53, 1007-1015). However, it is recognised that if exons associated with disease-causing mutations can be specifically deleted from some genes, a shortened protein product can sometimes be produced that has similar biological properties of the native protein or has sufficient biological activity to ameliorate the disease caused by mutations associated with the target exon (Lu Q L, et al., (2003) *Nature Medicine* 9, 1009-1014; Aartsma-Rus A et al., (2004) *Am J Hum Genet* 74: 83-92).

This process of targeted exon skipping is likely to be particularly useful in long genes where there are many exons and introns, where there is redundancy in the genetic constitution of the exons or where a protein is able to function without one or more particular exons (e.g. with the dystrophin gene, which consists of 79 exons; or possibly some collagen genes which encode for repeated blocks of sequence or the huge nebulin or titin genes which are comprised of ~80 and over 370 exons, respectively).

Efforts to redirect gene processing for the treatment of genetic diseases associated with truncations caused by mutations in various genes have focused on the use of antisense oligonucleotides that either: (1) fully or partially overlap with the elements involved in the splicing process; or (2) bind to the pre-mRNA at a position sufficiently close to the element to disrupt the binding and function of the splicing factors that would normally mediate a particular splicing reaction which occurs at that element (e.g., binds to the pre-mRNA at a position within 3, 6, or 9 nucleotides of the element to be blocked).

For example, modulation of mutant dystrophin pre-mRNA splicing with antisense oligoribonucleotides has been reported both in vitro and in vivo. In one type of dystrophin mutation reported in Japan, a 52-base pair deletion mutation causes exon 19 to be removed with the flanking introns during the splicing process (Matsuo et al., (1991) *J Clin Invest.*, 87:2127-2131). An in vitro minigene splicing system has been used to show that a 31-mer 2'-O-methyl oligoribonucleotide complementary to the 5' half of the deleted sequence in dystrophin Kobe exon 19 inhibited splicing of wild-type pre-mRNA (Takeshima et al. (1995), *J. Clin. Invest.*, 95, 515-520). The same oligonucleotide was used to induce exon skipping from the native dystrophin gene transcript in human cultured lymphoblastoid cells.

Dunckley et al., (1997) *Nucleosides & Nucleotides*, 16, 1665-1668 described in vitro constructs for analysis of splicing around exon 23 of mutated dystrophin in the mdx mouse mutant, a model for muscular dystrophy. Plans to analyse these constructs in vitro using 2' modified oligonucleotides targeted to splice sites within and adjacent to mouse dystrophin exon 23 were discussed, though no target sites or sequences were given.

2'-O-methyl oligoribonucleotides were subsequently reported to correct dystrophin deficiency in myoblasts from the mdx mouse from this group. An antisense oligonucleotide targeted to the 3' splice site of murine dystrophin intron 22 was reported to cause skipping of the mutant exon as well as several flanking exons and created a novel in-frame dystrophin transcript with a novel internal deletion. This mutated dystrophin was expressed in 1-2% of antisense treated mdx myotubes. Use of other oligonucleotide modifications such as 2'-O-methoxyethyl phosphodiesters are described (Dunckley et al. (1998) *Human Mol. Genetics*, 5, 1083-90).

Thus, antisense molecules may provide a tool in the treatment of genetic disorders such as Duchenne Muscular Dystrophy (DMD). However, attempts to induce exon skipping using antisense molecules have had mixed success. Studies on dystrophin exon 19, where successful skipping of that exon from the dystrophin pre-mRNA was achieved using a variety of antisense molecules directed at the flanking splice sites or motifs within the exon involved in exon definition as described by Errington et al. (2003) *J Gen Med* 5, 518-527".

In contrast to the apparent ease of exon 19 skipping, the first report of exon 23 skipping in the mdx mouse by Dunckley et al., (1998) is now considered to be reporting only a naturally occurring revertant transcript or artefact rather than any true antisense activity. In addition to not consistently generating transcripts missing exon 23, Dunckley et al., (1998) did not show any time course of induced exon skipping, or even titration of antisense oligonucleotides, to demonstrate dose dependent effects where the levels of exon skipping corresponded with increasing or decreasing amounts of antisense oligonucleotide. Furthermore, this work could not be replicated by other researchers.

The first example of specific and reproducible exon skipping in the mdx mouse model was reported by Wilton et al., (1999) *Neuromuscular Disorders* 9, 330-338. By directing an antisense molecule to the donor splice site, consistent and efficient exon 23 skipping was induced in the dystrophin mRNA within 6 hours of treatment of the cultured cells. Wilton et al, (1999), also describe targeting the acceptor region of the mouse dystrophin pre-mRNA with longer antisense oligonucleotides and being unable to repeat the published results of Dunckley et al., (1998). No exon skipping, either 23 alone or multiple removal of several flanking exons, could be reproducibly detected using a selection of antisense oligonucleotides directed at the acceptor splice site of intron 22.

While the first antisense oligonucleotide directed at the intron 23 donor splice site induced consistent exon skipping in primary cultured myoblasts, this compound was found to be much less efficient in immortalized cell cultures expressing higher levels of dystrophin. However, with refined targeting and antisense oligonucleotide design, the efficiency of specific exon removal was increased by almost an order of magnitude (see Mann C J et al., (2002) *J Gen Med* 4, 644-654).

Thus, there remains a need to provide antisense oligonucleotides capable of binding to and modifying the splicing of a target nucleotide sequence. Simply directing the antisense oligonucleotides to motifs presumed to be crucial for splicing is no guarantee of the efficacy of that compound in a therapeutic setting.

SUMMARY OF THE INVENTION

The present invention provides antisense molecule compounds and compositions suitable for binding to RNA motifs involved in the splicing of pre-mRNA that are able to induce specific and efficient exon skipping and a method for their use thereof.

The choice of target selection plays a crucial role in the efficiency of exon skipping and hence its subsequent application of a potential therapy. Simply designing antisense molecules to target regions of pre-mRNA presumed to be involved in splicing is no guarantee of inducing efficient and specific exon skipping. The most obvious or readily defined targets for splicing intervention are the donor and acceptor splice sites although there are less defined or conserved motifs including exonic splicing enhancers, silencing elements and branch points.

The acceptor and donor splice sites have consensus sequences of about 16 and 8 bases respectively (see FIG. 1 for schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process).

According to a first aspect, the invention provides antisense molecules capable of binding to a selected target to induce exon skipping. For example, to induce exon skipping in exons 3 to 8, 10 to 16, 19 to 40, 42 to 44, 46, 47, and 50 to 53 in the Dystrophin gene transcript the antisense molecules are preferably selected from the group listed in Table 1A.

In a further example, it is possible to combine two or more antisense oligonucleotides of the present invention together to induce multiple exon skipping in exons 19-20, and 53. This is a similar concept to targeting of a single exon. A combination or "cocktail" of antisense oligonucleotides are directed at adjacent exons to induce efficient exon skipping.

In another example, to induce exon skipping in exons 19-20, 31, 34 and 53 it is possible to improve exon skipping of a single exon by joining together two or more antisense oligonucleotide molecules. This concept is termed by the inventor as a "weasel", an example of a cunningly designed antisense oligonucleotide. A similar concept has been described in Aartsma-Rus A et al., (2004) *Am J Hum Genet* 74: 83-92).

According to a second aspect, the present invention provides antisense molecules selected and or adapted to aid in the prophylactic or therapeutic treatment of a genetic disorder comprising at least an antisense molecule in a form suitable for delivery to a patient.

According to a third aspect, the invention provides a method for treating a patient suffering from a genetic disease wherein there is a mutation in a gene encoding a particular

protein and the affect of the mutation can be abrogated by exon skipping, comprising the steps of: (a) selecting an antisense molecule in accordance with the methods described herein; and (b) administering the molecule to a patient in need of such treatment.

The invention also addresses the use of purified and isolated antisense oligonucleotides of the invention, for the manufacture of a medicament for treatment of a genetic disease.

The invention further provides a method of treating a condition characterised by Duchenne muscular dystrophy, which method comprises administering to a patient in need of treatment an effective amount of an appropriately designed antisense oligonucleotide of the invention, relevant to the particular genetic lesion in that patient. Further, the invention provides a method for prophylactically treating a patient to prevent or at least minimise Duchene muscular dystrophy, comprising the step of: administering to the patient an effective amount of an antisense oligonucleotide or a pharmaceutical composition comprising one or more of these biological molecules.

The invention also provides kits for treating a genetic disease, which kits comprise at least a antisense oligonucleotide of the present invention, packaged in a suitable container and instructions for its use.

Other aspects and advantages of the invention will become apparent to those skilled in the art from a review of the ensuing description, which proceeds with reference to the following figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** Schematic representation of motifs and domains involved in exon recognition, intron removal and the splicing process (SEQ ID NOS: 213 and 214).

FIG. **2**. Diagrammatic representation of the concept of antisense oligonucleotide induced exon skipping to by-pass disease-causing mutations (not drawn to scale). The hatched box represents an exon carrying a mutation that prevents the translation of the rest of the mRNA into a protein. The solid black bar represents an antisense oligonucleotide that prevents inclusion of that exon in the mature mRNA.

FIG. **3** Gel electrophoresis showing differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. The preferred compound [H8A(−06+18)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured normal human muscle cells. The less preferred antisense oligonucleotide [H8A(−06+14)] also induces efficient exon skipping, but at much higher concentrations. Other antisense oligonucleotides directed at exon 8 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

FIG. **4** Gel electrophoresis showing differing efficiencies of two antisense molecules directed at internal domains within exon 7, presumably exon splicing enhancers. The preferred compound [H7A(+45+67)] induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells. The less preferred antisense oligonucleotide [H7A(+2+26)] induces only low levels of exon skipping at the higher transfection concentrations. Other antisense oligonucleotides directed at exon 7 either only induced lower levels of exon skipping or no detectable skipping at all (not shown).

FIG. **5** Gel electrophoresis showing an example of low efficiency exon 6 skipping using two non-preferred antisense molecules directed at human exon 6 donor splice site. Levels of induced exon 6 skipping are either very low [H6D(+04−21)] or almost undetectable [H6D(+18−04)]. These are examples of non-preferred antisense oligonucleotides to demonstrate that antisense oligonucleotide design plays a crucial role in the efficacy of these compounds.

FIG. **6** Gel electrophoresis showing strong and efficient human exon 6 skipping using an antisense molecules [H6A (+69+91)] directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells.

FIG. **7** Gel electrophoresis showing strong human exon 4 skipping using an antisense molecule H4A(+13+32) directed at an exon 6 internal domain, presumably an exon splicing enhancer. This preferred compound induces strong and consistent exon skipping at a transfection concentration of 20 nanomolar in cultured human muscle cells,

FIG. **8** Gel electrophoresis showing (**8**B) strong human exon 11 skipping using antisense molecule H11A(+75+97) directed at an exon 11 internal domain; and (**8**A) strong human exon 12 skipping using antisense molecule H12A(+52+75) directed at exon 12 internal domain.

FIG. **9** Gel electrophoresis showing (**9**A) strong human exon 15 skipping using antisense molecules H15A(+48+71) and H15A(−12+19) directed at an exon 15 internal domain; and (**9**B) strong human exon 16 skipping using antisense molecules H16A(−12+19) and H16A(−06+25).

FIG. **10** Gel electrophoresis showing human exon 19/20 skipping using antisense molecules H20A(+44+71) and H20A(+149+170) directed at an exon 20 and a "cocktail" of antisense oligonucleotides H19A(+35+65, H20A(+44+71) and H20A(+149+170) directed at exons 19/20.

FIG. **11** Gel electrophoresis showing human exon 19/20 skipping using "weasels" directed at exons 19 and 20.

FIG. **12** Gel electrophoresis showing exon 22 skipping using antisense molecules H22A(+125+106), H22A(+47+69), H22A(+80+101) and H22D(+13−11) directed at exon 22.

FIG. **13** Gel electrophoresis showing exon 31 skipping using antisense molecules H31D(+01−25) and H31D(+03−22); and a "cocktail" of antisense molecules directed at exon 31.

FIG. **14** Gel electrophoresis showing exon 33 skipping using antisense molecules H33A(+30+56) and H33A(+64+88) directed at exon 33.

FIG. **15** Gel electrophoresis showing exon 35 skipping using antisense molecules H35A(+141+161), H35A(+116+135), and H35A(+24+43) and a "cocktail of two antisense molecules, directed at exon 35.

FIG. **16** Gel electrophoresis showing exon 36 skipping using antisense molecules H32A(+49+73) and H36A(+26+50) directed at exon 36.

FIG. **17** Gel electrophoresis showing exon 37 skipping using antisense molecules H37A(+82+105) and H37A(+134+157) directed at exon 37.

FIG. **18** Gel electrophoresis showing exon 38 skipping using antisense molecule H38A(+88+112) directed at exon 38.

FIG. **19** Gel electrophoresis showing exon 40 skipping using antisense molecule H40A(−05+17) directed at exon 40.

FIG. **20** Gel electrophoresis showing exon 42 skipping using antisense molecule H42A(−04+23) directed at exon 42.

FIG. **21** Gel electrophoresis showing exon 46 skipping using antisense molecule H46A(+86+115) directed a# exon 46

FIG. **22** Gel electrophoresis showing exon 51, exon 52 and exon 53 skipping using various antisense molecules directed at exons 51, 52 and 53, respectively. A "cocktail" of antisense molecules is also shown directed at exon 53.

BRIEF DESCRIPTION OF THE SEQUENCE LISTINGS

TABLE 1A

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
1	H8A(-06 + 18)	GAU AGG UGG UAU CAA CAU CUG UAA
2	H8A(-03 + 18)	GAU AGG UGG UAU CAA CAU CUG
3	H8A(-07 + 18)	GAU AGG UGG UAU CAA CAU CUG UAA G
4	H8A(-06 + 14)	GGU GGU AUC AAC AUC UGU AA
5	H8A(-10 + 10)	GUA UCA ACA UCU GUA AGC AC
6	H7A(+45 + 67)	UGC AUG UUC CAG UCG UUG UGU GG
7	H7A(+02 + 26)	CAC UAU UCC AGU CAA AUA GGU CUG G
8	H7D(+15 - 10)	AUU UAC CAA CCU UCA GGA UCG AGU A
9	H7A(-18 + 03)	GGC CUA AAA CAC AUA CAC AUA
10	C6A(-10 + 10)	CAU UUU UGA CCU ACA UGU GG
11	C6A(-14 + 06)	UUU GAC CUA CAU GUG GAA AG
12	C6A(-14 + 12)	UAC AUU UUU GAC CUA CAU GUG GAA AG
13	C6A(-13 + 09)	AUU UUU GAC CUA CAU GGG AAA G
14	CH6A(+69 + 91)	UAC GAG UUG AUU GUC GGA CCC AG
15	C6D(+12 - 13)	GUG GUC UCC UUA CCU AUG ACU GUG G
16	C6D(+06 - 11)	GGU CUC CUU ACC UAU GA
17	H6D(+04 - 21)	UGU CUC AGU AAU CUU CUU ACC UAU
18	H6D(+18 - 04)	UCU UAC CUA UGA CUA UGG AUG AGA
19	H4A(+13 + 32)	GCA UGA ACU CUU GUG GAU CC
20	H4D(+04 - 16)	CCA GGG UAC UAC UUA CAU UA
21	H4D(-24 - 44)	AUC GUG UGU CAC AGC AUC CAG
22	H4A(+11 + 40)	UGU UCA GGG CAU GAA CUC UUG UGG AUC CUU
23	H3A(+30 + 60)	UAG GAG GCG CCU CCC AUC CUG UAG GUC ACU G
24	H3A(+35 + 65)	AGG UCU AGG AGG CGC CUC CCA UCC UGU AGG U
25	H3A(+30 + 54)	GCG CCU CCC AUC CUG UAG GUC ACU G
26	H3D(+46 - 21)	CUU CGA GGA GGU CUA GGA GGC GCC UC
27	H3A(+30 + 50)	CUC CCA UCC UGU AGG UCA CUG
28	H3D(+19 - 03)	UAC CAG UUU UUG CCC UGU CAG G
29	H3A(-06 + 20)	UCA AUA UGC UGC UUC CCA AAC UGA AA
30	H3A(+37 + 61)	CUA GGA GGC GCC UCC CAU CCU GUA G

TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
31	H5A(+20 + 50)	UUA UGA UUU CCA UCU ACG AUG UCA GUA CUU C
32	H5D(+25 - 05)	CUU ACC UGC CAG UGG AGG AUU AUA UUC CAA A
33	H5D(+10 - 15)	CAU CAG GAU UCU UAC CUG CCA GUG G
34	H5A(+10 + 34)	CGA UGU CAG UAC UUC CAA UAU UCA C
35	H5D(-04 - 21)	ACC AUU CAU CAG GAU UCU
36	H5D(+16 - 02)	ACC UGC CAG UGG AGG AUU
37	H5A(-07 + 20)	CCA AUA UUC ACU AAA UCA ACC UGU UAA
38	H5D(+18 - 12)	CAG GAU UGU UAC CUG CCA GUG GAG GAU UAU
39	H5A(+05 + 35)	ACG AUG UCA GUA CUU CCA AUA UUC ACU AAA U
40	H5A(+15 + 45)	AUU UCC AUC UAC GAU GUC AGU ACU UCC AAU A
41	H10A(-05 + 16)	CAG GAG CUU CCA AAU GCU GCA
42	H10A(-05 + 24)	CUU GUC UUC AGG AGC UUC CAA AUG CUG CA
43	H10A(+98 + 119)	UCC UCA GCA GAA AGA AGC CAC G
44	H10A(+130 + 149)	UUA GAA AUC UCU CCU UGU GC
45	H10A(-33 - 14)	UAA AUU GGG UGU UAC ACA AU
46	H11D(+26 + 49)	CCC UGA GGC AUU CCC AUC UUG AAU
47	H11D(+11 - 09)	AGG ACU UAC UUG CUU UGU UU
48	H11A(+118 + 140)	CUU GAA UUU AGG AGA UUC AUC UG
49	H11A(+75 + 97)	CAU CUU CUG AUA AUU UUC CUG UU
50	H12A(+52 + 75)	UCU UCU GUU UUU GUU AGC CAG UCA
51	H12A(-10 + 10)	UCU AUG UAA ACU GAA AAU UU
52	H12A(+11 + 30)	UUC UGG AGA UCC AUU AAA AC
53	H13A(+77 + 100)	CAG CAG UUG CGU GAU CUC CAC UAG
54	H13A(+55 + 75)	UUC AUC AAC UAC CAC CAC CAU
55	H13D(+06 - 19)	CUA AGC AAA AUA AUC UGA CCU UAA G
56	H14A(+37 + 64)	CUU GUA AAA GAA CCC AGC GGU CUU CUG U
57	H14A(+14 + 35)	CAU CUA CAG AUG UUU GCC CAU C
58	H14A(+51 + 73)	GAA GGA UGU CUU GUA AAA GAA CC
59	H14D(-02 + 18)	ACC UGU UCU UCA GUA AGA CG
60	H14D(+14 - 10)	CAU GAC ACA CCU GUU CUU CAG UAA
61	H14A(+61 + 80)	CAU UUG AGA AGG AUG UCU UG
62	H14A(-12 + 12)	AUC UCC CAA UAC CUG GAG AAG AGA

TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
63	H15A(-12 + 19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA CAU U
64	H15A(+48 + 71)	UCU UUA AAG CCA GUU GUG UGA AUC
65	H15A(+08 + 28)	UUU CUG AAA GCC AUG CAC UAA
66	H15D(+17 - 08)	GUA CAU ACG GCC AGU UUU UGA AGA C
67	H16A(-12 + 19)	CUA GAU CCG CUU UUA AAA CCU GUU AAA ACA A
68	H16A(-06 + 25)	UCU UUU CUA GAU CCG CUU UUA AAA CCU GUU A
69	H16A(-06 + 19)	CUA GAU CCG CUU UUA AAA CCU GUU A
70	H16A(+87 + 109)	CCG UCU UCU GGG UCA CUG ACU UA
71	H16A(-07 + 19)	CUA GAU CCG CUU UUA AAA CCU GUU AA
72	H16A(-07 + 13)	CCG CUU UUA AAA CCU GUU AA
73	H16A(+12 + 37)	UGG AUU GCU UUU UCU UUU CUA GAU CC
74	H16A(+92 + 116)	CAU GCU UCC GUC UUC UGG GUC ACU G
75	H16A(+45 + 67)	G AUC UUG UUU GAG UGA AUA CAG U
76	H16A(+105 + 126)	GUU AUC CAG CCA UGC UUC CGU C
77	H16D(+05 - 20)	UGA UAA UUG GUA UCA CUA ACC UGU G
78	H16D(+12 - 11)	GUA UCA CUA ACC UGU GCU GUA C
79	H19A(+35 + 53)	CUG CUG GCA UCU UGC AGU U
80	H19A(+35 + 65)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U
81	H20A(+44 + 71)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C
82	H20A(+147 + 168)	CAG CAG UAG UUG UCA UCU GCU C
83	H20A(+185 + 203)	UGA UGG GGU GGU GGG UUG G
84	H20A(-08 + 17)	AUC UGC AUU AAC ACC CUC UAG AAA G
85	H20A(+30 + 53)	CCG GCU GUU CAG UUG UUC UGA GGC
86	H20A(-11 + 17)	AUC UGC AUU AAC ACC CUC UAG AAA GAA A
87	H20D(+08 - 20)	GAA GGA GAA GAG AUU CUU ACC UUA CAA A
88	H20A(+44 + 63)	AUU CGA UCC ACC GGC UGU UC
89	H20A(+149 + 168	CAG CAG UAG UUG UCA UCU GC
90	H21A(-06 + 16)	GCC GGU UGA CUU CAU CCU GUG C
91	H21A(+85 + 106)	CUG CAU CCA GGA ACA UGG GUC C
92	H21A(+85 + 108)	GUC UGC AUC CAG GAA CAU GGG UC
93	H21A(+08 + 31)	GUU GAA GAU CUG AUA GCC GGU UGA
94	H21D(+18 - 07)	UAC UUA CUG UCU GUA GCU CUU UCU

TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
95	H22A(+22 + 45)	CAC UCA UGG UCU CCU GAU AGC GCA
96	H22A(+125 + 106)	CUG CAA UUC CCC GAG UCU CUG C
97	H22A(+47 + 69)	ACU GCU GGA CCC AUG UCC UGA UG
98	H22A(+80 + 101)	CUA AGU UGA GGU AUG GAG AGU
99	H22D(+13 - 11)	UAU UCA CAG ACC UGC AAU UCC CC
100	H23A(+34 + 59)	ACA GUG GUG CUG AGA UAG UAU AGG CC
101	H23A(+18 + 39)	UAG GCC ACU UUG UUG CUC UUG C
102	H23A(+72 + 90)	UUC AGA GGG CGC UUU CUU C
103	H24A(+48 + 70)	GGG CAG GCC AUU CCU CCU UCA GA
104	H24A(-02 + 22)	UCU UCA GGG UUU GUA UGU GAU UCU
105	H25A(+9 + 36)	CUG GGC UGA AUU GUC UGA AUA UCA CUG
106	H25A(+131 + 156)	CUG UUG GCA CAU GUG AUC CCA CUG AG
107	H25D(+16 - 08)	GUC UAU ACC UGU UGG CAC AUG UGA
108	H26A(+132 + 156)	UGC UUU CUG UAA UUC AUC UGG AGU U
109	H26A(-07 + 19)	CCU CCU UUC UGG CAU AGA CCU UCC AC
110	H26A(+68 + 92)	UGU GUC AUC CAU UCG UGC AUC UCU G
111	H27A(+82 + 106)	UUA AGG CCU CUU GUG CUA CAG GUG G
112	H27A(-4 + 19)	GGG GCU CUU CUU UAG CUC UCU GA
113	H27D(+19 - 03)	GAC UUC CAA AGU CUU GCA UUU C
114	H28A(-05 + 19)	GCC AAC AUG CCC AAA CUU CCU AAG
115	H28A(+99 + 124)	CAG AGA UUU CCU CAG CUC CGC CAG GA
116	H28D(+16 - 05)	CUU ACA UCU AGC ACC UCA GAG
117	H29A(+57 + 81)	UCC GCC AUC UGU UAG GGU CUG UGC C
118	H29A(+18 + 42)	AUU UGG GUU AUC CUC UGA AUG UCG C
119	H29D(+17 - 05)	CAU ACC UCU UCA UGU AGU UCC C
120	H30A(+122 + 147)	CAU UUG AGC UGC GUC CAC CUU GUC UG
121	H30A(+25 + 50)	UCC UGG GCA GAC UGG AUG CUC UGU UC
122	H30D(+19 - 04)	UUG CCU GGG CUU CCU GAG GCA UU
123	H31D(+06 - 18)	UUC UGA AAU AAC AUA UAC CUG UGC
124	H31D(+03 - 22)	UAG UUU CUG AAA UAA CAU AUA CCU G
125	H31A(+05 + 25)	GAC UUG UCA AAU CAG AUU GGA
126	H31D(+04 - 20)	GUU UCU GAA AUA ACA UAU ACC UGU
127	H32D(+04 - 16)	CAC CAG AAA UAC AUA CCA CA
128	H32A(+151 + 170)	CAA UGA UUU AGC UGU GAC UG

TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pré-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
129	H32A(+10 + 32)	CGA AAC UUC AUG GAG ACA UCU UG
130	H32A(+49 + 73)	CUU GUA GAC GCU GCU CAA AAU UGG C
131	H33D(+09 - 11)	CAU GCA CAC ACC UUU GCU CC
132	H33A(+53 + 76)	UCU GUA CAA UCU GAC GUC CAG UCU
133	H33A(+30 + 56)	GUC UUU AUC ACC AUU UCC ACU UCA GAC
134	H33A(+64 + 88)	CCG UCU GCU UUU UCU GUA CAA UCU G
135	H34A(+83 + 104)	UCC AUA UCU GUA GCU GCC AGC C
136	H34A(+143 + 165)	CCA GGC AAC UUC AGA AUC CAA AU
137	H34A(-20 + 10)	UUU CUG UUA CCU GAA AAG AAU UAU AAU GAA
138	H34A(+46 + 70)	CAU UCA UUU CCU UUC GCA UCU UAC G
139	H34A(+95 + 120)	UGA UCU CUU UGU CAA UUC CAU AUC UG
140	H34D(+10 - 20)	UUC AGU GAU AUA GGU UUU ACC UUU CCC CAG
141	H34A(+72 + 96)	CUG UAG CUG CCA GCC AUU CUG UCA AG
142	H35A(+141 + 161)	UCU UCU GCU CGG GAG GUG ACA
143	H35A(+116 + 135)	CCA GUU ACU AUU CAG AAG AC
144	H35A(+24 + 43)	UCU UCA GGU GCA CCU UCU GU
145	H36A(+26 + 50)	UGU GAU GUG GUC CAC AUU CUG GUC A
146	H36A(-02 + 18)	CCA UGU GUU UCU GGU AUU CC
147	H37A(+26 + 50)	CGU GUA GAG UCC ACC UUU GGG CGU A
148	H37A(+82 + 105)	UAC UAA UUU CCU GCA GUG GUC ACC
149	H37A(+134 + 157)	UUC UGU GUG AAA UGG CUG CAA AUC
150	H38A(-01 + 19)	CCU UCA AAG GAA UGG AGG CC
151	H38A(+59 + 83)	UGC UGA AUU UCA GCC UCC AGU GGU U
152	H38A(+88 + 112)	UGA AGU CUU CCU CUU UCA GAU UCA C
153	H39A(+62 + 85)	CUG GCU UUC UCU CAU CUG UGA UUC
154	H39A(+39 + 58)	GUU GUA AGU UGU CUC CUC UU
155	H39A(+102 + 121)	UUG UCU GUA ACA GCU GCU GU
156	H39D(+10 - 10)	GCU CUA AUA CCU UGA GAG CA
157	H40A(-05 + 17)	CUU UGA GAC CUC AAA UCC UGU U
158	H40A(+129 + 153)	CUU UAU UUU CCU UUC AUC UCU GGG C
159	H42A(-04 + 23)	AUC GUU UCU UCA CGG ACA GUG UGC UGG
160	H42A(+86 + 109)	GGG CUU GUG AGA CAU GAG UGA UUU
161	H42D(+19 - 02)	A CCU UCA GAG GAC UCC UCU UGC

TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
162	H43D(+10 - 15)	UAU GUG UUA CCU ACC CUU GUC GGU C
163	H43A(+101 + 120)	GGA GAG AGC UUC CUG UAG CU
164	H43A(+78 + 100)	UCA CCC UUU CCA CAG GCG UUG CA
165	H44A(+85 + 104)	UUU GUG UCU UUC UGA GAA AC
166	H44D(+10 - 10)	AAA GAC UUA CCU UAA GAU AC
167	H44A(-06 + 14)	AUC UGU CAA AUC GCC UGC AG
168	H46D(+16 - 04)	UUA CCU UGA CUU GCU CAA GC
169	H46A(+90 + 109)	UCC AGG UUC AAG UGG GAU AC
170	H47A(+76 + 100)	GCU CUU CUG GGC UUA UGG GAG CAC U
171	H47D(+25 - 02)	ACC UUU AUC CAC UGG AGA UUU GUC UGC
172	H47A(-9 + 12)	UUC CAC CAG UAA CUG AAA CAG
173	H50A(+02 + 30)	CCA CUC AGA GCU CAG AUC UUC UAA CUU CC
174	H50A(+07 + 33)	CUU CCA CUC AGA GCU CAG AUC UUC UAA
175	H50D(+07 - 18)	GGG AUC CAG UAU ACU UAC AGG CUC C
176	H51A(-01 + 25)	ACC AGA GUA ACA GUC UGA GUA GGA GC
177	H51D(+16 - 07)	CUC AUA CCU UCU GCU UGA UGA UC
178	H51A(+111 + 134)	UUC UGU CCA AGC CCG GUU GAA AUC
179	H51A(+61 + 90)	ACA UCA AGG AAG AUG GCA UUU CUA GUU UGG
180	H51A(+66 + 90)	ACA UCA AGG AAG AUG GCA UUU CUA G
181	H51A(+66 + 95)	CUC CAA CAU CAA GGA AGA UGG CAU UUC UAG
182	H51D(+08 - 17)	AUC AUU UUU UCU CAU ACC UUC UGC U
183	H51A/D(+08 - 17) & (-15+)	AUC AUU UUU UCU CAU ACC UUC UGC UAG GAG CUA AAA
184	H51A(+175 + 195)	CAC CCA CCA UCA CCC UCU GUG
185	H51A(+199 + 220)	AUC AUC UCG UUG AUA UCC UCA A
186	H52A(-07 + 14)	UCC UGC AUU GUU GCC UGU AAG
187	H52A(+12 + 41)	UCC AAC UGG GGA CGC CUC UGU UCC AAA UCC
188	H52A(+17 + 37)	ACU GGG GAC GCC UCU GUU CCA
189	H52A(+93 + 112)	CCG UAA UGA UUG UUC UAG CC
190	H52D(+05 - 15)	UGU UAA AAA ACU UAC UUC GA
191	H53A(+45 + 69)	CAU UCA ACU GUU GCC UCC GGU UCU G
192	H53A(+39 + 62)	CUG UUG CCU CCG GUU CUG AAG GUG
193	H53A(+39 + 69)	CAU UCA ACU GUU GCC UCC GGU UCU GAA

TABLE 1A-continued

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA-like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
		GGU G
194	H53D(+14 - 07)	UAC UAA CCU UGG UUU CUG UGA
195	H53A(+23 + 47)	CUG AAG GUG UUC UUG UAC UUC AUC C
196	H53A(+150 + 176)	UGU AUA GGG ACC CUC CUU CCA UGA CUC
197	H53D(+20 - 05)	CUA ACC UUG GUU UCU GUG AUU UUC U
198	H53D(+09 - 18)	GGU AUC UUU GAU ACU AAC CUU GGU UUC
199	H53A(-12 + 10)	AUU CUU UCA ACU AGA AUA AAA G
200	H53A(-07 + 18)	GAU UCU GAA UUC UUU CAA CUA GAA U
201	H53A(+07 + 26)	AUC CCA CUG AUU CUG AAU UC
202	H53A(+124 + 145)	UUG GCU CUG GCC UGU CCU AAC A
203	H46A(+86 + 115)	CUC UUU UCC AGG UUC AAG UGG GAU ACU AGC
204	H46A(+107 + 137)	CAA GCU UUU CUU UUA GUU GCU GCU CUU UUC C
205	H46A(-10 + 20)	UAU UCU UUU GUU CUU CUA GCC UGG AGA AAG
206	H46A(+50 + 77)	CUG CUU CCU CCA ACC AUA AAA CAA AUU C
207	H45A(-06 + 20)	CCA AUG CCA UCC UGG AGU UCC UGU AA
208	H45A(+91 + 110)	UCC UGU AGA AUA CUG GCA UC
209	H45A(+125 + 151)	UGC AGA CCU CCU GCC ACC GCA GAU UCA
210	H45D(+16 - 04)	CUA CCU CUU UUU UCU GUC UG
211	H45A(+71 + 90)	UGU UUU UGA GGA UUG CUG AA

TABLE 1B

Description of a cocktail of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
81	H20A(+44 + 71)	CUG GCA GAA UUC GAU CCA CCG GCU
82	H20A(+147 + 168)	GUU C
		CAG CAG UAG UUG UCA UCU GCU C
80	H19A(+35 + 65)	GCC UGA GCU GAU CUG CUG GCA UCU
81	H20A(+44 + 71)	UGC
82	H20A(+147 + 168)	AGU U
		CUG GCA GAA UUC GAU CCA CCG GCU
		GUU C
		CAG CAG UAG UUG UCA UCU GCU C
194	H53D(+14 - 07)	UAC UAA CCU UGG UUU CUG UGA
195	H53A(+23 + 47)	CUG AAG GUG UUC UUG UAC UUC AUC C

TABLE 1B-continued

Description of a cocktail of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
196	H53A(+150 + 175)	UGU AUA GGG ACC CUC CUU CCA UGA CUC

TABLE 1C

Description of a "weasel" of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA.

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
81	H20A(+44 + 71)-	CUG GCA GAA UUC GAU CCA CCG GCU GUU C-
82	H20A(+147 + 168)	CAG CAG UAG UUG UCA UCU GCU C
80	H19A(+35 + 65)-	GCC UGA GCU GAU CUG CUG GCA UCU UGC AUU U
88	H20A(+44 + 63)-	-AUU CGA UCC ACC GGC UGU UC-
79	H20A(+149 + 168)	CUG CUG GCA UCU UGC AGU U
80	H19A(+35 + 65)-	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U
88	H20A(+44 + 63)	-AUU CGA UCC ACC GGC UGU UC-
80	H19A(+35 + 65)-	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U
79	H20A(+149 + 168)	-CUG CUG GCA UCU UGC AGU U
138	H34A(+46 + 70)-	CAU UCA UUU CCU UUC GCA UCU UAC G-
139	H34A(+94 + 120)	UGA UCU CUU UGU CAA UUC CAU AUC UG
124	H31D(+03 - 22)- UU-	UAG UUU CUG AAA UAA CAU AUA CCU G- UU-
144	H35A(+24 + 43)	UCU UCA GGU GCA CCU UCU GU
195	H53A(+23 + 47)- AA-	CUG AAG GUG UUC UUG UAC UUC AUC C-
196	H53A(+150 + 175)- AA-	UGU AUA GGG ACC CUC CUU CCA UGA CUC- AA-
194	H53D(+14 - 07)	UAC UAA CCU UGG UUU CUG UGA
- 212	Aimed at exons 19/20/20	CAG CAG UAG UUG UCA UCU GCU CAA CUG GCA GAA UUC GAU CCA CCG GCU GUU CAA GCC UGA GCU GAU CUG CUC GCA UCU UGC AGU

DETAILED DESCRIPTION OF THE INVENTION

General

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variation and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally equivalent products, compositions and methods are clearly within the scope of the invention as described herein.

Sequence identity numbers (SEQ ID NO:) containing nucleotide and amino acid sequence information included in

this specification are collected at the end of the description and have been prepared using the programme PatentIn Version 3.0. Each nucleotide or amino acid sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (e.g. <210>1, <210>2, etc.). The length, type of sequence and source organism for each nucleotide or amino acid sequence are indicated by information provided in the numeric indicator fields <211>, <212> and <213>, respectively. Nucleotide and amino acid sequences referred to in the specification are defined by the information provided in numeric indicator field <400> followed by the sequence identifier (e.g. <400>1, <400>2, etc.).

An antisense molecules nomenclature system was proposed and published to distinguish between the different antisense molecules (see Mann et al., (2002) *J Gen Med* 4, 644-654). This nomenclature became especially relevant when testing several slightly different antisense molecules, all directed at the same target region, as shown below:

H#A/D(x:y).

The first letter designates the species (e.g. H: human, M: murine, C: canine) "#" designates target dystrophin exon number.

"A/D" indicates acceptor or donor splice site at the beginning and end of the exon, respectively.

(x y) represents the annealing coordinates where "-" or "+" indicate intronic or exonic sequences respectively. As an example, A(-6+18) would indicate the last 6 bases of the intron preceding the target exon and the first 18 bases of the target exon. The closest splice site would be the acceptor so these coordinates would be preceded with an "A". Describing annealing coordinates at the donor splice site could be D(+2-18) where the last 2 exonic bases and the first 18 intronic bases correspond to the annealing site of the antisense molecule. Entirely exonic annealing coordinates that would be represented by A(+65+85), that is the site between the 65th and 85th nucleotide from the start of that exon.

The entire disclosures of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference. No admission is made that any of the references constitute prior art or are part of the common general knowledge of those working in the field to which this invention relates.

As used necessarily herein the term "derived" and "derived from" shall be taken to indicate that a specific integer may be obtained from a particular source albeit not directly from that source.

Throughout this specification, unless the context requires o#herwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

Description of the Preferred Embodiment

When antisense molecule(s) are targeted to nucleotide sequences involved in splicing in exons within pre-mRNA sequences, normal splicing of the exon may be inhibited causing the splicing machinery to by-pass the entire mutated exon from the mature mRNA. The concept of antisense oligonucleotide induced exon skipping is shown in FIG. 2. In many genes, deletion of an entire exon would lead to the production of a non-functional protein through the loss of important functional domains or the disruption of the reading frame. In some proteins, however, it is possible to shorten the protein by deleting one or more exons, without disrupting the reading frame, from within the protein without seriously altering the biological activity of the protein. Typically, such proteins have a structural role and or possess functional domains at their ends. The present invention describes antisense molecules capable of binding to specified dystrophin pre-mRNA targets and re-directing processing of that gene.

Antisense Molecules

According to a first aspect of the invention, there is provided antisense molecules capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules are preferably selected from the group of compounds shown in Table 1A. There is also provided a combination or "cocktail" of two or more antisense oligonucleotides capable of binding to a selected target to induce exon skipping. To induce exon skipping in exons of the Dystrophin gene transcript, the antisense molecules in a "cocktail" are preferably selected from the group of compounds shown in Table 1B. Alternatively, exon skipping may be induced by antisense oligonucleotides joined together "weasels" preferably selected from the group of compounds shown in Table 1C.

Designing antisense molecules to completely mask consensus splice sites may not necessarily generate any skipping of the targeted exon. Furthermore, the inventors have discovered that size or length of the antisense oligonucleotide itself is not always a primary factor when designing antisense molecules. With some targets such as exon 19, antisense oligonucleotides as short as 12 bases were able to induce exon skipping, albeit not as efficiently as longer (20-31 bases) oligonucleotides. In some other targets, such as murine dystrophin exon 23, antisense oligonucleotides only 17 residues long were able to induce more efficient skipping than another overlapping compound of 25 nucleotides.

The inventors have also discovered that there does not appear to be any standard motif that can be blocked or masked by antisense molecules to redirect splicing. In some exons, such as mouse dystrophin exon 23, the donor splice site was the most amenable to target to re-direct skipping of that exon. It should be noted that designing and testing a series of exon 23 specific antisense molecules to anneal to overlapping regions of the donor splice site showed considerable variation in the efficacy of induced exon skipping. As reported in Mann et al., (2002) there was a significant variation in the efficiency of bypassing the nonsense mutation depending upon antisense oligonucleotide annealing ("Improved antisense oligonucleotide induced exon skipping in the mdx mouse model of muscular dystrophy". *J Gen Med* 4: 644-654). Targeting the acceptor site of exon 23 or several internal domains was not found to induce any consistent exon 23 skipping.

In other exons targeted for removal, masking the donor splice site did not induce any exon skipping. However, by directing antisense molecules to the acceptor splice site (human exon 8 as discussed below), strong and sustained exon skipping was induced. It should be noted that removal of human exon 8 was tightly linked with the co-removal of exon 9. There is no strong sequence homology between the exon 8 antisense oligonucleotides and corresponding regions of exon 9 so it does not appear to be a matter of cross reaction. Rather the splicing of these two exons is inextricably linked. This is not an isolated instance as the same effect is observed in canine cells where targeting exon 8 for removal also resulted in the skipping of exon 9. Targeting exon 23 for removal in the mouse dystrophin pre-mRNA also results in

the frequent removal of exon 22 as well. This effect occurs in a dose dependent manner and also indicates close coordinated processing of 2 adjacent exons.

In other targeted exons, antisense molecules directed at the donor or acceptor splice sites did not induce exon skipping while annealing antisense molecules to intra-exonic regions (i.e. exon splicing enhancers within human dystrophin exon 6) was most efficient at inducing exon skipping. Some exons, both mouse and human exon 19 for example, are readily skipped by targeting antisense molecules to a variety of motifs. That is, targeted exon skipping is induced after using antisense oligonucleotides to mask donor and acceptor splice sites or exon splicing enhancers.

To identify and select antisense oligonucleotides suitable for use in the modulation of exon skipping, a nucleic acid sequence whose function is to be modulated must first be identified. This may be, for example, a gene (or mRNA transcribed form the gene) whose expression is associated with a particular disorder or disease state, or a nucleic acid molecule from an infectious agent. Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites, or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

Preferably, the present invention aims to provide antisense molecules capable of binding to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping. Duchenne muscular dystrophy arises from mutations that preclude the synthesis of a functional dystrophin gene product. These Duchenne muscular dystrophy gene defects are typically nonsense mutations or genomic rearrangements such as deletions, duplications or micro-deletions or insertions that disrupt the reading frame. As the human dystrophin gene is a large and complex gene with the 79 exons being spliced together to generate a mature mRNA with an open reading frame of approximately 11,000 bases, there are many positions where these mutations can occur. Consequently, a comprehensive antisense oligonucleotide based therapy to address many of the different disease-causing mutations in the dystrophin gene will require that many exons can be targeted for removal during the splicing process.

Within the context of the present invention, preferred target site(s) are those involved in mRNA splicing (i.e. splice donor sites, splice acceptor sites or exonic splicing enhancer elements). Splicing branch points and exon recognition sequences or splice enhancers are also potential target sites for modulation of mRNA splicing.

The oligonucleotide and the DNA or RNA are complementary to each other when a sufficient number of corresponding positions in each molecule are occupied by nucleotides which can hydrogen bond with each other. Thus, "specifically hybridisable" and "complementary" are terms which are used to indicate a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target. It is understood in the art that the sequence of an antisense molecule need not be 100% complementary to that of its target sequence to be specifically hybridisable. An antisense molecule is specifically hybridisable when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under conditions in which specific binding is desired, i.e., under physiological conditions in the case of in vivo assays or therapeutic treatment, and in the case of in vitro assays, under conditions in which the assays are performed.

While the above method may be used to select antisense molecules capable of deleting any exon from within a protein that is capable of being shortened without affecting its biological function, the exon deletion should not lead to a reading frame shift in the shortened transcribed mRNA. Thus, if in a linear sequence of three exons the end of the first exon encodes two of three nucleotides in a codon and the next exon is deleted then the third exon in the linear sequence must start with a single nucleotide that is capable of completing the nucleotide triplet for a codon. If the third exon does not commence with a single nucleotide there will be a reading frame shift that would lead to the generation of truncated or a non-functional protein.

It wilt be appreciated that the codon arrangements at the end of exons in structural proteins may not always break at the end of a codon, consequently there may be a need to delete more than one exon from the pre-mRNA to ensure in-frame reading of the mRNA. In such circumstances, a plurality of antisense oligonucleotides may need to be selected by the method of the invention wherein each is directed to a different region responsible for inducing splicing in the exons that are to be deleted.

The length of an antisense molecule may vary so long as it is capable of binding selectively to the intended location within the pre-mRNA molecule. The length of such sequences can be determined in accordance with selection procedures described herein. Generally, the antisense molecule will be from about 10 nucleotides in length up to about 50 nucleotides in length. It will be appreciated however that any length of nucleotides within this range may be used in the method. Preferably, the length of the antisense molecule is between 17 to 30 nucleotides in length.

In order to determine which exons can be connected in a dystrophin gene, reference should be made to an exon boundary map. Connection of one exon with another is based on the exons possessing the same number at the 3' border as is present at the 5' border of the exon to which it is being connected. Therefore, if exon 7 were deleted, exon 6 must connect to either exons 12 or 18 to maintain the reading frame. Thus, antisense oligonucleotides would need to be selected which redirected splicing for exons 7 to 11 in the first instance or exons 7 to 17 in the second instance. Another and somewhat simpler approach to restore the reading frame around an exon 7 deletion would be to remove the two flanking exons. Induction of exons 6 and 8 skipping should result in an in-frame transcript with the splicing of exons 5 to 9. In practise however, targeting exon 8 for removal from the pre-mRNA results in the co-removal of exon 9 so the resultant transcript would have exon 5 joined to exon 10. The inclusion or exclusion of exon 9 does not alter the reading frame. Once the antisense molecules to be tested have been identified, they are prepared according to standard techniques known in the art. The most common method for producing antisense molecules is the methylation of the 2' hydroxyribose position and the incorporation of a phosphorothioate backbone produces molecules that superficially resemble RNA but that are much more resistant to nuclease degradation.

To avoid degradation of pre-mRNA during duplex formation with the antisense molecules, the antisense molecules used in the method may be adapted to minimise or prevent cleavage by endogenous RNase H. This property is highly preferred as the treatment of the RNA with the unmethylated oligonucleotides either intracellularly or in crude extracts that contain RNase H leads to degradation of the pre-mRNA: antisense oligonucleotide duplexes. Any form of modified

antisense molecules that is capable of by-passing or not inducing such degradation may be used in the present method. An example of antisense molecules which when duplexed with RNA are not cleaved by cellular RNase H is 2'-O-methyl derivatives. 2'-O-methyl-oligoribonucleotides are very stable in a cellular environment and in animal tissues, and their duplexes with RNA have higher Tm values than their ribo- or deoxyribo-counterparts.

Antisense molecules that do not activate RNase H can be made in accordance with known techniques (see, e.g., U.S. Pat. No. 5,149,797). Such antisense molecules, which may be deoxyribonucleotide or ribonucleotide sequences, simply contain any structural modification which sterically hinders or prevents binding of RNase H to a duplex molecule containing the oligonucleotide as one member thereof, which structural modification does not substantially hinder or disrupt duplex formation. Because the portions of the oligonucleotide involved in duplex formation are substantially different from those portions involved in RNase H binding thereto, numerous antisense molecules that do not activate RNase H are available. For example, such antisense molecules may be oligonucleotides wherein at least one, or all, of the inter-nucleotide bridging phosphate residues are modified phosphates, such as methyl phosphonates, methyl phosphorothioates, phosphoromorpholidates, phosphoropiperazidates and phosphoramidates. For example, every other one of the internucleotide bridging phosphate residues may be modified as described. In another non-limiting example, such antisense molecules are molecules wherein at least one, or all, of the nucleotides contain a 2' lower alkyl moiety (e.g., C_1-C_4, linear or branched, saturated or unsaturated alkyl, such as methyl, ethyl, ethenyl, propyl, 1-propenyl, 2-propenyl, and isopropyl). For example, every other one of the nucleotides may be modified as described.

While antisense oligonucleotides are a preferred form of the antisense molecules, the present invention comprehends other oligomeric antisense molecules, including but not limited to oligonucleotide mimetics such as are described below.

Specific examples of preferred antisense compounds useful in this invention include oligonucleotides containing modified backbones or non-natural inter-nucleoside linkages. As defined in this specification, oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their inter-nucleoside backbone can also be considered to be oligonucleosides.

In other preferred oligonucleotide mimetics, both the sugar and the inter-nucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleo-bases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone.

Modified oligonucleotides may also contain one or more substituted sugar moieties. Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. Certain nucleo-bases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. and are presently preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

Another modification of the oligonucleotides of the invention involves chemically linking to the oligonucleotide one or more moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety, cholic acid, a thioether, e.g., hexyl-S-tritylthiol, a thiocholesterol, an aliphatic chain, e.g., dodecandiol or undecyl residues, a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate, a polyamine or a polyethylene glycol chain, or adamantane acetic acid, a palmityl moiety, or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety.

It is not necessary far all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds that are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this invention, are antisense molecules, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the increased resistance to nuclease degradation, increased cellular uptake, and an additional region for increased binding affinity for the target nucleic acid.

Methods of Manufacturing Antisense Molecules

The antisense molecules used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). One method for synthesising oligonucleotides on a modified solid support is described in U.S. Pat. No. 4,458,066.

Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates–and alkylated derivatives. In one such automated embodiment, diethyl-phosphoramidites are used as starting materials and may be synthesized as described by Beaucage, et al., (1981) *Tetrahedron Letters,* 22:1859-1862.

The antisense molecules of the invention are synthesised in vitro and do not include antisense compositions of biological origin, or genetic vector constructs designed to direct the in vivo synthesis of antisense molecules. The molecules of the invention may also be mixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor targeted molecules, oral, rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption.

Therapeutic Agents

The present invention also can be used as a prophylactic or therapeutic, which may be utilised for the purpose of treatment of a genetic disease.

Accordingly, in one embodiment the present invention provides antisense molecules that bind to a selected target in the dystrophin pre-mRNA to induce efficient and consistent exon skipping described herein in a therapeutically effective amount admixed with a pharmaceutically acceptable carrier, diluent, or excipient.

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similarly untoward reaction, such as gastric upset and the like, when administered to a patient. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in Martin, *Remington's Pharmaceutical Sciences,* 18th Ed., Mack Publishing Co., Easton, Pa., (1990).

In a more specific form of the invention there are provided pharmaceutical compositions comprising therapeutically effective amounts of an antisense molecule together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvants and/or carriers. Such compositions include diluents of various buffer content (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength and additives such as detergents and solubilizing agents (e.g., Tween 80, Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., Thimersol, benzyl alcohol) and bulking substances (e.g., lactose, mannitol). The material may be incorporated into particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hylauronic acid may also be used. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Martin, *Remington's Pharmaceutical Sciences,* 18th Ed. (1990, Mack Publishing Co., Easton, Pa. 18042) pages 1435-1712 that are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilised form.

It will be appreciated that pharmaceutical compositions provided according to the present invention may be administered by any means known in the art. Preferably, the pharmaceutical compositions for administration are administered by injection, orally, or by the pulmonary, or nasal route. The antisense molecules are more preferably delivered by intravenous, intra-arterial, intraperitoneal, intramuscular, or subcutaneous routes of administration.

Antisense Molecule Based Therapy

Also addressed by the present invention is the use of antisense molecules of the present invention, for manufacture of a medicament for modulation of a genetic disease.

The delivery of a therapeutically useful amount of antisense molecules may be achieved by methods previously published. For example, intracellular delivery of the antisense molecule may be via a composition comprising an admixture of the antisense molecule and an effective amount of a block copolymer. An example of this method is described in US patent application US 20040248833.

Other methods of delivery of antisense molecules to the nucleus are described in Mann C J et al., (2001) ["*Antisense-induced exon skipping and the synthesis of dystrophin in the mdx mouse*". Proc., Natl. Acad. Science, 98(1) 42-47J and in Gebski et al., (2003). Human Molecular Genetics, 12(15): 1801-1811.

A method for introducing a nucleic acid molecule into a cell by way of an expression vector either as naked DNA or complexed to lipid carriers, is described in U.S. Pat. No. 6,806,084.

It may be desirable to deliver the antisense molecule in a colloidal dispersion system. Colloidal dispersion systems include macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes or liposome formulations.

Liposomes are artificial membrane vesicles which are useful as delivery vehicles in vitro and in vivo. These formulations may have net cationic, anionic or neutral charge characteristics and are useful characteristics with in vitro, in vivo and ex vivo delivery methods. It has been shown that large unilamellar vesicles (LUV), which range in size from 0.2-4.0.PHI.m can encapsulate a substantial percentage of an aqueous buffer containing large macromolecules. RNA, and DNA can be encapsulated within the aqueous interior and be delivered to cells in a biologically active form (Fraley, et al., Trends Biochem. Sci., 6:77, 1981).

In order for a liposome to be an efficient gene transfer vehicle, the following characteristics should be present: (1) encapsulation of the antisense molecule of interest at high efficiency while not compromising their biological activity; (2) preferential and substantial binding to a target cell in comparison to non-target cells; (3) delivery of the aqueous contents of the vesicle to the target cell cytoplasm at high efficiency; and (4) accurate and effective expression of genetic information (Mannino, et al., Biotechniques, 6:682, 1988).

The composition of the liposome is usually a combination of phospholipids, particularly high-phase-transition-temperature phospholipids, usually in combination with steroids, especially cholesterol. Other phospholipids or other lipids may also be used. The physical characteristics of liposomes depend on pH, ionic strength, and the presence of divalent cations.

Alternatively, the antisense construct may be combined with other pharmaceutically acceptable carriers or diluents to produce a pharmaceutical composition. Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition may be formulated for parenteral, intramuscular, intravenous, subcutaneous, intraocular, oral or transdermal administration.

The routes of administration described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and any dosage for any particular animal and condition. Multiple approaches for introducing functional new genetic material into cells, both in vitro and in vivo have been attempted (Friedmann (1989) Science, 244:1275-1280).

These approaches include integration of the gene to be expressed into modified retroviruses (Friedmann (1989) supra; Rosenberg (1991) Cancer Research 51(18), suppl.: 5074S-5079S); integration into non-retrovirus vectors (Rosenfeld, et al. (1992) Cell, 68:143-155; Rosenfeld, et al. (1991) Science, 252:431-434); or delivery of a transgene linked to a heterologous promoter-enhancer element via liposomes (Friedmann (1989), supra; Brigham, et al. (1989) Am. J. Med. Sci., 298:278-281; Nabel, et al. (1990) Science, 249: 1285-1288; Hazinski, et al. (1991) Am. J. Resp. Cell Molec. Biol., 4:206-209; and Wang and Huang (1987) Proc. Natl. Acad. Sci. (USA), 84:7851-7855); coupled to ligand-specific,

cation-based transport systems (Wu and Wu (1988) J. Biol. Chem., 263:14621-14624) or the use of naked DNA, expression vectors (Nabel et al. (1990), supra); Wolff et al. (1990) Science, 247:1465-1468). Direct injection of transgenes into tissue produces only localized expression (Rosenfeld (1992) supra); Rosenfeld et al. (1991) supra; Brigham et al. (1989) supra; Nabel (1990) supra; and Hazinski et al. (1991) supra). The Brigham et al. group (Am. J. Med. Sci. (1989) 298:278-281 and Clinical Research (1991) 39 (abstract)) have reported in vivo transfection only of lungs of mice following either intravenous or intratracheal administration of a DNA liposome complex. An example of a review article of human gene therapy procedures is: Anderson, Science (1992) 256:808-813.

The antisense molecules of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal including a human, is capable of providing (directly or indirectly) the biologically active metabolite or residue thereof. Accordingly, for example, the disclosure is also drawn to prodrugs and pharmaceutically acceptable salts of the compounds of the invention, pharmaceutically acceptable salts of such pro-drugs, and other bioequivalents.

The term "pharmaceutically acceptable salts" refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto.

For oligonucleotides, preferred examples of pharmaceutically acceptable salts include but are not limited to (a) salts formed with cations such as sodium, potassium, ammonium, magnesium, calcium, polyamines such as spermine and spermidine, etc.; (b) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; (c) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, malefic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; and (d) salts formed from elemental anions such as chlorine, bromine, and iodine. The pharmaceutical compositions of the present invention may be administered in a number of ways depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including rectal delivery), pulmonary, e.g., by inhalation or insufflation of powders or aerosols, (including by nebulizer, intratracheal, intranasal, epidermal and transdermal), oral or parenteral. Parenteral administration includes intravenous, intra-arterial, subcutaneous, intraperitoneal or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Oligonucleotides with at least one 2'-O-methoxyethyl modification are believed to be particularly useful for oral administration.

The pharmaceutical formulations of the present invention, which may conveniently be presented in unit dosage form, may be prepared according to conventional techniques well known in the pharmaceutical industry. Such techniques include the step of bringing into association the active ingredients with the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Kits of the Invention

The invention also provides kits for treatment of a patient with a genetic disease which kit comprises at least an antisense molecule, packaged in a suitable container, together with instructions for its use.

In a preferred embodiment, the kits will contain at least one antisense molecule as shown in Table 1A, or a cocktail of antisense molecules as shown in Table 1B or a "weasel" compound as shown in Table 1C. The kits may also contain peripheral reagents such as buffers, stabilizers, etc.

Those of ordinary skill in the field should appreciate that applications of the above method has wide application for identifying antisense molecules suitable for use in the treatment of many other diseases.

EXAMPLES

The following Examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for carrying out various aspects of the invention. It is understood that these Examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. The references cited herein are expressly incorporated by reference.

Methods of molecular cloning, immunology and protein chemistry, which are not explicitly described in the following examples, are reported in the literature and are known by those skilled in the art. General texts that described conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art, included, for example: Sambrook et al, *Molecular Cloning: A Laboratory Manual*, Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989); Glover ed., *DNA Cloning: A Practical Approach*, Volumes I and II, MRL Press, Ltd., Oxford, U.K. (1985); and Ausubel, F., Brent, R., Kingston, R. E., Moore, D. D., Seidman, J. G., Smith, J. A., Struhl, K. *Current Protocols in Molecular Biology*. Greene Publishing Associates/Wiley Intersciences, New York (2002).

Determining Induced Exon Skipping in Human Muscle Cells

Attempts by the inventors to develop a rational approach in antisense molecules design were not completely successful as there did not appear to be a consistent trend that could be applied to all exons. As such, the identification of the most effective and therefore most therapeutic antisense molecules compounds has been the result of empirical studies.

These empirical studies involved the use of computer programs to identify motifs potentially involved in the splicing process. Other computer programs were also used to identify regions of the pre-mRNA which may not have had extensive secondary structure and therefore potential sites for annealing of antisense molecules. Neither of these approaches proved completely reliable in designing antisense oligonucleotides for reliable and efficient induction of exon skipping.

Annealing sites on the human dystrophin pre-mRNA were selected for examination, initially based upon known or predicted motifs or regions involved in splicing. 2OMe antisense oligonucleotides were designed to be complementary to the target sequences under investigation and were synthesised on an Expedite 8909 Nucleic Acid Synthesiser. Upon completion of synthesis, the oligonucleotides were cleaved from the support column and de-protected in ammonium hydroxide before being desalted. The quality of the oligonucleotide synthesis was monitored by the intensity of the trityl signals upon each deprotection step during the synthesis as detected

in the synthesis log. The concentration of the antisense oligonucleotide was estimated by measuring the absorbance of a diluted aliquot at 260 nm.

Specified amounts of the antisense molecules were then tested for their ability to induce exon skipping in an in vitro assay, as described below.

Briefly, normal primary myoblast cultures were prepared from human muscle biopsies obtained after informed consent. The cells were propagated and allowed to differentiate into myotubes using standard culturing techniques. The cells were then transfected with the antisense oligonucleotides by delivery of the oligonucleotides to the dells as cationic lipoplexes, mixtures of antisense molecules or cationic liposome preparations.

The cells were then allowed to grow for another 24 hours, after which total RNA was extracted and molecular analysis commenced. Reverse transcriptase amplification (RT-PCR) was undertaken to study the targeted regions of the dystrophin pre-mRNA or induced exonic re-arrangements.

For example, in the testing of an antisense molecule for inducing exon 19 skipping the RT-PCR test scanned several exons to detect involvement of any adjacent exons. For example, when inducing skipping of exon 19, RT-PCR was carried out with primers that amplified across exons 17 and 21. Amplifications of even larger products in this area (i.e. exons 13-26) were also carried out to ensure that there was minimal amplification bias for the shorter induced skipped transcript. Shorter or exon skipped products tend to be amplified more efficiently and may bias the estimated of the normal and induced transcript.

The sizes of the amplification reaction products were estimated on an agarose gel and compared against appropriate size standards. The final confirmation of identity of these products was carried out by direct DNA sequencing to establish that the correct or expected exon junctions have been maintained.

FIG. 3 shows differing efficiencies of two antisense molecules directed at exon 8 acceptor splice site. H8A(−06+18) [SEQ ID NO:1], which anneals to the last 6 bases of intron 7 and the first 18 bases of exon 8, induces substantial exon 8 and 9 skipping when delivered into cells at a concentration of 20 nM. The shorter antisense molecule, H8A(−06+14) [SEQ ID NO: 4] was only able to induce exon 8 and 9 skipping at 300 nM, a concentration some 15 fold higher than H8A(−06+18), which is the preferred antisense molecule.

This data shows that some particular antisense molecules induce efficient exon skipping while another antisense molecule, which targets a near-by or overlapping region, can be much less efficient. Titration studies show one compound is able to induce targeted exon skipping at 20 nM while the less efficient antisense molecules only induced exon skipping at concentrations of 300 nM and above. Therefore, we have shown that targeting of the antisense molecules to motifs involved in the splicing process plays a crucial role in the overall efficacy of that compound.

Efficacy refers to the ability to induce consistent skipping of a target exon. However, sometimes skipping of the target exons is consistently associated with a flanking exon. That is, we have found that the splicing of some exons is tightly linked. For example, in targeting exon 23 in the mouse model of muscular dystrophy with antisense molecules directed at the donor site of that exon, dystrophin transcripts missing exons 22 and 23 are frequently detected. As another example, when using an antisense molecule directed to exon 8 of the human dystrophin gene, all induced transcripts are missing both exons 8 and 9. Dystrophin transcripts missing only exon 8 are not observed.

Table 2 below discloses antisense molecule sequences that induce exon 8 (and 9) skipping.

TABLE 2

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
1	H8A(-06 + 18)	5'-GAU AGG UGG UAU CAA CAU CUG UAA	Very strong to 20 nM
2	H8A(-03 + 18)	5'-GAU AGG UGG UAU CAA CAU CUG	Very strong skipping to 40 nM
3	H8A(-07 + 18)	5'-GAU AGG UGG UAU CAA CAU CUG UAA G	Strong skipping to 40 nM
4	H8A(-06 + 14)	5'-GGU GGU AUC AAC AUC UGU AA	Skipping to 300 nM
5	H8A(-10 + 10)	5'-GUA UCA ACA UCU GUA AGC AC	Patchy/weak skipping to 100 nm

Once efficient exon skipping had been induced with one antisense molecule, subsequent overlapping antisense molecules may be synthesized and then evaluated in the assay as described above. Our definition of an efficient antisense molecule is one that induces strong and sustained exon skipping at transfection concentrations in the order of 300 nM or less.

Antisense Oligonucleotides Directed at Exon 8

Antisense oligonucleotides directed at exon 8 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense Oligonucleotides Directed at Exon 7

Antisense oligonucleotides directed at exon 7 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 4 shows the preferred antisense molecule, H7A(+45+67) [SEQ ID NO: 6], and another antisense molecule, H7A (+2+26) [SEQ ID NO: 7], inducing exon 7 skipping. Nested amplification products span exons 3 to 9. Additional products above the induced transcript missing exon 7 arise from amplification from carry-over outer primers from the RT-PCR as well as heteroduplex formation.

Table 3 below discloses antisense molecule sequences for induced exon 7 skipping.

TABLE 3

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
6	H7A(+45 + 67)	5'- UGC AUG UUC CAG UCG UUG UGU GG	Strong skipping to 20 nM
7	H7A(+02 + 26)	5'- CAC UAU UCC AGU CAA AUA GGU CUG G	Weak skipping at 100 nM
8	H7D(+15 - 10)	5'-AUU UAC CAA CCU UCA GGA UCG AGU A	Weak skipping to 300 nM
9	H7A(-18 + 03)	5'- GGC CUA AAA CAC AUA CAC AUA	Weak skipping to 300 nM

Antisense Oligonucleotides Directed at Exon 6

Antisense oligonucleotides directed at exon 6 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 5 shows an example of two non-preferred antisense molecules inducing very low levels of exon 6 skipping in cultured human cells. Targeting this exon for specific removal was first undertaken during a study of the canine model using the oligonucleotides as listed in Table 4, below. Some of the human specific oligonucleotides were also evaluated, as shown in FIG. 5. In this example, both antisense molecules target the donor splice site and only induced low levels of exon 6 skipping. Both H6D(+4-21) [SEQ ID NO: 17] and H6D(+18-4) [SEQ ID NO: 18] would be regarded as non-preferred antisense molecules.

One antisense oligonucleotide that induced very efficient exon 6 skipping in the canine model, C6A(+69+91) [SEQ ID NO: 14], would anneal perfectly to the corresponding region in human dystrophin exon 6. This compound was evaluated, found to be highly efficient at inducing skipping of that target exon, as shown in FIG. 6 and is regarded as the preferred compound for induced exon 6 skipping. Table 4 below discloses antisense molecule sequences for induced exon 6 skipping.

TABLE 4

SEQ ID	Antisense Oligo name	Sequence	Ability to induce skipping
10	C6A(-10 + 10)	5' CAU UUU UGA CCU ACA UGU GG	No skipping
11	C6A(-14 + 06)	5' UUU GAC CUA CAU GUG GAA AG	No skipping
12	C6A(-14 + 12)	5' UAC AUU UUU GAC CUA CAU GUG GAA AG	No skipping
13	C6A(-13 + 09)	5' AUU UUU GAC CUA CAU GGG AAA G	No skipping
14	CH6A(+69 + 91)	5' UAC GAG UUG AUU GUC GGA CCC AG	Strong skipping to 20 nM
15	C6D(+12 - 13)	5' GUG GUC UCC UUA CCU AUG ACU GUG G	Weak skipping at 300 nM
16	C6D(+06 - 11)	5' GGU CUC CUU ACC UAU GA	No skipping
17	H6D(+04 - 21)	5' UGU CUC AGU AAU CUU CUU ACC UAU	Weak skipping to 50 nM
18	H6D(+18 - 04)	5' UCU UAC CUA UGA CUA UGG AUG AGA	Very weak skipping to 300 nM

Antisense Oligonucleotides Directed at Exon 4

Antisense oligonucleotides directed at exon 4 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 7 shows an example of a preferred antisense molecule inducing skipping of exon 4 skipping in cultured human cells. In this example, one preferred antisense compound, H4A(+13+32) [SEQ ID NO:19], which targeted a presumed exonic

splicing enhancer induced efficient exon skipping at a concentration of 20 nM while other non-preferred antisense oligonucleotides failed to induce even low levels of exon 4 skipping. Another preferred antisense molecule inducing skipping of exon 4 was H4A(+111+40) [SEQ ID NO:22], which induced efficient exon skipping at a concentration of 20 nM.

Table 5 below discloses antisense molecule sequences for inducing exon 4 skipping.

TABLE 5

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
19	H4A(+13 + 32)	5' GCA UGA ACU CUU GUG GAU CC	Skipping to 20 nM
22	H4A(+11 + 40)	5' UGU UCA GGG CAU GAA CUC UUG UGG AUC CUU	Skipping to 20 nM
20	H4D(+04 - 16)	5' CCA GGG UAC UAC UUA CAU UA	No skipping
21	H4D(-24 - 44)	5' AUC GUG UGU CAC AGC AUC CAG	No skipping

Antisense Oligonucleotides Directed at Exon 3

Antisense oligonucleotides directed at exon 3 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H3A(+30+60) [SEQ ID NO:23] induced substantial exon 3 skipping when delivered into cells at a concentration of 20 nM to 600 nM. The antisense molecule, H3A(+35+65) [SEQ ID NO: 24] induced exon skipping at 300 nM.

Table 6 below discloses antisense molecule sequences that induce exon 3 skipping.

TABLE 6

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
23	H3A(+30 + 60)	UAG GAG GCG CCU CCC AUC CUG UAG GUC ACU G	Moderate skipping to 20 to 600 nM
24	H3A(+35 + 65)	AGG UCU AGG AGG CGC CUC CCA UCC UGU AGG U	Working to 300 nM
25	H3A(+30 + 54)	GCG CCU CCC AUC CUG UAG GUC ACU G	Moderate 100-600 nM
26	H3D(+46 - 21)	CUU CGA GGA GGU CUA GGA GGC GCC UC	No skipping
27	H3A(+30 + 50)	CUC CCA UCC UGU AGG UCA CUG	Moderate 20-600 nM
28	H3D(+19 - 03)	UAC CAG UUU UUG CCC UGU CAG G	No skipping
29	H3A(-06 + 20)	UCA AUA UGC UGC UUCCCA AAC UGA AA	No skipping
30	H3A(+37 + 61)	CUA GGA GGC GCC UCC CAU CCU GUA G	No skipping

Antisense Oligonucleotides Directed at Exon 5

Antisense oligonucleotides directed at exon 5 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H5A(+20+50) [SEQ ID NO:31] induces substantial exon 5 skipping when delivered into cells at a concentration of 100 nM. Table 7 below shows other antisense molecules tested. The majority of these antisense molecules were not as effective at exon skipping as H5A(+20+50). However, H5A(+15+45) [SEQ ID NO: 40] was able to induce exon 5 skipping at 300 nM.

Table 7 below discloses antisense molecule sequences that induce exon 5 skipping.

TABLE 7

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
31	H5A(+20 + 50)	UUA UGA UUU CCA UCU ACG AUG UCA GUA CUU C	Working to 100 nM
32	H5D(+25 - 05)	CUU ACC UGC CAG UGG AGG AUU AUA UUC CAA A	No skipping
33	H5D(+10 - 15)	CAU CAG GAU UCU UAC CUG CCA GUG G	Inconsistent at 300 nM
34	H5A(+10 + 34)	CGA UGU CAG UAC UUC CAA UAU UCA C	Very weak
35	H5D(-04 - 21)	ACC AUU CAU CAG GAU UCU	No skipping
36	H5D(+16 - 02)	ACC UGC CAG UGG AGG AUU	No skipping
37	H5A(-07 + 20)	CCA AUA UUC ACU AAA UCA ACC UGU UAA	No skipping
38	H5D(+18 - 12)	CAG GAU UCU UAC CUG CCA GUG GAG GAU UAU	No skipping

TABLE 7-continued

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
39	H5A(+05 + 35)	ACG AUG UCA GUA CUU CCA AUA UUC ACU AAA U	No skipping
40	H5A(+15 + 45)	AUU UCC AUC UAC GAU GUC AGU ACU UCC AAU A	Working to 300 nM

Antisense Oligonucleotides Directed at Exon 10

Antisense oligonucleotides directed at exon 10 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H10A(-05+16) [SEQ ID NO:41] induced substantial exon 10 skipping when delivered into cells. Table 8 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was variable. Table 8 below discloses antisense molecule sequences that induce exon 10 skipping.

TABLE 8

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
41	H10A(-05 + 16)	CAG GAG CUU CCA AAU GCU GCA	Not tested
42	H10A(-05 + 24)	CUU GUC UUC AGG AGC UUC CAA AUG CUG CA	Not tested
43	H10A(+98 + 119)	UCC UCA GCA GAA AGA AGC CAC G	Not tested
44	H10A(+130 + 149)	UUA GAA AUC UCU CCU UGU GC	No skipping
45	H10A(-33 - 14)	UAA AUU GGG UGU UAC ACA AU	No skipping

Antisense Oligonucleotides Directed at Exon 11

Antisense oligonucleotides directed at exon 11 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 8B shows an example of H11A(+75+97) [SEQ ID NO:49] antisense molecule inducing exon 11 skipping in cultured human cells. H11A(+75+97) induced substantial exon 11 skipping when delivered into cells at a concentration of 5 nM. Table 9 below shows other antisense molecules tested. The antisense molecules ability to induce exon skipping was observed at 100 nM.

TABLE 9

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
46	H11D(+26 + 49)	CCC UGA GGC AUU CCC AUC UUG AAU	Skipping at 100 nM
47	H11D(+11 - 09)	AGG ACU UAC UUG CUU UGU UU	Skipping at 100 nM

TABLE 9-continued

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
48	H11A(+118 + 140)	CUU GAA UUU AGG AGA UUC AUC UG	Skipping at 100 nM
49	H11A(+75 + 97)	CAU CUU CUG AUA AUU UUC CUG UU	Skipping at 100 nM
46	H11D(+26 + 49)	CCC UGA GGC AUU CCC AUC UUG AAU	Skipping at 5 nM

Antisense Oligonucleotides Directed at Exon 12

Antisense oligonucleotides directed at exon 12 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H12A(+52+75) [SEQ ID NO:50] induced substantial exon 12 skipping when delivered into cells at a concentration of 5 nM, as shown in FIG. 8A. Table 10 below shows other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The antisense molecules ability to induce exon skipping was variable.

TABLE 10

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
50	H12A(+52+75)	UCU UCU GUU UUU GUU AGC CAG UCA	Skipping at 5 nM
51	H12A(-10+10)	UCU AUG UAA ACU GAA AAU UU	Skipping at 100 nM
52	H12A(+11+30)	UUC UGG AGA UCC AUU AAA AC	No skipping

Antisense Oligonucleotides Directed at Exon 13

Antisense oligonucleotides directed at exon 13 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H13A(+77+100) [SEQ ID NO:53] induced substantial exon 13 skipping when delivered into cells at a concentration of 5 nM. Table 11 below includes two other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These other antisense molecules were unable to induce exon skipping.

TABLE 11

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
53	H13A(+77+100)	CAG CAG UUG CGU GAU CUC CAC UAG	Skipping at 5 nM
54	H13A(+55+75)	UUC AUC AAC UAC CAC CAC CAU	No skipping
55	H13D(+06-19)	CUA AGC AAA AUA AUC UGA CCU UAA G	No skipping

Antisense Oligonucleotides Directed at Exon 14

Antisense oligonucleotides directed at exon 14 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H14A(+37+64) [SEQ ID NO:56] induced weak exon 14 skipping when delivered into cells at a concentration of 100 nM. Table 12 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. The other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

TABLE 12

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
56	H14A(+37+64)	CUU GUA AAA GAA CCC AGC GGU CUU CUG U	Skipping at 100 nM
57	H14A(+14+35)	CAU CUA CAG AUG UUU GCC CAU C	No skipping
58	H14A(+51+73)	GAA GGA UGU CUU GUA AAA GAA CC	No skipping
59	H14D(-02+18)	ACC UGU UCU UCA GUA AGA CG	No skipping
60	H14D(+14-10)	CAU GAC ACA CCU GUU CUU CAG UAA	No skipping
61	H14A(+61+80)	CAU UUG AGA AGG AUG UCU UG	No skipping
62	H14A(-12+12)	AUC UCC CAA UAC CUG GAG AAG AGA	No skipping

Antisense Oligonucleotides Directed at Exon 15

Antisense oligonucleotides directed at exon 15 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H15A(-12+19) [SEQ ID NO:63] and H15A(+48+71) [SEQ ID NO:64] induced substantial exon 15 skipping when delivered into cells at a concentration of 10 Nm, as shown in FIG. 9A. Table 13 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 Nm. These other antisense molecules were unable to induce exon skipping at any of the concentrations tested.

TABLE 13

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
63	H15A(-12+19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA CAU U	Skipping at 5 Nm
64	H15A(+48+71)	UCU UUA AAG CCA GUU GUG UGA AUC	Skipping at 5 Nm
65	H15A(+08+28)	UUU CUG AAA GCC AUG CAC UAA	No skipping
63	H15A(-12+19)	GCC AUG CAC UAA AAA GGC ACU GCA AGA CAU U	No skipping
66	H15D(+17-08)	GUA CAU ACG GCC AGU UUU UGA AGA C	No skipping

Antisense Oligonucleotides Directed at Exon 16

Antisense oligonucleotides directed at exon 16 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H16A(−12+19) [SEQ ID NO:67] and H16A(−06+25) [SEQ ID NO:68] induced substantial exon 16 skipping when delivered into cells at a concentration of 10 nM, as shown in FIG. 9B. Table 14 below includes other antisense molecules tested. H16A(−06+19) [SEQ ID NO:69] and H16A(+87+109) [SEQ ID NO:70] were tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These two antisense molecules were able to induce exon skipping at 25 nM and 100 nM, respectively. Additional antisense molecules were tested at 100, 200 and 300 nM and did not result in any exon skipping.

TABLE 14

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
67	H16A(-12+19)	CUA GAU CCG CUU UUA AAA CCU GUU AAA ACA A	Skipping at 5 nM
68	H16A(-06+25)	UCU UUU CUA GAU CCG CUU UUA AAA CCU GUU A	Skipping at 5 nM
69	H16A(-06+19)	CUA GAU CCG CUU UUA AAA CCU GUU	ASkipping at 25 nM
70	H16A(+87+109)	CCG UCU UCU GGG UCA CUG ACU UA	Skipping at 100 nM
71	H16A(-07+19)	CUA GAU CCG CUU UUA AAA CCU GUU AA	No skipping
72	H16A(-07+13)	CCG CUU UUA AAA CCU GUU AA	No skipping
73	H16A(+12+37)	UGG AUU GCU UUU UCU UUU CUA GAU CC	No skipping
74	H16A(+92+116)	CAU GCU UCC GUC UUC UGG GUC ACU G	No skipping
75	H16A(+45+67)	G AUC UUG UUU GAG UGA AUA CAG U	No skipping
76	H16A(+105+126)	GUU AUC CAG CCA UGC UUC CGU C	No skipping
77	H16D(+05-20)	UGA UAA UUG GUA UCA CUA ACC UGU G	No skipping
78	H16D(+12-11)	GUA UCA CUA ACC UGU GCU GUA C	No skipping

Antisense Oligonucleotides Directed at Exon 19

Antisense oligonucleotides directed at exon 19 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H19A(+35+65) [SEQ ID NO:79] induced substantial exon 19 skipping when delivered into cells at a concentration of 10 nM. This antisense molecule also showed very strong exon skipping at concentrations of 25, 50, 100, 300 and 600 nM.

FIG. 10 illustrates exon 19 and 20 skipping using a "cocktail" of antisense oligonucleotides, as tested using gel electrophoresis. It is interesting to note that it was not easy to induce exon 20 skipping using single antisense oligonucleotides H20A(+44+71) [SEQ ID NO:81] or H20A(+149+170) [SEQ ID NO:82], as illustrated in sections 2 and 3 of the gel shown in FIG. 10. Whereas, a "cocktail" of antisense oligonucleotides was more efficient as can be seen in section 4 of FIG. 10 using a "cocktail" of antisense oligonucleotides H20A(+44+71) and H20A(+149+170). When the cocktail was used to target exon 19, skipping was even stronger (see section 5, FIG. 10).

FIG. 11 illustrates gel electrophoresis results of exon 19/20 skipping using "weasels" The "weasels" were effective in skipping exons 19 and 20 at concentrations of 25, 50, 100, 300 and 600 nM. A further "weasel" sequence is shown in the last row of Table 3C. This compound should give good results.

Antisense Oligonucleotides Directed at Exon 20

Antisense oligonucleotides directed at exon 20 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

None of the antisense oligonucleotides tested induced exon 20 skipping when delivered into cells at a concentration of 10, 25, 50, 300 or 600 nM (see Table 15). Antisense molecules H20A(−11+17) [SEQ ID NO:86] and H20D(+08−20) [SEQ ID NO:87] are yet to be tested.

However, a combination or "cocktail" of H20A(+44+71) [SEQ ID NO: 81] and H20(+149+170) [SEQ ID NO:82] in a ratio of 1:1, exhibited very strong exon skipping at a concentration of 100 nM and 600 nM. Further, a combination of antisense molecules H19A(+35+65) [SEQ ID NO:79], H20A (+44+71) [SEQ ID NO:81] and H20A(+149+170) [SEQ ID NO:82] in a ratio of 2:1:1, induced very strong exon skipping at a concentration ranging from 10 nM to 600 nM.

TABLE 15

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
81	H20A(+44+71)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C	No skipping
82	H20A(+147+168)	CAG CAG UAG UUG UCA UCU GCU C	No skipping
83	H20A(+185+203)	UGA UGG GGU GGU GGG UUG G	No skipping
84	H20A(-08+17)	AUC UGC AUU AAC ACC CUC UAG AAA G	No skipping
85	H20A(+30+53)	CCG GCU GUU CAG UUG UUC UGA GGC	No skipping
86	H20A(-11+17)	AUC UGC AUU AAC ACC CUC UAG AAA GAA A	Not tested yet
87	H20D(+08-20)	GAA GGA GAA GAG AUU CUU ACC UUA CAA A	Not tested yet
81 & 82	H20A(+44+71) & H20A(+147+168)	CUG GCA GAA UUC GAU CCA CCG GCU GUU C CAG CAG UAG UUG UCA UCU GCU C	Very strong skipping
80, 81 & 82	H19A(+35+65); H20A(+44+71); H20A(+147+168)	GCC UGA GCU GAU CUG CUG GCA UCU UGC AGU U; CUG GCA GAA UUC GAU CCA CCG GCU GUU C; CAG CAG UAG UUG UCA UCU GCU C	Very strong skipping

Antisense Oligonucleotides Directed at Exon 21

Antisense oligonucleotides directed at exon 21 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H21A(+85+108) [SEQ ID NO:92] and H21A(+85+106) [SEQ ID NO:91] induced exon 21 skipping when delivered into cells at a concentration of 50 nM. Table 16 below includes other antisense molecules tested at a concentration range of 5, 25, 50, 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping

TABLE 16

SEQ ID	Antisense Oligonucleotide name	Sequence	Ability to induce skipping
90	H21A(-06+16)	GCC GGU UGA CUU CAU CCU GUG C	Skips at 600 nM
91	H21A(+85+106)	CUG CAU CCA GGA ACA UGG GUC C	Skips at 50 nM
92	H21A(+85+108)	GUC UGC AUC CAG GAA CAU GGG UC	Skips at 50 nM
93	H21A(+08+31)	GUU GAA GAU CUG AUA GCC GGU UGA	Skips faintly to
94	H21D(+18-07)	UAC UUA CUG UCU GUA GCU CUU UCU	No skipping

Antisense Oligonucleotides Directed at Exon 22

Antisense oligonucleotides directed at exon 22 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 12 illustrates differing efficiencies of two antisense molecules directed at exon 22 acceptor splice site. H22A(+125+106) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO: 98] induce strong exon 22 skipping from 50 nM to 600 nM concentration.

H22A(+125+146) [SEQ ID NO:96] and H22A(+80+101) [SEQ ID NO:98] induced exon 22 skipping when delivered into cells at a concentration of 50 nM. Table 17 below shows other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 17

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
95	H22A(+22+45)	CAC UCA UGG UCU CCU GAU AGC GCA	No skipping
96	H22A(+125+146)	CUG CAA UUC CCC GAG UCU CUG C	Skipping to 50 nM
97	H22A(+47+69)	ACU GCU GGA CCC AUG UCC UGA UG	Skipping to 300 nM
98	H22A(+80+101)	CUA AGU UGA GGU AUG GAG AGU	Skipping to 50 nM
99	H22D(+13-11)	UAU UCA CAG ACC UGC AAU UCC CC	No skipping

Antisense Oligonucleotides Directed at Exon 23

Antisense oligonucleotides directed at exon 23 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 18 below shows antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed no ability to induce exon skipping or are yet to be tested.

TABLE 18

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
100	H23A(+34+59)	ACA GUG GUG CUG AGA UAG UAU AGG CC	No skipping
101	H23A(+18+39)	UAG GCC ACU UUG UUG CUC UUG C	No Skipping
102	H23A(+72+90)	UUC AGA GGG CGC UUU CUU C	No Skipping

Antisense Oligonucleotides Directed at Exon 24

Antisense oligonucleotides directed at exon 24 were prepared using similar methods as described above. Table 19 below outlines the antisense oligonucleotides directed at exon 24 that are yet to be tested for their ability to induce exon 24 skipping.

TABLE 19

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
103	H24A(+48+70)	GGG CAG GCC AUU CCU CCU UCA GA	Needs testing
104	H24A(-02+22)	UCU UCA GGG UUU GUA UGU GAU UCU	Needs testing

Antisense Oligonucleotides Directed at Exon 25

Antisense oligonucleotides directed at exon 25 were prepared using similar methods as described above. Table 20 below shows the antisense oligonucleotides directed at exon 25 that are yet to be tested for their ability to induce exon 25 skipping.

TABLE 20

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
105	H25A(+9+36)	CUG GGC UGA AUU GUC UGA AUA UCA CUG	Needs testing
106	H25A(+131+156)	CUG UUG GCA CAU GUG AUC CCA CUG AG	Needs testing
107	H25D(+16-08)	GUC UAU ACC UGU UGG CAC AUG UGA	Needs testing

Antisense oligonucleotides Directed at Exon 26

Antisense oligonucleotides directed at exon 26 were prepared using similar methods as described above. Table 21 below outlines the antisense oligonucleotides directed at exon 26 that are yet to be tested for their ability to induce exon 26 skipping.

TABLE 21

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
108	H26A(+132+156)	UGC UUU CUG UAA UUC AUC UGG AGU U	Needs testing
109	H26A(-07+19)	CCU CCU UUC UGG CAU AGA CCU UCC AC	Needs testing
110	H26A(+68+92)	UGU GUC AUC CAU UCG UGC AUC UCU G	Faint skipping at 600 nM

Antisense oligonucleotides Directed at Exon 27

Antisense oligonucleotides directed at exon 27 were prepared using similar methods as described above. Table 22 below outlines the antisense oligonucleotides directed at exon 27 that are yet to be tested for their ability to induce exon 27 skipping.

TABLE 22

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
111	H27A(+82+106)	UUA AGG CCU CUU GUG CUA CAG GUG G	Needs testing

TABLE 22-continued

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
112	H27A(-4+19)	GGG CCU CUU CUU UAG CUC UCU GA	Faint skipping at 600 and 300 nM
113	H27D(+19-03)	GAC UUC CAA AGU CUU GCA UUU C	v. strong skipping at 600 and 300 nM

Antisense Oligonucleotides Directed at Exon 28

Antisense oligonucleotides directed at exon 28 were prepared using similar methods as described above. Table 23 below outlines the antisense oligonucleotides directed at exon 28 that are yet to be tested for their ability to induce exon 28 skipping.

TABLE 23

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
114	H28A(-05+19)	GCC AAC AUG CCC AAA CUU CCU AAG	v. strong skipping at 600 and 300 nM
115	H28A(+99+124)	CAG AGA UUU CCU CAG CUC CGC CAG GA	Needs testing
116	H28D(+16-05)	CUU ACA UCU AGC ACC UCA GAG	v. strong skipping at 600 and 300 nM

Antisense Oligonucleotides Directed at Exon 29

Antisense oligonucleotides directed at exon 29 were prepared using similar methods as described above. Table 24 below outlines the antisense oligonucleotides directed at exon 29 that are yet to be tested for their ability to induce exon 29 skipping.

TABLE 24

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
117	H29A(+57+81)	UCC GCC AUC UGU UAG GGU CUG UGC C	Needs testing
118	H29A(+18+42)	AUU UGG GUU AUC CUC UGA AUG UCG C	v. strong skipping at 600 and 300 nM
119	H29D(+17-05)	CAU ACC UCU UCA UGU AGU UCC C	v. strong skipping at 600 and 300 nM

Antisense Oligonucleotides Directed at Exon 30

Antisense oligonucleotides directed at exon 30 were prepared using similar methods as described above. Table 25 below outlines the antisense oligonucleotides directed at exon 30 that are yet to be tested for their ability to induce exon 30 skipping.

TABLE 25

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
120	H30A(+122+147)	CAU UUG AGC UGC GUC CAC CUU GUC UG	Needs testing
121	H30A(+25+50)	UCC UGG GCA GAC UGG AUG CUC UGU UC	Very strong skipping at 600 and 300 nM.
122	H30D(+19-04)	UUG CCU GGG CUU CCU GAG GCA UU	Very strong skipping at 600 and 300 nM.

Antisense Oligonucleotides Directed at Exon 31

Antisense oligonucleotides directed at exon 31 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 13 illustrates differing efficiencies of two antisense molecules directed at exon 31 acceptor splice site and a "cocktail" of exon 31 antisense oligonucleotides at varying concentrations. H31D(+03-22) [SEQ ID NO:124] substantially induced exon 31 skipping when delivered into cells at a concentration of 20 nM. Table 26 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 26

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
123	H31D(+06-18)	UUC UGA AAU AAC AUA UAC CUG UGC	Skipping to 300 nM
124	H31D(+03-22)	UAG UUU CUG AAA UAA CAU AUA CCU G	Skipping to 20 nM
125	H31A(+05+25)	GAC UUG UCA AAU CAG AUU GGA	No skipping
126	H31D(+04-20)	GUU UCU GAA AUA ACA UAU ACC UGU	Skipping to 300 nM

Antisense oligonucleotides Directed at Exon 32

Antisense oligonucleotides directed at exon 32 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H32D(+04-16) [SEQ ID NO:127] and H32A(+49+73) [SEQ ID NO:130] induced exon 32 skipping when delivered into cells at a concentration of 300 nM. Table 27 below also shows other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules did not show an ability to induce exon skipping.

TABLE 27

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
127	H32D(+04-16)	CAC CAG AAA UAC AUA CCA CA	Skipping to 300 nM
128	H32A(+151+170)	CAA UGA UUU AGC UGU GAC UG	No skipping
129	H32A(+10+32)	CGA AAC UUC AUG GAG ACA UCU UG	No skipping

TABLE 27-continued

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
130	H32A(+49+73)	CUU GUA GAC GCU GCU CAA AAU UGG C	Skipping to 300 nM

Antisense Oligonucleotides Directed at Exon 33

Antisense oligonucleotides directed at exon 33 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 14 shows differing efficiencies of two antisense molecules directed at exon 33 acceptor splice site. H33A(+64+88) [SEQ ID NO:134] substantially induced exon 33 skipping when delivered into cells at a concentration of 10 nM. Table 28 below includes other antisense molecules tested at a concentration of 100, 200 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 28

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
131	H33D(+09-11)	CAU GCA CAC ACC UUU GCU CC	No skipping
132	H33A(+53+76)	UCU GUA CAA UCU GAC GUC CAG UCU	Skipping to 200 nM
133	H33A(+30+56)	GUG UUU AUC ACC AUU UCC ACU UCA GAC	Skipping to 200 nM
134	H33A(+64+88)	GCG UCU GCU UUU UCU GUA CAA UCU G	Skipping to 10 nM

Antisense Oligonucleotides Directed at Exon 34

Antisense oligonucleotides directed at exon 34 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Table 29 below includes antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed a variable ability to induce exon skipping.

TABLE 29

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
135	H34A(+83+104)	UCC AUA UCU GUA GCU GGC AGC C	No skipping
136	H34A(+143+165)	CCA GGC AAC UUC AGA AUC CAA AU	No skipping
137	H34A(-20+10)	UUU CUG UUA CCU GAA AAG AAU UAU AAU GAA	Not tested
138	H34A(+46+70)	CAU UCA UUU CCU UUC GCA UCU UAC G	Skipping to 300 nM
139	H34A(+95+120)	UGA UCU CUU UGU CAA UUC CAU AUC UG	Skipping to 300 nM
140	H34D(+10-20)	UUC AGU GAU AUA GGU UUU ACC UUU CCC CAG	Not tested

TABLE 29-continued

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
141	H34A(+72+96)	CUG UAG CUG CCA GCC AUU CUG UCA AG	No skipping

Antisense Oligonucleotides Directed at Exon 35

Antisense oligonucleotides directed at exon 35 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 15 shows differing efficiencies of antisense molecules directed at exon 35 acceptor splice site. H35A(+24+43) [SEQ ID NO:144] substantially induced exon 35 skipping when delivered into cells at a concentration of 20 nM. Table 30 below also includes other antisense molecules tested at a concentration of 100 and 300 nM. These antisense molecules showed no ability to induce exon skipping.

TABLE 30

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
142	H35A(+141+161)	UCU UCU GCU CGG GAG GUG ACA	Skipping to 20 nM
143	H35A(+116+135)	CCA GUU ACU AUU CAG AAG AC	No skipping
144	H35A(+24+43)	UCU UCA GGU GCA CCU UCU GU	No skipping

Antisense Oligonucleotides Directed at Exon 36

Antisense oligonucleotides directed at exon 36 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense molecule H36A(+26+50) [SEQ ID NO:145] induced exon 36 skipping when delivered into cells at a concentration of 300 nM, as shown in FIG. 16.

Antisense Oligonucleotides Directed at Exon 37

Antisense oligonucleotides directed at exon 37 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 17 shows differing efficiencies of two antisense molecules directed at exon 37 acceptor splice site. H37A(+82+105) [SEQ ID NO:148] and H37A(+134+157) [SEQ ID NO:149] substantially induced exon 37 skipping when delivered into cells at a concentration of 10 nM. Table 31 below shows the antisense molecules tested.

TABLE 31

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
147	H37A(+26+50)	CGU GUA GAG UCC ACC UUU GGG CGU A	No skipping
148	H37A(+82+105)	UAC UAA UUU CCU GCA GUG GUC ACC	Skipping to 10 nM
149	H37A(+134+157)	UUC UGU GUG AAA UGG CUG CAA AUC	Skipping to 10 nM

Antisense Oligonucleotides Directed at Exon 38

Antisense oligonucleotides directed at exon 38 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. **18** illustrates antisense molecule H38A(+88+112) [SEQ ID NO:152], directed at exon 38 acceptor splice site. H38A(+88+112) substantially induced exon 38 skipping when delivered into cells at a concentration of 10 nM. Table 32 below shows the antisense molecules tested and their ability to induce exon skipping.

TABLE 32

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
150	H38A(-01+19)	CCU UCA AAG GAA UGG AGG CC	No skipping
151	H38A(+59+83)	UGC UGA AUU UCA GCC UCC AGU GGU U	Skipping to 10 nM
152	H38A(+88+112)	UGA AGU CUU CCU CUU UCA GAU UCA C	Skipping to 10 nM

Antisense Oligonucleotides Directed at Exon 39

Antisense oligonucleotides directed at exon 39 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H39A(+62+85) [SEQ ID NO:153] induced exon 39 skipping when delivered into cells at a concentration of 100 nM. Table 33 below shows the antisense molecules tested and their ability to induce exon skipping.

TABLE 33

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
153	H39A(+62+85)	CUG GCU UUC UCU CAU CUG UGA UUC	Skipping to 100 nM
154	H39A(+39+58)	GUU GUA AGU UGU CUC CUC UU	No skipping
155	H39A(+102+121)	UUG UCU GUA ACA GCU GCU GU	No skipping
156	H39D(+10-10)	GCU CUA AUA CCU UGA GAG CA	Skipping to 300 nM

Antisense Oligonucleotides Directed at Exon 40

Antisense oligonucleotides directed at exon 40 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. **19** illustrates antisense molecule H40A(-05+17) [SEQ ID NO:157] directed at exon 40 acceptor splice site. H40A(-05+17) and H40A(+129+153) [SEQ ID NO:158] both substantially induced exon 40 skipping when delivered into cells at a concentration of 5 nM.

Antisense Oligonucleotides Directed at Exon 42

Antisense oligonucleotides directed at exon 42 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 20 illustrates antisense molecule H42A(−04+23) [SEQ ID NO:159], directed at exon 42 acceptor splice site. H42A(−4+23) and H42D(+19−02) [SEQ ID NO:161] both induced exon 42 skipping when delivered into cells at a concentration of 5 nM. Table 34 below shows the antisense molecules tested and their ability to induce exon 42 skipping.

TABLE 34

SEQ ID	Antisense afigonucleotide name	Sequence	Ability to induce skipping
159	H42A(-4+23)	AUC GUU UCU UCA CGG ACA GUG UGG UGC	Skipping to 5 nM
160	H42A(+86+109)	GGG CUU GUG AGA CAU GAG UGA UUU	Skipping to 100 nM
161	H42D(+19-02)	A CCU UCA GAG GAC UCC UCU UGC	Skipping to 5 nM

Antisense Oligonucleotides Directed at Exon 43

Antisense oligonucleotides directed at exon 43 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H43A(+101+120) [SEQ ID NO:163] induced exon 43 skipping when delivered into cells at a concentration of 25 nM. Table 35 below includes the antisense molecules tested and their ability to induce exon 43 skipping.

TABLE 35

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
162	H43D(+10-15)	UAU GUG UUA CCU ACC CUU GUC GGU C	Skipping to 100 nM
163	H43A(+101+120)	GGA GAG AGC UUC CUG UAG CU	Skipping to 25 nM
164	H43A(+78+100)	UCA CCC UUU CCA CAG GCG UUG CA	Skipping to 200 nM

Antisense Oligonucleotides Directed at Exon 44

Antisense oligonucleotides directed at exon 44 were prepared using similar methods as described above. Testing for the ability of these antisense molecules to induce exon 44 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 165 to 167 in Table 1A.

Antisense Oligonucleotides Directed at Exon 45

Antisense oligonucleotides directed at exon 45 were prepared using similar methods as described above. Testing for the ability of these antisense molecules to induce exon 45 skipping is still in progress. The antisense molecules under review are shown as SEQ ID Nos: 207 to 211 in Table 1A.

Antisense Oligonucleotides Directed at Exon 46

Antisense oligonucleotides directed at exon 46 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 21 illustrates the efficiency of one antisense molecule directed at exon 46 acceptor splice site. Antisense oligonucleotide H46A(+86+115) [SEQ ID NO:203] showed very strong ability to induce exon 46 skipping. Table 36 below includes antisense molecules tested. These antisense molecules showed varying ability to induce exon 46 skipping.

TABLE 36

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
168	H46D(+16-04)	UUA CCU UGA CUU GCU CAA GC	No skipping
169	H46A(+90+109)	UCC AGG UUC AAG UGG GAU AC	No skipping
203	H46A(+86+115)	CUC UUU UCC AGG UUC AAG UGG GAU ACU AGC	Good skipping to 100 nM
204	H46A(+107+137)	CAA GCU UUU CUU UUA GUU GCU GCU CUU UUC C	Good skipping to 100 nM
205	H46A(-10+20)	UAU UCU UUU GUU CUU CUA GCC UGG AGA AAG	Weak skipping
206	H46A(+50+77)	CUG CUU CCU CCA ACC AUA AAA CAA AUU C	Weak skipping

Antisense Oligonucleotides Directed at Exon 47

Antisense oligonucleotides directed at exon 47 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

H47A(+76+100) [SEQ ID NO:170] and H47A(-09+12) [SEQ ID NO:172] both induced exon 47 skipping when delivered into cells at a concentration of 200 nM. H47D(+25-02) [SEQ ID NO: 171] is yet to be prepared and tested.

Antisense Oligonucleotides Directed at Exon 50

Antisense oligonucleotides directed at exon 50 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

Antisense oligonucleotide molecule H50A(+02+30) [SEQ ID NO: 173] was a strong inducer of exon skipping. Further, H50A(+07+33) [SEQ ID NO:174] and H50D(+07-18) [SEQ ID NO:175] both induced exon 50 skipping when delivered into cells at a concentration of 100 nM.

Antisense Oligonucleotides Directed at Exon 51

Antisense oligonucleotides directed at exon 51 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 illustrates differing efficiencies of two antisense molecules directed at exon 51 acceptor splice site. Antisense oligonucleotide H51A(+66+90) [SEQ ID NO:180] showed the stronger ability to induce exon 51 skipping. Table 37 below includes antisense molecules tested at a concentration range of 25, 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 51 skipping. The strongest inducers of exon skipping were antisense oligonucleotide H51A(+61+90) [SEQ ID NO: 179] and H51A (+66+95) [SEQ ID NO: 181].

TABLE 37

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
176	H51A(-01+25)	ACC AGA GUA ACA GUC UGA GUA GGA GC	Paint skipping
177	H51D(+16-07)	CUC AUA CCU UCU GCU UGA UGA UC	Skipping at 300 nM
178	H51A(+111+134)	UUC UGU CCA AGC CCG GUU GAA AUC	Needs re- testing
179	H51A(+61+90)	ACA UCA AGG AAG AUG GCA UUU CUA GUU UGG	Very strong skipping

TABLE 37-continued

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
180	H51A(+66+90)	ACA UCA AGG AAG AUG GCA UUU CUA G	skipping
181	H51A(+66+95)	CUC CAA CAU CAA GGA AGA UGG CAU UUC UAG	Very strong skipping
182	H51D(+08-17)	AUC AUU UUU UCU CAU ACC UUC UGC U	No skipping
183	H51A/D(+08-17) & (-15+?)	AUC AUU UUU UCU CAU ACC UUC UGC UAG GAG CUA AAA	No skipping
184	H51A(+175+195)	CAC CCA CCA UCA GCC UCU GUG	No skipping
185	H51A(+199+220)	AUC AUC UCG UUG AUA UCC UCA A	No skipping

Antisense Oligonucleotides Directed at Exon 52

Antisense oligonucleotides directed at exon 52 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 also shows differing efficiencies of four antisense molecules directed at exon 52 acceptor splice site. The most effective antisense oligonucleotide for inducing exon 52 skipping was H52A(+17+37) [SEQ ID NO:188).

Table 38 below shows antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 50 skipping. Antisense molecules H52A(+12+41) [SEQ ID NO:187] and H52A(+17+37) [SEQ ID NO:188] showed the strongest exon 50 skipping at a concentration of 50 nM.

Antisense Oligonucleotides Directed at Exon 53

Antisense oligonucleotides directed at exon 53 were prepared and tested for their ability to induce exon skipping in human muscle cells using similar methods as described above.

FIG. 22 also shows antisense molecule H53A(+39+69) [SEQ ID NO:193] directed at exon 53 acceptor splice site. This antisense oligonucleotide was able to induce exon 53 skipping at 5, 100, 300 and 600 nM. A "cocktail" of three exon 53 antisense oligonucleotides: H53A(+23+47) [SEQ ID NO:195], H53A(+150+176) [SEQ ID NO:196] and H53D(+14-07) [SEQ ID NO:194], was also tested, as shown in FIG. 20 and exhibited an ability to induce exon skipping.

Table 39 below includes other antisense molecules tested at a concentration range of 50, 100, 300 and 600 nM. These antisense molecules showed varying ability to induce exon 53 skipping. Antisense molecule H53A(+39+69) [SEQ ID NO:193] induced the strongest exon 53 skipping.

TABLE 38

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
186	H52A(-07+14)	UCC UGC AUU GUU GCC UGU AAG	No skipping
187	H52A(+12+41)	UCC AAC UGG GGA CGC CUC UGU UCC AAA UCC	Very strong skipping
188	H52A(+17+37)	ACU GGG GAC GCC UCU GUU CCA	Skipping to 50 nM
189	H52A(+93+112)	CCG UAA UGA UUG UUC UAG CC	No skipping
190	H52D(+05-15)	UGU UAA AAA ACU UAC UUC GA	No skipping

TABLE 39

SEQ ID	Antisense oligonucleotide name	Sequence	Ability to induce skipping
191	H53A(+45+69)	CAU UCA ACU GUU GCC UCC GGU UCU G	Faint skipping at 50 nM
192	H53A(+39+62)	CUG UUG CCU CCG GUU CUG AAG GUG	Faint skipping at 50 nM
193	H53A(+39+69)	CAU UCA ACU GUU GCC UCC GGU UCU GAA GGU G	Strong skipping to 50 nM
194	H53D(+14-07)	UAC UAA CCU UGG UUU CUG UGA	Very faint skipping to 50 nM
195	H53A(+23+47)	CUG AAG GUG UUC UUG UAC UUC AUC C	Very faint skipping to 50 nM
196	H53A(+150+176)	UGU AUA GGG ACC CUC CUU CCA UGA CUC	Very faint skipping to 50 nM
197	H53D(+20-05)	CUA ACC UUG GUU UCU GUG AUU UUC U	Not made yet
198	H53D(+09-18)	GGU AUC UUU GAU ACU AAC CUU GGU UUC	Faint at 600 nM
199	H53A(-12+10)	AUU CUU UCA ACU AGA AUA AAA G	No skipping
200	H53A(-07+18)	GAU UCU GAA UUG UUU CAA CUA GAA U	No skipping
201	H53A(+07+26)	AUC CCA CUG AUU CUG AAU UC	No skipping
202	H53A(+124+145)	UUG GCU CUG GCC UGU CCU AAG A	No skipping

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 32

cuuaccugcc aguggaggau uauauuccaa a 31

<210> SEQ ID NO 33
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 33

caucaggauu cuuaccugcc agugg 25

<210> SEQ ID NO 34
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 34

cgaugucagu acuuccaaua uucac 25

<210> SEQ ID NO 35
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 35

accauucauc aggauucu 18

<210> SEQ ID NO 36
<211> LENGTH: 18
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 36

accugccagu ggaggauu 18

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<210> SEQ ID NO 37
<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 37

ccaauauuca cuaaaucaac cuguuaa 27

<210> SEQ ID NO 38
<211> LENGTH: 30
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 38

caggauucuu accugccagu ggaggauuau 30

<210> SEQ ID NO 39
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 39

acgaugucag uacuuccaau auucacuaaa u 31

<210> SEQ ID NO 40
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 40

auuuccaucu acgaugucag uacuuccaau a 31

<210> SEQ ID NO 41
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 41

caggagcuuc caaaugcugc a 21

<210> SEQ ID NO 42
<211> LENGTH: 29
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense

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oligonucleotide

<400> SEQUENCE: 42

cuugucuuca ggagcuucca aaugcugca 29

<210> SEQ ID NO 43
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 43

uccucagcag aaagaagcca cg 22

<210> SEQ ID NO 44
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 44

uuagaaaucu cuccuugugc 20

<210> SEQ ID NO 45
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 45

uaaauugggu guuacacaau 20

<210> SEQ ID NO 46
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 46

cccugaggca uucccaucuu gaau 24

<210> SEQ ID NO 47
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 47

aggacuuacu ugcuuuguuu 20

<210> SEQ ID NO 48
<211> LENGTH: 23

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 48

cuugaauuua ggagauucau cug 23

<210> SEQ ID NO 49
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 49

caucuucuga uaauuuuccu guu 23

<210> SEQ ID NO 50
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 50

ucuucuguuu uuguuagcca guca 24

<210> SEQ ID NO 51
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 51

ucuauguaaa cugaaaauuu 20

<210> SEQ ID NO 52
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 52

uucuggagau ccauuaaaac 20

<210> SEQ ID NO 53
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 53

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cagcaguugc gugaucucca cuag 24

<210> SEQ ID NO 54
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 54

uucaucaacu accaccacca u 21

<210> SEQ ID NO 55
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 55

cuaagcaaaa uaaucugacc uuaag 25

<210> SEQ ID NO 56
<211> LENGTH: 28
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 56

cuuguaaaag aacccagcgg ucuucugu 28

<210> SEQ ID NO 57
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 57

caucuacaga uguuugccca uc 22

<210> SEQ ID NO 58
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 58

gaaggauguc uuguaaaaga acc 23

<210> SEQ ID NO 59
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 59

accuguucuu caguaagacg 20

<210> SEQ ID NO 60
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 60

caugacacac cuguucuuca guaa 24

<210> SEQ ID NO 61
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 61

cauuugagaa ggaugucuug 20

<210> SEQ ID NO 62
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 62

aucucccaau accuggagaa gaga 24

<210> SEQ ID NO 63
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 63

gccaugcacu aaaaaggcac ugcaagacau u 31

<210> SEQ ID NO 64
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 64

ucuuuaaagc caguugugug aauc 24

<210> SEQ ID NO 65

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<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 65

uuucugaaag ccaugcacua a 21

<210> SEQ ID NO 66
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 66

guacauacgg ccaguuuuug aagac 25

<210> SEQ ID NO 67
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 67

cuagauccgc uuuuaaaacc uguuaaaaca a 31

<210> SEQ ID NO 68
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 68

ucuuuucuag auccgcuuuu aaaaccuguu a 31

<210> SEQ ID NO 69
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 69

cuagauccgc uuuuaaaacc uguua 25

<210> SEQ ID NO 70
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 70

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ccgucuucug ggucacugac uua 23

<210> SEQ ID NO 71
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 71

cuagauccgc uuuuaaaacc uguuaa 26

<210> SEQ ID NO 72
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 72

ccgcuuuuaa aaccuguuaa 20

<210> SEQ ID NO 73
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 73

uggauugcuu uuucuuuucu agaucc 26

<210> SEQ ID NO 74
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 74

caugcuuccg ucuucugggu cacug 25

<210> SEQ ID NO 75
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 75

gaucuuguuu gagugaauac agu 23

<210> SEQ ID NO 76
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 76

guuauccagc caugcuuccg uc 22

<210> SEQ ID NO 77
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 77

ugauaauugg uaucacuaac cugug 25

<210> SEQ ID NO 78
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 78

guaucacuaa ccugugcugu ac 22

<210> SEQ ID NO 79
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 79

cugcuggcau cuugcaguu 19

<210> SEQ ID NO 80
<211> LENGTH: 31
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 80

gccugagcug aucugcuggc aucuugcagu u 31

<210> SEQ ID NO 81
<211> LENGTH: 28
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 81

cuggcagaau ucgauccacc ggcuguuc 28

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<210> SEQ ID NO 82
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 82

cagcaguagu ugucaucugc uc 22

<210> SEQ ID NO 83
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 83

ugauggggug guggguugg 19

<210> SEQ ID NO 84
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 84

aucugcauua acacccucua gaaag 25

<210> SEQ ID NO 85
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 85

ccggcuguuc aguuguucug aggc 24

<210> SEQ ID NO 86
<211> LENGTH: 28
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 86

aucugcauua acacccucua gaaagaaa 28

<210> SEQ ID NO 87
<211> LENGTH: 28
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

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<400> SEQUENCE: 87

gaaggagaag agauucuuac cuuacaaa 28

<210> SEQ ID NO 88
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 88

auucgaucca ccggcuguuc 20

<210> SEQ ID NO 89
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 89

cagcaguagu ugucaucugc 20

<210> SEQ ID NO 90
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 90

gccgguugac uucauccugu gc 22

<210> SEQ ID NO 91
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 91

cugcauccag gaacaugggu cc 22

<210> SEQ ID NO 92
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 92

gucugcaucc aggaacaugg guc 23

<210> SEQ ID NO 93
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 93

guugaagauc ugauagccgg uuga 24

<210> SEQ ID NO 94
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 94

uacuuacugu cuguagcucu uucu 24

<210> SEQ ID NO 95
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 95

cacucauggu cuccugauag cgca 24

<210> SEQ ID NO 96
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 96

cugcaauucc ccgagucucu gc 22

<210> SEQ ID NO 97
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 97

acugcuggac ccauguccug aug 23

<210> SEQ ID NO 98
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 98

cuaaguugag guauggagag u 21

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<210> SEQ ID NO 99
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 99

uauucacaga ccugcaauuc ccc 23

<210> SEQ ID NO 100
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 100

acaguggugc ugagauagua uaggcc 26

<210> SEQ ID NO 101
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 101

uaggccacuu uguugcucuu gc 22

<210> SEQ ID NO 102
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 102

uucagagggc gcuuucuuc 19

<210> SEQ ID NO 103
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 103

gggcaggcca uuccuccuuc aga 23

<210> SEQ ID NO 104
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

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<400> SEQUENCE: 104

ucuucagggu uuguauguga uucu 24

<210> SEQ ID NO 105
<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 105

cugggcugaa uugucugaau aucacug 27

<210> SEQ ID NO 106
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 106

cuguuggcac augugauccc acugag 26

<210> SEQ ID NO 107
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 107

gucuauaccu guuggcacau guga 24

<210> SEQ ID NO 108
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 108

ugcuuucugu aauucaucug gaguu 25

<210> SEQ ID NO 109
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 109

ccuccuuucu ggcauagacc uuccac 26

<210> SEQ ID NO 110
<211> LENGTH: 25
<212> TYPE: RNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 110

ugugucaucc auucgugcau cucug 25

<210> SEQ ID NO 111
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 111

uuaaggccuc uugugcuaca ggugg 25

<210> SEQ ID NO 112
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 112

gggccucuuc uuuagcucuc uga 23

<210> SEQ ID NO 113
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 113

gacuuccaaa gucuugcauu uc 22

<210> SEQ ID NO 114
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 114

gccaacaugc ccaaacuucc uaag 24

<210> SEQ ID NO 115
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 115

cagagauuuc cucagcuccg ccagga 26

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<210> SEQ ID NO 116
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 116

cuuacaucua gcaccucaga g 21

<210> SEQ ID NO 117
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 117

uccgccaucu guuagggucu gugcc 25

<210> SEQ ID NO 118
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 118

auuuggguua uccucugaau gucgc 25

<210> SEQ ID NO 119
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 119

cauaccucuu cauguaguuc cc 22

<210> SEQ ID NO 120
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 120

cauuugagcu gcguccaccu ugucug 26

<210> SEQ ID NO 121
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense

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oligonucleotide

<400> SEQUENCE: 121

uccugggcag acuggaugcu cuguuc 26

<210> SEQ ID NO 122
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 122

uugccugggc uuccugaggc auu 23

<210> SEQ ID NO 123
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 123

uucugaaaua acauauaccu gugc 24

<210> SEQ ID NO 124
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 124

uaguuucuga aauaacauau accug 25

<210> SEQ ID NO 125
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 125

gacuugucaa aucagauugg a 21

<210> SEQ ID NO 126
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 126

guuucugaaa uaacauauac cugu 24

<210> SEQ ID NO 127
<211> LENGTH: 20

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<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 127

caccagaaau acauaccaca 20

<210> SEQ ID NO 128
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 128

caaugauuua gcugugacug 20

<210> SEQ ID NO 129
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 129

cgaaacuuca uggagacauc uug 23

<210> SEQ ID NO 130
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 130

cuuguagacg cugcucaaaa uuggc 25

<210> SEQ ID NO 131
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 131

caugcacaca ccuuugcucc 20

<210> SEQ ID NO 132
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 132

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ucuguacaau cugacgucca gucu 24

<210> SEQ ID NO 133
<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 133

gucuuuauca ccauuuccac uucagac 27

<210> SEQ ID NO 134
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 134

ccgucugcuu uuucuguaca aucug 25

<210> SEQ ID NO 135
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 135

uccauaucug uagcugccag cc 22

<210> SEQ ID NO 136
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 136

ccaggcaacu ucagaaucca aau 23

<210> SEQ ID NO 137
<211> LENGTH: 30
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 137

uuucuguuac cugaaaagaa uuauaaugaa 30

<210> SEQ ID NO 138
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 138

cauucauuuc cuuucgcauc uuacg 25

<210> SEQ ID NO 139
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 139

ugaucucuuu gucaauucca uaucug 26

<210> SEQ ID NO 140
<211> LENGTH: 30
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 140

uucagugaua uagguuuuac cuuuccccag 30

<210> SEQ ID NO 141
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 141

cuguagcugc cagccauucu gucaag 26

<210> SEQ ID NO 142
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 142

ucuucugcuc gggaggugac a 21

<210> SEQ ID NO 143
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 143

ccaguuacua uucagaagac 20

<210> SEQ ID NO 144

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<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 144

ucuucaggug caccuucugu 20

<210> SEQ ID NO 145
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 145

ugugaugugg uccacauucu gguca 25

<210> SEQ ID NO 146
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 146

ccauguguuu cugguauucc 20

<210> SEQ ID NO 147
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 147

cguguagagu ccaccuuugg gcgua 25

<210> SEQ ID NO 148
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 148

uacuaauuuc cugcaguggu cacc 24

<210> SEQ ID NO 149
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 149

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uucuguguga aauggcugca aauc 24

<210> SEQ ID NO 150
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 150

ccuucaaagg aauggaggcc 20

<210> SEQ ID NO 151
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 151

ugcugaauuu cagccuccag ugguu 25

<210> SEQ ID NO 152
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 152

ugaagucuuc cucuuucaga uucac 25

<210> SEQ ID NO 153
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 153

cuggcuuucu cucaucugug auuc 24

<210> SEQ ID NO 154
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 154

guuguaaguu gucuccucuu 20

<210> SEQ ID NO 155
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 155

uugucuguaa cagcugcugu 20

<210> SEQ ID NO 156
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 156

gcucuaauac cuugagagca 20

<210> SEQ ID NO 157
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 157

cuuugagacc ucaaauccug uu 22

<210> SEQ ID NO 158
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 158

cuuuauuuuc cuuucaucuc ugggc 25

<210> SEQ ID NO 159
<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 159

aucguuucuu cacggacagu gugcugg 27

<210> SEQ ID NO 160
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 160

gggcuuguga gacaugagug auuu 24

<210> SEQ ID NO 161

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<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 161

accuucagag gacuccucuu gc 22

<210> SEQ ID NO 162
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 162

uauguguuac cuacccuugu cgguc 25

<210> SEQ ID NO 163
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 163

ggagagagcu uccuguagcu 20

<210> SEQ ID NO 164
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 164

ucacccuuuc cacaggcguu gca 23

<210> SEQ ID NO 165
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 165

uuugugucuu ucugagaaac 20

<210> SEQ ID NO 166
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 166

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aaagacuuac cuuaagauac 20

<210> SEQ ID NO 167
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 167

aucugucaaa ucgccugcag 20

<210> SEQ ID NO 168
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 168

uuaccuugac uugcucaagc 20

<210> SEQ ID NO 169
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 169

uccagguuca agugggauac 20

<210> SEQ ID NO 170
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 170

gcucuucugg gcuuauggga gcacu 25

<210> SEQ ID NO 171
<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 171

accuuuaucc acuggagauu ugucugc 27

<210> SEQ ID NO 172
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 172

uuccaccagu aacugaaaca g 21

<210> SEQ ID NO 173
<211> LENGTH: 29
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 173

ccacucagag cucagaucuu cuaacuucc 29

<210> SEQ ID NO 174
<211> LENGTH: 27
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 174

cuuccacuca gagcucagau cuucuaa 27

<210> SEQ ID NO 175
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 175

gggauccagu auacuuacag gcucc 25

<210> SEQ ID NO 176
<211> LENGTH: 26
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 176

accagaguaa cagucugagu aggagc 26

<210> SEQ ID NO 177
<211> LENGTH: 23
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 177

cucauaccuu cugcuugaug auc 23

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<210> SEQ ID NO 178
<211> LENGTH: 24
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 178

uucuguccaa gcccgguuga aauc 24

<210> SEQ ID NO 179
<211> LENGTH: 30
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 179

acaucaagga agauggcauu ucuaguuugg 30

<210> SEQ ID NO 180
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 180

acaucaagga agauggcauu ucuag 25

<210> SEQ ID NO 181
<211> LENGTH: 30
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 181

cuccaacauc aaggaagaug gcauuucuag 30

<210> SEQ ID NO 182
<211> LENGTH: 25
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 182

aucauuuuuu cucauaccuu cugcu 25

<210> SEQ ID NO 183
<211> LENGTH: 36
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

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<400> SEQUENCE: 183

aucauuuuuu cucauaccuu cugcuaggag cuaaaa 36

<210> SEQ ID NO 184
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 184

cacccaccau cacccucugu g 21

<210> SEQ ID NO 185
<211> LENGTH: 22
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 185

aucaucucgu ugauauccuc aa 22

<210> SEQ ID NO 186
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 186

uccugcauug uugccuguaa g 21

<210> SEQ ID NO 187
<211> LENGTH: 30
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 187

uccaacuggg gacgccucug uuccaaaucc 30

<210> SEQ ID NO 188
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 188

acuggggacg ccucuguucc a 21

<210> SEQ ID NO 189
<211> LENGTH: 20
<212> TYPE: RNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic Human 2'-O-methyl phosphorothioate antisense oligonucleotide

<400> SEQUENCE: 189

ccguaaugau uguucuagcc 20

<210> SEQ ID NO 190
<211> LENGTH: 20
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What is claimed is:

1. An antisense oligonucleotide of 30 bases comprising the base sequence CUCCAACAUC AAGGAAGAUG GCAUUUCUAG (SEQ ID NO: 181), in which the uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

2. A pharmaceutical composition comprising an antisense oligonucleotide of 30 bases comprising the base sequence CUCCAACAUC AAGGAAGAUG GCAUUUCUAG (SEQ ID NO: 181), in which the uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, and a pharmaceutically acceptable carrier.

* * * * *

EXHIBIT F

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

Exhibit F

PTO/AIA/26 (04-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) AVN-008CN25

In re Application of: Stephen Donald WILTON *et al.*

Application No.: 14/316,603-Conf. #2157

Filed: June 26, 2014

For: ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

The applicant, The University of Western Australia, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. (see attached) as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. [ ] The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. [X] The undersigned is an attorney or agent of record. Reg. No. 36,207

/Amy E. Mandragouras, Esq./ — Signature
February 26, 2015 — Date

Amy E. Mandragouras, Esq. — Typed or printed name

Attorney for Applicant(s) — Title
(617) 202-4626 — Telephone Number

[X] Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: February 26, 2015 — Electronic Signature for Amy E. Mandragouras, Esq.: /Amy E. Mandragouras, Esq./

SUPPLEMENTAL SHEET FOR TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) AVN-008CN25

Prior patent Nos. applicable to this terminal disclaimer (referenced on first page):

7,807,816
7,960,541
8,486,907

EXHIBIT G

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

Exhibit G

United States Patent and Trademark Office

Office of the Commissioner for Patents

ANTISENSE OLIGONUCLEOTIDES FOR INDUCING EXON SKIPPING AND METHODS OF USE THEREOF

PATENT #	APPLICATION #	FILING DATE	ISSUE DATE
9018368	14316603	06/26/2014	04/28/2015

Payment Window Status

WINDOW	STATUS	FEES
3.5 Year	Not Open	Not Due

No maintenance fees are due at this time. 3.5 year window opens on 04/28/2018.

Window	First Day to Pay	Surcharge Starts	Last Day to Pay	Status	Fees
3.5 Year	04/28/2018	10/30/2018	04/29/2019	Not Open	Not Due
7.5 Year	04/28/2022	10/29/2022	04/28/2023	Not Open	Not Due
11.5 Year	04/28/2026	10/29/2026	04/28/2027	Not Open	Not Due

Patent Holder Information

Customer # 123147

Entity Status SMALL

Phone Number 6175734700

Address Nelson Mullins Riley & Scarborough LLP/Sarepta
One Post Office Square
Boston, MA 02109
UNITED STATES

EXHIBIT H

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

EXHIBIT H
CLAIMS 1 and 2 OF U.S. PATENT NO. 9,018,368
READ ON EXONDYS 51™ (eteplirsen)

Claims	EXONDYS 51™ Properties and Description
1. An antisense oligonucleotide of 30 bases comprising the base sequence CUCCAACAUC AAGGAAGAUG GCAUUUCUAG (SEQ ID NO: 181), in which the uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.	Claim 1 reads on the approved product. Claim 1 claims an antisense oligonucleotide that is the active ingredient of EXONDYS 51™, which is eteplirsen. Eteplirsen is an antisense oligonucleotide that contains 30 phosphorodiamidate morpholino subunits that has a sequence of bases CUCCAACAUC AAGGAAGAUG GCAUUUCUAG SEQ ID NO: 181 in which the uracil bases are thymine bases. Eteplirsen is chemically linked to a polyethylene glycol chain at the 5' end.
2. A pharmaceutical composition comprising an antisense oligonucleotide of 30 bases comprising the base sequence CUCCAACAUC AAGGAAGAUG GCAUUUCUAG (SEQ ID NO: 181), in which the uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide is chemically linked to a polyethylene glycol chain, and a pharmaceutically acceptable carrier.	Claim 2 reads on the approved product. Claim 2 claims a pharmaceutical composition comprising an antisense oligonucleotide that is the active ingredient of EXONDYS 51™, which is eteplirsen. Eteplirsen is an antisense oligonucleotide that contains 30 phosphorodiamidate morpholino subunits that has a sequence of bases CUCCAACAUC AAGGAAGAUG GCAUUUCUAG SEQ ID NO: 181, in which the uracil bases are thymine bases. Eteplirsen is chemically linked to a polyethylene glycol chain at the 5' end. The approved product, EXONDYS 51™ (eteplirsen) injection is formulated with a pharmaceutically acceptable carrier.

EXHIBIT I

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

AVI BioPharma

Exhibit I

August 2, 2007

Russell Katz, M.D.
Director, Division of Neurology Products
Center For Drugs Research and Evaluation
Food and Drug Administration
5901-B Ammendale Rd
Beltsville, MD 20705-1266

Re: IND 77,427 SN 000 and Fast-Track Designation Request

Dear Dr. Katz:

AVI BioPharma, Inc. (AVI), Portland, OR, is pleased to provide you with an Investigational New Drug Application for the clinical development of AVI-4658, a phosphorodiamidate Morpholino oligomer (PMO) in patients with Duchenne Muscular Dystrophy (DMD) a frame-shift mutation upstream of or just after exon 51. This mutation leads to either a profound reduction or absence of dystrophin in striated and cardiac muscles in DMD patients. Frame-shift mutations in one or more of 12 exons account for ≥ 65% of the causes for this disease. Those with deletions of exons 50, 45-50, 48-50, 49-50, 52, and 52-63 could benefit from skipping exon 51, and account for the the majority (~12 to 18%) of all genetic-causes in DMD. A drug able to induce skipping of exon 51 is the initial focus of AVI's experimental therapeutic program to manage this disease.

AVI-4658 has been studied in muscle explants from DMD patients and confirmed to elicit *de novo* dystrophin production in this *ex vivo* model. The ability of other similar PMOs to elicit *de novo* dystrophin production in the *mdx* mouse DMD model and golden retriever and beagle dog models of DMD by a putative exon skipping mechanism have definitively been demonstrated by multiple investigators throughout the world. Therefore, AVI-4658 is a rational target in this DMD patient subpopulation. As you know, DMD is a severely debilitating and lethal disease afflicting males: death typically occurs by the early twenties.

Background

Duchenne Muscular Dystrophy (DMD) is the most common X-linked lethal pediatric disease worldwide. It is exclusively a human disease without an identical correlate in animals. Dystrophin is a 427 kD protein that is an essential component of the sarcolemma and pivotal for overall striated muscle cell function. A mutation is located in the gene for dystrophin, and causes either nonsense or frame shift errors, resulting in early termination of the protein production pathway. Frame-shift mutations are the predominant cause of DMD, with duplications and a premature stop codon accounting for the remainder. These errors result in early termination of dystrophin production pathway. Frame-shift mutations in one or more of 12 exons account for ≥ 65% of the causes for this disease. Those with deletions of exons 50, 45-50, 48-50, 49-50, 52, and 52-63 could benefit from skipping exon 51, and account for the the majority (~[redacted]%) of all genetic-causes in DMD. A drug able to induce skipping exon 51 is the initial focus of AVI's experimental therapeutic program to manage this disease.

The consequence of a frame-shift mutation upstream of or just after exon 51 leads to prematurely aborted dystrophin production. This leads to either a profound reduction or absence of dystrophin in

striated and cardiac muscles in DMD patients. The lack of functional dystrophin production leads to membrane leakage and fiber damage, ultimately leading to degeneration and death of the muscle fiber. This occurs despite the fact that there is a corresponding over-production of another plasma-membrane-bound protein (viz., utrophin) that performs similar tasks as dystrophin at the neuromuscular junction. The end result of a frame-shift mutation in exon 51 in the dystrophin gene is the same as all other causes of DMD: muscle wasting, progressive debilitation and early death.

The pathogenesis and natural course of DMD is relevant in rational clinical protocol design to assess potential therapeutically valuable experimental modalities. There is continuous striated muscle injury (inclusive of cardiac muscle cells) due to a lack of functional dystrophin within the sarcolemma. This causes on-going dystrophic changes in muscle cells: fat infiltration, fibrosis and death of affected muscle cells. Once the fatty infiltration has occurred, there is presumptively permanent muscle dysfunction and ultimately muscle wasting. Many early diagnoses of DMD occur in infancy due to the observation of weak neck muscle function. Thereafter, other DMD diagnoses occur because of muscle weakness of the legs and pelvis by the age of 5 years. There is also a relative "honeymoon" period among boys with DMD between early detection of the disease and until 7 years of age due to hypertrophy of viable muscle cells and bellies. It is assumed that this apparent improvement in muscle function relates to the effect of muscle conditioning due to mechanical stress. This phenomenon wanes as greater muscle wasting occurs.

There is eventually a progressive decline in the ability to walk independently, inability to run, difficulty getting out of a chair, and reduced physical stamina. By age 10 years, DMD patients are usually unable to walk well unless supported by braces and by age 12 years most (69%) are confined to a wheelchair. Even the function of hands and fingers is eventually impaired such that the patients are unable to use a "joy" stick to maneuver their automated wheelchairs or to use other electronic devices. This is a well-recognized major quality of life problem that requires novel approaches to modulate this impairment. By or during the third decade, a fatal outcome will occur as a consequence of respiratory failure unless mechanical ventilation is utilized and/or cardiac causes. In summary, there is progressive muscle wasting in boys with DMD that is manifested over time in incremental muscle function decline. Proper design of clinical trials to provide benefit to the major subgroups of boys with DMD will entail different strategies.

These data provide the scientific basis to use a PMO to target a specific exon in DMD patients with a specific mutation. It may provide benefit by reducing the functional and respiratory decline and early death in this patient population. Ultimately, it may be prudent and therapeutically desired to use a PMO or PMOs to target multiple exons in a single patient, based on their specific genetic deletions. This strategy would set the stage for a personalized therapeutic approach for DMD patients.

The drug, AVI-4658, is a PMO and has a sequence designed to "skip" exon 51, thus theoretically enabling dystrophin production to occur in human striated muscle in DMD patients with a corresponding exon defect. A PMO platform process, in which the arrangement and number of the subunits affixed to the backbone vary, is used to produce AVI-4658. This PMO drug class has been the subject of three successful IND applications in the USA and a series of clinical studies in the United States and EU (see Table 1, below). A total of 19 studies in over 400 subjects have been performed in both healthy and patient populations. In general, this class of drugs has been well-tolerated without evidence of clinically significant toxicity.

Table 1: Summary of PMO Drugs used in Human Clinical Studies

IND Number	Drug Name	Indication	Sequence	Length
59,255	AVI-[redacted]	Restenosis (target: *c-myc*)	[redacted]	[redacted]
66,219	AVI-[redacted]	West Nile virus (encephalopathy)	[redacted]	[redacted]
69,015	AVI-[redacted]	Hepatitis C virus	[redacted]	[redacted]
N/A	AVI-[redacted]	Metabolic Redirection (CYP3A4 or P450)	[redacted]	[redacted]
77,429	AVI-4658	DMD (Exon 51 of dystrophin [+66+95])	CTC CAA CAT CAA GGA AGA TGG CAT TTC TAG	30

FAST-TRACK DESIGNATION REQUEST

In addition to submitting this IND, we are also seeking Fast-Track Designation of AVI-4658 to induce exon skipping patients with due to a frame shift mutation upstream of or just after exon 51 of the dystrophin gene. We believe that AVI-4658 meets the requirements for Fast-Track Designation, as indicated below.

Duchenne Muscular Dystrophy is a Serious Life-Threatening Condition

Duchenne Muscular Dystrophy (DMD) is a devastating X-linked degenerative and lethal muscle disease in males due to mutation(s) of the dystrophin gene. Dystrophin is encoded by the largest gene in the human body. It has a long half-life and is required for proper muscle function. Without dystrophin, the connections between the muscle fibers and cell membrane are not properly aligned. This leads to uncontrolled leakage at the plasma membrane, eventually causing rupture of the muscle cell. Once rupture has occurred, calcium easily enters the muscle cell resulting in contraction at the damaged sites and continued muscle fiber breakage. As this process is repeated, the muscle deteriorates, eventually becoming fibrotic and replaced by fat.

Therefore, DMD is a serious disease consistent with 21 CFR 312.81(a), in that patients with DMD experience a gradual loss of the ability to move their muscles starting early in life, ultimately resulting in early death. Patients are usually diagnosed between the ages of 2 to 5. By age 12, 69% of DMD patients solely rely on a wheel chair for mobility. There is no cure for DMD and there are no approved treatments to address the underlying cause of DMD at a genetic level. As such, care is palliative in nature, e.g., mechanical ventilation. These patients experience continued decline through their lives; death is usually due to respiratory or cardiac failure.

AVI-4658 is Intended to Treat a Serious Condition

AVI-4658 is to be used only in DMD patients with a mutation at or upstream of exon 51 of the dystrophin gene. The subunit sequence in AVI-4658 has been designed to "bridge" the missing exon (+66+95) thus enabling the mRNA to read the message, resulting in the expression of a truncated, yet functional dystrophin. Multiple animal model studies have shown that PMOs [redacted] effectively skip targeted exons and result in truncated dystrophin production. The intent of the AVI-4658 clinical development program is to demonstrate that the induction of exon 51 skipping will allow truncated, yet functional dystrophin to be produced in these DMD patients. Thus, we believe the development program meets the definition of demonstrating "an effect on a serious aspect of the condition."

AVI-4658 has the Potential to Address an Unmet Medical Need

Although a variety of disease mitigating modalities have been tried, care remains palliative in nature. There are no therapeutic approaches that address the underlying genetic defect. The current standard of care consists of prednisone (up to 40 mg/day) and physical therapy. Although

prednisone aids in addressing the inflammation associated with DMD, it does not ameliorate the continued decline of muscle activity over the course of the patient's life. As the disease progresses, supplemental oxygen and other respiratory treatments, mechanical ventilation, and cardiac therapeutics are required.

A number of approaches have attempted to address correction of the errant gene in DMD through myogenic or stem cell transplant, viral vector delivery of the gene correction, and PTC 124 which is a stop codon drug designed to address nonsense mutation in certain DMD patients. Preclinical research (see below) suggests that a PMO-based exon-skipping approach to DMD has potential to address the fundamental genetic problem of this disease.

AVI-4658 has the Potential to Address DMD

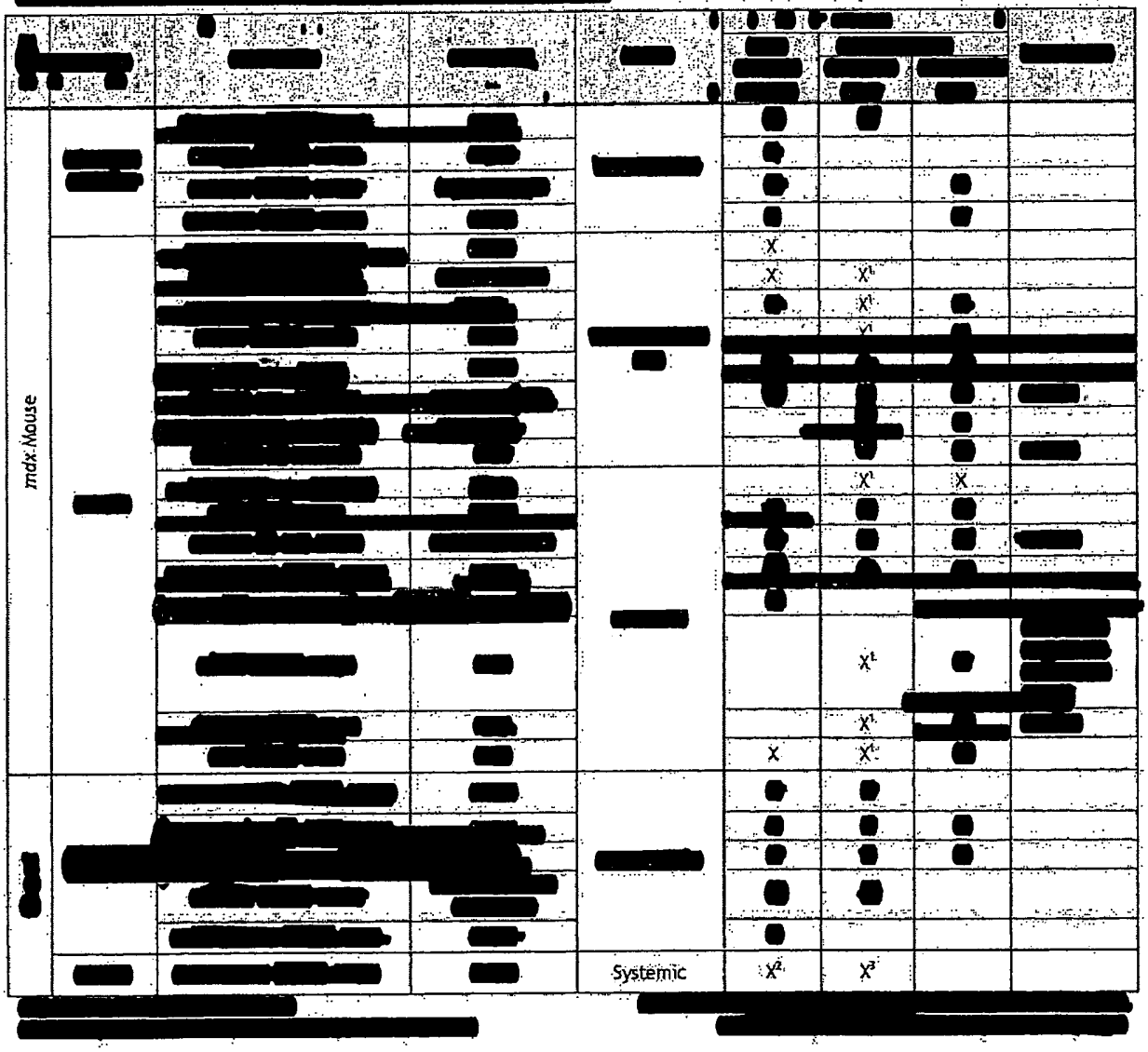
As the understanding of Duchenne Muscular Dystrophy (DMD) has grown, a variety of approaches to therapeutically address the underlying genetic basis for this lethal disease have advanced with technology. This has evolved from the understanding of the dystrophin gene: the concept of exon-skipping, the application of antisense compounds to effect an exon skip in cell cultures of muscle explants from DMD patients, proof of concept in animal models of DMD, and finally, to conclusive evidence of the ability of antisense compounds to lead to a robust production of a functional truncated dystrophin. [redacted]

The *mdx* mouse carries a nonsense mutation in exon 23 of its dystrophin gene. The skipping of this exon restores the reading frame and is associated with functional dystrophin production. The first studies were carried out in cultured myoblasts from the *mdx* mice. Subsequently, antisense compounds were administered intramuscularly to *mdx* mice. This administration was followed by the restoration of dystrophin expression at sarcolemma. A number of different antisense chemistries, including PMOs, have been used in these studies.

More recently, studies have been performed in the *mdx* mouse following the systemic administration of antisense via the intraperitoneal or intravascular route. For example, Alter *et al.*, repeated intravenous administration of a PMO at weekly intervals in the *mdx* mouse, resulting in dystrophin expression in dystrophin-deficient skeletal muscles and improvement in muscle function without

evidence of adverse experiences. Intravenous administration of 2OMe antisense targeting the abnormal exon 23 in this *mdx* mouse model has resulted in dystrophin-deficient muscle fibers maintaining dystrophin expression for at least 2 months after the last dose of drug administration. However the longevity of *de novo* dystrophin production was significantly improved following the administration of a PMO when compared to a 2OMe-based antisense, with levels of expression that only start to decline after 14 weeks following a single intramuscular injection. A recent study reported similar results of antisense directed exon skipping to induce dystrophin expression in cultured myoblast cultures in a canine model of DMD (viz., golden retriever muscular dystrophy [GRMD]). Unlike the *mdx* mouse, which develops only limited weakness and does not die from the consequences of limited muscle weakness, GRMD dogs suffer a rapidly accelerated death due to muscle wasting with eventual fibrosis, contractures and weakness in all muscle groups. This DMD dog model is clinically more similar to DMD although there are a minimum of three defect dystrophin exons to account for this disease. In these experiments, relevant exon skips were followed by expression of dystrophin protein. Immunohistochemistry techniques were used to confirm dystrophin localized within the sarcolemma. Table 2 summarizes the results of these various published preclinical studies.

[redacted]



In summary, it has been established in primary cell cultures both from animal models and DMD patients that antisense administration is effective at promoting exon skipping, resulting in significant *de novo* dystrophin production that is correctly localized at the sarcolemma. The efficacy by local and systemic delivery has been established in the *mdx* mouse including significant functional improvement of previously diseased affected muscle groups. The evidence from the preclinical studies suggests that the CTC CAA CAT CAA GGA AGA TGG CAT TTC TAG sequence (which targets nucleotides +66+95 of the dystrophin gene and is the sequence of AVI-4658), is a good choice for effectively skipping exon 51.

Experiments performed by groups in the United Kingdom and Australia comparing the relative efficacy of the 2OMe modified phosphorothioate and PMO have been performed in cultured cells, and *in vivo* in a transgenic mouse model. The results of these experiments clearly indicate that the PMO was significantly more potent than the 2OMe modified phosphorothioate antisense chemistry.

References

1. Alter J, F Lou, A Rabinowitz, H Yin, J Rosenfeld, SD Wilton, TA Partridge, QL Lu. 2006. Systemic Delivery of Morpholino Oligonucleotide Restores Dystrophin Expression Bodywide and Improves Dystrophic Pathology. Nat Med **12**(2): 175-177.
2. Bushby K, J Bourke, R Bullock, M Eagle, M Gobson, J Quinby. 2005. The Multidisciplinary Management of Duchenne Muscular Dystrophy. Current Paediatrics **15**: 292-300.
3. Centers for Disease Control and Prevention. 2006. Causes of Duchenne/Becker Muscular Dystrophy.
4. Centers for Disease Control and Prevention. 2005. CDC Duchenne/Becker Muscular Dystrophy (DBMD) Activities – Update 2005.
5. Fall Abbie M, R Johnson, K Honeyman, P Iversen, S Fletcher, SD Wilton. 2006. Induction of Revertant fibres in the *mdx* mouse using Antisense Oligonucleotides. Genetic Vaccines and Therapy **4**:3.
6. Fletcher Susan, K Honeyman, A M Fall, PL Harding, RD Johnsen, SD Wilton. 2006. Dystrophin Expression in the *mdx* Mouse after Localised and Systemic Administration of a Morpholino Antisense Oligonucleotide. J Gene Med **8**:207-216.
7. Garcia, Sherry. 2005. Presentation: Duchenne Muscular Dystrophy: Walk a Mile in Their shoes. CDC's 2005 Science Ambassador Program.
8. Gebski Bianca L, CJ Mann, S Fletcher, SD Wilton. 2003. Morpholino Antisense Oligonucleotide Induced Dystrophin Exon 23 Skipping in *mdx* Mouse Muscle. Human Molecular Genetics **12**(15): 1801-1811.
9. Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review. Revision 2. FDA, January 2006.
10. Koenig M, AH Beggs, M Moyer, S Scherpf, K Heindrich, T Bettecken, G Meng *et al.* 1989. The Molecular Basis for Duchenne versus Becker Muscular dystrophy: Correlation of Severity with Type of Deletion. Am J Genet **45**:498-506.
11. Kole Rizard, T Williams, L Cohen. 2004. RNA Modulation, Repair and Remodeling by Slice Switching Oligonucleotides. Acta Biochemica Polonica **51**(2/2004):373-378.
12. Lu QL, CJ Mann, Fang Lou, G Bou-Gharios, GE Morris, S Xue, S Fletcher, TA Partridge, SD Wilton. 2003. Functional Amounts of Dystrophin Produced by Skipping the Mutated Exon in the *mdx* Dystrophic Mouse. Nat Med 9(8): 1009-1014.
13. Lu QL, GE Morris, SD Wilton, T Ly, OV Artem'yeva, P Strong, TA Partirdge. 2000. Massive Idiosyncratic Exon Skipping Corrects the Nonsense Mutation in Dystrophic Mouse Muscle and Produces Functional Revertant Fibers by Clonal Expression. J Cell Biology **148**(5):985-995.
14. Lu QL, A Rabinowitz, YC Chen, T Yokota, HF Yin, J Alter, A Jadoon, G Bou-Gharios, TA Partridge. 2005. Systemic Delivery of Antisense Oligonucleotide Restores Dystrophin Expression in Body-wide Skeletal Muscles. PNAS **102**(1):198-203.

15. Mann CJ, K Honeyman, AJ Cheng, T Ly, F Lloyd, S Fletcher, JE Morgan, TA Partridge, SD Wilton. 2001. Antisense-induced Exon Skipping and Synthesis of Dystrophin in the *mdx* Mouse. PNAS **98**(1):42-47.

16. McClorey G, AM Fall, HM Moulton, PL Iversen, JE Rasko, M Ryan, S Fletcher, SD Wilton. 2006. Induced Dystrophin Exon Skipping in Human Muscle Explants. Neuromuscular Disorders. **16**(9-10):583-590.

17. Sherratt TG, T Vulliamy, V Dubowitz, CA Sewry, PN Strong. 1993. Exon Skipping and Translation in Patients with Frameshift Deletions in the Dystrophin Gene. Am J Genet **53**:1007-1015.

18. National Human genome Research Institute. 2007. Learning About Duchenne Muscular Dystrophy. http://www.genome.gov/19518854

19. Wilton SD, AM Fall, PL Harding, G McClorey, C Coleman, S Fletcher. 2007. Antisense Oligonucleotide-Induced Exon Skipping Across the Human Dystrophin Gene Transcript. Mol Therapy. Advance online publication, Feb 2007.

Fast-Track Designation Contact:

Janet R. Christensen, M.S.P.H., R.A.C.
Vice President, Regulatory Affairs and Quality
AVI BioPharma, Inc.
One SW Columbia Street, Ste 200
Portland, OR 97258
[redacted] (office)
[redacted] fax)
[redacted] e-mail)

Should you have any questions, please contact me using the same contact information provided above for the Fast-Track Designation. Should I not be available, please contact [redacted] at the same telephone and fax numbers.

Best regards,

Janet R. Christensen, M.S.P.H., R.A.C.
Vice President, Regulatory Affairs and Quality

EXHIBIT J

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

Exhibit J

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 77,429

REMOVE FULL CLINICAL HOLD

AVI Biopharma
Attention: Jacqueline A. Dombroski, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
3450 Monte Villa Parkway
Bothell, WA 98021

Dear Dr. Dombroski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AVI-4658.

We also refer to your amendment dated May 21, 2010 which provide a complete response to our January 29, 2008, letter which cited the reasons for placing this IND on clinical hold and the information needed to resolve the clinical hold issues.

We have completed the review of your submission, and have concluded that your clinical trial may be initiated.

A letter providing non-hold comments and recommendations, regarding your study protocol, will follow in a separate communication.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations).

Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

If you have any questions, contact Stephanie N. Keefe, Regulatory Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-77429	ORIG-1	AVI BIOPHARMA INC	AVI 4658

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
06/25/2010

EXHIBIT K

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

Exhibit K

SAREPTA
THERAPEUTICS

26 June 2015

Billy Dunn, MD
Director, Division of Neurology Drug Products, ODE I
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA Number:	NDA 206488
Product:	EXONDYS 51™ (eteplirsen) Injection
Proposed Indication:	EXONDYS 51™ is an exon skipping phosphorodiamidate morpholino oligomer (PMO) which restores the mRNA reading frame to produce dystrophin protein and is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping. This indication is approved on an intermediate endpoint demonstrating delayed disease progression as measured by the 6 minute walk test. Continued benefit will be evaluated through confirmatory trials.

NDA Sequence Number: 0001

Subject: **FINAL SUBMISSION OF ROLLING NDA**

For the Attention of Fannie Choy, RPh, Regulatory Project Manager

Dear Dr. Dunn,

Pursuant to 21 CFR 314.50, Sarepta Therapeutics, Inc., (Sarepta) is submitting a New Drug Application for EXONDYS 51™ (eteplirsen) Injection. The active pharmaceutical ingredient of EXONDYS 51 Injection is eteplirsen, an exon skipping phosphorodiamidate morpholino oligomer which restores the mRNA reading frame to induce the production of dystrophin protein.

An application for Priority Review Designation (Module 1.2) is included as part of this NDA submission. Investigation of eteplirsen (code name: AVI-4658) for DMD was designated as a Fast Track development program on 27 November 2007.

As agreed by Sarepta and the Division at the 19 May 2015 Type B pre-NDA meeting (Memorandum of Meeting Minutes dated 09 June 2015, Reference ID 3776938), this NDA is being submitted for rolling review; this submission provides the complete clinical content contained in Modules 2 and 5. Sequence No. 0000, dated 20 May 2015, contained the complete nonclinical and chemistry, manufacturing and controls content. This submission therefore completes the NDA.

As requested by the FDA at the meeting, we plan to amend this NDA [redacted] The Division agreed that these items of data are not necessary for filing this NDA, but should be submitted as available.

The additional clinical items will be submitted on the following schedule:

Table 1: Planned Amendments to NDA 206,488

NDA Amendment	Approximate Submission Date
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

This NDA also contains reviewer's guides for the following topics:

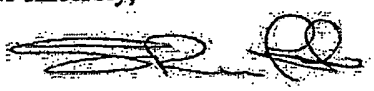
- Clinical information
- Nonclinical information
- Chemistry, manufacturing, and controls information

As discussed at the pre-NDA meeting, we also plan to hold an orientation meeting with the Agency to facilitate navigation of the NDA contents in [redacted]

In parallel with this eCTD submission, we are sending an external hard drive containing [redacted] as requested at the 18 September 2014 Type B pre-NDA meeting (Memorandum of Meeting Minutes dated 20 October 2014, Reference ID 3645985). The drive is navigable via a hyperlinked table of contents, contained on the drive in both PDF and Excel format. The drive also contains a reviewer's guide for [redacted]

Please do not hesitate to contact me by telephone at [redacted] or by electronic mail at [redacted] if you have any questions about this submission. If ESUB or the Division has any technical issues with this electronic submission or the external drive, please contact [redacted] by telephone at [redacted] or by electronic mail at [redacted]

Yours sincerely,



Shamim Ruff
Vice President, Regulatory Affairs and Quality
Sarepta Therapeutics, Inc.

Electronic Submission Specifications

This submission is compliant with FDA's Guideline for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway. This eCTD has been generated by Accenture, LLP (formerly Octagon Research Solutions Inc.), who has filed an acceptable eCTD pilot with the Center (Pilot Number 900777).

Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	11.0.5002.333
Virus Definition Date	06/22/2015 rev. 41
Submission Size	Approx. 2375.9 MB

The IT point of contact for this submission is:

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

EXHIBIT L

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

Exhibit L

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA206488

PRIORITY REVIEW DESIGNATION

Sarepta Therapeutics, Inc.
Attention: Shamim Ruff, MSc.
Vice President, Regulatory Affairs and Quality
215 First Street, Suite 415
Cambridge, MA 02142

Dear Ms. Ruff:

Please refer to your New Drug Application (NDA) dated June 26, 2015, received June 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Exondys 51 (eteplirsen) injection, 50 mg/mL.

We also refer to your submissions dated June 25, 2015, July 13, 2015, July 24, 2015, and July 31, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is February 26, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 25, 2016.

While conducting our filing review, we identified potential review issues that were communicated to you on August 6, 2015, by email.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURIE A KELLEY
08/20/2015

WILLIAM H Dunn
08/20/2015

EXHIBIT M

In re patent of Stephen Donald Wilton et al.
USP 9,081,368 B2
Approved Product: EXONDYS 51™ (eteplirsen)
Application for Patent Term Extension
Customer No. 123147

Exhibit M

Eteplirsen (AVI-4658) for treatment of Duchenne muscular dystrophy (DMD)				
Date	Doc From	Doc To	Document Description	Application Identifier
18-May-2007	AVI	FDA	Letter: Type B IND meeting request	IND 077429
31-May-2007	FDA	AVI	Email: Pre-IND# assigned, meeting confirmation for 24-Jul-07 [redacted]	IND 077429
4-Sep-2007	AVI	FDA	RoC: Not [redacted] to proceed	IND 077429
17-Sep-2007	AVI	FDA	Email: AVI has not received follow-up letter from 4-Sep-2007 telecon	IND 077429
20-Sep-2007	FDA	AVI	Email: FDA is actively working on follow-up letter	IND 077429
27-Nov-2007	FDA	AVI	Letter: Fast track designation is granted	IND 077429
29-Jan-2008	FDA	AVI	Letter: Proposed study is under full clinical hold; request for information	IND 077429
18-Apr-2008	AVI	FDA	JRR informed [redacted] Complete Response had been sent 4/17/08 [redacted]	IND 077429
16-May-2008	FDA	AVI	Email: Serial 0002 is not a complete response, letter forthcoming	IND 077429
16-May-2008	AVI	FDA	Email: Thanks	IND 077429
22-May-2008	FDA	AVI	Email/letter: Serial 0002 is not a complete response; CMC and nonclinical comments	IND 077429
22-May-2008	AVI	FDA	Email: Safety pharm draft report and DP CoA were provided in serials 0001 and 0002 respectively	IND 077429
23-May-2008	FDA	AVI	Email: Request for clarification on CoA; agree that safety pharm draft report was provided	IND 077429
23-May-2008	AVI	FDA	Email: Clarification on CoA	IND 077429
10-Feb-2009	AVI	FDA	RoC: Discussion with FDA on how to make a complete response to the clinical hold; [redacted]	IND 077429
26-Feb-2009	AVI	FDA	RoC: Extra copies requested for upcoming submission	IND 077429
23-Mar-2009	FDA	AVI	RoC: Reponse to serial 0006 will be verbal only; desk copies of serial 0006 and IND volume 1 requested	IND 077429
24-Mar-2009	AVI	FDA	Email: Tcon arrangements for serial 0006 discussion and desk copies	IND 077429
24-Mar-2009	FDA	AVI	Email: Thanks	IND 077429
24-Mar-2009	AVI	FDA	Email: Request for clarification on whether post-meeting call will be a group discussion	IND 077429
24-Mar-2009	FDA	AVI	Email: Telecon will be informal; AVI team should be available for questions and clarifications	IND 077429
24-Mar-2009	AVI	FDA	Email: Dial-in information for telecon	IND 077429
25-Mar-2009	FDA	AVI	Email: Desk copies received; internal FDA meeting to discuss IND will be rescheduled	IND 077429
3-Apr-2009	AVI	FDA	Email: Dial-in information for telecon	IND 077429
24-Apr-2009	AVI	FDA	Email/RoC: [redacted] taking over as RPM of IND	IND 077429
1-May-2009	AVI	FDA	Email: Dial-in and follow-up instructions for tcon	IND 077429
6-May-2009	FDA	AVI	RoC: Minutes of tcon with FDA re AVI questions in serial 0006	IND 077429
8-Jun-2009	FDA	AVI	Email: S. Keefe taking over as RPM of IND	IND 077429
28-Mar-2010	FDA	AVI	Fax: CD-ROM for serial 0008 is blank/unreadable	IND 077429
2-Apr-2010	FDA	AVI	Fax: CD-ROM for serial 0009 is blank/unreadable	IND 077429
6-Apr-2010	FDA	AVI	Email: Stephanie Keefe contact information; desk copy CD-ROM is blank/unreadable	IND 077429
6-Apr-2010	AVI	FDA	Email: Replacement CD will be sent	IND 077429
6-Apr-2010	FDA	AVI	Email: Replacement CD will also need to be submitted archivally to the IND, marked "Complete Response to Full Clinical Hold"; 30-day review clock will start upon receipt	IND 077429
6-Apr-2010	AVI	FDA	Email: Request for clarification on requirement for archive CD and stopping of review clock	IND 077429
6-Apr-2010	FDA	AVI	Email: CDs for serials 0008 and 0009 both blank, 30-day clock cannot proceed until nonclin study reports received	IND 077429
7-Apr-2010	AVI	FDA	Email: CDs will be resubmitted	IND 077429
8-Apr-2010	AVI	FDA	RoC: Serials 0008 and 0009 inadvertantly sent on DVDs rather than CD-ROMs; AVI will resubmit readable CDs	IND 077429
25-May-2010	FDA	AVI	Email: Request desk copies of serial 0011	IND 077429
21-Jun-2010	FDA	AVI	Email: Inquiry into AVI availability to discuss complete response to clinical hold	IND 077429
21-Jun-2010	AVI	FDA	Email: Availability to discuss complete response to clinical hold	IND 077429
24-Jun-2010	FDA	AVI	Email: Response letter being drafted	IND 077429
24-Jun-2010	AVI	FDA	Email: Acknowledgement of status update on response letter	IND 077429
24-Jun-2010	AVI	FDA	Email: Letter is in final stages of sign-off, PDF will be emailed	IND 077429
25-Jun-2010	FDA	AVI	FDA letter to remove full clinical hold on IND for AVI-4658	IND 077429
30-Jun-2010	AVI	FDA	Email: Request for update on response letter	IND 077429
30-Jun-2010	FDA	AVI	Email: Response letter was mailed 25-Jun-2010	IND 077429
6-Jul-2010	AVI	FDA	Email: Acknowledgement of receipt of remove full clinical hold letter; request update on status of "non-hold comments and recommendations" letter	IND 077429
6-Jul-2010	FDA	AVI	Letter: Remove full clinical hold on IND	IND 077429
8-Jul-2010	FDA	AVI	Email: Second letter with comments will be sent	IND 077429
8-Jul-2010	AVI	FDA	Email: Request second letter as soon as possible	IND 077429
19-Jul-2010	FDA	AVI	Email: Clinical Hold comments in final stages, will be sent ASAP	IND 077429
19-Jul-2010	AVI	FDA	Email: Acknowledgement of response re comments	IND 077429
29-Jul-2010	FDA	AVI	Email: Nonclinical team adding comments to letter, hope to have update by 2-Aug-2010	IND 077429
29-Jul-2010	AVI	FDA	Email: Acknowledgement of update	IND 077429
5-Aug-2010	FDA	AVI	Email/letter: Non-hold clinical and nonclinical comments	IND 077429
5-Aug-2010	AVI	FDA	Email: Acknowledge receipt of letter; inquiry whether hard copy will be sent also	IND 077429
29-Oct-2010	AVI	FDA	Email: Inquiry whether there are comments re new clinical protocol 4658-us-201; in the absence of comments AVI plans to start the study within the next month	IND 077429
4-Nov-2010	AVI	FDA	Email: Electronic copy of serial 0014 as requested	IND 077429
4-Nov-2010	FDA	AVI	Email: Comments are in process, request follow-up from AVI in 1 week	IND 077429
4-Nov-2010	FDA	AVI	Email: Request for PDF of serial 0014	IND 077429
4-Nov-2010	AVI	FDA	Email: [redacted] will send PDF of serial 0014; [redacted] delegated to sign forms on [redacted] behalf, inquiry whether IND amendment should be filed reflecting this change	IND 077429
9-Nov-2010	AVI	FDA	Email: [redacted] is no longer with AVI, [redacted] is now regulatory contact; request for update on serial 00014	IND 077429
10-Nov-2010	FDA	AVI	Email: Confirmation of change on sponsor authorized contact, request for amendment to IND reflecting change	IND 077429
16-Nov-2010	AVI	FDA	Email: Follow-up on [redacted] email from 29-Oct-2010 re forthcoming FDA response to serial 0014	IND 077429

16-Nov-2010	FDA	AVI	Email: FDA nonclinical team working on the response; request for AVI to wait for response before proceeding with study	IND 077429
29-Nov-2010	FDA	AVI	Email: FDA will meet internally to discuss serial 0014; inquiry re AVI availability for telecon with FDA during meeting; request for contact number	IND 077429
29-Nov-2010	AVI	FDA	Email: Contact number for	IND 077429
1-Dec-2010	FDA	AVI	Email: availability	IND 077429
1-Dec-2010	AVI	FDA	Email: will be out of office, will be contact for telecon	IND 077429
2-Dec-2010	AVI	FDA	Email: Follow-up to email that will be telecon contact, not 4658-us-201 remains on hold until FDA comments are received	IND 077429
3-Dec-2010	FDA	AVI	Email: FDA will issue a letter with comments, in next couple weeks; 4658-us-201 may proceed at any time	IND 077429
3-Dec-2010	AVI	FDA	Email: Acknowledgement of FDA decision	IND 077429
29-Dec-2010	AVI	FDA	Email: Inquiry re when comments from FDA meeting on 1-Dec-2010 can be expected	IND 077429
2-Jan-2011	FDA	AVI	Email: will follow up with review team	IND 077429
14-Jan-2011	AVI	FDA	Email: Follow-up to voicemail inquiry re when comments from FDA meeting on 1-Dec-2010 can be expected	IND 077429
18-Jan-2011	FDA	AVI	Email: Director was out of the office, should be reviewing response letter for finalization this week	IND 077429
21-Jan-2011	FDA	AVI	Letter: Nonclinical and clinical comments on 4658-us-201	IND 077429
6-Apr-2011	AVI	FDA	Email: Inquiry re status of meeting request	IND 077429
6-Apr-2011	FDA	AVI	Email: has meeting request, will be in touch	IND 077429
8-Apr-2011	AVI	FDA	Email: Inquiry re status of meeting request	IND 077429
8-Apr-2011	FDA	AVI	Email: Goal date for responding to meeting request is 11-Apr-2011	IND 077429
11-Apr-2011	AVI	FDA	Email: Inquiry re status of meeting request	IND 077429
11-Apr-2011	FDA	AVI	Email: Meeting request granted 14-Jun-2011; teleconference only	IND 077429
15-Apr-2011	AVI	FDA	Email: Inquiry re status of meeting request	IND 077429
15-Apr-2011	FDA	AVI	Email: Request for EOP1 meeting on 14-Jun-2011 granted; meeting package due 17-May-2011	IND 077429
24-May-2011	FDA	AVI	Email: Acknowledgement of receipt of serial 0019	IND 077429
9-Jun-2011	AVI	FDA	Email: Notification of submission of serial 0020; request for feedback on serial 0019	IND 077429
12-Jun-2011	FDA	AVI	Email: FDA's preliminary responses on EOP1 meeting package	IND 077429
14-Jun-2011	FDA	AVI	Email: EOP1 meeting FDA attendees list	IND 077429
29-Jul-2011	FDA	AVI	Letter: FDA 14-Jun-2011 EOP1 meeting minutes	IND 077429
7-Feb-2012	AVI	FDA	Email: Electronic copy of serial 0027	IND 077429
8-Feb-2012	FDA	AVI	Email: F. Choy taking over as RPM of IND	IND 077429
29-Feb-2012	AVI	FDA	Email: Electronic copy of serial 0029; 3674	IND 077429
5-Mar-2012	FDA	AVI	Email: Forwarding serial 0029 to nonclinical review team; contact information for F. Choy	IND 077429
2-Apr-2012	AVI	FDA	Email: Request update on status of serial 0029 review	IND 077429
2-Apr-2012	FDA	AVI	Email: Serial 0029 still under review	IND 077429
25-Apr-2012	AVI	FDA	Email: 15-day IND safety report forthcoming; request method of transmission	IND 077429
25-Apr-2012	FDA	AVI	Email: Paper amendment with electronic copy sent by email is fine	IND 077429
26-Apr-2012	AVI	FDA	Email: Electronic copy of serial 0031	IND 077429
1-May-2012	AVI	FDA	Email: Inquiry regarding existence of formal letter assigning IND number	IND 077429
2-May-2012	FDA	AVI	Email: No such letter issued	IND 077429
3-May-2012	AVI	FDA	Email: Cover letter for serial 0032	IND 077429
3-May-2012	FDA	AVI	Email: Thanks	IND 077429
1-Jun-2012	AVI	FDA	Email: Further follow-up on IND safety report is forthcoming; draft histology subreport for 4658-tox-001 will be submitted by	IND 077429
1-Jun-2012	FDA	AVI	Email: Request IND number for reference	IND 077429
4-Jun-2012	AVI	FDA	Email: IND number is 077429	IND 077429
6-Jun-2012	AVI	FDA	Email: Serial 0033 electronic copy	IND 077429
19-Jun-2012	AVI	FDA	Email: Request update on status of serial 0029 review	IND 077429
20-Jun-2012	FDA	AVI	Email: PK studies under INDs are reviewed by clinical pharmacology team; Serial 0029 review is underway	IND 077429
21-Jun-2012	AVI	FDA	Email: Thanks	IND 077429
12-Jul-2012	SRPT	FDA	Email: Sponsor name change	IND 077429
12-Jul-2012	FDA	SRPT	Email: Thanks	IND 077429
27-Jul-2012	SRPT	FDA	Email: Request update on status of serial 0029 review	IND 077429
13-Aug-2012	FDA	SRPT	Email: Inquiry on status of serial 0029 review will be forwarded to team	IND 077429
16-Aug-2012	SRPT	FDA	Email: Electronic copy of serial 0035	IND 077429
16-Aug-2012	FDA	SRPT	Letter: Acknowledgement of sponsor name change	IND 077429
20-Aug-2012	FDA	SRPT	Email: Serial 0029 still under review	IND 077429
23-Aug-2012	SRPT	FDA	Email: Serial 0036 electronic copy	IND 077429
24-Aug-2012	SRPT	FDA	Email: Notification of serial 0037	IND 077429
5-Nov-2012	SRPT	FDA	Email: Request update on status of serial 0029 review	IND 077429
6-Nov-2012	FDA	SRPT	Email: Inquiry on status of serial 0029 review will be forwarded to team	IND 077429
13-Nov-2012	FDA	SRPT	RoC: Inquiry re	IND 077429
14-Nov-2012	FDA	SRPT	Email: Request teleconference to discuss next steps in development of eteplirsen	IND 077429
14-Nov-2012	SRPT	FDA	Email: Propose 1:1 call between and	IND 077429
15-Nov-2012	FDA	SRPT	Email: 1:1 discussion is acceptable; available times	IND 077429
15-Nov-2012	SRPT	FDA	Email: Request clarification on time zone	IND 077429
15-Nov-2012	FDA	SRPT	Email: Times are EST; 2-3:30 pm time slot is available	IND 077429
15-Nov-2012	SRPT	FDA	Email: 3:00 pm EST is acceptable;	IND 077429
15-Nov-2012	FDA	SRPT	Email: R. Katz will call now	IND 077429
15-Nov-2012	SRPT	FDA	Email: Acknowledgement of receipt of previous email	IND 077429
15-Nov-2012	FDA	SRPT	Email: Call between and to clarify comments in next steps in development of eteplirsen	IND 077429

28-Nov-2012	SRPT	FDA	Email: Serial 0038 electronic copy	IND 077429
5-Dec-2012	SRPT	FDA	Email: [redacted] on leave of absence; [redacted] is primary sponsor's authorized representative until further notice	IND 077429
6-Dec-2012	FDA	SRPT	Email: Thanks	IND 077429
11-Dec-2012	SRPT	FDA	Email: Serial 0039 cover letter	IND 077429
14-Dec-2012	FDA	SRPT	Email: Request call to discuss EOP2 meeting request	IND 077429
14-Dec-2012	FDA	SRPT	RoC: Inquiry into plans for clinical development and EOP2 meeting request	IND 077429
17-Dec-2012	SRPT	FDA	Email: Targetting late February to early March for clinical EOP2 meeting	IND 077429
18-Dec-2012	FDA	SRPT	Email: Thanks	IND 077429
27-Dec-2012	SRPT	FDA	Email: Serial 0040 electronic copy	IND 077429
27-Dec-2012	SRPT	FDA	Email: 4658-us-202 v02 protocol in serial 0038 contained errors; request corrective action	IND 077429
2-Jan-2013	FDA	SRPT	Email: Protocol should be resubmitted with new serial number and explanation of cause of errors	IND 077429
4-Jan-2013	FDA	SRPT	Email: Propose 13-Mar-2013 4:00-5:00 pm EST as date for EOP2 meeting	IND 077429
4-Jan-2013	FDA	SRPT	Email: Request that the meeting package for the EOP2 meeting be submitted one week in advance of the usual deadline, i.e. sometime Feb 4-8	IND 077429
8-Jan-2013	FDA	SRPT	Email: Request confirmation of 13-Mar-2013 EOP2 meeting date	IND 077429
8-Jan-2013	SRPT	FDA	Email: Confirm 13-Mar-2013 EOP2 meeting date	IND 077429
8-Jan-2013	FDA	SRPT	Letter: Type B clinical EOP2 meeting request granted 13-Mar-2013	IND 077429
8-Jan-2013	SRPT	FDA	Email: Acknowledge receipt of Meeting Request Granted letter	IND 077429
9-Jan-2013	SRPT	FDA	Email: Serial 0041 electronic copy	IND 077429
10-Jan-2013	FDA	SRPT	Email: Thanks	IND 077429
16-Jan-2013	SRPT	FDA	Email: Inquiry if 3 CD-ROMs would be needed for the meeting briefing document or only 1	IND 077429
17-Jan-2013	FDA	SRPT	Email: Only 1 disc necessary	IND 077429
17-Jan-2013	SRPT	FDA	Email: Inquiry if all CD-ROM-based submissions require only 1 disc to be submitted	IND 077429
18-Jan-2013	FDA	SRPT	Email: Only 1 disc necessary	IND 077429
18-Jan-2013	SRPT	FDA	Email: Serial 0042 electronic copy	IND 077429
6-Feb-2013	SRPT	FDA	Email: Serial 0043 electronic copy; EOP2 meeting attendees and questions	IND 077429
7-Feb-2013	FDA	SRPT	Email: Acknowlege receipt of EOP2 BD electronic copy and attendees and questions Word document	IND 077429
7-Feb-2013	SRPT	FDA	Email: FedEx unable to deliver desk copy package on first attempt	IND 077429
7-Feb-2013	FDA	SRPT	Email: Inform FedEx that FDA follows operation status of federal government and insist they re-deliver the desk copy package ASAP	IND 077429
8-Feb-2013	SRPT	FDA	RoC: FedEx delivery issues	IND 077429
8-Feb-2013	SRPT	FDA	Email: Request confirmation of desk copy address	IND 077429
8-Feb-2013	FDA	SRPT	Email: Desk copy address is correct	IND 077429
11-Feb-2013	SRPT	FDA	Email: FedEx tracking number	IND 077429
11-Feb-2013	FDA	SRPT	Email: Package not yet received	IND 077429
11-Feb-2013	SRPT	FDA	Email: Request acknowledgement of receipt of desk copy package	IND 077429
11-Feb-2013	FDA	SRPT	Email: Confirmation of receipt	IND 077429
11-Feb-2013	SRPT	FDA	Email: Thanks	IND 077429
13-Feb-2013	FDA	SRPT	Email: First set of comments on serial 0043 (EOP2 BD); request response by morning 18-Feb-2013	IND 077429
13-Feb-2013	SRPT	FDA	Email: Acknowlege receipt of comments on serial 0043	IND 077429
15-Feb-2013	SRPT	FDA	Email: Unable to submit response to 13-Feb-2013 comments until 19-Feb-2013	IND 077429
18-Feb-2013	FDA	SRPT	Email: Provide response to 13-Feb-2013 comments by 19-Feb-2013 10am EST	IND 077429
18-Feb-2013	SRPT	FDA	Email: Response to 13-Feb-2013 comments will be emailed by 19-Feb-2013 10am EST	IND 077429
18-Feb-2013	SRPT	FDA	Email: Serial 0044 electronic copy	IND 077429
19-Feb-2013	SRPT	FDA	Email: Serial 0045 electronic copy	IND 077429
19-Feb-2013	FDA	SRPT	Email: Meeting preliminary comments typically emailed 24-48 hours in advance	IND 077429
19-Feb-2013	SRPT	FDA	Email: Serial 0046 electronic copy	IND 077429
25-Feb-2013	SRPT	FDA	Email: New sponsor phone numbers	IND 077429
6-Mar-2013	FDA	SRPT	Email: Comments on serial 0044	IND 077429
6-Mar-2013	FDA	SRPT	Email: Scheduled visit notification form	IND 077429
7-Mar-2013	FDA	SRPT	Email: Request confirmation of receipt of 06-Mar-2013 comments	IND 077429
7-Mar-2013	SRPT	FDA	Email: Request method of follow-up to DMEPA reviewer's comment on serial 0044	IND 077429
7-Mar-2013	FDA	SRPT	Email: Submit response as IND amendment	IND 077429
7-Mar-2013	SRPT	FDA	Email: Serial 0047 electronic copy	IND 077429
8-Mar-2013	SRPT	FDA	Email: Updated attendee list for 13-Mar-2013 meeting	IND 077429
8-Mar-2013	FDA	SRPT	Email: Internal meeting to discuss serial 0043 rescheduled	IND 077429
11-Mar-2013	FDA	SRPT	Email: Second set of comments on serial 0043 (EOP2 BD); request response by 12-Mar-2013 noon EST	IND 077429
11-Mar-2013	SRPT	FDA	Email: Acknowledge receipt of 11-Mar-2013 comments on serial 0043	IND 077429
11-Mar-2013	FDA	SRPT	Email: Request regarding serial 0043 page 24 forthcoming	IND 077429
11-Mar-2013	SRPT	FDA	Email: Serial 0043 page 24 request coming today?	IND 077429
11-Mar-2013	FDA	SRPT	Email: Serial 0043 page 24 request will come today	IND 077429
11-Mar-2013	FDA	SRPT	Email: Serial 0043 page 24 request will come tomorrow	IND 077429
12-Mar-2013	SRPT	FDA	Email: When to expect serial 0043 page request?	IND 077429
12-Mar-2013	FDA	SRPT	Email: Third set of comments on serial 0043 (EOP2 BD); request prompt response	IND 077429
12-Mar-2013	FDA	SRPT	Email: Internal FDA follow-up meeting scheduled at 3pm	IND 077429
12-Mar-2013	SRPT	FDA	Email: Acknowledge receipt of 12-Mar-2013 comments on serial 0043	IND 077429
12-Mar-2013	SRPT	FDA	Email: Responses to 11-Mar-2013 comments	IND 077429
12-Mar-2013	FDA	SRPT	Email: Acknowledge receipt	IND 077429
12-Mar-2013	SRPT	FDA	Email: Responses to 12-Mar-2013 comments	IND 077429

12-Mar-2013	FDA	SRPT	Email: Acknowledge receipt; plan to send preliminary comments on serial 0043 today	IND 077429
12-Mar-2013	FDA	SRPT	Letter: Preliminary responses to 13-Mar-2013 EOP2 meeting questions (serial 0043) and list of FDA participants	IND 077429
13-Mar-2013	SRPT	FDA	Email: Acknowledge receipt	IND 077429
13-Mar-2013	SRPT	FDA	Email: 13-Mar-2013 EOP2 meeting slides	IND 077429
19-Mar-2013	SRPT	FDA	Email: Serial 0048 electronic copy	IND 077429
22-Mar-2013	SRPT	FDA	Email: Serial 0049 electronic copy	IND 077429
25-Mar-2013	FDA	SRPT	Email: FDA attendees at 13-Mar-2013 EOP2 meeting	IND 077429
4-Apr-2013	SRPT	FDA	RoC: FDA 13-Mar-2013 EOP2 meeting minutes expected around 12-Apr-2013; request general correspondence amendment with Sarepta's new address	IND 077429
4-Apr-2013	SRPT	FDA	Email: Serial 0050 electronic copy	IND 077429
5-Apr-2013	SRPT	FDA	Email: Study 4658-us-202[redacted]	IND 077429
11-Apr-2013	SRPT	FDA	Email: Request data format for study 4658-us-201/202[redacted]	IND 077429
12-Apr-2013	FDA	SRPT	Letter: Memorandum of 13-Mar-2013 Clinical EOP2 meeting minutes	IND 077429
12-Apr-2013	SRPT	FDA	Email: Acknowledge receipt	IND 077429
15-Apr-2013	SRPT	FDA	Email: Serial 0051 cover letter	IND 077429
15-Apr-2013	FDA	SRPT	Email: Still on track to submit[redacted] by end of week?	IND 077429
16-Apr-2013	SRPT	FDA	Email: Targeting[redacted] submission by end of April	IND 077429
17-Apr-2013	FDA	SRPT	Email:[redacted] data should be submitted both SAS and CSV format	IND 077429
19-Apr-2013	FDA	SRPT	Email: Fannie Choy OOO 4/22-24 and 5/1-3; interim contact is Susan Daughtery	IND 077429
19-Apr-2013	SRPT	FDA	Email: Thanks	IND 077429
23-Apr-2013	SRPT	FDA	Email: Serial 0052 electronic copy	IND 077429
23-Apr-2013	FDA	SRPT	Email: Serial 0052 will be forwarded to nonclinical reviewer	IND 077429
26-Apr-2013	FDA	SRPT	Letter: Acknowledge address change	IND 077429
29-Apr-2013	SRPT	FDA	Email: Target date for role of[redacted] is week of May 6	IND 077429
29-Apr-2013	FDA	SRPT	Email: Request expected submission date for[redacted]	IND 077429
29-Apr-2013	SRPT	FDA	Email: Will follow up on submission date for[redacted]	IND 077429
6-May-2013	SRPT	FDA	Email:[redacted] to be submitted 15-May-2013; request follow-up EOP2 meeting by end of June	IND 077429
9-May-2013	SRPT	FDA	RoC: EOP2 follow-up meeting aimed for mid-July	IND 077429
24-May-2013	SRPT	FDA	Email: Serial 0053 electronic copy	IND 077429
24-May-2013	SRPT	FDA	Email: Request confirmation of 22- or 23-Jul-2013 follow-up meeting date	IND 077429
28-May-2013	FDA	SRPT	Email: Meeting tenatively scheduled for 23-Jul-2013	IND 077429
29-May-2013	SRPT	FDA	Email: Serial 0054 electronic copy	IND 077429
4-Jun-2013	FDA	SRPT	Email: Comments on serial 0052 (4658-pkd-006 outline)	IND 077429
4-Jun-2013	SRPT	FDA	Email: Acknowledge receipt	IND 077429
13-Jun-2013	FDA	SRPT	Email: Request that briefing package desk copies for 23-Jul-2013 meeting be sent with or soon after meeting request	IND 077429
13-Jun-2013	SRPT	FDA	Email: Meeting request will be sent next week in order to include desk copies	IND 077429
13-Jun-2013	FDA	SRPT	Email: Send meeting request tomorrow in order to confirm date	IND 077429
13-Jun-2013	SRPT	FDA	Email: Meeting request will be sent tomorrow	IND 077429
14-Jun-2013	SRPT	FDA	Email: Serial 0055 electronic copy; 3 references missing from CD-ROM	IND 077429
17-Jun-2013	SRPT	FDA	Email: Desk copies should arrive 18-Jun-2013; included CD-ROM of references is complete	IND 077429
17-Jun-2013	FDA	SRPT	Email: Thanks	IND 077429
26-Jun-2013	FDA	SRPT	Efax: 23-Jul-2013 Type C EOP2 followup meeting request granted	IND 077429
9-Jul-2013	SRPT	FDA	Email: Serial 0056 electronic copy	IND 077429
10-Jul-2013	FDA	SRPT	Email: Thanks	IND 077429
16-Jul-2013	FDA	SRPT	Email: CMC EOP2 meeting request should be submitted to IND; meeting scheduling will be managed by ONDQA project manager	IND 077429
16-Jul-2013	SRPT	FDA	Email: Request contact info of ONDQA PM	IND 077429
17-Jul-2013	FDA	SRPT	Email: ONDQA PM Teshara Boule contact info	IND 077429
22-Jul-2013	FDA	SRPT	Efax: 23-Jul-2013 Type C EOP2 followup meeting preliminary comments	IND 077429
22-Jul-2013	SRPT	FDA	Email: Acknolwedge receipt of preliminary comments	IND 077429
22-Jul-2013	SRPT	FDA	Email: Meeting attendees and question in Word format	IND 077429
23-Jul-2013	FDA	SRPT	Email:[redacted] and[redacted] removed from attendees list; request meeting slides	IND 077429
23-Jul-2013	SRPT	FDA	Email: 23-Jul-2013 EOP2 followup meeting slides	IND 077429
24-Jul-2013	FDA	SRPT	Email: Request copy of backup slide on study 4658-301 design	IND 077429
29-Jul-2013	FDA	SRPT	Email: Request teleconference to discuss proposed trade name for eteplirsen ([redacted]	IND 077429
29-Jul-2013	SRPT	FDA	Email: Availability for teleconference	IND 077429
30-Jul-2013	FDA	SRPT	Email: Confirm teleconference time and date	IND 077429
31-Jul-2013	SRPT	FDA	RoC: Trade name[redacted] not acceptable	IND 077429
6-Aug-2013	FDA	SRPT	Email: Decision reached re regulatory options for trade name review?	IND 077429
6-Aug-2013	SRPT	FDA	Email: Serial 0057 electronic copy	IND 077429
7-Aug-2013	FDA	SRPT	Email: 31-Jul-2013 teleconference FDA attendees	IND 077429
12-Aug-2013	SRPT	FDA	Email: 23-Jul-2013 EOP2 followup meeting minutes; request timing of feedback to serial 0056	IND 077429
14-Aug-2013	FDA	SRPT	Email: Will forward request to Quality RPM[redacted]	IND 077429
14-Aug-2013	SRPT	FDA	Email: Thanks	IND 077429
14-Aug-2013	FDA	SRPT	Email: Will have responses to serial 0056 by end of week	IND 077429
15-Aug-2013	FDA	SRPT	Efax: Responses to serial 0056	IND 077429
16-Aug-2013	FDA	SRPT	Letter: Proprietary name request unacceptable	IND 077429
16-Aug-2013	FDA	SRPT	Email: Request Sarepta attendees at 31-Jul-2013 teleconference	IND 077429
16-Aug-2013	SRPT	FDA	Email: 31-Jul-2013 teleconference Sarepta attendees	IND 077429

Exhibit M

16-Aug-2013	FDA	SRPT	Email: Thanks	IND 077429
22-Aug-2013	FDA	SRPT	Email: Propose 02-Oct-2013 for CMC EOP2 meeting (2 emails)	IND 077429
22-Aug-2013	SRPT	FDA	Email: Propose week of 07-Oct-2013 for CMC EOP2 meeting	IND 077429
23-Aug-2013	FDA	SRPT	Email: Available 09-Oct-2013	IND 077429
23-Aug-2013	SRPT	FDA	Email: Will get back ASAP	IND 077429
23-Aug-2013	SRPT	FDA	Email: Confirm 09-Oct-2013 for CMC EOP2 meeting	IND 077429
23-Aug-2013	FDA	SRPT	Email: Meeting request granted letter will be issued next week	IND 077429
23-Aug-2013	SRPT	FDA	Email: Serial 0058 electronic copy	IND 077429
27-Aug-2013	SRPT	FDA	Email: Include serial 0035 with paper desk copies?	IND 077429
27-Aug-2013	FDA	SRPT	Email: Request serial 0035 be provided as appendix with BD desk copies	IND 077429
29-Aug-2013	SRPT	FDA	Email: Request number of desk copies needed	IND 077429
29-Aug-2013	FDA	SRPT	Efax: 7 desk copies of BD needed; CMC EOP2 meeting request granted	IND 077429
30-Aug-2013	FDA	SRPT	Email: CMC EOP2 meeting tentatively rescheduled to 17-Oct-2013	IND 077429
10-Sep-2013	SRPT	FDA	Email: Request confirmation of 17-Oct-2013 meeting date	IND 077429
10-Sep-2013	SRPT	FDA	Email: Serial 0059 electronic copy	IND 077429
12-Sep-2013	FDA	SRPT	Email: Confirm 17-Oct-2013 CMC EOP2 meeting date and desk copy address for [redacted]	IND 077429
12-Sep-2013	SRPT	FDA	Email: Request BD due date	IND 077429
12-Sep-2013	FDA	SRPT	Email: BD due 17-Sep-2013	IND 077429
13-Sep-2013	SRPT	FDA	Email: Serial 0035, 0056, and 0060 electronic copies	IND 077429
13-Sep-2013	FDA	SRPT	Email: Thanks	IND 077429
15-Sep-2013	FDA	SRPT	Email: Acknowledge receipt of Type C meeting request	IND 077429
25-Sep-2013	FDA	SRPT	Email: Type C meeting tentatively scheduled 09-Dec-2013; requested planned date for enrolling patients in [redacted]	IND 077429
25-Sep-2013	SRPT	FDA	Email: Accept 09-Dec-2013 Type C meeting date	IND 077429
25-Sep-2013	FDA	SRPT	Efax: Type C meeting request granted letter	IND 077429
25-Sep-2013	SRPT	FDA	Email: Planning to start [redacted]	IND 077429
27-Sep-2013	FDA	SRPT	Email: Rescheduled Type C meeting 07-Nov-2013	IND 077429
27-Sep-2013	SRPT	FDA	Email: Confirm Type C meeting as teleconference and 08-Nov-2013 meeting date	IND 077429
2-Oct-2013	FDA	SRPT	Email: Confirm 08-Nov-2013 Type C meeting date; request BD submission by 08-Oct-2013	IND 077429
2-Oct-2013	SRPT	FDA	Email: Acknolwedge receipt	IND 077429
4-Oct-2013	SRPT	FDA	Email: 17-Oct-2013 CMC EOP2 meeting attendees and questions	IND 077429
8-Oct-2013	SRPT	FDA	Email: Updated attendees for 17-Oct-2013 CMC EOP2 meeting; request status of meeting in light of government shutdown	IND 077429
8-Oct-2013	FDA	SRPT	Email: 17-Oct-2013 CMC EOP2 will be held as scheduled	IND 077429
8-Oct-2013	FDA	SRPT	Email: Government shutdown auto-reply	IND 077429
8-Oct-2013	FDA	SRPT	Email: Request electronic copy of serial 0061	IND 077429
8-Oct-2013	SRPT	FDA	Email: Serial 0061 electronic copy	IND 077429
8-Oct-2013	FDA	SRPT	Email: Thanks	IND 077429
8-Oct-2013	FDA	SRPT	Email: Information request re serial 0061	IND 077429
8-Oct-2013	SRPT	FDA	Email: Acknowlege receipt	IND 077429
9-Oct-2013	SRPT	FDA	Email: Will send 4658-us-201/202 [redacted] data today	IND 077429
9-Oct-2013	FDA	SRPT	Email: Thanks	IND 077429
9-Oct-2013	SRPT	FDA	Email: Serial 0062 electronic copy	IND 077429
9-Oct-2013	FDA	SRPT	Email: Acknowlege receipt	IND 077429
10-Oct-2013	FDA	SRPT	Email: 2nd information request re serial 0061	IND 077429
10-Oct-2013	SRPT	FDA	Email: Will have requested graphs today	IND 077429
10-Oct-2013	FDA	SRPT	Email: Thanks	IND 077429
10-Oct-2013	SRPT	FDA	Email: Serial 0063 electronic copy	IND 077429
10-Oct-2013	FDA	SRPT	Email: Acknowledge receipt	IND 077429
11-Oct-2013	SRPT	FDA	Email: Updated attendees for 17-Oct-2013 CMC EOP2 meeting	IND 077429
11-Oct-2013	FDA	SRPT	Email: LobbyGuard notification coming soon	IND 077429
14-Oct-2013	SRPT	FDA	Email: Request FDA attendees and preliminary comments ETA for 17-Oct-2013 CMC EOP2 meeting	IND 077429
15-Oct-2013	FDA	SRPT	Email: Tentative list of FDA attendees	IND 077429
15-Oct-2013	FDA	SRPT	Efax: 17-Oct-2013 Type B CMC EOP2 meeting preliminary comments	IND 077429
15-Oct-2013	FDA	SRPT	Email: LobbyGuard form	IND 077429
15-Oct-2013	SRPT	FDA	Email: Confirm 17-Oct-2013 CMC EOP2 meeting date	IND 077429
16-Oct-2013	FDA	SRPT	Email: Meeting agenda?	IND 077429
17-Oct-2013	SRPT	FDA	Email: 17-Oct-2013 CMC EOP2 meeting slides v1	IND 077429
17-Oct-2013	SRPT	FDA	Email: 17-Oct-2013 CMC EOP2 meeting slides v2	IND 077429
17-Oct-2013	FDA	SRPT	Email: Request laptop to project slides	IND 077429
21-Oct-2013	FDA	SRPT	Email: 17-Oct-2013 CMC EOP2 meeting attendees	IND 077429
28-Oct-2013	FDA	SRPT	Letter: 17-Oct-2013 Type B CMC EOP2 meeting minutes	IND 077429
1-Nov-2013	FDA	SRPT	Email: 08-Nov-2013 Type C teleconference extended to 4:00-5:30 pm	IND 077429
1-Nov-2013	SRPT	FDA	Email: 08-Nov-2013 Type C teleconference attendees and questions	IND 077429
1-Nov-2013	FDA	SRPT	Email: Acknowledge receipt	IND 077429
4-Nov-2013	SRPT	FDA	Email: 17-Oct-2013 Type B CMC EOP2 meeting minutes	IND 077429
5-Nov-2013	SRPT	FDA	Email: Additional agenda item for 08-Nov-2013 Type C teleconference: update on [redacted]	IND 077429
6-Nov-2013	FDA	SRPT	Efax: 08-Nov-2013 Type C teleconference preliminary comments	IND 077429
6-Nov-2013	FDA	SRPT	Email: [redacted] may attend 08-Nov-2013 teleconference	IND 077429

7-Nov-2013	FDA	SRPT	Email: Acknowledge receipt	IND 077429
7-Nov-2013	SRPT	FDA	Email: Updated attendees and dial-in	IND 077429
7-Nov-2013	SRPT	FDA	Email: [redacted] calling into 08-Nov-2013 meeting	IND 077429
8-Nov-2013	SRPT	FDA	Email: 6 in-person Sarepta attendees	IND 077429
8-Nov-2013	FDA	SRPT	Email: Meeting room	IND 077429
8-Nov-2013	FDA	SRPT	Email: Building 22 entry instructions	IND 077429
8-Nov-2013	SRPT	FDA	Email: Thanks	IND 077429
8-Nov-2013	SRPT	FDA	RoC: 08-Nov-2013 Type C meeting transcript	IND 077429
8-Nov-2013	FDA	SRPT	Email: Propose 15-Nov-2013 for follow-up meeting	IND 077429
8-Nov-2013	SRPT	FDA	Email: Will confirm availability of personnel by Monday	IND 077429
11-Nov-2013	SRPT	FDA	Email: Confirm 15-Nov-2013 follow-up meeting date	IND 077429
12-Nov-2013	FDA	SRPT	Email: Thanks	IND 077429
12-Nov-2013	SRPT	FDA	Email: Request list of FDA attendees	IND 077429
12-Nov-2013	FDA	SRPT	Email: Will try to send today	IND 077429
12-Nov-2013	SRPT	FDA	Email: 15-Nov-2013 teleconference dial-in	IND 077429
13-Nov-2013	FDA	SRPT	Email: 08-Nov-2013 Type C meeting attendees	IND 077429
15-Nov-2013	SRPT	FDA	PPT: 15-Nov-2013 teleconference slides	IND 077429
15-Nov-2013	SRPT	FDA	RoC: 15-Nov-2013 teleconference transcript	IND 077429
18-Nov-2013	FDA	SRPT	Email: Information request re 4658-us-202[redacted] Site 01 contact info	IND 077429
18-Nov-2013	SRPT	FDA	Email: Acknowledge receipt	IND 077429
19-Nov-2013	SRPT	FDA	Email: Propose dates for follow-up meeting/teleconference	IND 077429
19-Nov-2013	FDA	SRPT	Email: Will follow up on teleconference date today; request prompt response on 18-Nov-2013 information request	IND 077429
19-Nov-2013	SRPT	FDA	Email: Will call today	IND 077429
19-Nov-2013	SRPT	FDA	Email: Follow-up teleconference BD will be submitted 01-Dec-2013	IND 077429
19-Nov-2013	SRPT	FDA	Email: Responses to 18-Nov-2013 information request	IND 077429
19-Nov-2013	FDA	SRPT	Email: Acknowledge receipt	IND 077429
20-Nov-2013	SRPT	FDA	RoC: OSI to inspect 4658-us-202 Site 01 next month; request additional info on site[redacted]	IND 077429
21-Nov-2013	SRPT	FDA	Email: Response to information request on 4658-us-202 Site 01[redacted]	IND 077429
21-Nov-2013	FDA	SRPT	Email: Thanks	IND 077429
22-Nov-2013	FDA	SRPT	Email: Propose 19-Dec-2013 for follow-up meeting	IND 077429
22-Nov-2013	SRPT	FDA	Email: Will confirm ASAP	IND 077429
22-Nov-2013	SRPT	FDA	Email: Confirm 19-Dec-2013 Type A meeting date	IND 077429
22-Nov-2013	SRPT	FDA	RoC: 19-Dec-2013 Type A teleconference BD logistics	IND 077429
26-Nov-2013	SRPT	FDA	Email: Questions regarding 4658-us-202 Site 01 inspection (2 emails)	IND 077429
26-Nov-2013	FDA	SRPT	Email: Acknowledge receipt	IND 077429
27-Nov-2013	FDA	SRPT	Email: Responses to information request re 4658-us-202 Site 01 inspection	IND 077429
27-Nov-2013	SRPT	FDA	Email: Thanks	IND 077429
2-Dec-2013	SRPT	FDA	Email: 08-Nov-2013 and 15-Nov-2013 Type C meeting minutes	IND 077429
2-Dec-2013	SRPT	FDA	Email: Serial 0065 electronic copy	IND 077429
2-Dec-2013	FDA	SRPT	Email: Request confirmation that 19-Dec-2013 Type A meeting will be teleconference	IND 077429
2-Dec-2013	SRPT	FDA	Email: Thanks	IND 077429
9-Dec-2013	FDA	SRPT	Email: Clinical information request re[redacted] data	IND 077429
9-Dec-2013	SRPT	FDA	RoC: Clinical information requests	IND 077429
9-Dec-2013	SRPT	FDA	Email: Will be able to send[redacted] data on 12/11	IND 077429
11-Dec-2013	SRPT	FDA	Email: Unmonitored[redacted] data	IND 077429
11-Dec-2013	FDA	SRPT	Email: Acknowledge receipt	IND 077429
12-Dec-2013	FDA	SRPT	Efax: 19-Dec-2013 Type A meeting granted	IND 077429
12-Dec-2013	SRPT	FDA	Email: Request 19-Dec-2013 teleconference be arranged as face-to-face meeting	IND 077429
12-Dec-2013	FDA	SRPT	Email: Acknowledge receipt	IND 077429
13-Dec-2013	SRPT	FDA	Email: 19-Dec-2013 Type A meeting attendees	IND 077429
13-Dec-2013	FDA	SRPT	Email: Clinical pharmacology information request	IND 077429
13-Dec-2013	SRPT	FDA	Email: Acknowledge receipt	IND 077429
16-Dec-2013	FDA	SRPT	Email: Clin pharm information request re CK data	IND 077429
16-Dec-2013	SRPT	FDA	Email: Acknowledge receipt	IND 077429
16-Dec-2013	SRPT	FDA	Email: Request ETA of 08-Nov and 15-Nov-2013 meeting minutes	IND 077429
17-Dec-2013	FDA	SRPT	Efax: 19-Dec-2013 Type A meeting preliminary comments	IND 077429
17-Dec-2013	SRPT	FDA	Email: Acknowledge receipt	IND 077429
18-Dec-2013	FDA	SRPT	Email: LobbyGuard form	IND 077429
18-Dec-2013	FDA	SRPT	Email: LobbyGuard form	IND 077429
18-Dec-2013	SRPT	FDA	Email: Meeting slides tomorrow	IND 077429
18-Dec-2013	FDA	SRPT	Email: Thanks	IND 077429
19-Dec-2013	FDA	SRPT	Email: Clinical information request re[redacted] data	IND 077429
19-Dec-2013	SRPT	FDA	Email: Meeting slides today	IND 077429
19-Dec-2013	SRPT	FDA	Email: 19-Dec-2013 Type A meeting slides	IND 077429
24-Dec-2013	FDA	SRPT	Email: Clin pharm information request re CK data	IND 077429
30-Dec-2013	FDA	SRPT	Email: Clin pharm information request re CK data (resent)	IND 077429
30-Dec-2013	SRPT	FDA	Email:[redacted] data	IND 077429

30-Dec-2013	FDA	SRPT	Email: Acknowledge receipt	IND 077429
3-Jan-2014	FDA	SRPT	Email: Clinical information request re CK data	IND 077429
3-Jan-2014	SRPT	FDA	Email: Request 19-Dec-2013 FDA attendees; problem with LobbyGuard form	IND 077429
6-Jan-2014	FDA	SRPT	Email: Reiteration of recent clinical and clin pharm information requests	IND 077429
6-Jan-2014	SRPT	FDA	Email: [redacted]CK data with time of day	IND 077429
7-Jan-2014	FDA	SRPT	Email: Acknowledge receipt	IND 077429
8-Jan-2014	SRPT	FDA	RoC: Sarepta will resubmit 02-Dec-2013 Type A request in order to schedule follow-up meeting; FDA requests Sarepta to provide estimated dates for responses to recent information requests ASAP	IND 077429
8-Jan-2014	FDA	SRPT	Email: 19-Dec-2013 FDA meeting attendees	IND 077429
8-Jan-2014	SRPT	FDA	Email: Acknowledge receipt	IND 077429
10-Jan-2014	SRPT	FDA	Email: Request identity of FDA scientist who offered 1:1 with [redacted]	IND 077429
13-Jan-2014	FDA	SRPT	Email: [redacted]reminder to respond to outstanding IRs	IND 077429
13-Jan-2014	SRPT	FDA	Email: Table of projected response dates to outstanding IRs	IND 077429
13-Jan-2014	FDA	SRPT	Email: Acknowledge receipt	IND 077429
14-Jan-2014	SRPT	FDA	Email: Serial 0067 electronic copy	IND 077429
17-Jan-2014	SRPT	FDA	Email: Serial 0072 shipment info; [redacted]timing update	IND 077429
21-Jan-2014	SRPT	FDA	Email: Status of 08-Nov-2013, 15-Nov-2013, and 19-Dec-2013 meeting minutes?	IND 077429
24-Jan-2014	FDA	SRPT	Email: Available for phone call today?	IND 077429
24-Jan-2014	SRPT	FDA	Email: Request phone call topic	IND 077429
24-Jan-2014	FDA	SRPT	Email: Topic is review of pending issues	IND 077429
24-Jan-2014	FDA	SRPT	Email: Expecting responses to clin-pharm IRs this week	IND 077429
24-Jan-2014	SRPT	FDA	Email/RoC: Sarepta available to meet with FDA 14 and 26-Feb-2014	IND 077429
24-Jan-2014	SRPT	FDA	Email: Serial 0068 cover letter	IND 077429
3-Feb-2014	FDA	SRPT	Email: Request [redacted]	IND 077429
3-Feb-2014	SRPT	FDA	Email: Acknowledge receipt	IND 077429
3-Feb-2014	FDA	SRPT	Email: Request [redacted]data	IND 077429
4-Feb-2014	FDA	SRPT	Email: Will follow up on meeting date later this week	IND 077429
4-Feb-2014	SRPT	FDA	Email/RoC: Will provide [redacted]graphs today	IND 077429
4-Feb-2014	SRPT	FDA	Email: [redacted]graphs in response to 03-Feb-2014 IRs	IND 077429
4-Feb-2014	FDA	SRPT	Email: Clarification of 03-Feb-2014 [redacted]graph IRs	IND 077429
5-Feb-2014	SRPT	FDA	Email: Revised [redacted]graphs	IND 077429
5-Feb-2014	FDA	SRPT	Email: Acknowledge receipt	IND 077429
6-Feb-2014	FDA	SRPT	Email: Request [redacted]and any other endpoints	IND 077429
6-Feb-2014	SRPT	FDA	RoC: FDA is meeting today to discuss eteplirsen and requests responses to [redacted]data and drug supply requests beforehand	IND 077429
6-Feb-2014	SRPT	FDA	Email/RoC: 03-Feb-2014 CMC IR response by 20-Feb-2014	IND 077429
6-Feb-2014	FDA	SRPT	Email: Request update on CMC IR response	IND 077429
6-Feb-2014	SRPT	FDA	Email: PFTs will be provided today	IND 077429
6-Feb-2014	FDA	SRPT	Email: Request clarification on target date for 03-Feb-2013 CMC IR response	IND 077429
6-Feb-2014	SRPT	FDA	Email: 03-Feb-2014 CMC IR response by 10-Feb-2014	IND 077429
6-Feb-2014	SRPT	FDA	Email: Response to 06-Feb-2014 clinical IR; [redacted]	IND 077429
6-Feb-2014	SRPT	FDA	RoC: FDA is ok with response to 03-Feb-2014 CMC IR by 10-Feb-2014 morning	IND 077429
6-Feb-2014	SRPT	FDA	Email: Sarepta attendees to 07-Feb-2014 ad hoc teleconference	IND 077429
7-Feb-2014	FDA	SRPT	Email: FDA attendees to 07-Feb-2014 ad hoc teleconference	IND 077429
7-Feb-2014	SRPT	FDA	RoC: 07-Feb-2014 ad hoc teleconference transcript	IND 077429
7-Feb-2014	SRPT	FDA	RoC: 07-Feb-2014 ad hoc teleconference sponsor minutes; FDA clin-pharm requests for study 4658-us-201/202 [redacted]data	IND 077429
7-Feb-2014	SRPT	FDA	Email: Timetable for delivery of [redacted]data	IND 077429
7-Feb-2014	FDA	SRPT	Email: Thanks	IND 077429
7-Feb-2014	SRPT	FDA	Email: Propose format for [redacted]data	IND 077429
7-Feb-2014	FDA	SRPT	Email: Contact eSUB for instructions on [redacted]data format	IND 077429
9-Feb-2014	SRPT	FDA	Email: Propose format for [redacted]data to eSUB	IND 077429
10-Feb-2014	FDA	SRPT	Email: Additional specification requests from A. Rao on [redacted]submission format	IND 077429
10-Feb-2014	FDA	SRPT	Email: Request from eSUB to submit [redacted]as compiled PDFs	IND 077429
10-Feb-2014	SRPT	FDA	Email: [redacted]order of submissions is driven by [redacted]availability	IND 077429
10-Feb-2014	SRPT	FDA	Email: [redacted]	IND 077429
10-Feb-2014	FDA	SRPT	Email: Request updated date for [redacted]	IND 077429
10-Feb-2014	FDA	SRPT	Email: Request explanation of [redacted]	IND 077429
10-Feb-2014	SRPT	FDA	Email: [redacted]should be submitted by tomorrow; explanation of [redacted]	IND 077429
11-Feb-2014	FDA	SRPT	Email: Request response to 03-Feb-2014 CMC IR ASAP	IND 077429
11-Feb-2014	SRPT	FDA	Email: Response to 03-Feb-2014 CMC IR	IND 077429
11-Feb-2014	FDA	SRPT	Email: Request status of response to 03-Feb-2014 [redacted]IR	IND 077429
11-Feb-2014	FDA	SRPT	Email: Request serial 0069 shipping info	IND 077429
11-Feb-2014	SRPT	FDA	Email: Serial 0069 shipping info	IND 077429
12-Feb-2014	SRPT	FDA	Email: Serial 0069 eNDA format navigation	IND 077429
12-Feb-2014	SRPT	FDA	Email: [redacted]reviewer's guide forthcoming	IND 077429
12-Feb-2014	SRPT	FDA	Email: [redacted]reviewer's guide	IND 077429
12-Feb-2014	FDA	SRPT	Email: Request status of outstanding 07-Feb-2014 clin pharm IRs	IND 077429
12-Feb-2014	SRPT	FDA	Email: Timing of [redacted]	IND 077429
12-Feb-2014	SRPT	FDA	Email: 03-Feb-2014 [redacted]response	IND 077429

12-Feb-2014	FDA	SRPT	Email: Request tracking info for remainder of IR responses	IND 077429
13-Feb-2014	SRPT	FDA	Email: [redacted] submission updated target dates	IND 077429
14-Feb-2014	FDA	SRPT	Email: Request status of [redacted] submission	IND 077429
14-Feb-2014	SRPT	FDA	Email: [redacted] submission timing and [redacted] submission challenges	IND 077429
14-Feb-2014	FDA	SRPT	Email: Delays in [redacted] submissions will impact timing of follow-up [redacted] meeting	IND 077429
19-Feb-2014	FDA	SRPT	Email: Acknowledge receipt of serial 0072	IND 077429
20-Feb-2014	FDA	SRPT	Email: Request status of [redacted] data etc.	IND 077429
20-Feb-2014	SRPT	FDA	Email: Serials 0073 and 0074 status updates	IND 077429
20-Feb-2014	SRPT	FDA	Email: Serials 0073 and 0074 going out today	IND 077429
20-Feb-2014	FDA	SRPT	Email: Thanks	IND 077429
20-Feb-2014	SRPT	FDA	Email: Serials 0073 and 0074 cover letters and shipping info	IND 077429
25-Feb-2014	SRPT	FDA	RoC: Follow-up meeting won't be held 26-Feb-2014; meeting is likely to be held by second week of March	IND 077429
27-Feb-2014	SRPT	FDA	Email: Available dates in March	IND 077429
27-Feb-2014	FDA	SRPT	Email: Will follow up by 07-March-2014	IND 077429
3-Mar-2014	FDA	SRPT	Email: ackn rcpt	IND 077429
3-Mar-2014	SRPT	FDA	Email: new contact info	IND 077429
10-Mar-2014	FDA	SRPT	fda Email: confirm 19mar14 mtg date	IND 077429
10-Mar-2014	SRPT	FDA	Email:19mar14 mtg attendees	IND 077429
10-Mar-2014	SRPT	FDA	Email:ackn rcpt	IND 077429
11-Mar-2014	SRPT	FDA	Email: ecld conversion	IND 077429
12-Mar-2014	FDA	SRPT	Email: ackn ecld conversion	IND 077429
13-Mar-2014	FDA	SRPT	Email: ackn rcpt	IND 077429
13-Mar-2014	SRPT	FDA	Email: updated 19mar14 mtg attendees	IND 077429
18-Mar-2014	FDA	SRPT	Email: 19mar14 mtg attendees	IND 077429
18-Mar-2014	SRPT	FDA	Email: inq attendees	IND 077429
19-Mar-2014	SRPT	FDA	roc 19mar14 brainstorming mtg transcript	IND 077429
22-Mar-2014	SRPT	FDA	Email: eteplirsen development proposal	IND 077429
24-Mar-2014	FDA	SRPT	Email: ackn rcpt	IND 077429
24-Mar-2014	FDA	SRPT	Email: lobbyguard form 1	IND 077429
24-Mar-2014	FDA	SRPT	Email: lobbyguard form 2	IND 077429
27-Mar-2014	FDA	SRPT	Letter nch inspection report	IND 077429
4-Apr-2014	FDA	SRPT	Email: thanks	IND 077429
4-Apr-2014	SRPT	FDA	Email: natural history study authors contact info	IND 077429
10-Apr-2014	FDA	SRPT	Email: propose round table logistics tcon	IND 077429
10-Apr-2014	SRPT	FDA	Email: thanks	IND 077429
11-Apr-2014	SRPT	FDA	Email: 23apr14 tcon attendees	IND 077429
15-Apr-2014	FDA	SRPT	eFax guidance letter	IND 077429
15-Apr-2014	FDA	SRPT	Email: 23apr14 tcon attendees	IND 077429
15-Apr-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
15-Apr-2014	SRPT	FDA	Email: dial in	IND 077429
17-Apr-2014	SRPT	FDA	RoC nda timing and content tcon	IND 077429
23-Apr-2014	SRPT	FDA	RoC: 23apr14 nch visit tcon minutes	IND 077429
23-Apr-2014	SRPT	FDA	RoC: 23apr14 nch visit tcon transcript	IND 077429
30-Apr-2014	SRPT	FDA	Email: inq status of seq 0077 review	IND 077429
1-May-2014	FDA	SRPT	Email: feedback by end of may	IND 077429
5-May-2014	SRPT	FDA	RoC: nch inspection dates etc	IND 077429
6-May-2014	SRPT	FDA	Email: nch inspection dates	IND 077429
12-May-2014	FDA	SRPT	Email: inq time to review 1 pt data set	IND 077429
12-May-2014	FDA	SRPT	Email: thanks	IND 077429
12-May-2014	SRPT	FDA	Email: 1 full day needed	IND 077429
12-May-2014	SRPT	FDA	Email: inq nch visit date	IND 077429
27-May-2014	FDA	SRPT	eFax cmc comments on seq 0077	IND 077429
27-May-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
27-May-2014	SRPT	FDA	Email: ind 118086 cross referencing	IND 077429
27-May-2014	SRPT	FDA	Email: inq cmc response to seq 0077 status	IND 077429
27-May-2014	SRPT	FDA	RoC: nch site visit on 29may14	IND 077429
29-May-2014	FDA	SRPT	Email: inter ind linking is acceptable	IND 077429
29-May-2014	SRPT	FDA	Email: thanks	IND 077429
2-Jun-2014	FDA	SRPT	Email: thanks	IND 077429
2-Jun-2014	SRPT	FDA	Email: clinical [redacted] mtg rqst soon	IND 077429
2-Jun-2014	SRPT	FDA	Email: cmc [redacted] mtg rqst this week	IND 077429
2-Jun-2014	SRPT	FDA	Email: response to 29may14 clin pharm questions	IND 077429
3-Jun-2014	FDA	SRPT	Email: no comments on 4658 301 a1	IND 077429
3-Jun-2014	FDA	SRPT	Email: [redacted] mtg topics	IND 077429
3-Jun-2014	SRPT	FDA	Email: thanks	IND 077429
11-Jun-2014	SRPT	FDA	Email: inq seq 0083 response	IND 077429
11-Jun-2014	SRPT	FDA	Email: inq seq 0084 response	IND 077429

Exhibit M

12-Jun-2014	FDA	SRPT	Email: will get back next week	IND 077429
17-Jun-2014	FDA	SRPT	Email: rqst update on [redacted] mtg rqst	IND 077429
18-Jun-2014	SRPT	FDA	Email: [redacted] mtg rqst this week	IND 077429
19-Jun-2014	FDA	SRPT	Email: no comments on 4658 us 202 06	IND 077429
19-Jun-2014	SRPT	FDA	Email: thanks	IND 077429
23-Jun-2014	FDA	SRPT	Email: seq 0089 rcvd	IND 077429
23-Jun-2014	SRPT	FDA	Email: clinical [redacted] mtg rqst today	IND 077429
24-Jun-2014	FDA	SRPT	Email: propose 03sep14 cmc [redacted] mtg date	IND 077429
25-Jun-2014	FDA	SRPT	Email: mtg granted letter next week	IND 077429
25-Jun-2014	SRPT	FDA	Email: confirm cmc [redacted] mtg date	IND 077429
2-Jul-2014	FDA	SRPT	Email: propose clinical [redacted] mtg date	IND 077429
2-Jul-2014	SRPT	FDA	Email: 18sep14 is acceptable	IND 077429
2-Jul-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
7-Jul-2014	FDA	SRPT	eFax clinical [redacted] mtg rqst granted and [redacted] mtg instructions	IND 077429
7-Jul-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
7-Jul-2014	SRPT	FDA	Email: rqst cmc [redacted] mtg granted letter	IND 077429
10-Jul-2014	FDA	SRPT	Email: rqst [redacted] data and analyses	IND 077429
10-Jul-2014	SRPT	FDA	Email: [redacted]	IND 077429
14-Jul-2014	FDA	SRPT	eFax 03sep14 cmc [redacted] mtg granted	IND 077429
14-Jul-2014	SRPT	FDA	Email: rqst cmc [redacted] mtg granted letter	IND 077429
17-Jul-2014	FDA	SRPT	Email: rqst 4658 tox 001 complement activation summary	IND 077429
17-Jul-2014	FDA	SRPT	Email: rqst update on [redacted] data submission	IND 077429
17-Jul-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
17-Jul-2014	SRPT	FDA	Email: will send [redacted] shortly	IND 077429
21-Jul-2014	FDA	SRPT	Email: finalizing comments on [redacted]	IND 077429
22-Jul-2014	FDA	SRPT	Email: rqst complement summar asap	IND 077429
22-Jul-2014	FDA	SRPT	Email: rqst update on 17jul14 pharm tox ir	IND 077429
22-Jul-2014	SRPT	FDA	Email: [redacted] this week	IND 077429
22-Jul-2014	SRPT	FDA	Email: pharm tox response this week	IND 077429
25-Jul-2014	FDA	SRPT	Email: ackn rcpt	IND 077429
25-Jul-2014	SRPT	FDA	Email: complement activation summary	IND 077429
29-Jul-2014	FDA	SRPT	eFax clin pharm info rqsts [redacted]	IND 077429
31-Jul-2014	FDA	SRPT	Email: rqst conf rcpt	IND 077429
31-Jul-2014	FDA	SRPT	Email: thanks	IND 077429
31-Jul-2014	SRPT	FDA	Email: [redacted] next week	IND 077429
4-Aug-2014	SRPT	FDA	Email: [redacted] request	IND 077429
7-Aug-2014	SRPT	FDA	Email: [redacted] and [redacted] on tuesday	IND 077429
21-Aug-2014	FDA	SRPT	eFax 03sep14 cmc [redacted] mtg preliminary comments	IND 077429
23-Aug-2014	SRPT	FDA	Email: [redacted] inspection rqst	IND 077429
29-Aug-2014	SRPT	FDA	Email: nda draft toc	IND 077429
3-Sep-2014	FDA	SRPT	Email: rqst 29may14 rfi response timelines	IND 077429
4-Sep-2014	FDA	SRPT	Email: ackn rcpt	IND 077429
4-Sep-2014	SRPT	FDA	Email: intial response to 29jul14 clin pharm rfi	IND 077429
5-Sep-2014	SRPT	FDA	Email: seq 0098 cover letter	IND 077429
8-Sep-2014	FDA	SRPT	Letter 03sep14 cmc [redacted] mtg minutes	IND 077429
15-Sep-2014	FDA	SRPT	Email: lobbyguard form	IND 077429
15-Sep-2014	SRPT	FDA	Email: 18sep14 mtg attendees and questions	IND 077429
17-Sep-2014	FDA	SRPT	eFax 18sep14 [redacted] mtg preliminary comments	IND 077429
17-Sep-2014	SRPT	FDA	Email: updated 18sep14 mtg attendees and questions	IND 077429
18-Sep-2014	FDA	SRPT	Email: [redacted] and [redacted]	IND 077429
18-Sep-2014	SRPT	FDA	Email: mtg slides	IND 077429
18-Sep-2014	SRPT	FDA	RoC: 18sep14 mtg transcript	IND 077429
18-Sep-2014	SRPT	FDA	RoC: 18sep14 type b [redacted] mtg minutes	IND 077429
19-Sep-2014	SRPT	FDA	Email: rqst 18sep14 mtg attendees	IND 077429
23-Sep-2014	FDA	SRPT	Email: clinical and clin pharm rfi	IND 077429
23-Sep-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
24-Sep-2014	FDA	SRPT	Email: ackn rcpt	IND 077429
24-Sep-2014	SRPT	FDA	Email: cmc [redacted] minutes [redacted]	IND 077429
24-Sep-2014	SRPT	FDA	Email: response to 23sep14 [redacted]	IND 077429
26-Sep-2014	SRPT	FDA	Email: clinical rfi response update	IND 077429
29-Sep-2014	FDA	SRPT	Email: rqst outstanding responses by tomorrow	IND 077429
29-Sep-2014	SRPT	FDA	Email: partial response to 23sep14 [redacted]	IND 077429
29-Sep-2014	SRPT	FDA	Email: [redacted] question for dr rao	IND 077429
30-Sep-2014	SRPT	FDA	Email: 2nd partial response to 23sep14 [redacted]	IND 077429
30-Sep-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
1-Oct-2014	FDA	SRPT	Email: clin pharm rfis	IND 077429
1-Oct-2014	FDA	SRPT	Email: cmc [redacted] minutes revision will be accepted	IND 077429

1-Oct-2014	SRPT	FDA	Email: 18sep14 [redacted] mtg minutes	IND 077429
1-Oct-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
2-Oct-2014	FDA	SRPT	Email: agree on [redacted]	IND 077429
2-Oct-2014	SRPT	FDA	Email: inq intent of [redacted]	IND 077429
2-Oct-2014	SRPT	FDA	Email: one [redacted] per Email:	IND 077429
2-Oct-2014	SRPT	FDA	Email: rqst clarification on [redacted]	IND 077429
3-Oct-2014	FDA	SRPT	Email: rqst cd and desk copy	IND 077429
3-Oct-2014	FDA	SRPT	Email: rqst [redacted] today	IND 077429
3-Oct-2014	FDA	SRPT	Email: security policy blocks ftp links	IND 077429
3-Oct-2014	SRPT	FDA	Email: images sent and tx assignment key	IND 077429
3-Oct-2014	SRPT	FDA	Email: [redacted] to ind monday	IND 077429
3-Oct-2014	SRPT	FDA	Email: intralinks	IND 077429
3-Oct-2014	SRPT	FDA	Email: partial response to 01oct14 clin pharm rfis	IND 077429
3-Oct-2014	SRPT	FDA	RoC: [redacted]	IND 077429
6-Oct-2014	FDA	SRPT	Email: rqst clin pharm responses by tomorrow	IND 077429
6-Oct-2014	FDA	SRPT	Email: seq 0099 not yet rcvd	IND 077429
6-Oct-2014	SRPT	FDA	Email: seq 0099 being compiled	IND 077429
6-Oct-2014	SRPT	FDA	Email: seq 0099 in esg	IND 077429
7-Oct-2014	SRPT	FDA	Email: partial responses to 01oct14 clin pharm rfis	IND 077429
8-Oct-2014	FDA	SRPT	Email: rqst update on rfi responses	IND 077429
8-Oct-2014	SRPT	FDA	Email: responses later today	IND 077429
10-Oct-2014	FDA	SRPT	Email: call will end at 10	IND 077429
10-Oct-2014	FDA	SRPT	Email: clin pharm rfis	IND 077429
10-Oct-2014	FDA	SRPT	Email: propose dr rao tcon date	IND 077429
10-Oct-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
10-Oct-2014	SRPT	FDA	Email: confirm 15oct14 tcon	IND 077429
13-Oct-2014	SRPT	FDA	Email: confirming responses with nch	IND 077429
15-Oct-2014	SRPT	FDA	RoC: [redacted] protocol tcon transcript	IND 077429
16-Oct-2014	SRPT	FDA	Email: sample [redacted]	IND 077429
20-Oct-2014	FDA	SRPT	eFax 18sep14 [redacted] mtg minutes	IND 077429
20-Oct-2014	FDA	SRPT	Email: ackn rcpt	IND 077429
20-Oct-2014	SRPT	FDA	Email: inq 18sep14 [redacted] mtg minutes	IND 077429
20-Oct-2014	SRPT	FDA	Email: [redacted] protocol	IND 077429
22-Oct-2014	SRPT	FDA	Email: [redacted] protocol corrected	IND 077429
24-Oct-2014	FDA	SRPT	Email: protocol update monday	IND 077429
24-Oct-2014	FDA	SRPT	Email: rescore protocol update later today	IND 077429
24-Oct-2014	SRPT	FDA	Email: [redacted] protocol review	IND 077429
27-Oct-2014	FDA	SRPT	Email: response tomorrow	IND 077429
27-Oct-2014	SRPT	FDA	Email: [redacted] ready	IND 077429
27-Oct-2014	SRPT	FDA	Email: thanks	IND 077429
28-Oct-2014	FDA	SRPT	Email: comments on [redacted] protocol	IND 077429
28-Oct-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
5-Nov-2014	SRPT	FDA	Email: [redacted] mtg jan2015	IND 077429
6-Nov-2014	FDA	SRPT	Email: propose 26feb14 mtg date	IND 077429
6-Nov-2014	SRPT	FDA	Email: will check date	IND 077429
7-Nov-2014	FDA	SRPT	Email: [redacted] mtg rqst not yet reviewed	IND 077429
7-Nov-2014	FDA	SRPT	Email: closed 11nov14	IND 077429
7-Nov-2014	SRPT	FDA	Email: revised [redacted] protocol next week	IND 077429
9-Nov-2014	FDA	SRPT	Letter proprietary name conditional approval	IND 077429
12-Nov-2014	FDA	SRPT	Email: rqst redline version	IND 077429
12-Nov-2014	SRPT	FDA	Email: [redacted] protocol redline	IND 077429
12-Nov-2014	SRPT	FDA	Email: revised [redacted] protocol	IND 077429
14-Nov-2014	FDA	SRPT	Email: [redacted] may proceed and data quality rfis	IND 077429
14-Nov-2014	FDA	SRPT	Email: team is reviewing [redacted] protocol	IND 077429
14-Nov-2014	SRPT	FDA	Email: inq more changes to [redacted] protocol	IND 077429
17-Nov-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
24-Nov-2014	FDA	SRPT	Email: [redacted] protocol stats comments	IND 077429
15-Dec-2014	FDA	SRPT	Email: rqst update on [redacted]	IND 077429
16-Dec-2014	FDA	SRPT	Email: thanks	IND 077429
16-Dec-2014	SRPT	FDA	Email: will update in a few days	IND 077429
17-Dec-2014	SRPT	FDA	Email: responses to 14nov14 and 24nov14 clin pharm rfis	IND 077429
18-Dec-2014	SRPT	FDA	Email: [redacted] update	IND 077429
22-Dec-2014	FDA	SRPT	Email: ackn rcpt	IND 077429
22-Dec-2014	SRPT	FDA	Email: [redacted] protocol	IND 077429
23-Dec-2014	FDA	SRPT	Email: comments on 18dec14 [redacted] response	IND 077429
23-Dec-2014	SRPT	FDA	Email: ackn rcpt	IND 077429
6-Jan-2015	FDA	SRPT	Email: feedback on [redacted] protocol planned by friday	IND 077429

6-Jan-2015	FDA	SRPT	Email: fwded tcon rqst to team	IND 077429
6-Jan-2015	FDA	SRPT	Email: Inq purpose of [redacted] protocol	IND 077429
6-Jan-2015	SRPT	FDA	Email: [redacted] tcon rqst	IND 077429
6-Jan-2015	SRPT	FDA	Email: [redacted] protocol for [redacted]	IND 077429
9-Jan-2015	FDA	SRPT	Email: [redacted] feedback forthcoming	IND 077429
9-Jan-2015	SRPT	FDA	Email: Inq comments by monday	IND 077429
14-Jan-2015	SRPT	FDA	Email: serial 0067 electronic copy	IND 077429
14-Jan-2015	SRPT	FDA	Email: additional [redacted] protocols forthcoming	IND 077429
16-Jan-2015	FDA	SRPT	Email: comments on [redacted] protocol	IND 077429
16-Jan-2015	SRPT	FDA	Email: ackn rcpt	IND 077429
22-Jan-2015	SRPT	FDA	Email: inq [redacted] tcon	IND 077429
23-Jan-2015	FDA	SRPT	Email: will update on [redacted] tcon next week	IND 077429
26-Jan-2015	FDA	SRPT	Email: rqst [redacted] technical contact	IND 077429
26-Jan-2015	FDA	SRPT	Email: thanks	IND 077429
26-Jan-2015	SRPT	FDA	Email: [redacted] technical contact is [redacted]	IND 077429
28-Jan-2015	SRPT	FDA	Email: [redacted] protocols	IND 077429
29-Jan-2015	FDA	SRPT	Email: [redacted] protocols fwded	IND 077429
29-Jan-2015	FDA	SRPT	Email: [redacted] rfi	IND 077429
29-Jan-2015	FDA	SRPT	Email: rqst [redacted] response by monday	IND 077429
10-Feb-2015	FDA	SRPT	Email: comments on [redacted] protocols	IND 077429
10-Feb-2015	SRPT	FDA	Email: ackn rcpt	IND 077429
10-Feb-2015	SRPT	FDA	Email: response to 29jan15 [redacted] questions	IND 077429
12-Feb-2015	FDA	SRPT	Email: Inq [redacted]	IND 077429
12-Feb-2015	FDA	SRPT	Email: rqst [redacted] results	IND 077429
12-Feb-2015	FDA	SRPT	Email: rqst [redacted] summary table	IND 077429
12-Feb-2015	SRPT	FDA	Email: [redacted] listing	IND 077429
12-Feb-2015	SRPT	FDA	Email: ackn rcpt	IND 077429
13-Feb-2015	FDA	SRPT	Email: rqst 4658 us 202 week [redacted]	IND 077429
13-Feb-2015	SRPT	FDA	Email: ackn rcpt	IND 077429
13-Feb-2015	SRPT	FDA	RoC: rqst [redacted] toc	IND 077429
16-Feb-2015	SRPT	FDA	Email: ackn rcpt	IND 077429
16-Feb-2015	SRPT	FDA	Email: responses to 12feb15 [redacted] rfis	IND 077429
18-Feb-2015	FDA	SRPT	Email: rqst update on avi 4658 [redacted] protocols	IND 077429
18-Feb-2015	SRPT	FDA	Email: Inq feedback on [redacted] protocol v2	IND 077429
19-Feb-2015	FDA	SRPT	Email: feedback on [redacted] protocol forthcoming	IND 077429
20-Feb-2015	SRPT	FDA	Email: avi 4658 [redacted] response forthcoming	IND 077429
23-Feb-2015	SRPT	FDA	Email: [redacted] data tomorrow	IND 077429
24-Feb-2015	FDA	SRPT	Email: ackn rcpt	IND 077429
24-Feb-2015	SRPT	FDA	Email: inq [redacted]	IND 077429
25-Feb-2015	FDA	SRPT	Email: [redacted] rationale	IND 077429
25-Feb-2015	FDA	SRPT	Email: disregard [redacted] question	IND 077429
25-Feb-2015	FDA	SRPT	Email: rqst clarification on [redacted]	IND 077429
25-Feb-2015	FDA	SRPT	Email: rqst clarification on [redacted]	IND 077429
25-Feb-2015	SRPT	FDA	Email: [redacted]	IND 077429
25-Feb-2015	SRPT	FDA	Email: ackn rcpt	IND 077429
25-Feb-2015	SRPT	FDA	Email: rqst [redacted] mtg	IND 077429
25-Feb-2015	SRPT	FDA	Email: updated timing of avi 4658 [redacted] forthcoming	IND 077429
26-Feb-2015	FDA	SRPT	Email: [redacted] protocol v2 comments	IND 077429
26-Feb-2015	SRPT	FDA	Email: ackn rcpt	IND 077429
4-Mar-2015	FDA	SRPT	Email: propose 19may15 [redacted] mtg date	IND 077429
4-Mar-2015	SRPT	FDA	Email: [redacted] mtg rqst forthcoming	IND 077429
5-Mar-2015	SRPT	FDA	Email: [redacted] control question	IND 077429
6-Mar-2015	FDA	SRPT	Email: [redacted] question not clear	IND 077429
6-Mar-2015	SRPT	FDA	Email: Inq response to avi 4658 [redacted]	IND 077429
6-Mar-2015	SRPT	FDA	Email: mtg rqst will be submitted next week	IND 077429
6-Mar-2015	SRPT	FDA	Email: [redacted] mtg rqst	IND 077429
9-Mar-2015	FDA	SRPT	Email: no response to [redacted]	IND 077429
9-Mar-2015	SRPT	FDA	Email: thanks	IND 077429
10-Mar-2015	SRPT	FDA	Email: responses to [redacted] and mtg rqst	IND 077429
16-Mar-2015	FDA	SRPT	Email: ackn rcpt	IND 077429
16-Mar-2015	FDA	SRPT	Email: [redacted] mtg 19may15	IND 077429
16-Mar-2015	SRPT	FDA	Email: [redacted] clarification	IND 077429
16-Mar-2015	SRPT	FDA	Email: confirm [redacted] mtg date	IND 077429
16-Mar-2015	SRPT	FDA	Email: Inq [redacted] protocols rcvd	IND 077429
16-Mar-2015	SRPT	FDA	Email: seq 0116 by tomorrow	IND 077429
20-Mar-2015	FDA	SRPT	eFax 19may15 [redacted] mtg granted	IND 077429
20-Mar-2015	SRPT	FDA	Email: ackn rcpt	IND 077429

23-Mar-2015	FDA	SRPT	Email: investigating now	IND 077429
23-Mar-2015	SRPT	FDA	Email: inq update on [redacted] protocols	IND 077429
23-Mar-2015	SRPT	FDA	Email: inq update on [redacted] protocols 2	IND 077429
26-Mar-2015	FDA	SRPT	Email: [redacted] protocols response by next week	IND 077429
30-Mar-2015	FDA	SRPT	Email: [redacted] may proceed	IND 077429
30-Mar-2015	SRPT	FDA	Email: ackn rcpt	IND 077429
2-Apr-2015	SRPT	FDA	Email: [redacted] proposal and 804 protocol	IND 077429
2-Apr-2015	SRPT	FDA	RoC: [redacted] bd [redacted] and 804 protocol	IND 077429
3-Apr-2015	FDA	SRPT	Email: thanks	IND 077429
10-Apr-2015	FDA	SRPT	Email: thanks	IND 077429
10-Apr-2015	SRPT	FDA	Email: [redacted] mtg bd in esq	IND 077429
4-May-2015	SRPT	FDA	Email: rqst rolling review	IND 077429
8-May-2015	SRPT	FDA	Email: inq feedback on [redacted]	IND 077429
11-May-2015	FDA	SRPT	Email: [redacted] feedback in [redacted] preliminary comments	IND 077429
14-May-2015	FDA	SRPT	Letter ackn rolling review rqst	IND 077429
15-May-2015	FDA	SRPT	eFax 19may15 [redacted] mtg preliminary comments	IND 077429
15-May-2015	FDA	SRPT	Email: inq same info in slides	IND 077429
15-May-2015	FDA	SRPT	Email: lobbyguard form	IND 077429
15-May-2015	SRPT	FDA	Email: [redacted] slides 1	IND 077429
15-May-2015	SRPT	FDA	Email: [redacted] slides 2	IND 077429
15-May-2015	SRPT	FDA	Email: ackn rcpt	IND 077429
15-May-2015	SRPT	FDA	Email: slide content identical	IND 077429
18-May-2015	FDA	SRPT	Email: ackn rcpt	IND 077429
18-May-2015	FDA	SRPT	Email: lobbyguard form	IND 077429
18-May-2015	SRPT	FDA	Email: mtg slides today	IND 077429
18-May-2015	SRPT	FDA	Email: mtg slides v1 and attendees	IND 077429
19-May-2015	FDA	SRPT	Email: inq same slides different order	IND 077429
19-May-2015	SRPT	FDA	Email: mtg slides v2	IND 077429
19-May-2015	SRPT	FDA	Email: slides substantively the same	IND 077429
19-May-2015	SRPT	FDA	Email: slight differences in content	IND 077429
19-May-2015	SRPT	FDA	RoC: 19may15 [redacted] type c mtg transcript	IND 077429
19-May-2015	SRPT	FDA	RoC: 19may15 type c [redacted] mtg minutes	IND 077429
20-May-2015	FDA	SRPT	Email: thanks	NDA 206488
20-May-2015	SRPT	FDA	Email: intent to submit nda	NDA 206488
21-May-2015	FDA	SRPT	Email: include xls and pdf nat hist	IND 077429
21-May-2015	SRPT	FDA	Email: req approval to send xlsx to nda	IND 077429
22-May-2015	FDA	SRPT	Email: submit xpt as well as xlsx	IND 077429
26-May-2015	FDA	SRPT	Email: mtg attendees	IND 077429
26-May-2015	FDA	SRPT	Email: pdf legibility confirmation	IND 077429
26-May-2015	SRPT	FDA	Email: confirm pdf legibility ok	IND 077429
26-May-2015	SRPT	FDA	Email: confirm xpt will be sub with xlsx	IND 077429
26-May-2015	SRPT	FDA	Email: inq [redacted] mtg attendees	IND 077429
27-May-2015	SRPT	FDA	Email: rqst metamorph version	NDA 206488
28-May-2015	FDA	SRPT	Email: metamorph nx v786	NDA 206488
28-May-2015	SRPT	FDA	Email: thanks	NDA 206488
2-Jun-2015	FDA	SRPT	Email: rqst updated toc	NDA 206488
2-Jun-2015	FDA	SRPT	Email: [redacted] clin pharm lrs	NDA 206488
2-Jun-2015	SRPT	FDA	Email: inq folder structure or toc	NDA 206488
4-Jun-2015	SRPT	FDA	RoC: nda timing and orientation	NDA 206488
5-Jun-2015	SRPT	FDA	Email: response to 02jun15 clin lr 1	NDA 206488
8-Jun-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
9-Jun-2015	FDA	SRPT	eFax 19may15 type c [redacted] mtg minutes	IND 077429
9-Jun-2015	SRPT	FDA	Email: ackn rcpt	IND 077429
9-Jun-2015	FDA	SRPT	Email: f choy on leave 10jun15 thru 23jun15	NDA 206488
11-Jun-2015	SRPT	FDA	Email: responses to 02jun15 clin irs 1 2	NDA 206488
12-Jun-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
12-Jun-2015	FDA	SRPT	Email: [redacted] missing	NDA 206488
12-Jun-2015	SRPT	FDA	Email: avi 4658 [redacted]	NDA 206488
12-Jun-2015	SRPT	FDA	Email: [redacted] screenshot	NDA 206488
16-Jun-2015	SRPT	FDA	Email: alert to esub re external drive	IND 077429
16-Jun-2015	SRPT	FDA	Email: pre alert external drive	NDA 206488
22-Jun-2015	SRPT	FDA	Email: clarify drive not shipped	NDA 206488
25-Jun-2015	SRPT	FDA	Email: alert esub external drive	NDA 206488
26-Jun-2015	SRPT	FDA	Email: inq 07jul15 orientation date	NDA 206488
30-Jun-2015	SRPT	FDA	RoC: confirm 07jul15 nda orientation	NDA 206488
2-Jul-2015	FDA	SRPT	Email: bldg 22	IND 077429
2-Jul-2015	FDA	SRPT	Email: navigate with sarepta pcs	IND 077429

Exhibit M

2-Jul-2015	SRPT	FDA	Email: 07jul15 orientation mtg slides	IND 077429
2-Jul-2015	SRPT	FDA	Email: inq bldg	IND 077429
2-Jul-2015	SRPT	FDA	Email: thanks	IND 077429
5-Jul-2015	FDA	SRPT	Email: lobbyguard form 1	NDA 206488
5-Jul-2015	FDA	SRPT	Email: lobbyguard form 2	NDA 206488
7-Jul-2015	FDA	SRPT	Email: no questions rcvd	NDA 206488
7-Jul-2015	SRPT	FDA	Email: inq advance orientation questions	NDA 206488
8-Jul-2015	FDA	SRPT	Email: 07jul15 nda orientation mtg attendees	NDA 206488
8-Jul-2015	SRPT	FDA	Email: rqst attendees	NDA 206488
9-Jul-2015	FDA	SRPT	Letter nda acknowledgement	NDA 206488
15-Jul-2015	FDA	SRPT	Email: clinical ir [redacted] 201 202	NDA 206488
15-Jul-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
24-Jul-2015	SRPT	FDA	Email: [redacted] not collected	NDA 206488
27-Jul-2015	SRPT	FDA	Email: [redacted] to cder	NDA 206488
29-Jul-2015	FDA	SRPT	Email: tcon today re external drive	NDA 206488
30-Jul-2015	FDA	SRPT	Email: 31jul15 tcon scheduled	NDA 206488
30-Jul-2015	FDA	SRPT	Email: rfarkas available for tcon	NDA 206488
30-Jul-2015	FDA	SRPT	Email: thanks	NDA 206488
30-Jul-2015	SRPT	FDA	Email: 31jul15 tcon screen sharing link	NDA 206488
30-Jul-2015	SRPT	FDA	Email: navigation tcon today	NDA 206488
30-Jul-2015	SRPT	FDA	Email: rqst [redacted] attend tcon	NDA 206488
30-Jul-2015	SRPT	FDA	Email: tcon dial in	NDA 206488
30-Jul-2015	SRPT	FDA	Email: will send tcon dial in	NDA 206488
30-Jul-2015	SRPT	FDA	RoC: screen sharing	NDA 206488
31-Jul-2015	FDA	SRPT	Email: 31jul15 tcon topics	NDA 206488
31-Jul-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
31-Jul-2015	SRPT	FDA	Email: updated screen sharing link	NDA 206488
4-Aug-2015	SRPT	FDA	Email: 07jul15 nda orientation mtg minutes	NDA 206488
5-Aug-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
5-Aug-2015	SRPT	FDA	Email: 201 202 [redacted] protocol nda location	NDA 206488
5-Aug-2015	SRPT	FDA	Email: 29 31jul15 tcon minutes	NDA 206488
5-Aug-2015	SRPT	FDA	Email: iss [redacted]	NDA 206488
5-Aug-2015	SRPT	FDA	Email: response to 30jul15 rfi re [redacted]	NDA 206488
6-Aug-2015	FDA	SRPT	eFax clinical irs re nda	NDA 206488
6-Aug-2015	FDA	SRPT	Email: rqst tcon topics	NDA 206488
6-Aug-2015	SRPT	FDA	Email: rqst tcon to discuss filing issues	NDA 206488
7-Aug-2015	FDA	SRPT	Email: fchoy on leave tcon rqst fwded	NDA 206488
7-Aug-2015	FDA	SRPT	Email: nda nav good issue at	NDA 206488
7-Aug-2015	FDA	SRPT	Email: rqst discussion outline asap	NDA 206488
7-Aug-2015	SRPT	FDA	Email: will provide responses 10aug15	NDA 206488
10-Aug-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
10-Aug-2015	FDA	SRPT	Email: proposed tcon times	NDA 206488
10-Aug-2015	FDA	SRPT	Email: tcon confirmed	NDA 206488
10-Aug-2015	FDA	SRPT	Email: tcon tentatively scheduled	NDA 206488
10-Aug-2015	FDA	SRPT	Email: will check	NDA 206488
10-Aug-2015	SRPT	FDA	Email: 11aug15 tcon agenda and preliminary responses	NDA 206488
10-Aug-2015	SRPT	FDA	Email: dial in info	NDA 206488
10-Aug-2015	SRPT	FDA	Email: propose wednesday	NDA 206488
10-Aug-2015	SRPT	FDA	Email: responses to 06aug15 clinical irs 1 2 3	NDA 206488
11-Aug-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
11-Aug-2015	FDA	SRPT	Email: clinical ir [redacted] markups	NDA 206488
11-Aug-2015	FDA	SRPT	Email: tcon attendees	NDA 206488
11-Aug-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
11-Aug-2015	SRPT	FDA	Email: ck data in nda	NDA 206488
11-Aug-2015	SRPT	FDA	Email: tcon attendees	NDA 206488
14-Aug-2015	SRPT	FDA	Email: 11aug15 ad hoc tcon minutes	NDA 206488
18-Aug-2015	FDA	SRPT	eFax nda cmc irs	NDA 206488
19-Aug-2015	FDA	SRPT	Email: clinical ir [redacted]	NDA 206488
20-Aug-2015	FDA	SRPT	Email: thanks	NDA 206488
20-Aug-2015	SRPT	FDA	Email: response to 19aug15 clinical ir	NDA 206488
21-Aug-2015	FDA	SRPT	Email: clinical irs [redacted] data	NDA 206488
25-Aug-2015	FDA	SRPT	eFax nda filed and priority review designation granted	NDA 206488
25-Aug-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
26-Aug-2015	FDA	SRPT	Email: rqst proprietary name rqst copied to nda	NDA 206488
27-Aug-2015	FDA	SRPT	Email: rqst proprietary name rqst copied to nda 2	NDA 206488
27-Aug-2015	SRPT	FDA	Email: will submit proprietary name rqst to nda	NDA 206488
2-Sep-2015	FDA	SRPT	Email: meth val request	NDA 206488

4-Sep-2015	FDA	SRPT	eFax filing communication	NDA 206488
8-Sep-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
9-Sep-2015	FDA	SRPT	Email: cmc info request	NDA 206488
16-Sep-2015	FDA	SRPT	Email: c breder available tomorrow	NDA 206488
16-Sep-2015	FDA	SRPT	Email: clinical ir[redacted]	NDA 206488
16-Sep-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
17-Sep-2015	FDA	SRPT	Email: c breder available today	NDA 206488
17-Sep-2015	FDA	SRPT	Email: attendees	NDA 206488
17-Sep-2015	SRPT	FDA	Email: dial in info	NDA 206488
17-Sep-2015	SRPT	FDA	Email: sarepta attendees	NDA 206488
17-Sep-2015	SRPT	FDA	Email: sarepta team can meet today	NDA 206488
21-Sep-2015	FDA	SRPT	Email: agree to hold tcon re[redacted]organization	NDA 206488
21-Sep-2015	FDA	SRPT	Email: new start time	NDA 206488
21-Sep-2015	SRPT	FDA	Email: confirm tcon	NDA 206488
21-Sep-2015	SRPT	FDA	Email: rqst tcon re[redacted]	NDA 206488
21-Sep-2015	SRPT	FDA	Email: tcon dial in	NDA 206488
23-Sep-2015	SRPT	FDA	Email: 17sep15 tcon minutes re safety lab ranges	NDA 206488
28-Sep-2015	FDA	SRPT	Email: clinical ir re 201 csr int table inputs	NDA 206488
28-Sep-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
29-Sep-2015	SRPT	FDA	Email: response to 28sep15 clinical ir re[redacted]table	NDA 206488
30-Sep-2015	SRPT	FDA	Email: 06oct15 tcon dial in	NDA 206488
30-Sep-2015	SRPT	FDA	Email: response to 17sep15 clinical ir re safety labs	NDA 206488
3-Oct-2015	FDA	SRPT	Letter proprietary name conditionally acceptable	NDA 206488
5-Oct-2015	FDA	SRPT	Email: mid cycle mtg 13oct15 mcc 22oct15	NDA 206488
5-Oct-2015	FDA	SRPT	Letter cmc rfi multi	NDA 206488
5-Oct-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
6-Oct-2015	SRPT	FDA	Email: confirm 22oct15 mcc tcon	NDA 206488
6-Oct-2015	SRPT	FDA	Email: esub clarify text excel	NDA 206488
7-Oct-2015	FDA	SRPT	Email: thanks	NDA 206488
8-Oct-2015	FDA	SRPT	Email: clin pharm ir re 201 202[redacted]methodology	NDA 206488
8-Oct-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
12-Oct-2015	SRPT	FDA	Email: response to clin pharm rfi re[redacted]methods	NDA 206488
15-Oct-2015	FDA	SRPT	Email: available before 1pm	NDA 206488
15-Oct-2015	FDA	SRPT	Email: clinical ir re[redacted]	NDA 206488
15-Oct-2015	FDA	SRPT	Email: rqst tcon re pcnsdac 22jan16 mtg	NDA 206488
15-Oct-2015	FDA	SRPT	Email: tcon must be today	NDA 206488
15-Oct-2015	FDA	SRPT	Email: will dial in now	NDA 206488
15-Oct-2015	FDA	SRPT	Email: will dial in now 2	NDA 206488
15-Oct-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
15-Oct-2015	SRPT	FDA	Email: dialed in now	NDA 206488
15-Oct-2015	SRPT	FDA	Email: dial in	NDA 206488
15-Oct-2015	SRPT	FDA	Email: propose tomorrow	NDA 206488
15-Oct-2015	SRPT	FDA	Email: rqst start time	NDA 206488
15-Oct-2015	SRPT	FDA	Email: will dial in later	NDA 206488
15-Oct-2015	SRPT	FDA	RoC:[redacted]mtg planning tcon	NDA 206488
16-Oct-2015	FDA	SRPT	eFax[redacted]pcnsdac mtg date and timeline	NDA 206488
16-Oct-2015	FDA	SRPT	Email: clin pharm ir re[redacted]	NDA 206488
16-Oct-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
19-Oct-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
19-Oct-2015	SRPT	FDA	Email: response to 15oct15 clinical ir re[redacted]	NDA 206488
21-Oct-2015	FDA	SRPT	eFax 22oct15 mcc tcon preliminary comments	NDA 206488
21-Oct-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
21-Oct-2015	FDA	SRPT	Email: b dunn will not attend mtg	NDA 206488
21-Oct-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
21-Oct-2015	SRPT	FDA	Email: mcc tcon attendees	NDA 206488
21-Oct-2015	SRPT	FDA	Email: mcc tcon dial in	NDA 206488
21-Oct-2015	SRPT	FDA	Email: response to 16oct15 clin pharm ir re[redacted]	NDA 206488
21-Oct-2015	SRPT	FDA	Email: rqst b dunn at mcc tcon	NDA 206488
22-Oct-2015	FDA	SRPT	Email: additional tcon attendee	NDA 206488
22-Oct-2015	FDA	SRPT	Email:[redacted]independent assessor	NDA 206488
22-Oct-2015	SRPT	FDA	Email: 22oct15 mcc tcon slides	NDA 206488
22-Oct-2015	SRPT	FDA	Email: final tcon attendees	NDA 206488
22-Oct-2015	SRPT	FDA	RoC: 22oct15 mcc tcon mtg minutes	NDA 206488
22-Oct-2015	SRPT	FDA	RoC: 22oct15 mcc tcon transcript	NDA 206488
23-Oct-2015	FDA	SRPT	Email: cmc request	NDA 206488
23-Oct-2015	FDA	SRPT	Email: post mcc mtg clin pharm irs re[redacted]	NDA 206488
23-Oct-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488

26-Oct-2015	SRPT	FDA	Email: fu to[redacted] material request from 2sep15	NDA 206488
27-Oct-2015	FDA	SRPT	Email: fu to[redacted] material request from 2sep15	NDA 206488
27-Oct-2015	SRPT	FDA	Email:[redacted] telecon call in info	NDA 206488
28-Oct-2015	FDA	SRPT	Email:[redacted] telecon call in recd	NDA 206488
28-Oct-2015	SRPT	FDA	Email: q to[redacted]	NDA 206488
30-Oct-2015	SRPT	FDA	Email:[redacted] shipment	NDA 206488
30-Oct-2015	SRPT	FDA	Email: responses by 02nov15	NDA 206488
2-Nov-2015	FDA	SRPT	Email: available tomorrow	NDA 206488
2-Nov-2015	SRPT	FDA	Email: confirm tcon	NDA 206488
2-Nov-2015	SRPT	FDA	Email: dial in info	NDA 206488
2-Nov-2015	SRPT	FDA	Email: rqst tcon re pcnsdac due dates	NDA 206488
3-Nov-2015	FDA	SRPT	Email: confirm tcon	NDA 206488
3-Nov-2015	SRPT	FDA	Email: investigator list	NDA 206488
3-Nov-2015	SRPT	FDA	Email: temptale instructions	NDA 206488
3-Nov-2015	SRPT	FDA	Email: thanks	NDA 206488
3-Nov-2015	SRPT	FDA	RoC: rqst[redacted] extension	NDA 206488
4-Nov-2015	FDA	SRPT	eFax[redacted] mtg date and timeline updated	NDA 206488
4-Nov-2015	FDA	SRPT	Email: issue connecting nonapproved devices	NDA 206488
4-Nov-2015	FDA	SRPT	Email: report from creedo box attached	NDA 206488
4-Nov-2015	FDA	SRPT	Email: rqst status of 23oct15[redacted]	NDA 206488
4-Nov-2015	FDA	SRPT	Email: thanks	NDA 206488
4-Nov-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
4-Nov-2015	SRPT	FDA	Email: min from 06oct15 telecon	NDA 206488
4-Nov-2015	SRPT	FDA	Email: was unaware there could be issue open temptale device	NDA 206488
4-Nov-2015	SRPT	FDA	Email: will respond by tomorrow	NDA 206488
4-Nov-2015	SRPT	FDA	Email: will submit bd by[redacted]	NDA 206488
5-Nov-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
5-Nov-2015	FDA	SRPT	Email: clinical ir re[redacted]	NDA 206488
5-Nov-2015	FDA	SRPT	Letter[redacted] received	NDA 206488
5-Nov-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
5-Nov-2015	SRPT	FDA	Email:[redacted] letter signature good	NDA 206488
5-Nov-2015	SRPT	FDA	Email: responses to 23oct15 clinical and clin pharm irs	NDA 206488
12-Nov-2015	FDA	SRPT	Email: clin pharm ir re[redacted] values	NDA 206488
12-Nov-2015	FDA	SRPT	Email: inq ad comm av vendor	NDA 206488
12-Nov-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
12-Nov-2015	SRPT	FDA	Email: av vendor[redacted]	NDA 206488
13-Nov-2015	SRPT	FDA	Email: response to 05nov15 clinical ir re[redacted]	NDA 206488
18-Nov-2015	FDA	SRPT	Email: pcnsdac av contact	NDA 206488
18-Nov-2015	SRPT	FDA	Email:[redacted] av contact	NDA 206488
18-Nov-2015	SRPT	FDA	Email:[redacted] will not visit great room	NDA 206488
18-Nov-2015	SRPT	FDA	Email: response to 12nov15 clin pharm ir re[redacted]	NDA 206488
19-Nov-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
19-Nov-2015	FDA	SRPT	Email: thanks	NDA 206488
19-Nov-2015	SRPT	FDA	Email: replacement lot of dtma	NDA 206488
20-Nov-2015	FDA	SRPT	eFax 22oct15 mcc tcon minutes	NDA 206488
20-Nov-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
23-Nov-2015	FDA	SRPT	Email: clin pharm ir re[redacted]	NDA 206488
23-Nov-2015	SRPT	FDA	RoC: responses to 23nov15 clin pharm irs	NDA 206488
24-Nov-2015	SRPT	FDA	Email: response to 23nov15 ind clin pharm ir	IND 077429
24-Nov-2015	SRPT	FDA	Email: response to 23nov15 nda clin pharm irs	NDA 206488
27-Nov-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
27-Nov-2015	FDA	SRPT	Email: clinical irs re[redacted]	NDA 206488
27-Nov-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
30-Nov-2015	FDA	SRPT	Email: clinical irs re annotated[redacted]	NDA 206488
30-Nov-2015	FDA	SRPT	Email: clin pharm ir re[redacted]	NDA 206488
30-Nov-2015	FDA	SRPT	Email: rqst ackn rcpt	NDA 206488
30-Nov-2015	SRPT	FDA	Email: ackn rcpt 1	NDA 206488
30-Nov-2015	SRPT	FDA	Email: ackn rcpt 2	NDA 206488
30-Nov-2015	SRPT	FDA	Email: replacement lot[redacted]	NDA 206488
1-Dec-2015	FDA	SRPT	Email: confirm sfty resp recd	NDA 206488
1-Dec-2015	SRPT	FDA	Email: resp to outstand[redacted] queries 27 30 nov	NDA 206488
2-Dec-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
2-Dec-2015	SRPT	FDA	Email: response to 30nov15 clin pharm irs re[redacted]	NDA 206488
3-Dec-2015	FDA	SRPT	Email: clinical ir re[redacted]	NDA 206488
3-Dec-2015	FDA	SRPT	Email: recd[redacted] reagent	NDA 206488
3-Dec-2015	FDA	SRPT	Email: pcnsdac breakout room	NDA 206488
3-Dec-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488

3-Dec-2015	SRPT	FDA	Email: [redacted] req conf of receipt	NDA 206488
4-Dec-2015	SRPT	FDA	Email: eteplirsen n206488 pcnsdac briefing book	NDA 206488
4-Dec-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
4-Dec-2015	FDA	SRPT	Email: clin pharm ir re [redacted]	NDA 206488
4-Dec-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
4-Dec-2015	SRPT	FDA	Email: response to 04dec15 clin pharm ir re [redacted]	NDA 206488
8-Dec-2015	FDA	SRPT	Email: clinical ir re study 202[redacted] dates	NDA 206488
8-Dec-2015	FDA	SRPT	Email: clin pharm ir re [redacted]	NDA 206488
8-Dec-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
8-Dec-2015	SRPT	FDA	Email: response to 03dec15 clinical irs re [redacted]	NDA 206488
9-Dec-2015	FDA	SRPT	eFax comments on carton and container	NDA 206488
9-Dec-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
9-Dec-2015	FDA	SRPT	Email: ackn rcpt ad comm bd	NDA 206488
9-Dec-2015	FDA	SRPT	Email: cmc change requests	NDA 206488
9-Dec-2015	SRPT	FDA	Email: response to 08dec15 clin pharm ir re [redacted]	NDA 206488
10-Dec-2015	FDA	SRPT	Email: reason for [redacted] rqst	NDA 206488
10-Dec-2015	FDA	SRPT	Email: rqst [redacted] data	NDA 206488
10-Dec-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
10-Dec-2015	SRPT	FDA	Email: rqst reason for [redacted] data rqst	NDA 206488
10-Dec-2015	SRPT	FDA	Email: accepts change requests by	NDA 206488
10-Dec-2015	SRPT	FDA	Email: we agree so cmc telecon unnecessary	NDA 206488
10-Dec-2015	SRPT	FDA	Email: response to clinical ir re [redacted] dates	NDA 206488
10-Dec-2015	SRPT	FDA	RoC: 202[redacted] timing clarification	NDA 206488
11-Dec-2015	SRPT	FDA	Email: [redacted] datasets by [redacted]	NDA 206488
14-Dec-2015	FDA	SRPT	Email: clinical ir re [redacted]	NDA 206488
14-Dec-2015	FDA	SRPT	Email: thanks	NDA 206488
14-Dec-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
14-Dec-2015	SRPT	FDA	Email: [redacted] data in esg by tonight	NDA 206488
15-Dec-2015	FDA	SRPT	Email: cant locate coa	NDA 206488
15-Dec-2015	SRPT	FDA	Email: attempting to locate coa	NDA 206488
15-Dec-2015	SRPT	FDA	Email: response to 14dec15 clinical ir re [redacted]	NDA 206488
16-Dec-2015	FDA	SRPT	Email: ackn rcpt	NDA 206488
16-Dec-2015	FDA	SRPT	Email: pcnsdac bd may be delayed	NDA 206488
16-Dec-2015	FDA	SRPT	Email: pcnsdac mtg date published 18dec15	NDA 206488
16-Dec-2015	SRPT	FDA	Email: 4 coas	NDA 206488
23-Dec-2015	FDA	SRPT	Email: ackn rcpt	IND 077429
23-Dec-2015	FDA	SRPT	Email: clin pharm ir re [redacted]	IND 077429
23-Dec-2015	SRPT	FDA	Email: response to 23nov15 clin pharm ir re [redacted]	IND 077429
23-Dec-2015	FDA	SRPT	Email: 22jan16 pcnsdac bd v1	NDA 206488
23-Dec-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
24-Dec-2015	FDA	SRPT	Email: thanks	NDA 206488
27-Dec-2015	SRPT	FDA	Email: inq addendum cds and hardcopies reqd	NDA 206488
28-Dec-2015	FDA	SRPT	Email: short document can be Email: only	NDA 206488
29-Dec-2015	FDA	SRPT	Email: 11jan16 fcm agenda	NDA 206488
29-Dec-2015	SRPT	FDA	Email: rqst [redacted] and [redacted] at fcm	NDA 206488
30-Dec-2015	FDA	SRPT	Email: 22jan16 pcnsdac bd v2	NDA 206488
30-Dec-2015	SRPT	FDA	Email: ackn rcpt	NDA 206488
4-Jan-2016	SRPT	FDA	Email: correction	NDA 206488
4-Jan-2016	SRPT	FDA	Email: fcm dial in	NDA 206488
5-Jan-2016	SRPT	FDA	Email: rqst pt level data	NDA 206488
6-Jan-2016	FDA	SRPT	Email: reference in bd	NDA 206488
6-Jan-2016	FDA	SRPT	Email: rqst presenters and agenda items	NDA 206488
6-Jan-2016	SRPT	FDA	Email: pcnsdac presenters and responders	NDA 206488
6-Jan-2016	SRPT	FDA	Email: will answer today	NDA 206488
7-Jan-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
7-Jan-2016	FDA	SRPT	Email: rqst update on addendum	NDA 206488
7-Jan-2016	FDA	SRPT	Email: rqst update on presentations	NDA 206488
7-Jan-2016	FDA	SRPT	Email: thanks	NDA 206488
7-Jan-2016	SRPT	FDA	Email: finalizing addendum today	NDA 206488
7-Jan-2016	SRPT	FDA	Email: pcnsdac bd addendum	NDA 206488
7-Jan-2016	SRPT	FDA	Email: presentation titles and speakers	NDA 206488
8-Jan-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
8-Jan-2016	FDA	SRPT	Email: will update lobbyguard	NDA 206488
8-Jan-2016	SRPT	FDA	Email: ackn rcpt lobbyguard	NDA 206488
8-Jan-2016	SRPT	FDA	Email: [redacted] to attend fcm	NDA 206488
8-Jan-2016	SRPT	FDA	Email: pcnsdac bd addendum revised	NDA 206488
11-Jan-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488

11-Jan-2016	FDA	SRPT	Email: bd and addendum [redacted]	NDA 206488
11-Jan-2016	FDA	SRPT	Email: pcnsdac breakout room logistics	NDA 206488
11-Jan-2016	SRPT	FDA	Email: 11jan16 lcm slides	NDA 206488
11-Jan-2016	SRPT	FDA	Email: will present slides today	NDA 206488
12-Jan-2016	FDA	SRPT	Email: bds to be posted 15jan16	NDA 206488
12-Jan-2016	FDA	SRPT	Email: pcnsdac bd will post [redacted]	NDA 206488
12-Jan-2016	FDA	SRPT	Email: pcnsdac industry representative	NDA 206488
12-Jan-2016	SRPT	FDA	Email: agree to bd posted [redacted]	NDA 206488
12-Jan-2016	SRPT	FDA	Email: thanks	NDA 206488
12-Jan-2016	SRPT	FDA	Email: thanks 2	NDA 206488
12-Jan-2016	SRPT	FDA	Email: will respond today	NDA 206488
14-Jan-2016	FDA	SRPT	Email: pcnsdac bd clearances not yet rcvd	NDA 206488
14-Jan-2016	SRPT	FDA	Email: inq time bds will be posted	NDA 206488
14-Jan-2016	SRPT	FDA	Email: thanks	NDA 206488
15-Jan-2016	FDA	SRPT	Email: clinical ir re [redacted] data	NDA 206488
15-Jan-2016	FDA	SRPT	Email: hope to post bds [redacted]	NDA 206488
15-Jan-2016	FDA	SRPT	Email: pcnsdac bds posted	NDA 206488
15-Jan-2016	FDA	SRPT	Email: thanks	NDA 206488
15-Jan-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
15-Jan-2016	SRPT	FDA	Email: rqst estimate of pcsndac mtg attendees	NDA 206488
15-Jan-2016	SRPT	FDA	Email: thanks	NDA 206488
18-Jan-2016	FDA	SRPT	Email: 400 copies of slides	NDA 206488
19-Jan-2016	FDA	SRPT	Email: 1 minute	NDA 206488
19-Jan-2016	FDA	SRPT	Email: inq ready now	NDA 206488
19-Jan-2016	FDA	SRPT	Email: inq telephone number	NDA 206488
19-Jan-2016	FDA	SRPT	Email: rqst tcon today	NDA 206488
19-Jan-2016	SRPT	FDA	Email: ready in 5min	NDA 206488
19-Jan-2016	SRPT	FDA	Email: ready now	NDA 206488
19-Jan-2016	SRPT	FDA	Email: ready now 2	NDA 206488
19-Jan-2016	SRPT	FDA	Email: ready now 3	NDA 206488
19-Jan-2016	SRPT	FDA	Email: telephone number	NDA 206488
19-Jan-2016	SRPT	FDA	Email: thanks	NDA 206488
20-Jan-2016	FDA	SRPT	Email: clinical irs re [redacted] data collection	NDA 206488
20-Jan-2016	FDA	SRPT	Email: inq security guards	NDA 206488
20-Jan-2016	SRPT	FDA	Email: 1 security guard	NDA 206488
20-Jan-2016	SRPT	FDA	Email: inq bldg 1 opening time	NDA 206488
20-Jan-2016	SRPT	FDA	Email: inq pcnsdac meeting weather decision	NDA 206488
20-Jan-2016	SRPT	FDA	Email: inq pcnsdac meeting weather decision 2	NDA 206488
20-Jan-2016	SRPT	FDA	Email: responses to 15jan16 clinical irs re [redacted]	NDA 206488
26-Jan-2016	SRPT	FDA	Email: response to 20jan16 clinical irs	NDA 206488
26-Jan-2016	SRPT	FDA	RoC: bd comm tentative date acceptable	NDA 206488
27-Jan-2016	FDA	SRPT	eFax 23feb16 pcnsdac mtg timeline	NDA 206488
27-Jan-2016	FDA	SRPT	Email: available at 11	NDA 206488
27-Jan-2016	FDA	SRPT	Email: rqst tcon re pcnsdac mtg rescheduling	NDA 206488
27-Jan-2016	FDA	SRPT	Email: will get back	NDA 206488
27-Jan-2016	SRPT	FDA	Email: available for tcon	NDA 206488
27-Jan-2016	SRPT	FDA	Email: have dialed in	NDA 206488
27-Jan-2016	SRPT	FDA	Email: inq bd paper copies	NDA 206488
27-Jan-2016	SRPT	FDA	Email: tcon dial in	NDA 206488
27-Jan-2016	SRPT	FDA	Email: will edit addendum only	NDA 206488
27-Jan-2016	SRPT	FDA	Email: will update addendum only	NDA 206488
28-Jan-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
28-Jan-2016	FDA	SRPT	Email: pcnsdac mtg bd paper copies due tomorrow	NDA 206488
28-Jan-2016	SRPT	FDA	Email: 23feb16 pcnsdac mtg investigator list	NDA 206488
29-Jan-2016	FDA	SRPT	Email: clinical ir re [redacted] source docs	NDA 206488
29-Jan-2016	FDA	SRPT	Email: rqst eta of electronic copies	NDA 206488
29-Jan-2016	FDA	SRPT	Email: thanks	NDA 206488
29-Jan-2016	SRPT	FDA	Email: 23feb16 pcnsdac mtg bd and addendum	NDA 206488
29-Jan-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
29-Jan-2016	SRPT	FDA	Email: cds to be delivered 01feb16	NDA 206488
29-Jan-2016	SRPT	FDA	Email: pcnsdac bd tracking no	NDA 206488
29-Jan-2016	SRPT	FDA	Email: pdfs by 4pm	NDA 206488
1-Feb-2016	FDA	SRPT	Email: inq [redacted] subject ids contain pt initials	NDA 206488
1-Feb-2016	FDA	SRPT	Email: pcnsdac fr announcement 04feb16	NDA 206488
1-Feb-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
1-Feb-2016	SRPT	FDA	Email: [redacted] subj ids should be redacted	NDA 206488
2-Feb-2016	FDA	SRPT	Email: pcnsdac 23feb16 mtg delayed	NDA 206488

Exhibit M

2-Feb-2016	FDA	SRPT	Email: pcnsdac bd cd copies rcvd	NDA 206488
2-Feb-2016	FDA	SRPT	Email: pcnsdac bd paper copies rcvd	NDA 206488
2-Feb-2016	FDA	SRPT	Email: pcnsdac mtg date not in fr tomorrow	NDA 206488
2-Feb-2016	SRPT	FDA	Email: rqst conf of pcnsdac mtg fr posting date	NDA 206488
3-Feb-2016	SRPT	FDA	Email: 23feb16 mtg cancellation notice from [redacted]	NDA 206488
4-Feb-2016	SRPT	FDA	Email: rqst tcon re pdufa date	NDA 206488
5-Feb-2016	FDA	SRPT	eFax new pdufa date is 26may16	NDA 206488
5-Feb-2016	FDA	SRPT	Email: dnp notified of postponement before panel	NDA 206488
5-Feb-2016	FDA	SRPT	Email: rqst shipping label for return pkg	NDA 206488
5-Feb-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
5-Feb-2016	SRPT	FDA	Email: return label	NDA 206488
7-Feb-2016	SRPT	FDA	Email: [redacted]	NDA 206488
8-Feb-2016	FDA	SRPT	Email: thanks	NDA 206488
8-Feb-2016	FDA	SRPT	Email: very factual	NDA 206488
9-Feb-2016	FDA	SRPT	Email: fu clinical ir re [redacted] inclusion dates	NDA 206488
9-Feb-2016	FDA	SRPT	Email: propose 25apr16 pcnsdac mtg date	NDA 206488
9-Feb-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
9-Feb-2016	SRPT	FDA	Email: ackn rcpt 2	NDA 206488
10-Feb-2016	FDA	SRPT	eFax 11jan16 tcm minutes	NDA 206488
10-Feb-2016	FDA	SRPT	eFax 25apr16 pcnsdac mtg timeline	NDA 206488
10-Feb-2016	FDA	SRPT	Email: pcnsdac bd return status	NDA 206488
10-Feb-2016	SRPT	FDA	Email: inq will edit pcnsdac bd	NDA 206488
10-Feb-2016	SRPT	FDA	Email: ok	NDA 206488
10-Feb-2016	SRPT	FDA	Email: pcnsdac mtg list of investigators	NDA 206488
11-Feb-2016	FDA	SRPT	Email: will check with dnp	NDA 206488
11-Feb-2016	SRPT	FDA	Email: rqst tcon re 29jan16 clinical irs	NDA 206488
12-Feb-2016	FDA	SRPT	Email: bd return pkg tracking no	NDA 206488
12-Feb-2016	FDA	SRPT	Email: clinical irs re [redacted]	NDA 206488
12-Feb-2016	FDA	SRPT	Email: fwded mtg rqst	NDA 206488
12-Feb-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
12-Feb-2016	SRPT	FDA	Email: thanks	NDA 206488
16-Feb-2016	FDA	SRPT	Email: propose 18feb16 tcon date	NDA 206488
16-Feb-2016	SRPT	FDA	Email: confirm 18feb16 tcon	NDA 206488
16-Feb-2016	SRPT	FDA	Email: tcon dial in	NDA 206488
17-Feb-2016	FDA	SRPT	Email: dnp probably wants to know [redacted]	NDA 206488
17-Feb-2016	FDA	SRPT	Email: inq pcnsdac av vendor	NDA 206488
17-Feb-2016	SRPT	FDA	Email: av vendor is [redacted]	NDA 206488
17-Feb-2016	SRPT	FDA	Email: response to 12feb16 clinical irs re [redacted]	NDA 206488
17-Feb-2016	SRPT	FDA	Email: rqst fu tcon	NDA 206488
18-Feb-2016	FDA	SRPT	Email: dnp has not decided whether to update pcnsdac bd	NDA 206488
18-Feb-2016	SRPT	FDA	Email: rqst tcon participants	NDA 206488
18-Feb-2016	SRPT	FDA	Email: thanks	NDA 206488
18-Feb-2016	SRPT	FDA	Email: we are dialed in	NDA 206488
18-Feb-2016	SRPT	FDA	RoC: 18feb16 ad hoc tcon minutes	NDA 206488
18-Feb-2016	SRPT	FDA	RoC: 18feb16 ad hoc tcon transcript	NDA 206488
25-Feb-2016	FDA	SRPT	Email: clinical ir re [redacted] site contact info	NDA 206488
25-Feb-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
29-Feb-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
29-Feb-2016	SRPT	FDA	Email: partial response to 25feb16 clinical ir re [redacted]	NDA 206488
3-Mar-2016	FDA	SRPT	Email: leuven nmrc site inspection 25 29apr16	NDA 206488
4-Mar-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
4-Mar-2016	FDA	SRPT	Email: rqst update on [redacted] registry contact info	NDA 206488
4-Mar-2016	FDA	SRPT	Email: thanks	NDA 206488
4-Mar-2016	SRPT	FDA	Email: contact info sent to aife	NDA 206488
4-Mar-2016	SRPT	FDA	Email: [redacted] contact info	NDA 206488
8-Mar-2016	FDA	SRPT	Email: propose agenda for leuven inspection	NDA 206488
8-Mar-2016	SRPT	FDA	Email: [redacted] availability	NDA 206488
8-Mar-2016	SRPT	FDA	Email: proposal acceptable to [redacted]	NDA 206488
9-Mar-2016	FDA	SRPT	Email: pcnsdac mtg date to be published 14mar16	NDA 206488
9-Mar-2016	FDA	SRPT	Email: rqst status update on [redacted] source docs	NDA 206488
9-Mar-2016	SRPT	FDA	Email: hope to get docs in next couple weeks	NDA 206488
9-Mar-2016	SRPT	FDA	Email: thanks	NDA 206488
10-Mar-2016	FDA	SRPT	Email: site inspections 1 day per pt	NDA 206488
11-Mar-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
11-Mar-2016	FDA	SRPT	Email: clinical ir [redacted]	NDA 206488
11-Mar-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
11-Mar-2016	SRPT	FDA	Email: response to 11mar16 clinical ir	NDA 206488

Exhibit M

14-Mar-2016	SRPT	FDA	Email: [redacted] site availability	NDA 206488
15-Mar-2016	FDA	SRPT	eFax labeling comments	NDA 206488
15-Mar-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
17-Mar-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
17-Mar-2016	SRPT	FDA	Email: responses to 29jan 12feb 18feb16 clinical irs	NDA 206488
18-Mar-2016	SRPT	FDA	Email: [redacted] data	NDA 206488
21-Mar-2016	FDA	SRPT	Email:confirm receipt [redacted] data	NDA 206488
22-Mar-2016	SRPT	FDA	Email: rqst pcnsdac bd extension	NDA 206488
25-Mar-2016	SRPT	FDA	Email: 25apr16 pcnsdac mtg bd	NDA 206488
28-Mar-2016	SRPT	FDA	Email: alert moon to fedex delivery delay	NDA 206488
29-Mar-2016	FDA	SRPT	Email: moon oooo but confirmed receipt of pkg	NDA 206488
5-Apr-2016	FDA	SRPT	Email: pcnsdac bd delayed	NDA 206488
5-Apr-2016	SRPT	FDA	Email: updated pcnsdac presenters and responders	NDA 206488
7-Apr-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
7-Apr-2016	SRPT	FDA	Email: rqst 2nd tcm	NDA 206488
12-Apr-2016	FDA	SRPT	eFax 25apr16 pcnsdac mtg bd	NDA 206488
13-Apr-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
13-Apr-2016	FDA	SRPT	Email: rqst logistics tcon	NDA 206488
13-Apr-2016	FDA	SRPT	Email: tcon time	NDA 206488
13-Apr-2016	FDA	SRPT	Email: thanks	NDA 206488
13-Apr-2016	SRPT	FDA	Email: available for call	NDA 206488
13-Apr-2016	SRPT	FDA	Email: confirm tcon	NDA 206488
13-Apr-2016	SRPT	FDA	Email: pcnsdac bd [redacted] rqsts	NDA 206488
13-Apr-2016	SRPT	FDA	Email: pcnsdac mtg headcount	NDA 206488
13-Apr-2016	SRPT	FDA	RoC: 25apr16 pcnsdac mtg logistics	NDA 206488
15-Apr-2016	FDA	SRPT	Email: rqst update on [redacted]	NDA 206488
15-Apr-2016	SRPT	FDA	Email: 25apr16 pcnsdac bd errata	NDA 206488
15-Apr-2016	SRPT	FDA	Email: inq timing of response to [redacted] rqsts	NDA 206488
15-Apr-2016	SRPT	FDA	Email: pcnsdac presentation titles and speakers	NDA 206488
18-Apr-2016	FDA	SRPT	Email: 800 to 1000 copies	NDA 206488
18-Apr-2016	FDA	SRPT	Email: final positions on pcnsdac bd [redacted]	NDA 206488
18-Apr-2016	FDA	SRPT	Email: [redacted]	NDA 206488
18-Apr-2016	FDA	SRPT	Email: pcnsdac bd redaction tcon	NDA 206488
18-Apr-2016	FDA	SRPT	Email: unable to dial in	NDA 206488
18-Apr-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
18-Apr-2016	SRPT	FDA	Email: inq tcon error message	NDA 206488
18-Apr-2016	SRPT	FDA	Email: rqst no of printed copies	NDA 206488
18-Apr-2016	SRPT	FDA	Email: tcon dial in	NDA 206488
19-Apr-2016	FDA	SRPT	Email: [redacted] data to be presented at pcnsdac	NDA 206488
19-Apr-2016	FDA	SRPT	Email: rqst update on [redacted]	NDA 206488
19-Apr-2016	FDA	SRPT	Email: rqst [redacted]	NDA 206488
19-Apr-2016	SRPT	FDA	Email: [redacted] still pending	NDA 206488
19-Apr-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
20-Apr-2016	FDA	SRPT	Email: rqst tcon	NDA 206488
20-Apr-2016	FDA	SRPT	Email: tcon time	NDA 206488
20-Apr-2016	SRPT	FDA	Email: rqst overview of presentation and conclusions	NDA 206488
20-Apr-2016	SRPT	FDA	Email: tcon availability	NDA 206488
20-Apr-2016	SRPT	FDA	Email: tcon number	NDA 206488
20-Apr-2016	SRPT	FDA	Email: will submit [redacted] asap	NDA 206488
20-Apr-2016	SRPT	FDA	RoC: pcnsdac mtg agenda and logistics tcon	NDA 206488
21-Apr-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
21-Apr-2016	FDA	SRPT	Email: pcnsdac industry rep mark gordon	NDA 206488
21-Apr-2016	SRPT	FDA	Email: thanks	NDA 206488
22-Apr-2016	FDA	SRPT	Email: you have had access to [redacted] data	NDA 206488
22-Apr-2016	SRPT	FDA	Email: we only have access to manuscript	NDA 206488
24-Apr-2016	FDA	SRPT	Email: wireless mic for [redacted]	NDA 206488
24-Apr-2016	SRPT	FDA	Email: inq podium access for [redacted]	NDA 206488
25-Apr-2016	FDA	SRPT	Email: clear 2nd row during oph	NDA 206488
3-May-2016	FDA	SRPT	Email: clinical irs re [redacted]	NDA 206488
3-May-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
4-May-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
4-May-2016	SRPT	FDA	Email: response to 03may16 clin pharm ir no 2	NDA 206488
5-May-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
5-May-2016	FDA	SRPT	Email: clinical irs re [redacted]	NDA 206488
5-May-2016	FDA	SRPT	Email: rqst update on [redacted]	NDA 206488
5-May-2016	FDA	SRPT	Email: thanks	NDA 206488
5-May-2016	SRPT	FDA	Email: response to 05may16 clinical ir re [redacted]	NDA 206488

5-May-2016	SRPT	FDA	Email: response to [redacted] rqst by tomorrow	NDA 206488
6-May-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
6-May-2016	FDA	SRPT	Email: clinical lr 202[redacted]	NDA 206488
6-May-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
6-May-2016	SRPT	FDA	Email: response to 06may16 clinical lr re 202[redacted]	NDA 206488
6-May-2016	SRPT	FDA	Email: [redacted] data by monday	NDA 206488
9-May-2016	SRPT	FDA	Email: response to 19apr16 clinical lr re [redacted] data v1	NDA 206488
10-May-2016	FDA	SRPT	Email: response v1 fwded to team	NDA 206488
10-May-2016	SRPT	FDA	Email: response to 19apr16 clinical lr re [redacted] v2	NDA 206488
24-May-2016	FDA	SRPT	Email: nda review will continue past pdufa date	NDA 206488
24-May-2016	FDA	SRPT	Email: thanks	NDA 206488
24-May-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
24-May-2016	SRPT	FDA	Email: revised proposed [redacted]	NDA 206488
27-May-2016	SRPT	FDA	Email: rqst update on [redacted] comments	NDA 206488
31-May-2016	FDA	SRPT	Email: unable to provide [redacted] comments timeline	NDA 206488
31-May-2016	SRPT	FDA	Email: thanks	NDA 206488
1-Jun-2016	FDA	SRPT	Email: rqst tcon to discuss [redacted] analysis	NDA 206488
1-Jun-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
2-Jun-2016	FDA	SRPT	Email: tcon rqst 2	NDA 206488
3-Jun-2016	FDA	SRPT	Email: tcon 06jun16 1pm	NDA 206488
3-Jun-2016	FDA	SRPT	Email: thanks	NDA 206488
3-Jun-2016	FDA	SRPT	Email: [redacted] comments pending	NDA 206488
3-Jun-2016	FDA	SRPT	Letter clinical lr re [redacted] analysis	NDA 206488
3-Jun-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
3-Jun-2016	SRPT	FDA	Email: confirm 1pm tcon	NDA 206488
3-Jun-2016	SRPT	FDA	Email: rqst tcon w ash rao re [redacted] protocol	NDA 206488
3-Jun-2016	SRPT	FDA	Email: tcon details monday morning	NDA 206488
4-Jun-2016	SRPT	FDA	Email: tcon dial in	NDA 206488
5-Jun-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
5-Jun-2016	FDA	SRPT	Email: rqst [redacted] protocol for tcon tomorrow	NDA 206488
5-Jun-2016	FDA	SRPT	Email: thanks	NDA 206488
5-Jun-2016	SRPT	FDA	Email: draft interim [redacted] protocols	NDA 206488
5-Jun-2016	SRPT	FDA	Email: [redacted] protocol tonight	NDA 206488
6-Jun-2016	FDA	SRPT	Email: attendees	NDA 206488
6-Jun-2016	FDA	SRPT	Email: internal discussion first	NDA 206488
6-Jun-2016	FDA	SRPT	Email: labeling comments 3	NDA 206488
6-Jun-2016	FDA	SRPT	Email: rqst confirmation of [redacted] addresses	NDA 206488
6-Jun-2016	FDA	SRPT	Email: thanks	NDA 206488
6-Jun-2016	SRPT	FDA	Email: 15 minutes late	NDA 206488
6-Jun-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
6-Jun-2016	SRPT	FDA	Email: confirm [redacted] addresses	NDA 206488
6-Jun-2016	SRPT	FDA	Email: rqst attendees	NDA 206488
6-Jun-2016	SRPT	FDA	Email: tcon slides and attendees	NDA 206488
6-Jun-2016	SRPT	FDA	Email: will reply asap	NDA 206488
7-Jun-2016	FDA	SRPT	Email: rqst [redacted] contacts	NDA 206488
7-Jun-2016	FDA	SRPT	Email: rqst [redacted] and ncs	NDA 206488
7-Jun-2016	SRPT	FDA	Email: 06jun16 ad hoc tcon minutes	NDA 206488
7-Jun-2016	SRPT	FDA	Email: [redacted] site contact	NDA 206488
8-Jun-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
8-Jun-2016	FDA	SRPT	Email: ackn rcpt 2	NDA 206488
8-Jun-2016	FDA	SRPT	Email: ackn rcpt 3	NDA 206488
8-Jun-2016	FDA	SRPT	Email: ackn rcpt 4	NDA 206488
8-Jun-2016	FDA	SRPT	Email: need [redacted] details to confirm inspections	NDA 206488
8-Jun-2016	FDA	SRPT	Email: rqst [redacted] site contact	NDA 206488
8-Jun-2016	SRPT	FDA	Email: 4658 us 202[redacted]	NDA 206488
8-Jun-2016	SRPT	FDA	Email: [redacted] site contact	NDA 206488
8-Jun-2016	SRPT	FDA	Email: nc details preliminary response	NDA 206488
8-Jun-2016	SRPT	FDA	Email: rqst feedback by 10jun16	NDA 206488
8-Jun-2016	SRPT	FDA	Email: updated [redacted] protocols	NDA 206488
9-Jun-2016	FDA	SRPT	Email: [redacted] under review by [redacted]	NDA 206488
9-Jun-2016	SRPT	FDA	Email: [redacted] protocols	NDA 206488
9-Jun-2016	SRPT	FDA	Email: rqst [redacted] comments	NDA 206488
9-Jun-2016	SRPT	FDA	Email: site visit dates	NDA 206488
9-Jun-2016	SRPT	FDA	Email: thanks	NDA 206488
9-Jun-2016	SRPT	FDA	RoC: rqst site visit dates	NDA 206488
10-Jun-2016	FDA	SRPT	Email: 06jun16 ad hoc tcon minutes	NDA 206488
10-Jun-2016	FDA	SRPT	Email: edited [redacted]	NDA 206488

10-Jun-2016	FDA	SRPT	Email: signature	NDA 206488
10-Jun-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
10-Jun-2016	SRPT	FDA	Email: ackn rcpt 2	NDA 206488
13-Jun-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
13-Jun-2016	FDA	SRPT	Email: adr table derivation	NDA 206488
13-Jun-2016	FDA	SRPT	Email: carton container proposal is acceptable	NDA 206488
13-Jun-2016	FDA	SRPT	Email: will discuss and provide response	NDA 206488
13-Jun-2016	SRPT	FDA	Email: [redacted]	NDA 206488
13-Jun-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
13-Jun-2016	SRPT	FDA	Email: ackn rcpt 2	NDA 206488
13-Jun-2016	SRPT	FDA	Email: rqst adr table reference	NDA 206488
13-Jun-2016	SRPT	FDA	Email: rqst confirmation of inspector at[redacted]	NDA 206488
13-Jun-2016	SRPT	FDA	Email: thanks	NDA 206488
15-Jun-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
15-Jun-2016	FDA	SRPT	Email: rqst dates of nonclin pmrs and cmc pmcs	NDA 206488
15-Jun-2016	SRPT	FDA	Email: [redacted]manual	NDA 206488
15-Jun-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
16-Jun-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
16-Jun-2016	SRPT	FDA	Email: proposed nonclin pmr and cmc pmc dates	NDA 206488
17-Jun-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
17-Jun-2016	FDA	SRPT	Email: ackn rcpt 2	NDA 206488
17-Jun-2016	FDA	SRPT	Email: [redacted]	NDA 206488
17-Jun-2016	FDA	SRPT	Email: [redacted]inspector roles	NDA 206488
17-Jun-2016	FDA	SRPT	Email: rqst final[redacted]protocol	NDA 206488
17-Jun-2016	FDA	SRPT	Email: rqst redline in word	NDA 206488
17-Jun-2016	FDA	SRPT	Email: thanks	NDA 206488
17-Jun-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
17-Jun-2016	SRPT	FDA	Email: final 4658[redacted]protocol	NDA 206488
17-Jun-2016	SRPT	FDA	Email: rqst confirmation of[redacted]	NDA 206488
17-Jun-2016	SRPT	FDA	Email: rqst inspector roles	NDA 206488
17-Jun-2016	SRPT	FDA	Email: thanks	NDA 206488
17-Jun-2016	SRPT	FDA	Email: updated[redacted]	NDA 206488
18-Jun-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
18-Jun-2016	SRPT	FDA	Email: updated[redacted]	NDA 206488
20-Jun-2016	FDA	SRPT	Email: clinical ir re[redacted]	NDA 206488
20-Jun-2016	FDA	SRPT	Letter: form 482 1	NDA 206488
20-Jun-2016	FDA	SRPT	Letter: form 482 2	NDA 206488
20-Jun-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
21-Jun-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
21-Jun-2016	SRPT	FDA	Email: [redacted]	NDA 206488
22-Jun-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
22-Jun-2016	FDA	SRPT	Email: inq[redacted]today	NDA 206488
22-Jun-2016	SRPT	FDA	Email: response to 20jun16 clinical ir re[redacted]	NDA 206488
22-Jun-2016	SRPT	FDA	Email: [redacted]today	NDA 206488
23-Jun-2016	FDA	SRPT	Email: clinical ir re[redacted]analysis sap	NDA 206488
23-Jun-2016	FDA	SRPT	Email: thanks	NDA 206488
23-Jun-2016	FDA	SRPT	RoC: rqst[redacted]	NDA 206488
23-Jun-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
23-Jun-2016	SRPT	FDA	Email: [redacted]	NDA 206488
23-Jun-2016	SRPT	FDA	Email: response to 23jun16 clinical ir re[redacted]sap	NDA 206488
24-Jun-2016	SRPT	FDA	Email: sq0042 contents	NDA 206488
26-Jun-2016	SRPT	FDA	Email: [redacted]	NDA 206488
27-Jun-2016	FDA	SRPT	Email: rqst notification when submission is in esg	NDA 206488
27-Jun-2016	SRPT	FDA	Email: sq0042 in esg	NDA 206488
5-Jul-2016	FDA	SRPT	Email: htm 25apr16 pcnsdac meeting minutes	NDA 206488
8-Jul-2016	SRPT	FDA	Email: inq sponsor rep title change procedure	NDA 206488
13-Jul-2016	FDA	SRPT	Email: rqst efficacy pmr pmc dates	NDA 206488
13-Jul-2016	FDA	SRPT	Email: rqst revised nonclinical pmr dates	NDA 206488
13-Jul-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
13-Jul-2016	SRPT	FDA	Email: ackn rcpt 2	NDA 206488
14-Jul-2016	FDA	SRPT	Email: need time for[redacted]process	NDA 206488
14-Jul-2016	FDA	SRPT	Email: revised eteplirsen[redacted]pmr	NDA 206488
14-Jul-2016	SRPT	FDA	Email: [redacted]pmr pmc dates	NDA 206488
14-Jul-2016	SRPT	FDA	Email: nonclinical revised pmr dates 1	NDA 206488
15-Jul-2016	FDA	SRPT	Email: nonclinical revised pmr dates acceptable	NDA 206488
15-Jul-2016	FDA	SRPT	Email: suggest 6 mos for[redacted]	NDA 206488
15-Jul-2016	SRPT	FDA	Email: eteplirsen[redacted]pmr revised dates	NDA 206488

15-Jul-2016	SRPT	FDA	Email: nonclinical revised pmr dates 2	NDA 206488
15-Jul-2016	SRPT	FDA	Email: accept [redacted] pmr pmc dates	NDA 206488
22-Jul-2016	FDA	SRPT	Email: rqst [redacted] pmr dates	NDA 206488
27-Jul-2016	SRPT	FDA	Email: [redacted] pmr dates	NDA 206488
28-Jul-2016	FDA	SRPT	Email: edited [redacted]	NDA 206488
29-Jul-2016	SRPT	FDA	Email: responses to [redacted]	NDA 206488
2-Aug-2016	FDA	SRPT	Email: [redacted] data median	NDA 206488
2-Aug-2016	FDA	SRPT	Email: [redacted]	NDA 206488
3-Aug-2016	FDA	SRPT	Email: [redacted] pmr dates acceptable	NDA 206488
6-Aug-2016	FDA	SRPT	Email: eteplirsen [redacted]	NDA 206488
16-Sep-2016	FDA	SRPT	Email: revised pmr pmc dates	NDA 206488
16-Sep-2016	FDA	SRPT	Email: rqst submission of revised pmr pmc dates	NDA 206488
16-Sep-2016	FDA	SRPT	Email: thanks	NDA 206488
16-Sep-2016	SRPT	FDA	Email: accept revised pmr pmc dates	NDA 206488
16-Sep-2016	SRPT	FDA	Email: pmrs pmcs will be submitted	NDA 206488
16-Sep-2016	SRPT	FDA	Email: submission available in esg	NDA 206488
19-Sep-2016	FDA	SRPT	Email:htm eteplirsen approval letter	NDA 206488
19-Sep-2016	FDA	SRPT	Email:htm eteplirsen summary review	NDA 206488
19-Sep-2016	FDA	SRPT	Email:htm eteplirsen uspi	NDA 206488
19-Sep-2016	FDA	SRPT	Letter: nda206488 action letter	NDA 206488
19-Sep-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
20-Sep-2016	FDA	SRPT	Email: rqst 4658 [redacted] demos	NDA 206488
20-Sep-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
21-Sep-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
21-Sep-2016	FDA	SRPT	Email: rqst response today	NDA 206488
21-Sep-2016	SRPT	FDA	Email: alt 4658 [redacted]	NDA 206488
26-Sep-2016	SRPT	FDA	Email: eudralink pre maa rapp mtg slides	NDA 206488
27-Sep-2016	FDA	SRPT	Email: rqst dmd study enrollment update	NDA 206488
27-Sep-2016	SRPT	FDA	Email: ackn rcpt	NDA 206488
28-Sep-2016	FDA	SRPT	Email: ackn rcpt	NDA 206488
28-Sep-2016	SRPT	FDA	Email: dmd study [redacted] update	NDA 206488
29-Sep-2016	FDA	SRPT	Email: E595:E1534letter acknowledgement of cbe 30	NDA 206488