Sponsor: Sanofi **Drug substance:** GZ402666 (neoGAA)	**Study Identifiers:** U1111-1144-7725; NCT01898364; EudraCT number: 2012-004167-42 **Study code:** TDR12857
Title of the study: An open-label, multicenter, multinational, ascending dose study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of repeated biweekly infusions of neoGAA in naïve and alglucosidase alfa treated late-onset Pompe disease patients	
Study centers: 17 centers: 7 in the USA, 3 in France, 1 in Belgium, 1 in Denmark, 1 in The Netherlands, 1 in the UK, and 3 in Germany	
Study period: Date first participant enrolled: 19/Aug/2013 Date last participant completed: 25/Feb/2015 Study Status: Completed	
Phase of development: 1	
Objectives: Group 1 To determine in treatment naïve patients with late-onset Pompe disease: • The safety and tolerability of neoGAA • The pharmacokinetic (PK) parameters of neoGAA • The pharmacodynamic (PD) effects of neoGAA on skeletal muscle • The effect of neoGAA on exploratory efficacy endpoints Group 2 To determine in alglucosidase alfa treated patients with late-onset Pompe disease: • The safety and tolerability of neoGAA • The PK parameters of neoGAA • The PD effects of neoGAA on skeletal muscle • The effect of neoGAA on exploratory efficacy endpoints	
Methodology: This was a multicenter, multinational, open-label, ascending dose, repeated every other week (qow) intravenous (IV) infusion study of neoGAA (3 dose levels) in late-onset Pompe disease patients naïve to treatment (Group 1) and in late-onset Pompe disease patients previously treated with alglucosidase alfa (Group 2). The groups were initiated simultaneously. Eligible patients in each group received an IV infusion of neoGAA at doses of 5, 10, or 20 mg/kg of body weight every other week (qow) for 24 weeks.	
Number of participants: Planned: 21 Treated: 24 **Evaluated:** Safety: 24 Pharmacokinetics: 24 Pharmacodynamics: 24 Efficacy: 24	

Diagnosis and criteria for inclusion: Male and female patients ≥18 years of age, with confirmed acid α-glucosidase (GAA) enzyme deficiency from any tissue source and/or confirmed GAA gene mutation, and without known cardiac hypertrophy. The patients were able to ambulate 50 m (approximately 160 feet) without stopping and without an assistive device. The patients had a forced vital capacity (FVC) in the upright position of ≥50% predicted. For Group 1, late-onset Pompe disease patients were naïve to treatment and for Group 2, late onset Pompe disease patients had been previously treated with alglucosidase alfa for at least 9 months.

Study treatments:

Investigational medicinal product: NeoGAA (recombinant human α-glucosidase conjugated with synthetic bis mannose 6 phosphate-Man6 glycan)

Formulation: A sterile, non-pyrogenic, lyophilized product in a single-use 20 mL vial. Each vial was reconstituted with sterile water and further diluted into dextrose.

Route of administration: IV infusion with a step-wise increase in infusion rate from 1 to 7 ml/kg/h

Dose regimen: 5 mg/kg, 10 mg/kg, or 20 mg/kg qow for 24 weeks

Duration of treatment: Thirteen infusions qow for 24 weeks (Week 1 to Week 25).

Duration of observation: Up to a maximum of approximately 42 weeks, including screening (within 90 days), 1 treatment period (24 weeks, including 13 IV infusions qow), a posttreatment evaluation visit (2 weeks after the last infusion; Week 27), and an end-of-study (EOS) visit (4 weeks after the last infusion; Week 29). The Week 27 visit was the EOS if the patient enrolled in an extension study or started treatment with a commercially available enzyme replacement therapy.

Criteria for evaluation:

Safety: Patients were monitored for safety via adverse events (AEs) spontaneously reported by the patients or observed by the Investigator, infusion associated reactions (IARs), standard clinical laboratory evaluations (biochemistry, hematology, urinalysis), vital signs (heart rate, systolic and diastolic blood pressure, oxygen saturation, and respiratory rate), temperature, 12 lead electrocardiogram (ECG; automatic readings), physical examination, immunogenicity (anti-neoGAA and anti alglucosidase alfa antibodies), and body weight.

Pharmacokinetics: The following PK parameters were calculated for plasma concentrations of neoGAA after single and multiple doses using noncompartmental methods: maximum plasma concentration observed (C_{max}), time to reach Cmax (t_{max}), area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time tlast (AUC_{last}), area under the plasma concentration versus time curve extrapolated to infinity (AUC), terminal half-life ($t_{1/2z}$), total body clearance (CL), and volume of distribution at steady state (V_{ss}).

Pharmacodynamics: The following PD parameters were assessed after single and multiple dose administration of neoGAA: skeletal muscle glycogen content, qualitative (T1-weighted Mercuri scoring) and quantitative (Dixon, T2) skeletal muscle magnetic resonance imaging (MRI), skeletal muscle, and urinary Hex4.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pharmacokinetics: Blood samples were collected for the determination of neoGAA concentrations in plasma at Weeks 1 (Day 1), 13, and 25, prior to the start of neoGAA infusion (predose), immediately before the infusion rate changed from 1 to 3 mg/kg/h, from 3 to 5 mg/kg/h, and from 5 to 7 mg/kg/h, immediately before the end of the infusion, and at 1, 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48 hours after the end of the infusion. Plasma concentrations of neoGAA were determined using a validated fluorometric assay using a 4-methylumbelliferyl-α-D-glucoside (4-MUG) substrate to detect neoGAA activity, with a lower limit of quantification of 13 ng/mL.

Pharmacodynamics: Magnetic resonance imaging and skeletal biopsies were performed at baseline (within 21 days) and at the posttreatment evaluation visit (Week 27). Sites were instructed to sample normal appearing muscle tissue (as determined by MRI guidance, if feasible) to prevent biopsy of fat or fibrotic tissue. Skeletal muscle glycogen content was measured by computer-assisted histomorphometry. To accurately represent the distribution of glycogen across the entire specimen, up to 10 blocks were processed per sample-time point for each patient. One slide from each block was analyzed; values obtained were then combined to obtain an average value and standard deviation for each patient-time point. Urine Hex4 samples were assessed at baseline (within 24 hours prior to the start of infusion), and qow prior to neoGAA infusion.

Immunogenicity: Blood samples for anti-neoGAA immunoglobulins G and M (IgG and IgM) and neutralizing antibodies in positive patients were collected at baseline (within 24 hours prior to the start of the first infusion) and Weeks 1, 5, 9, 13, 17, 21, 25, 27, and 29. In addition, for Group 2 patients, samples at Weeks 1 and 25 were analyzed for anti-alglucosidase alfa IgG antibodies.

Pharmacogenetics: Pharmacogenetic samples were collected at baseline (within 24 hours prior to the start of the first infusion) for mRNA and miRNA analysis, serum expression analysis, and optional DNA analysis. Samples for GAA and angiotensin converting enzyme (ACE) genotyping were also taken at baseline (within 24 hours prior to infusion), if historical samples were not available.

Statistical methods: The full analysis set study population was used for all analyses, including safety, PD, PK, and efficacy. This analysis set consisted of all patients who received at least 1 complete infusion of neoGAA.

Safety: The safety evaluation was based on the review of descriptive statistics (summary tables) and individual data for AEs, immunogenicity, clinical laboratory, vital sign, and ECG parameters. Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 17.1) and numbers of patients with treatment-emergent adverse events (TEAEs) were summarized by system-organ class (SOC), preferred term (PT), and relationship to study drug for each group and dose level. Infusion associated reactions, defined as those considered to be treatment related by the investigator, and those that occurred within 24 hours after the start of infusion, were summarized by SOC and PT for each group and dose level, and individual events were listed. In addition, summary tables of AEs and IARs, which occurred ≤2 hours, from >2 to ≤24 hours, from >24 to ≤48 hours, and >48 hours postinfusion, were presented by SOC and PT for each group and dose level. Descriptive statistics by study visit, group, and dose level were presented for actual values and changes from baseline for clinical laboratory and vital sign parameters. In addition, a subset of clinical laboratory data were summarized in shift tables. Electrocardiogram data were listed.

Analysis of anti-neoGAA antibody titers during the course of the study was used to determine the time to patients becoming anti-neoGAA antibody positive (seroconverted), and their maximum titer value during the study (peak titer). Anti-neoGAA antibody titers over time, peak titer, and time to seroconversion were summarized (descriptive statistics) and listed for each group and dose level. Patients with titers classified as "sustained and elevated" (peak titer ≥25,600 and a last titer value ≥peak titer, or were 1 dilution level lower than the peak titer), "diminished" (seroconverted patient with a last titer at least 2-fold dilutions lower than the peak titer), or "tolerized" (seroconverted patient who subsequently has ≥2 consecutive samples that were negative) were presented in a frequency table. The presence/absence of inhibitory antibodies to neoGAA were listed by group and dose level.

Pharmacokinetics: NeoGAA plasma concentrations and PK parameters were summarized using descriptive statistics by group, dose level, and study week.

Pharmacodynamics: For each of the 3 PD variables studied (glycogen content in quadriceps muscle tissues, skeletal muscle MRI assessments, and urinary Hex4), descriptive statistics for both observed and changes from baseline for each study week assessed were calculated overall, by group, and by dose level.

Efficacy: For each of the 7 functional efficacy variables studied (6MWT, GSGC, GMFM-88, QMFT, HHD, PedsQL, and PFT), changes from baseline to Week 13 and change from baseline to Week 25 were calculated. For each group, patient results and changes from baseline were plotted over time with a mean population line and 95% confidence intervals (CI). For each variable, results were provided overall, by group, and by dose level.

Each PD and efficacy functional endpoint was summarized using a Spearman rank correlation.

Summary Results:

Population characteristics:

Group 1: A total of 10 patients were enrolled and treated, and 9 completed the study (5 mg/kg, n = 3; 10 mg/kg, n = 3; 20 mg/kg, n =3). The mean age at enrollment was 44.8 years, and 3 (30.0%) of the patients were male. The mean age at Pompe disease diagnosis was 43.3 years and 20.0% used some kind of walking device at baseline. One patient (5 mg/kg) discontinued treatment due to serious adverse events (SAE) occurring during the ninth neoGAA infusion.

Group 2: A total of 14 patients were enrolled, treated, and 12 completed the study (5 mg/kg, n =3; 10 mg/kg, n = 4; 20 mg/kg, n = 5). The mean age at enrollment was 46.7 years, and 9 (64.3%) of the patients were male. The mean age at Pompe disease diagnosis was 36.3 years, and 21.4% used some kind of walking device at baseline. Two patients withdrew consent from the study for non AE related-reasons; 1 patient (5 mg/kg) following the last neoGAA infusion and 1 patient (20 mg/kg) following their eighth neoGAA infusion.

Safety results:

Group 1: There were no deaths and 2 drug-related SAEs (respiratory distress and chest discomfort) reported in 1 patient (5 mg/kg) who subsequently discontinued treatment. Both SAEs resolved without sequelae. Eight (80.0%) patients reported at least 1 TEAE for a total of 83 AEs, with the majority of TEAEs being mild across all dose levels. Across all doses, common TEAEs regardless of relationship included headache (8 events in 4 patients), rash (8 events in 3 patients), dizziness (7 events in 3 patients), nausea (4 events in 3 patients), oral herpes (4 events in 1 patient), dysmenorrhea (4 events in 2 patients), and diarrhea (3 events in 3 patients).

Related treatment-emergent adverse events by preferred term in Group 1 patients – Full analysis set

Preferred Term	Group 1: 5 mg/kg (N=4) n (%)	Group 1: 10 mg/kg (N=3) n (%)	Group 1: 20 mg/kg (N=3) n (%)	Group 1: Combined (N=10) n (%)
Any Events	3 (75.0)	2 (66.7)	1 (33.3)	6 (60.0)
Fatigue	0	2 (66.7)	0	2 (20.0)
Nausea	2 (50.0)	0	0	2 (20.0)
Chest discomfort	1 (25.0)	0	0	1 (10.0)
Cough	1 (25.0)	0	0	1 (10.0)
Dizziness	1 (25.0)	0	0	1 (10.0)
Dyspnoea	1 (25.0)	0	0	1 (10.0)
Erythema	0	0	1 (33.3)	1 (10.0)
Flushing	1 (25.0)	0	0	1 (10.0)
Gastrooesophageal reflux disease	1 (25.0)	0	0	1 (10.0)
Headache	0	1 (33.3)	0	1 (10.0)
Myalgia	0	1 (33.3)	0	1 (10.0)
Rash	1 (25.0)	0	0	1 (10.0)
Respiratory distress	1 (25.0)	0	0	1 (10.0)

Note: Group 1 = Naive Pompe disease patients, Group 2 = Pompe disease patients previously treated with alglucosidase alfa

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Overall, 11 IAR events were reported in 4 of the Group 1 patients. All IARs were non-serious except 2 IARs/SAEs of respiratory distress and chest discomfort in 1 patient. The most commonly reported IAR event was flushing (2 out of 11 events), with all other IAR events occurring once.

One IAR event of erythema was reported in 1 patient at 20 mg/kg in association with their fourth infusion. Samples collected following this event were negative for anti-neoGAA IgE antibodies and complement activation and within the normal range for tryptase (2.4 µg/L, normal range ≤12.5 µg/L). Six IAR events including chest discomfort, cough, respiratory distress, flushing, dizziness, and nausea were reported in 1 patient at 5 mg/kg during their ninth neoGAA infusion (Week 17). Samples collected following these events were negative for anti-neoGAA IgE antibodies, positive for complement activation, and within the normal range for tryptase (3.6 µg/L). This patient was negative for anti-neoGAA antibodies at screening, and seroconverted at Week 13 with a titer of 1600, and a titer of 3200 immediately prior to the 6 IAR events that occurred during their ninth infusion.

No adverse reactions associated with clinical laboratory abnormalities or ECG assessments were reported. Nine (90.0%) patients developed antibodies to neoGAA during the treatment period, with a maximum titer of 25600 observed across all of Group 1. One patient (5 mg/kg) tested positive for antibodies that inhibited enzyme uptake at Week 27; none of the anti neoGAA antibodies inhibited enzymatic activity.

Group 2: There were no deaths and 1 unrelated SAE of gastrointestinal hemorrhage (5 mg/kg) reported in 1 patient, which resolved without sequelae. Twelve (85.7%) patients reported at least 1 TEAE for a total of 93 AEs, with the majority of TEAEs being mild across all dose levels. Across all doses, common TEAEs regardless of relationship included headache (10 events in 3 patients), myalgia (6 events in 1 patient), musculoskeletal pain (4 events in 3 patients), falls (4 events in 2 patients), and nasopharyngitis (3 events in 3 patients).

Related treatment-emergent adverse events by preferred term in Group 2 patients – Full analysis set

Preferred Term	Group 2: 5 mg/kg (N=4) n (%)	Group 2: 10 mg/kg (N=4) n (%)	Group 2: 20 mg/kg (N=6) n (%)	Group 2: Combined (N=14) n (%)
Any Events	3 (75.0)	1 (25.0)	3 (50.0)	7 (50.0)
Abdominal pain	0	1 (25.0)	0	1 (7.1)
Asthenia	0	0	1 (16.7)	1 (7.1)
Balanoposthitis	0	0	1 (16.7)	1 (7.1)
Diarrhoea	0	1 (25.0)	0	1 (7.1)
Dizziness	1 (25.0)	0	0	1 (7.1)
Dyspnoea	1 (25.0)	0	0	1 (7.1)
Facial pain	1 (25.0)	0	0	1 (7.1)
Fatigue	1 (25.0)	0	0	1 (7.1)
Headache	1 (25.0)	0	0	1 (7.1)
Hypersensitivity	0	0	1 (16.7)	1 (7.1)
Hypotension	1 (25.0)	0	0	1 (7.1)
Infusion site reaction	0	1 (25.0)	0	1 (7.1)
Muscle spasms	1 (25.0)	0	0	1 (7.1)
Myalgia	1 (25.0)	0	0	1 (7.1)
Pruritus	0	0	1 (16.7)	1 (7.1)
Pulmonary function test decreased	1 (25.0)	0	0	1 (7.1)
Rash generalised	0	0	1 (16.7)	1 (7.1)
Somnolence	0	0	1 (16.7)	1 (7.1)

Note: Group 1 = Naive Pompe disease patients, Group 2 = Pompe disease patients previously treated with alglucosidase alfa

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Overall, 14 IAR events were reported in 4 of the Group 2 patients. All IARs were non-serious. The most commonly reported IAR events included myalgia (6 out of 14 events, in 1 patient) and headache (2 out of 14 events in 1 patient), with all other IAR events occurring once.

Three IAR events (hypersensitivity, pruritus, and generalized rash) were reported in 1 patient at 20 mg/kg during their thirteenth neoGAA infusion. Samples collected in association with the events were negative for anti-neoGAA IgE antibodies, positive for complement activation, and within the normal range for tryptase (4.7 µg/L).

There were no adverse reactions associated with ECG assessments reported.

In Group 2 patients, immunogenicity assessments included evaluations for antibodies against neoGAA and for IgG antibodies against alglucosidase alfa. Five (35.7%) Group 2 patients tested positive for antibodies to neoGAA at Screening and Week 1, with a maximum titer of 1600 observed at Week 1. Of the 9 patients testing negative at Screening and Week 1 for anti neoGAA antibodies, 2 patients seroconverted with antibodies to neoGAA during the neoGAA treatment period with a maximum titer of 1600. None of the anti-neoGAA antibodies inhibited enzyme uptake or enzymatic activity.

For the alglucosidase alfa, 7 (50.0%) Group 2 patients tested positive for IgG antibodies to alglucosidase alfa at Week 1, with a maximum titer of 6400 observed across all patients. Of the 7 Group 2 patients testing negative at Week 1 for anti alglucosidase alfa antibodies, 3 patients seroconverted with antibodies to alglucosidase alfa during the neoGAA treatment period, with a maximum observed titer of 3200.

Pharmacokinetic results:

Group 1: NeoGAA plasma concentrations appeared to decline mono-exponentially after the end of the IV infusion with a mean terminal half-life ($t_{1/2z}$) of approximately 1.0 hour. NeoGAA exposure increased with dose; the mean systemic plasma clearance (CL) ranged from 0.92 to 1.28 L/h; and the mean steady state volume of distribution (V_{ss}) ranged from 2.40 to 3.02 L. The PK parameters appeared similar at Week 1, Week 13, and Week 25, indicating no apparent effect of qow dosing on neoGAA PK.

Mean ±SD (geometric mean) [CV%] of neoGAA PK parameters for Group 1 at Week 1 and Week 25

	Week 1 (1st infusion) Dose			Week 25 (13th infusion) Dose		
Parameter	5 mg/kg (n=4)	10 mg/kg (n=3)	20 mg/kg (n=3)	5 mg/kg (n=3)	10 mg/kg (n=3)	20 mg/kg (n=3)
C_{max} (ng/mL)	82300 ± 6690 (82100) [8.1]	190000 ± 40100 (187000) [21.1]	302000 ± 107000 (291000) [35.6]	89100 ± 11000 (88600) [12.3]	162000 ± 26500 (161000) [16.4]	350000 ± 105000 (341000) [29.9]
t_{max}[a] (hr)	1.71 (1.47 - 2.58)	2.30 (2.23 - 2.30)	3.83 (3.75 - 4.00)	1.43 (1.43 - 1.62)	2.35 (2.35 - 2.45)	3.92 (3.75 - 4.50)
AUC_{last} (ng•h/mL)	259000 ± 37600 (259000) [14.5]	529000 ± 79600 (525000) [15.0]	1520000 ± 806000 (1400000) [53.0]	264000 ± 50200 (261000) [19.0]	565000 ± 89800 (560000) [15.9]	1560000 ± 637000 (1490000) [40.7]
AUC (ng•h/mL)	259000 ± 37600 (257000) [14.5]	529000 ± 79600 (525000) [15.0]	1520000 ± 806000 (1400000) [53.0]	264000 ± 50200 (261000) [19.0]	565000 ± 89800 (560000) [15.9]	1560000 ± 637000 (1490000) [40.7]
$t_{1/2z}$ (hr)	0.784 ± 0.369 (0.727) [47.1]	0.833 ± 0.493 (0.750) [59.2]	0.778 ± 0.217 (0.757) [27.9]	0.777 ± 0.0455 (0.776) [5.9]	0.856 ± 0.235 (0.835) [27.5]	1.03 ± 0.242 (1.01) [23.5]
CL (mL/h)	1260 ± 203 (1240) [16.2]	1240 ± 386 (1190) [31.3]	989 ± 278 (959) [28.1]	1230 ± 229 (1220) [18.5]	1180 ± 176 (1170) [14.9]	917 ± 214 (901) [23.4]
V_{ss} (mL)	2620 ± 396 (2600) [15.1]	2480 ± 626 (2420) [25.3]	2900 ± 439 (2870) [15.2]	2400 ± 316 (2390) [13.1]	2670 ± 109 (2670) [4.1]	2930 ± 233 (2930) [7.9]

a Median (Min - Max)

Group 2: NeoGAA plasma concentrations appeared to decline mono-exponentially after the end of the IV infusion with a mean terminal half-life ($t_{1/2z}$) of approximately 1.0 hour. NeoGAA exposure increased with dose; the mean systemic plasma clearance (CL) ranged from 1.0 to 1.57 L/h; and the mean steady state volume of distribution (V_{ss}) ranged from 2.83 to 3.71 L. The PK parameters appeared similar at Week 1, Week 13, and Week 25, indicating no apparent effect of qow dosing on neoGAA PK.

Mean ±SD (geometric mean) [CV%] of neoGAA PK parameters for Group 2 at Week 1 and Week 25

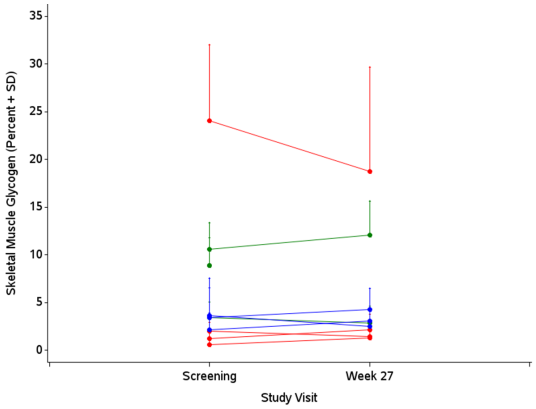
	Week 1 (1st infusion) Dose (mg/kg)			Week 25 (13th infusion) Dose (mg/kg)		
Parameter	5 mg/kg (n=4)	10 mg/kg (n=4)	20 mg/kg (n=6)	5 mg/kg (n=4)	10 mg/kg (n=4)	20 mg/kg (n=5)
C_{max} (ng/mL)	77400 ± 22400 (74800) [29.0]	168000 ± 36800 (165000) [21.9]	321000 ± 125000 (303000) [38.9]	97100 ± 36400 (90900) [37.6]	164000 ± 19100 (163000) [11.6]	299000 ± 47500 (296000) [15.9]
t_{max}[a] (hr)	1.84 (1.38 - 2.60)	2.27 (1.75 - 2.43)	3.83 (3.68 - 4.73)	1.97 (1.50 - 2.62)	2.51 (2.25 - 3.35)	3.83 (3.68 - 5.58)
AUC_{last} (ng•h/mL)	246000 ± 81500 (236000) [33.1]	631000 ± 118000 (622000) [18.7]	1500000 ± 502000 (1430000) [33.4]	306000 ± 79900 (298000) [26.1]	642000 ± 46900 (641000) [7.3]	1530000 ± 434000 (1480000) [28.5]
AUC (ng•h/mL)	246000 ± 81500 (236000) [33.1]	631000 ± 118000 (622000) [18.7]	1500000 ± 502000 (1430000) [33.4]	306000 ± 79900 (298000) [26.1]	642000 ± 46900 (641000) [7.3]	1530000 ± 434000 (1480000) [28.5]
$t_{1/2z}$ (hr)	0.668 ± 0.299 (0.628) [44.8]	1.03 ± 0.628 (0.920) [61.1]	0.876 ± 0.232 (0.852) [26.5]	1.53 ± 0.520 (1.47) [33.8]	0.712 ± 0.103 (0.706) [14.5]	1.06 ± 0.435 (1.00) [40.9]
CL (mL/h)	1570 ± 362 (1530) [23.1]	1280 ± 246 (1270) [19.2]	1060 ± 198 (1050) [18.6]	1240 ± 342 (1210) [27.7]	1230 ± 56.3 (1230) [4.6]	998 ± 204 (982) [20.5]
V_{ss} (mL)	3710 ± 1520 (3490) [40.9]	3210 ± 839 (3140) [26.1]	3310 ± 731 (3250) [22.1]	2880 ± 704 (2820) [24.4]	3060 ± 114 (3060) [3.7]	3290 ± 755 (3210) [23.0]

a Median (Min - Max)

Pharmacodynamic results:

Group 1: Quadriceps biopsies were available at both baseline and at Week 27 for 9 of the Group 1 patients that completed the study. Sites were instructed to sample normal appearing muscle tissue (as determined by MRI guidance, if feasible) to prevent biopsy of fat or fibrotic tissue. Across all Group 1 patients the mean (SD) skeletal muscle glycogen level at baseline was 6.0% (7.13%), with reduced levels from baseline in 4 out of 9 patients at Week 27 (decrease of 5.34% and 0.57% in 2 respective patients at 5 mg/kg; decrease of 0.55% in 1 patient at 10 mg/kg; and decrease of 1.12% in 1 patient at 20 mg/kg).

Individual +SD skeletal muscle glycogen levels at baseline and at Week 27 in Group 1 patients



Group 1: 5 mg/kg (red), 10 mg/kg (green), 20 mg/kg (blue)

Evaluation of intact muscle and fatty replacement in the upper and lower leg with Mercuri scores, Dixon, and T2 MRI with and without B1 mapping, demonstrated minimal changes throughout the study. Mean percentage reductions (SD) from baseline at Week 25 in urinary Hex4 concentrations were 30.3% (18.63%), 36.0% (6.87%), and 13.2% (40.63%) in the respective 5, 10, and 20 mg/kg neoGAA groups.

Evaluation of intact muscle and fatty replacement by MRI in Group 1 patients [Mean (SD)] – Full analysis set

	Group 1:5 mg/kg (N=4)		Group 1:10 mg/kg (N=3)		Group 1:20 mg/kg (N=3)	
	Baseline	Week 27	Baseline	Week 27	Baseline	Week 27
Lower Leg Assessment						
Mercuri Grading	1.4 (0.39)	1.4 (0.38)	1.1 (0.07)	1.1 (0.07)	1.5 (0.71)	1.5 (0.71)
Dixon	5.5 (2.62)	5.8 (2.86)	4.5 (0.66)	4.8 (0.91)	7.8 (4.11)	7.8 (3.00)
T2 with B1	37.1 (2.04)	37.5 (3.25)	36.6 (2.02)	36.2 (2.83)	37.9 (1.83)	37.5 (2.60)
T2 without B1	37.6 (2.22)	38.1 (3.02)	36.7 (1.93)	36.4 (2.89)	37.9 (1.69)	37.7 (2.19)
Upper Leg Assessment						
Mercuri Grading	2.4 (0.33)	2.6 (0.30)	1.2 (0.03)	1.3 (0.08)	2.0 (1.02)	2.0 (1.02)
Dixon	9.6 (4.26)	11.2 (4.28)	6.3 (0.62)	7.1 (0.59)	7.8 (2.41)	9.0 (2.17)
T2 with B1	36.7 (1.31)	37.4 (3.20)	38.4 (1.30)	36.9 (0.50)	36.3 (1.50)	34.7 (2.49)
T2 without B1	37.0 (1.67)	38.1 (2.30)	39.0 (0.77)	37.4 (0.92)	36.5 (1.55)	35.1 (2.68)

Note: Group 1 = Naive Pompe disease patients, Group 2 = Pompe disease patients previously treated with alglucosidase alfa

Mercuri Grading (1) Normal appearance, 2) Mild involvement, 3) Moderate involvement, and 4) Severe involvement), Dixon (% fat): degree of fatty infiltration.

T2 with B1 (ms) with abnormal value defined as >39ms, T2 without B1 (ms), and Trophicity Index (ms)
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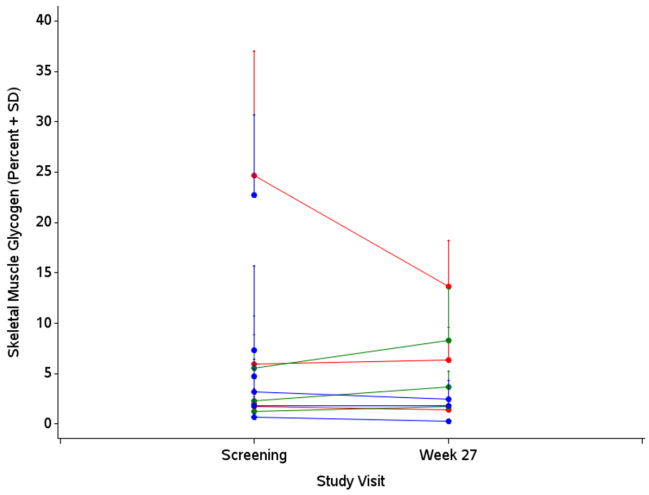
Group 2: Quadriceps biopsies were available at both baseline and at Week 27 for 9 Group 2 patients that completed the study. Across all Group 2 patients the mean (SD) skeletal muscle glycogen level at baseline was 6.5% (7.92%), with reduced levels from baseline in 5 out of 9 patients at Week 27 (decreases of 0.34% and 11.03% in 2 respective patients at 5 mg/kg; and decreases of 0.01%, 0.40%, and 0.77% in 3 respective patients at 20 mg/kg).

Individual mean +SD skeletal muscle glycogen levels at baseline and at Week 27 in Group 2 patients



Group 2: 5 mg/kg (red), 10 mg/kg (green), 20 mg/kg (blue)

Evaluation of intact muscle and fatty replacement in the upper and lower leg with Mercuri scores, Dixon, and T2 MRI with and without B1 mapping demonstrated minimal change throughout the study in Group 2 patients. Mean percentage reductions (SD) from baseline at Week 25 in urinary Hex4 concentrations were 7.5% (38.77%), 12.0% (29.72%), and 20.5% (27.77%) in the respective 5, 10, and 20 mg/kg neoGAA groups.

Evaluation of intact muscle and fatty replacement by MRI in Group 2 patients [Mean (SD)] – Full analysis set

	Group 2:5 mg/kg (N=4)		Group 2:10 mg/kg (N=4)		Group 2:20 mg/kg (N=6)	
	Baseline	Week 27	Baseline	Week 27	Baseline	Week 27
Lower Leg Assessment						
Mercuri Grading	1.1 (0.06)	1.3 ()	1.5 (0.44)	1.3 (0.36)	1.4 (0.37)	1.4 (0.39)
Dixon	6.9 (1.49)	5.1 ()	6.3 (2.04)	6.7 (2.39)	8.0 (2.52)	8.2 (2.43)
T2 with B1	41.5 (3.53)	43.2 (3.87)	39.4 (2.54)	39.8 (2.21)	37.4 (2.90)	38.3 (2.77)
T2 without B1	41.8 (3.77)	43.7 (4.16)	38.7 (0.83)	38.1 (1.19)	37.5 (2.74)	37.8 (2.81)
Upper Leg Assessment						
Mercuri Grading	2.6 (0.72)	1.5 ()	2.4 (0.73)	2.3 (0.86)	2.1 (0.60)	2.1 (0.70)
Dixon	29.4 (23.24)	14.5 (11.55)	8.8 (7.60)	8.6 (6.35)	15.1 (10.79)	18.5 (12.47)
T2 with B1	37.4 (1.36)	41.3 (1.66)	37.9 (1.64)	39.0 (1.66)	35.4 (3.75)	35.3 (5.77)
T2 without B1	38.0 (0.97)	42.4 (1.71)	38.8 (1.73)	37.5 (1.11)	36.1 (3.82)	35.5 (5.55)

Note: Group 1 = Naive Pompe disease patients, Group 2 = Pompe disease patients previously treated with alglucosidase alfa

Mercuri Grading (1) Normal appearance, 2) Mild involvement, 3) Moderate involvement, and 4) Severe involvement), Dixon (% fat): degree of fatty infiltration,

T2 with B1 (ms) with abnormal value defined as >39ms, T2 without B1 (ms), and Trophicity Index (ms)

PGM=PRODOPS/GZ402666/TDR12857/CSR/REPORT/PGM/mri_mean_sd_t.sas
OUT=REPORT/OUTPUT/mri_mean_sd_t_grp2_i.rtf (23JUL2015 - 18:03)

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