Name of Sponsor/Company: Prosensa Therapeutics B.V.	**Individual Study Table Referring to Study Report:**	
Name of Finished Product: drisapersen solution 200 mg/mL	DMD114117	
Name of Active Ingredient: drisapersen		

Title of Study:

A phase II, double blind, exploratory, parallel-group, placebo-controlled clinical study to assess two dosing regimens of GSK2402968 for efficacy, safety, tolerability and pharmacokinetics in ambulant subjects with Duchenne muscular dystrophy

Investigators:

Multi-centre study

Study centre(s):

This study was conducted at 13 centres in 9 countries in Australia, Belgium, France, Germany, Israel, Netherlands, Spain, Turkey, and the United Kingdom (UK).

Publication (reference):

None at the time of this report

Studied period (years):	**Phase of development:**
(date of first enrolment) 01 September 2010 **(date of last completed)** 12 September 2012	Phase II

Objectives:

The primary objective of this study was to assess the efficacy of 2 different dosing regimens of subcutaneous drisapersen (GSK2402968, drisapersen sodium) administered over 24 weeks in ambulant subjects with Duchenne muscular dystrophy (DMD).

Secondary objectives were:

- To assess the safety and tolerability of 2 different dosing regimens of subcutaneous drisapersen administered over 48 weeks in ambulant subjects with DMD.
- To assess the pharmacokinetics (PK) of 2 different dosing regimens of subcutaneous drisapersen administered over 48 weeks in ambulant subjects with DMD.
- To assess long term efficacy of 2 different dosing regimens of subcutaneous drisapersen administered over 48 weeks in ambulant subjects with DMD.

Methodology:

This was a phase II, double-blind, exploratory, parallel-group, placebo-controlled clinical study in ambulant subjects with DMD resulting from a mutation that can be corrected by exon skipping induced by drisapersen. There were 2 parallel cohorts. Each cohort included subjects on drisapersen and matched placebo in a 2:1 ratio. The active doses were:

- Continuous regimen; 6 mg/kg drisapersen once weekly
- Intermittent regimen; 6 mg/kg drisapersen twice weekly on 1st, 3rd and 5th weeks, once weekly on 2nd, 4th and 6th weeks, and no active drug on 7th to 10th week of each 10 week cycle

All subjects received a loading dosing regimen of twice weekly dosing with 6 mg/kg drisapersen for the first 3 weeks of treatment only. The intermittent regimen cycles started after completion of the loading dosing regimen (i.e. from Week 4).

The study was fully blinded with respect to active and placebo in each cohort, however the different regimens were not fully blinded. Subjects allocated to the continuous dosing regimen received a total of 51 doses of drisapersen or placebo, whereas subjects allocated to the intermittent regimen received a total of 50 doses of drisapersen or placebo.

Subjects were treated for 48 weeks (including the loading dose period) following a 2 to 4 week screening period. At the end of the treatment period, subjects who completed the study had the option to enter an open-label extension study (Study DMD114349). Any subjects who did not enter the extension study, for whatever reason, were monitored as clinically indicated but for a minimum of 20 weeks after the last dose of drisapersen/placebo. A formal follow-up visit was conducted 20 weeks after the last dose of drisapersen/placebo.

Safety and efficacy were measured at intervals throughout the study. An Independent Data Monitoring Committee (IDMC) oversaw the study and regularly evaluated safety and tolerability, according to the IDMC charter.

The primary efficacy analysis for this study was conducted when all subjects had completed 24 weeks of dosing (Week 25). All subjects remained on study until the final efficacy evaluations after 48 weeks of dosing (Week 49).

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Number of patients (planned and analysed):
It was planned to randomise 54 subjects, which assuming a drop-out rate of approximately 10%, would provide 48 evaluable subjects (2 active: 1 placebo regimen matched per cohort).

Population	Placebo (combined)	6 mg/kg drisapersen continuous	6 mg/kg drisapersen intermittent	Total
Planned, N	18	18	18	54
Randomised, N	18	18	17	53

Demographic characteristics were similar across treatment groups with the intermittent group being older and having slightly higher mean height and weight values. Baseline DMD characteristics were relatively balanced across treatment groups and were as expected with the eligibility criteria. The time since first symptoms and diagnosis in the intermittent group was slightly longer than the other two treatment groups which are consistent with the older mean age of this group.

	Placebo (combined) (N=18)	6 mg/kg drisapersen continuous (N=18)	6 mg/kg drisapersen intermittent (N=17)	Total (N=53)
Age (yrs)				
Mean (SD)	6.9 (1.18)	7.2 (1.66)	7.7 (1.49)	7.3 (1.47)
Median	7.0	6.5	8.0	7.0
Min., Max.	5, 9	5, 11	5, 10	5, 11
Sex, n (%)				
Male	18 (100)	18 (100)	17 (100)	53 (100)
Ethnicity, n (%)[a]				
n	16	17	15	48
Not Hispanic/Latino	16 (100)	17 (100)	14 (93)	47 (98)
Hispanic/Latino	0	0	1 (7)	1 (2)
Race, n (%)[a]				
n	16	17	15	48
White – White/Caucasian/European Heritage	13 (81)	15 (88)	14 (93)	42 (88)
White –Arabic/North African Heritage	0	2 (12)	0	2 (4)
American Indian or Alaska Native	0	0	1 (7)	1 (2)
Asian – South East Asian Heritage	1 (6)	0	0	1 (2)
Native Hawaiian or other Pacific Islander	1 (6)	0	0	1 (2)
Mixed Race	1 (6)	0	0	1 (2)
Height (cm)				
Mean (SD)	118.69 (8.137)	118.42 (10.459)	120.60 (10.267)	NA
Weight (kg)				
Mean (SD)	25.03 (5.226)	25.05 (7.390)	28.39 (9.811)	NA
Time Since First Symptoms (months)[b]				
Mean (SD)	63.5 (24.00)	61.1 (24.86)	64.5 (24.56)	63.0 (24.04)
Median	73.3	57.4	63.1	62.2
Min., Max.	15, 95	27, 112	27, 105	15, 112
Time Since Diagnosis (months)[b]				
Mean (SD)	44.4 (21.61)	44.6 (27.69)	47.8 (26.48)	45.5 (24.93)
Median	35.5	41.4	47.0	43.4
Min., Max.	12, 82	3, 96	3, 105	3, 105

NA=Not available
a. Race and ethnicity were not collected for subjects from France per country specific clinical trial guideline.
b. Date of first dose used to calculate number of months for each subject.

Diagnosis and main criteria for inclusion:

Participants in this study were ambulant male subjects at least 5 years of age with a life expectancy of at least 1 year, with DMD resulting from a mutation in the DMD gene, confirmed by a state-of-the-art DNA diagnostic technique covering all DMD gene exons, including but

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not limited to MLPA (Multiplex Ligation-dependent Probe Amplification), and correctable by drisaperseninduced DMD exon 51 skipping; able to rise from floor in ≤ 7 seconds (without aids/orthoses); able to complete the 6 minute walking distance (6MWD) test with a distance of at least 75 m (results of the 6MWD were to be within 20% at each pre-drug visit); receiving glucocorticoids for a minimum of 6 months immediately prior to screening, with no significant change in total daily dosage or dosing regimen for a minimum of 3 months immediately prior to screening and a reasonable expectation that total daily dosage and dosing regimen would not change significantly for the duration of the study; QT interval corrected for heart rate (QTc) <450 msec (based on single or average QTc value of triplicate electrocardiogram [ECGs] obtained over a brief recording period). Subjects with any additional missing exon for DMD that could not be treated with drisapersen were excluded from the study.

Test product, dose and mode of administration, batch number:

Drisapersen (Batch numbers: 091236424, 101244308, 101273846 and 111285814) was supplied as 3 mL vials containing 1 mL sterile solution for subcutaneous injection.

Each subject received drisapersen subcutaneously in accordance with their allocated dosing regimen. Dosing was preferably to be conducted in the morning, but after completion of any safety and efficacy assessments. The dose volume was calculated on the basis of the individual subject's most recent body weight.

Multiple injections may have been required, depending on the subject's weight. As there was the potential for injection site reactions with drisapersen administration, it was strongly recommended to try and minimize any skin reactions by defined rotation of the injection site.

The syringe was to be filled shortly before injection to protect the study treatments from exposure to light. There were no food restrictions with regards to dosing.

Duration of treatment:

24 weeks

Reference therapy, dose and mode of administration, batch number:

Placebo (Batch numbers: 101239530 and 101266022) was supplied as mL vials containing 1 mL sterile solution for subcutaneous injection

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint was the change from baseline at Week 25 in the 6 minute walking distance (6MWD) test.

Secondary efficacy endpoints included: Timed function tests (times and grading): rise from floor, 10 m walk/run, 4-stair climb/descent; muscle strength (total score): knee flexors, knee extensors, elbow flexors, elbow extensors, shoulder abductors and hip flexors (as determined by handheld dynamometry); North Star Ambulatory Assessment (NSAA); frequency of accidental falls (during 6MWD); time to loss of ambulation; creatine kinase (CK) serum concentrations; pulmonary function (Forced Expiratory Volume [FEV1], Forced Vital Capacity [FVC], Maximum Inspiratory Pressure [MIP], Maximum Expiratory Pressure [MEP], Peak Cough Flow [PCF] and Peak Flow [PF]); and dystrophin expression (muscle biopsies).

Safety:

Safety endpoints included adverse events (AEs); physical examination including local tolerability; vital signs, ECG parameters; safety haematology and biochemistry parameters including non-standard parameters such as coagulation parameters (in particular activated partial thromboplastin time [aPTT]), cystatin C, Complement factor C3, haptoglobulin, fibrinogen, high sensitivity C-reactive protein (CRP); urinalysis (including quantitative protein, creatinine and ratio in urine and α1-microglobulin, cystatin C and Kidney Injury Molecule 1 [KIM-1]); and echocardiogram.

Pharmacokinetics:

PK endpoints included maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), area under concentration-time curve from time zero (predose) to 24 hours postdose (AUC(0-24h)) and area under concentration-time curve from time zero (predose) to last time of quantifiable concentration (AUC(0-t)) using the PK-data obtained at Week 29.

Statistical methods:

The sample size of 48 evaluable subjects was not based on statistical considerations, but was considered sufficient to provide adequate PK data for each of the dosing regimens, and to provide information on trends with respect to efficacy and safety.

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drisapersen		

For efficacy parameters the primary time point of interest was Week 25. The data were re-analysed at Week 49 for supportive purposes.

Each of the two treatment regimens were compared separately to placebo, and to account for multiplicity, the Bonferroni-Holm adjustment was employed for the analysis of the primary endpoint, the change from baseline in the 6MWD at Week 25.

Primary and secondary continuous efficacy variables (with the exception of frequency of accidental falls, pulmonary function variables and dystrophin expression) were analysed using a mixed model with repeated measures (MMRM). Treatment differences, 95% confidence intervals and p-values are presented.

Insufficient numbers of subjects lost ambulation during the study to enable an analysis of the time to loss of ambulation.

All other efficacy, safety and PK variables were summarised.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS

In the primary efficacy MMRM analysis of change from Baseline in 6MWD at Week 25, a statistically significant and clinically meaningful treatment benefit (35.09 m; p<0.025) over placebo in 6MWD was observed for the continuous regimen. No statistically significant or clinically meaningful treatment benefit over placebo at Week 25 was observed for the intermittent regimen.

Whilst treatment differences of 35.84 m and 27.08 m were observed for the continuous and intermittent groups respectively, statistical significance at the Week 49 timepoint was not reached for either drisapersen treatment group versus combined placebo. It should be noted that the study was not designed to have sufficient power to detect a 30 m treatment difference as being statistically significant (based on an assumed standard deviation).

MMRM Analysis of Change from Baseline in 6MWD (m)

	Placebo (combined) (N=18)	6 mg/kg drisapersen continuous (N=18)	6 mg/kg drisapersen intermittent (N=17)
Baseline			
N	18	18	17
Mean (SD)	403.18 (45.131)	427.61 (70.045)	394.57 (66.952)
Week 25 Primary Analysis			
N	16	16	15
Adjusted mean change (SE)	-3.6 (9.73)	31.5 (9.75)	-0.1 (10.34)
Adjusted mean difference vs. placebo		35.09	3.51
95% CI		(7.59, 62.60)	(-24.34, 31.35)
p-value		0.014	0.801
Week 49			
N	17	18	15
Adjusted mean change (SE)	-24.7 (12.75)	11.2 (12.64)	2.4 (13.63)
Adjusted mean difference vs. placebo		35.84	27.08
95% CI		(-0.11, 71.78)	(-9.83, 63.99)
p-value		0.051	0.147

There were trends in favour of the continuous group compared with placebo at Week 25 for the majority of the secondary endpoints (timed function tests [rise from floor, 10 m walk/run, and 4 stair climb/descent], NSAA and CK). Little change was seen in total muscle strength, compared to slight improvements with placebo, and changes in pulmonary function measures were small and variable in both treatment groups.

There were inconsistent, non-statistically significant results for the intermittent treatment regimen group compared with placebo, across secondary efficacy endpoints at Week 25.

There were trends in favour of the continuous and intermittent groups compared with placebo at Week 49 for timed function tests (rise from floor, 10 m walk/run, and 4 stair climb/descent), NSAA and CK. Similar, small increases were observed in total muscle strength for the continuous and placebo regimens, and little change was observed with the intermittent regimen. Changes in pulmonary function measures were small and variable in all treatment groups.

Measurement of exon skipping and dystrophin protein expression by Western Blot (WB) and dystrophin restoration at the membrane as

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measured by a reproducible analysis of at least 1000 individual fibre membranes by immunofluorescence assay (IFA) indicates that a pharmacodynamic effect is associated with drisapersen treatment. When defining a positive pharmacodynamic response as an increase from baseline in dystrophin at Week 25 by at least one testing method (IFA, WB or exon skipping), the majority of active drug-treated subjects (continuous group: 72%; intermittent group: 59%) showed a positive response compared to only 1 (6%) placebo subject. Further investigation is needed to better understand the individual variability of treated subjects.

Summary of Key Secondary Efficacy Results

	Placebo (N=18)	6 mg/kg drisapersen continuous (N=18)	6 mg/kg drisapersen intermittent (N=17)
Rise from floor (s)			
Baseline, n	18	18	17
Mean (SD)	4.67 (1.018)	4.83 (1.627)	5.79 (2.917)
Week 25, n	16	16	15
Adjusted mean change (SE)	0.96 (0.710)	0.06 (0.698)	2.14 (0.747)
Week 49, n	17	18	16
Adjusted mean change (SE)	3.81 (1.190)	0.89 (1.162)	2.89 (1.262)
10 meter walk/run (s)			
Baseline, n	18	18	17
Mean (SD)	4.96 (0.788)	4.98 (1.175)	5.65 (1.802)
Week 25, n	16	16	15
Adjusted mean change (SE)	0.47 (0.228)	-0.02 (0.227)	0.20 (0.242)
Week 49, n	17	18	15
Adjusted mean change (SE)	0.76 (0.259)	0.09 (0.253)	0.33 (0.279)
4 stair climb – ascent time (s)			
Baseline, n	18	18	17
Mean (SD)	3.50 (1.576)	3.14 (1.152)	4.29 (2.949)
Week 25, n	16	16	15
Adjusted mean change (SE)	0.23 (0.348)	-0.34 (0.350)	0.65 (0.367)
Week 49, n	17	18	16
Adjusted mean change (SE)	1.02 (0.517)	0.77 (0.511)	0.52 (0.548)
4 stair climb – descent time (s)			
Baseline, n	18	18	17
Mean (SD)	2.81 (0.951)	2.98 (0.795)	3.68 (1.591)
Week 25, n	16	16	15
Adjusted mean change (SE)	0.15 (0.358)	-0.28 (0.351)	0.07 (0.373)
Week 49, n	17	18	16
Adjusted mean change (SE)	0.33 (0.419)	-0.00 (0.407)	0.15 (0.445)
Total muscle strength (lbs)			
Baseline, n	17	18	17
Mean (SD)	122.01 (27.952)	124.29 (22.705)	124.26 (31.564)
Week 25, n	15	16	15
Adjusted mean change (SE)	6.23 (4.621)	-0.99 (4.411)	-1.76 (4.681)
Week 49, n	16	18	16
Adjusted mean change (SE)	7.49 (4.915)	5.93 (4.628)	0.08 (4.978)
North Star Ambulatory Assessment (total score)			
Baseline, n	18	18	17
Mean (SD)	26.1 (4.40)	26.9 (4.48)	24.9 (6.43)
Week 25, n	16	16	15
Adjusted mean change (SE)	-1.4 (0.84)	0.2 (0.83)	0.4 (0.89)
Week 49, n	17	18	16
Adjusted mean change (SE)	-2.7 (1.06)	-0.2 (1.04)	-0.4 (1.12)
Creatine kinase serum concentration (IU/L)			

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Baseline, n	18	18	17
Mean (SD)	9525.2 (5415.45)	12267.1 (6297.37)	14023.4 (7560.97)
Week 25, n	16	17	16
Adjusted mean change (SE)	-62.1 (1290.13)	-3268.3 (1272.97)	-4093.0 (1389.94)
Week 48, n	18	18	14
Adjusted mean change (SE)	-2114.8 (1209.87)	-3850.8 (1168.97)	-4055.7 (1361.20)
DMD Exon 51 Skip Muscle Biopsy Data			
Week 25, n (%)			
N	17	17	17
Increase	0	2 (12)	5 (29)
No increase	0	2 (12)	0
Inconclusive	0	0	0
Below reporting level	17 (100)	12 (71)	11 (65)
No result[a]	0	1 (6)	1 (6)
Dystrophin Expression - Relative Intensity (All muscles)			
Immunofluorescence assay (IFA)			
Week 25, n (%)			
N	18	17	17
Strong increase	0	4 (24)	4 (24)
Increase	1 (6)	5 (29)	4 (24)
No change	9 (50)	4 (24)	3 (18)
Decrease	7 (39)	2 (12)	4 (24)
Inconclusive	0	0	1 (6)
No result[a]	1 (6)	2 (12)	1 (6)
Western blot (WB)			
Week 25, n (%)			
N	18	18	17
Increase	0	5 (28)	5 (29)
No increase	14 (78)	11 (61)	9 (53)
Inconclusive	1 (6)	0	0
Below reporting level	0	1 (6)	2 (12)
No result[a]	3 (17)	1 (6)	1 (6)
Increase from Baseline in Dystrophin at Week 25 by at least one testing method (IFA, WB or Exon Skipping), n (%)	1 (6)	13 (72)	10 (59)

a. Some subjects could not be analysed with all methods due to poor quality (IFA) or the biopsy being too small to perform all analyses (WB and exon skip analysis), therefore these are stated as “no result”.

SAFETY RESULTS:

AEs for this study were classified into on-treatment AEs and follow-up AEs. The majority of subjects in each treatment group reported an on-treatment AE. An AE (nasopharyngitis) was reported during the follow-up phase in 1 (6%) subject in the intermittent treatment group compared to 0 subjects with AEs during the follow-up phase in the continuous and placebo groups. The incidence of drug-related AEs (per the investigator’s judgment) was higher in the continuous and intermittent groups compared with the placebo group.

The incidence of serious adverse events (SAEs) was comparable across treatment groups. Only one SAE was considered related to investigational product by the investigator, a case of haematuria in 1 subject in the intermittent group which was initially reported as related to investigational product but subsequently changed to relationship unknown. There were no fatal AEs or AEs leading to permanent discontinuation of investigational product or withdrawal from the study.

Summary of All AEs by Treatment in DMD114117 (Safety Population)

	Number (%) of Subjects

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	Placebo (combined) (N=18)	6 mg/kg drisapersen continuous (N=18)	6 mg/kg drisapersen intermittent (N=17)	Total (N=53)
Any AE by Phase				
On-Treatment AE	18 (100)	17 (94)	17 (100)	52 (98)
AE during Follow-up period	0	0	1 (6)	1 (2)
Drug-related AE (per investigator judgment	11 (61)	16 (89)	15 (88)	42 (79)
Deaths	0	0	0	0
Non-fatal SAE	2 (11)	1 (6)	2 (12)	5 (9)
Glossitis	1 (6)	0	0	1 (2)
Vomiting	0	1 (6)	0	1 (2)
Myocarditis	0	0	1 (6)	1 (2)
Oedema peripheral	0	1 (6)	0	1 (2)
Head injury	1 (6)	0	0	1 (2)
Pain in extremity	0	1 (6)	0	1 (2)
Haematuria	0	0	1 (6)	1 (2)
AE resulting in investigational product discontinuation or study withdrawal	0	0	0	0
AE of special interest	13 (72)	16 (89)	15 (88)	44 (83)
Injection site reaction	6 (33)	14 (78)	15 (88)	35 (66)
Renal toxicity	7 (39)	13 (72)	12 (71)	32 (60)
Inflammation	9 (50)	10 (56)	6 (35)	25 (47)
Coagulation abnormalities	4 (22)	2 (11)	0	6 (11)
Hepatic toxicity	1 (6)	2 (11)	0	3 (6)
Thrombocyte counts	0	0	0	0

The most commonly reported on-treatment AEs of special interest were injection site reaction AEs and renal AEs which occurred more frequently in the drisapersen treated groups than placebo. The most common AEs were injection site discolouration, injection site erythema, injection site haematoma, pyrexia and vomiting.

Most Common On-Treatment Adverse Events Reported in ≥2 Subjects in any Treatment Group (Safety Population)

	Number (%) of Subjects		
Preferred Term	**Placebo (combined) (N=18)**	**6 mg/kg drisapersen continuous (N=18)**	**6 mg/kg drisapersen intermittent (N=17)**
Any event	**18 (100)**	**17 (94)**	**17 (100)**
Injection site discolouration	1 (6)	9 (50)	8 (47)
Injection site erythema	2 (11)	8 (44)	8 (47)
Injection site haematoma	4 (22)	8 (44)	6 (35)
Pyrexia	5 (28)	8 (44)	5 (29)
Vomiting	6 (33)	7 (39)	5 (29)
Nasopharyngitis	4 (22)	9 (50)	3 (18)
Protein urine present	2 (11)	6 (33)	8 (47)
Headache	6 (33)	7 (39)	2 (12)
Abdominal pain	3 (17)	7 (39)	4 (24)
Cough	7 (39)	3 (17)	4 (24)
Diarrhoea	4 (22)	8 (44)	2 (12)
Fall	7 (39)	5 (28)	2 (12)
Upper respiratory tract infection	7 (39)	5 (28)	1 (6)
Rhinitis	6 (33)	5 (28)	1 (6)
Urine protein/creatinine ratio increased	2 (11)	4 (22)	5 29)
Procedural pain	3 (17)	3 (17)	4 (24)
Red blood cells urine positive	1 (6)	5 (28)	4 (24)

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Cytostatin C increased	3 (17)	3 (17)	3 (18)
Rash	7 (39)	1 (6)	1 (6)
Injection site pain	2 (11)	2 (11)	4 (24)
Injection site pruritis	0	5 (28)	3 (18)
Oropharyngeal pain	7 (39)	1 (6)	0
Back pain	5 (28)	0	2 (12)
Excoriation	4 (22)	1 (6)	2 (12)
Gastroenteritis	0	4 (22)	3 (18)
Proteinuria	2 (11)	2 (11)	3 (18)
Constipation	3 (17)	3 (17)	0
Ligament sprain	3 (17)	1 (6)	2 (12)
Haematuria	0	2 (11)	3 (18)
Injection site swelling	0	2 (11)	3 (18)
Nausea	2 (11)	2 (11)	1 (6)
Red blood cell count increased	1 (6)	4 (22)	0
Red blood cells urine	1 (6)	1 (6)	3 (18)
Rhinorrhoea	2 (11)	2 (11)	1 (6)
Blood fibrinogen decreased	2 (11)	2 (11)	0
Contusion	2 (11)	1 (6)	1 (6)
Fatigue	1 (6)	0	3 (18)
Haematoma	2 (11)	1 (6)	1 (6)
Injection site atrophy	0	1 (6)	3 (18)
Injection site induration	1 (6)	0	3 (18)
Injection site rash	1 (6)	3 (17)	0
Joint injury	1 (6)	1 (6)	2 (12)
Pain in extremity	0	1 (6)	3 (18)
Abdominal pain upper	0	1 (6)	2 (12)
Arthralgia	1 (6)	0	2 (12)
Chest pain	3 (17)	0	0
Gastroenteritis viral	2 (11)	1 (6)	0
Influenza like illness	2 (11)	1 (6)	0
Injection site macule	0	1 (6)	2 (12)
Injection site reaction	0	0	3 (18)
International normalised ratio increased	2 (11)	1 (6)	0
Laceration	3 (17)	0	0
Prothrombin time prolonged	3 (17)	0	0
Sinusitis	1 (6)	2 (11)	0
Vitamin D deficiency	2 (11)	1 (6)	0
White blodd cells urine positive	0	1 (6)	2 (12)
Aggression	2 (11)	0	0
Balanitis	0	2 (11)	0
Bronchitis	0	0	2 (12)
Myalgia	2 (11)	0	0
Post procedural discharge	0	2 (11)	0
Seasonal allergy	2 (11)	0	0
White blood cells urine	0	0	2 (12)

Note: One subject randomised to the placebo group experienced AEs of injection site haematoma and injection site pain at Day 56. PK data indicate that this subject inadvertently received active treatment on this date. These AEs have been reported for the placebo group.

AEs of special interest were defined as AEs resulting from any of the Laboratory Safety Parameter Stopping Criteria for hepatic or renal toxicity, thrombocyte counts, inflammation and coagulation abnormalities occurring and also any AEs resulting from injection site reactions.

A total of 13 (72%) subjects in the placebo group, 16 (89%) subjects in the continuous group and 15 (88%) subjects in the intermittent group had an AE of special interest. The most common AEs of special interest were injection site reactions and renal toxicity events. There were no clinically meaningful treatment differences in AEs related to inflammation, coagulation (aPTT), thrombocyte counts or

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hepatotoxicity.

Injection site reactions were observed in 33%, 78% and 88% of subjects in the placebo, continuous and intermittent treatment groups respectively. The most frequently reported injection site reaction AEs in the continuous and intermittent treatment groups were injection site discolouration, injection site erythema, and injection site haematoma. None were reported as a 'severe' or as a 'serious' adverse event. The intermittent treatment group in this study did not appear to result in a less frequent occurrence of injection site reactions.

Renal AEs were observed in 39%, 72% and 71% of subjects in the placebo, continuous and intermittent treatment groups respectively. The most frequently reported renal AEs in the continuous and intermittent treatment groups were protein urine present, urine protein/creatinine ratio increased, and red blood cells urine positive. As for the injection site reactions, the intermittent treatment group in this study did not appear to result in a less frequent occurrence of renal AEs.

Summary of Adverse Events of Special Interest (Safety Population)

	Number (%) of Subjects		
Special Interest Category Preferred Term	**Placebo (combined) (N=18)**	**6 mg/kg drisapersen continuous (N=18)**	**6 mg/kg drisapersen intermittent (N=17)**
Any event	**13 (72)**	**16 (89)**	**15 (88)**
Injection site reaction			
Any event	**6 (33)**	**14 (78)**	**15 (88)**
Injection site discolouration	1 (6)	9 (50)	8 (47)
Injection site erythema	2 (11)	8 (44)	8 (47)
Injection site haematoma	4 (22)	8 (44)	6 (35)
Injection site pain	2 (11)	2 (11)	4 (24)
Injection site pruritus	0	5 (28)	3 (18)
Injection site swelling	0	2 (11)	3 (18)
Injection site atrophy	0	1 (6)	3 (18)
Injection site induration	1 (6)	0	3 (18)
Injection site rash	1 (6)	3 (17)	0
Injection site macule	0	1 (6)	2 (12)
Injection site reaction	0	0	3 (18)
Injection site inflammation	0	1 (6)	1 (6)
Injection site urticarial	0	1 (6)	1 (6)
Injection site mass	0	1 (6)	0
Injection site oedema	0	0	1 (6)
Injection site scab	0	1 (6)	0
Skin lesion	1 (6)	0	0
Renal toxicity			
Any event	**7 (39)**	**13 (72)**	**12 (71)**
Protein urine present	2 (11)	6 (33)	8 (47)
Urine protein/creatinine ratio increased	2 (11)	4 (22)	5 (29)
Red blood cells urine positive	1 (6)	5 (28)	4 (24)
Cystatin C increased	3 (17)	3 (17)	3 (18)
Proteinuria	2 (11)	2 (11)	3 (18)
Haematuria	0	2 (11)	3 (18)
Red blood cells urine	1 (6)	1 (6)	3 (18)
White blood cells urine positive	0	1 (6)	2 (12)
White blood cells urine	0	0	2 (12)
Albuminuria	0	0	1 (6)
Myoglobinuria	0	1 (6)	0
Protein total increased	0	0	1 (6)
Urine analysis abnormal	1 (6)	0	0
Inflammation			
Any event	**9 (50)**	**10 (56)**	**6 (35)**
Pyrexia	5 (28)	8 (44)	5 (29)

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Influenza like illness	2 (11)	1 (6)	0
Blood fibrinogen increased	1 (6)	1 (6)	0
Blood fibrinogen abnormal	0	0	1 (6)
Body temperature increased	0	1 (6)	0
Complement factor C3 decreased	0	1 (6)	0
Haptoglobin increased	1 (6)	0	0
Neutrophil toxic granulation present	1 (6)	0	0
Coagulation abnormalities			
Any event	**4 (22)**	**2 (11)**	**0**
Blood fibrinogen decreased	2 (11)	2 (11)	0
International normalised ratio increased	2 (11)	1 (6)	0
Prothrombin time prolonged	3 (17)	0	0
Activated partial thromboplastin time prolonged	1 (6)	1 (6)	0
Coagulation time prolonged	1 (6)	1 (6)	0
Hepatic toxicity			
Any event	**1 (6)**	**2 (11)**	**0**
Alanine aminotransferase increased	1 (6)	1 (6)	0
Hepatitis	1 (6)	0	0
Hepatomegaly	0	1 (6)	0
Ultrasound liver abnormal	0	1 (6)	0
Thrombocyte counts			
Any event	**0**	**0**	**0**

PHARMACOKINETICS RESULTS:

At Week 29 the median concentration-time profiles of both dosing regimens largely overlapped, apart from the predose levels, as at Week 29 the last dose in a cycle for the intermittent regimen was given, and therefore the predose level for this regimen was higher than for the continuous regimen. In concordance with the largely overlapping concentration-time profiles, the PK parameters of AUC, Cmax and tmax were also similar. Population PK modelling would be needed, however, to conclude if the average systemic exposure is the same between both treatment groups.

Summary of Drisapersen Pharmacokinetic Parameters following administration of Drisapersen 3 or 6 mg/kg/wk at Week 23

	6 mg/kg drisapersen continuous		6 mg/kg drisapersen intermittent	
Parameter	**n**	**Value**	**n**	**Value**
Cmax (ng/mL)[a]	18	4852 (47.2%)	17	4806 (47.7%)
AUC[0-t] (ng.hr/mL)[a]	18	50614 (30.9%)	17	60688 (42.5%)
AUC[0-24] (ng.hr/mL)[a]	18	45538 (29.0%)	17	52495 (38.8%)
Tmax (hr)[b]	18	2.00 (1.98-4.03)	17	2.00 (0.33-4.00)

a. Geometric mean (CV%)
b. Median (range)

As expected, the predose concentrations of drisapersen for the continuous dosing regimen increased over time to a steady state. The predose concentrations for the intermittent dosing regimen increased and decreased over time, but this was in a consistent pattern with the dosing cycles.

After 24 weeks of either continuous or intermittent dosing at 6 mg/kg, there appeared not to be a relationship between the individual predose plasma concentrations and drug concentrations in muscle at Week 25. However, a weak relationship between the muscle concentrations and the effect on dystrophin as measured by immunofluorescence was observed at Week 25.

CONCLUSION:

- At Week 29, the pharmacokinetic parameters Cmax, tmax and AUC are similar between the continuous and intermittent arms. Population PK modelling is required to confirm if this also means that the average systemic exposure is the same for both dosing regimens.
- At Week 25, there was a weak relationship between muscle concentrations and percentage difference in dystrophin compared to baseline as measured by immunofluorescence, but there was no clear relationship between muscle concentrations and corresponding trough levels in plasma.

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- At Week 25, for the primary efficacy analysis of change from Baseline in 6MWD, a statistically significant and clinically meaningful treatment benefit (35.09 m) over placebo in 6MWD was observed for the continuous regimen.
- At Week 49, a clinically meaningful treatment difference (similar magnitude to Week 25 of 35.84 m) over placebo in 6MWD was observed for the continuous regimen, though the results were no longer statistically significant due to increased variability.
- The difference in mean 6MWD observed for subjects treated with continuous drisapersen versus placebo at Week 25 was maintained at Week 49. Following an initial improvement in 6MWD during the first 24 weeks of the study, subjects receiving continuous treatment showed a mean decrease, approaching baseline values by Week 49, compared to a gradual decrease throughout the study for subjects receiving placebo.
- The 6MWD results for the continuous regimen were supported by trends in favour of drisapersen (compared to placebo) for the majority of the secondary endpoints at Week 25 and Week 49 (timed function tests [rise from floor, 10 m walk/run, and 4 stair climb/descent], NSAA and CK) and suggests beneficial effects of the drug administered weekly.
- At Week 25, no statistically significant or clinically meaningful treatment benefit (3.51 m) over placebo in 6MWD was observed for the intermittent regimen.
- At Week 49, a treatment benefit (27.08 m) over placebo in 6MWD was observed for the intermittent regimen, although the results were not statistically significant.
- There was little change from baseline in the mean 6MWD throughout the 48 weeks of the study in the intermittent regimen, leading to a benefit over placebo by Week 49.
- There were inconsistent results for the intermittent regimen across secondary efficacy endpoints at Week 25. At Week 49, there were trends in favour of the intermittent group (compared to placebo) for timed function tests (rise from floor, 10 m walk/run, and 4 stair climb/descent), NSAA and CK.
- Measurement of exon skipping and dystrophin protein expression by WB and dystrophin restoration at the membrane as measured by a reproducible analysis of at least 1000 individual fibre membranes by IFA indicates that a pharmacodynamics effect is associated with drisapersen treatment. Further investigation is needed to better understand the individual variability of treated subjects.
- Drisapersen 6 mg/kg administered weekly or intermittently was generally well tolerated, though the majority of subjects treated with drisapersen reported AEs related to injection site reactions and renal toxicity (subclinical proteinuria).
- There were no clinically meaningful treatment differences in AEs related to inflammation, coagulation/haematology (aPTT and thrombocytes) or hepatotoxicity.
- There were no withdrawals from the study because of AEs and there were no significant safety concerns related to drisapersen identified.
- The intermittent regimen used in this 48-week study did not appear to confer any safety advantages over a continuous regimen.
- No new safety signals were detected in this study. Safety issues that have been identified during this clinical study for drisapersen are manageable and thus the current safety profile with drisapersen is considered acceptable given the benefits that may be afforded to patients with DMD.

Date of the report:

29-AUG--2013