CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761194Orig1s000

INTEGRATED REVIEW

BLA Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	BLA
Application number	761194
Priority or standard	Priority review with major amendment
Submit date	9/18/2020
Received date	9/18/2020
PDUFA goal date	8/18/2021
Division	Division of Rare Diseases and Medical Genetics (DRDMG)
Review completion date	8/5/2021
Established/proper name	Avalglucosidase alfa-ngpt
(Proposed) proprietary name	Nexviazyme
Pharmacologic class	Enzyme replacement therapy
Code name	GZ402666
Applicant	Genzyme Corporation
Dosage form	Powder for solution for infusion, 100 mg/vial
Dosing regimen	20 mg per kg of actual body weight administered every two weeks as intravenous infusion for patients 30 kg and greater with late-onset Pompe disease and 40 mg per kg of actual body weight administered every two weeks as intravenous infusion for patients less than 30 kg
Applicant proposed indication(s)/ population(s)	Pompe disease
Proposed SNOMED indication	274864009, Glycogen Storage Disease, Type II
Regulatory action	Approval
Approved dosage (if applicable)	20 mg per kg of actual body weight administered every two weeks as intravenous infusion for patients 30 kg and greater with late-onset Pompe disease and 40 mg per kg of actual body weight administered every two weeks as intravenous infusion for patients less than 30 kg
Approved indication(s)/ population(s) (if applicable)	Treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal alpha-glucosidase [GAA] deficiency)
Approved SNOMED term for indication (if applicable)	722343009, Glycogen storage disease type II late onset (disorder)

Table of Contents

Table of Tables vi
Table of Figures x
Glossary 1
I. Executive Summary 3
1. Summary of Regulatory Action 3
2. Benefit-Risk Assessment 5
2.1. Benefit-Risk Framework 5
2.2. Conclusions Regarding Benefit-Risk 8
II. Interdisciplinary Assessment 10
3. Introduction 10
3.1. Review Issue List 11
3.1.1. Key Review Issues Relevant to Evaluation of Benefit 11
3.1.2. Key Review Issues Relevant to Evaluation of Risk 11
3.2. Approach to the Review 12
4. Patient Experience Data 16
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology 17
5.1. Nonclinical Assessment of Potential Effectiveness 22
6. Assessment of Effectiveness 22
6.1. Dose and Dose Responsiveness 22
6.1.1. Proposed Dosage Regimen 22
6.1.2. Dose Selection for the Clinical Studies in Patients With LOPD 22
6.1.3. Dose Selection for the Clinical Studies in Patients With IOPD 23
6.1.4. Pharmacodynamics in Patients With LOPD 23
6.1.5. Pharmacodynamics in Patients With IOPD 25
6.1.6. Exposure-Response Relationship for Efficacy in Patients With LOPD 25
6.1.7. Exposure-Response for Safety 26
6.2. Clinical Trials Intended to Demonstrate Efficacy 26
6.2.1. EFC14028 (COMET) 26
6.2.1.1. Design, EFC14028 (COMET) 26
6.2.1.2. Eligibility Criteria, EFC14028 (COMET) 27
6.2.1.3. Statistical Analysis Plan, EFC14028 (COMET) 28
6.2.1.4. Results of Analyses, EFC14028 (COMET) 31
6.2.2. TDR12857 and LTS13769 43
6.2.2.1. Design, TDR12857 and LTS13769 43
6.2.2.2. Eligibility Criteria, TDR12857 and LTS13769 44
6.2.2.3. Statistical Analysis Plan, TDR12857 and LTS13769 44

Reference ID: 4836879

6.2.2.4. Results of Analyses, TDR12857 and LTS13769 44
6.2.3. ACT14132 48
6.2.3.1. Design, ACT14132 48
6.2.3.2. Eligibility Criteria, ACT14132 48
6.2.3.3. Statistical Analysis Plan, ACT14132 49
6.2.3.4. Results of Analyses, ACT14132 49
6.2.4. Conclusions Regarding Effectiveness 50
6.3. Key Review Issues Relevant to Evaluation of Benefit 51
6.3.1. Confirmatory Evidence 51
6.3.2. Extrapolation of Efficacy to Patients Less Than 16 Years of Age With LOPD 52
6.3.3. Evidence of Efficacy in Patients With IOPD 55
6.3.4. Long-Term Effectiveness 64
7. Risk and Risk Management 66
7.1. Potential Risks or Safety Concerns Based on Nonclinical Data 66
7.1.1. Overall Safety Concern 66
7.1.2. Safety Pharmacology 66
7.1.3. ADME 67
7.1.4. General Toxicology 67
7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors 68
7.3. Potential Safety Concerns Identified Through Postmarket Experience 68
7.4. FDA Approach to the Safety Review 68
7.5. Adequacy of Clinical Safety Database 69
7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database 71
7.6.1. Safety Findings and Concerns, Integrated Safety Set 72
7.6.1.1. Overall Adverse Event Summary, Integrated Safety Set 72
7.6.1.2. Deaths, Integrated Safety Set 73
7.6.1.3. Serious Adverse Events, Integrated Safety Set 73
7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, Integrated Safety Set 76
7.6.1.5. Treatment-Emergent Adverse Events, Integrated Safety Set 77
7.6.1.6. Laboratory Findings, Integrated Safety Set 80
7.6.2. Safety Findings and Concerns, EFC14028 (COMET) 84
7.6.2.1. Overall Adverse Event Summary, EFC14028 84
7.6.2.2. Deaths, EFC14028 84
7.6.2.3. Serious Adverse Events, EFC14028 84

Reference ID: 4836879

7.6.2.4. Dropouts and/or Discontinuations Due to Adverse Events, EFC14028 ... 84
7.6.2.5. Treatment-Emergent Adverse Events, EFC14028 ... 85
7.6.2.6. Laboratory Findings, EFC14028 ... 88
7.6.3. Safety Findings and Concerns, ACT14132 (Mini-COMET) ... 88
7.6.3.1. Overall Adverse Event Summary, ACT14132 ... 88
7.6.3.2. Deaths, ACT14132 ... 88
7.6.3.3. Serious Adverse Events, ACT14132 ... 88
7.6.3.4. Dropouts and/or Discontinuations Due to Adverse Events, ACT41432 ... 89
7.6.3.5. Treatment-Emergent Adverse Events, ACT14132 ... 89
7.6.3.6. Laboratory Findings, ACT14132 ... 93
7.7. Key Review Issues Relevant to Evaluation of Risk ... 93
7.7.1. Hypersensitivity Reactions (Including Anaphylaxis) and Infusion-Associated Reactions ... 93
7.7.2. Safety in Patients 12 Months of Age and Younger With IOPD ... 96
7.7.3. Risk to Fetus During Pregnancy and Infant During Lactation ... 97
7.7.4. Hepatotoxicity ... 98
7.7.5. Manufacturing Site Inspection ... 101
7.7.6. Clinical Site Inspections ... 102
8. Therapeutic Individualization ... 103
8.1. Intrinsic Factors ... 103
8.1.1. Renal Impairment or Hepatic Impairment ... 105
8.2. Drug Interactions ... 105
8.3. Plans for Pediatric Drug Development ... 105
8.4. Pregnancy and Lactation ... 105
9. Product Quality ... 108
9.1. Device or Combination Product Considerations ... 110
10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure ... 110
11. Advisory Committee Summary ... 111
III. Appendices ... 112
12. Summary of Regulatory History ... 112
13. Pharmacology Toxicology: Additional Information and Assessment ... 115
13.1. Summary Review of Studies Submitted Under the IND ... 115
13.1.1. Pharmacology (Primary and Secondary) ... 115
13.1.2. Safety Pharmacology ... 116
13.1.3. ADME/PK/TK ... 116
13.1.3.1. Single-Dose Pharmacokinetics ... 116

Reference ID: 4836879

13.1.3.2. Repeat-Dose Pharmacokinetics 118
13.1.3.3. Distribution 121
13.1.3.4. Metabolism 121
13.1.3.5. Elimination and Excretion 122
13.1.3.6. General Toxicology 122
13.1.3.7. Genetic Toxicology 125
13.2. Individual Reviews of Studies Submitted to the BLA 126
13.2.1.1. ADME/TK 126
13.2.1.2. Carcinogenicity 128
13.2.1.3. Reproductive Toxicology 129
13.2.1.4. Impurities/Degradants 142
14. Clinical Pharmacology: Additional Information and Assessment 150
14.1. In Vitro Studies 150
14.2. In Vivo Studies 151
14.3. Immunogenicity Summary 152
14.4. Bioanalytical Methods 159
14.5. Pharmacometrics Review 169
14.5.1. Population PK Analyses 169
14.5.2. Exposure-Response Analyses 177
14.5.2.1. Exposure-Response Analyses for Efficacy 177
14.5.2.2. Exposure-Response Analyses for Safety 179
14.5.3. Pediatric Dose Selection 180
15. Trial Design: Additional Information and Assessment 184
16. Efficacy: Additional Information and Assessment 185
17. Clinical Safety: Additional Information and Assessment 195
18. Mechanism of Action/Drug Resistance: Additional Information and Assessment 201
19. Other Drug Development Considerations: Additional Information and Assessment 201
20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections) 202
20.1. Biopharmaceutical Inspection 202
21. Labeling Summary of Considerations and Key Additional Information 203
22. Postmarketing Requirements and Commitments 204
23. Financial Disclosure 205
24. References 206
25. Review Team 209

Reference ID: 4836879

Table of Tables

Table 1. Administrative Application Information i
Table 2. Benefit-Risk Framework 5
Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Avalglucosidase Alfa 14
Table 4. Patient Experience Data Submitted or Considered 16
Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics 17
Table 6. Patient Disposition, Trial EFC14028 (COMET) 31
Table 7. Baseline Demographics, Trial EFC14028 (COMET) 32
Table 8. Baseline Data of Key Efficacy Parameters, Trial EFC14028 (COMET) 33
Table 9. Change in FVC (% Predicted) From Baseline to Week 49, mITT Population, Trial EFC14028 (COMET) 35
Table 10. Change in Distance in 6MWT From Baseline to Week 49, mITT Population, Trial EFC14028 (COMET) 39
Table 11. Mean Change From Baseline to Week 49 in Other Secondary Endpoints 43
Table 12. Patient Disposition (n), Trials TDR12857 and LTS13769 45
Table 13. Baseline Demographics and Characteristics, Trials TDR12857 and LTS13769 46
Table 14. Patient Disposition, Trial ACT14132 49
Table 15. Baseline Demographics, Trial ACT14132 50
Table 16. Change From Baseline to Week 25 in GMFM-88 Total Percent Score, Trial ACT14132 56
Table 17. Change From Baseline to Week 25 in QMFT Total Score, Trial ACT14132 57
Table 18. Change From Baseline to Week 25 in Pompe-PEDI Total Raw Score, Trial ACT14132 58
Table 19. Change From Baseline to Week 25 in LVM Z-Score, Trial ACT14132 59
Table 20. Change From Baseline to Week 25 in Interpalpebral Fissure Distance (Left Eye; Without Flash), Trial ACT14132 60
Table 21. Change From Baseline to Week 25 in Interpalpebral Fissure Distance (Right Eye; Without Flash), Trial ACT14132 60
Table 22. Safety Margins From Pivotal Toxicology Studies 66
Table 23. Baseline Demographic and Clinical Characteristics, Integrated Summary of Safety 69
Table 24. Duration of Exposure, Safety Population, Integrated Summary of Safety 71
Table 25. Overview of Adverse Events for Avalglucosidase Alfa, Integrated Safety Population 72
Table 26. Exposure-Adjusted Incidence Rate of TEAE(S), Integrated Safety Population 73

Reference ID: 4836879

Table 27. Deaths in the Integrated Safety Population in Patients Receiving Avalglucosidase Alfa 73
Table 28. Serious Adverse Events, Integrated Safety Population 74
Table 29. Adverse Events Leading to Discontinuation, Integrated Safety Population 76
Table 30. Common Adverse Events Occurring at ≥2% Frequency, Safety Population, Integrated Safety Set 77
Table 31. Overview of Adverse Events, Controlled Trial Safety Population, Trial EFC14028 (COMET) 84
Table 32. Treatment-Emergent Adverse Events[1] Occurring at ≥2% Frequency, Trial EFC14028 (COMET) 85
Table 33. Serious Adverse Events Occurring in Patients Treated With Avalglucosidase Alfa at 20 mg/kg qow and 40 mg/kg qow, Trial ACT14132 (Cohorts 1, 2 and 3) 89
Table 34. Treatment-Emergent Adverse Events Occurring at a Higher Frequency in Patient Treated With Avalglucosidase Alfa Than Alglucosidase Alfa, Trial ACT14132 (Cohort 3) 90
Table 35. Treatment-Emergent Adverse Events Occurring in Patients Treated With Avalglucosidase Alfa at 20 mg/kg qow and 40 mg/kg qow, Trial ACT14132 (Cohort 1 and 2) 91
Table 36. Infusion Associated Reactions Occurring in Patients Treated With Avalglucosidase Alfa at 20 mg/kg qow and 40 mg/kg qow, Trial ACT14132 (Cohort 1, 2 and 3) 93
Table 37. Potential DILI, Safety Population, Integrated Safety Set 98
Table 38. Exposure Comparison by Patient Body Weight for Avalglucosidase Alfa at 20 mg/kg and 40 mg/kg qow in Patients With IOPD and LOPD (Based on Updated Population PK Model) 104
Table 39. Juvenile Toxicity Safety Margin 105
Table 40. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation 106
Table 41. Reproductive and Developmental Toxicity Safety Margins 107
Table 42. Pharmacology Studies 115
Table 43. Safety Pharmacology Assessment 116
Table 44. Single-Dose Pharmacokinetics, Studies 08-2344, 10-00813, and 10-05540 116
Table 45. Repeat-Dose Pharmacokinetics, General Toxicology, Study 10-00183 118
Table 46. Repeat-Dose Pharmacokinetics, General Toxicology, Study 1213-004 119
Table 47. Repeat-Dose Pharmacokinetics, General Toxicology, Study 0658-11097 120
Table 48. Pharmacokinetics Studies, Distribution, Studies 10-00818 and 09-3559 121
Table 49. Methods, Study 0658-11097 122
Table 50. Observations and Results, Study 0658-11097 123

Reference ID: 4836879

Table 51. Nonpivotal General Toxicology Studies 124
Table 52. Genetic Toxicology Studies 125
Table 53. Juvenile Toxicology Study Review, Study JUV0033 126
Table 54. Reproductive Toxicology Study Review, Study TER0685 127
Table 55. Reproductive Toxicology Study Review, Study TER0686 128
Table 56. Methods, Reproductive and Developmental Toxicology (Fertility and Early Embryonic Development), Study FER0511 129
Table 57. Observations and Results, Study FER0511 130
Table 58. Study Methods, Reproductive and Developmental Toxicology (Embryonic and Fetal Development), Study FER0685 132
Table 59. Observations and Results, Study FER0685 133
Table 60. Study Methods, Reproductive and Developmental Toxicology (Embryonic and Fetal Development), Study FER0686 134
Table 61. Observations and Results, Study FER0686 135
Table 62. Study Methods, Reproductive and Developmental Toxicology (Prenatal and Postnatal Development), Study DPN0378 136
Table 63. Observations and Results, Study DPN0378 137
Table 64. Study Methods, Juvenile Toxicity, Study JUV0033 138
Table 65. Observations and Results, Study JUV0033 140
Table 66. Summary of Drug Substance-Related Impurities of Avalglucosidase Alfa Drug Product Using the Proposed Commercial Process 142
Table 67. Toxicological and Risk Assessments of Avalglucosidase Alfa Leachables 143
Table 68. General Toxicology (Impurity), Study No. TXC1530 144
Table 69. Other Special Toxicology Studies, Genotoxicity (Impurity) 145
Table 70. Potential Genotoxic Impurities Per ICH M7[1]: Class I 147
Table 71. Potential Genotoxic Impurities Per ICH M7[1]: Class III 148
Table 72. Incidence of Antidrug Antibody Responses in Patients With LOPD and IOPD 154
Table 73. Summary of Treatment-Emergent Adverse Events by Antidrug Antibody Status in Treatment-Naïve Patients 158
Table 74. Summary of Treatment-Emergent Adverse Events by Antidrug Antibody Peak Titer Category for Treatment-Naïve Patients (N=61) 158
Table 75. Bioanalytical Method Life Cycle Information 159
Table 76. Summary Method Performance, Study ITR-629-0413 161
Table 77. Summary Method Performance, Study DOH1429 163
Table 78. Summary Method Performance, Study DOH1626 165
Table 79. Summary Method Performance, Trials TDR12857, LTS13769, ACT14132, and EFC14028 167

Reference ID: 4836879

Table 80. Summary of Clinical Trials Included in the Population PK Analysis 169
Table 81. Demographic Characteristics (Baseline Values) of the Patients Included in the PopPK Analysis 170
Table 82. Descriptive Statistics on Continuous Demographic or Covariate at Baseline for Patients Included in the PopPK Analysis 171
Table 83. Summary of the Final PopPK Model Parameters and Bootstrap Results 172
Table 84. Inferential Statistics of Efficacy Parameters Versus Exposure Linear Regressions 178
Table 85. Overview of the Baseline Demographic and Disease Characteristics by Avalglucosidase Alfa AUCτ Quartile, Trial EFC14028 (COMET) 179
Table 86. Logistic Regression Representing the Probability of Experiencing a TEAE as Function of AUC or log(AUC) Adjusted by Baseline Covariates (Age at Baseline, Disease Type/Treatment-Naïve/Treatment Experienced) 180
Table 87. Tipping Point Analysis of FVC (% Predicted), Trial EFC14028 (COMET) . 186
Table 88. Change in FVC (% Predicted) From Baseline to Week 49 by Subgroups of Baseline FVC (% Predicted), mITT Population, Trial EFC14028 (COMET)..... 187
Table 89. Adverse Events by System Organ Class and FDA Medical Query (Narrow), Integrated Safety Population 195
Table 90. Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial EFC14028 (COMET)..... 198
Table 91. Drug Product Batches and Batch History..... 201
Table 92. Major Prescribing Information Changes..... 203
Table 93. Covered Clinical Studies: EFC14028, ACT14132..... 205
Table 94. Reviewers of Integrated Assessment..... 209
Table 95. Additional Reviewers of Application..... 210
Table 96. Signatures of Reviewers 210

Reference ID: 4836879

Table of Figures

Figure 1. Mean (SE) Percentage Change From Baseline in Urinary Hex4 in Patients With LOPD Receiving Avalglucosidase Alfa or Alglucosidase Alfa 20 mg/kg qow, Trial EFC14028 (COMET) 24
Figure 2. Mean (SE) Percentage Change From Baseline in Urinary Hex4 in Patients With IOPD Receiving Avalglucosidase Alfa 20 mg/kg and 40 mg/kg qow, Trial ACT14132 25
Figure 3. Trial Design (PAP and ETP), Trial EFC14028 (COMET) 27
Figure 4. Mean (±SE) Change From Baseline in FVC (% Predicted) Over Time (All Randomized) 36
Figure 5. Subgroup Analyses of Change From Baseline to Week 49 in FVC (% Predicted) 37
Figure 6. Mean (±SE) Change From Week 49 in FVC (% Predicted) Over Time (All Randomized) 38
Figure 7. Mean (±SE) Change From Baseline in 6MWT Distance (in Meters) Over Time (All Randomized) 40
Figure 8. Subgroup Analyses of Change From Baseline to Week 49 in Distance (in Meters) Walked in 6MWT 41
Figure 9. Mean (±SE) Change From Week 49 in 6MWT Distance (in Meters) Over Time (All Randomized) 42
Figure 10. Mean (±SD) Change From Baseline in FVC (% Predicted) and 6MWT Distance Over Time 47
Figure 11. Simulated Avalglucosidase Alfa AUC_{2W} and C_{max} by Body Weight Category at 20 mg/kg and 40 mg/kg Every Other Week in Patients With LOPD 54
Figure 12. GMFM-88 Total Percent Score and Mean Change From Baseline Over Time 56
Figure 13. QMFT Total Percent Score and Mean Change From Baseline Over Time 57
Figure 14. Pompe-PEDI Mobility Domain Raw Score and Mean Change From Baseline Over Time 58
Figure 15. LVM Z-Score From M-Mode Echocardiography and Mean Change From Baseline Over Time 59
Figure 16. Interpalpebral Fissure Distance (Left Eye) and Mean Change From Baseline Over Time 61
Figure 17. Interpalpebral Fissure Distance (Right Eye) and Mean Change From Baseline Over Time 61
Figure 18. Effect of ERT on Pulmonary Function During Treatment With Alglucosidase Alfa 65
Figure 19. Effect of ERT on Distance Walked During Treatment With Alglucosidase Alfa 65

Reference ID: 4836879

Figure 20. Drug-Induced Liver Injury Case Screening Plot, Safety Population, Integrated Safety Set 99
Figure 21. Schematic of One Glycan E13 Conjugated to Alglucosidase Alfa 109
Figure 22. Urinary Hex4 Over Time After Avalglucosidase Alfa 5, 10 and 20 mg/kg qow in Treatment-Naïve Patients with LOPD, Trial TDR12857 152
Figure 23. Avalglucosidase Alfa Exposure by ADA Peak Titer Category, Trial EFC14028 (COMET) 155
Figure 24. Avalglucosidase Alfa Exposure by Neutralizing Antibody Status, Trial EFC14028 (COMET) 155
Figure 25. The Percent Change of Hex4 From Baseline by Antidrug Antibody Peak Titer Categories for Treatment-Naïve Patients 156
Figure 26. Change From Baseline of FVC (% Predicted) Upright by Antidrug Antibody Status and Peak Titer Categories in Treatment-Naïve Patients 157
Figure 27. Change From Baseline of 6MWT (Distance Walked) by Antidrug Antibody Peak Titer Categories in Treatment-Naïve Patients 157
Figure 28. Visual Predictive Check Results of All Data (Semi-Log Scale) 173
Figure 29. Visual Predictive Check Results Stratified by Study (Semi-Log Scale) 173
Figure 30. Goodness-of-Fit Plots of the Final PopPK Model (All Subjects) 174
Figure 31. Goodness-of-Fit Plots of the Final PopPK Model Stratified by Naive/Non-Naïve Patient Population 175
Figure 32. Goodness-of-Fit Plots of the Final PopPK Model Stratified by Study 175
Figure 33. Goodness-of-Fit Plots of the Final PopPK Model Stratified by ADA Status (Constant, Not Time-Varying) 176
Figure 34. Goodness-of-Fit Plots of the Final PopPK Model Stratified by Disease Type 176
Figure 35. Percent Predicted FVC and 6MWT Change Versus Baseline as Function of AUCτ, Week 9 177
Figure 36. Body Weight in Virtual Patients by Age Group 181
Figure 37. Simulated Avalglucosidase Alfa $AUC_{0\text{-}2W}$ and C_{max} by Age Category (1 to <2 Years, 2 to <6 Years, 6 to <12 Years, 12 to <18 Years, and ≥18 Years Old) at 20 mg/kg Every Other Week in Patients With LOPD 182
Figure 38. Estimated Treatment Difference by Excluding One Site at a Time 187
Figure 39. Scatter Plot of Baseline FVC (% Predicted) by Change From Baseline to Week 49 (or Last Visit) in FVC (% Predicted) 188
Figure 40. Analyses of FVC (% Predicted) in Subgroups by Baseline Score 189
Figure 41. Mean and Mean Change Over Time in FVC (% Predicted), Group 1, Trial TDR12857 190
Figure 42. Mean and Mean Change Over Time in FVC (% Predicted), Group 2, Trial TDR12857 190

Reference ID: 4836879

Figure 43. Mean and Mean Change Over Time in 6MWT (Meters), Group 1, Trial TDR12857 191
Figure 44. Mean and Mean Change Over Time in 6MWT (Meters), Group 2, Trial TDR12857 192
Figure 45. FVC (% Predicted) Over Time for Patients Having Missing Value at Week 49, Trial EFC14028 (COMET) 193
Figure 46. Pompe-PEDI Mobility Domain Normative Standard Score and Mean Change From Baseline Over Time, Trial ACT14132 194

Reference ID: 4836879

Glossary

ADA	antidrug antibodies
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AOAH	2-(aminooxy) acetohydrazide
AST	aspartate aminotransferase
AUC	area under the curve
BLA	biologics license application
BTDR	Breakthrough Therapy Designation Request
CFR	Code of Federal Regulations
CE	confirmatory evidence
CI	confidence interval
COMET	Comparing an Operation to Monitoring, With or Without Endocrine Therapy
CRIM	cross-reactive immunologic material
DILI	drug-induced liver injury
DPH	diphenhydramine
DP	drug product
DS	drug substance
eGFR	estimated glomerular filtration rate
EKG	electrocardiogram
E-R	exposure-response
ERT	enzyme replacement therapy
ETP	extension treatment period
FDA	Food and Drug Administration
FMQ	FDA medical query
FVC	forced vital capacity
GAA	alpha-glucosidase
GD	gestation day
Glc4	glucose tetrasaccharide
GLP	good laboratory practice
GMFM-88	Gross Motor Function Measure-88
HBH	4-hydroxybutyric acid hydrazide
HHD	hand-held dynamometry
IAR	infusion-associated reaction
ICH	International Conference on Harmonisation
IND	investigational new drug
IOPD	infantile-onset Pompe disease
ISS	integrated summary of safety
ITI	immune tolerance induction
IV	intravenous
LC-MS/MS	liquid chromatography with tandem mass spectroscopy
LLOQ	lower limit of quantitation

Reference ID: 4836879

LOPD	late-onset Pompe disease
LVMI	left ventricular mass index
MAR	missing-at-random
MCS	mental component summary
MEP	maximal expiratory pressure
MIP	maximal inspiratory pressure
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
NI	noninferiority
NOAEL	no observed adverse effect level
PAD	pharmacologically active dose
PAP	primary analysis period
PCS	physical component summary
PD	Pompe disease
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
Pompe-PEDI	Pompe Pediatric Evaluation of Disability Inventory
PRO	patient-reported outcome
QMFT	Quick Motor Function Test
qow	every other week
rhGAA	recombinant human acid alpha-glucosidase
RRA	remote regulatory assessments
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
TEAE	treatment-emergent adverse event
TK	toxicokinetics
WRO	Written Responses Only

Reference ID: 4836879

I. Executive Summary

1. Summary of Regulatory Action

Genzyme (Applicant) submitted this biologics license application (BLA) for avalglucosidase alfa (tradename Nexviazyme), seeking approval of this second-generation enzyme replacement therapy for Pompe disease (PD), a rare lysosomal storage disorder. Patients with PD have an enzyme deficiency that leads to glycogen accumulation in skeletal and cardiac muscle, causing muscle weakness, respiratory failure, and heart failure. The BLA was reviewed by a multidisciplinary review team. Each discipline recommends approval for patients with late-onset PD (LOPD) and the signatory authority for this application concurs with those recommendations.

Substantial evidence of effectiveness for avalglucosidase alfa in patients with LOPD was established using data from one adequate and well-controlled trial with confirmatory evidence (CE). A single trial in treatment-naive patients greater than 16 years of age with LOPD showed a large and clinically significant numerical improvement in lung function that was statistically noninferior compared to treatment with alglucosidase alfa. CE providing strong mechanistic support includes the well-established etiology of the disease, the mechanism of action of the therapy, and animal studies showing reduced glycogen in tissues and improved muscle function in GAAKO mice. Extrapolation of efficacy from older patients with LOPD to patients younger than 16 years of age with LOPD is supported by similar pathophysiology, mechanism of action, and disease manifestations across patients with LOPD. (b) (4)

The available safety data show that avalglucosidase alfa is safe for its intended use. Common adverse reactions included headache, fatigue, diarrhea, nausea, arthralgia, dizziness, myalgia, pruritus, vomiting, dyspnea, erythema, paresthesia, and urticaria. Serious adverse reactions include anaphylaxis, a known class effect for enzyme replacement therapies (ERTs). Although not initially proposed by the Applicant, a Boxed Warning for hypersensitivity reactions, including anaphylaxis, will be included in the product labeling to mitigate this known risk with ERTs. All the identified safety risks for avalglucosidase alfa can be adequately mitigated through labeling and further evaluated during routine pharmacovigilance.

The BLA includes appropriate preapproval nonclinical studies, and no additional nonclinical studies or clinical pharmacology studies will be conducted as postmarketing requirements. We are requiring a postmarketing study to evaluate the outcomes of pregnancies in women exposed to avalglucosidase. Labeling will note that data regarding these risks are not available currently.

Reference ID: 4836879

As described in the Benefit/Risk Framework below, we conclude that the improvement in lung function observed with use of avalglucosidase alfa outweighs the risks when avalglucosidase alfa is used as recommended in the approved labeling.

Reference ID: 4836879

Reference ID: 4836879

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pompe disease (PD) is an autosomal recessive, lysosomal storage disease that results in deficient activity of alpha glucosidase (GAA), the enzyme that degrades glycogen in lysosomes. Enzyme deficiency leads to myopathy, respiratory weakness, physical disability, and premature death. • There are two forms of PD caused by deficiency of the same enzyme: infantile-onset and late-onset. Infantile-onset Pompe disease (IOPD) is associated with severe left ventricular hypertrophy and a high mortality rate within the first year of life (Gupta et al. 2020). Late-onset Pompe disease (LOPD) is associated with limb girdle and respiratory muscle weakness, and premature death due to respiratory insufficiency (Gupta et al. 2020). • The incidence of PD in the United States is approximately 1:40,000 births.	• PD is a rare and serious disease that can lead to death from cardiac or respiratory failure if untreated in the infantile-onset form and to motor impairment and premature death from respiratory failure in the late-onset form.
Current Treatment Options	• Enzyme replacement therapy (ERT) with recombinant alpha glucosidase (alglucosidase alfa) is the only approved therapy. However, the improvements seen with alglucosidase alfa are not sustained. Patients can regress back to their baseline pulmonary function within 3 years (Schoser et al. 2017). • Patients with IOPD have shown improvement in cardiac variables, such as left ventricular hypertrophy and improved survival, with available ERT if treatment is initated before 6 months of age. • Patients with LOPD have shown improvement in forced vital capacity and 6-minute walk test with available ERT.	• Improvements seen with the currently approved ERT, alglucosidase alfa, are not sustained; therefore, the treatment and cure of Pompe disease continue to represent unmet needs.

Reference ID: 4836879

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Nexviazyme (avalglucosidase alfa) is a modified recombinant human GAA intended for use as ERT in LOPD. • Avalglucosidase alfa is manufactured by conjugating bis-mannose-6-phosphate (M6P) to oxidized sialic acid residues on alglucosidase alfa. This modification is hypothesized to improve its cellular uptake. As a recombinant form of GAA, the proposed indication is to replace the endogenous GAA and degrade glycogen. • The efficacy of avalglucosidase was evaluated in an adequate and well-controlled trial (EFC14028) in LOPD. Changes in lung function (forced vital capacity [FVC] % predicted) were compared between patients with LOPD randomly assigned to avalglucosidase alfa at 20 mg/kg every other week (qow; N=51) or alglucosidase alfa at 20 mg/kg qow (N=49). • The estimated treatment difference in the mean change in FVC (% predicted) from baseline to week 49 was 2.4% (95% confidence interval [CI]: -0.1 to 5.0), favoring avalglucosidase alfa and meeting pre-established noninferiority criteria. This level of change in lung function is expected to affect how patients feel and function. • Confirmatory evidence (CE) of effectiveness for LOPD is derived from mechanistic support including the well-established etiology of the disease, the mechanism of action of the therapy, and animal studies showing that avalglucosidase alfa reduces glycogen levels in tissues and improves muscle function in GAAKO mice, consistent with the pathophysiology for this disease. • The estimated treatment difference in the distance walked in the 6-minute walk test (6MWT), a key secondary endpoint in EFC14028, was 30 meters (95% CI: 1.3 to 58.7), favoring avalglucosidase and supporting improved walking distance.	• Avalglucosidase alfa demonstrated a large and clinically meaningful numerical improvement in lung function in treatment-naïve patients greater than 16 years of age with LOPD. • The clinical trial design and lung function endpoint were appropriate given the rarity and severity of PD. The improvement in lung function supports effectiveness of avalglucosidase alpha in patients greater than 16 years of age with LOPD. • An improvement from baseline in walking distance is suggestive that avalglucosidase alfa is effective, but no formal statistical analysis was performed since the superiority test of the primary endpoint did not reach statistical significance. • Effectiveness of avalglucosidase alfa in patients younger than 16 years of age with LOPD is based on our findings of effectiveness for patients greater than 16 years of age with LOPD (which is scientifically justified by the similar disease pathophysiology, mechanism of action, and disease manifestations). • (b) (4)

Reference ID: 4836879

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• An open-label trial (ACT14132) to evaluate safety enrolled 22 patients greater than 12 months of age with IOPD who had been treated with alglucosidase alfa for at least 6 months and either showed clinical decline (n=11) or had a suboptimal response (n=11). No meaningful difference in secondary endpoints (gross motor function measure-88, quick motor function test, Pompe pediatric evaluation of disability inventory, and left ventricular mass Z-score) was shown in patients with a previous suboptimal response on alglucosidase alfa for avalglucosidase alfa at 40 mg/kg qow (n=5) compared to those continuing on alglucosidase alfa at the patient's previous stable dose (n=6).	
Risk and Risk Management	• Safety was assessed in 138 patients with Pompe disease who received avalglucosidase alfa. This included treatment-naïve (61) and treatment-experienced (77) patients; adult (118) and pediatric (19) patients; and patients with LOPD (119) and IOPD (19). • Total cumulative duration of exposure was 274.2 patient-years; 124 patients (90%) had greater than 48 weeks of exposure; and 17 patients (12%) had greater than 240 weeks of exposure. • Serious adverse events (SAEs) were reported in 25% (35/138) of patients treated with avalglucosidase alfa; SAEs reported in 2 or more patients included pneumonia, chills, pyrexia, respiratory distress, respiratory failure, and eyelid ptosis. • The most common adverse reactions (ARs) were hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions, which presented most often as abdominal pain, arthralgia, back pain, chills, cough, diarrhea, dizziness, dyspnea, erythema, fatigue, headache, hypertension, musculoskeletal pain, myalgia, nausea, pain, pain in extremity, pruritus, pyrexia, rash, urticaria and vomiting.	• The safety database was adequate for a safety assessment of avalglucosidase alfa for the proposed indication, patient population, dosage regimen, and duration. • The identified safety concerns do not outweigh the benefit of improved lung function and can be adequately mitigated with labeling alone. • Safety risks of hypersensitivity, including anaphylaxis and infusion-associated reactions, are known risks with ERT. These risks with avalglucosidase alfa are not clinically different from those of alglucosidase and can be addressed through labeling and routine pharmacovigilence. • We are requiring a pregnancy and lactation study postapproval. Labeling will note that data regarding pregnancy and lactation are not available.

Reference ID: 4836879

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Four patients treated with avalglucosidase alfa met the clinical criteria for anaphylaxis, and all patients developed symptoms within 2 hours of the initiation of the infusion. One patient was withdrawn from the trial. There were no deaths associated with anaphylaxis. • Thirty percent of patients reported 1 or more infusion-associated reaction (IAR). The most frequently reported IARs were pruritus, rash, and urticaria. Most of the IARs occurred within 2 hours after the infusion started. • Treatment-naïve patients were more likely to develop antidrug antibodies (ADA) compared to treatment-experienced patients. • The most frequent laboratory abnormalities included aspartate transaminase (AST) and alanine aminotransferase (ALT) elevations.	

2.2. Conclusions Regarding Benefit-Risk

Pompe disease (PD) is a rare and serious lysosomal storage disease caused by autosomal recessive variants in the *GAA* gene. The resulting enzyme deficiency of GAA results in accumulation of glycogen in cells and leads to myopathy, respiratory weakness, physical disability, and can lead to premature death. The two forms of PD present differently: IOPD is associated with severe left ventricular hypertrophy and high mortality within the first year of life and LOPD is associated with limb girdle and respiratory muscle weakness. The only approved therapy is a recombinant alpha glucosidase, alglucosidase alfa, which does not lead to a sustained improvement in muscle weakness and thus, impending respiratory failure. Therefore, treatment and cure of PD continue to represent unmet needs.

Avalglucosidase alfa has more bis-mannose-6-phosphate (M6P) moieties compared to alglucosidase alfa. The Applicant's earlier preclinical studies in a Pompe disease mouse model have suggested that avalglucosidase alfa has a higher binding affinity to M6P receptors and increased uptake compared to alglucosidase alfa (Pena et al. 2019; Zhu et al. 2005).

The benefit of avalglucosidase alfa, a hydrolytic lysosomal glycogen-specific enzyme, is based on comparison of FVC (% predicted) in 100 treatment-naive patients greater than 16 years of age with LOPD randomized either to avalglucosidase alfa at 20 mg/kg every other week (n=51) or alglucosidase alfa at 20 mg/kg every other week (n=49). The estimated treatment difference in the mean change in FVC (% predicted) from baseline to week 49 was 2.4% (95% CI: -0.1 to 5.0), favoring the avalglucosidase alfa arm and meeting the

Reference ID: 4836879

established criteria for noninferiority. Confirmatory evidence of effectiveness for LOPD is derived from mechanistic support including the etiology of the disease, the mechanism of action of the therapy, and animal studies that show avalglucosidase alfa reduces glycogen levels in tissues in GAAKO mice. Patients on avalglucosidase alfa also showed an improvement from baseline in the distance walked on their 6-minute walk test (6MWT) compared to patients on alglucosidase alfa, but no formal statistical test was performed since the primary endpoint met statistical significance for noninferiority test but not for the superiority test. Per the statistical analysis plan, the formal superiority test for the 6MWT endpoint would be performed only if the primary endpoint met the superiority test.

Extrapolation of efficacy to patients less than 16 years of age with LOPD is supported by the similar disease pathophysiology within LOPD, mechanism of action of avalglucosidase alfa, and clinical disease manifestations. However, data to support extrapolation to patients with IOPD was inadequate due to differences in clinical presentation and potential immunogenicity concerns.

Safety concerns for ERTs include hypersensitivity reactions (including anaphylaxis) and IARs. The safety profile of avalglucosidase alfa as assessed in 138 patients with PD appears to be similar to that of the currently available therapy, alglucosidase alfa. Despite the high incidence of adverse events (91% of patients), most patients did not discontinue due to adverse events. Elevations of aspartate transaminase (AST) and alanine aminotransferase (ALT) were reported in 28% of patients receiving avalglucosidase, but the majority of these patients also had elevations at baseline, and most, but not all, showed improvement in these measures during the course of the trial. The most common adverse reactions (ARs) were hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions, which presented most often as abdominal pain, arthralgia, back pain, chills, cough, diarrhea, dizziness, dyspnea, erythema, fatigue, headache, hypertension, musculoskeletal pain, myalgia, nausea, pain, pain in extremity, pruritus, pyrexia, rash, urticaria and vomiting. The risk of hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions can be addressed through labeling and routine pharmacovigilance.

Uncertainties with regard to safety include safety in patients with PD who are less than 1 year of age, as well as the risk to a fetus during pregnancy and to infants during lactation. Labeling will note the lack of this safety information, and a postmarketing study will assess the uncertainties related to exposure during pregnancy and lactation.

In summary, we conclude that the benefits of avalglucosidase alfa outweigh its risks when used according to the agreed-upon labeling. The availability of avalglucosidase alfa provides a second-generation ERT with equal or greater effectiveness for patients 1 year of age and older with LOPD.

II. Interdisciplinary Assessment

3. Introduction

Pompe disease (PD), also known as acid maltase deficiency or glycogen storage disease type II, is a rare, autosomal recessive disease caused by the deficiency of lysosomal alpha-glucosidase (GAA). GAA cleaves alpha-1,4 and alpha-1,6 linkages in glycogen under the acidic conditions of the lysosome. In this lysosomal disorder, glycogen accumulation in affected tissue (skeletal and/or cardiac muscle) can result in progressive hypotonia, respiratory failure, and cardiomyopathy. The disease spectrum ranges from the severe, rapidly progressive infantile-onset Pompe disease (IOPD) to the slowly progressive, heterogeneous late-onset Pompe disease (LOPD).

During a virtual Patient-Focused Drug Development meeting on July 13, 2020, sponsored by the Muscular Dystrophy Association in partnership with the Acid Maltase Deficiency Association and the United Pompe Foundation, members of the Pompe patient community (both patients and caregivers) shared their perspectives on disease symptoms and daily impacts of IOPD and LOPD, as well as current experiences with treatment and expectations for potential future treatments. The Voice of the Patient Report is not yet available, but the meeting recording is available online (Muscular Dystrophy Association 2020). The age of diagnosis for most patients was between 0 to 5 years of age (35%) or 31 to 50 years of age (35%). The activities most impacted in patients with Pompe disease included exercising or participating in sports, walking, self-care/self-feeding, and socializing. Over 50% of patients reported participating in a clinical trial with experimental treatment, and the most important targets for drug treatment included improving lower body muscle strength, respiratory/pulmonary strength, and stabilizing or slowing further progression from current state.

First-generation enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme, biologics license application [BLA 125141]) was approved in April 2006 for patients diagnosed with IOPD, based upon improvement in ventilator-free survival compared to the well-described natural history of the disease. Lumizyme (BLA 125291) was approved for patients with LOPD in May 2010 based on improvements in lung function (FVC % predicted) and six-minute walk distance compared to placebo. Lumizyme and Myozyme are both alglucosidase alfa products produced by the same Applicant but produced at different bioreactor scales. The indication for Lumizyme was subsequently extended to all patients with PD (SUPPL-136 in August 2014) based on the physicochemical comparability of Myozyme and Lymizyme. Currently, alglucosidase alfa (Lumizyme; Myozyme is no longer manufactured in the United States) is the only approved therapy for PD.

Patients with LOPD have substantial unmet medical need as lung function improves within the first few months of ERT, but gradually returns to baseline at 36 months, with a slight decline after 36 months (Schoser et al. 2017). Similarly, in a prospective study conducted by Harlaar et al (2019), 30 patients with LOPD who had been treated with alglucosidase alfa had improved walking distances on the 6MWT during the first 3 years of treatment. After the first three years, the patients experienced a decline; at the 10-year assessment, the average 6MWT distance was lower than the distance walked at the start of treatment.

Reference ID: 4836879

Avalglucosidase alfa is a second-generation ERT that provides an exogenous source of GAA and is a modification of alglucosidase alfa. While alglucosidase alfa has seven hexamannose structures, each containing two terminal mannose-6-phosphate (M6P) moieties conjugated to oxidized sialic acid residues, avalglucosidase alfa has a 15-fold increase in mannose-6-phosphate (M6P) moieties. The Applicant hypothesizes that these differences may lead to increased uptake of avalglucosidase alfa into the diaphragm and other skeletal muscles compared to that of alglucosidase alfa.

In terms of the product's regulatory history, the Applicant submitted the investigational new drug (IND) opening protocol (IND 109569) to the U.S. Food and Drug Administration (FDA) in March 2013. The program was developed to compare avalglucosidase alfa with alglucosidase alfa. In November 2013, avalglucosidase alfa was granted an Orphan Drug designation, followed by a Fast Track designation in August 2019, and a Breakthrough Therapy designation in June 2020. The type B pre-BLA teleconference was held in June 2020, and a rolling review submission request was granted. The application met the criteria for a priority review because avalglucosidase alfa would provide a clinically significant improvement in the effectiveness of the treatment for PD, a serious condition.

The application contains four clinical trials: three in patients with LOPD and one in patients with IOPD. The pivotal trial, EFC14028, was a randomized, double-blind, comparator-controlled trial in treatment-naïve patients 3 years of age and older with LOPD, comparing avalglucosidase alfa to alglucosidase alfa.

3.1. Review Issue List

The review team identified the key review issues listed in Sections 3.1.1 and 3.1.2 below relevant to the evaluation of benefit and risk, respectively. In-depth assessment of these benefit and risk issues can be found in Sections 6.3 and 7.7, respectively.

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

- Confirmatory Evidence
- Extrapolation of Efficacy to Patients Less Than 16 Years of Age With LOPD
- Evidence of Efficacy in Patients With IOPD
- Long-Term Effectiveness

3.1.2. Key Review Issues Relevant to Evaluation of Risk

- Hypersensitivity Reactions (Including Anaphylaxis) and Infusion-Associated Reactions
- Safety in Patients 12 Months of Age and Younger With IOPD
- Risk to Fetus During Pregnancy and Infant During Lactation
- Hepatotoxicity
- Manufacturing Site Inspection

Reference ID: 4836879

- Clinical Site Inspections

3.2. Approach to the Review

The Applicant submitted data from three trials that involved patients with LOPD and one trial that involved patients with IOPD (summarized in Table 3) that form the basis of the benefit-risk assessment of avalglucosidase alfa in patients diagnosed with IOPD and LOPD. The review of BLA 761194 is based on the current understanding of Pompe disease, including IOPD and LOPD forms, as described in the literature.

Determination of Efficacy

At a Type C presubmission meeting held in February 20, 2020, the Applicant and the Agency agreed that a summary of results from the individual trials (EFC14038, ACT14132, TDR12857, and LTS13769) would be provided instead of a separate Integrated Summary of Efficacy. Evaluating the efficacy results in the individual trials, rather than pooling the efficacy results, is an acceptable approach because each of the trials evaluate avalglucosidase alfa in different populations and use different trial designs.

To evaluate the efficacy of avalglucosidase alfa, the review team evaluated data presented from 146 patients who received either avalglucosidase alfa or alglucosidase alfa: 124 patients with LOPD and 22 patients with IOPD. For short-term efficacy in treatment of patients with LOPD, we reviewed FVC (% predicted) and the 6MWT in patients who received avalglucosidase alfa compared to those who received alglucosidase alfa in trial EFC14028. For long-term efficacy in patients with LOPD who received avalglucosidase alfa, we evaluated the FVC (% predicted) and 6MWT at 2 years in EFC14028 and at 6 years in LTS13769. For short-term efficacy in the treatment of patients with IOPD, we reviewed the Gross Motor Function Measure-88 (GMFM-88), Quick Motor Function Test (QMFT), Pompe Pediatric Evaluation of Disability Inventory (Pompe-PEDI), Left Ventricular Mass Index (LVMI), and LVM Z-score. For long-term efficacy in patients with IOPD who received avalglucosidase alfa, we reviewed the same endpoints at 2 years.

Determination of Safety

All four trials were reviewed to determine the safety of avalglucosidase alfa in patients with Pompe disease. The safety data from these trials were pooled by the Applicant and presented as the Integrated Summary of Safety. This population of 138 patients with Pompe disease received avalglucosidase alfa, including 95 patients with LOPD from EFC14028, 5 patients with LOPD from TDR12857, 19 patients with LOPD from LTS13769, and 19 pediatric patients with IOPD from ACT14132. Three additional pediatric patients with IOPD were included in the 120-day safety report.

The analysis of general safety—assessment of adverse events, laboratory evaluations, vital signs, and electrocardiograms—was based on descriptive summaries and review of source data. Case report forms and patient narratives were reviewed for anaphylaxis, death, discontinuations, and withdrawals. Clinical trial data were independently analyzed using JMP and Python software. All safety assessments and conclusions are those of the clinical review team unless otherwise specified.

We also evaluated safety in EFC14028 and ACT14132 where avalglucosidase alfa was compared directly to alglucosidase alfa. In the primary analysis period, EFC14028 started with 51 patients who received avalglucosidase alfa and 49 patients who received alglucosidase alfa. Four patients in the latter group later discontinued their participation. In stage 2, six patients received avalglucosidase alfa and five received alglucosidase alfa.

Reference ID: 4836879

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Avalglucosidase Alfa

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized[2]	No. of Centers and Countries
EFC14028 (NCT02782741)	Treatment-naïve patients with LOPD ≥3 years of age	Control type: Active Randomization: Randomized Blinding: Double-blind Innovative design features: 12 month PAP study followed by a long-term open label ETP	Drug: Avalglucosidase alfa Dosage: 20 mg/kg qow Number treated: 51 Duration: 49 wk Drug: Alglucosidase alfa Dosage: 20 mg/kg qow Number treated: 49 Duration: 49 wk	Primary: Effect of avalglucosidase alfa treatment on FVC (% predicted) compared to alglucosidase alfa Secondary: Functional endurance using the 6MWT, inspiratory muscle strength (MIP), expiratory muscle strength (MEP), lower extremity muscle strength, motor function and health-related quality of life	96, 100	69 centers in 26 countries
ACT14132 (NCT03019406)	Patients with IOPD previously treated with alglucosidase alfa, with either clinical decline or suboptimal response	Control type: Active Randomization: Actual enrolled Blinding: None Innovative design features: Multistage, open-label, ascending dose cohort, repeated IV study with long-term open label ETP. There were three cohorts in this study.	Drug: Avalglucosidase alfa Stage 1 Dosage: Cohort 1: 20 mg/kg qow; Cohort 2: 40 mg/kg qow Stage 2 Dosage: Cohort 3 40 mg/kg qow or the previous prestudy dose Number treated: Cohort 1: 6; Cohort 2: 10 Duration: 25 wk Drug: Alglucosidase alfa Dosage: 20-40 mg/kg/qow Number treated: 6 Duration: 25 wk	Primary: Evaluate safety profile of avalglucosidase alfa in patients with IOPD previously treated with alglucosidase alfa Secondary: Characterize PK profile and evaluate preliminary efficacy compared to alglucosidase alfa	20, 22	10 centers in 5 countries

Reference ID: 4836879

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized[2]	No. of Centers and Countries
TDR12857 (NCT01898364)	Treatment-naïve and treatment-experienced patients with LOPD	Control type: Uncontrolled Randomization: Actual enrolled Blinding: None Biomarkers: Skeletal muscle glycogen content Innovative design features: Open-label, ascending dose study with repeated IV infusions of avalglucosidase alfa	Drug: Avalglucosidase alfa Dosage: 5, 10, 20 mg/kg qow Number treated: Group 1: 10; Group 2: 14 Duration: 41 wk	Primary: Assess safety and tolerability of avalglucosidase alfa and characterize PD and PK after repeat infusions in patients with LOPD	21, 24	17 centers in 7 countries
LTS13769 (NCT02032524)	Treatment-naïve and treatment-experienced patients with LOPD from trial TDR12857	Control type: Uncontrolled Randomization: Actual enrolled Blinding: None Biomarkers: Skeletal muscle glycogen content Innovative design features: Open-label extension study with patients who finished trial TDR12857	Drug: Avalglucosidase alfa Dosage: 5, 10, 20 mg/kg qow Number treated: 19 Duration: 6 y	Primary: Assess long-term safety and PK of avalglucosidase alfa in patients with LOPD Secondary: Assess the long-term effect of avalglucosidase alfa on PD and exploratory efficacy variables to assess if the benefits of the drug were maintained and to assess the time course of response	24, 19	16 centers in 7 countries

Source: Clinical review team
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: 6MWT, 6-minute walk test; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; DB, double-blind; ETP, extension treatment period; FVC, forced vital capacity; Hex4, hexose tetrasaccharide; IOPD, infantile-onset Pompe disease; IV, intravenous; LOPD, late-onset Pompe disease; LTE, long-term extension study; MC, multicenter; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; N, number of subjects; OL, open-label; PAP, primary analysis period; PC, placebo-controlled; PD, pharmacodynamics; PG, parallel group; PK, pharmacokinetics; qow, every other week; R, randomized; wk, week

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	2.1, 6.2, and 12
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☒	Performance outcome	2.1 and 6.2
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☒	Patient-focused drug development meeting summary report	3
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The pharmacologic activity, pharmacokinetics (PK), and clinical pharmacology of avalglucosidase alfa that are relevant to the interpretation of benefit and risk are summarized in Table 5.

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Avalglucosidase alfa is a hydrolytic lysosomal glycogen-specific enzyme.
Mechanism of action	Pompe disease (also known as glycogen storage disease type II, acid maltase deficiency, and glycogenosis type II) is an inherited disorder of glycogen metabolism caused by deficiency of lysosomal enzyme alpha-glucosidase (GAA), which results in intralysosomal accumulation of glycogen in various tissues. Avalglucosidase alfa provides an exogenous source of GAA. The M6P on avalglucosidase alfa mediates binding to M6P receptors on the cell surface, after which it is internalized and transported into lysosomes where it undergoes proteolytic cleavage that results in increased enzymatic activity. Avalglucosidase alfa then exerts enzymatic activity in cleaving glycogen.
Active moieties	Avalglucosidase alfa is created by conjugating bis-mannose-6-phosphate (bis-M6P) to oxidized sialic acid residues on alglucosidase alfa. Alglucosidase alfa is a recombinant human acid alpha-glucosidase (rhGAA).
	General Information
Bioanalysis	Avalglucosidase alfa concentrations in human plasma were determined using two validated enzymatic activity assays: study DOH1429 with a lower limit of quantification (LLOQ) of 0.0125 µg/mL and study DOH1626 with a LLOQ of 0.0120 µg/mL. The two methods were cross-validated.
Healthy subjects versus patients	PK of avalglucosidase alfa has not been assessed in healthy subjects.
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	LOPD: The mean ± SD plasma C_{max} and AUC_{last} of avalglucosidase alfa at week 1 and week 49 following IV infusion of 20 mg/kg every other week in patients with LOPD are summarized below: **Mean+SD Plasma C_{max} and AUC_{last} of Avalglucosidase Alfa at Weeks 1 and 49 Following IV Infusion of 20 mg/kg Every Other Week in Patients With LOPD** Parameter / Week 1 / Week 49 N / 49 / 48 C_{max} (µg/mL) / 259±72 / 242±81 AUC_{last} (µg•hr/mL) / 1290±420 / 1250±433

Characteristic	Drug Information

IOPD: The mean ± SD plasma C_{max} and AUC_{last} of avalglucosidase alfa at week 1 and week 25 following 20 mg/kg every other week in patients with IOPD (clinical decliners) are summarized below:

Mean+SD Plasma C_{max} and AUC_{last} of Avalglucosidase Alfa at Weeks 1 and 25 Following 20 mg/kg Every Other Week in Patients With IOPD (Clinical Decliners)

Parameter	Week 1	Week 25
N	5	5
C_{max} (µg/mL)	189±57	175±66
AUC_{last} (µg•hr/mL)	923±352	805±295

The mean ± SD plasma C_{max} and AUC_{last} of avalglucosidase alfa at week 1 and week 25 following 40 mg/kg every other week in patients with IOPD are summarized below:

Mean+SD Plasma C_{max} and AUC_{last} of Avalglucosidase Alfa at Weeks 1 and 25 Following 40 mg/kg Every Other Week in Patients With IOPD

	Clinical Decliners		Suboptimal Response	
Parameter	Week 1	Week 25	Week 1	Week 25
N	4	5	4	5
C_{max} (µg/mL)	403±171	297±60	250±45	356±85
AUC_{last} (µg•hr/mL)	2630±972	1930±348	1720±255	2200±533

Source of data: Table 43, CSR of trial EFC14028; Tables 31 and 32, CSR of trial ACT14132. AUC_{last} = area under the concentration-time curve from time 0 to the last measurable drug concentration up to approximately 8 hr post dosing; C_{max} = maximum plasma concentration

Range of effective dosage(s) or exposure

LOPD: The recommended dose of avalglucosidase alfa is 20 mg/kg of actual body weight administered every other week as intravenous infusion for patients ≥30 kg and 40 mg/kg of actual body weight administered every two weeks as intravenous infusion for patients <30 kg.

IOPD: A therapeutic dose of avalglucosidase alfa in IOPD cannot be recommended at this time. Two dosage regimens of avalglucosidase alfa, i.e., 40 mg/kg and 20 mg/kg of actual body weight administered every other week as IV infusion, were tested in trial ACT14132; however, the available data is not adequate to demonstrate an evidence of effectiveness of avalglucosidase alfa in IOPD.

Maximally tolerated dosage (MTD) or exposure

An MTD was not determined. The highest evaluated dosage was 40 mg/kg every other week across the clinical trials in patients with LOPD and IOPD.

Dosage proportionality

LOPD: Following 5, 10, and 20 mg/kg IV infusions every other week, no major deviation from dose proportionality was observed for C_{max} and AUC.

IOPD: Following 20 and 40 mg/kg IV infusions every other week, no major deviation from dose proportionality was observed for C_{max} and AUC.

Reference ID: 4836879

Characteristic	Drug Information
Accumulation	LOPD: No accumulation of avalglucosidase alfa was observed following 5, 10 and 20 mg/kg IV infusions every other week. IOPD: No accumulation of avalglucosidase alfa was observed following 20 and 40 mg/kg IV infusions every other week.
	Distribution
Volume of distribution	LOPD: 3.4 L IOPD: 4.0 to 5.4 L
Plasma protein binding	Plasma protein binding of avalglucosidase alfa has not been characterized.
	Elimination
Clearance	LOPD: 0.9 L/h IOPD: 0.5 to 0.7 L/h
Terminal Half-life	LOPD: 1.6 h IOPD: 0.8 to 1.2 h
Metabolic pathway(s)	The metabolic pathway of avalglucosidase alfa has not been characterized. The protein portion of avalglucosidase alfa is expected to be degraded into small peptides or amino acids via catabolic pathways.
Primary excretion pathways (% dosage)	No specific excretion studies were conducted.
	Intrinsic Factors and Specific Populations
Body weight	The population pharmacokinetics (popPK) analysis including patients with LOPD and IOPD identified body weight as a significant covariate influencing avalglucosidase alfa PK. Within the same dosage regimen (e.g., 20 mg/kg IV every other week), the exposure of avalglucosidase alfa was lower in patients with lower body weight compared to patients with higher body weight.
Age	The popPK analysis indicated that age was not a significant covariant influencing avalglucosidase alfa PK.
Renal impairment	No dedicated trial of the effect of renal impairment on the PK of avalglucosidase alfa was conducted. Based on 6 patients with a mild renal impairment (eGFR 60-89 mL/min at baseline), the popPK analysis indicated that eGFR was not a significant covariant influencing avalglucosidase alfa PK. No data are available in patients with moderate or severe renal impairment.
Hepatic impairment	No dedicated trial of the effect of hepatic impairment on the PK of avalglucosidase alfa was conducted.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	No specific drug-drug interaction studies were conducted with avalglucosidase alfa.
Inhibition/induction of transporter systems	No specific drug-drug interaction studies were conducted with avalglucosidase alfa.

Characteristic	Drug Information
	Immunogenicity
Bioanalysis	Immunogenicity for trial TDR12857 and the initial component of trial LTS13769 was assessed using a qualified enzyme linked immunosorbent assay to screen samples for antidrug antibodies (ADA) and a separate radio-immunoprecipitation assay to confirm the specificity of the response (ITR-708-0414 and ITR-636-0513, respectively). In trials EFC14028 (LOPD), LTS13769 (long-term extension; for samples collected after June 2016), and ACT14132 (IOPD), the assay format was updated to utilize a floating cut point and drug competition confirmatory assay (DOH1430 (ITR-822-0216)).
Incidence	• Among treatment-naïve patients (n=61), 58 (95%) patients developed treatment-emergent ADA with a median time to seroconversion of 8 weeks and a median peak titer of 3200. The majority patients had low or intermediate response (36 patients, 59%); 13 (22%) patients had a high response with a peak titer ≥12,800. • Among treatment-naïve patients (n=61), 17 (28%) patients developed neutralizing antibody (NAb) that inhibited avalglucosidase alfa catalytic activity, 24 (39%) patients developed NAb that inhibited cellular uptake, and 13 (21%) patients developed NAb that inhibited avalglucosidase alfa catalytic activity and also inhibited cellular uptake. The median duration for NAb positivity for catalytic activity inhibition was 12 weeks, and the median duration for NAb positivity for cellular uptake inhibition was 52 weeks. • Among adult patients previously treated with alglucosidase alfa (n=58), the majority (43 patients, 74%) had pre-existing ADA at baseline, and 32 (55%) patients developed treatment-emergent ADA. • Among adult patients previously treated with alglucosidase alfa (n=58), 10 (18%) patients developed NAb that inhibited avalglucosidase alfa catalytic activity, 12 patients (21%) developed NAb that inhibited cellular uptake, and 3 (5%) patients developed NAb that inhibited both avalglucosidase alfa catalytic activity and inhibited cellular uptake. • Among the pediatric patients previously treated with alglucosidase alfa (n=16), 2 patients had pre-existing ADA at baseline. One of the 6 (17%) patients treated with 20 mg/kg avalglucosidase alfa developed treatment-emergent ADA. Of the 10 patients treated with 40 mg/kg avalglucosidase alfa, 5 (50%) developed treatment emergent ADA. • One pediatric patient (10%) treated with 40 mg/kg avalglucosidase alfa (n=10) developed NAb that inhibited cellular uptake.
Clinical impact	**Cross-Reactivity** ADA cross-reactivity studies showed that antibodies to avalglucosidase alfa are cross-reactive to alglucosidase alfa. **Impact on PK** • No apparent change in median AUC was observed between week 1 and week 49 irrespective of ADA peak titer category. • The population PK analysis including 75 patients with LOPD did not identify ADA as a significant covariate influencing avalglucosidase alfa PK (study POH0703).

Characteristic	Drug Information
	Impact on PD and efficacy • A trend toward decreased pharmacodynamic response as measured by percent change of urinary glucose tetrasaccharides from baseline was observed in patients with ADA peak titer ≥12,800. • The development of ADA did not have an apparent impact on clinical efficacy. The change from baseline to week 49 for FVC (% predicted) for treatment-naïve patients (n=55) with treatment-emergent ADA was a median of 3.72 (mean [SD] of 2.98 [7.08]) compared to the 2 always negative patients who had a median of 2.62 (mean [SD] of 2.62 [2.15]). The distribution of the FVC (% predicted) by ADA peak titer category in treatment-naïve patients was generally overlapping between different ADA peak titer categories. **Impact on safety** *Hypersensitivity and infusion-associated reactions* • In avalglucosidase alfa-treated patients, the incidence of infusion-associated reactions (IAR) was 62% (8/13) in those with an ADA peak titer ≥12,800, compared with incidences of 19% (8/43) in those with ADA peak titer <12,800 and 33% (1/3) in those who were ADA-negative. • Increased incidence of hypersensitivity reactions was observed in patients with higher ADA titers (4/13, 31%) compared to lower ADA titers (2/14, 14%). • In enzyme replacement therapy (ERT)–experienced adult patients, the occurrences of IARs and hypersensitivity reactions were higher in patients who developed ADA compared to patients who were ADA-negative. • One (1) treatment-naive patient (ADA peak titer 3,200) and 2 treatment-experienced patients (ADA peak titers; 800 and 12,800, respectively) developed anaphylaxis. *Overall treatment emergent adverse events* • Among treatment-naïve patients, the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and IARs were similar between patients with ADA-negative status (n=3) and treatment-emergent ADA (n=58). See Section 14.3 for additional immunogenicity results.

Abbreviations: ADA, antidrug antibodies; AUC, area under the concentration-time curve; IAR, infusion-associated reactions; IOPD, infantile-onset Pompe disease; IV, intravenous; LOPD, late-onset Pompe disease; SD, standard deviation; eGFR, estimated glomerular filtration rate

5.1. Nonclinical Assessment of Potential Effectiveness

The pharmacodynamic effects of avalglucosidase alfa were assessed in GAA knockout (GAAKO) mice, a mouse model of Pompe disease in which both alleles of GAA are inactivated by homologous recombination. Intravenous (IV) bolus administration was used in all primary pharmacodynamic studies. These studies were conducted to evaluate the efficacy of avalglucosidase alfa by assessing depletion of glycogen from target tissues. Tissue glycogen content was measured biochemically and histologically. These studies demonstrated that (1) avalglucosidase alfa could effectively deplete glycogen from the heart (pharmacological active dose [PAD] of 4 mg/kg IV), diaphragm, and other skeletal muscles (PAD of 12 mg/kg IV), and (2) avalglucosidase alfa appeared to be approximately 3- to 7-fold more potent than alglucosidase alfa in terms of glycogen reduction when compared on a dose basis.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

The recommended dosage regimens in patients with LOPD are based on the individual patient's body weight. For details on dose selection, refer to Section 6.3.2 and Appendix 14.5.

6.1.1. Proposed Dosage Regimen

Nexviazyme (avalglucosidase alfa) is proposed as an ERT for the treatment of patients with Pompe disease (alpha-glucosidase deficiency). Avalglucosidase alfa is administered as an intravenous infusion. The proposed dosage regimen in patients with LOPD is 20 mg/kg of body weight administered every other week. (b) (4) The proposed dosage regimens have been tested in a phase 3 clinical trial in patients with LOPD (trial EFC14028) and a phase 2 clinical trial in patients with IOPD (trial ACT14132).

6.1.2. Dose Selection for the Clinical Studies in Patients With LOPD

Phase 1/2 First-in-Human Trial TDR12857 (NEO-1)

The starting dose (5 mg/kg) for trial TDR12857 in adult patients with LOPD was based on the no observed adverse effect level (NOAEL) determined in a 26-week cynomolgus monkey study (200 mg/kg qow) and the observed pharmacologically active dose (PAD) of avalglucosidase alfa in nonclinical studies. The maximum recommended starting dose was 20 mg/kg qow by applying a safety factor of 10. Based on the Pompe disease mouse model, PAD was defined as the minimum level of avalglucosidase alfa associated with glycogen clearance. Four weekly infusions of avalglucosidase alfa at 4 mg/kg reduced tissue glycogen in the heart by approximately 50%, whereas 12 mg/kg reduced skeletal muscle glycogen by approximately 25% to 70% depending on the muscle evaluated (quadriceps, psoas, triceps, and diaphragm). In addition, two nonclinical studies (study 07-1948 and study 10-00587) demonstrated that

avalglucosidase alfa is as at least 3- to 7-fold more potent in terms of tissue glycogen reduction in the GAA knockout mouse relative to alglucosidase alfa, following four weekly IV doses.

- The starting dose administered to treatment-naïve patients with LOPD (group 1) and in patients with LOPD previously treated for a minimum of 9 months with alglucosidase alfa (group 2) was 5 mg/kg qow. An ascending dose process was used, allowing the monitoring of potential safety signals and taking into consideration the difference in PAD between cardiac and skeletal muscles, and patients could proceed to the next dose level (from 5 mg/kg to 10 mg/kg, and then to 20 mg/kg qow).
- At week 25, the percentage predicted FVC showed an apparent increase relative to baseline in patients who received avalglucosidase alfa 10 or 20 mg/kg qow and remained stable in patients who received 5 mg/kg qow.

Phase 3 Trial EFC14028 (COMET)

Based on results obtained from the phase 1/2 trial TDR12857, avalglucosidase alfa dose of 20 mg/kg qow was selected for treatment-naïve patients with LOPD in trial EFC14028. After 49 weeks of treatment, patients continued in the trial for the 144-week open-label extension treatment period (ETP), during which all patients received a 20 mg/kg avalglucosidase alfa qow.

6.1.3. Dose Selection for the Clinical Studies in Patients With IOPD

Phase 2 Trial ACT14132 (Mini-COMET)

The ACT14132 trial enrolled male and female pediatric patients diagnosed with IOPD, who had been treated with alglucosidase alfa and had demonstrated clinical decline or suboptimal clinical response. Avalglucosidase alfa was administered in an ascending dose manner in cohort 1 (20 mg/kg qow) and cohort 2 (40 mg/kg qow). The dose of 40 mg/kg was selected based on previous experience with alglucosidase alfa where patients with IOPD are often treated with a higher dose when not responding to 20 mg/kg dosing regimen. Cohort 3 was initiated after determination of the highest tolerated avalglucosidase alfa dose in cohorts 1 and 2. Cohort 3 patients were randomized 1:1 to receive either avalglucosidase alfa 40 mg/kg qow or their stable dose of alglucosidase alfa (dose range: 20 mg/kg qow to 40 mg/kg qw) that they had been administered regularly for a minimum of 6 months. After 6 months of randomized treatment, all patients continued on a long-term avalglucosidase alfa treatment and follow-up in an ETP for up to 3 years.

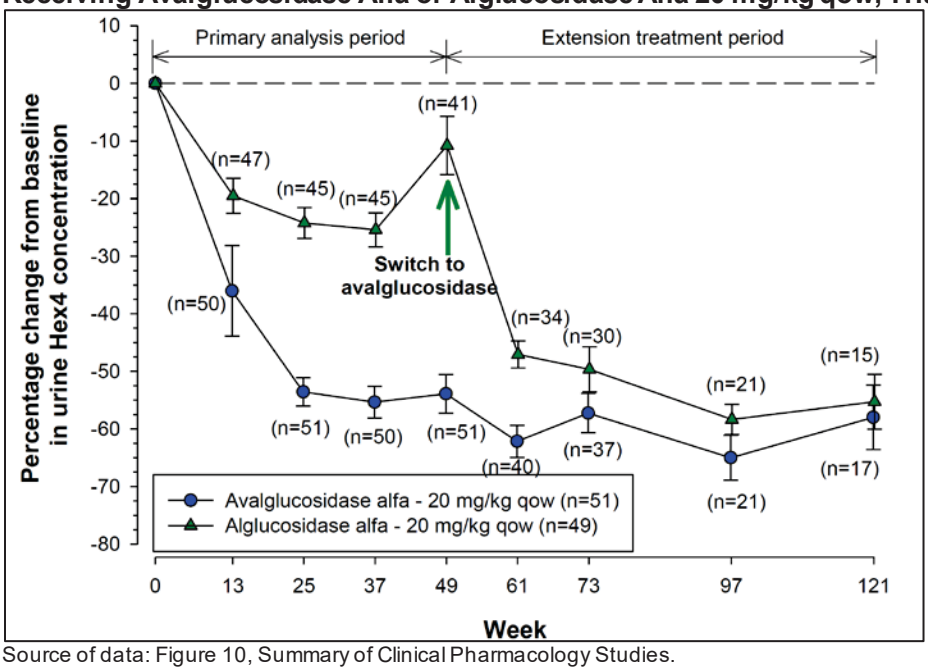
6.1.4. Pharmacodynamics in Patients With LOPD

In patients with Pompe disease, excess glycogen is degraded to hexose tetrasaccharide (Hex4). Patients with Pompe disease have higher Hex4 concentrations in urine compared to healthy subjects. Glucose tetrasaccharide (Glc4) is the major component of Hex4. The Applicant assayed urinary Glc4 (which is also referred to as urinary Hex4) to assess the pharmacodynamic effect of avalglucosidase alfa or alglucosidase alfa in clinical trials. Glc4 urine concentrations were quantified using a validated liquid chromatography with tandem mass spectroscopy (LC-MS/MS) method with a LLOQ of 0.5 µg/mL (study ITR-580-0312).

Reference ID: 4836879

In the phase 3 trial EFC14028 (COMET), urinary Hex4 was assessed in patients with LOPD following treatment with avalglucosidase alfa or alglucosidase alfa 20 mg/kg qow for 49 weeks (i.e., the primary analysis period). After week 49, in the extension treatment period, patients treated with alglucosidase alfa switched to avalglucosidase alfa at the same dosage regimen of 20 mg/kg qow. Mean (SE) percentage changes from baseline in urinary Hex4 in both the primary analysis period and extension treatment period are shown in Figure 1. In the primary analysis period, a greater mean reduction in urinary Hex4 was observed in patients treated with avalglucosidase alfa than in patients treated with alglucosidase alfa. In the extension treatment period, mean urinary Hex4 level in patients switching from alglucosidase alfa to avalglucosidase alfa reduced to a level similar to patients who initiated treatment with avalglucosidase alfa during the primary analysis period.

Figure 1. Mean (SE) Percentage Change From Baseline in Urinary Hex4 in Patients With LOPD Receiving Avalglucosidase Alfa or Alglucosidase Alfa 20 mg/kg qow, Trial EFC14028 (COMET)



Source of data: Figure 10, Summary of Clinical Pharmacology Studies.
At baseline, the mean ± SD value of urinary Hex4 was 12.71±10.10 mmol/mol in the avalglucosidase alfa group and 8.74±5.04 mmol/mol in the alglucosidase alfa group.

The exposure-response (E-R) relationship between avalglucosidase alfa exposure (area under the curve $(AUC)_{2W}$ and C_{max}) and urinary Hex4 levels was explored in patients with LOPD receiving the 20 mg/kg qow dosage in trial EFC14028 (COMET); however, no evidence of an E-R relationship was observed.

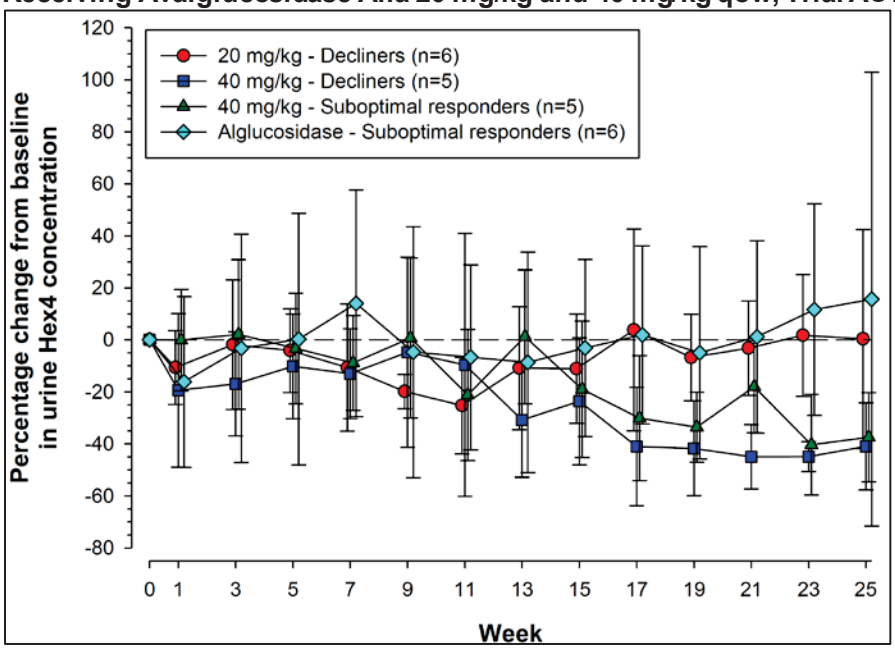
Of note, in phase 1/2 trial TDR12857, no clear dose-response relationship for reduction of urinary Hex4 was observed across the avalglucosidase alfa doses of 5 mg/kg (n=4), 10 mg/kg (n=3), and 20 mg/kg (n=3) qow for 25 weeks of treatment. This is potentially affected by small sample size and imbalance in baseline urinary Hex4 levels across dose groups (Figure 22). For details refer to Section 14.2.

6.1.5. Pharmacodynamics in Patients With IOPD

In the phase 2 trial ACT14132, urinary Hex4 was assessed in patients with IOPD following treatment with avalglucosidase alfa at 20 mg/kg and 40 mg/kg qow or alglucosidase alfa at previously received stable doses ranging from 20 mg qow to 40 mg/kg qw. Mean (SE) percentage changes from baseline in urinary Hex4 in the primary analysis period are shown in Figure 2. A trend for greater reductions in urinary Hex4 was observed in decliners and suboptimal responders to alglucosidase alfa who were treated with avalglucosidase alfa 40 mg/kg qow, as compared to decliners to alglucosidase alfa treated with avalglucosidase alfa 20 mg/kg qow. Patients treated with 40 mg/kg qow showed greater reductions in urinary Hex4 as compared to patients treated with a stable dose of alglucosidase alfa.

The relationship between avalglucosidase alfa exposures (AUC_{2w} and C_{max}) and urinary Hex4 levels was explored in patients with IOPD receiving 20 mg/kg or 40 mg/kg qow (trial ACT14132). Consistent with the dose-response relationship, a trend for lower Hex4 levels was observed with increasing avalglucosidase alfa exposures.

Figure 2. Mean (SE) Percentage Change From Baseline in Urinary Hex4 in Patients With IOPD Receiving Avalglucosidase Alfa 20 mg/kg and 40 mg/kg qow, Trial ACT14132



Source of data: Figure 11, Summary of Clinical Pharmacology Studies.
The mean value of urinary Hex4 level at baseline was 80.25 mmol/mol in clinical decliners to alglucosidase alfa treated with avalglucosidase alfa 20 mg/kg qow, 63.43 mmol/mol in clinical decliners to alglucosidase alfa treated with avalglucosidase alfa 40 mg/kg qow, 54.81 mmol/mol in suboptimal responders to alglucosidase alfa treated with avalglucosidase alfa 40 mg/kg qow, and 52.16 mmol/mol in suboptimal responders treated with a stable dose of alglucosidase alfa.

6.1.6. Exposure-Response Relationship for Efficacy in Patients With LOPD

The Applicant conducted exploratory exposure-response analyses evaluating the relationship between avalglucosidase alfa exposures (AUC_{2w} and C_{max}) and efficacy endpoints including FVC (% predicted) and 6MWT. The E-R analyses were performed by linear regressions for the patients with LOPD treated with avalglucosidase alfa 20 mg/kg qow in the phase 3 trial

EFC14028 (COMET). The exposure parameters C_{max} and AUC_{2W} were determined based on individual PK simulations using a population PK model (study POH0703). The efficacy endpoints were FVC (% predicted) and 6MWT change from baseline at week 49. The exposure-response analyses did not identify any positive relationship between the exposure and efficacy endpoints (see Section 14.5.2.1)

6.1.7. Exposure-Response for Safety

The E-R analyses for safety were performed in all patients and each subgroup of patients with IOPD, patients with LOPD, treatment-naïve and non-naïve patients. For safety endpoints included in the Applicant's E-R analyses, no significant relationship between adverse event incidence and exposure was observed. Refer to Section 14.5 for more information.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. EFC14028 (COMET)

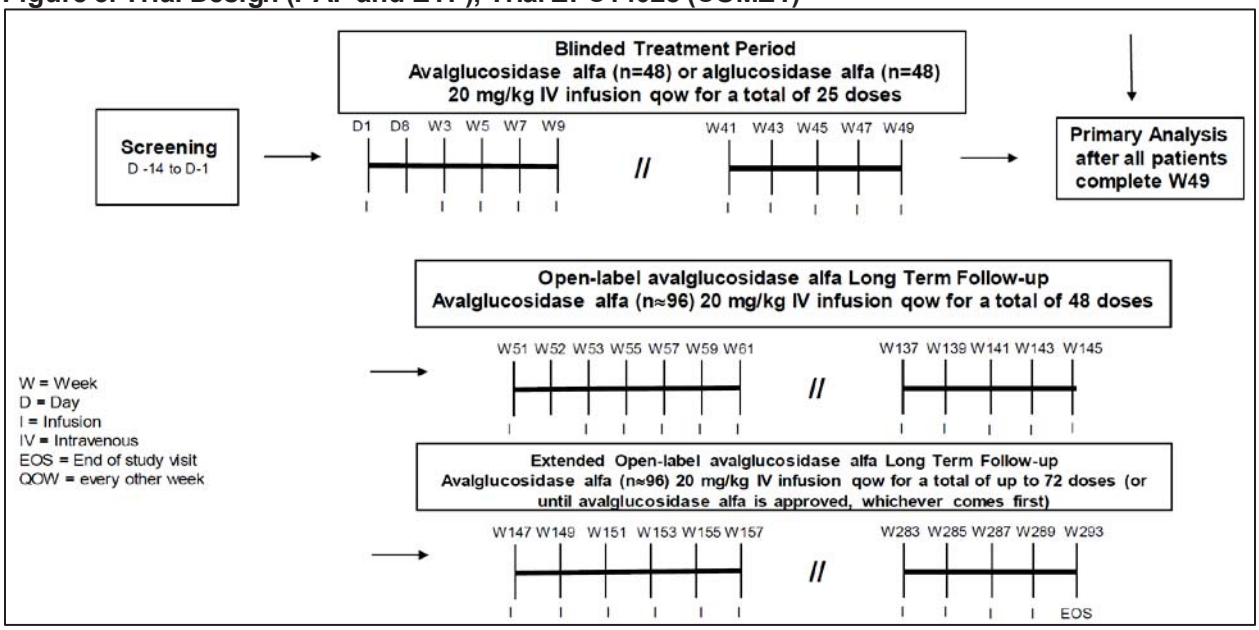
6.2.1.1. Design, EFC14028 (COMET)

The pivotal trial, EFC14028 (COMET), conducted in 69 centers in 26 countries, was a randomized, double blind, comparator-controlled study in treatment-naïve patients 3 years of age or older with LOPD, although the youngest enrolled patient was 16 years of age. The primary objective of this trial was to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by FVC (% predicted) in the upright position compared to alglucosidase alfa. The key secondary objectives included efficacy evaluation in functional endurance as measured by the Six Minute Walk Test (6MWT), as well as on inspiratory muscle strength (measured as maximum inspiratory pressure [MIP]), expiratory muscle strength (measured as maximum expiratory pressure [MEP]), lower extremity muscle strength (measured via hand-held dynamometry [HHD]), motor function (assessed using the Quick Motor Function Test [QMFT]) and the health-related quality of life (assessed using Medical Outcomes Study 12 Item Short Form Health Survey [SF-12]).

A total of 100 patients were randomized 1:1 to receive either avalglucosidase alfa or alglucosidase alfa at 20 mg/kg qow for a 12-month double-blind treatment period referred to as the PAP. Upon completion of the PAP, the patients continued in an open-label ETP, during which they all received avalglucosidase alfa (Figure 3). Randomization was stratified by baseline FVC (<55% or ≥55%), sex, age (<18 years and ≥18 years) and country (Japan or not-Japan).

The duration of the trial included a 14-day screening period, a 49-week blinded treatment period, an open-label treatment period up to 144 weeks with avalglucosidase alfa for all trial participants, regardless of their original randomization group, and a post-treatment observation period of up to 4 weeks. Data from 49 patients receiving avalglucosidase alfa were collected to evaluate PK.

Figure 3. Trial Design (PAP and ETP), Trial EFC14028 (COMET)



Source: Figure 1 of the Clinical Study Report for trial EFC14028.
Abbreviations: ETP, extension treatment period; PAP, primary analysis period

Primary Efficacy Endpoint

The primary efficacy endpoint for the PAP is the change from baseline to week 49 in FVC (% predicted) in the upright position.

Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the change from baseline to week 49 in total distance (meters) walked during the 6MWT to measure functional endurance. Additional secondary efficacy endpoints include the following (also see Sections 6.2.1.3.3 and 6.2.1.4.4):

- Pulmonary function testing: Maximum expiratory pressure (MEP): expiratory muscle strength and maximum inspiratory pressure (MIP): inspiratory muscle strength
- Hand-held dynamometry (HHD, lower extremity strength): muscle strength
- Quick motor function test (QMFT, total score): motor function
- A 12-item short-form health survey (the physical component summary (PCS) and mental component summary (MCS) scales from the survey): health-related quality of life

6.2.1.2. Eligibility Criteria, EFC14028 (COMET)

Key eligibility criteria are summarized in this section.

Inclusion Criteria

- Males and females with confirmed GAA enzyme deficiency from any tissue source and/or two confirmed *GAA* gene variants.

Exclusion Criteria

- Age <3 years.
- Known Pompe-specific cardiac hypertrophy.
- Wheelchair dependence, inability to ambulate 40 meters without stopping and without an assistive device. Use of assistive device for community ambulation was allowed.
- Dependence on invasive ventilation (noninvasive ventilation was allowed).
- Inability to perform repeated FVC (% predicted) measurements in upright position of ≥30% predicted and ≤85% predicted.
- Previous treatment with alglucosidase alfa or any investigational therapy for Pompe disease.
- Prior or current use of immune tolerance induction therapy.

6.2.1.3. Statistical Analysis Plan, EFC14028 (COMET)

The final statistical analysis plan (SAP; version 3) was submitted to the Agency on May 1, 2020. The SAP-defined primary estimand for the primary efficacy endpoint is a treatment-policy estimand which is estimated by a mixed model for repeated measures (MMRM). Although the treatment-policy estimand is acceptable, the Agency stated that the final acceptability of its estimation based on the MMRM would be a review issue.

6.2.1.3.1. Analysis for Primary Endpoint

The SAP-defined primary analysis method for the primary efficacy endpoint was a MMRM, which included baseline FVC (% predicted), age, gender, treatment group, visit, and treatment-by-visit interaction. The visits included in the MMRM model were weeks 13, 25, 37, and 49. An unstructured covariance matrix was used to capture correlations among repeated measures within the same patient.

Per the SAP, the primary analysis was performed on the modified intent-to-treat (mITT) population defined as all randomized patients receiving at least one infusion. In the trial, every randomized patient received at least one infusion and thus the mITT population includes all randomized patients.

Noninferiority (NI) of avalglucosidase alfa to alglucosidase alfa was tested using the results from the MMRM. If the lower bound of the two-sided 95% confidence interval (CI) for the difference between the two treatment arms was larger than -1.1% (the prespecified NI margin), the trial was considered to meet the NI of avalglucosidase alfa to alglucosidase alfa. If the NI was met, then a superiority test was to be performed at a two-sided alpha level of 0.05.

Determination of NI Margin

Per the SAP, the NI margin of -1.1% was determined using the results of trial AGLU02704 (LOTS), a phase 3, randomized, double-blinded, placebo-controlled, superiority trial of alglucosidase alfa. At the IND stage, the Agency investigated the treatment effect of alglucosidase alfa over placebo at 12 months (52 weeks) observed in trial LOTS to assess the proposed NI margin. The mean change (standard deviation) from baseline in FVC (% predicted)

at 12 months was 1.7% (5.0%) for the alglucosidase alfa arm and -2.0% (4.4%) for the placebo arm. The estimated treatment difference (alglucosidase alfa minus placebo) was 3.7% [95% CI: (1.7%, 5.6%)]. In this estimation, the last available values prior to week 52 were used for patients who had missing values at week 52. The estimated treatment difference appeared to be robust given that other methods of handling missing values led to similar results: 3.6% [95% CI: (1.4%, 5.8%)]. In the other methods, missing data were handled by an MMRM model or only observed values at week 52 were used. As the lower bounds of the 95% CIs were larger than 1.1%, the proposed NI margin of -1.1% was considered acceptable by the Agency.

Primary Estimand

The primary estimand was a treatment-policy estimand. The SAP stated that "Estimand for this trial is defined as the difference between avalglucosidase alfa treatment and alglucosidase alfa in mean FVC (% predicted) change from baseline to week 49 regardless of whether intercurrent events have occurred." All observed data during the trial that include the data collected after study treatment discontinuation were used in the analyses.

Handling of Missing Data

The Applicant's primary MMRM analysis did not explicitly impute any missing data. The MMRM analysis relied on the assumption that missing data can be reasonably explained by nonmissing data in the trial, referred to as the missing-at-random (MAR) assumption.

Sensitivity Analyses

The SAP specified the following sensitivity analyses to assess the impact of missing data and robustness of the primary analysis results.

A Tipping Point Analysis to Assess Robustness to Departure From the MAR Assumption

This analysis investigated how severe departures from the MAR assumption must be in order to overturn the NI conclusion from the primary analysis. The tipping point analysis proceeds as follows:

- Step 1: Missing values for the primary endpoint (change from baseline to week 49 in FVC (% predicted)) were explicitly imputed based on the MAR assumption using multiple imputation (MI) methods. See details of the MI methods in Section 16.
- Step 2: The imputed values in step 1 were shifted in favor of alglucosidase alfa. In particular, the imputed values in the avalglucosidase alfa arm were decreased by δ_1 (>0) while the imputed values in the alglucosidase alfa arm were increased by δ_2 (>0). Note that a higher value of the primary endpoint was indicative of a better improvement in FVC (% predicted).
- Step 3: The values of (δ_1, δ_2) that overturn the NI conclusion were identified. Larger values of δ_1 and δ_2 indicated stronger robustness of the primary analysis results.

Different Analysis Models to Assess Robustness of the Primary Analysis Results

The SAP specified the following additional analysis methods to investigate robustness of the NI conclusion from the primary analysis:

- The primary efficacy endpoint was analyzed using an analysis of covariance (ANCOVA) model. The ANCOVA model included baseline FVC (% predicted), age, gender, and treatment group as covariates. For patients who prematurely discontinued the trial prior to week 49 or had missing values at week 49, their last available values were used in the analysis.
- A Wilcoxon-Mann-Whitney model was applied to compare change from baseline in FVC (% predicted) at week 49. Missing values at week 49 were imputed by baseline or last assessment for the subject, whichever was worse.

Supportive Analyses

As a supportive analysis, the SAP specified a linear mixed effects model. The linear mixed effects model included fixed effects of age, gender, treatment, time (in years as a continuous variable), and treatment by time interaction as well as subject-specific random intercept and random slope.

The review team also conducted an additional supportive analysis to assess the impact of a single site on the primary analysis results. The treatment difference was estimated by excluding one site at a time using the MMRM.

Subgroup Analyses

The SAP specifies analyses for the following subgroups: age (<18 years, 18 to <45 years, and ≥45 years), gender, baseline FVC (<55% and ≥55%), race, ethnicity, region (United States versus non-United States), baseline use of walking device, baseline 6MWT, and duration of disease. The same MMRM model for the primary analysis was used while excluding the subgroup factor from the covariates. For example, age was excluded from the covariates for the MMRM models for the age subgroups. The review team conducted additional subgroup analyses defined by baseline FVC (% predicted). Various values (from 45% to 80%) for the threshold of baseline FVC (% predicted) to define subgroups were used (see Section 16 for the results).

6.2.1.3.2. Analysis for Key Secondary Endpoint

The key secondary efficacy endpoint was analyzed using a MMRM model. The MMRM included distance walked in 6MWT at baseline, baseline FVC (% predicted), age, gender, treatment group, visit, and treatment-by-visit interaction. The visits included in the MMRM model were weeks 13, 25, 37, and 49. An unstructured covariance matrix was used to capture correlations among repeated measures within the same patient. The primary analysis of the key secondary endpoint was performed on the mITT population. Subgroup analyses were planned similarly to the primary efficacy endpoint. If the trial met superiority for the primary efficacy endpoint, a formal superiority test for the key secondary endpoint was conducted based on the results from the MMRM model.

6.2.1.3.3. Analysis for Other Secondary Endpoints

The other secondary efficacy endpoints were analyzed using MMRM models. The variables to be included in the MMRM models were as follows:

- The change from baseline in MIP (% predicted) and MEP (% predicted): baseline value of the corresponding response variable (either MIP or MEP), age, gender, treatment group, visit, and treatment by visit interaction
- Change from baseline in lower extremity muscle strength composite score: baseline lower extremity score, baseline FVC (% predicted), age, gender, treatment group, visit, and treatment-by-visit interaction
- Change from baseline in total score of QMFT: total QMFT score at baseline, baseline FVC (% predicted), age, gender, treatment group, visit, and treatment-by-visit interaction
- Change from baseline in PCS and MCS: baseline score (PCS or MCS), baseline FVC (% predicted), age, gender, treatment group, visit, and treatment-by-visit interaction

6.2.1.4. Results of Analyses, EFC14028 (COMET)

This section presents patient disposition, baseline demographics, and results of the efficacy analyses for the primary and secondary efficacy endpoints.

6.2.1.4.1. Disposition and Baseline Demographics

Patient Disposition

Disposition information is presented in Table 6. A total of 100 patients were randomized. Five patients in the alglucosidase alfa arm and no patients in the avalglucosidase alfa arm prematurely discontinued the PAP. Of the five patients in the alglucosidase alfa arm, four patients discontinued the trial due to adverse events and one patient withdrew consent. All 95 patients who completed the PAP entered the ETP, during which they received avalglucosidase alfa. At the time of data cutoff (March 19, 2020), 91 patients continued to receive avalglucosidase alfa in the ongoing ETP.

Table 6. Patient Disposition, Trial EFC14028 (COMET)

Patient Disposition	Avalgluco	Alglu	Total
Randomized	N=51	N=49	N=100
Primary analysis period (PAP)			
Completed PAP	51 (100.0)	44 (89.8)	95 (95.0)
Discontinued PAP	0 (0.0)	5 (10.2)	5 (5.0)
Adverse event	0 (0.0)	4 (8.2)	4 (4.0)
Consent withdrawal	0 (0.0)	1 (2.0)	1 (1.0)
Extension treatment period (ETP)			
Entered into ETP	51 (100.0)	44 (89.8)	95 (95.0)
Ongoing ETP	48 (94.1)	43 (87.8)	91 (91.0)
Discontinued ETP	3 (5.9)	1 (2.0)	4 (4.0)
Adverse event	2 (3.9)	1 (2.0)	3 (3.0)
Consent withdrawal	1 (2.0)	0 (0.0)	1 (1.0)

Source: Table 9 of Clinical Study Report. This table was produced by review team based on the adsl.xpt dataset located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
All values are expressed as n (%) unless stated otherwise.
Abbreviations: alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa

Baseline Demographics

Patient demographic information is presented in Table 7. The mean age was 48.1 years, and the majority of patients were White (94%). Gender was well balanced between the two treatment arms. The mean and median ages in the avalglucosidase alfa arm were slightly lower than those in the alglucosidase alfa arm. Hispanic or Latino ethnicity was represented more in the alglucosidase alfa group (24.5%) than in the avalglucosidase alfa group (5.9%). However, given the low number of Hispanic or Latino patients in the trial (n=15), the review team concluded that this difference between groups would not likely impact the efficacy results.

Table 7. Baseline Demographics, Trial EFC14028 (COMET)

Characteristic	Avalgluco (N=51)	Alglu (N=49)	Total (N=100)
Age at enrollment (years)			
Mean (SD)	46.0 (14.5)	50.3 (13.7)	48.1 (14.2)
Median	47.7	48.9	48.5
Min, max	16.5, 78.2	19.5, 77.5	16.5, 78.2
Disease duration [1] (years)			
Mean (SD)	13.4 (11.0)	12.6 (10.1)	13.0 (10.5)
Median	11.5	10.4	10.7
Min, max	0.9, 58.2	0.4, 38.2	0.4, 58.2
Gender, n (%)			
Female	24 (47.1)	24 (49.0)	48 (48.0)
Male	27 (52.9)	25 (51.0)	52 (52.0)
Race, n (%)			
White	47 (92.2)	47 (95.9)	94 (94.0)
Black or African American	1 (2.0)	2 (4.1)	3 (3.0)
Asian	3 (5.9)	0 (0.0)	3 (3.0)
Ethnic, n (%)			
Not Hispanic or Latino	44 (86.3)	32 (65.3)	76 (76.0)
Hispanic or Latino	3 (5.9)	12 (24.5)	15 (15.0)
Not reported	4 (7.8)	5 (10.2)	9 (9.0)
Region, n (%)			
Europe	31 (60.8)	21 (42.9)	52 (52.0)
North America	14 (27.5)	20 (40.8)	34 (34.0)
Latin America	2 (3.9)	7 (14.3)	9 (9.0)
Asia-Pacific	4 (7.8)	1 (2.0)	5 (5.0)

Source: Table 10 of Clinical Study Report. This table was produced by review team based on the adsl.xpt dataset located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
[1] Disease duration (years) is calculated as time from first symptom of Pompe disease to first infusion of study drug.
Abbreviation: alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; SD, standard deviation

Baseline Key Efficacy Variables

Baseline data of the key efficacy variables are presented in Table 8. The mean and median FVC (% predicted) and distance walked in the 6MWT at baseline were slightly higher in the avalglucosidase alfa arm than in the alglucosidase alfa arm. The other secondary efficacy variables appeared to be well balanced between the two treatment arms, except the following: MIP (% predicted) and HHD lower extremity composite score. The avalglucosidase alfa arm showed lower baseline MEP (% predicted) and lower baseline HHD lower extremity composite score than the alglucosidase alfa arm.

The majority (83%) of the patients reported no walking device. Seven patients in the avalglucosidase alfa arm and 10 patients in the alglucosidase alfa arm used a walking device. The most common type of walking device was a straight cane (seven patients).

Table 8. Baseline Data of Key Efficacy Parameters, Trial EFC14028 (COMET)

Parameter Statistic	Avalgluco N=51	Alglu N=49	Total N=100
FVC (% predicted)			
N	51	49	100
Mean (SD)	62.5 (14.4)	61.6 (12.4)	62.1 (13.4)
Median	65.5	60.8	63.2
Min, max	32.1, 84.8	39.3, 84.5	32.1, 84.8
Distance in 6MWT (m)			
N	51	49	100
Mean (SD)	399.3 (110.9)	378.1 (116.2)	388.9 (113.5)
Median	415.7	387.0	403.5
Min, max	118.0, 630.0	138.0, 592.0	118.0, 630.0
MIP (% predicted)			
N	50	49	99
Mean (SD)	59.9 (47.1)	60.6 (41.0)	60.3 (44.0)
Median	47.6	51.1	48.1
Min, max	9.0, 262.8	17.7, 233.6	9.0, 262.8
MEP (% predicted)			
N	50	49	99
Mean (SD)	65.8 (39.0)	74.8 (35.2)	70.3 (37.3)
Median	54.2	68.0	59.6
Min, max	28.7, 232.5	19.7, 201.1	19.7, 232.5
HHD lower extremity			
N	50	46	96
Mean (SD)	1330.5 (625.4)	1466.2 (604.9)	1395.5 (616.2)
Median	1193.5	1427.5	1290.0
Min, max	323.0, 3522.0	329.0, 3218.0	323.0, 3522.0
QMFT			
N	51	46	97
Mean (SD)	41.3 (10.1)	42.3 (10.6)	41.8 (10.3)
Median	41.0	43.5	41.0
Min, max	17.0, 63.0	19.0, 63.0	17.0, 63.0
SF-12 (PCS)			
N	50	48	98
Mean (SD)	35.9 (7.8)	36.8 (9.4)	36.3 (8.6)
Median	35.0	36.0	35.4
Min, max	17.8, 55.9	16.3, 57.3	16.3, 57.3
SF-12 (MCS)			
N	50	48	98
Mean (SD)	48.3 (10.1)	50.6 (8.7)	49.4 (9.5)
Median	47.5	52.2	50.2
Min, max	24.2, 70.8	30.4, 65.0	24.2, 70.8
GMFCS, n(%)			
N	51	49	100
LEVEL I	10 (19.6)	14 (28.6)	24 (24.0)
LEVEL II	36 (70.6)	27 (55.1)	63 (63.0)
LEVEL III	5 (9.8)	8 (16.3)	13 (13.0)

Parameter Statistic	Avalgluco N=51	Alglu N=49	Total N=100
Walking device on 6MWT, n(%)			
N	51	49	100
None	44 (86.3)	39 (79.6)	83 (83.0)
Straight cane	4 (7.8)	3 (6.1)	7 (7.0)
Wide-based cane	1 (2.0)	1 (2.0)	2 (2.0)
One crutch	0 (0.0)	2 (4.1)	2 (2.0)
Rolling walker	0 (0.0)	3 (6.1)	3 (3.0)
Other	2 (3.9)	1 (2.0)	3 (3.0)

Source: Table 11 of Clinical Study Report. This table was produced by review team based on the following data sets: adsl.xpt, adre.xpt, adft.xpt, adqs.xpt, and adcc.xpt. They can be located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
Abbreviations: 6MWT, 6-minute walking test; alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; FVC, forced vital capacity; GMFCS, Gross Motor Function Classification System; HHD, hand-held dynamometry; MCS, Mental Component Summary Scale Score; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; PCS, Physical Component Summary Scale Score; QMFT, quick motor function test; SD, standard deviation; SF-12, 12-item short form health survey

6.2.1.4.2. Efficacy Results for FVC (% Predicted)

Primary Efficacy Results

The estimated mean change from baseline in FVC (% predicted) to week 49 was higher in the avalglucosidase alfa arm (Table 9): 2.9% (avalglucosidase alfa) versus 0.5% (alglucosidase alfa). The estimated treatment difference was 2.4% (95% CI: -0.1 to 5.0; p-value=0.06) favoring the avalglucosidase alfa arm. As the lower bound of the 95% CI for the difference is larger than the prespecified NI margin of -1.1%, the trial met noninferiority for the primary efficacy endpoint. The p-value for the superiority test was 0.06, slightly larger than the prespecified significance level of 0.05. Note: the primary efficacy results were not driven by the imbalance in the baseline FVC (% predicted) values between the two treatment arms (see details in the Subgroup Analyses section below).

Table 9. Change in FVC (% Predicted) From Baseline to Week 49, mITT Population, Trial EFC14028 (COMET)

Time Point Parameter	Avalgluco	Alglu	Difference[1] (95% CI)	Superiority P-Value
Baseline	N=51	N=49		
Mean (SD)	62.5 (14.4)	61.6 (12.4)		
Median	65.5	60.8		
Min, max	32.1, 84.8	39.3, 84.5		
Week 49	N=49	N=43		
Mean (SD)	65.5 (17.4)	61.2 (13.5)		
Median	69.7	59.5		
Min, max	22.4, 89.0	39.4, 84.0		
Change from baseline to Week 49				
Mean (SD)	3.0 (6.8)	-0.0 (5.8)		
Median	3.2	-0.8		
Min, max	-24.1, 19.4	-13.3, 14.1		
LS mean change[2]	**2.89 (0.88)**	**0.46 (0.93)**	**2.43 (-0.13, 4.99)**	**0.0626**

Source: Tables 11 and 12 of Clinical Study Report. This table was produced by review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
[1] Estimated difference (avalglucosidase alfa – alglucosidase alfa) and 95% confidence interval
[2] LS mean change from baseline to week 49 estimated by mixed model for repeated measures (MMRM) including treatment, visit, treatment-by-visit interaction, baseline FVC (% predicted), age (continuous), and gender; an unstructured covariance matrix was used.
Abbreviations: alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; CI, confidence interval; LS, least squares; SD, standard deviation

Two patients (4%) in the avalglucosidase alfa arm and six patients (12%) in the alglucosidase alfa arm had missing FVC (% predicted) value at week 49. See Figure 45 for the time profile of the FVC (% predicted) for the eight patients. Robustness of the primary analysis results is supported by the results of the following two sensitivity analyses that used different methods to handle missing data:

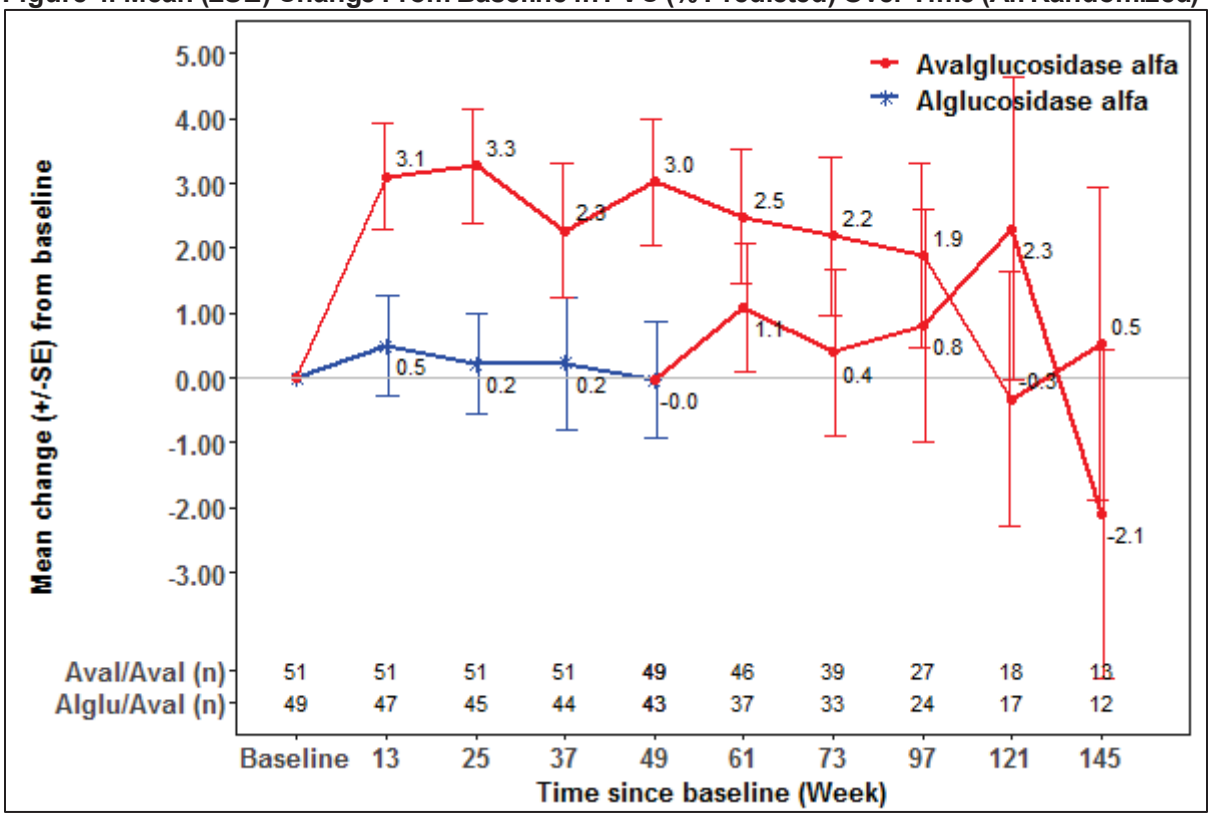
- The Applicant's tipping point analyses explicitly imputed missing values in two steps: (1) missing values were imputed based on the MAR assumption using multiple imputation methods, and (2) the imputed values were shifted such that the resulting treatment differences became less favorable to the avalglucosidase alfa arm. In particular, some (δ_1) reduction was added to the imputed values for the avalglucosidase alfa arm while a different (δ_2) increase was added to the imputed values for the alglucosidase alfa arm. In these analyses, the NI was still met with 15 of δ_1 and 2 of δ_2, which supports robustness of the primary analysis results. See Table 87 in Appendices for the full tipping point analysis results.
- The ANCOVA analysis was performed with the last available values for the patients with missing values at week 49. The estimated treatment difference from the ANCOVA analysis was 2.2% (95% CI: -0.3 to 4.7; p-value=0.09) favoring the avalglucosidase alfa arm. The NI conclusion remain the same as the lower bound of the 95% CI is larger than the NI margin of -1.1%.

  Statistical reviewer note: The Applicant's ANCOVA analysis excluded two patients in the alglucosidase alfa arm having no postbaseline FVC (% predicted) values (one discontinued the trial at day 6 and the other at day 26 from the first dose). If their baseline values were used for values at week 49, then the estimated treatment difference by the ANCOVA was 2.2% (95% CI: -0.3 to 4.7; p-value=0.09).

The nominal p-value from the nonparametric Wilcoxon-Mann-Whitney test for superiority was 0.02. The estimated rate of change from the linear mixed model was 2.6 (%/year) for the avalglucosidase alfa arm and 0.5 (%/year) for alglucosidase alfa arm. The estimated difference in the rate of change was 2.1% (95% CI: -0.5 to 4.7; p-value=0.11), numerically favoring the avalglucosidase alfa arm and supporting the results of the primary analysis. The review team's additional analyses excluding one site at a time did not alter the NI conclusion as the lower bounds of 95% CIs for the differences were larger than -1.1% (Figure 38).

Figure 4 depicts the mean change in FVC (% predicted) over time by the randomized arms. At each time point, the vertical bar presents ± standard error (SE). The red and blue lines present the mean change from baseline over time in the avalglucosidase alfa arm and the alglucosidase alfa arm, respectively. The rows "Aval/Aval (n)" and "Alglu/Aval (n)" present the number of patients with available FVC (% predicted) value at each time point for the avalglucosidase alfa arm and the alglucosidase alfa arm, respectively. The difference between the two groups was observed at week 13 (the time of the first postbaseline assessment) and maintained through week 49.

Figure 4. Mean (±SE) Change From Baseline in FVC (% Predicted) Over Time (All Randomized)



Source: Table 5 and Figure 3 of Clinical Study Report Addendum. This figure was produced by review team based on the adrew97.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
Abbreviations: FVC, forced vital capacity; SE, standard error

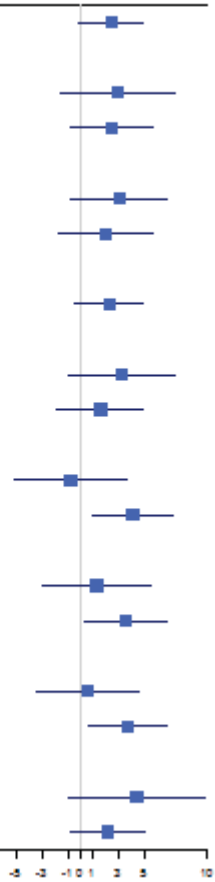
Subgroup Analyses

Figure 5 presents the results of the subgroup analyses. The estimated treatment differences numerically favor the avalglucosidase alfa arm in all subgroups except the subgroup of patients with baseline FVC (% predicted) <55%. In the subgroup of patients with baseline FVC (% predicted) <55%, the unfavorable results of the mean change for the avalglucosidase alfa arm

were majorly driven by one patient in the avalglucosidase alfa arm who had a decrease of 24.1% (Table 88 in Section 16). In this subgroup, the median change from baseline to week 49 was 1.9% for the avalglucosidase alfa arm and 1.6% for the alglucosidase alfa arm, which numerically favors the avalglucosidase alfa arm. Note that 55% was the prespecified threshold in the SAP for the subgroups by baseline FVC. The review team conducted additional subgroup analyses by varying the threshold values (from 45% to 80%). See Figure 40 in Section 16 for the results. These additional analyses did not identify any notable pattern indicating that the estimated treatment effect could be biasedly affected by the imbalance in baseline FVC (% predicted) between the treatment arms. The scatter plot (Figure 39 in Section 16) of baseline FVC (% predicted) by change from baseline in FVC (% predicted) also indicates no strong relationship between baseline FVC (% predicted) and change from baseline in FVC (% predicted). For the subgroup of Black or African American (n=3) and Asian (n=3), the primary analysis model did not converge due to the limited sample size.

Figure 5. Subgroup Analyses of Change From Baseline to Week 49 in FVC (% Predicted)

Subgroup	Aval N / Mean	Alglu N / Mean	Difference 95% CI
Overall	51 / 2.89	49 / 0.46	2.43 (-0.13, 4.99)
Age (year)			
18 to < 45	23 / 3.78	19 / 0.80	2.99 (-1.52, 7.49)
>= 45	27 / 2.32	30 / -0.14	2.46 (-0.84, 5.77)
Gender			
Female	24 / 4.20	24 / 1.15	3.06 (-0.77, 6.88)
Male	27 / 1.64	25 / -0.32	1.96 (-1.70, 5.63)
Race			
White	47 / 2.77	47 / 0.48	2.29 (-0.39, 4.97)
Region			
USA	12 / 1.81	20 / -1.47	3.28 (-0.87, 7.43)
Non-USA	39 / 3.30	29 / 1.73	1.58 (-1.81, 4.97)
Baseline FVC (%)			
< 55	16 / 0.85	19 / 1.61	-0.76 (-5.23, 3.71)
>=55	35 / 3.99	30 / -0.11	4.10 (0.95, 7.26)
Baseline 6MWT (m)			
< 403.5	22 / 1.99	28 / 0.72	1.27 (-3.03, 5.57)
>= 403.5	29 / 3.77	21 / 0.19	3.58 (0.36, 6.81)
Disease duration (year)			
< 10.7	24 / 1.62	25 / 1.03	0.59 (-3.41, 4.59)
>= 10.7	26 / 4.01	24 / 0.30	3.71 (0.64, 6.77)
Use of Walking Device			
Yes	7 / 4.77	10 / 0.32	4.44 (-1.00, 9.88)
No	44 / 2.69	39 / 0.51	2.19 (-0.76, 5.13)



Source: Figure 3 of Clinical Study Report. This figure was produced by review team based on the adrew97.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
Abbreviations: 6MWT, 6-minute walk test; CI, confidence interval; FVC, forced vital capacity

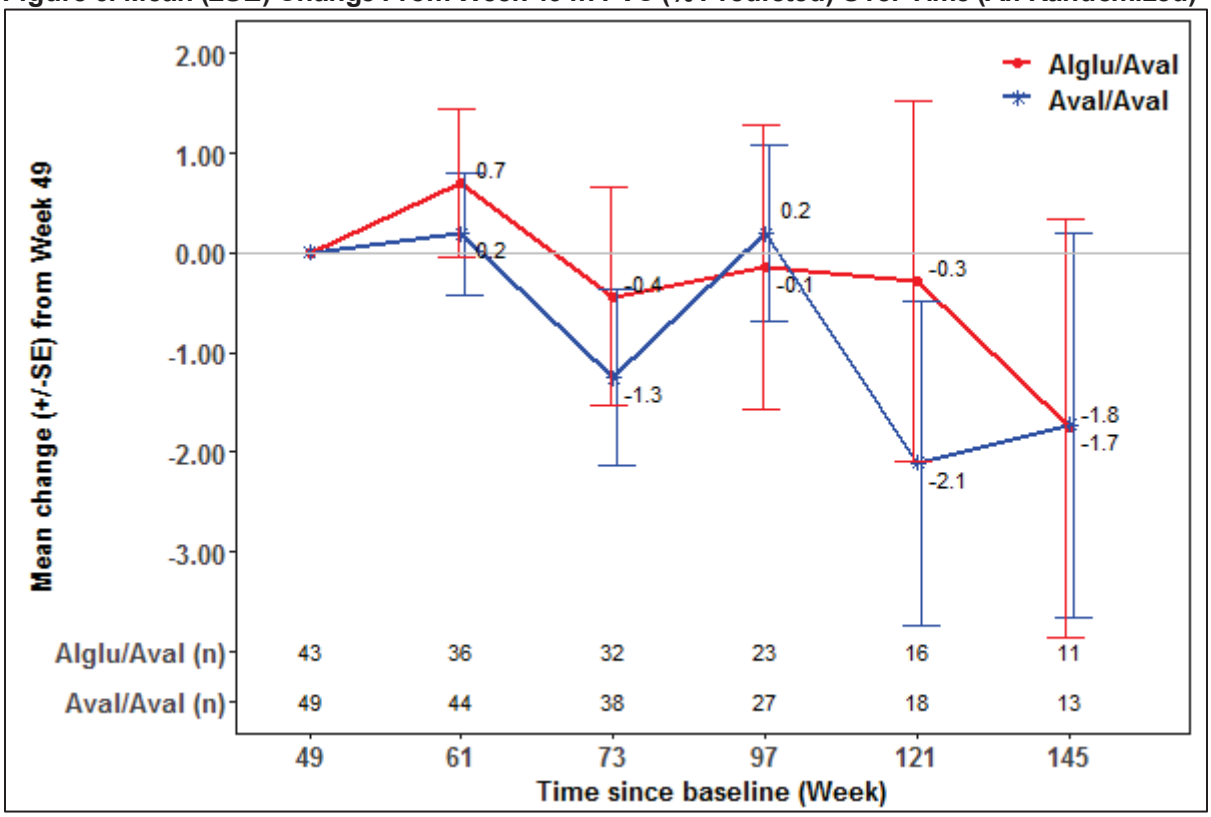
Patients Who Switched From Alglucosidase Alfa in PAP to Avalglucosidase Alfa in ETP

Of the 49 patients initially randomized to the alglucosidase alfa arm for the PAP, 44 entered the ETP and switched to avalglucosidase alfa at week 49. At the IND stage, the Applicant proposed to conduct a one-sample superiority test for the mean change in FVC (% predicted) from week 49 to week 97 for the switched patients. The one-sample superiority test was intended to provide confirmatory efficacy evidence of avalglucosidase alfa for ERT-experienced patients.

Of the 44 patients who were initially randomized to alglucosidase alfa and then were crossed over to avalglucosidase alfa, 23 patients had available FVC (% predicted) value at week 97 (as of the most recent data cutoff of July 3, 2020). The mean change in FVC (% predicted) from week 49 to week 97 among the 23 patients was -0.1% (95% CI: -3.2 to 2.8; p-value=0.92), which failed to show a statistically significant improvement.

Figure 6 depicts the mean change from week 49 in FVC (% predicted) over time by the randomized arms. At each time point, the vertical bar presents ± SE. The red and blue lines indicate the alglucosidase alfa arm and the avalglucosidase alfa arm, respectively. Overall, the data during the ETP did not show any notable improvement in FVC (% predicted) after the switch to avalglucosidase alfa at week 49.

Figure 6. Mean (±SE) Change From Week 49 in FVC (% Predicted) Over Time (All Randomized)



Source: This figure was produced by review team based on the adrew97.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
Abbreviations: FVC, forced vital capacity; SE, standard error

6.2.1.4.3. Efficacy Results for 6MWT

The estimated mean change from baseline to week 49 in distance walked in 6MWT was higher in the avalglucosidase alfa arm (Table 10): 32.2 meters (avalglucosidase alfa) versus 2.2 meters (alglucosidase alfa). The estimated treatment difference was 30.0 meters (95% CI: 1.3 to 58.7; p-value=0.04), favoring the avalglucosidase alfa arm. These results suggest that avalglucosidase alfa is effective in improving distance walked in 6MWT. However, as the superiority test for the primary endpoint did not meet the significance level of 0.05, no formal superiority test was conducted for the key secondary endpoint.

Table 10. Change in Distance in 6MWT (in Meters) From Baseline to Week 49, mITT Population, Trial EFC14028 (COMET)

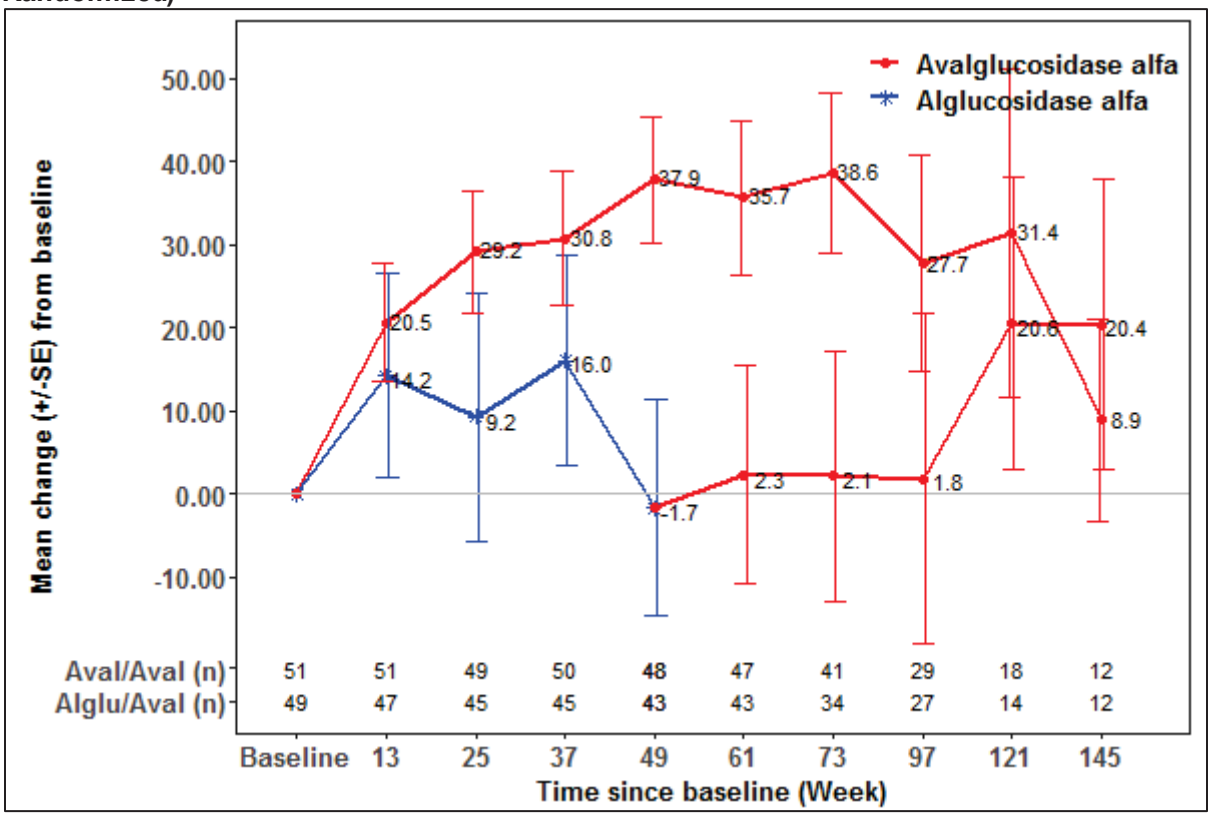
Time Point Parameter	Avalgluco	Alglu	Difference[1] (95% CI)	Superiority P-Value
Baseline	N=51	N=49		
Mean (SD)	399.3 (110.9)	378.1 (116.2)		
Median	415.7	387.0		
Min, max	118.0, 630.0	138.0, 592.0		
Week 49	N=48	N=43		
Mean (SD)	441.3 (109.8)	383.6 (141.1)		
Median	471.5	400.0		
Min, max	131.0, 636.0	86.0, 690.0		
Change from baseline to week 49				
Mean (SD)	37.9 (52.8)	-1.7 (85.2)		
Median	29.6	16.0		
Min, max	-31.0, 262.9	-394.0, 193.0		
LS mean change[2]	**32.21 (9.93)**	**2.19 (10.40)**	**30.01 (1.33, 58.69)**	0.0405

Source: Tables 11 and 16 of Clinical Study Report. This table was produced by review team based on the adft.xpt dataset located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
[1] Estimated difference (avalglucosidase alfa – alglucosidase alfa) and 95% confidence interval
[2] Least squares (LS) mean change from baseline to week 49 estimated by mixed model for repeated measures (MMRM) including treatment, visit, treatment-by-visit interaction, baseline 6MWT, baseline FVC (% predicted), age (continuous), and gender; an unstructured covariance matrix was used.
Abbreviations: 6MWT, 6-minute walk test; alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; CI, confidence interval; mITT, modified intent-to-treat; SD, standard deviation

Three patients (6%) in the avalglucosidase alfa arm and six patients (12%) in the alglucosidase alfa arm had missing values for 6MWT at week 49. To investigate robustness of the results for 6MWT, the review team conducted an ANCOVA analysis. The ANCOVA model included treatment and the same covariates used in the MMRM. The last available values prior to week 49 were used for the patients who had missing values at week 49. The estimated treatment difference from the ANCOVA analysis was 28.7 meters (95% CI: 0.8 to 56.6; p-value=0.04), which is similar to the results from the MMRM.

Figure 7 depicts the mean change in distance walked in 6MWT over time by the randomized arms. At each time point, the vertical bar presents ± SE. The red and blue lines indicate avalglucosidase alfa treatment and alglucosidase alfa treatment, respectively. The rows "Aval/Aval (n)" and "Alglu/Aval (n)" present the number of patients with available 6MWT value at each time point for the avalglucosidase alfa arm and the alglucosidase alfa arm, respectively. The largest difference between the two arms was observed at week 49.

Figure 7. Mean (±SE) Change From Baseline in 6MWT Distance (in Meters) Over Time (All Randomized)



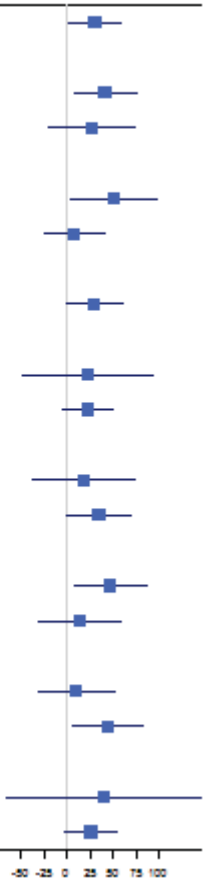
Source: Table 5 and Figure 4 of Clinical Study Report Addendum. This figure was produced by review team based on the adftw97.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
Abbreviations: 6MWT, 6-minute walk test; SE, standard error

Subgroup Analyses

Figure 8 presents the results of the subgroup analyses. The estimated treatment differences numerically favor the avalglucosidase alfa arm in all subgroups. For the subgroup of Black or African American (n=3) and Asian (n=3), the primary analysis model did not converge due to the limited sample size.

Figure 8. Subgroup Analyses of Change From Baseline to Week 49 in Distance (in Meters) Walked in 6MWT

Subgroup	Aval N / Mean	Alglu N / Mean	Difference 95% CI
Overall	51 / 32.21	49 / 2.19	30.01 (1.33, 58.69)
Age (year)			
18 to < 45	23 / 47.74	19 / 6.79	40.95 (7.06, 74.84)
>= 45	27 / 21.60	30 / -5.53	27.12 (-20.48, 74.73)
Gender			
Female	24 / 41.74	24 / -8.48	50.22 (2.89, 97.54)
Male	27 / 23.21	25 / 16.15	7.07 (-25.68, 39.81)
Race			
White	47 / 32.81	47 / 3.42	29.39 (-0.80, 59.58)
Region			
USA	12 / 3.56	20 / -19.46	23.01 (-48.34, 94.37)
Non-USA	39 / 41.17	29 / 18.62	22.55 (-4.03, 49.14)
Baseline FVC (%)			
< 55	16 / 32.77	19 / 15.45	17.32 (-38.14, 72.78)
>=55	35 / 37.46	30 / 3.07	34.40 (-0.88, 69.67)
Baseline 6MWT (m)			
< 403.5	22 / 45.39	28 / -1.08	46.47 (7.16, 85.78)
>= 403.5	29 / 15.32	21 / 1.06	14.26 (-30.26, 58.77)
Disease duration (year)			
< 10.7	24 / 26.93	25 / 17.53	9.40 (-32.04, 50.85)
>= 10.7	26 / 33.17	24 / -11.38	44.55 (5.80, 83.31)
Use of Walking Device			
Yes	7 / 18.04	10 / -21.78	39.81 (-65.65, 145.27)
No	44 / 35.48	39 / 9.60	25.88 (-3.02, 54.78)



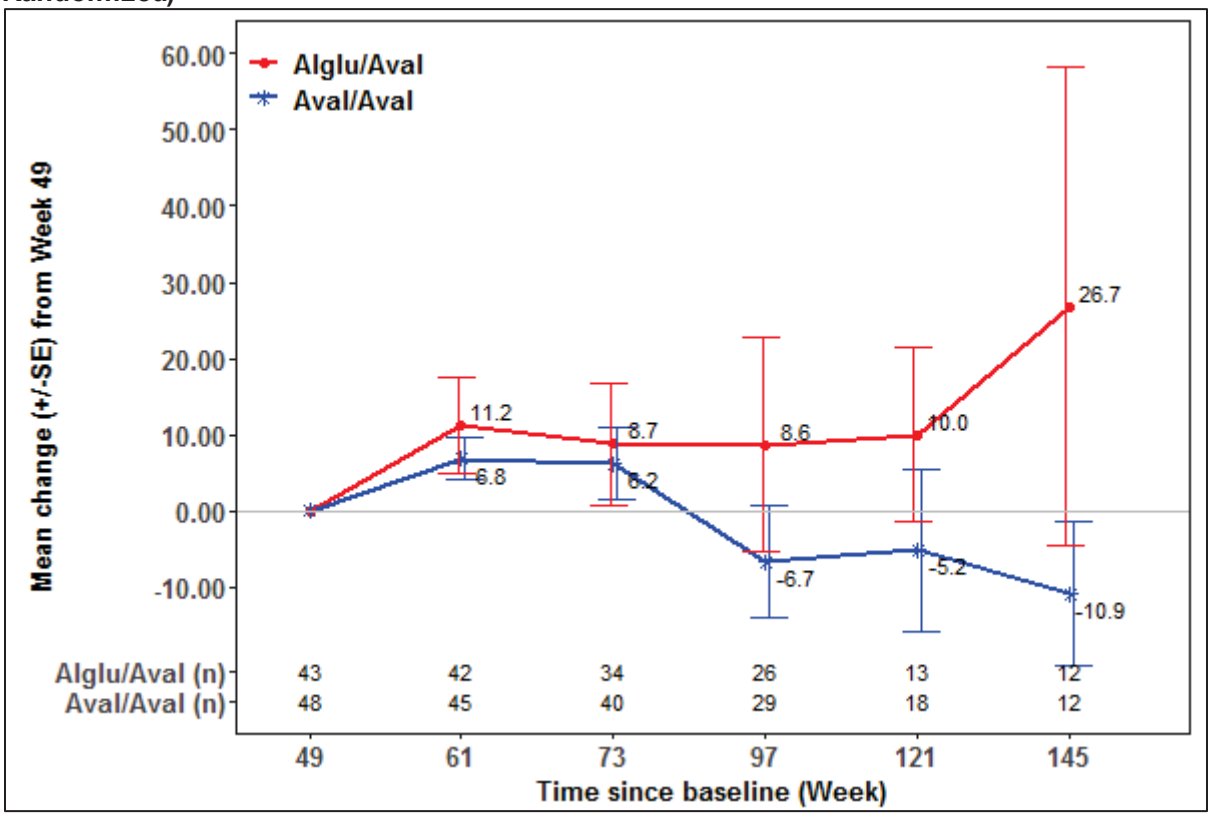
Source: Figure 6 of Clinical Study Report. This figure was produced by review team based on the adftw97 xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
Abbreviations: 6MWT, 6-minute walk test; CI, confidence interval; FVC, forced vital capacity

Patients Who Switched From Alglucosidase Alfa in PAP to Avalglucosidase Alfa in ETP

Of the 44 patients who were initially randomized to alglucosidase alfa and then crossed over to avalglucosidase alfa, 26 patients had available 6MWT value at week 97 (as of the most recent data cutoff of July 3, 2020). The mean change in distance walked in 6MWT from week 49 to week 97 among the 26 patients was 8.6 meters (95% CI: -20.4 to 37.5; p-value=0.55), which failed to show a statistically significant improvement.

Figure 9 depicts the mean change from week 49 in distance walked in 6MWT over time by the randomized arms. At each time point, the vertical bar presents ± standard error (SE). The red and blue lines indicate the alglucosidase alfa arm and the avalglucosidase alfa arm, respectively. The mean changes from week 49 over time for the switched patients were greater than zero.

Figure 9. Mean (±SE) Change From Week 49 in 6MWT Distance (in Meters) Over Time (All Randomized)



Source: This figure was produced by review team based on the adftw97.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
Abbreviations: 6MWT, 6-minute walk test; SE, standard error

6.2.1.4.4. Results for Other Secondary Endpoints

Table 11 summarizes baseline mean and mean change from baseline to week 49 for the other secondary efficacy endpoints. The estimated treatment differences for all other secondary endpoints except MEP (% predicted) numerically favor the avalglucosidase alfa arm.

Regarding MIP and MEP values, the clinical study report states the following:

"Nonphysiologic MIP and MEP values of 200 cm H2O at baseline were noted after DBL in 4 patients and may reflect erroneous use of the device used to assess respiratory pressures or may reflect incorrect data entry. This was likely due to errors in data entry not corrected in spite of repeated queries."

The Applicant conducted post hoc analyses for MIP and MEP by excluding the four patients (two patients in each arm). In the post hoc analyses, the estimated treatment difference was 4.4% (95% CI: -1.6 to 10.4; p-value=0.15) for MIP and 2.5% (95% CI: -5.7 to 10.7; p-value=0.55) for MEP.

Table 11. Mean Change From Baseline to Week 49 in Other Secondary Endpoints

Parameter	Avalgluco	Alglu	Difference[1] (95% CI)	P-Value
MIP (% predicted)				
Mean (SD) at baseline	59.9 (47.1)	60.6 (41.0)		
Estimated change (SE)	-0.3 (3.8)	-2.9 (4.0)	2.6 (-8.5, 13.7)	0.6451
MEP (% predicted)				
Mean (SD) at baseline	65.8 (39.0)	74.8 (35.2)		
Estimated change (SE)	2.4 (4.0)	5.0 (4.2)	-2.6 (-14.2, 9.0)	0.6557
HHD lower extremity score				
Mean (SD) at baseline	1330.5 (625.4)	1466.2 (604.9)		
Estimated change (SE)	260.7 (46.1)	153.7 (48.5)	107.0 (-26.6, 240.5)	0.115
QMFT total score				
Mean (SD) at baseline	41.3 (10.1)	42.3 (10.6)		
Estimated change (SE)	4.0 (0.6)	1.9 (0.7)	2.1 (0.2, 3.9)	0.0288
SF-12 PCS				
Mean (SD) at baseline	35.9 (7.8)	36.8 (9.4)		
Estimated change (SE)	2.4 (1.0)	1.6 (1.1)	0.8 (-2.1, 3.7)	0.5996
SF-12 MCS				
Mean (SD) at baseline	48.3 (10.1)	50.6 (8.7)		
Estimated change (SE)	2.9 (1.2)	0.8 (1.3)	2.1 (-1.5, 5.7)	0.2427

Source: Table 3 of Summary of Clinical Efficacy. This table was produced by review team based on the following data sets: adsl.xpt, adre.xpt, adft.xpt, and adqs.xpt. They can be located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
[1] Differences were estimated by MMRM models descr bed in Section 6.2.1.3.3.
Abbreviations: alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; CI, confidence interval; HHD, hand-held dynamometry; MCS, Mental Component Summary Scale Score; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; PCS, Physical Component Summary Scale Score; QMFT, quick motor function test; SD, standard deviation; SE, standard error; SF-12, 12-item short form health survey

6.2.2. TDR12857 and LTS13769

6.2.2.1. Design, TDR12857 and LTS13769

TDR12857 was an open-label ascending dose trial of the safety, tolerability, PK, pharmacodynamic, and exploratory efficacy of repeated biweekly infusions of avalglucosidase alfa in patients with LOPD. This trial was conducted in 17 centers in 7 countries. A total of 24 patients with LOPD were enrolled in two groups: group 1 included 10 patients who were treatment-naïve, and group 2 included 14 patients who were previously treated with alglucosidase alfa. They received one of three dose levels (5, 10, or 20 mg/kg) qow for 13 doses.

LTS13769 was a 6-year open-label extension of TDR12857. Among the 21 patients who completed TDR12857, 19 were enrolled in LTS13769. After the dose of 20 mg/kg qow was selected as the optimal dose from TDR12857, patients initially receiving doses of 5 or 10 mg/kg qow had to provide consent to switch to the 20 mg/kg qow regimen for the remaining duration of LTS13769. Patients initially on 20 mg/kg continued with this dose.

Exploratory Efficacy Measures

The 6MWT and pulmonary function testing were conducted as exploratory efficacy measures. This review presents the following data:

- Mean change from baseline over time in FVC (% predicted)
- Mean change from baseline over time in distance walked in 6MWT

Baseline was defined as the last observation prior to the first infusion in TDR12857.

6.2.2.2. Eligibility Criteria, TDR12857 and LTS13769

Key eligibility criteria for TDR12857 are summarized as follows:

Inclusion Criteria

- Males and females ≥18 years old with confirmed GAA enzyme deficiency from any tissue source and/or two confirmed *GAA* gene variants and without known cardiac hypertrophy.
- Patients were able to ambulate 50 meters without stopping and without an assistive device.
- Patients had an FVC (% predicted) in the upright position of ≥50% predicted.

Exclusion Criteria

- Patients were wheelchair-dependent or required invasive ventilation.
- Patients could not be in group 1 if they had received previous treatment with alglucosidase alfa or any other ERT for Pompe disease.
- Patients could not be in group 2 if they had a high risk for a severe allergic reaction to avalglucosidase alfa.

The key eligibility criterion for LTS13769 was as follows:

- Patients with LOPD who previously completed trial TDR12857

6.2.2.3. Statistical Analysis Plan, TDR12857 and LTS13769

No formal statistical hypothesis tests were planned. The data of FVC (% predicted) and 6MWT are graphically presented in Section 6.2.2.4.2.

6.2.2.4. Results of Analyses, TDR12857 and LTS13769

This section presents the patient disposition, baseline demographics, and the descriptive summaries of FVC (% predicted) and 6MWT data.

6.2.2.4.1. Disposition and Baseline Demographics, TDR12857 and LTS13769

Patient Disposition

Disposition information is presented in Table 12. Among the 21 patients who completed TDR12857, 19 were enrolled in LTS13769. Two patients prematurely discontinued LTS13769; the reasons for discontinuation were: wish to withdraw and other. A total of 17 patients remained on LTS13769 at the time of the data cutoff (February 27, 2020). LTS13769 is ongoing.

Table 12. Patient Disposition (n), Trials TDR12857 and LTS13769

Enrolled Trial	Group 1				Group 2			
Patient Disposition Reason for Disc.	5 mg/kg	10 mg/kg	20 mg/kg	Total	5 mg/kg	10 mg/kg	20 mg/kg	Total
Enrolled in TDR12857	4	3	3	10	4	4	6	14
Completed	3	3	3	9	3	4	5	12
Discontinued	1	0	0	1	1	0	1	2
Adverse event	1	0	0	1	1	0	1	2
Wish to withdraw	0	0	0	0	0	0	0	
Enrolled in LTS13769	3	2	3	8	3	3	5	11
Completed	0	0	0	0	0	0	0	0
Discontinued	0	1	0	1	0	0	1	1
Wish to withdraw	0	1	0	1	0	0	0	0
Other	0	0	0	0	0	0	1	1

Source: Table 6 of Clinical Study Report.
Abbreviation: Disc, discontinuation

Baseline Demographics

Patient demographic information is presented in Table 13. The mean age at enrollment was 44.8 years for group 1 and 46.7 years for group 2. The majority of patients were White (80% for group 1 and 92.9% for group 2). Most patients (90% in group 1 and 92.9% in group 2) were not Hispanic or Latino. Due to the limited sample size, baseline demographics were not well balanced among dose groups.

Table 13. Baseline Demographics and Characteristics, Trials TDR12857 and LTS13769

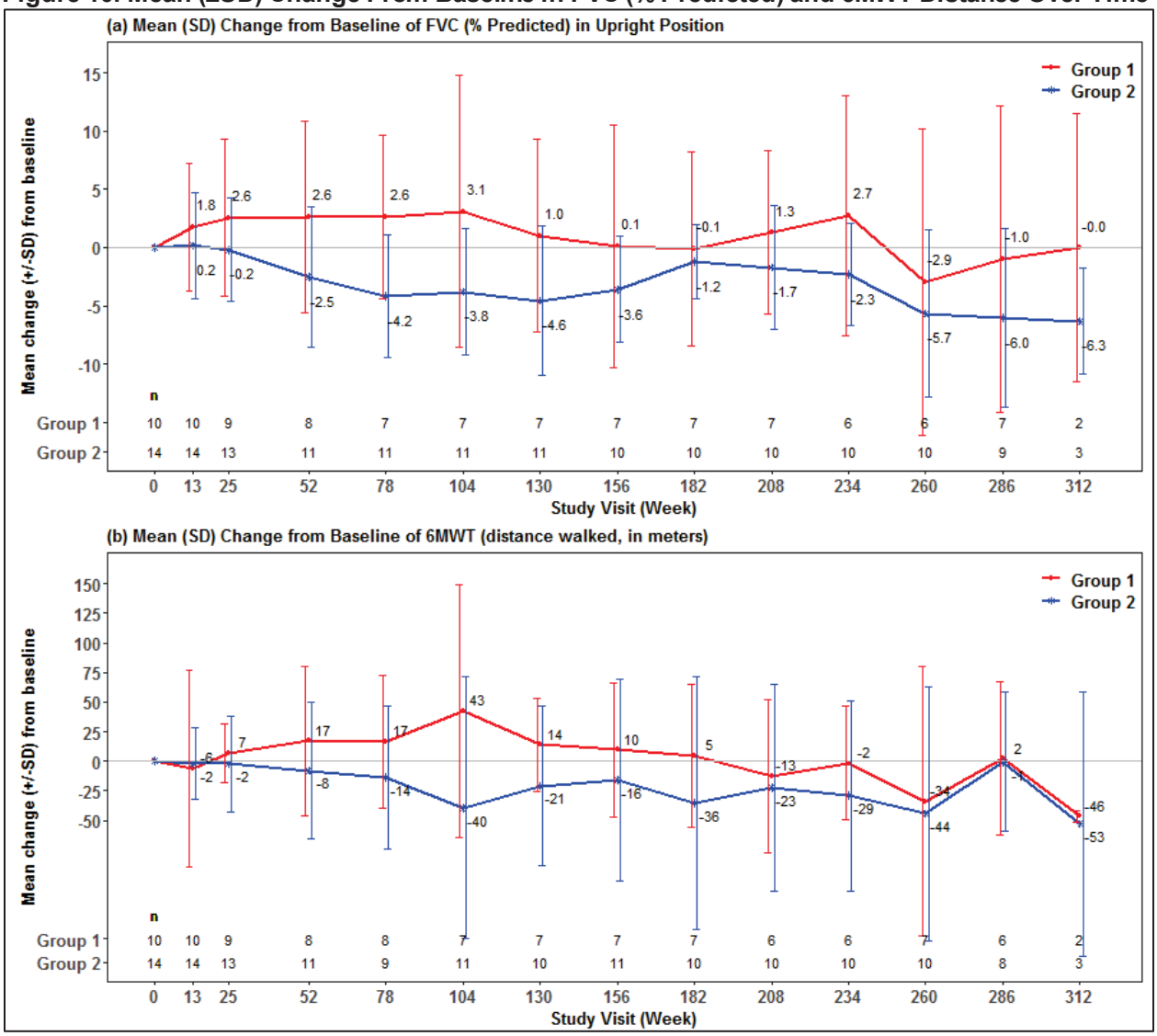
	Group 1				Group 2			
Demographics or Characteristics	**5 mg/kg N=4**	**10 mg/kg N=3**	**20 mg/kg N=3**	**Total N=10**	**5 mg/kg N=4**	**10 mg/kg N=4**	**20 mg/kg N=6**	**Total N=14**
Age at enrollment (yrs.)								
Mean (SD)	55.8 (14.7)	26.0 (8.2)	49.1 (25.6)	44.8 (20.3)	50.6 (13.9)	47.2 (12.1)	43.8 (17.0)	46.7 (14.1)
Median	56.0	22.8	38.5	38.3	50.7	44.6	41.4	46.2
Min, max	38.2, 73.0	19.8, 35.3	30.5, 78.3	19.8, 78.3	33.6, 67.5	36.4, 63.3	20.5, 67.1	20.5, 67.5
Gender, n (%)								
Female	3 (75.0)	3 (100.0)	1 (33.3)	7 (70.0)	2 (50.0)	1 (25.0)	2 (33.3)	5 (35.7)
Male	1 (25.0)	0 (0.0)	2 (66.7)	3 (30.0)	2 (50.0)	3 (75.0)	4 (66.7)	9 (64.3)
Race, n (%)								
White	4 (100.0)	1 (33.3)	3 (100.0)	8 (80.0)	4 (100.0)	3 (75.0)	6 (100.0)	13 (92.9)
Black or AA	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (7.1)
Multiple	0 (0.0)	1 (33.3)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not reported	0 (0.0)	1 (33.3)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnic, n (%)								
Not Hispanic or Latino	4 (100.0)	2 (66.7)	3 (100.0)	9 (90.0)	4 (100.0)	4 (100.0)	5 (83.3)	13 (92.9)
Not reported	0 (0.0)	1 (33.3)	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (7.1)
FVC (% predicted)								
Mean (SD)	62.5 (13.6)	83.6 (26.1)	63.7 (16.3)	69.2 (19.3)	77.4 (11.5)	86.0 (20.2)	71.5 (16.7)	77.3 (16.5)
Median	58.6	87.6	55.2	58.7	73.4	78.3	70.6	75.9
Min, max	51.0, 81.8	55.8, 107.5	53.4, 82.6	51.0, 107.5	68.9, 93.8	71.4, 115.8	50.9, 96.2	50.9, 115.8
Distance in 6MWT (m)								
Mean (SD)	366.0 (124.1)	506.7 (35.1)	502.7 (125.0)	449.2 (118.4)	332.5 (107.1)	484.0 (151.1)	483.2 (134.6)	440.4 (141.0)
Median	374.5	510.0	555.0	488.5	350.5	542.5	482.5	439.0
Min, max	208.0, 507.0	470.0, 540.0	360.0, 593.0	208.0, 593.0	201.0, 428.0	260.0, 591.0	331.0, 657.0	201.0, 657.0

Source: Table 8 of Clinical Study Report. This table was produced by review team based on the dataset adsl.xpt that can be located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\lts13769\analysis\adam\datasets.
Abbreviations: 6MWT, 6-minute walk test; AA, African American; FVC, forced vital capacity; SD, standard deviation; yrs., years

6.2.2.4.2. Efficacy Results, TDR12857 and LTS13769

Figure 10 represents the mean change from baseline in FVC (% predicted) and 6MWT over time by group. At each time point, the vertical bar represents ± standard deviation (SD). The red and blue lines indicate group 1 (treatment-naïve patients) and group 2 (patients previously treated with alglucosidase alfa), respectively. Given the high level of uncertainty (large SD), it is difficult to make any conclusive statement. See Figure 41 to Figure 44 for the mean change from baseline by initial dose within each group.

Figure 10. Mean (±SD) Change From Baseline in FVC (% Predicted) and 6MWT Distance Over Time



Source: This figure was produced by review team based on the datasets adre.xpt and adft.xpt that can be located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\lts13769\analysis\adam\datasets.
Abbreviations: 6MWT, 6-minute walking test; FVC, forced vital capacity; SD, standard deviation

6.2.3. ACT14132

6.2.3.1. Design, ACT14132

This was a phase 2, open-label ascending dose trial in alglucosidase alfa-experienced pediatric patients with IOPD, conducted in 10 centers in 5 countries in two stages: stage 1 and stage 2. A total of 22 patients with IOPD who showed clinical decline or suboptimal clinical response in respiratory function, motor skills, cardiac parameters, and/or new onset of ptosis were enrolled.

In stage 1, a total of 11 patients who showed clinical decline in respiratory function, motor skills, cardiac parameters, and/or new onset of ptosis were enrolled. They received avalglucosidase alfa at 20 mg/kg qow (cohort 1; n=6) or 40 mg/kg qow (cohort 2; n=5) for 6 months. After the highest tolerated dose was determined in stage 1, 11 new patients who showed suboptimal clinical response while on alglucosidase alfa with respect to respiratory function, motor skills, cardiac parameters, and/or new onset of ptosis were enrolled in stage 2, into cohort 3. The patients in cohort 3 were randomized 1:1 and stratified by sex to receive either avalglucosidase alfa 40 mg/kg qow (n=5) or their current stable dose of alglucosidase alfa (n=6) for 6 months. The PAP at the 6-month treatment duration was followed by an open-label ETP.

The primary objective of this trial was to evaluate the safety profile of avalglucosidase alfa in patients with IOPD who were previously treated with alglucosidase alfa. Additional objectives were to determine the effect of avalglucosidase alfa treatment on functional endurance, respiratory function, health-related quality of life, pain, developmental disability, and hearing in patients with IOPD.

Secondary Efficacy Variables

The prespecified secondary efficacy variables included the following (also see Section 6.3.3):

- GMFM-88 and Gross Motor Function Classification System - Expanded and Revised
- Quick Motor Function Test (QMFT)
- Pompe Pediatric Evaluation of Disability Inventory (Pompe-PEDI) Functional Skills Scale: Mobility Domain
- Echocardiography left ventricular mass index (LVMI) and left ventricular mass (LVM) Z-score
- Eyelid position measurements (interpalpebral fissure distance, margin reflex distance-1, and margin pupil distance)

6.2.3.2. Eligibility Criteria, ACT14132

Key eligibility criteria are summarized in this section.

Inclusion Criteria

- Males and females with confirmed GAA enzyme deficiency from any tissue source and/or two confirmed *GAA* gene variants.
- Patient had to be <18 years old.

- Patient had cardiomyopathy at time of diagnosis: i.e., LVMI equivalent to mean age specific LVMI plus two standard deviations.
- Patient had been receiving a stable dose of alglucosidase alfa regularly for at least 6 months immediately before trial entry.
- For stage 1 (cohorts 1 and 2), patients must have met the criteria for demonstrating decline and for stage 2 (cohort 3), patients must have met criteria for demonstrating suboptimal response.

Exclusion Criteria

- Patient had a high antibody titer at two consecutive time points, not less than 1 month apart.
- Previous participation in any cohort of ACT14132.
- Patient had a high risk for severe allergic reaction to avalglucosidase alfa.

6.2.3.3. Statistical Analysis Plan, ACT14132

The final SAP (version 2) explicitly stated that "This phase 2 study is not considered as a confirmatory clinical study." All secondary efficacy variables were summarized descriptively by dose cohort and treatment group.

6.2.3.4. Results of Analyses, ACT14132

This section presents patient disposition, baseline demographics, and descriptive summaries of the secondary efficacy variables.

6.2.3.4.1. Disposition and Baseline Demographics, ACT14132

Patient Disposition

Disposition information is presented in Table 14. No patients discontinued in the PAP or ETP up to the data cutoff date (September 30, 2019). All patients were ongoing in the ETP, although three patients in the alglucosidase alfa arm of cohort 3 had not received the first infusion of avalglucosidase alfa in the ETP as of the data cutoff date.

Table 14. Patient Disposition, Trial ACT14132

			Cohort 3		
Patient Disposition	**Cohort 1**	**Cohort 2**	**Avalgluco**	**Alglu**	**Total**
Enrolled or randomized	N=6	N=5	N=5	N=6	N=11
Primary analysis period (PAP)					
Completed PAP	6 (100)	5 (100)	5 (100)	6 (100)	11 (100)
Discontinued PAP	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Extension treatment period (ETP)					
Entered into ETP	6 (100)	5 (100)	5 (100)	3 (50)	8 (73)
Did not enter into ETP	0 (0)	0 (0)	0 (0)	3 (50)	3 (27)

Source: Table 5 of Clinical Study Report
Cohort 1: avalgluco at 20 mg/kg qow; Cohort 2: avalgluco 40 mg/kg qow; Cohort 3: avalgluco 40 mg/kg qow or current stable dose of alglu
Abbreviations: Alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa

Baseline Demographics

Patient demographic information is presented in Table 15. The mean age at enrollment was 6.77 years, and the majority of patients were White (54.5%) and Asian (36.4%). Most patients (86.4%) were not Hispanic or Latino. Given the limited sample size, baseline demographics were not well balanced among cohorts and treatment arms. The mean and median ages in the alglucosidase alfa arm within cohort 3 were lower than those in the other arms.

Table 15. Baseline Demographics, Trial ACT14132

			Cohort 3		
Demographics	**Cohort 1**	**Cohort 2**	**Avalgluco**	**Alglu**	**Total**
Number of patients	N=6	N=5	N=5	N=6	N=22
Age at enrollment (years)					
Mean (SD)	7.60 (3.36)	8.11 (4.13)	6.93 (2.68)	4.67 (3.16)	6.77 (3.40)
Median	8.2	9.8	8.0	3.6	7.0
Min, max	2, 11	1, 12	4, 10	1, 10	1, 12
Gender, n (%)					
Female	1 (16.7)	2 (40.0)	3 (60.0)	4 (66.7)	10 (45.5)
Male	5 (83.3)	3 (60.0)	2 (40.0)	2 (33.3)	12 (54.5)
Race, n (%)					
White	3 (50.0)	2 (40.0)	3 (60.0)	4 (66.7)	12 (54.5)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	2 (9.1)
Asian	3 (50.0)	3 (60.0)	2 (40.0)	0 (0.0)	8 (36.4)
Ethnic, n (%)					
Not Hispanic or Latino	6 (100.0)	4 (80.0)	4 (80.0)	5 (83.3)	19 (86.4)
Hispanic or Latino	0 (0.0)	1 (20.0)	1 (20.0)	1 (16.7)	3 (13.6)

Source: Table 7 of the Clinical Study Report. This table was produced by review team based on the dataset adsl.xpt that can be located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\act14132\analysis\adam\datasets. The variable used for age was 'AGEENRO' which presents age at enrollment.
Cohort 1: avalgluco at 20 mg/kg qow; Cohort 2: avalgluco 40 mg/kg qow; Cohort 3: avalgluco 40 mg/kg qow or current stable dose of alglu
Abbreviations: Alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; SD, standard deviation

6.2.3.4.2. Efficacy Results, ACT14132

Descriptive summaries and graphical presentations of the secondary efficacy variables are presented in Section 6.3.3. Due to the small sample size and high variability in the data, it is difficult to make conclusive statement regarding the effects of avalglucosidase alfa on the secondary efficacy variables in patients with IOPD.

6.2.4. Conclusions Regarding Effectiveness

In summary, we conclude that substantial evidence of effectiveness for LOPD is established based on:

- One adequate and well-controlled trial (EFC14028) showing improvement in lung function in patients greater than 16 years of age with LOPD. The trial data included clinical assessments in treatment-naïve patients and patients who switched from alglucosidase alfa to avalglucosidase alfa at Week 49. The totality of the data is adequate to support approval for the treatment of patients 1 year of age and older with LOPD.
- Confirmatory evidence derived from mechanistic support including the well-established etiology of the disease, the mechanism of action of the therapy, and animal studies

showing that avalglucosidase alfa reduces glycogen levels in tissues and improves muscle function in GAAKO mice, consistent with the pathophysiology for this disease.

- Effectiveness in patients younger than 16 years of age with LOPD is based on extrapolation of our findings of effectiveness for patients greater than 16 years of age with LOPD and leveraging of safety data from pediatric patients 1 year of age and older with IOPD who received a higher dose than used in patients with LOPD. This approach is scientifically justified by the similar pathophysiology, mechanism of action, and disease manifestations across the age spectrum of patients with LOPD.
- Data supporting effectiveness in patients with IOPD was inadequate due to differences in severity of clinical presentation and potential immunogenicity concerns. Therefore, we conclude that substantial evidence of effectiveness for IOPD is not established.

See Section 6.3 for key review issues relevant to the evaluation of benefit and how they were resolved.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Confirmatory Evidence

Issue

Providing confirmatory evidence that avalglucosidase alfa is effective in the treatment of LOPD in addition to the results from one adequate and well-controlled trial (EFC14028).

Background and Assessment

Substantial evidence of effectiveness under 21 Code of Federal Regulations (CFR) 314.126 can be established with a single adequate and well-controlled clinical investigation supported by confirmatory evidence (CE), under certain circumstances (section 115(a) of FDAMA). Data that provide strong mechanistic support is one option for CE (see the guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). To support the effectiveness of avalglucosidase alfa, CE is derived from the well-established etiology of the disease, the mechanism of action of the therapy, and studies in an animal model of disease.

Pompe disease is caused by variants in the *GAA* gene that result in absence or reduction of lysosomal alpha-glucosidase (GAA). GAA enzyme deficiency leads to glycogen accumulation in the lysosome, resulting in cellular dysfunction. Avalglucosidase alfa provides an exogenous source of GAA, thereby replacing the missing enzyme. Treatment of the animal model of Pompe disease (GAAKO mice) with neo-recombinant human acid alpha-glucosidase (rhGAA) (avalglucosidase alfa) resulted in greater clearance of glycogen from heart, diaphragm and skeletal muscle compared to unmodified rhGAA (alglucosidase alfa) (Zhu et al. 2005).

The GAAKO (alpha glucosidase knock out) mice are genetically engineered to be unable to produce GAA, are the most widely used animal model of Pompe disease, and are considered an acceptable animal model by the review team. The GAAKO mouse was used in all four primary

Reference ID: 4836879

pharmacodynamic studies of avalglucosidase (studies 07-1948, 10-00587, 09-3981, and 11-02367). The in vivo repeat-dose pharmacodynamic studies were conducted to evaluate the efficacy of avalglucosidase alfa by assessing depletion of glycogen from target tissues. Tissue glycogen content was measured biochemically and histologically.

In GAAKO mice treated with avalglucosidase alfa, glycogen depletion in heart, quadriceps, and triceps was assessed using a biochemical glycogen assay. The pharmacological active dose (PAD) for heart tissue is 4 mg/kg IV of avalglucosidase alfa, as substantial glycogen clearance was noted at this dose level. In contrast, at least 12 mg/kg IV avalglucosidase alfa is necessary to elicit a significant effect on glycogen accumulation in diaphragm and other skeletal muscles (quadriceps, triceps, and psoas). In addition, avalglucosidase alfa was at least 3 to 7-fold more potent in terms of tissue glycogen reduction relative to alglucosidase alfa, following 4 weekly IV doses.

Conclusion

In addition to the one single adequate and well-controlled clinical investigation (EFC14028), the available CE for the efficacy of avalglucosidase alfa provide strong mechanistic evidence to support approval.

6.3.2. Extrapolation of Efficacy to Patients Less Than 16 Years of Age With LOPD

Issue

Pediatric patients less than 16 years old with LOPD were not enrolled in trial EFC14028.

Background

While patients 3 years of age and older with LOPD were eligible for participation in trial EFC14028, the youngest patient was 16 years old at enrollment. Therefore, children with LOPD were not well represented in this application. The review team had previously discussed with the Applicant that extrapolation of efficacy from adult patients with LOPD to pediatric patients with LOPD could be considered. In order to assess if this extrapolation was reasonable to perform, the review team asked that the Applicant to provide any available PK and safety data in pediatric patients with PD.

There is a spectrum of disease, ranging from severe, rapidly progressive IOPD to slowly progressive, heterogeneous LOPD, but PD is classified into two forms based on age of onset, organ involvement, severity, and rate of progression (Leslie and Bailey 2007). Major defining features of the two PD forms are the presence or absence of cardiomyopathy and the risk of immunogenicity. While there are differences in the clinical symptoms, severity, and time course between IOPD and LOPD, patients across the age groups with LOPD have similar natural history and clinical manifestations, with the majority of patients lacking cardiac involvement. In addition, Angelini and colleagues showed that in a group of 74 patients with LOPD who were treated with alglucosidase alfa and whose ages ranged from 7 to 72 years at trial entry, the mean distance walked in the 6MWT increased independent of age at onset or the age at first infusion. After treatment, there was no difference in FVC (% predicted) compared to the patients' baselines (Angelini et al. 2012; van der Meijden et al. 2018).

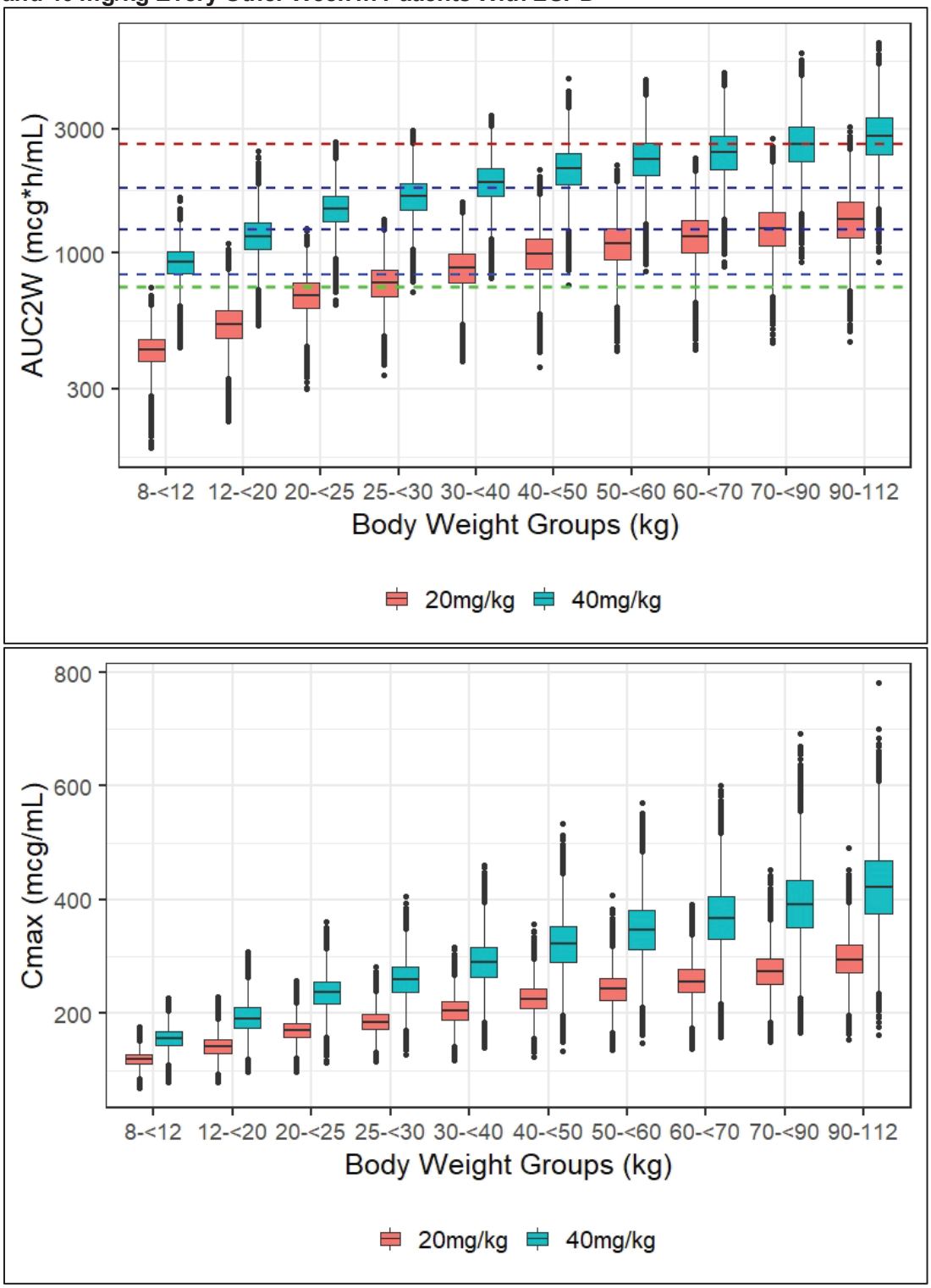
Assessment

The Applicant provided efficacy data from one 16-year-old patient with LOPD as part of the initial application, in addition to data from adult patients with LOPD. The Applicant also shared that an additional pediatric patient aged 9 years with LOPD was subsequently enrolled in August 2020 per the amended clinical trial protocol (version 3); however, PK data are not available until the patient reaches week 49. These data alone are not adequate to demonstrate efficacy in pediatric patients with LOPD. However, the review team concluded that the clinical disease similarities (in terms of similar pathophysiology and disease course) and the similarity in treatment responses in patients with LOPD across the age spectrum provides justification for extrapolation of efficacy using PK data.

The population PK data submitted in December 2020 showed similar PK across all included patients with PD, and baseline characteristics such as age and disease type (LOPD or IOPD) did not affect avalglucosidase alfa PK. To determine whether the dosing regimen of 20 mg/kg qow is appropriate across different age or body weight groups, the Applicant conducted simulation to evaluate the exposure following 20 mg/kg for patients with LOPD who were 1 year of age and older upon FDA's request. The virtual population for pediatric age groups (<18 years) was generated based on CDC weight-for-age growth chart. The virtual population for adults (≥18 years) was consistent with body weight from the available adult patients from trials TDR12857 and EFC14028 (n=74) (for details refer to Section 14.5). Based on the Applicant's simulation, for the 20 mg/kg dose, patients with lower body weights tended to have lower exposures than patients with higher body weight. Compared to the median exposures in adult patients, pediatric patients within 1 to <2, 2 to <6, 6 to <12 and 12 to <18 years of age are expected to have approximately 60%, 50%, 30% and 12% lower exposure, respectively.

The Applicant's simulation indicated that pediatric patients with lower body weights will likely need a higher dose to achieve a comparable exposure to adult patients. Thus, PK extrapolation approach based on modeling and simulation was utilized to select the appropriate dosing regimen for pediatric patients with LOPD. FDA conducted an independent simulation to compare the exposures at 40 mg/kg and 20 mg/kg, respectively, across different body weight groups. As shown in Figure 11, for subjects with body weight <30 kg, 40 mg/kg qow is expected to provide comparable exposure (AUC_{2W}) to that in adult patients receiving 20 mg/kg qow (target exposure, blue dash lines), also within the observed range from the patients with IOPD received 40 mg/kg in trial ACT14132. Similarly, for subjects weighing 30 kg and above, 20 mg/kg qow is expected to be an acceptable dosing regimen given the exposure associated is predicted to be within the observed range in patients with LOPD from trial EFC14028.

Figure 11. Simulated Avalglucosidase Alfa AUC_{2W} and C_{max} by Body Weight Category at 20 mg/kg and 40 mg/kg Every Other Week in Patients With LOPD



Source: FDA independent analysis
Note: Blue lines: 5th percentile (bottom), median (middle) and 95th percentile (top) of simulated AUC_{2W} in adults following 20 mg/kg; green line: minimum of AUC_{2W} in patients with LOPD in the trial EFC14028 following 20 mg/kg; red line: maximum of AUC_{2W} in patients with IOPD in the trial ACT14132 following 40 mg/kg
Abbreviations: AUC_{2W}, area under the concentration-time curve over the first two weeks; C_{max}, maximum plasma drug concentration; LOPD, late-onset Pompe disease

Additionally, safety data obtained in pediatric patients with IOPD, whose ages varied between 1 year and 11 years, can be leveraged to support approval in pediatric patients with LOPD, since these IOPD patients were more severely affected, treatment-experienced, and received higher doses of avalglucosidase alfa over an adequate period of time to assess safety (see Section 7.7). No apparent E-R relationship was identified for safety endpoints based on pooled data from patients with IOPD and LOPD following the studied dosing regimen of 20 or 40 mg/kg qow. Thus, based on the totality of evidence, FDA recommends 40 mg/kg for pediatric patients weighing <30 kg, and 20 mg/kg for patients weighing ≥30 kg. For details of pediatric dose selection, refer to Appendix 14.5 Pharmacometrics Review.

Conclusion

The review team concluded that extrapolation of efficacy from adult patients with LOPD to pediatric patients with LOPD is justified and acceptable.

6.3.3. Evidence of Efficacy in Patients With IOPD

Issue

The submitted data for IOPD from trial ACT14132 do not show convincing evidence to support efficacy of avalglucosidase alfa in patients with IOPD. To support efficacy in patients with IOPD, the Applicant needs to provide evidence from a controlled trial in patients with IOPD or scientifically justify pediatric extrapolation of efficacy with a scientific bridge between LOPD and IOPD.

Background

ACT14132 is the only trial to evaluate avalglucosidase alfa in patients with IOPD in this application. The trial was open-label and was designed to assess safety rather than efficacy. During the PAP, 22 patients were enrolled in 3 cohorts. Cohort 1 patients (n=6) received avalglucosidase alfa at 20 mg/kg qow and cohort 2 patients (n=5) received avalglucosidase alfa at 40 mg/kg qow. These 11 patients previously experienced a clinical decline on alglucosidase alfa. The patients in cohort 3 were randomized 1:1 to receive either avalglucosidase alfa 40 mg/kg qow (n=5) or their current stable dose of alglucosidase alfa (n=6) for 6 months. These 11 patients previously had a suboptimal response to alglucosidase alfa. The PAP was 6 months long and was followed by an open-label ETP. The primary endpoint was safety, not efficacy. No safety data is available for patients 12 months of age or younger to support approval in that population (see Section 7.7.2). Descriptive summaries and graphical presentations of the secondary efficacy variables are presented below.

Gross Motor Function Measure-88

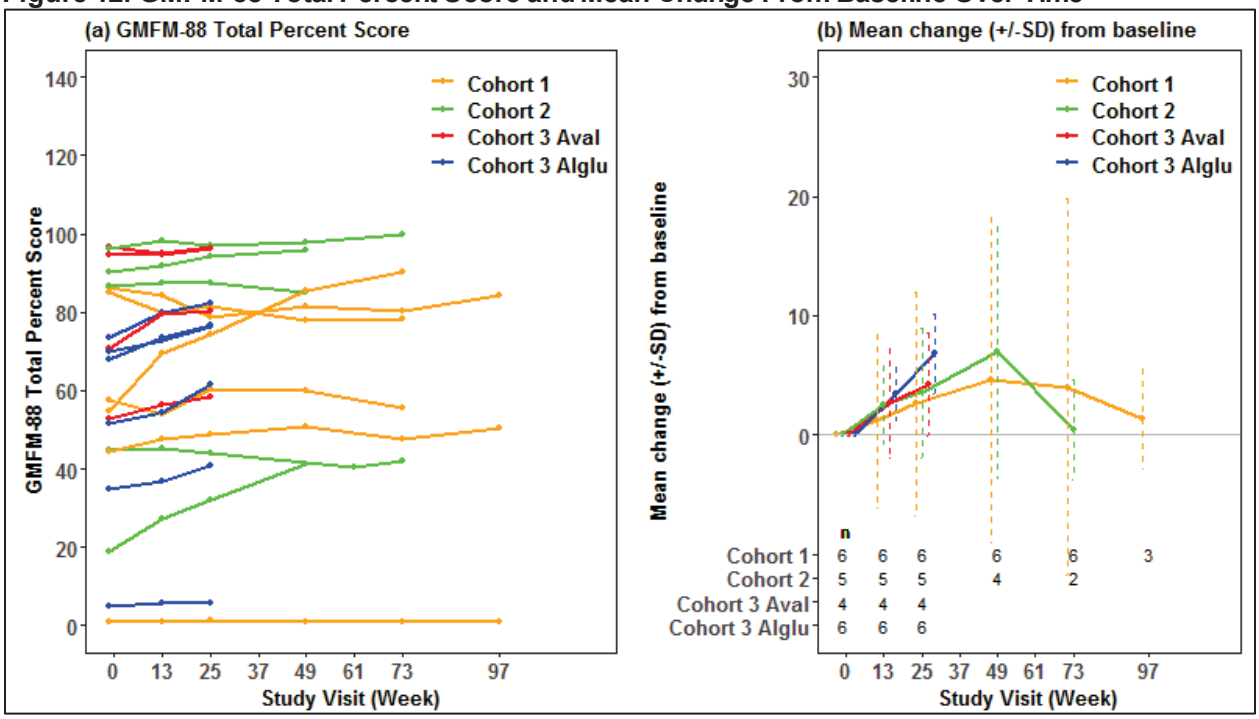
Table 16 presents the change from baseline to week 25 in the GMFM-88 total percent score using observed (available) data. In all cohorts, the mean change from baseline to week 25 was numerically positive: 2.6 for cohort 1 (n=6), 3.5 for cohort 2 (n=5), 4.2 for cohort 3 avalglucosidase alfa group (n=4), and 6.8 for cohort 3 alglucosidase alfa group (n=6). As shown in Figure 12, there is high variability in this data.

Table 16. Change From Baseline to Week 25 in GMFM-88 Total Percent Score, Trial ACT14132

Timepoint			Cohort 3	
Parameter	Cohort 1	Cohort 2	Avalgluco	Alglu
Baseline	N=6	N=5	N=4	N=6
Mean (SD)	54.8 (31.4)	67.4 (33.8)	78.7 (21.0)	50.4 (26.4)
Median (min, max)	56.2 (0.8, 86.2)	86.6 (19.1, 96.3)	82.8 (52.6, 96.6)	59.6 (5.1, 73.4)
Week 25	N=6	N=5	N=4	N=6
Mean (SD)	57.4 (30.2)	71.0 (30.7)	82.9 (18.0)	57.3 (29.3)
Median (min, max)	67.4 (1.2, 81.4)	87.4 (31.9, 97.1)	88.2 (58.4, 96.8)	68.9 (5.9, 82.4)
Change from baseline	N=6	N=5	N=4	N=6
Mean (SD)	2.6 (9.3)	3.5 (5.5)	4.2 (4.3)	6.8 (3.3)
Median (min, max)	1.7 (-7.7, 19.4)	0.8 (-0.8, 12.8)	3.5 (0.1, 9.6)	7.7 (0.8, 9.9)

Source: Tables 16.2.6.1.1.3 of the Clinical Study Report. This table was produced by review team based on the dataset adft.xpt at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\act14132\analysis\adam\datasets.
Cohort 1: avalgluco at 20 mg/kg qow; Cohort 2: avalgluco 40 mg/kg qow; Cohort 3: avalgluco 40 mg/kg qow or current stable dose of alglu
Abbreviations: Alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; GMFM-88, Gross Motor Function Measure-88; SD, standard deviation

Figure 12. GMFM-88 Total Percent Score and Mean Change From Baseline Over Time



Source: Sections 16.2.6.1.1.9 and 16.2.6.1.1.10 of Clinical Study Report. This figure was produced by review team based on the adft.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
Abbreviations: Alglu, alglucosidase alfa; Aval, avalglucosidase alfa; GMFM-88, Gross Motor Function Measure-88; SD, standard deviation

Quick Motor Function Test

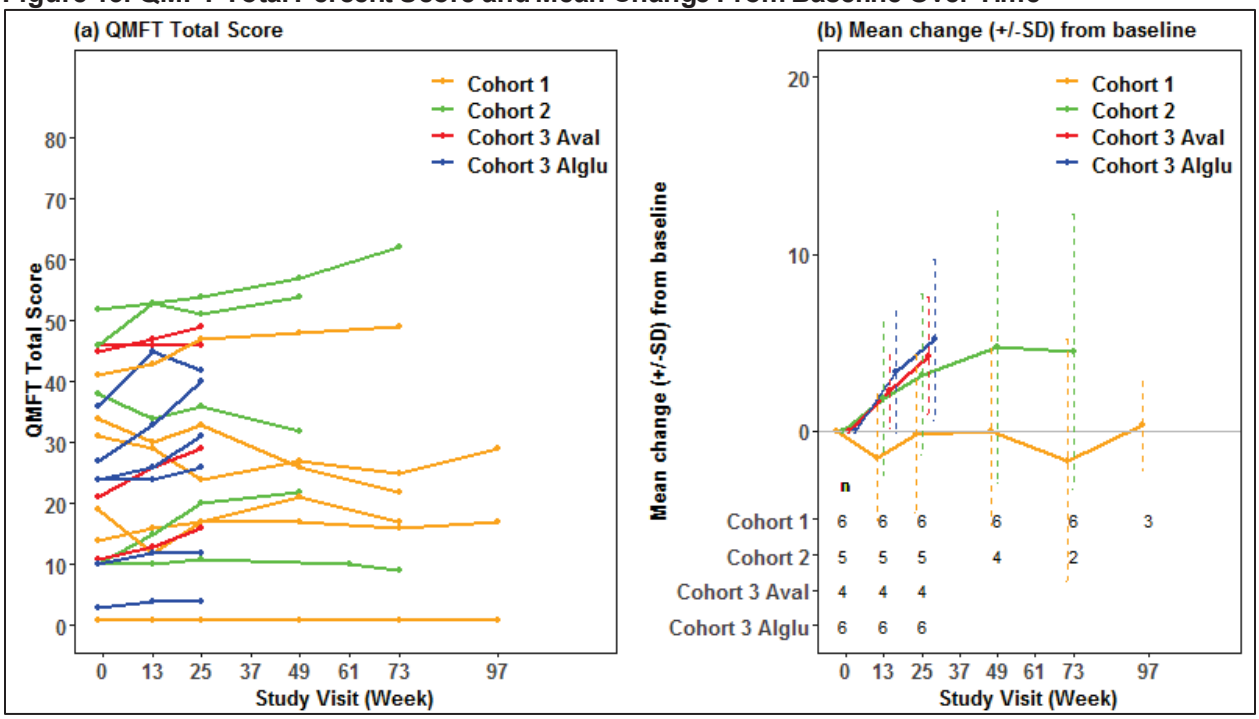
Table 17 presents the change from baseline to week 25 in the QMFT total score using observed (available) data. In cohorts 2 and 3, the mean change from baseline to week 25 was numerically positive: 3.2 for cohort 2 (n=5), 4.3 for cohort 3 avalglucosidase alfa group (n=4), and 5.2 for cohort 3 alglucosidase alfa group (n=6). For cohort 1 (n=6), the mean change from baseline to week 25 was numerically negative (-0.2). As shown in Figure 13, there is high variability in this data.

Table 17. Change From Baseline to Week 25 in QMFT Total Score, Trial ACT14132

Timepoint			Cohort 3	
Parameter	Cohort 1	Cohort 2	Avalgluco	Alglu
Baseline	N=6	N=5	N=4	N=6
Mean (SD)	23.3 (14.8)	31.2 (20.0)	30.8 (17.5)	20.7 (12.0)
Median (min, max)	25.0 (1.0, 41.0)	38.0 (10.0, 52.0)	33.0 (11.0, 46.0)	24.0 (3.0, 36.0)
Week 25	N=6	N=5	N=4	N=6
Mean (SD)	23.2 (15.7)	34.4 (18.8)	35.0 (15.4)	25.8 (15.2)
Median (min, max)	20.5 (1.0, 47.0)	36.0 (11.0, 54.0)	37.5 (16.0, 49.0)	28.5 (4.0, 42.0)
Change from baseline	N=6	N=5	N=4	N=6
Mean (SD)	-0.2 (4.4)	3.2 (4.5)	4.2 (3.3)	5.2 (4.5)
Median (min, max)	-0.5 (-7.0, 6.0)	2.0 (-2.0, 10.0)	4.5 (0.0, 8.0)	4.0 (1.0, 13.0)

Source: Tables 16.2.6.1.2.1 and 16.2.6.1.2.2 of the Clinical Study Report. This table was produced by review team based on the dataset adft.xpt at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\act14132\analysis\adam\datasets.
Abbreviations: Alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; QMFT, Quick Motor Function Test; SD, standard deviation

Figure 13. QMFT Total Percent Score and Mean Change From Baseline Over Time



Source: Sections 16.2.6.1.2.4 and 16.2.6.1.2.5 of Clinical Study Report. This figure was produced by review team based on the adft.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets
Abbreviations: Alglu, alglucosidase alfa; Aval, avalglucosidase alfa; QMFT, Quick Motor Function Test; SD, standard deviation

Pompe Pediatric Evaluation of Disability Inventory (Pompe-PEDI)

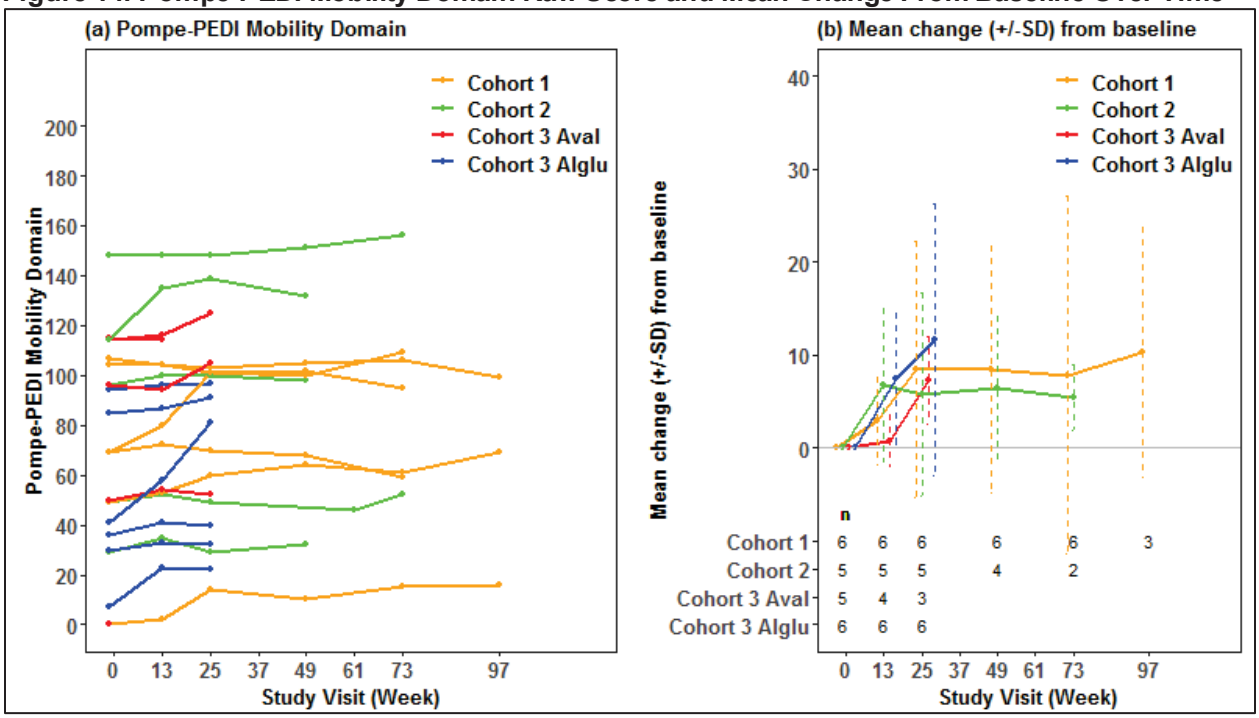
Table 18 presents the change from baseline to week 25 in the Pompe-PEDI total raw score using observed (available) data. In all cohorts, the mean change from baseline to week 25 was numerically positive: 8.5 for cohort 1 (n=6), 5.8 for cohort 2 (n=5), 7.3 for cohort 3 avalglucosidase alfa group (n=3), and 11.7 for cohort 3 alglucosidase alfa group (n=6). As shown in Figure 14, there is high variability in this data.

Table 18. Change From Baseline to Week 25 in Pompe-PEDI Total Raw Score, Trial ACT14132

Timepoint			Cohort 3	
Parameter	Cohort 1	Cohort 2	Avalgluco	Alglu
Baseline	N=6	N=5	N=5	N=6
Mean (SD)	66.3 (39.5)	87.2 (48.3)	75.0 (49.5)	48.8 (33.7)
Median (min, max)	69.0 (0.0, 107.0)	96.0 (29.0, 148.0)	96.0 (0.0, 115.0)	38.5 (7.0, 94.0)
Week 25	N=6	N=5	N=3	N=6
Mean (SD)	74.8 (34.9)	93.0 (53.0)	94.0 (37.7)	60.5 (32.9)
Median (min, max)	85.5 (14.0, 103.0)	100.0 (29.0, 148.0)	105.0 (52.0, 125.0)	60.5 (22.0, 97.0)
Change from baseline	N=6	N=5	N=3	N=6
Mean (SD)	8.5 (13.8)	5.8 (10.9)	7.3 (4.7)	11.7 (14.7)
Median (min, max)	6.0 (-6.0, 32.0)	0.0 (0.0, 25.0)	9.0 (2.0, 11.0)	5.0 (2.0, 40.0)

Source: Tables 16.2.6.1.3.1 and 16.2.6.1.3.2 of the Clinical Study Report. This table was produced by review team based on the dataset adcc.xpt at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\act14132\analysis\adam\datasets.
Abbreviations: Alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; SD, standard deviation

Figure 14. Pompe-PEDI Mobility Domain Raw Score and Mean Change From Baseline Over Time



Source: Sections 16.2.6.1.3.10 and 16.2.6.1.3.13 of Clinical Study Report. This figure was produced by review team based on the adcc.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets
Abbreviations: alglu, alglucosidase alfa; aval, avalglucosidase alfa; SD, standard deviation

Left Ventricular Mass (LVM) Z-Score From M-Mode Echocardiography

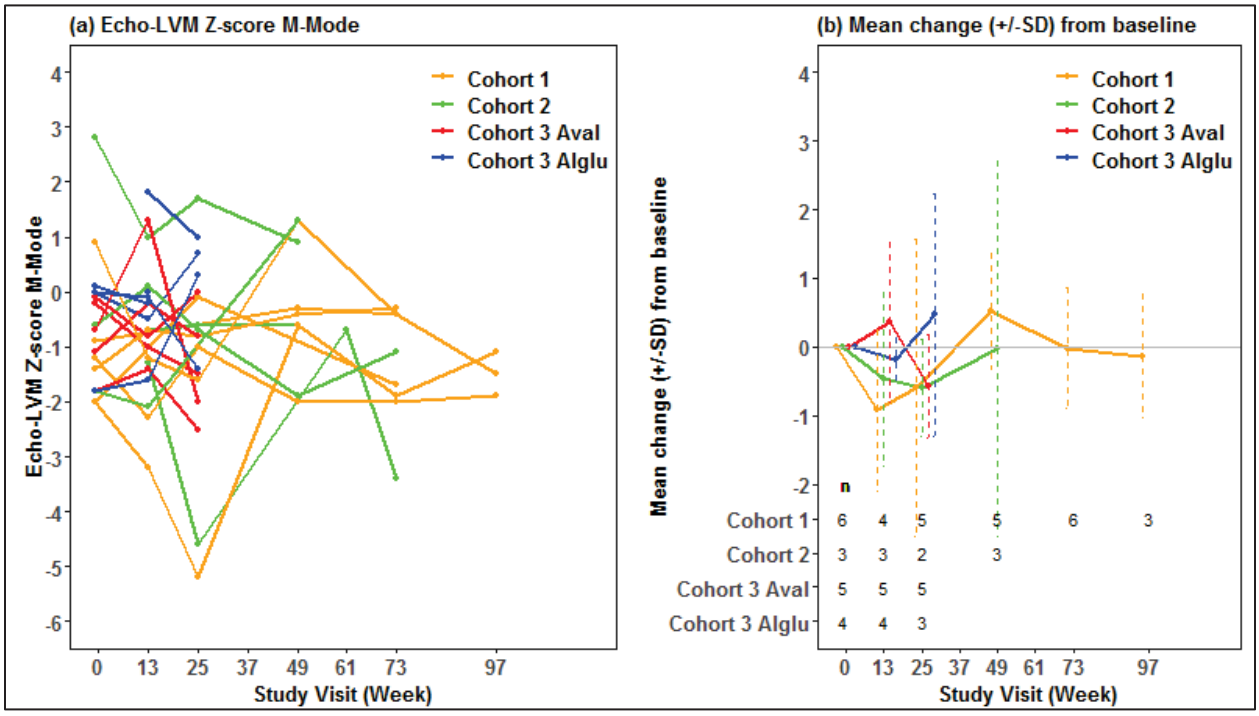
Table 19 and Figure 15 present descriptive summaries and graphical presentation of the LVM Z-score from M-Mode echocardiography using observed (available) data.

Table 19. Change From Baseline to Week 25 in LVM Z-Score, Trial ACT14132

Timepoint			Cohort 3	
Parameter	Cohort 1	Cohort 2	Avalgluco	Alglu
Baseline	N=6	N=3	N=5	N=4
Mean (SD)	-1.1 (1.1)	0.1 (2.4)	-0.8 (0.7)	-0.4 (0.9)
Median (min, max)	-1.3 (-2.0, 0.9)	-0.6 (-1.8, 2.8)	-0.7 (-1.8, -0.1)	0.0 (-1.8, 0.1)
Week 25	N=5	N=4	N=5	N=4
Mean (SD)	-1.7 (2.0)	-1.0 (2.6)	-1.4 (1.0)	0.2 (1.1)
Median (min, max)	-1.0 (-5.2, -0.1)	-0.6 (-4.6, 1.7)	-1.5 (-2.5, 0.0)	0.5 (-1.4, 1.0)
Change from baseline	N=5	N=2	N=5	N=3
Mean (SD)	-0.6 (2.2)	-0.6 (0.7)	-0.6 (0.8)	0.5 (1.8)
Median (min, max)	0.2 (-3.2, 1.9)	-0.6 (-1.1, -0.1)	-0.7 (-1.3, 0.3)	0.7 (-1.4, 2.1)

Source: Tables 16.2.6.1.4.1 and 16.2.6.1.4.2 of the Clinical Study Report. This table was produced by review team based on the dataset adcv.xpt at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\act14132\analysis\adam\datasets.
Abbreviations: Alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; LVM, left ventricular mass; SD, standard deviation

Figure 15. LVM Z-Score From M-Mode Echocardiography and Mean Change From Baseline Over Time



Source: Sections 16.2.6.1.4.11 and 16.2.6.1.4.15 of Clinical Study Report. This figure was produced by review team based on the adcv.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets
Abbreviations: alglu, alglucosidase alfa; aval, avalglucosidase alfa; LVM, left ventricular mass; SD, standard deviation

At enrollment, most patients (94%) had normal LVM Z-scores (-2 to 2) without any cardiac hypertrophy; we do not know these patients' LVM Z-scores at birth or whether treatment with alglucosidase alfa improved their muscle thickness prior to enrollment in ACT14132. One patient from cohort 2 had a baseline LVM Z-score of 2.8, which improved to less than 2 by week 25. The rest of the patients' LVM Z-scores remained normal at week 25. Although one patient's

LVM Z-score improved, there is insufficient data to conclude that avalglucosidase alfa affects cardiac hypertrophy in this patient population, a defining feature of IOPD.

Eyelid Position Measurements

Descriptive summary statistics for the interpalpebral fissure distance (without flash) using observed (available) data are presented in Table 20 (left eye) and Table 21 (right eye). Figure 16 and Figure 17 provide graphical presentation of the interpalpebral fissure distance data.

Table 20. Change From Baseline to Week 25 in Interpalpebral Fissure Distance (Left Eye; Without Flash), Trial ACT14132

Timepoint			Cohort 3	
Parameter	Cohort 1	Cohort 2	Avalgluco	Alglu
Baseline	N=6	N=5	N=5	N=6
Mean (SD)	8.5 (2.0)	7.3 (1.0)	7.5 (1.7)	8.2 (1.4)
Median (min, max)	9.5 (5.5, 10.0)	7.5 (6.0, 8.5)	8.0 (5.5, 9.0)	8.0 (6.5, 10.0)
Week 25	N=6	N=5	N=5	N=6
Mean (SD)	7.8 (1.6)	8.6 (1.6)	8.8 (1.2)	7.7 (1.5)
Median (min, max)	8.0 (5.5, 10.0)	8.0 (7.0, 11.0)	9.0 (7.0, 10.0)	7.5 (5.5, 10.0)
Change from baseline	N=6	N=5	N=5	N=6
Mean (SD)	-0.7 (1.5)	1.3 (1.5)	1.3 (0.8)	-0.5 (0.8)
Median (min, max)	-0.5 (-3.0, 1.5)	1.5 (-0.5, 3.5)	1.0 (0.5, 2.5)	-0.5 (-1.5, 0.5)

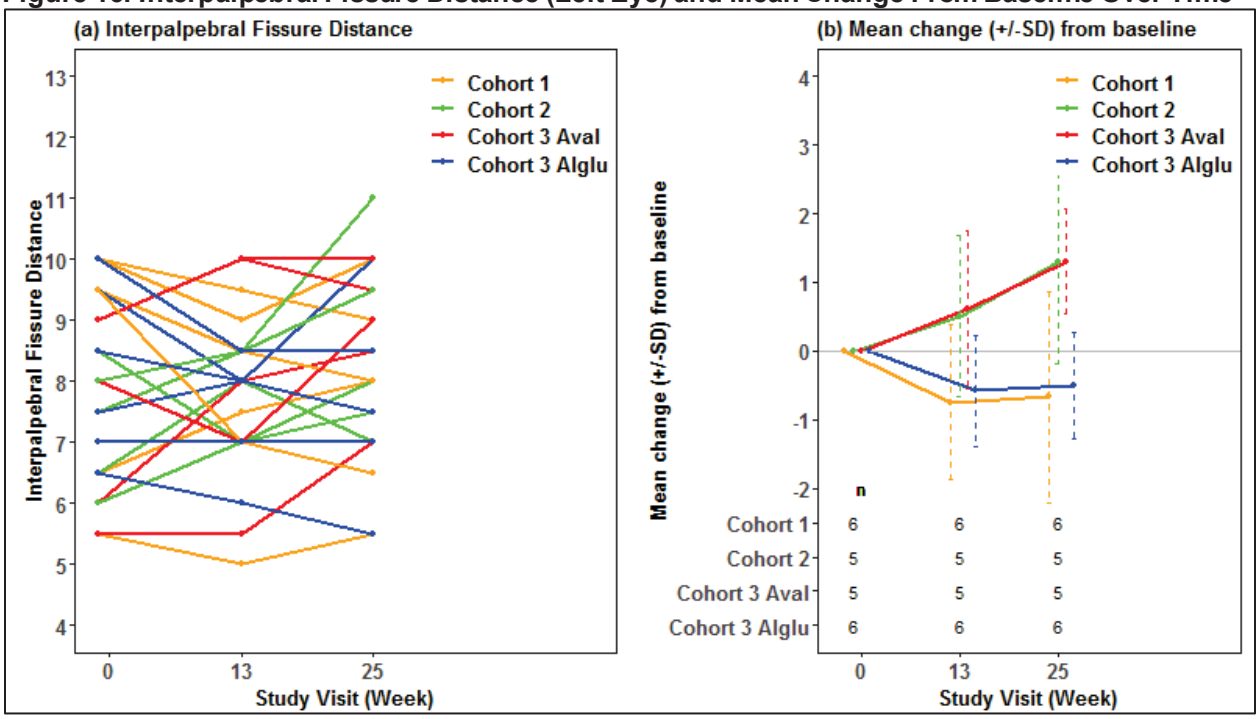
Source: Tables 16.2.6.1.5.7 and 16.2.6.1.5.8 of the Clinical Study Report. This table was produced by review team based on the dataset 'adoe.xpt' at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\act14132\analysis\adam\datasets.
Abbreviations: Alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; SD, standard deviation

Table 21. Change From Baseline to Week 25 in Interpalpebral Fissure Distance (Right Eye; Without Flash), Trial ACT14132

Timepoint			Cohort 3	
Parameter	Cohort 1	Cohort 2	Avalgluco	Alglu
Baseline	N=6	N=5	N=5	N=6
Mean (SD)	8.1 (2.1)	7.2 (1.0)	7.7 (1.3)	7.8 (1.4)
Median (min, max)	9.0 (5.0, 10.0)	7.5 (5.5, 8.0)	7.5 (6.0, 9.0)	8.0 (6.0, 9.5)
Week 25	N=6	N=5	N=5	N=6
Mean (SD)	7.2 (1.9)	7.9 (1.2)	8.6 (1.0)	7.6 (1.8)
Median (min, max)	6.8 (5.0, 10.5)	7.5 (7.0, 10.0)	8.5 (7.5, 10.0)	7.8 (4.5, 10.0)
Change from baseline	N=6	N=5	N=5	N=6
Mean (SD)	-0.9 (1.7)	0.7 (1.3)	0.9 (1.1)	-0.2 (1.1)
Median (min, max)	-0.8 (-3.0, 1.0)	0.0 (-0.5, 2.5)	1.0 (-0.5, 2.0)	-0.5 (-1.5, 1.5)

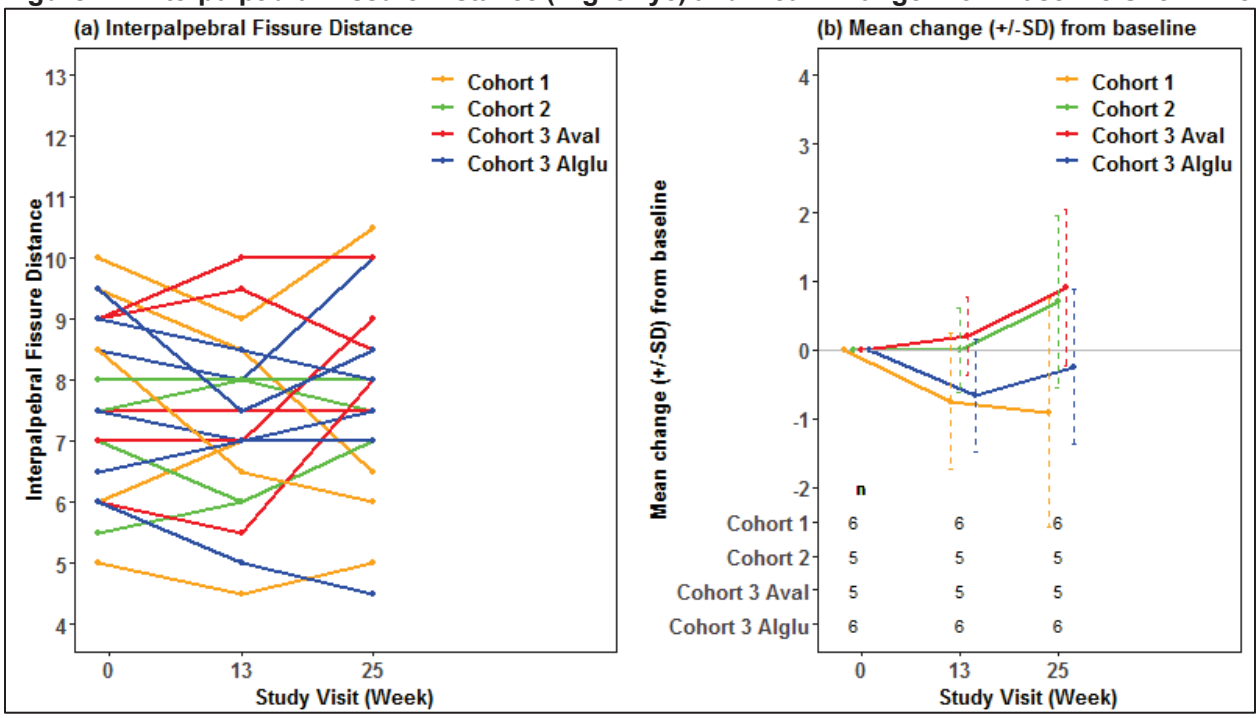
Source: Tables 16.2.6.1.5.9 and 16.2.6.1.5.10 of the Clinical Study Report. This table was produced by review team based on the dataset 'adoe.xpt' at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\act14132\analysis\adam\datasets.
Abbreviations: Alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; SD, standard deviation

Figure 16. Interpalpebral Fissure Distance (Left Eye) and Mean Change From Baseline Over Time



Source: Sections 16.2.6.1.5.21 and 16.2.6.1.5.28 of Clinical Study Report. This figure was produced by review team based on the adoe.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets
Abbreviations: alglu, alglucosidase alfa; aval, avalglucosidase alfa; SD, standard deviation

Figure 17. Interpalpebral Fissure Distance (Right Eye) and Mean Change From Baseline Over Time



Source: Sections 16.2.6.1.5.22 and 16.2.6.1.5.30 of Clinical Study Report. This figure was produced by review team based on the adoe.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets
Abbreviations: alglu, alglucosidase alfa; aval, avalglucosidase alfa; SD, standard deviation

An improvement in interpalpebral fissure distance is demonstrated by an increase in this distance. However, in the literature, this is not a validated parameter for assessing patients with IOPD. In the ACT14132, interpalpebral fissure distance increased in patients receiving 40 mg/kg qow of avalglucosidase alfa (cohort 2 and the avalglucosidase alfa arm of cohort 3) suggesting a potential impact of avalglucosidase alfa on this parameter. However, the clinical significance of this finding is not clear, and the reproducibility of this endpoint is not established in patients with IOPD.

While overall there were numerical improvements or no worsening from baseline in the numerical scores used for Gross Motor Function Measure-88 (GMFM-88), Quick Motor Function Test (QMFT), and eyelid position movements, the interpretation of this data is limited due to the high variability and small sample size. The final SAP explicitly stated that this study "is not considered as a confirmatory clinical study," and these secondary efficacy variables were only summarized descriptively by dose cohort and treatment group. Additionally, at baseline, all except one patient had a normal LVMI on echocardiogram (Z-scores between 2 and -2). This parameter improved in the one patient who started with a z-score of 3 but did not change in the rest of the patients who received avalglucosidase alfa.

Given that the data from ACT14132 were not adequate to establish efficacy of avalglucosidase alfa in IOPD, another option was for the Applicant to provide data to support pediatric extrapolation from LOPD to IOPD. (b) (4)

To establish a similarity between LOPD and IOPD, the Applicant's response emphasized:

- Both forms of the disease are caused by autosomal recessive defects of the *GAA* gene and that the age of onset correlates with patients' residual GAA levels.
- Although the clinical manifestations in IOPD and LOPD are different, both diseases are multisystemic and the same organ systems can be affected in both. For example, IOPD and LOPD can have cardiac manifestations. Patients with IOPD most commonly have hypertrophic cardiomyopathy while patients with LOPD can have aortic aneurysms, arrhythmias, and cardiac dysfunction.
- There is a similar unmet need in both forms of the disease. While patients with either form initially improve with the currently available therapy, alglucosidase alfa, their improvement in muscle weakness and respiratory dysfunction can plateau or regress.
- Based on data from the Pompe Registry, the Applicant attempted to show that long-term outcome data on alglucosidase alfa are similar in patients with IOPD or LOPD. However, in this registry, patients are categorized according to age at symptom onset. The patients whose symptoms began before the age of 2 years are assumed to have IOPD. The patients whose symptoms began after 2 years of age, between 2 and 12 years of age, between 12 and 18 years of age and finally, after 18 years of age are assumed to have LOPD.
- During the course of treatment with alglucosidase alfa in the Pompe Registry, there were more patients with IOPD who received respiratory support at their last follow-up compared to their baseline, while a similar proportion of patients with LOPD required respiratory support at baseline and at their last follow-up. At baseline, 88% of patients whose symptoms began before the age of 2 years had cardiac enlargement, 83% had cardiomyopathy, and 75% had cardiac hypertrophy or enlargement. From baseline to the

last follow up, the percentage of these patients with cardiac enlargement, cardiomyopathy, and any cardiac hypertrophy or enlargement decreased during treatment. Cardiac disease was not commonly present in the patients whose symptoms began after the age of 2 years.

Assessment

The secondary efficacy variables used in ACT14132 do not capture the manifestations of IOPD that have the most impact on survival, such as respiratory failure and cardiac hypertrophy. Respiratory function was an exploratory endpoint in ACT14132. Perhaps because all the patients enrolled in this trial had already been exposed to alglucosidase alfa, at baseline most had normal left ventricular mass indices. Twenty-one of 22 patients did not have cardiac hypertrophy on entry into the trial, and after 25 weeks of treatment, the LVMI remained normal.

Furthermore, as the trial progressed, there were fewer patients with data available at each of the time points after 25 weeks (see Figure 12, Figure 13, Figure 14, Figure 15, Figure 16, and Figure 17), which limited assessment of the effects of avalglucosidase alfa in this population.

The review team concluded that the data from the open-label, controlled trial (ACT14132) in patients with IOPD did not provide convincing evidence for the effectiveness of avalglucosidase alfa at 40 mg/kg qow in this population. (b) (4) If pediatric extrapolation could be justified, the review team asked the Applicant to specify which data would be used to bridge the efficacy of avalglucosidase alfa between LOPD and IOPD populations. (b) (4)

In our assessment, the Applicant provided insufficient evidence to establish a similarity between LOPD and IOPD (b) (4) While the etiology of both forms of Pompe disease results from defects within the *GAA* gene, LOPD and IOPD have remarkably different phenotypes. For instance, hypertrophic cardiomyopathy is a hallmark of IOPD that contributes to the morbidity and mortality in patients with IOPD (Kishnani et al. 2007). This difference is emphasized by the findings in the Pompe Registry that, in patients whose symptom onset was after the age of 2 years, cardiac disease was not as prevalent or significant. Additionally, in the Pompe Registry, data are classified by the age at which symptoms started, rather than by whether a patient was established by their healthcare team to have IOPD or LOPD.

Conclusion

There is inadequate data to support the effectiveness of avalglucosidase alfa in the treatment of patients with IOP (b) (4) In order to establish effectiveness in this population, the Applicant should come to agreement with the Agency on a trial in treatment-naïve patients with IOPD, including pre-specified regimens and criteria for the use of immune tolerance induction (ITI).For example, the Applicant could compare treatment with avalglucosidase alfa to alglucosidase alfa, assessing efficacy endpoints, such as cardiac hypertrophy, survival, and ventilator-free survival, with an

Reference ID: 4836879

anticipated duration longer than 52 weeks in order to capture differences between the two treatment groups.

6.3.4. Long-Term Effectiveness

Issue

Evidence to support long-term sustainability of the efficacy of avalglucosidase alfa.

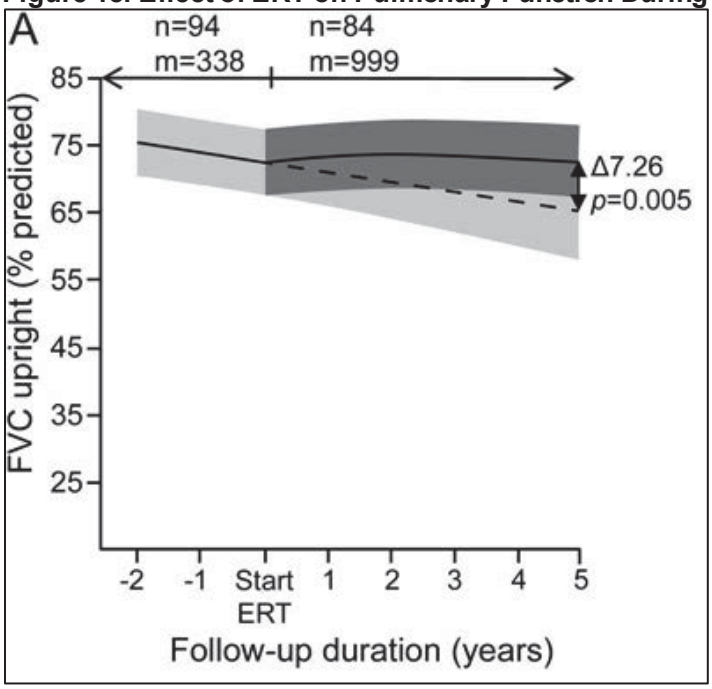
Background and Assessment

At the time of submission in September 2020, patients with LOPD enrolled in trials EFC14028 and LTS1379 (the extension trial for patients from TDR12857) had up to 3 years and 6 years of exposure to avalglucosidase alfa, respectively. However, for each of these trials, few patients had efficacy data available at these time points. In EFC14028, 13 patients had data for the FVC (% predicted) endpoint, and 12 patients had data for the 6-minute walk test (6MWT) endpoint at 2 years. At the 6-year time point in LTS13769, which was the extension treatment period portion of TDR12857, only four patients had data for both FVC (% predicted) and the 6MWT: two treatment-naive patients who had started at the 5 mg/kg qow dose and two treatment-experienced patients, one who had started at 5 mg/kg qow and one who had started at 10 mg/kg qow. Additional data is necessary to assess the long-term effectiveness of avalglucosidase alfa before including statements in the prescribing information.

In patients treated with alglucosidase alfa, a peak treatment effect is seen at two to three years for pulmonary function and muscle strength (Kuperus et al. 2017). Figure 18 and Figure 19 show that pulmonary function and muscle strength, respectively, decline over 5 years of treatment with alglucosidase alfa. More long-term data is necessary to determine whether patients treated with avalglucosidase alfa will experience a similar decline in effectiveness over time or whether the gains they achieved initially with avalglucosidase alfa treatment will persist after 2-3 years. Based on the unmet need for long-term treatment in LOPD with alglucosidase alfa, the review team concluded that it is reasonable to approve avalglucosidase alfa for treatment of patients 1 year of age and older with LOPD.

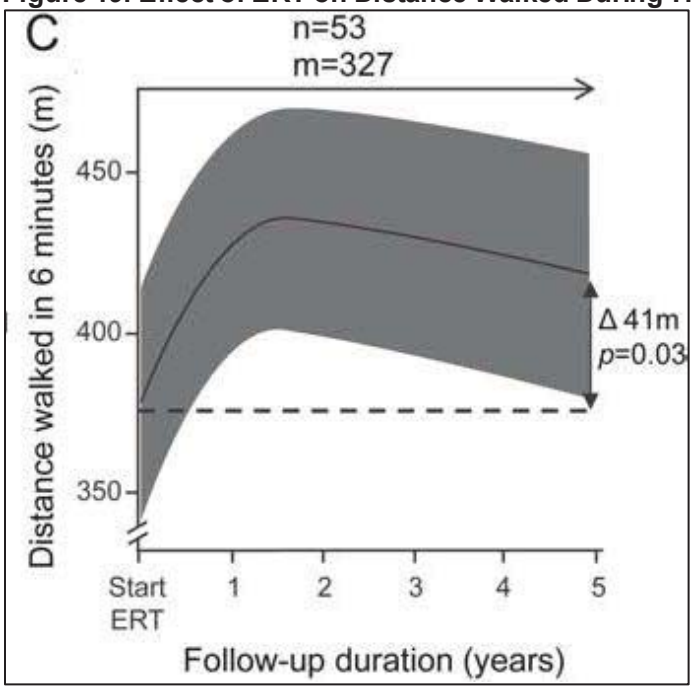
Reference ID: 4836879

Figure 18. Effect of ERT on Pulmonary Function During Treatment With Alglucosidase Alfa



Source: Kuperus et al., 2017, Figure 2A
Solid lines represent the measured natural course of the disease and/or the course during treatment. Dashed line represents the natural course extrapolated based on natural history data. The 95% confidence intervals are shown in gray. Δ = difference between treatment data and extrapolated natural course at 5 years.
Abbreviations: ERT, enzyme replacement therapy; FVC, forced vital capacity; m, number of measurements

Figure 19. Effect of ERT on Distance Walked During Treatment With Alglucosidase Alfa



Source: Kuperus et al., 2017, Figure 1C
Solid lines represent the measured natural course of the disease and/or the course during treatment. Dashed line represents the natural course extrapolated based on natural history data or baseline level. The 95% confidence intervals are shown in gray. Δ = difference between treatment data and extrapolated natural course at 5 years.
Abbreviations: ERT, enzyme replacement therapy; m, number of measurements; (m), meters

Conclusion

The review team concluded that it is premature to include any statement regarding long-term effectiveness in the prescribing information.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

7.1.1. Overall Safety Concern

There were no nonclinical safety issues of significant concern as assessed by the toxicology studies conducted during the development program, and the nonclinical data support marketing of avalglucosidase alfa. Nonclinical safety was evaluated in the following studies during development: (1) repeat dose toxicity studies in mice (up to 28 days) and monkeys (up to 26 weeks, Table 22); (2) an in vivo genotoxicity study in mice (up to 150 mg/kg IV); (3) reproductive and developmental toxicity studies, including fertility studies in male and female mice, embryo-fetal development studies in mice and rabbits, and a pre- and postnatal development study in mice; (4) a juvenile study in mice; and (5) in vitro and in vivo impurity studies. No additional nonclinical study will be conducted as a postmarketing requirement.

Table 22. Safety Margins From Pivotal Toxicology Studies

Study	NOAEL	AUC[1]	Safety Margin[2] (Based on AUC)
26-week monkey study Reductions in body weight gain (9%) and organ weights at 200 mg/kg without any microscopic findings	200 mg/kg IV every other week[3]	28162 µg•h/mL	23X

Source: Study 0658-11097 study report submitted under eCTD 001 module 4.2.3.2.
[1] $AUC_{0\text{-}inf}$ value was used to determine the clinical safety margin.
[2] Exposure multiples were based on pharmacokinetics analysis from trial EFC14028, where the maximum clinical dose (20 mg/kg IV every other week in patients with LOPD) resulted in systemic exposure of $AUC_{0\text{-}2w}$ =1230 µg•h/mL.
[3] Highest dose tested
Abbreviations: AUC, area under the curve; IV, intravenous; NOAEL, no observed adverse effect level

7.1.2. Safety Pharmacology

The effects of avalglucosidase alfa in the central nervous system, pulmonary system, and cardiovascular system were evaluated in the 26-week IV toxicity study in monkeys. There were no drug-related changes in central nervous system evaluation (activity level, fasciculations, movement of facial muscles, and visual field), respiratory rate, core temperatures, and electrocardiogram (heart rate, RR, QT, and QTc intervals). Hemodynamic data (systolic, diastolic, and mean arterial pressure) were not monitored in this study. However, the Applicant noted that hemodynamics will be monitored closely in clinical trials.

Reference ID: 4836879

7.1.3. ADME

Pharmacokinetic studies were conducted in CD-1 mice and cynomolgus monkeys. Single-dose PK studies showed avalglucosidase alfa prolonged circulating half-life and an increase in systemic exposure with a corresponding decrease in clearance, indicating saturation. The $t_{½}$ appeared similar across species. Repeat-dose PK studies showed no differences in PK parameters between the first and fourth doses at 40 mg/kg avalglucosidase alfa in the 28-day IV mouse study and the 4-week IV monkey study. However, there were differences in PK parameters at 120 mg/kg avalglucosidase alfa (i.e., decreased clearance and increased exposure) in monkeys. Moreover, in the 26-week monkey study, changes in PK parameters were also noted at the seventh and thirteenth infusions (i.e., increased half-life, increased maximal concentrations, increased exposure, and decreased clearance). Lastly, distribution studies in GAA knockout (GAAKO) mice showed that the majority of avalglucosidase alfa distributed to the liver, followed by a lesser amount to the heart, and less still to the skeletal muscle.

7.1.4. General Toxicology

No target organs were identified. Repeat dose toxicity studies done in mice (up to 120 mg/kg/week for 28 days) and monkeys (up to 200 mg/kg every other week for 26 weeks) showed that avalglucosidase alfa was generally well tolerated. Due to hypersensitivity reactions to avalglucosidase alfa, especially in mice pretreated with diphenhydramine (DPH), the chronic toxicity study was performed in monkeys only. Despite reductions in body weight gain (9%) and organ weights (without microscopic findings) at 200 mg/kg, the NOAEL was 200 mg/kg IV every other week in monkeys, corresponding to an area under the concentration-time curve $(AUC)_{0\text{-inf}}$ of 28162 µg·h/mL (23 times the human safety AUC obtained from the recommended biweekly dose of 20 mg/kg for patients with LOPD). In addition, local tolerance of avalglucosidase alfa (IV infusion sites) was assessed in the repeat-dose toxicity studies in monkeys. No macroscopic and microscopic findings were observed at injection sites.

Genotoxicity studies for avalglucosidase alfa were not conducted, per International Conference on Harmonisation (ICH) guidance *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012) and the guidance for industry *Investigational Enzyme Replacement Therapy Products, Nonclinical Assessment* (October 2019). However, a non-good laboratory practice (non-good laboratory practice (GLP)) in vivo micronucleus test was conducted in GAAKO mice up to 150 mg/kg IV, where genotoxicity was not observed. Carcinogenicity studies were not conducted. The Applicant provided a carcinogenicity risk assessment for avalglucosidase alfa, including (1) an evaluation of avalglucosidase alfa nonclinical toxicity; (2) a review of marketed Pompe disease drugs; (3) a review of the impurity [redacted] (b) (4) published literature, a repeat dose toxicity study in monkeys, and in vitro genotoxicity studies; and (4) an evaluation of the potential release of [redacted] (b) (4) containing compounds in the avalglucosidase alfa drug product.

Potential genotoxic impurities and impurities/degradants of avalglucosidase alfa were evaluated. In particular, the potential toxicity of [redacted] (b) (4) in the drug product was evaluated in a 13-week monkey study [redacted] (b) (4) IV infusion every other week spiked up to [redacted] (b) (4) There was no difference between the groups administered avalglucosidase alfa with various amounts of spiked [redacted] (b) (4)

[redacted] (b) (4) for males and females, respectively. The calculated maximal theoretical amount of linker in a 20 mg/kg dose of avalglucosidase alfa [redacted] (b) (4) was below the acceptable limit of lifetime adjusted acceptable intake of [redacted] (b) (4) µg/kg per dose. Moreover, the genotoxic potential of [redacted] (b) (4) was evaluated by Ames and chromosomal aberration assays, and found to be negative, suggesting that [redacted] (b) (4) was not genotoxic.

According to the ERT guidance (October 2019), "evaluating carcinogenic potential generally is not needed to support a marketing application. However, chemically modified ERT products (e.g., a recombinant human enzyme conjugated with a chemical linker) may need an assessment to address the potential for genotoxicity and/or [redacted] (b) (4) herefore, per the ERT guidance, a chemical linker within avalglucosidase alfa would warrant a carcinogenic assessment. However, given the negative genotoxic findings [redacted] (b) (4) tested negative in the Ames test and chromosomal aberration assay) and the lack of histopathology findings in the 26-week toxicity study in monkeys, a weight-of-evidence approach to address carcinogenic potential is the most appropriate approach, and a postmarketing carcinogenicity study is not warranted.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Avalglucosidase alfa is an enzyme replacement therapy and potential risks with this class of drugs include hypersensitivity reactions including anaphylaxis, infusion associated reactions, and immunogenicity (see Section 7.7.1)

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Not applicable. This product has not been approved in the United States or in any foreign markets. Therefore, no postmarketing experience is available at the time of this review.

7.4. FDA Approach to the Safety Review

Safety data from the following trials were pooled and submitted to support the safety of avalglucosidase alfa:

- Trial EFC14028 (100 patients)
- Trial ACT14132 (22 patients)
- Trial TDR12857 (24 patients)
- Trial LST13769 (19 patients who finished TDR12857)

The avalglucosidase alfa combined safety population consisted of 138 patients from the four trials listed above: 119 patients with LOPD who were 16 years or older and 19 patients with

IOPD who were between 1 year to 11 years old. The safety data are shown by events occurring in treatment-naïve and treatment-experienced patients; adult and pediatric patients; all patients; and treatment arm within individual trials. There was a total of 118 adults and 20 pediatric patients. Sixty-one patients were treatment-naïve and 77 were treatment-experienced, having received alglucosidase alfa previously. Three additional pediatric patients with IOPD were included in the 120-day safety report.

First, the integrated summary of safety (ISS) dataset was examined for the required and standardized components and for completeness of the data. Then, the review team confirmed that the 2,947 adverse events (AEs) reported by the Applicant accurately described the AEs reported by the investigators.

Once accuracy was confirmed, the frequencies of each AE were assessed and described both by occurrence and exposure-adjusted rates. The review team reviewed all deaths, adverse events of special interest (AESI), SAEs, discontinuations, withdrawals, and patients lost to follow-up.

In addition, the review team separately assessed data from the two comparator-controlled trials: EFC14028 and stage 2 (cohort 3) of ACT14132. These two trials provided data to compare the incidences of adverse effects between avalglucosidase alfa and the current standard of care, alglucosidase alfa.

7.5. Adequacy of Clinical Safety Database

The safety database was adequate for a sufficient safety assessment of avalglucosidase alfa for the indication of LOPD (b) (4) in children who are older than 1 year. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review. No major issues were identified with respect to the coding of adverse events.

Table 23 shows the baseline demographic and clinical characteristics of the safety population. The most notable imbalances occur in the age groups that are represented in the safety population. For instance, there are only 20 children in the safety set. There are no children younger than 1 year of age. Additionally, there is only one pediatric patient with LOPD, a 16-year-old male. The limited number of children affects the approvability of avalglucosidase alfa in patients with IOPD and in patients younger than 1 year of age with LOPD (see Section 6.3.2 and 6.3.3).

The majority of the patients (88%) were White, and this is not representative of the population with PD, as there is an incidence of 1:14,000 among African Americans (Leslie and Bailey 2007). However, this imbalance was present in the earlier alglucosidase alfa trials as well (Hahn et al. 2018; van der Ploeg et al. 2010).

Table 23. Baseline Demographic and Clinical Characteristics, Integrated Summary of Safety

Characteristic	Naive N=61	Experienced N=77	Adult N=118	Pediatric N=20	All patients N=138
Sex, n (%)					
F	31 (50.8)	33 (42.9)	56 (47.5)	8 (40.0)	64 (46.4)
M	30 (49.2)	44 (57.1)	62 (52.5)	12 (60.0)	74 (53.6)

Characteristic	Naive N=61	Experienced N=77	Adult N=118	Pediatric N=20	All patients N=138
Age, years					
Mean (SD)	45.3 (15.4)	38.1 (21.9)	47.1 (14.5)	7.0 (3.8)	41.3 (19.5)
Median (min, max)	47.0	41.0	47.0	7.5	43.5
Min, max	16.0, 78.0	1.0, 77.0	19.0, 78.0	1.0, 16.0	1.0, 78.0
Age group					
>6 months to <1 year	0	0	0	0	0
1 to <6 years	0	6 (7.8)	0	6 (30.0)	6 (4.3)
≥6 to <18 years	1 (1.6)	13 (16.9)	0	14 (70.0)	14 (10.1)
≥18 to <45 years	29 (47.5)	25 (32.5)	54 (45.8)	0	54 (39.1)
≥45 to <65 years	24 (39.3)	23 (29.9)	47 (39.8)	0	47 (34.1)
≥65 years	7 (11.5)	10 (13.0)	17 (14.4)	0	17 (12.3)
Ethnicity, n (%)					
Hispanic or Latino	3 (4.9)	12 (15.6)	12 (10.2)	3 (15.0)	15 (10.9)
Not Hispanic or Latino	53 (86.9)	59 (76.6)	95 (80.5)	17 (85.0)	112 (81.2)
Not reported	5 (8.2)	6 (7.8)	11 (9.3)	0	11 (8.0)
Race, n (%)					
Asian	3 (4.9)	8 (10.4)	2 (1.7)	9 (45.0)	11 (8.0)
Black or African American	1 (1.6)	2 (2.6)	3 (2.5)	0	3 (2.2)
Multiple	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Not reported	1 (1.6)	0	1 (0.8)	0	1 (0.7)
White	55 (90.2)	67 (87.0)	111 (94.1)	11 (55.0)	122 (88.4)
Country					
Argentina	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Australia	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Austria	2 (3.3)	0	2 (1.7)	0	2 (1.4)
Brazil	1 (1.6)	5 (6.5)	6 (5.1)	0	6 (4.3)
Canada	2 (3.3)	0	2 (1.7)	0	2 (1.4)
Germany	7 (11.5)	3 (3.9)	10 (8.5)	0	10 (7.2)
Spain	4 (6.6)	0	3 (2.5)	1 (5.0)	4 (2.9)
France	9 (14.8)	9 (11.7)	15 (12.7)	3 (15.0)	18 (13.0)
United Kingdom	3 (4.9)	5 (6.5)	6 (5.1)	2 (10.0)	8 (5.8)
Hungary	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Italy	2 (3.3)	3 (3.9)	5 (4.2)	0	5 (3.6)
Japan	1 (1.6)	2 (2.6)	1 (0.8)	2 (10.0)	3 (2.2)
Netherlands	4 (6.6)	3 (3.9)	7 (5.9)	0	7 (5.1)
Poland	2 (3.3)	0	2 (1.7)	0	2 (1.4)
Portugal	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Russia	4 (6.6)	2 (2.6)	6 (5.1)	0	6 (4.3)
Turkey	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
United States	14 (23.0)	34 (44.2)	41 (34.7)	7 (35.0)	48 (34.8)
Belgium	0	3 (3.9)	3 (2.5)	0	3 (2.2)
Czech Republic	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Denmark	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Taiwan	0	5 (6.5)	0	5 (25.0)	5 (3.6)

Source: adsl.xpt; Software: Python
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Table 24 summarizes the avalglucosidase alfa exposure for the pooled safety population. Patients treated with avalglucosidase alfa for 48 weeks or greater but less than 96 weeks (41%) comprise the largest cohort in the safety database. The second largest patient cohort were those treated for 96 weeks or greater but less than 144 weeks (21%).

Table 24. Duration of Exposure, Safety Population, Integrated Summary of Safety

	Patient Description				
Variable	Naive N=61	Experienced N=77	Adult N=118	Pediatric N=20	All N=138
Duration of treatment (wks)					
Mean (SD)	122.4 (77.3)	88.9 (95.4)	111.16 (93.6)	59.5 (29.8)	103.7 (89.1)
Median	98.16	66.9	86.7	69.74	81.0
(Min, max)	(17.1; 329.3)	(2.0, 340.5)	(2.0, 340.5)	(12.0, 102.2)	(2.0, 240.5)
Patients treated, by duration, n (%)					
<48 wks	3 (4.9)	11 (14.3)	6 (5.1)	8 (40.0)	14 (10.1)
≥48 to <96 wks	27 (44.3)	30 (39.0)	48 (40.7)	9 (45.0)	57 (41.3)
≥96 to <144 wks	13 (21.3)	16 (20.8)	26 (22.0)	3 (15.0)	29 (21.0)
≥144 to <192 wks	11 (18.0)	10 (13.0)	21 (17.8)	0	21 (15.2)
≥192 to <240 wks	0	0	0	0	0
≥240 to <300 wks	3 (4.9)	2 (2.6)	5 (4.2)	0	5 (3.6)
≥300 to <500 wks	4 (6.6)	8 (10.4)	12 (10.2)	0	12 (8.7)

Source: adex.xpt; Software: Python
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

Overall Summary

The demonstrated safety profile of avalglucosidase alfa is acceptable at the dose of 20 mg/kg qow in patients with LOPD, as well as at the dose of 40 mg/kg qow in patients with IOPD who are 1 year of age and older. No safety data is available for patients 12 months of age or younger. The most common adverse reactions (ARs) were hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions, which presented most often as abdominal pain, arthralgia, back pain, chills, cough, diarrhea, dizziness, dyspnea, erythema, fatigue, headache, hypertension, musculoskeletal pain, myalgia, nausea, pain, pain in extremity, pruritus, pyrexia, rash, urticaria and vomiting.

During the course of the trials, 28% (38/138) of patients with either LOPD or IOPD had peak elevated liver enzymes that met criteria for Temple's Corollary, and thus were at possible increased risk of drug induced liver injury (DILI). While ALT and AST did not normalize by the last measurement for most patients, most ALT and AST levels at the last measurement were lower than the patient's baseline measurement. The bilirubin levels for the 38 patients remained within the normal range throughout the trial (see Section 7.7.4 for details.)

During the safety review, the review team also assessed adverse events of special interest (AESI); as with most ERTs, hypersensitivity events (including anaphylaxis) and IARs were identified with avalglucosidase alfa treatment. No data on pregnancy and lactation are available with avalglucosidase alfa. There was one death on avalglucosidase alfa during the trials, which was assessed as unrelated. The review team concluded that labeling, including a boxed warning, and routine pharmacovigilance monitoring is adequate to monitor identified safety risks.

7.6.1. Safety Findings and Concerns, Integrated Safety Set

7.6.1.1. Overall Adverse Event Summary, Integrated Safety Set

Table 25 provides a summary of AEs reported in the ISS. One or more treatment-emergent adverse events (TEAEs) were reported by 91% (126/138) of the patients. A higher proportion of treatment-naïve patients (95%, 58/61) reported TEAEs compared to treatment-experienced patients (88%, 68/77). Similarly, a higher proportion of treatment-naïve patients (71%, 43/61) reported moderate or severe AEs compared to treatment-experienced patients (62%, 48/77). However, this could be related to the difference in exposure times. As shown in Table 24, treatment-naïve patients were exposed to avalglucosidase alfa for longer than treatment-experienced patients during these trials. A higher proportion of pediatric patients (40%, 8/20) had SAEs compared to the rest of the groups. This finding could, however, be related to the small number of pediatric patients reported in the LOPD trials (n=1) and IOPD trials (n=19).

Table 25. Overview of Adverse Events for Avalglucosidase Alfa, Integrated Safety Population

	Patient Description				
Adverse Event Category	Naive N=61 n (%)	Experienced N=77 n (%)	Adult N=118 n (%)	Pediatric N=20 n (%)	All N=138 n (%)
Any AE	58 (95.1)	68 (88.3)	106 (89.8)	20 (100.0)	126 (91.3)
Moderate or severe AE	43 (70.5)	48 (62.3)	78 (66.1)	13 (65.0)	91 (65.9)
Any SAE	18 (29.5)	17 (22.1)	27 (22.9)	8 (40.0)	35 (25.4)
SAE with fatal outcome	0	1 (1.3)	1 (0.8)	0	1 (0.7)
AE leading to discontinuation	4 (6.6)	0	4 (3.4)	0	4 (2.9)
AE leading to dose modification	20 (32.8)	23 (29.9)	39 (33.1)	4 (20.0)	43 (31.2)
Leading to interruption	20 (32.8)	23 (29.9)	39 (33.1)	4 (20.0)	43 (31.2)
Leading to reduction	1 (1.6)	1 (1.3)	2 (1.7)	0	2 (1.4)
Leading to delay	0	0	0	0	0

Source: adae.xpt; Software: Python
Treatment-emergent adverse events are defined as AEs that developed, worsened or became serious during the treatment epoch, ISS.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

However, the exposure-adjusted incidence rate of any TEAEs was greater in treatment-experienced patients (486 per 100 person-years) than in treatment-naïve patients (250 per 100 person-years) as shown in Table 26. This is not unexpected given treatment-experienced patients' previous exposure to ERT. In addition, the exposure-adjusted incidence rate for SAEs and moderate or severe AEs was similar for the two groups.

Table 26. Exposure-Adjusted Incidence Rate of TEAE(S), Integrated Safety Population

Adverse Event Category	Patient Description: Naive N=61	Experienced N=77	Adult N=118	Pediatric N=20	All Patients N=138
Any AE	58 (250)	68 (485.7)	106 (305.5)	20 (800)	126 (338.7)
Any SAE	18 (16)	17 (15.9)	27 (13.3)	8 (50)	35 (15.9)
Moderate or severe AEs	43 (29.6)	48 (35.7)	78 (30.4)	13 (55.1)	91 (32.5)

Source: adae3.xpt; Software: R
All values are expressed as n (EAIR per 100 person-years).
Abbreviations: AE, adverse event; EAIR, exposure-adjusted incident rate; SAE, serious adverse event; TEAE, treatment-emergent adverse event

The most commonly reported TEAE was nasopharyngitis, occurring in 30% of the patients. The most common system organ class with TEAE was infections and infestations (68%). However, the review team does not assess these as likely related to avalglucosidase alfa. The most common adverse reactions (ARs) were hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions, which presented most often as abdominal pain, arthralgia, back pain, chills, cough, diarrhea, dizziness, dyspnea, erythema, fatigue, headache, hypertension, musculoskeletal pain, myalgia, nausea, pain, pain in extremity, pruritus, pyrexia, rash, urticaria and vomiting (See Section 7.7.1).

7.6.1.2. Deaths, Integrated Safety Set

Table 27 describes the deaths among trial patients receiving avalglucosidase alfa. During the clinical trials, a total of two patients died: one patient receiving avalglucosidase alfa and one receiving alglucosidase alfa. Both patients participated in trial EFC14028.

Table 27. Deaths in the Integrated Safety Population in Patients Receiving Avalglucosidase Alfa

Preferred Term	Patient Description: Naive N=61 n (%)	Experienced N=77 n (%)	Adult N=118 n (%)	Pediatric N=20 n (%)	All Patients N=138 n (%)
Any AE leading to death	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Adenocarcinoma pancreas	0	1 (1.3)	1 (0.8)	0	1 (0.7)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as AEs that developed or worsened or became serious during the treatment epoch
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

The narrative for the one death on avalglucosidase alfa is provided in Section 7.7.4.

In the 120-day safety update, one additional death was reported in a 78-year-old male patient (b) (6) who had withdrawn from the trial. His last infusion was on (b) (6) On (b) (6) he developed acute respiratory failure and died 7 days later. The investigator assessed this death as unrelated to avalglucosidase alfa, and the review team agrees with this assessment.

7.6.1.3. Serious Adverse Events, Integrated Safety Set

Table 28 lists the 77 SAEs reported in 35 patients (25%) in the ISS. SAEs occurring in 2 or more patients included pneumonia, chills, pyrexia, respiratory distress, respiratory failure, and eyelid ptosis. The SAEs in six patients were related to hypersensitivity (including anaphylaxis) or IARs (see Section 7.7.1).

Table 28. Serious Adverse Events, Integrated Safety Population

	Patient Description				
Preferred Term	**Naive N=61 n (%)**	**Experienced N=77 n (%)**	**Adult N=118 n (%)**	**Pediatric N=20 n (%)**	**All Patients N=138 n (%)**
Any SAE	18 (29.5)	17 (22.1)	27 (22.9)	8 (40.0)	35 (25.4)
Pneumonia	2 (3.3)	3 (3.9)	2 (1.7)	3 (15.0)	5 (3.6)
Chills	2 (3.3)	0	2 (1.7)	0	2 (1.4)
Pyrexia	1 (1.6)	1 (1.3)	1 (0.8)	1 (5.0)	2 (1.4)
Respiratory distress	1 (1.6)	1 (1.3)	1 (0.8)	1 (5.0)	2 (1.4)
Respiratory failure	1 (1.6)	1 (1.3)	2 (1.7)	0	2 (1.4)
Acute myocardial infarction	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Aortic aneurysm	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Aortic dilatation	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Arteritis	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Bacteremia	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Basal cell carcinoma	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Blood pressure increased	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Body temperature increased	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Breast cyst	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Calculus urinary	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Chest discomfort	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Cholecystitis	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Cholelithiasis	1 (1.6)	0	1 (0.8)	0	1 (0.7)
CIDP	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Cystitis	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Dyspnea	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Gastric ulcer	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Headache	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Heart rate increased	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Hydronephrosis	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Hyponatremia	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Hypotension	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Hypoventilation	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Infection	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Ischemic stroke	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Labor pain	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Moyamoya disease	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Myalgia	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Myocardial ischemia	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Nausea	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Oxygen saturation decreased	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Pelvi-ureteric obstruction	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Peripheral artery stenosis	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Postimplantation syndrome	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Rectal hemorrhage	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Renal colic	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Renal oncocytoma	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Respiratory acidosis	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Skin discoloration	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Subarachnoid hemorrhage	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Syncope	1 (1.6)	0	1 (0.8)	0	1 (0.7)
VIIIth nerve injury	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Eyelid ptosis	0	2 (2.6)	0	2 (10.0)	2 (1.4)
Adenoidal hypertrophy	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Atrial thrombosis	0	1 (1.3)	0	1 (5.0)	1 (0.7)

	Patient Description				
Preferred Term	Naive N=61 n (%)	Experienced N=77 n (%)	Adult N=118 n (%)	Pediatric N=20 n (%)	All Patients N=138 n (%)
Device malfunction	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Femur fracture	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Gastroenteritis	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Influenza	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Otitis media	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Postprocedural hemorrhage	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Respiratory tract infection viral	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Strabismus	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Tonsillar hypertrophy	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Tympanic membrane perforation	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Adenocarcinoma pancreas	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Angina pectoris	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Bipolar disorder	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Deep vein thrombosis	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Diverticulitis	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Electrocardiogram q wave abnormal	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Extravasation blood	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Fall	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Fractured sacrum	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Gastrointestinal hemorrhage	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Hip fracture	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Lumbar vertebral fracture	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Lung carcinoma cell type unspecified stage iv	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Noncardiac chest pain	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Renal cell carcinoma	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Vertigo	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Volvulus	0	1 (1.3)	1 (0.8)	0	1 (0.7)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as AEs that developed or worsened or became serious during the treatment epoch
Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event

The narrative of one patient experiencing an SAE that the review team disagreed with the Applicant's assessment is provided below.

- (b) (6) A 24-year-old male in trial EFC14028 who received avalglucosidase alfa. On day 260, 7 hours after an avalglucosidase alfa infusion, the patient was hospitalized for hypoventilation with a chest x-ray showing mild alveolar hypoventilation. During this hospitalization, the patient's noninvasive ventilation equipment showed that he had lower inspiratory pressures in the lateral decubitus position. This event did not result in any changes to the patient's later infusions. The review team disagrees with the investigator's assessment that this event is unrelated to avalglucosidase alfa, because this event cannot be distinguished from the infusion causing fluid overload resulting in mild pulmonary edema. In the Labeling, caution is advised for patients with cardiac or pulmonary disease that places them at increased risk for developing pulmonary edema.

The SAEs listed below were considered AESIs. The review team agreed with the Applicant that these events are related to avalglucosidase alfa. These cases are discussed in Section 7.7.1.

- [redacted] (b) (6) A 62-year-old female in trial EFC14028 with syncope.
- [redacted] (b) (6) A 44-year-old female in trial EFC14028 with nausea on two separate days.
- [redacted] (b) (6) A 52-year-old female in trial EFC14028 with dyspnea.
- [redacted] (b) (6) A 68-year-old male in trial EFC14028 with increased blood pressure, increased heart rate, headache, chills, increased body temperature, decreased oxygen saturation, and skin discoloration.
- [redacted] (b) (6) A 51-year-old female in trial LTS13769 with chest discomfort, respiratory distress, flushing, dizziness, and nausea.
- [redacted] (b) (6) A 78-year-old male in trial LTS13769 with pyrexia and chills.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, Integrated Safety Set

Nine patients who received avalglucosidase alfa discontinued participation during the clinical trials: four patients discontinued due to TEAEs and five patients withdrew for reasons other than AEs (i.e., enrolled in a gene therapy study [1], withdrew due to the difficulty of visits [1] and other [3]).

As shown in Table 29, the TEAEs in two of the four patients who discontinued avalglucosidase alfa due to TEAEs were assessed by the review team as being related to avalglucosidase alfa, which was consistent with the investigator's assessment.

Table 29. Adverse Events Leading to Discontinuation, Integrated Safety Population

Patient ID Number	AE Leading to Study Discontinuation	Relationship to Drug
[redacted] (b) (6)	Anaphylaxis	Related
	IAR	Related
	Non-ST elevation myocardial infarction	Not related
	Pregnancy	Not related

Source: adae.xpt; Software: JMP 15
Abbreviations: AE, adverse event, IAR, infusion associated reaction.

As described in the narratives below, the patients with TEAEs related to avalglucosidase alfa and resulting in discontinuation from the trial had hypersensitivity events including anaphylaxis, ocular hyperemia, and erythema.

Narratives of patients discontinuing due to AEs related to avalglucosidase alfa:

- [redacted] (b) (6) (TDR12857): A 51-year-old woman who experienced anaphylaxis during her ninth infusion and was discontinued from the trial. See Section 7.7.1 for the patient narrative.
- [redacted] (b) (6) (EFC14028): A 51-year-old man who was receiving avalglucosidase alfa at 20 mg/kg qow. He had a history of mild-to-moderate IARs during five previous infusions, including dyspepsia, nausea, and abdominal pain. On day 479, during an infusion, he experienced abdominal pain which prompted an interruption of the infusion. An hour after re-initiating the infusion, the patient developed ocular hyperemia and

erythema. He did not receive any interventions for these symptoms. Avalglucosidase alfa was discontinued after development of ocular hyperemia and erythema, which the review team assessed as related to the study drug. The patient discontinued his participation in the trial on day 505.

- [redacted] (b) (6) (EFC14028): A 47-year-old man who was receiving avalglucosidase alfa at 20 mg/kg qow. He had a previous history of past tobacco use, sleep disorder, and hypertension. At enrollment, his medications included lisinopril, hydrochlorothiazide, and fish oil. On day 677, the patient was diagnosed with a non-ST elevation myocardial infarction. He underwent a cardiac catheterization with pacemaker placement. During his hospitalization, he also experienced severe respiratory failure and severe acute kidney injury. Avalglucosidase alfa was discontinued due to this event. Based on his past medical history, the myocardial infarct does not seem related to his exposure to avalglucosidase alfa.
- [redacted] (b) (6) (LTS13769): A 19-year-old woman who was receiving avalglucosidase alfa at 10 mg/kg qow. She found out that she was pregnant on day 154 and received her last dose of avalglucosidase alfa on day 183. The review team agrees with the Applicant that this event is unrelated to avalglucosidase alfa.

In the 120-day safety update, the Applicant noted that another patient had discontinued treatment. This patient, [redacted] (b) (6) (EFC14028), was a 34-year-old woman who discontinued treatment due to a pregnancy. The review team assessed this event as unrelated to avalglucosidase alfa.

7.6.1.5. Treatment-Emergent Adverse Events, Integrated Safety Set

The frequency and severity of TEAEs were evaluated in the ISS to assess the general safety profile of avalglucosidase alfa. TEAEs are AEs that developed, worsened or became serious during the treatment period.

The review team assessed frequent AEs to be ARs if they could be explained by avalglucosidase alfa's drug class (ERT) (see Section 7.6.2.5 for assessment of TEAEs relative to the active comparator) or its mechanism of action. Table 30 shows TEAEs that occurred in ≥2% of all patients with PD who received avalglucosidase alfa. As shown in Table 25, only two adult patients required a reduction in their dose of avalglucosidase alfa due to ARs, while 43 adult and pediatric patients required interruptions in their infusions. This may reflect the fact that most of the events were not very severe.

Refer to Section 7.7.1 for a discussion of hypersensitivity (including anaphylaxis) and IARs.

Table 30. Common Adverse Events Occurring at ≥2% Frequency, Safety Population, Integrated Safety Set

	Patient Description				All
Preferred Term	Naive N=61 n (%)	Experienced N=77 n (%)	Adult N=118 n (%)	Pediatric N=20 n (%)	Patients N=138 n (%)
Any AE	58 (95.1)	68 (88.3)	106 (89.8)	20 (100.0)	126 (91.3)
Nasopharyngitis	22 (36.1)	20 (26.0)	41 (34.7)	1 (5.0)	42 (30.4)
Headache	19 (31.1)	19 (24.7)	34 (28.8)	4 (20.0)	38 (27.5)
Back pain	19 (31.1)	13 (16.9)	30 (25.4)	2 (10.0)	32 (23.2)

	Patient Description				All
Preferred Term	Naive N=61 n (%)	Experienced N=77 n (%)	Adult N=118 n (%)	Pediatric N=20 n (%)	Patients N=138 n (%)
Diarrhea	17 (27.9)	18 (23.4)	31 (26.3)	4 (20.0)	35 (25.4)
Nausea	17 (27.9)	11 (14.3)	26 (22.0)	2 (10.0)	28 (20.3)
Influenza	16 (26.2)	7 (9.1)	21 (17.8)	2 (10.0)	23 (16.7)
Pain in extremity	14 (23.0)	11 (14.3)	22 (18.6)	3 (15.0)	25 (18.1)
Fatigue	13 (21.3)	9 (11.7)	21 (17.8)	1 (5.0)	22 (15.9)
Fall	12 (19.7)	18 (23.4)	25 (21.2)	5 (25.0)	30 (21.7)
Arthralgia	12 (19.7)	11 (14.3)	22 (18.6)	1 (5.0)	23 (16.7)
Myalgia	12 (19.7)	8 (10.4)	19 (16.1)	1 (5.0)	20 (14.5)
Muscle spasms	12 (19.7)	7 (9.1)	19 (16.1)	0	19 (13.8)
Dizziness	12 (19.7)	6 (7.8)	18 (15.3)	0	18 (13.0)
Contusion	10 (16.4)	5 (6.5)	14 (11.9)	1 (5.0)	15 (10.9)
URI	9 (14.8)	16 (20.8)	19 (16.1)	6 (30.0)	25 (18.1)
Rash	9 (14.8)	15 (19.5)	18 (15.3)	6 (30.0)	24 (17.4)
Vomiting	9 (14.8)	12 (15.6)	16 (13.6)	5 (25.0)	21 (15.2)
Pyrexia	9 (14.8)	10 (13.0)	13 (11.0)	6 (30.0)	19 (13.8)
Musculoskeletal pain	7 (11.5)	11 (14.3)	17 (14.4)	1 (5.0)	18 (13.0)
Abdominal pain	7 (11.5)	8 (10.4)	11 (9.3)	4 (20.0)	15 (10.9)
Pruritus	6 (9.8)	10 (13.0)	16 (13.6)	0	16 (11.6)
Urinary tract infection	6 (9.8)	7 (9.1)	10 (8.5)	3 (15.0)	13 (9.4)
Oropharyngeal pain	6 (9.8)	7 (9.1)	11 (9.3)	2 (10.0)	13 (9.4)
Erythema	6 (9.8)	4 (5.2)	8 (6.8)	2 (10.0)	10 (7.2)
Abdominal pain upper	6 (9.8)	4 (5.2)	10 (8.5)	0	10 (7.2)
Chills	6 (9.8)	2 (2.6)	8 (6.8)	0	8 (5.8)
Influenza like illness	6 (9.8)	1 (1.3)	7 (5.9)	0	7 (5.1)
Cough	5 (8.2)	8 (10.4)	9 (7.6)	4 (20.0)	13 (9.4)
Urticaria	5 (8.2)	5 (6.5)	9 (7.6)	1 (5.0)	10 (7.2)
Dyspnea	5 (8.2)	5 (6.5)	10 (8.5)	0	10 (7.2)
Hypertension	5 (8.2)	3 (3.9)	8 (6.8)	0	8 (5.8)
Edema peripheral	5 (8.2)	2 (2.6)	6 (5.1)	1 (5.0)	7 (5.1)
Peripheral swelling	5 (8.2)	2 (2.6)	7 (5.9)	0	7 (5.1)
Cystitis	5 (8.2)	0	5 (4.2)	0	5 (3.6)
Gastroenteritis	4 (6.6)	6 (7.8)	9 (7.6)	1 (5.0)	10 (7.2)
Tonsillitis	4 (6.6)	3 (3.9)	6 (5.1)	1 (5.0)	7 (5.1)
Hypotension	4 (6.6)	3 (3.9)	7 (5.9)	0	7 (5.1)
Dyspepsia	4 (6.6)	2 (2.6)	6 (5.1)	0	6 (4.3)
Paresthesia	4 (6.6)	2 (2.6)	6 (5.1)	0	6 (4.3)
Syncope	4 (6.6)	2 (2.6)	6 (5.1)	0	6 (4.3)
Noncardiac chest pain	4 (6.6)	1 (1.3)	4 (3.4)	1 (5.0)	5 (3.6)
Procedural pain	4 (6.6)	1 (1.3)	4 (3.4)	1 (5.0)	5 (3.6)
Insomnia	4 (6.6)	1 (1.3)	5 (4.2)	0	5 (3.6)
Vitamin D deficiency	4 (6.6)	1 (1.3)	5 (4.2)	0	5 (3.6)
Seasonal allergy	4 (6.6)	0	4 (3.4)	0	4 (2.9)
Neck pain	3 (4.9)	4 (5.2)	7 (5.9)	0	7 (5.1)
Asthenia	3 (4.9)	3 (3.9)	5 (4.2)	1 (5.0)	6 (4.3)
Constipation	3 (4.9)	3 (3.9)	5 (4.2)	1 (5.0)	6 (4.3)
ALT increased	3 (4.9)	3 (3.9)	6 (5.1)	0	6 (4.3)
Anxiety	3 (4.9)	2 (2.6)	5 (4.2)	0	5 (3.6)
Respiratory failure	3 (4.9)	2 (2.6)	5 (4.2)	0	5 (3.6)
Basal cell carcinoma	3 (4.9)	1 (1.3)	4 (3.4)	0	4 (2.9)
Dysmenorrhea	3 (4.9)	1 (1.3)	4 (3.4)	0	4 (2.9)
Lower respiratory tract infection	3 (4.9)	1 (1.3)	4 (3.4)	0	4 (2.9)
Oral herpes	3 (4.9)	1 (1.3)	4 (3.4)	0	4 (2.9)

	Patient Description				All
Preferred Term	Naive N=61 n (%)	Experienced N=77 n (%)	Adult N=118 n (%)	Pediatric N=20 n (%)	Patients N=138 n (%)
Renal colic	3 (4.9)	1 (1.3)	4 (3.4)	0	4 (2.9)
Sciatica	3 (4.9)	1 (1.3)	4 (3.4)	0	4 (2.9)
Vertigo	3 (4.9)	1 (1.3)	4 (3.4)	0	4 (2.9)
Catheter site erythema	3 (4.9)	0	3 (2.5)	0	3 (2.2)
Flank pain	3 (4.9)	0	3 (2.5)	0	3 (2.2)
Herpes zoster	3 (4.9)	0	3 (2.5)	0	3 (2.2)
Hypoesthesia	3 (4.9)	0	3 (2.5)	0	3 (2.2)
Viral URI	3 (4.9)	0	3 (2.5)	0	3 (2.2)
Pneumonia	2 (3.3)	8 (10.4)	5 (4.2)	5 (25.0)	10 (7.2)
Pain	2 (3.3)	7 (9.1)	9 (7.6)	0	9 (6.5)
Toothache	2 (3.3)	5 (6.5)	5 (4.2)	2 (10.0)	7 (5.1)
Gastroenteritis viral	2 (3.3)	5 (6.5)	7 (5.9)	0	7 (5.1)
Sinusitis	2 (3.3)	5 (6.5)	7 (5.9)	0	7 (5.1)
Epistaxis	2 (3.3)	4 (5.2)	3 (2.5)	3 (15.0)	6 (4.3)
Nasal congestion	2 (3.3)	4 (5.2)	5 (4.2)	1 (5.0)	6 (4.3)
Dysuria	2 (3.3)	3 (3.9)	4 (3.4)	1 (5.0)	5 (3.6)
Anemia	2 (3.3)	3 (3.9)	5 (4.2)	0	5 (3.6)
Oxygen saturation decreased	2 (3.3)	3 (3.9)	5 (4.2)	0	5 (3.6)
Post-traumatic pain	2 (3.3)	3 (3.9)	5 (4.2)	0	5 (3.6)
Rhinorrhea	2 (3.3)	2 (2.6)	2 (1.7)	2 (10.0)	4 (2.9)
Malaise	2 (3.3)	2 (2.6)	3 (2.5)	1 (5.0)	4 (2.9)
Muscle strain	2 (3.3)	2 (2.6)	3 (2.5)	1 (5.0)	4 (2.9)
Chest discomfort	2 (3.3)	2 (2.6)	4 (3.4)	0	4 (2.9)
Tachycardia	2 (3.3)	2 (2.6)	4 (3.4)	0	4 (2.9)
GGT increased	2 (3.3)	1 (1.3)	2 (1.7)	1 (5.0)	3 (2.2)
Thermal burn	2 (3.3)	1 (1.3)	2 (1.7)	1 (5.0)	3 (2.2)
Burning sensation	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Chest pain	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Dizziness postural	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Ear infection	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
GERD	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Hematoma	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Infusion site pain	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Infusion site rash	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Iron deficiency	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Lymphadenopathy	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Muscular weakness	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Neuralgia	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Palpitations	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Rhinitis allergic	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Skin laceration	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Somnolence	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Tremor	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Bronchitis	1 (1.6)	6 (7.8)	5 (4.2)	2 (10.0)	7 (5.1)
Musculoskeletal chest pain	1 (1.6)	4 (5.2)	4 (3.4)	1 (5.0)	5 (3.6)
Joint swelling	1 (1.6)	4 (5.2)	5 (4.2)	0	5 (3.6)
Arthropod bite	1 (1.6)	3 (3.9)	3 (2.5)	1 (5.0)	4 (2.9)
Infusion site extravasation	1 (1.6)	3 (3.9)	4 (3.4)	0	4 (2.9)
Migraine	1 (1.6)	3 (3.9)	4 (3.4)	0	4 (2.9)
Musculoskeletal stiffness	1 (1.6)	3 (3.9)	4 (3.4)	0	4 (2.9)
Pharyngitis	1 (1.6)	3 (3.9)	4 (3.4)	0	4 (2.9)
Bronchitis viral	1 (1.6)	2 (2.6)	1 (0.8)	2 (10.0)	3 (2.2)

	Patient Description				All
Preferred Term	Naive N=61 n (%)	Experienced N=77 n (%)	Adult N=118 n (%)	Pediatric N=20 n (%)	Patients N=138 n (%)
Ear pain	1 (1.6)	2 (2.6)	2 (1.7)	1 (5.0)	3 (2.2)
Feeling hot	1 (1.6)	2 (2.6)	2 (1.7)	1 (5.0)	3 (2.2)
Infusion site swelling	1 (1.6)	2 (2.6)	2 (1.7)	1 (5.0)	3 (2.2)
Ligament sprain	1 (1.6)	2 (2.6)	2 (1.7)	1 (5.0)	3 (2.2)
Osteopenia	1 (1.6)	2 (2.6)	2 (1.7)	1 (5.0)	3 (2.2)
Skin abrasion	1 (1.6)	2 (2.6)	2 (1.7)	1 (5.0)	3 (2.2)
Abdominal discomfort	1 (1.6)	2 (2.6)	3 (2.5)	0	3 (2.2)
Angina pectoris	1 (1.6)	2 (2.6)	3 (2.5)	0	3 (2.2)
Blood pressure increased	1 (1.6)	2 (2.6)	3 (2.5)	0	3 (2.2)
Facial pain	1 (1.6)	2 (2.6)	3 (2.5)	0	3 (2.2)
Gout	1 (1.6)	2 (2.6)	3 (2.5)	0	3 (2.2)
Hyperhidrosis	1 (1.6)	2 (2.6)	3 (2.5)	0	3 (2.2)
Hypokalemia	1 (1.6)	2 (2.6)	3 (2.5)	0	3 (2.2)
Otitis media	0	5 (6.5)	2 (1.7)	3 (15.0)	5 (3.6)
Eye irritation	0	4 (5.2)	2 (1.7)	2 (10.0)	4 (2.9)
Rhinitis	0	4 (5.2)	3 (2.5)	1 (5.0)	4 (2.9)
Conjunctival hemorrhage	0	4 (5.2)	4 (3.4)	0	4 (2.9)
Device occlusion	0	3 (3.9)	1 (0.8)	2 (10.0)	3 (2.2)
Eyelid ptosis	0	3 (3.9)	1 (0.8)	2 (10.0)	3 (2.2)
Vision blurred	0	3 (3.9)	3 (2.5)	0	3 (2.2)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as AEs that developed or worsened or became serious during the treatment epoch
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 89 shows the AEs according to the system organ class based on FDA medical query (FMQ). Within these systems, AEs related to hypersensitivity reactions were prevalent, suggesting that these are related to either avalglucosidase alfa or to its administration. AEs from Table 30 that may be associated with hypersensitivity reactions include: tachycardia, diarrhea, nausea, abdominal pain, vomiting, dyspepsia, fatigue, pyrexia, local administration reactions, peripheral edema, angioedema, back pain, myalgia, arthritis, arthralgia, dizziness, paresthesia, syncope, tremor, dyspnea, cough, bronchospasm, rash, pruritus, erythema, urticaria, and hypotension (see Section 7.7.1).

7.6.1.6. Laboratory Findings, Integrated Safety Set

Overall Summary

Routine safety monitoring blood work (hematology, clinical chemistry, creatine kinase, lactate dehydrogenase, triglycerides), and urinalysis were obtained throughout the trials. Except for hepatic function, the mean values for most of these tests remained within normal ranges. The review team performed additional analyses to discern the prevalence and severity of elevated liver enzyme levels during the trials, focusing on ALT and AST. ALT or AST were noted to be elevated at baseline in more than half of the patients in the ISS. Review of potential Hy's Law and Temple's Corollary cases did not identify an increased risk of drug induced liver injury related to treatment with avalglucosidase alfa. Over the course of the trials, ALT and AST levels decreased without normalizing in the majority of patients (see Section 7.7.4).

Hematological Analyses

The review team focused on the following hematological bloodwork obtained during this trial: hemoglobin, hematocrit, platelets, leukocytes, and neutrophils. In most cases, baseline data for these components of the complete blood count were available for 117 adult and 19 pediatric patients. As follow-up time increased, however, there were fewer patients with available data to review. At week 80, for instance, there were only 3 pediatric patients with data, and by week 240, there were only 16 adult patients with data.

In the majority of adults, the mean values for hemoglobin, hematocrit, platelets, leukocytes, and neutrophils remained normal throughout their exposure to avalglucosidase alfa. Twenty-one adult patients were anemic at least once, with hemoglobin levels lower than the lower limit of normal. On their last hemoglobin checks, 16 of these 21 patients had normal or near normal hemoglobin levels and 5 of the 21 patients had hemoglobin levels ≤105 g/L (normal 110 to 130 g/L) (Beutler and Waalen 2006). Three of these five patients were also anemic at baseline, but 2 of the 5 patients had normal hemoglobin levels at baseline. No interventions were reported as having been performed for these 2 patients. It seems unlikely that new-onset anemia in 2 out of 119 adult patients is a side effect of avalglucosidase alfa.

In pediatric patients, the mean values for hemoglobin, hematocrit, platelets, leukocytes, and neutrophils remained normal throughout their exposure to avalglucosidase alfa. While several patients had abnormally high and low values at different times for each of these hematological tests, most patients' levels normalized by the end of the trial while still on treatment. In cases where the results did not normalize, the review team concluded that the levels were not clinically significant. Therefore, the abnormal results were likely normal variations with frequent testing or reflective of a transient change in the patients.

In pediatric patients, the mean values for hemoglobin, hematocrit, platelets, leukocytes, and neutrophils remained normal throughout their exposure to avalglucosidase alfa. While several patients had abnormally high and low values at different times for each of these hematological tests, most patients' levels normalized by the end of the trial while still on treatment. In cases where the results did not normalize, the review team concluded that the levels were not clinically significant. Therefore, the abnormal results were likely normal variations with frequent testing or reflective of a transient change in the patients.

Liver Function

Refer to Section 7.7.4 for a discussion of potential hepatoxicity.

Kidney Function

Kidney function remained normal throughout the trials in the majority of patients. As with the hematological data, there were few patients with data at later time points, and no pediatric patients with data after week 20.

One adult patient had a single creatinine level of 256 µmol/L and a BUN of 15 mmol/L, but the rest of his creatinine and BUN levels were normal, ranging between 36 to 62 µmol/L and 3 to 7 mmol/L, respectively. Thus, the elevated values were not part of an abnormal trend in this patient.

Six other adult patients and three pediatric patients had creatinine levels increase above baseline levels by 1.5 times or more during the trials, but these values all remained within the normal range. By the end of the trials, only one pediatric patient still had creatinine elevated 1.5 times the child's baseline. Therefore, these findings do not suggest a risk of renal impairment with use of avalglucosidase alfa, and the review team does not recommend any additional monitoring.

Electrolyte Trends

Sodium, potassium, chloride, calcium, and blood glucose levels were followed throughout the trials. While several patients had tests with abnormally high and low values, these results were not clinically significant, especially with respect to potassium, chloride, calcium, and blood glucose.

Eleven patients developed hyponatremia with levels less than 134 mEq/L; however, only four patients had moderate-to-severe hyponatremia with levels less than 130 mEq/L. One of these patients, who had a history of hyponatremia, required hospitalization with the administration of tolvaptan, a vasopressin V2 receptor antagonist, for severe hyponatremia (111 mEq/L). Seventeen patients had mild hypernatremia with sodium levels greater than 145 mEq/L, but these patients did not require treatment, and by the end of their respective trials, their levels returned to normal. In the PAP of EFC14028, the occurrence of hyponatremia was balanced between the avalglucosidase alfa and the alglucosidase alfa arms; therefore, the review team concludes that hyponatremia is not related to avalglucosidase alfa.

Electrocardiogram (EKG) Trends

All 138 patients had EKGs with PR, QRS and QTc interval data to review. Because pediatrics and adult EKGs are interpreted differently, they will be discussed separately.

Among adult patients, nine had prolonged PR intervals, which in isolation, is considered a variant of normal. Twenty-five patients who received avalglucosidase alfa had at least one EKG with a prolonged QTc interval (>450ms) after their baseline EKG assessment. Six of these 25 patients had abnormal QTc intervals at baseline. Two of these six patients had normal QTc intervals on their last EKGs. The QTc intervals on the last EKGs for the 4 remaining patients, while still prolonged and abnormal, were shorter than their baseline measurements. Nineteen of the 25 patients with at least one abnormal QTc interval had normal QTc intervals at baseline. Sixteen of the 19 patients had normal QTc intervals on their last EKG. Three of the 19 patients still had prolonged QTc intervals on their last EKG, but the QTc intervals were very mildly longer than normal (>450ms) and clinically not significant.

Twenty-seven adult patients who received avalglucosidase alfa had at least one EKG with a prolonged QRS interval (>110ms). However, several adult guidelines suggest that it is a QRS interval >120ms that is associated with adverse cardiovascular events such as heart failure, sudden cardiac death, and mortality in older adults; the risk with intermediate degrees of QRS interval prolongation has not been clearly established (Ilkhanoff et al. 2012). Eight of these 27 patients had QRS intervals >120 ms at least once during the trials. Five of these eight patients had baseline QRS intervals >120 ms; one patient's final QRS interval normalized, and two patients' final QRS interval was shorter than at baseline. However, two patients' QRS intervals were longer than at baseline; one of these patients had no adverse events reported, and the other patient experienced tachycardia associated with a prolonged QRS duration. The other 3 of eight

Reference ID: 4836879

patients with QRS intervals >120 ms had normal baseline QRS durations but had prolonged QRS durations on their last EKGs. One of these three patients had ventricular arrhythmias while on treatment *before* the QRS prolongation occurred, while the other two had no adverse events reported.

There is no consensus on the cardiac manifestations of LOPD; it may or may not be associated with electrical abnormalities (Forsha et al. 2011; Tarnopolsky et al. 2016). Forsha and colleagues studied EKGs in 85 patients with LOPD and found 3 patients with QRS duration prolongation, right bundle branch block, and left bundle branch block and 3 patients with prolonged QTc intervals. Therefore, we are unable to determine, with certainty, whether the findings of prolonged QRS intervals and QTc intervals in the patients who received avalglucosidase alfa are similar to what would be seen in patients with PD. The review team does not recommend additional cardiac monitoring or follow up in addition to what is already recommended for untreated patients with LOPD.

Among pediatric patients, one patient had a prolonged PR interval, which, in isolation, is considered a variant of normal. One patient had a short PR interval, which is a finding associated with IOPD. Two patients had prolonged QRS intervals (>100ms), but these measurements normalized on their last EKGs. Five patients had at least one QTc interval which was prolonged (>450 ms). Two of these five patients had prolonged QTc intervals at baseline, but their last EKGs had normal QTc intervals. Three of the five patients had normal QTc intervals at baseline. On their last EKGs, one of these three patients had a normal QTc interval, while the other two patients had only very mildly prolonged QTc intervals of 453ms and 454ms. These findings are not clinically significant, and therefore, the review team would not recommend cardiac monitoring or follow up in addition to what is already recommended for pediatric patients with IOPD (ACMG Work Group on Management of Pompe Disease et al. 2006).

Vital Sign Trends

The review team focused on the following vital signs heart rates, and systolic and diastolic blood pressures. Because abnormalities in oxygen saturation, body temperature, and respiratory rate would be more reflective of hypersensitivity reactions (including anaphylaxis) and infusion associated reactions, these abnormalities are included in the narratives in Section 7.7.1.

In adults, the majority of the patients had heart rates between 60-105 beats per minute (bpm), There were outliers heart rates that varied between 105-167 bpm for 58 patients. Each of these patients had a wide range of heart rates with most being within the normal range. Pediatric heart rates were all within the age appropriate ranges.

The mean adult systolic and diastolic blood pressures were approximately 120 and 75 mm Hg, respectively and did not change throughout the course of the trials. The mean pediatric systolic and diastolic pressures were approximately 105 and 65 mm Hg, respectively, and also did not change throughout the course of the trial.

Therefore, while vital signs should be monitored during infusions, especially due to the risk for hypersensitivity reactions (including anaphylaxis) and infusion associated reactions, there were no specific changes in vital signs noted with avalglucosidase alfa treatment.

Reference ID: 4836879

7.6.2. Safety Findings and Concerns, EFC14028 (COMET)

7.6.2.1. Overall Adverse Event Summary, EFC14028

EFC14028 was divided into the primary analysis period (PAP) and the extension treatment period (ETP). During the PAP, 51 patients with LOPD received avalglucosidase alfa at 20 mg/kg qow and 49 patients with LOPD received alglucosidase alfa, the active comparator, at either 20 mg/kg qow or at their previous dose, for 49 weeks. During the ETP, the remaining 95 patients received avalglucosidase alfa for a 144-week open label treatment period. The review team focused on the safety analysis of the PAP data, which allowed comparison based on the treatment received. In this section, safety data are displayed by treatment arm (avalglucosidase or alglucosidase). In addition, the risk difference (95% CI) is shown.

As Table 31 shows, one or more TEAEs were reported by 44 (86%) of the patients treated with avalglucosidase alfa compared to 45 (92%) of the patients treated with alglucosidase alfa. Fewer patients in the avalglucosidase alfa arm had moderate or severe AEs (29, 57%) and SAEs (8, 16%) than the alglucosidase arm, moderate or severe AEs (34, 69%) and SAEs (12, 25%).

Table 31. Overview of Adverse Events, Controlled Trial Safety Population, Trial EFC14028 (COMET)

Event Category	Avalgluco N=51 n (%)	Alglu N=49 n (%)	Risk Difference (95% CI)[1]
Any AE	44 (86.3)	45 (91.8)	-5.5 (-17.7, 6.7)
Moderate or severe AEs	29 (56.9)	34 (69.4)	-12.5 (-31.2, 6.2)
Any SAE	8 (15.7)	12 (24.5)	-8.8 (-24.4, 6.8)
SAE with fatal outcome	0	1 (2.0)	-2.0 (-6.0, 2.0)
AE leading to discontinuation of study drug	0	4 (8.2)	-8.2 (-15.9, -0.5)
AE leading to dose modification of study drug	11 (21.6)	13 (26.5)	-4.9 (-21.6, 11.8)
AE leading to interruption of study drug	11 (21.6)	13 (26.5)	-4.9 (-21.6, 11.8)
AE leading to reduction of study drug	1 (2.0)	0	2.0 (-1.8, 5.8)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as AEs that developed or worsened or became serious during the treatment epoch
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.2.2. Deaths, EFC14028

See Section 7.6.1.2 for discussion and narratives of reported deaths.

7.6.2.3. Serious Adverse Events, EFC14028

See Section 7.6.1.3 for discussion and narratives of reported SAEs.

7.6.2.4. Dropouts and/or Discontinuations Due to Adverse Events, EFC14028

See Section 7.6.1.2 for discussion and narratives of patients who discontinued.

7.6.2.5. Treatment-Emergent Adverse Events, EFC14028

As shown in Table 32, the most commonly reported TEAEs in ≥5% patients who received avalglucosidase alfa in trial EFC14028 were influenza, fatigue, nausea, diarrhea, dizziness, myalgia, arthralgia, upper respiratory tract infection, vomiting, pruritus, noncardiac chest pain, influenza-like illness, urticaria, paresthesia, dyspepsia, erythema, peripheral edema, dyspnea, pain in extremity, and muscle spasms. These TEAEs were also noted in the integrated safety set (Table 29), but noncardiac chest pain, paresthesia, and dyspepsia were not as common. Certain TEAEs occurred in more than 5% of the avalglucosidase alfa-treated patients, but either occurred at higher or similar rates in the alglucosidase alfa-treated patients (fall, contusion) or could not be explained by the mechanism of action or drug class of ERTs (cystitis).

During the PAP, four patients on avalglucosidase alfa and two on alglucosidase alfa experienced anaphylaxis. One additional patient experienced anaphylaxis while on avalglucosidase alfa in the ETP. These reactions are discussed in more details in Section 7.7.1. Sixteen patients (31%) who received avalglucosidase alfa had infusion associated reactions compared to 23 (46%) who received alglucosidase alfa. Three of the IAR events in avalglucosidase alfa treated patients were categorized as severe reactions (Section 7.7.1).

Table 32. Treatment-Emergent Adverse Events[1] Occurring at ≥2% Frequency, Trial EFC14028 (COMET)

Preferred Term	Avalgluco N=51 n (%)	Alglu N=49 n (%)	Risk Difference (95% CI)[2]
Any AE	44 (86.3)	45 (91.8)	-5.5 (-17.7, 6.7)
Influenza	9 (17.6)	2 (4.1)	13.5 (1.7, 25.3)
Back pain	12 (23.5)	5 (10.2)	13.3 (-1.1, 27.7)
Cystitis	3 (5.9)	0	5.9 (-0.6, 12.4)
Noncardiac chest pain	3 (5.9)	0	5.9 (-0.6, 12.4)
Influenza like illness	3 (5.9)	1 (2.0)	3.9 (-3.7, 11.5)
Urticaria	3 (5.9)	1 (2.0)	3.9 (-3.7, 11.5)
Basal cell carcinoma	2 (3.9)	0	3.9 (-1.4, 9.2)
Dizziness postural	2 (3.9)	0	3.9 (-1.4, 9.2)
Dysuria	2 (3.9)	0	3.9 (-1.4, 9.2)
Electrocardiogram abnormal	2 (3.9)	0	3.9 (-1.4, 9.2)
Lymphadenopathy	2 (3.9)	0	3.9 (-1.4, 9.2)
Renal colic	2 (3.9)	0	3.9 (-1.4, 9.2)
Rhinitis allergic	2 (3.9)	0	3.9 (-1.4, 9.2)
Sciatica	2 (3.9)	0	3.9 (-1.4, 9.2)
Throat irritation	2 (3.9)	0	3.9 (-1.4, 9.2)
Vitamin d deficiency	2 (3.9)	0	3.9 (-1.4, 9.2)
URTI	4 (7.8)	2 (4.1)	3.7 (-5.5, 12.9)
Fatigue	9 (17.6)	7 (14.3)	3.3 (-11.0, 17.6)
Angioedema	1 (2.0)	0	2.0 (-1.8, 5.8)
Aortic dilatation	1 (2.0)	0	2.0 (-1.8, 5.8)
Bacteriuria	1 (2.0)	0	2.0 (-1.8, 5.8)
Blood pressure fluctuation	1 (2.0)	0	2.0 (-1.8, 5.8)
Blood sodium decreased	1 (2.0)	0	2.0 (-1.8, 5.8)
Breast cyst	1 (2.0)	0	2.0 (-1.8, 5.8)
Bronchitis viral	1 (2.0)	0	2.0 (-1.8, 5.8)
Calculus urinary	1 (2.0)	0	2.0 (-1.8, 5.8)
Catheter site bruise	1 (2.0)	0	2.0 (-1.8, 5.8)
Catheter site erythema	1 (2.0)	0	2.0 (-1.8, 5.8)
Catheter site hematoma	1 (2.0)	0	2.0 (-1.8, 5.8)

Preferred Term	Avalgluco N=51 n (%)	Alglu N=49 n (%)	Risk Difference (95% CI)[2]
Catheter site irritation	1 (2.0)	0	2.0 (-1.8, 5.8)
Catheter site related reaction	1 (2.0)	0	2.0 (-1.8, 5.8)
Catheter site swelling	1 (2.0)	0	2.0 (-1.8, 5.8)
Conjunctival hyperemia	1 (2.0)	0	2.0 (-1.8, 5.8)
Cyanosis	1 (2.0)	0	2.0 (-1.8, 5.8)
Decreased appetite	1 (2.0)	0	2.0 (-1.8, 5.8)
Depressed mood	1 (2.0)	0	2.0 (-1.8, 5.8)
Dermatosis	1 (2.0)	0	2.0 (-1.8, 5.8)
Diabetes mellitus	1 (2.0)	0	2.0 (-1.8, 5.8)
Dislocation of vertebra	1 (2.0)	0	2.0 (-1.8, 5.8)
Ear pruritus	1 (2.0)	0	2.0 (-1.8, 5.8)
ECG pq interval prolonged	1 (2.0)	0	2.0 (-1.8, 5.8)
Eye infection	1 (2.0)	0	2.0 (-1.8, 5.8)
Furuncle	1 (2.0)	0	2.0 (-1.8, 5.8)
Genital candidiasis	1 (2.0)	0	2.0 (-1.8, 5.8)
Groin pain	1 (2.0)	0	2.0 (-1.8, 5.8)
Hydronephrosis	1 (2.0)	0	2.0 (-1.8, 5.8)
Hypoesthesia	1 (2.0)	0	2.0 (-1.8, 5.8)
Hypotonia	1 (2.0)	0	2.0 (-1.8, 5.8)
Hypoventilation	1 (2.0)	0	2.0 (-1.8, 5.8)
Infusion site joint pain	1 (2.0)	0	2.0 (-1.8, 5.8)
Infusion site rash	1 (2.0)	0	2.0 (-1.8, 5.8)
Iron deficiency	1 (2.0)	0	2.0 (-1.8, 5.8)
Joint swelling	1 (2.0)	0	2.0 (-1.8, 5.8)
Laryngeal inflammation	1 (2.0)	0	2.0 (-1.8, 5.8)
Ligament sprain	1 (2.0)	0	2.0 (-1.8, 5.8)
Limb injury	1 (2.0)	0	2.0 (-1.8, 5.8)
Macular degeneration	1 (2.0)	0	2.0 (-1.8, 5.8)
Medial tibial stress syndrome	1 (2.0)	0	2.0 (-1.8, 5.8)
Menstruation delayed	1 (2.0)	0	2.0 (-1.8, 5.8)
Menstruation irregular	1 (2.0)	0	2.0 (-1.8, 5.8)
Muscle contracture	1 (2.0)	0	2.0 (-1.8, 5.8)
Muscle rupture	1 (2.0)	0	2.0 (-1.8, 5.8)
Muscle twitching	1 (2.0)	0	2.0 (-1.8, 5.8)
Odynophagia	1 (2.0)	0	2.0 (-1.8, 5.8)
Oral herpes	1 (2.0)	0	2.0 (-1.8, 5.8)
Osteopenia	1 (2.0)	0	2.0 (-1.8, 5.8)
Osteoporosis	1 (2.0)	0	2.0 (-1.8, 5.8)
Oxygen saturation decreased	1 (2.0)	0	2.0 (-1.8, 5.8)
Pelvic fracture	1 (2.0)	0	2.0 (-1.8, 5.8)
Polyneuropathy	1 (2.0)	0	2.0 (-1.8, 5.8)
Prostatitis	1 (2.0)	0	2.0 (-1.8, 5.8)
Pruritus genital	1 (2.0)	0	2.0 (-1.8, 5.8)
Respiratory failure	1 (2.0)	0	2.0 (-1.8, 5.8)
Respiratory symptom	1 (2.0)	0	2.0 (-1.8, 5.8)
Sensation of foreign body	1 (2.0)	0	2.0 (-1.8, 5.8)
Skin laceration	1 (2.0)	0	2.0 (-1.8, 5.8)
Spinal flattening	1 (2.0)	0	2.0 (-1.8, 5.8)
Spinal osteoarthritis	1 (2.0)	0	2.0 (-1.8, 5.8)
Stress	1 (2.0)	0	2.0 (-1.8, 5.8)
Supraventricular extrasystoles	1 (2.0)	0	2.0 (-1.8, 5.8)
Syncope	1 (2.0)	0	2.0 (-1.8, 5.8)
Tachycardia	1 (2.0)	0	2.0 (-1.8, 5.8)

Preferred Term	Avalgluco N=51 n (%)	Alglu N=49 n (%)	Risk Difference (95% CI)[2]
Tension headache	1 (2.0)	0	2.0 (-1.8, 5.8)
Toothache	1 (2.0)	0	2.0 (-1.8, 5.8)
Tremor	1 (2.0)	0	2.0 (-1.8, 5.8)
Upper limb fracture	1 (2.0)	0	2.0 (-1.8, 5.8)
Ventricular extrasystoles	1 (2.0)	0	2.0 (-1.8, 5.8)
Vessel puncture site pain	1 (2.0)	0	2.0 (-1.8, 5.8)
Viral URI	1 (2.0)	0	2.0 (-1.8, 5.8)
Gastroenteritis viral	2 (3.9)	1 (2.0)	1.9 (-4.7, 8.5)
Urinary tract infection	2 (3.9)	1 (2.0)	1.9 (-4.7, 8.5)
Paresthesia	3 (5.9)	2 (4.1)	1.8 (-6.7, 10.3)
Vomiting	4 (7.8)	3 (6.1)	1.7 (-8.3, 11.7)
Contusion	5 (9.8)	4 (8.2)	1.6 (-9.6, 12.8)
Dizziness	5 (9.8)	4 (8.2)	1.6 (-9.6, 12.8)
Pain in extremity	8 (15.7)	7 (14.3)	1.4 (-12.6, 15.4)
Abdominal pain	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Anxiety	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Burning sensation	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
GGT increased	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Herpes zoster	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Hyponatremia	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Infusion site pain	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Insomnia	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Malaise	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Meralgia paraesthetica	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Ocular hyperemia	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Pharyngitis	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Rash erythematous	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Sleep apnea syndrome	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Dyspepsia	3 (5.9)	3 (6.1)	-0.2 (-9.5, 9.1)
Erythema	3 (5.9)	3 (6.1)	-0.2 (-9.5, 9.1)
Edema peripheral	3 (5.9)	3 (6.1)	-0.2 (-9.5, 9.1)
Asthenia	2 (3.9)	2 (4.1)	-0.2 (-7.9, 7.5)
Peripheral swelling	2 (3.9)	2 (4.1)	-0.2 (-7.9, 7.5)
Pruritus	4 (7.8)	4 (8.2)	-0.4 (-11.0, 10.2)
Nasopharyngitis	12 (23.5)	12 (24.5)	-1.0 (-17.7, 15.7)
Depression	1 (2.0)	2 (4.1)	-2.1 (-8.8, 4.6)
Dysmenorrhea	1 (2.0)	2 (4.1)	-2.1 (-8.8, 4.6)
Gastroenteritis	1 (2.0)	2 (4.1)	-2.1 (-8.8, 4.6)
Musculoskeletal pain	1 (2.0)	2 (4.1)	-2.1 (-8.8, 4.6)
Pneumonia	1 (2.0)	2 (4.1)	-2.1 (-8.8, 4.6)
Abdominal pain upper	2 (3.9)	3 (6.1)	-2.2 (-10.8, 6.4)
ALT increased	2 (3.9)	3 (6.1)	-2.2 (-10.8, 6.4)
Dyspnea	3 (5.9)	4 (8.2)	-2.3 (-12.3, 7.7)
Nausea	6 (11.8)	7 (14.3)	-2.5 (-15.7, 10.7)
Chills	1 (2.0)	3 (6.1)	-4.1 (-11.8, 3.6)
Hypertension	1 (2.0)	3 (6.1)	-4.1 (-11.8, 3.6)
Muscle spasms	3 (5.9)	5 (10.2)	-4.3 (-15.0, 6.4)
Cough	2 (3.9)	4 (8.2)	-4.3 (-13.6, 5.0)
Pyrexia	2 (3.9)	4 (8.2)	-4.3 (-13.6, 5.0)
Rash	2 (3.9)	4 (8.2)	-4.3 (-13.6, 5.0)
Diarrhea	6 (11.8)	8 (16.3)	-4.5 (-18.1, 9.1)
Myalgia	5 (9.8)	7 (14.3)	-4.5 (-17.3, 8.3)
Oropharyngeal pain	2 (3.9)	5 (10.2)	-6.3 (-16.3, 3.7)

Preferred Term	Avalgluco N=51 n (%)	Alglu N=49 n (%)	Risk Difference (95% CI)[2]
Pain	2 (3.9)	5 (10.2)	-6.3 (-16.3, 3.7)
Arthralgia	5 (9.8)	8 (16.3)	-6.5 (-19.7, 6.7)
Fall	7 (13.7)	10 (20.4)	-6.7 (-21.4, 8.0)
Nasal congestion	1 (2.0)	5 (10.2)	-8.2 (-17.5, 1.1)
Headache	11 (21.6)	16 (32.7)	-11.1 (-28.4, 6.2)

Source: adae2.xpt; Software: Python
[1] Treatment-emergent adverse events defined as AEs that developed or worsened or became serious during the treatment epoch
[2] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; alglu, alglucosidase alfa; ALT, alanine aminotransferase; avalgluco, avalglucosidase alfa; CI, confidence interval; ECG, electrocardiogram; GGT, gamma-glutamyltransferase; N, number of subjects in treatment arm; n, number of subjects with adverse event; URTI, upper respiratory tract infection

Table 90 shows the AEs according to the system organ class based on FMQ. Within these systems, AEs related to hypersensitivity reactions were prevalent, suggesting that these are related to either avalglucosidase alfa or to its administration. AEs from Table 90 that may be associated with hypersensitivity reactions include: abdominal pain, angioedema, anxiety, arthralgia, back pain, cough, diarrhea, dizziness, dyspepsia, dyspnea, erythema, fatigue, headache, local administration reactions, myalgia, nausea, paresthesia, peripheral edema, pruritus, pyrexia, rash, syncope, systemic hypertension, tachycardia, tremor, urticaria, vomiting (see Section 7.7.1).

7.6.2.6. Laboratory Findings, EFC14028

See Section 7.6.1.6 for discussion of hematological bloodwork results, renal function, electrolyte trends, EKG findings, and vital signs. Analysis of hepatotoxicity is in Section 7.7.4.

7.6.3. Safety Findings and Concerns, ACT14132 (Mini-COMET)

7.6.3.1. Overall Adverse Event Summary, ACT14132

ACT14132 was divided into cohort 1, cohort 2 and cohort 3. Patients with IOPD in cohorts 1 and 2 both received avalglucosidase alfa at 20 mg/kg qow (n=6) and 40 mg/kg qow (n=5), respectively. Cohort 3 enrolled 11 new patients who had shown suboptimal clinical response on alglucosidase alfa. Five patients received avalglucosidase alfa at 40 mg/kg qow and six patients received alglucosidase alfa at the dose used before trial enrollment. The cohort 3 PAP duration was 25 weeks and was followed by the open label ETP.

One or more TEAEs were reported by all 5 (100%) of the patients treated with avalglucosidase alfa and by all 6 (100%) of the patients treated with alglucosidase alfa. While SAEs were reported by patients who received both avalglucosidase alfa and alglucosidase alfa, none were assessed as related to the either drug by the Investigators, and the review team agreed with them.

7.6.3.2. Deaths, ACT14132

No deaths occurred during ACT14132.

7.6.3.3. Serious Adverse Events, ACT14132

No SAEs related to avalglucosidase alfa occurred during ACT14132.

Although the review team assessed all of the SAEs as unrelated to avalglucosidase alfa, the SAEs that occurred on the different doses of avalglucosidase alfa (20 and 40 mg/kg qow) were reviewed as shown in Table 33. Four of the 10 children on avalglucosidase alfa at 40 mg/kg qow had 8 SAEs compared to 3 of the 6 children on 20 mg/kg qow who had 10 SAEs; however, the small number of patients in each group precludes any meaningful comparison of SAEs between these two groups.

Table 33. Serious Adverse Events Occurring in Patients Treated With Avalglucosidase Alfa at 20 mg/kg qow and 40 mg/kg qow, Trial ACT14132 (Cohorts 1, 2 and 3)

	SAE Event		
Patient ID Number	**Avalglucosidase alfa 20 mg/kg qow**	**Avalglucosidase alfa 40 mg/kg qow**	**Number of Events**
(b) (6)	Influenza		1
	Pneumonia		1
	Tympanic membrane perforation		1
(b) (6)	Post-procedural hemorrhage		1
(b) (6)	Adenoidal hypertrophy		1
	Atrial thrombosis		1
	Device malfunction		1
	Otitis media		1
	Respiratory tract infection viral		4
	Tonsillar hypertrophy		1
(b) (6)		Eyelid ptosis	1
		Pneumonia	1
		Strabismus	1
(b) (6)		Gastroenteritis	2
		Pyrexia	6
		Respiratory distress	1
(b) (6)		Femur fracture	1
(b) (6)		Eyelid ptosis	1

Source: Review team
Abbreviation: qow, every other week; SAE, serious adverse event

7.6.3.4. Dropouts and/or Discontinuations Due to Adverse Events, ACT41432

No patients discontinued their participation during ACT14132.

7.6.3.5. Treatment-Emergent Adverse Events, ACT14132

All of the TEAES shown in Table 34, occurred in at least one patient who received avalglucosidase alfa in Cohort 3. Because of the small number of patients in each group (n=5 and n=6), the differences in rates of each TEAE are not meaningful. The TEAEs occurring in at least two patients on avalglucosidase alfa were cough, device occlusion, diarrhea, eye irritation, headache, tachypnea, pyrexia, rhinorrhea, URI, rash, and vomiting. Except for tachypnea, these TEAEs were also noted in the integrated safety set (Table 30). Tachypnea did not occur in ≥2% of the integrated safety set.

No pediatric patients on avalglucosidase alfa or alglucosidase alfa experienced anaphylaxis. Two patients (40%) on avalglucosidase alfa experienced IARs, including tachypnea and rash. No patients on alglucosidase alfa experienced IARs.

Table 34. Treatment-Emergent Adverse Events Occurring at a Higher Frequency in Patient Treated With Avalglucosidase Alfa Than Alglucosidase Alfa, Trial ACT14132 (Cohort 3)

Preferred Term	Avalgluco N=5 n (%)	Alglu N=6 n (%)	Risk Difference (95% CI)[1]
Any AE	5 (100)	6 (100)	0 (0, 0)
Cough	2 (40.0)	0 (0)	40 (-2.9, 82.9)
Device occlusion	2 (40.0)	0 (0)	40 (-2.9, 82.9)
Diarrhea	2 (40.0)	0 (0)	40 (-2.9, 82.9)
Eye irritation	2 (40.0)	0 (0)	40 (-2.9, 82.9)
Headache	2 (40.0)	0 (0)	40 (-2.9, 82.9)
Tachypnea	2 (40.0)	0 (0)	40 (-2.9, 82.9)
Pyrexia	2 (40.0)	1 (16.7)	23.3 (-28.9, 75.6)
Rhinorrhea	2 (40.0)	1 (16.7)	23.3 (-28.9, 75.6)
URI	2 (40.0)	1 (16.7)	23.3 (-28.9, 75.6)
Abdominal pain	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Aphthous ulcer	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Arthropod bite	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Asthenia	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Dermatitis contact	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Eye discharge	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Fatigue	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Feeling hot	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Increased upper airway secretion	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Lacrimation increased	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Malaise	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Muscle strain	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Nasal congestion	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Nightmare	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Procedural pain	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Respiratory tract congestion	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Urinary tract infection bacterial	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Wound	1 (20.0)	0 (0)	20 (-15.1, 55.1)
Rash	2 (40.0)	2 (33.3)	6.7 (-50.5, 63.8)
Fall	1 (20.0)	1 (16.7)	3.3 (-42.7, 49.4)
Middle ear effusion	1 (20.0)	1 (16.7)	3.3 (-42.7, 49.4)
Nausea	1 (20.0)	1 (16.7)	3.3 (-42.7, 49.4)
Pain in extremity	1 (20.0)	1 (16.7)	3.3 (-42.7, 49.4)
Vomiting	2 (40.0)	3 (50.0)	-10 (-68.7, 48.7)

Source: adae2.xpt; Software: R
Treatment-emergent adverse events defined as AEs that developed or worsened or became serious during the treatment epoch
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

Because we are recommending that patients with LOPD who weigh less than 30 kg receive avalglucosidase alfa at 40 mg/kg qow, we also assessed for any differences in TEAEs and AESIs (IARs) between children who received avalglucoisdase alfa at 20 mg/kg qow and 40 mg/kg qow.

Among the children who received avalglucosidase alfa at 20 mg/kg qow, no TEAEs were reported in more than one patient; reported events include upper respiratory tract infection, fall, pneumonia, bronchitis, influenza, otitis media and tympanic membrane perforation. In children

who received avalglucosidase alfa at 40 mg/kg qow, at least two patients experienced pyrexia, rash, vomiting, abdominal pain, cough, diarrhea, headache, upper respiratory tract infection, device occlusion, epistaxis, eye irritation, eyelid ptosis, fall, oropharyngeal pain, rhinorrhea, and tachypnea.

Table 35 suggests that more TEAEs occurred in patients who received avalglucosidase alfa at 40 mg/kg qow compared to 20 mg/kg qow. However, there was a small number of patients in each group: 5 patients received avalglucosidase alfa at 20 mg/kg qow and 6 patients received avalglucosidase alfa at 40 mg/kg qow, and this precludes any meaningful conclusion on a potential dose-response relationship.

Table 35. Treatment-Emergent Adverse Events Occurring in Patients Treated With Avalglucosidase Alfa at 20 mg/kg qow and 40 mg/kg qow, Trial ACT14132 (Cohort 1 and 2)

	Cohort 1 (20 mg/kg, n=5)		Cohort 2 (40 mg/kg, n=6)	
Adverse Events	**Events**	**Patients**	**Events**	**Patients**
Pyrexia	0	0	18	4
Rash	0	0	8	4
Vomiting	0	0	8	4
Abdominal pain	0	0	3	3
Cough	0	0	5	3
Diarrhea	0	0	6	3
Headache	0	0	3	3
Upper respiratory tract infection	1	1	4	3
Device occlusion	0	0	2	2
Epistaxis	0	0	3	2
Eye irritation	0	0	2	2
Eyelid ptosis	0	0	3	2
Fall	2	1	4	2
Oropharyngeal pain	0	0	3	2
Rhinorrhea	0	0	2	2
Tachypnea	0	0	2	2
Abdominal pain upper	0	0	1	1
Aphthous ulcer	0	0	1	1
Arthralgia	0	0	1	1
Arthropod bite	0	0	1	1
Arthropod sting	0	0	5	1
Asthenia	0	0	1	1
Back pain	0	0	1	1
Bronchitis viral	0	0	1	1
Catheter site oedema	0	0	2	1
Conjunctivo-chalasis	0	0	1	1
Constipation	0	0	1	1
Contusion	0	0	2	1
Dermatitis contact	0	0	2	1
Dermatitis diaper	0	0	3	1
Dysphagia	0	0	1	1
Ear pain	0	0	1	1
Erythema	0	0	1	1
Eye discharge	0	0	1	1
Fatigue	0	0	1	1
Feeling hot	0	0	1	1
Foot deformity	0	0	1	1
Gastroenteritis	0	0	3	1
Increased upper airway secretion	0	0	1	1
Infusion site swelling	0	0	2	1

Adverse Events	Cohort 1 (20 mg/kg, n=5) Events	Patients	Cohort 2 (40 mg/kg, n=6) Events	Patients
Keratopathy	0	0	1	1
Lacrimation increased	0	0	1	1
Laryngeal oedema	0	0	1	1
Ligament sprain	0	0	1	1
Malaise	0	0	1	1
Middle ear disorder	0	0	1	1
Middle ear effusion	0	0	1	1
Muscle strain	0	0	1	1
Musculoskeletal pain	0	0	1	1
Nasal congestion	0	0	1	1
Nasopharyngitis	0	0	1	1
Nausea	0	0	1	1
Neutropenia	0	0	1	1
Nightmare	0	0	1	1
Pain in extremity	0	0	1	1
Pneumonia	1	1	2	1
Procedural pain	0	0	1	1
Regurgitation	0	0	1	1
Respiratory distress	0	0	1	1
Respiratory tract congestion	0	0	1	1
Scab	0	0	1	1
Scratch	0	0	1	1
Seizure	0	0	1	1
Sepsis	0	0	1	1
Skin abrasion	0	0	3	1
Strabismus	0	0	1	1
Sunburn	0	0	1	1
Thermal burn	0	0	1	1
Tinea pedis	0	0	1	1
Tonsillar hypertrophy	0	0	1	1
Toothache	0	0	6	1
Urinary tract infection	0	0	1	1
Urinary tract infection bacterial	0	0	1	1
Urticaria	0	0	1	1
Wound	0	0	1	1
Bronchitis	2	1	0	0
Influenza	2	1	0	0
Otitis media	1	1	0	0
Tympanic membrane perforation	1	1	0	0

Source: Review team
Abbreviation: qow, every other week

Among children who received avalglucosidase alfa at 20mg/kg qow, 1 patient (17%) in Cohort 1 had an AESI, which was an infusion associated reaction (IAR) with eczema and rash. In children who received avalglucosidase alfa at 40 mg/kg qow, 4 patients (40%) in Cohorts 2 and 3 experienced an IAR. Their symptoms included: tachypnea, rash, laryngeal edema, and urticaria (Table 36). As with SAEs and TEAEs discussed above, the small number of patients in each group precludes any meaningful conclusions on a potential dose-response relationship.

Table 36. Infusion Associated Reactions Occurring in Patients Treated With Avalglucosidase Alfa at 20 mg/kg qow and 40 mg/kg qow, Trial ACT14132 (Cohort 1, 2 and 3)

Patient ID Number	AESI:IAR		Number of Events	Action Taken With Avalglucosidase Alfa Infusion
	Avalglucosidase Alfa at 20 mg/kg qow	Avalglucosidase Alfa at 40 mg/kg qow		
(b) (6)		Tachypnea	1	Continued
(b) (6)		Rash	2	Continued
(b) (6)	Eczema		1	Continued
	Rash		1	Continued
(b) (6)		Rash	2	Interrupted and then resumed
		Rash	1	Interrupted twice and resumed at a lower rate
		Laryngeal edema	1	Interrupted and then resumed
(b) (6)		Urticaria	1	Discontinued infusion
		Rash	1	Interrupted and then resumed

Source: Review team
Abbreviations: AESI, adverse event of special interest; IAR, infusion-associated reaction; qow, every other week

7.6.3.6. Laboratory Findings, ACT14132

See Section 7.6.1.6 for discussion of hematological bloodwork results, renal function, electrolyte trends, EKG findings, and vital signs. Analysis of hepatotoxicity is in Section 7.7.4.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Hypersensitivity Reactions (Including Anaphylaxis) and Infusion-Associated Reactions

Issue

There is a risk of hypersensitivity reactions (including anaphylaxis) and infusion associated reactions (IAR) during treatment with avalglucosidase alfa. Enzyme replacement therapies (ERTs), as a class, include a boxed warning in labeling for these risks, but the Applicant did not include a boxed warning in the proposed labeling.

Background

Among the patients treated with avalglucosidase alfa, 48% (67/141) experienced hypersensitivity reactions. The symptoms that occurred in more than one patient consisted of rash, pruritus, erythema, urticaria, flushing, blisters, eye swelling, infusion site rash, lip swelling, erythematous rash, allergic rhinitis, asthma, choking, conjunctivitis, contact dermatitis, drug hypersensitivity, eczema, mouth ulceration, respiratory distress, and swollen tongue. Six of these hypersensitivity reactions (9%, 6/67) were severe reactions consisting of respiratory distress, erythema, urticaria, tongue edema, and rash.

Based on the review team's assessment of patient narratives, three patients who received avalglucosidase alfa met Sampson's criteria for anaphylaxis (Sampson et al. 2006): one patient from EFC14028 and two patients from TDR12857. Their symptoms included chest discomfort, cough, increase in creatine, decreased breath sounds, dizziness, dysphagia, erythema, nausea,

Reference ID: 4836879

oxygen desaturation, pruritus, premature ventricular contractions, rash, redness on feet, redness on palms, respiratory distress, , swollen lower lip, swollen tongue, and throat tightness.

Assessment

Anaphylaxis

Two patients (1%) who received avalglucosidase alfa had anaphylaxis. Symptoms of anaphylaxis were considered moderate in severity except for chest discomfort in patient (b) (6), which was severe. The symptoms in these 2 patients are described in the narratives below.

On January 15, 2021, the Applicant submitted an updated summary of clinical safety, an updated USPI document, and updated ISS and ISI appendices with 1 new case of anaphylaxis, bringing the total number of anaphylaxis cases to 3/141 (2%).

Anaphylaxis Narratives

- (b) (6): A 51-year-old woman in trial TDR12857 who was receiving avalglucosidase alfa at 5 mg/kg qow. On day 109, shortly after her ninth infusion began, she began coughing and complained of severe chest pressure, tightness in her throat which worsened, respiratory distress, dizziness and nausea. She received supplemental oxygen, diphenhydramine hydrochloride, epinephrine, normal saline and ondansetron hydrochloride, nebulized albuterol, and later, famotidine. This episode, according to the Applicant, met Sampson criteria for anaphylaxis and the review team agreed. While her symptoms resolved three days later, the patient was discontinued from the trial on day 144.
- (b) (6) A 44-year-old woman in trial TDR12857 who was receiving avalglucosidase alfa at 20 mg/kg qow. On day 351, during an infusion, she developed decreased breath sounds, oxygen desaturation, premature ventricular contractions, redness on feet, redness on palms, and swollen lower lip. The infusion was stopped, she received methylprednisone, salbutamol, ranitidine, normal saline, and oxygen. On blood work obtained later, her creatinine had increased to >1.5x her baseline. On day 373, during another infusion, she developed lip swelling, pruritus, palmar erythema, and desaturation which led to the infusion being stopped. She received prednisone. This episode, according to the Applicant, met Sampson criteria for anaphylaxis, and the review team agreed.
- (b) (6) A 48-year-old female in trial EFC14028 who was receiving avalglucosidase alfa at 20 mg/kg qow. On day 665, she developed erythema, respiratory distress, dysphagia, chest discomfort, tongue edema and nausea during an infusion. The infusion was stopped, and she received cetirizine, hydrocortisone, and chlorphenamine maleate. The respiratory distress, tongue edema, erythema, dysphagia and chest discomfort were considered severe, while the nausea was considered mild. The episode, according to the Applicant, met Sampson criteria for anaphylaxis, and the review team agreed.

There were 2 additional patients who had mild and moderate symptoms suggestive of possible anaphylaxis according to the review team, but not considered anaphylaxis by the Applicant.

However, with the available data, the review team was unable to definitively assess these episodes as anaphylaxis per the Sampson criteria. The narratives are below.

- (b) (6): A 47-year-old man in trial EFC14028 who was receiving avalglucosidase alfa at 20 mg/kg qow. On day 114, he developed pruritus, rash, sensation of a foreign body and headache during an infusion. His infusion was interrupted, and he received diphenhydramine chloride, paracetamol, and other unspecified treatments. This event included both skin (pruritus) and respiratory (sensation of foreign body) symptoms. However, in the description of the event, the "sensation of foreign body" was not severe enough to warrant classifications as respiratory compromise to meet Sampson criteria for anaphylaxis.
- (b) (6): A 19-year-old woman in trial EFC14028 who was receiving avalglucosidase alfa at 20 mg/kg qow. On day 882, she developed rash, cough, and pruritus during an infusion. Her infusion was interrupted, and she received diphenhydramine hydrochloride, and paracetamol. This event included both skin (pruritus, rash) and respiratory (cough) symptoms. However, in the description of the event, the cough resolved within half an hour and was not severe enough to warrant classification as respiratory compromise to meet Sampson criteria for anaphylaxis.

AESI: IARs

Forty-two patients (30%) who received avalglucosidase alfa had infusion associated reactions (IARs). The majority of these were mild to moderate in severity. The symptoms occurring in more than one patient consisted of pruritus, rash, headache, urticaria, chills, nausea, erythema, cough, dizziness, fatigue, chest discomfort, diarrhea, hyperhidrosis, influenza like illness, lip swelling, ocular hyperemia, decreased oxygen saturation, pain, pain in extremity, palmar erythema, erythematous rash, swollen tongue, tachycardia, tremor, and vomiting. Five patients had severe IARs, which consisted of hypertension, increased body temperature, chest discomfort, chills, dyspnea, headache, tachycardia, nausea, decreased oxygen saturation, pyrexia, respiratory distress, and skin discoloration.

On December 14, 2020, the Applicant updated the ISS and ISI to add 6 additional cases of IARs from patients in LTS13769. These cases occurred before the data lock for BLA submission on September 18, 2020. On January 15, 2021, the Applicant submitted an updated summary of clinical safety, an updated USPI document, and ISS and ISI appendices with 6 new cases of IARs, bringing the total number of patients with IARs to 48/141 (34%).

AESI: SAEs Narratives

- (b) (6): A 44-year-old female in trial EFC14028 who started the trial on avalglucosidase alfa. On days 396 and 424, during avalglucosidase alfa infusions, the patient developed severe nausea. In both instances, the infusion was interrupted, and the nausea resolved.
- (b) (6) A 52-year-old female in trial EFC14028 who started the trial on avalglucosidase alfa. On day 72, during an infusion of avalglucosidase alfa, the patient developed shortness of breath, tachycardia and cyanosis with an oxygen saturation of 85%. She was hospitalized; her only treatment was supplemental oxygen.

- (b) (6): A 68-year-old male in trial EFC14028 who started the trial on avalglucosidase alfa. On day 1009, during an infusion of avalglucosidase alfa, the patient developed increased blood pressure, increased heart rate, headache, chills, increased body temperature, decreased oxygen saturation, and skin discoloration. The infusion was interrupted, and the patient received supplemental oxygen, intravenous famotidine, diphenhydramine, and paracetamol.

Conclusion

Hypersensitivity reactions (including anaphylaxis) and IARs are known risks with ERTs. The review team recommended including a boxed warning in the labeling about this increased risk, and recommended changes to the text of the labeling to provide better details about the symptoms of hypersensitivity reactions (including anaphylaxis) and infusion-associated reactions.

7.7.2. Safety in Patients 12 Months of Age and Younger With IOPD

Issue

Patients 12 months of age and younger with IOPD were not enrolled in trial ACT14132, the only trial including patients with IOPD in this application.

Background

While patients age 6 months and older with IOPD were eligible for participation in trial ACT14132, the youngest patient was 1 year of age at the time of enrollment. According to the inclusion criteria, all patients previously received alglucosidase alfa. Therefore, infants who were 12 months of age and younger and treatment-naïve were not represented in this trial. The safety of avalglucosidase alfa in this population has not been established.

(b) (4)

Assessment

Within the IOPD population, infants aged 12 months and younger are at a higher risk of death compared to their older counterparts. Severe cardiac hypertrophy, at times including left ventricular outflow tract obstruction, can also increase their risk for arrhythmias and sudden cardiac death. The patients enrolled in ACT14132 were previously exposed to alglucosidase alfa, which may have improved cardiac hypertrophy that may be present at birth.

Patients with a complete absence of GAA are classified as negative for cross-reactive immunologic material (CRIM) and are likely to develop antibodies to ERT, which can make them resistant to treatment or place them at a higher risk for hypersensitivity events such as anaphylaxis. They are, therefore, likely to need immune tolerizing therapies. The patients enrolled in ACT14132 were previously exposed to alglucosidase alfa, which likely affects development of antidrug antibodies to avalglucosidase alfa.

Thus, while the population of patients included in ACT14132 were those who were declining clinically or responding suboptimally on alglucosidase alfa, they do not reflect the severity of disease in treatment-naïve infants 12 months of age and younger with IOPD.

Conclusion

Given the lack of safety data in this population, the review team concluded that there is inadequate support for approval of avalglucosidase alfa for children less than 12 months of age.

(b) (4)

7.7.3. Risk to Fetus During Pregnancy and Infant During Lactation

Issue

Limited data are available on the risks of avalglucosidase alfa on maternal and fetal health during pregnancy and on infants through their exposure to breast milk.

Background

Pregnant and lactating women were excluded from clinical trials with avalglucosidase alfa. The available data from 9 reported cases of inadvertent pregnancy exposure during the clinical development program (5 in female trial participants and 4 in female partners of male trial participants) are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Additionally, there are no available data on the presence of avalglucosidase alfa in human or animal milk, the effects on the breastfed infant, or the effects on milk product.

(b) (4)

Assessment

Review of existing Pompe pregnancy subregistry data for Lumizyme and Myozyme revealed limited data from only 8 pregnancies in 6 enrolled patients between 2006 to 2018. During the same timeframe, 108 cases were reported to the Applicant's global pharmacovigilance database (Dinatale 2019). While the review team agrees that the pharmacovigilance database may be a more robust source of data than the Pompe pregnancy subregistry, 38 of the reported pregnancy outcomes (35%) in the pharmacovigilance database were unknown.

The review team initially also indicated the need for a clinical lactation study (milk only) to assess concentrations of avalglucosidase alfa in breast milk using a validated assay. However, the Applicant provided acceptable justification that a study to assess concentrations of avalglucosidase alfa in breast milk is not needed, based on previous scientific experience with ERT related to lactation (Sekijima et al. 2010) and breastfeeding and the conclusions that alglucosidase alfa is compatible with lactation (de Vries et al. 2011).

Conclusion

The review team concluded that use of the existing Pompe patient registry and routine pharmacovigilance would be insufficient to adequately assess the risks of avalglucosidase alfa on maternal and fetal health during pregnancy and on infants through their exposure to breast milk. The review team indicated the need for a worldwide, descriptive, single-arm pregnancy safety study to collect outcome data in women and their offspring who are exposed to avalglucosidase alfa during pregnancy and lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant as a postmarketing requirement. See Section 22 for details about the Postmarketing Requirement.

7.7.4. Hepatotoxicity

Issue

There was a concern for potential hepatotoxicity in patients receiving avalglucosidase alfa, based on elevated transaminase levels with one potential Hy's Law case and 38 Temple's Corollary cases, as shown in Table 37.

Table 37. Potential DILI, Safety Population, Integrated Safety Set

Quadrant	Adult patients N=118 n (%)	Pediatric patients N=20 n (%)
Potential Hy's Law (right upper)	1 (0.8)	0
Cholestasis (left upper)	0	0
Temple's Corollary* (right lower)	22 (18.6)	16 (80)
Total	23 (19.5)	16 (80)

Source: adlb.xpt; Software: R
Note: The DILI Screening Plot and this table are generated using maximum treatment-emergent liver test abnormalities.
Abbreviations: DILI, drug-induced liver injury; N, number of patients in treatment arm; n, number of patients meeting criteria

Background

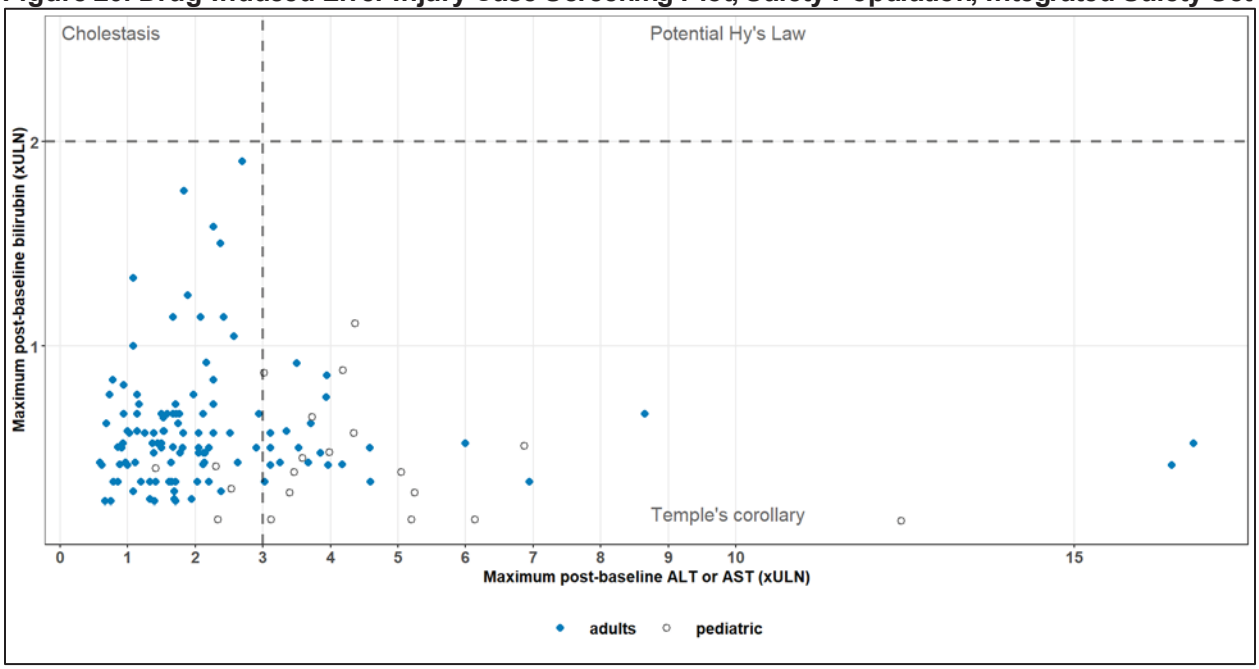
In the review team's analysis for drug induced liver injury, one potential Hy's Law case was identified, but another explanation for the elevated AST, ALT and total bilirubin was identified.

- [redacted] (b) (6): This patient was a 62-year-old woman with LOPD who was enrolled in trial EFC14028. She started treatment with alglucosidase alfa in the PAP and was switched to avalglucosidase alfa in the ETP. She received avalglucosidase alfa for 56 days, and her last dose was given on day 393. She had normal AST, ALT, and bilirubin results at baseline and at the beginning of the ETP, when she was switched to avalglucosidase alfa.

  During the ETP, on day 399, after developing severe abdominal pain and nausea, the patient was diagnosed with pancreatic adenocarcinoma. She was noted to have elevated liver function enzymes and bilirubin concurrently. On day 428, she underwent bile duct stent insertion due to biliary obstruction, and our analysis showed that her liver enzymes began to improve. Her status subsequently declined, and she did not tolerate chemotherapy. She died due to complications of her diagnosis on day 495. The Applicant assessed this death as being due to complications of her diagnosis and unrelated to avalglucosidase alfa; the review team agreed with this assessment.

During the course of the trials, 38 patients (28%) with either LOPD or IOPD had peak elevated liver enzymes (AST or ALT) which placed them in the Temple's Corollary quadrant, and thus at possible increased risk of severe DILI. Figure 20 shows the 22 adult and 16 pediatric patients who met criteria for Temple's Corollary. The pediatric cases included a 16-year-old patient with LOPD from trial EFC14028. This figure does not include the Hy's Law case because it occurred during the ETP of trial EFC14028.

Figure 20. Drug-Induced Liver Injury Case Screening Plot, Safety Population, Integrated Safety Set



Source: adlb.xpt; Software: R
Note: The Hy's Law screening plot is generated using maximum treatment-emergent liver test abnormalities.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; DILI, drug-induced liver injury; ULN, upper limit of normal; ALP, alkaline phosphatase

All 38 patients had abnormally elevated ALT and AST levels at baseline, and 37 of 38 patients had elevated CK levels. The abnormal liver functions at baseline could be reflective of muscle or general hepatocellular damage due to PD pathology (Hoeksma et al. 2007). By the end of the trials, 12 (32%) of the 38 patients had normal ALT levels and 10 (26%) had normal AST levels. Of the remaining patients, 22 (58%) and 24 (63%) patients had ALT and AST levels that were less than baseline, respectively. At the end of the trials, five patients had ALT or AST levels that were higher than their baseline values, 3 of whom had elevations of both. These five patients' total bilirubin (TB) levels remained normal throughout the trial, they continued on avalglucosidase alfa, and there were no reported signs of liver failure.

- [redacted] (b) (6) A 67-year-old female whose ALT and AST increased from baseline by the end of her participation. Her baseline ALT and AST levels were 50 and 49 IU/L, respectively, with peaks of 559 and 389 IU/L on day 119. At the end of the trial, her ALT and AST levels were 106 and 71 IU/L.
- [redacted] (b) (6) A 52-year-old female whose ALT and AST increased from baseline by the end of her participation. Her baseline ALT and AST levels were 76 and 59 IU/L, respectively with peaks of 105 (day 203) and 57 IU/L on day 35. At the end of the trial, her ALT and AST levels were 99 and 31 IU/L.
- [redacted] (b) (6) A 6-year-old male whose ALT and AST increased from baseline by the end of his participation. His baseline ALT and AST levels were 98 and 104 IU/L. At the end of the trial, his ALT and AST levels were 110 and 115 IU/L.
- [redacted] (b) (6): A 3-year-old male whose ALT and AST increased from his baseline values from the time he switched to avalglucosidase alfa until the end of his participation. His ALT and AST levels were 149 and 292 IU/L at the time of switching drugs. At the end of the trial, his ALT and AST levels were 155 and 302 IU/L.
- [redacted] (b) (6) A 19-year-old female whose ALT and AST increased from baseline by the end of her participation. On day 154, the patient found out that she was pregnant. Avalglucosidase alfa was discontinued on day 183. The patient's participation ended on day 542. Her baseline ALT and AST levels were 101 and 140 IU/L, respectively, with peaks of 104 (day 63) and 128 (day 35) IU/L, respectively. The patient's total bilirubin remained normal throughout the trial. After discontinuing avalglucosidase alfa on day 183, her subsequent ALT and AST levels were 56 and 74 IU/L. Her last ALT and AST levels were obtained after avalglucosidase alfa had been discontinued, and were 98 and 116 IU/L, respectively.

With respect to TB, 37 of the 38 patients with abnormally elevated ALT and AST levels at baseline had TB levels within the normal range throughout the course of the trial. One patient (narrative below) had intermittent elevation of his TB, but it was within the normal range at the end of the trial without modification to his avalglucosidase alfa dose.

- [redacted] (b) (6) A 10-year-old male with increases in his TB levels to 18.6 and 19 μmol/L during the course of the trial, which decreased to 10.1 μmol/L at the end of the trial. His baseline TB level was 6.3 μmol/L (normal <17.1 μmol/L). The elevated bilirubin levels did not correlate with his peak ALT and AST levels. There were no reported clinical signs of liver failure, and he remained on avalglucosidase alfa.

Three patients in Temple's Corollary later discontinued the trial for reasons unrelated to liver function. The details of their discontinuation are discussed in Section 7.6.1.4.

Assessment

On review of the narratives of the patient who potentially met Hy's Law criteria, the review team concluded that her liver injury was associated with her diagnosis of pancreatic adenocarcinoma and unrelated to her exposure to avalglucosidase alfa.

All 38 patients who met criteria for Temple's Corollary had abnormal baseline values for AST and ALT. All but one had normal total bilirubin levels throughout the trial. This patient's abnormal total bilirubin levels did not correlate with the patient's peak AST and ALT values and returned to normal at the end of the trial.

The review team concluded that avalglucosidase alfa is unlikely to cause hepatotoxicity. In the five cases where the ALT and AST increased from baseline at the last measurement, the increase was ≤2 times the baseline and the TB was normal, and the patients were continued on avalglucosidase alfa.

Conclusion

While liver function should be followed regularly in patients with Pompe disease, no additional hepatic monitoring is recommended in patients due to treatment with avalglucosidase alfa.

7.7.5. Manufacturing Site Inspection

Issue

Delay in timing of manufacturing site inspections due to travel restrictions to the COVID19 pandemic.

Background

A prelicensure inspection of the drug substance manufacturing facility (Genzyme Flanders NV, Belgium) was assessed as necessary for approval of this marketing application. This issue was communicated to the Applicant in the midcycle communication. In response, the Applicant submitted a proposal on November 20, 2020, for a virtual site inspection and provided recent inspection history by the Belgian regulatory health authority.

Assessment

The review team initiated a review of records under section 704(a)(4) to determine whether a virtual assessment or an on-site inspection would be required. Assessment of these records and other information from the manufacturing facility was completed. No issues were identified.

Conclusion

The review team concluded that an on-site inspection of the manufacturing facility (Genzyme Flanders NV, Belgium) is not warranted at this time following the successful review of records under section 704(a)(4) in combination with review of the relevant inspection report by the Belgian health authority, through Mutual Recognition Agreement.

7.7.6. Clinical Site Inspections

Issue

Delay in timing of clinical site inspections due to travel restrictions related to the COVID19 pandemic.

Background

Selection of clinical sites for inspection was based on risk ranking, number of patients enrolled, and geographic location. EFC14028 (COMET) was the pivotal trial for LOPD at 55 sites, with no single site enrolling more than 6 patients. Five sites for trial EFC 14028 within the United States were selected for onsite inspection: Durham, NC (site ID 8400001), Fairfax, VA (site ID 8400005), Orange, CA (site ID 8400011), Chicago, IL (site ID 8400023), and Pittsburgh, PA (site ID 8400025).

ACT14132 (mini-COMET) was a phase 2 open-label trial at 10 sites, with no single site enrolling more than 5 patients. Two sites for trial ACT14132 within the United States were selected for onsite inspections: Durham, NC (site ID 8400006) and Valhalla, NY (site ID 8400002).

Given low treatment arm participation at the selected U.S. sites (only 3 of 13 patients are in the treatment arm), inclusion of two international sites would include a larger number of patients in the treatment arm: Barcelona, Spain (site ID 7240002) included three patients in the treatment arm and Moscow, Russia (site ID 6430001) included four patients in the treatment arm. In addition, the Spain site was selected for inspection because the treatment efficacy rate was twice the overall study rate. Due to the uncertainty of international travel during the COVID19 pandemic, the team investigated alternative methods of inspection for these foreign sites. Remote regulatory assessments (RRA) required extensive collaboration with the data privacy office of each institution and were successfully arranged at the clinical sites in Russia and Spain.

Unfortunately, the site in Spain (site ID 7240002) was not available to complete the RRA within the PDUFA timeline. In addition, the site in VA (site ID 8400005), which enrolled two patients in the alglucosidase alfa arm, was not included in the inspection, since it was recently inspected in October 2020.

Assessment

The review team conducted a sensitivity analysis to assess the impact of the data from the site in Spain (site ID 7240002) on the primary efficacy results. Specifically, the data from the site in Spain were excluded, and then the primary MMRM analysis (Section 6.2.1.3.1) was repeated. In this sensitivity analysis, the estimated mean change from baseline in FVC (% predicted) to week 49 was 2.6 for the avalglucosidase alfa arm and 0.4 for the alglucosidase alfa arm. The estimated treatment difference was 2.2 (95% CI: -0.4 to 4.8; p=0.09), favoring the avalglucosidase alfa arm. As the lower bound of the 95% CI for the difference was larger than the prespecified NI margin of -1.1%, the trial still met noninferiority for the primary efficacy endpoint.

Removal of the site in VA (site ID 8400005) resulted in the removal of two patients in the alglucosidase alfa arm. Thus, inspection of 6 clinical sites and review of data from 25 patients,

including 12 who received avalglucosidase alfa, the study drug, was felt to be adequate by the review team.

For trial EFC14028, the inspection of site 8400023 identified a data discrepancy regarding a protocol violation for the use of protocol prohibited methotrexate, rituximab, immunoglobulins and other immunosuppressants involving all three subjects enrolled at the trial site. The submitted protocol deviation data listings include the protocol violation for all three subjects; however, according to the records at the site, and according to the CRFs submitted by the Applicant, none of the three subjects at the site had taken the prohibited medications. The review team concluded that these discrepancies would not affect our analysis.

The inspection of site 8400023 additionally found that spirometry results at baseline and week 49 for subject (b) (6) were available but were omitted from the submitted data listings. This subject was in the study drug arm of the trial. The primary endpoint for this subject, change in forced vital capacity (FVC) (% predicted) from baseline to week 49 showed a decrease of 6.7%. Further inspection established that the week 49 spirometry results for this subject were obtained past the week 49 window. Consequently, the week 49 spirometry was remapped to week 61 in the Applicant's analysis dataset per the SAP. The review team conducted a sensitivity analysis to assess the impact of this remapping on the primary efficacy results. Specifically, the decrease of 6.7% was included as the primary endpoint value for this subject, and the primary MMRM analysis was repeated. In the sensitivity analysis, the estimated treatment difference was 2.2 (95% CI: -0.3 to 4.8; p-value=0.09) favoring the avalglucosidase alfa arm. As the lower bound of the 95% CI for the difference is larger than the prespecified NI margin of -1.1%, the trial still met noninferiority for the primary efficacy endpoint.

Conclusion

The review team concluded that inspection of the five sites in the United States and the RRA at the one site in Russia was sufficient to assess the data quality and integrity. The Office of Scientific Investigations concluded that other than the data discrepancies described above, the clinical data generated by the inspected investigators appear reliable. No significant trial conduct issues or regulatory violations were identified at any of the inspected entities. Overall, the improvement in pulmonary function is minimally affected by the identified discrepancies and would not change our regulatory decision.

8. Therapeutic Individualization

The recommended dosage regimens in patients with LOPD are based on the individual patient's body weight. The currently available data do not support a need for further therapeutic individualization based on other intrinsic factors. For details on dose selection, refer to Section 6.3.2 and Appendix 14.5.

8.1. Intrinsic Factors

Age

Based on the population pharmacokinetics (popPK) analysis of 75 patients with LOPD aged 16 to 78 years (with 1 patient <18 years of age and 16% of patients ≥65 years of age) who received

20 mg/kg qow avalglucosidase alfa, age was not determined to be a significant covariant influencing PK of avalglucosidase alfa (study POH0703).

Sex

Based on the popPK analysis of 75 patients (36 female and 39 male) with LOPD who received 20 mg/kg qow avalglucosidase alfa, sex was not determined to be a significant covariant influencing PK of avalglucosidase alfa (study POH0703).

Race

The popPK analysis with data from 68 Caucasians (91% of the population), 3 Asians (4%), 2 Blacks (3%), and 2 other races (3%), who received 20 mg/kg qow avalglucosidase alfa, did not identify race as a significant covariate influencing PK of avalglucosidase alfa (study POH0703).

Body Weight

The popPK analysis, including 75 patients with LOPD weighing between 38 and 129 kg, and 16 patients with IOPD weighing between 10 and 64 kg, identified body weight as a significant covariate on CL, V1 and Vm. Within the same dosing regimen, the exposure appears to be lower in subjects with lower body weight (Table 38).

Table 38. Exposure Comparison by Patient Body Weight for Avalglucosidase Alfa at 20 mg/kg and 40 mg/kg qow in Patients With IOPD and LOPD (Based on Updated Population PK Model)

	Avalglucosidase Alfa 20 mg/kg qow			Avalglucosidase Alfa 40 mg/kg qow		
Body Weight (kg)	n	C_{max} (µg/mL)	AUC_{2W} (µg·h/mL)	n	C_{max} (µg/mL)	AUC_{2W} (µg·h/mL)
10–29	3	149 (5%)	543 (11%)	5	234 (12%)	1532 (13%)
30–49	8	218 (9%)	903 (11%)	4	336 (8%)	2298 (8%)
50–99	55	262 (13%)	1185 (21%)	1	382 (NA)	2449 (NA)
≥100	10	323 (11%)	1456 (23%)	0	NA	NA

Source: Adapted from Table 4, Response to FDA Clinical Information Request, Information on Topics Dated on 13-Nov-2020
Descriptive statistics are mean (CV%)
Body weight used for exposure computation, i.e., body weight at the time patients received their first avalglucosidase alfa 20 mg/kg qow dose for patients with LOPD and body weight at the time patients received their last dose for patients with IOPD
Abbreviations: AUC_{2W}, area under the concentration-time curve over the first two weeks; C_{max}, maximum plasma drug concentration; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; NA, not applicable; PK, pharmacokinetic; qow, every other week

Patients With IOPD Versus Patients With LOPD

At the 20 mg/kg dose, a trend of lower exposures was observed in patients with IOPD than in patients with LOPD, based on direct comparison of PK data from trial EFC14028 (LOPD) and trial ACT14132 (IOPD). When comparing exposures in patients with IOPD (body weight range: 10 to 64 kg) with the 15 patients with LOPD who had a lower body weight range of ≤64 kg (range: 38 to 62 kg), the two populations showed overlapping exposures. Based on popPK analysis, no clinically relevant difference in PK was identified between patients with IPOD versus patients with LOPD, after body weight was accounted for.

8.1.1. Renal Impairment or Hepatic Impairment

The effect of renal impairment or hepatic impairment on the PK of avalglucosidase alfa has not been studied in dedicated clinical pharmacology studies. Intact avalglucosidase alfa is unlikely to be filtered by kidney or excreted in urine. Metabolism by CYP enzymes or secretion into bile is generally not a significant contributor to the elimination of therapeutic proteins such as avalglucosidase alfa.

Based on the popPK analysis in 75 patients with LOPD who received 20 mg/kg qow avalglucosidase alfa, including six patients with mild renal impairment (eGFR 60 to 89 mL/min at baseline), eGFR and creatinine clearance was not determined to be a significant covariant influencing PK of avalglucosidase alfa (study POH0703). No data are available in patients with moderate or severe renal impairment.

8.2. Drug Interactions

No specific drug-drug interaction studies were conducted with avalglucosidase alfa.

Previous treatment with alglucosidase alfa was not identified as a significant covariate influencing PK of avalglucosidase alfa in the popPK analyses (study POH0703).

8.3. Plans for Pediatric Drug Development

Avalglucosidase alfa was granted orphan-drug designation in November 2013 for the treatment of patients with a confirmed diagnosis of Pompe disease. Avalglucosidase alfa is exempt from the Pediatric Research Equity Act (21 U.S.C.355c), (b) (4)

Nonclinical

Nonclinical safety for pediatric patients was evaluated in repeat dose toxicity studies conducted in juvenile mice for 9 weeks. No adverse effects were observed in this study.

Table 39. Juvenile Toxicity Safety Margin

Study	NOAEL	AUC[1]	Safety Margins[2] (Based on AUC)
9-week juvenile mouse study	100 mg/kg IV every other week[3]	8140 µg•h/mL (male) 5400 µg•h/mL (female)	3.7X (male) 2.5X (female)

Source: Study JUV0033 study report submitted under eCTD001 module 4.2.3.5.4.
[1] $AUC_{0\text{-}24hr}$ values were used to determine the clinical safety margin.
[2] Exposure multiples were based on pharmacokinetics analysis from trial ACT14132, where the maximum clinical dose (40 mg/kg IV every other week in patients with IOPD) resulted in systemic exposure of $AUC_{0\text{-}2w}$ =2200 µg•h/mL.
[3] Highest dose tested
Abbreviations: AUC, area under the curve; IV, intravenous; NOAEL, no observed adverse effect level

8.4. Pregnancy and Lactation

The following nonclinical information was used in support of the drug's labeling. Additional details are available in Section 13.

Reference ID: 4836879

Table 40. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation
	(b) (4)

Labeling Section	Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	(b) (4)

(b) (4)

Table 41. Reproductive and Developmental Toxicity Safety Margins

Study	NOAEL	AUC[1]	Safety Margins (Based on AUC)
Embryonic and fetal development mouse study:	50 mg/kg/day (maternal)[2]	2080 µg•h/mL (GD 6)	1.7X[3]
Maternal toxicity related to an immunologic response (including anaphylactoid response). Postimplantation loss and late resorptions at 50 mg/kg/day. No placenta transfers.	20 mg/kg/day (developmental)	582 µg•h/mL (GD 6)	0.5X[3]
Embryonic and fetal development rabbit study:	30 mg/kg/day (maternal)	1260 µg•h/mL (GD 19)	1.0X[3]
Lower mean maternal body weight and food consumption at 60 and 100 mg/kg/day.	100 mg/kg/day (developmental)[2]	7910 µg•h/mL (GD 19)	6.4X[3]
9-week juvenile mouse study: No adverse effect	100 mg/kg IV qow[2]	M: 8140 µg•h/mL F: 5400 µg•h/mL	M: 3.7X[4] F: 2.5X[4]

Source: Study TER0685 and study TER0686 study reports submitted under eCTD0001 module 4.2.3.5.2. and study JUV0033 study report submitted under eCTD 0001 module 4.2.3.5.4.
[1] $AUC_{0\text{-}24hr}$ values were used to determine the clinical safety margin.
[2] Highest dose tested
[3] Exposure multiples were based on pharmacokinetics analysis from trial EFC14028, where the maximum clinical dose (20 mg/kg IV every other week in patients with LOPD) resulted in systemic exposure of $AUC_{0\text{-}2w}$ =1230 µg•h/mL.
[4] Exposure multiples were based on pharmacokinetics analysis from trial ACT14132, where the maximum clinical dose (40 mg/kg IV every other week in patients with IOPD) resulted in systemic exposure of $AUC_{0\text{-}2w}$ =2200 µg•h/mL.
Abbreviations: AUC, area under the curve; GD, gestation day; IV, intravenous; NOAEL, no observed adverse effect level; qow, every other week

Pregnancy

Pregnant women were excluded from clinical trials with avalglucosidase alfa. Available data from the nine reported cases of inadvertent pregnancy exposure during the clinical development program (five in female trial participants and four in female partners of male trial participants) are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. However, available data from postmarketing reports and published case reports of alglucosidase alfa use in pregnant women have not identified a drug-associated risk of adverse pregnancy outcomes (see Section 7.7.3).

Subsection 8.1 of labeling for Nexviazyme will include a risk summary that describes the available human pregnancy data for both avalglucosidase alfa and alglucosidase alfa considering the similarities between these two ERTs. A clinical consideration will also be included to inform

prescribers that untreated Pompe disease is associated with worsening of respiratory and musculoskeletal symptoms in some pregnant women.

Pompe disease is a rare condition that affects females of reproductive potential. Thus, exposure to avalglucosidase alfa in pregnant women is anticipated, but is likely to be rare in the postmarketing setting. Given that available data from inadvertent pregnancy exposure cases during the clinical development program are insufficient to evaluate the safety of avalglucosidase alfa use in pregnant women, it will be important to collect pregnancy safety data postapproval.

Lactation

Lactating women were excluded from clinical trials with avalglucosidase alfa, and no lactation exposures were reported. Overall, there are no available data on the presence of avalglucosidase alfa in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Avalglucosidase alfa is a large glycoprotein that is likely degraded in the infant's gastrointestinal tract, suggesting systemic exposure by the breastfed infant is likely to be minimal. Therefore, the following benefit-risk statement will be included in subsection 8.2 of labeling for Nexviazyme: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Nexviazyme and any potential adverse effects on the breastfed infant from Nexviazyme or from the underlying maternal condition."

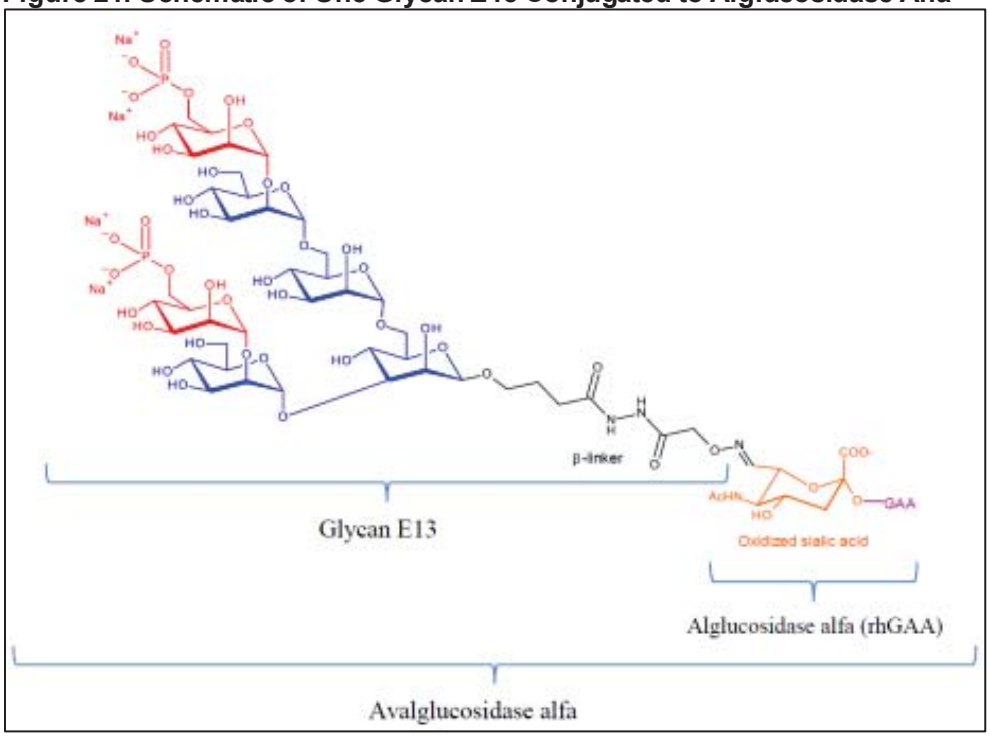
Based on the lack of available data and the anticipated use of avalglucosidase alfa in females of reproductive potential including lactating women, it will be important to collect safety data in this population postapproval (see Section 7.7.3).

9. Product Quality

Avalglucosidase alfa-ngpt is a modified form of human α-glucosidase (alglucosidase alfa) conjugated with multiple copies of synthetic glycan E13, a synthetic bis-mannose-6-phosphate-tetra-mannose glycan (bisM6P), linked to sialic acid residues in the enzyme. (b) (4) [redacted] he structure was confirmed by NMR experiments and Mass Spectrometry. (b) (4) [redacted]

One molecule of avalglucosidase contains approximately seven glycan E13 conjugated to the oxidized sialic acid residues in alglucosidase alfa. For clarity purposes, Figure 21 shows the structure of avalglucosidase alfa with only one glycan E13 conjugated to alglucosidase alfa (rhGAA).

Figure 21. Schematic of One Glycan E13 Conjugated to Alglucosidase Alfa



Source: Structure section submitted under module 3.2.S.1.2.
Glycan E13 contains 2 bisM6P in red, 4 mannose molecules in blue, and the linker in black, attached to the sialic acid (orange) on the alglucosidase alfa protein (pink). The glycan is conjugated to alglucosidase alfa through an aminoxy nitrogen to carbon double bond (oxime), with the nitrogen (N) coming from the glycan linker and the carbon from the carbon at position 7 (C7) of oxidized sialic acid of alglucosidase alfa.

Recombinant human alglucosidase alfa is expressed, secreted, and purified from CHO cells as a fully glycosylated 110 kDa molecule. Avalglucosidase alfa-ntpg is produced by conjugation of oxidized alglucosidase alfa and glycan E13. The manufacturing process (b) (4)

Avalglucosidase alfa-ntpg drug product is supplied in a single-use (b) (4) glass vial containing 100 mg lyophilized product per vial. Reconstituted drug product contains 10 mg/mL avalglucosidase alfa in 10mM L-histidine/L-histidine hydrochloride monohydrate, 2% (w/v) glycine, 2% (w/v) mannitol, and 0.01% (w/v) polysorbate 80 at pH 6.2.

The data submitted in this Biologics License Application support the conclusion that the manufacture of avalglucosidase alfa-ngpt, is well controlled and leads to a product that is safe, pure, and potent. The process is under adequate microbial control, and sterility assurance of the drug product has been demonstrated. The product is free from endogenous and adventitious infectious agents and meets the standards recommended by the FDA. The conditions used in the manufacturing process were adequately validated, and the product was consistently manufactured from multiple production runs.

The stability data are sufficient to support an expiration dating period of (b) (4) months for avalglucosidase alfa-ngpt drug substance when stored at (b) (4) °C and an expiration dating period of 48 months for lyophilized avalglucosidase alfa-ngpt drug product when stored at 5±3°C.

A review of Genzyme Flanders NV, Geel Belgium (FEI: 3003623839) drug substance manufacturing documents was performed using the FDA's authority under Section 704(a)(4) of the FD&C Act in advance or in lieu of an inspection. It was determined that a prelicense inspection was not needed and based on the 704(a)(4) review a recommendation for approval was made for this facility.

An inspection of Genzyme Ireland Limited, Waterford, Ireland (FEI: 3003809840) for drug product manufacturing operations was waived based on the history of the facility.

All other proposed manufacturing and testing facilities are acceptable based on their current GMP compliance status and recent relevant inspectional coverage.

The Applicant has provided sufficient CMC information to assure the identity, strength, purity, potency, and safety of lyophilized avalglucosidase alfa-ngpt drug product.

The Office of Pharmaceutical Manufacturing Assessment has made a final overall "Approval" recommendation for the facilities involved in this application.

The Office of Biotechnology Products Immunogenicity team has no bioanalytical assay related approvability issues for avalglucosidase alfa-ntpg and considers that supporting immunogenicity data are acceptable pending concurrence from Clinical and Clinical Pharmacology teams.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling is satisfactory from the CMC perspective.

Therefore, from the OPQ perspective, this BLA is recommended for "**Approval**."

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections / Clinical Site and Other Good Clinical Practice Inspections / Financial Disclosure

Human Subjects Protections

As stated by the Applicant, the clinical trials were conducted in substantial conformance with International Council for Harmonization good clinical practice requirements and with applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and protection of human subjects participating in biomedical research. All studies submitted in this application were conducted according to FDA requirements, under investigational new drug (IND) 109569.

Clinical Site Inspections

FDA clinical site inspections were performed on-site at five sites within the United States and at one site remotely in Russia (refer to Section 20 for details).

Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance *Financial Disclosure by Clinical Investigators* (February 2013) (see Section 23), and by 21 CFR 54.4. None of the investigators of the four studies were employed by the Applicant, and none disclosed financial interests with the Applicant. In conclusion, the likelihood that trial results were biased on financial interests is minimal and should not affect the approvability of the application.

11. Advisory Committee Summary

An advisory committee was not held for this application. It did not raise challenging efficacy or safety issues that needed external input.

Reference ID: 4836879

III. Appendices

12. Summary of Regulatory History

Genzyme Corporation (Genzyme) had the first interaction with the FDA on the development program of GZ402666, also referred as avalglucosidase alfa or neoGAA, in a pre-IND meeting on October 27, 2010 (PIND 109569). Avalglucosidase alfa is recombinant human GAA conjugated with a synthetic bis-mannose-6-phosphate-Man6-glycan. This modification of the enzyme results in the conjugation of a number of hexamannose structures containing two terminal mannose-6-phosphate (M6P) moieties to oxidized sialic acid residues on GAA, thereby increasing M6P levels on the molecule.

Genzyme proposed to develop avalglucosidase alfa intravenous injection as a second-generation enzyme replacement therapy (ERT) for the treatment of patients with a confirmed diagnosis of Pompe disease (PD) (GAA deficiency). The clinical development program for avalglucosidase alfa was designed to demonstrate clinical benefit over the first generation ERT, alglucosidase alfa, which is marketed under the trade names Myozyme (alglucosidase alfa), BLA 125141, and Lumizyme (alglucosidase alfa), BLA 125291.

A phase 1 protocol, trial TDR12857 titled "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," was received on March 28, 2013.

An informal teleconference was held with Genzyme on April 25, 2013, to discuss the nonclinical concerns on the proposed upper limit. Genzyme agreed to the Agency's recommended upper limit of 50 µg/mL and submitted an updated protocol to reflect this agreement on April 26, 2013. Trial TDR12857, under IND 109569, was determined to be "safe to proceed."

On November 19, 2013, Genzyme received Orphan Drug designation for avalglucosidase alfa for the treatment of Pompe disease.

A phase 2 protocol, trial LTS13769 titled "An open-label, multicenter, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of neoGAA in patients with Pompe disease," was received on October 25, 2013. This protocol described a long-term safety extension trial to collect safety, pharmacokinetic, pharmacodynamic, pharmacogenetic, and exploratory efficacy data. Protocol amendments 1, 2, 3, 4, 5, 6, 7, and 8 were received on January 3 and August 7, 2014, February 16, 2016, January 12 and August 28, 2018, September 23, 2019, February 21 and November 12, 2020, respectively.

A Written Responses Only (WRO) meeting document was issued on August 25, 2014, which provided guidance on the proposed juvenile toxicity study design to support future pediatric clinical trials of neoGAA.

On September 8, 2015, an end-of-phase 2 meeting took place to discuss the overall development program for avalglucosidase; specifically the nonclinical program, completion of the phase 1/2 protocol (trial TDR12857), plans for phase 2 protocol (trial ACT14132) in patients with infantile-onset Pompe disease (IOPD), and the phase 3 protocol (trial EFC14028) for patients with late-onset Pompe disease (LOPD). In response to Genzyme's proposed plan to not conduct

Reference ID: 4836879

carcinogenicity studies, the FDA recommended that the they submit an assessment of the carcinogenic potential for avalglucosidase in their marketing application for review. The FDA also stated that a juvenile toxicity study is needed to support the inclusion of pediatric patients less than 6 years old. (b) (4) [redacted] The FDA also provided recommendations on the proposed phase 3 protocol for LOPD, assessments of pharmacokinetic and immunogenicity, and a statistical analysis plan. The meeting minutes were issued on September 16, 2015.

A WRO was issued on September 23, 2015, and the Office of Pharmaceutical Quality provided guidance on the manufacturing development of neoGAA (b) (4) [redacted]

Genzyme submitted a meeting request on November 10, 2015, to obtain feedback on their revised plan for phase 2 protocol in patients with IOPD and phase 3 protocol in patients with LOPD. A WRO was issued on January 25, 2016, which provided comments on the revised trial design and efficacy analysis plan.

On December 22, 2015, Genzyme submitted a meeting request to obtain feedback on their proposed plan to use the Pompe Disease Symptom Scale and the Pompe Disease Impact Scale patient-reported outcome (PRO) instruments as the primary endpoints for the avalglucosidase alfa clinical development program. The FDA issued a WRO dated March 2, 2016, and an advice letter dated July 27, 2016, providing their recommendations. Based on the FDA feedback, Genzyme changed the Pompe Disease Impact Scale and Pompe Disease Symptom Scale Pompe PRO tools to exploratory endpoints.

A phase 3 protocol, trial EFC14028 titled "A Phase 3, randomized, multicenter, multinational, double-blinded study comparing the efficacy and safety of repeated biweekly infusions of neoGAA (GZ402666) and alglucosidase alfa in treatment-naïve patients with late onset Pompe disease" was received April 11, 2016. The FDA commented on the endpoints, pharmacokinetic (PK) assessment and efficacy analysis in an advice letter dated June 13, 2016. A protocol amendment was received August 5, 2016.

A statistical analysis plan (SAP) for the pivotal trial, EFC14028, was received on August 29, 2016. FDA correspondences on the SAP included advice letters dated September 2, 2016, July 19, 2019, January 13, 2020, and April 13, 2020. Additional communications between the FDA and Genzyme resulted in a final SAP being submitted on April 16, 2020.

A phase 2 protocol, trial ACT14132 titled "An open-label ascending dose cohort study to assess the safety, pharmacokinetics, and preliminary efficacy of neoGAA (GZ402666) in patients with infantile-onset Pompe disease treated with alglucosidase alfa who demonstrate clinical decline or suboptimal clinical response," was received on November 11, 2016. The FDA had concerns on the trial design and indicated that efficacy from patients with LOPD cannot be extrapolated to patients with IOPD, (b) (4) [redacted] The discussion on the proposed pediatric program, particularly trial ACT14132, occurred in multiple forums, and a final protocol for trial ACT14132 was received on May 1, 2020.

Reference ID: 4836879

To study pediatric patients with IOPD from 0 to 6 months of age, Genzyme proposed a postmarket phase 3 protocol, trial EFC14462 titled "An open label, multinational, multicenter intravenous infusion study of the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of avalglucosidase alfa in treatment-naïve pediatric patients less than or equal to 6 months of age with infantile onset Pompe disease (IOPD)." The FDA issued a WRO on July 6, 2018, regarding trial EFC14462 in addition to the previously presented clinical data in trials ACT14132 and EFC14028. These data did not support an indication in all pediatric patients with a confirmed diagnosis of Pompe disease.

Genzyme submitted a Breakthrough Therapy designation request (BTD) on February 7, 2019. This BTDR was withdrawn on March 4, 2019, after an informal teleconference wherein the FDA expressed concerns regarding the interpretability of the submitted data. Genzyme resubmitted their BTDR on May 19, 2020. The FDA granted BTD for avalglucosidase alfa for the treatment of patients with a confirmed diagnosis of Pompe disease (alpha-glucosidase deficiency) on June 3, 2020.

On August 14, 2019, the FDA granted Fast Track designation of avalglucosidase alfa for the treatment of Pompe disease.

On December 10, 2019, Genzyme submitted a request for a review of the proposed proprietary name Nexviazyme. The FDA found Nexviazyme to be conditionally acceptable on June 3, 2020.

On May 6, 2020, Genzyme requested a pre-BLA meeting to discuss their proposed marketing application. A teleconference took place on June 30, 2020. The FDA stated that preliminary results from trial EFC14028 appear supportive of improved efficacy of avalglucosidase alfa over alglucosidase alfa in treatment-naïve patients with LOPD. However, the FDA reiterated that the indication for avalglucosidase alfa will be considered based upon the data submitted for patients with IOPD and LOPD to the BLA and will not include patients aged 0 to 6 months of age. The meeting minutes were issued on July 14, 2020.

On June 9, 2020, Genzyme had a teleconference with the FDA to discuss trial EFC14462. Genzyme anticipated that the results of trial EFC14462 and natural history study NCOMPC09701, in combination with trial ACT14132 (patients with IOPD <18 years of age) and trial EFC14028 (treatment of patients with LOPD ≥3 years of age) would ultimately inform labeling across the full range of patients with a confirmed diagnosis of Pompe disease. The FDA commented that trials EFC14028 and ACT14132 may enable labeling for the treatment of LOPD and IOPD except for treatment-naïve patients with IOPD <6 months of age. The meeting minutes were issued on June 16, 2020.

Rolling review designation was requested on June 17, 2020, and granted for the BLA on June 24, 2020.

Genzyme submitted BLA 761194 for avalglucosidase for the treatment of Pompe disease in two parts: part 1, which contained the nonclinical modules, was received on July 17, 2020, and part 2, which contained the clinical and chemistry, manufacturing, and controls modules, was received on September 18, 2020. The Division determined that the review classification for BLA 761194 is priority because avalglucosidase is a drug for a serious disease and, on its face, appeared to be an important advance in therapy.

Reference ID: 4836879

On September 18, 2020, Genzyme requested a suffix "ngpt" for the nonproprietary name avalglucosidase alfa, and the FDA found avalglucosidase alfa-ngpt conditionally acceptable on February 1, 2021.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

13.1.1. Pharmacology (Primary and Secondary)

Table 42. Pharmacology Studies

Study Number	Study Purpose/Dose/Route	Major Findings
Study No. 07-1948	To determine potency of neoGAA relative to alglucosidase alfa by measuring glycogen content in GAAKO mouse tissues [n =6 (3M/3F)] Dose/Route: 4, 12, and 20 mg/kg, 4 weekly doses, IV bolus	NeoGAA was 5-7X more potent than alglucosidase alfa. ADA were identified in all dose groups. No adverse effects were observed in the live, kidney, lung, or quadriceps. One mouse showed mild multifocal myocardial necrosis at 20 mg/kg.
Study No. 09-3981	To determine how many glycans (0 to 7 per mole of neoGAA) were needed to significantly increase potency of neoGAA by measuring glycogen content in GAAKO mouse tissues [n =12 (6M/6F)] Dose/Route: 20 mg/kg, 4 weekly doses, IV bolus	A minimum of 3 glycans were required to obtain a substantial increase in potency of neoGAA relative to alglucosidase alfa.
Study No. 09-3981	To determine potency of neoGAA relative to alglucosidase alfa by measuring glycogen content in GAAKO mouse tissues [n =12 (6M/6F)] Dose/Route: 4, 12, and 20 mg/kg, 4 weekly doses, IV bolus	NeoGAA reduced glycogen levels in heart, quadriceps, triceps, psoas, and diaphragm at doses 3-5X lower than those with alglucosidase alfa.
Study No. 11-02367	To compare potency of neoGAA with different sialic acid levels at 5.5 or 7.2 mole/mole by measuring glycogen content in GAAKO mouse tissues [n =6 (3M/3F)] Dose/Route: 4 and 12 mg/kg, 4 weekly doses, IV bolus	There was no difference in tissue glycogen reduction when neoGAA was provided with 5.5 or 7.2 mol/mol sialic acid.

Abbreviations: ADA, antidrug antibodies; F, female; IV, intravenous; M, male; neoGAA, avalglucosidase alfa

13.1.2. Safety Pharmacology

Table 43. Safety Pharmacology Assessment

Study	Findings
Study No.: 0658-11097 Study Title: A 26-week intravenous infusion GLP toxicity study of neoGAA in cynomolgus monkeys Species/Strain: Cynomolgus monkey Number/Sex/Group: 6/sex/group Dose: 50 and 200 mg/kg Route of Administration: IV infusion (6 hours) Dosing Frequency: Every other week (13 doses)	• Safety pharmacology assessment was incorporated into the 26-week toxicity monkey study. • No adverse findings were noted in CNS parameters (activity level, fasciculations, movements of facial muscles and visual field), respiratory rate, core temperatures, and ECG parameters (heart rate, RR, QT, QTc intervals). • NOAEL =200 mg/kg with $AUC_{0\text{-}inf}$ =28162 µg•h/mL (23 times the human safety AUC obtained from the recommended biweekly dose of 20 mg/kg for patients with LOPD)

Source: Study No 0658-11097 study report submitted under module 4.2.3.2
Abbreviations: AUC, area under the curve; CNS, central nervous system; ECG, electrocardiogram; GLP, good laboratory practice; IV, intravenous; NOAEL, no observed adverse effect level

13.1.3. ADME/PK/TK

13.1.3.1. Single-Dose Pharmacokinetics

Table 44. Single-Dose Pharmacokinetics, Studies 08-2344, 10-00813, and 10-05540

Single-dose PK data: GAAKO mouse						
Study no:	08-2344		10-00813		10-05540	
Study design:	GAAKO mouse, IV bolus single dose, 20 mg/kg, N=10 (5M/5F)					
Lot No.: NeoGAA	08-BD-0019		NE006		15679-186-33 (5SA) 15679-186-22/16 (7SA)	
Vehicle:	(b) (4) mannitol (b) (4) Tween-80, pH 6.2 (b) (4)		10mM-L-Histidine, 2% glycine, 2% mannitol, 0.01 Tween-80, pH 6.2		(b) (4) mannitol, (b) (4) Tween-80, pH 6.25	
	Test Article					
PK Parameters	NeoGAA	Alglu	NeoGAA	Alglu	NeoGAA-5SA	NeoGAA-7SA
$AUC_{0\text{-}inf}$ (µg•h/mL)	612	667	317	379	399	467
C_{max} (µg/mL)	569	446	303	326	349	349
$t_{½}$ (hr)	0.61	2.42	0.59	1.78	0.7	0.74
CL (mL/h/kg)	33.3	28.9	65.6	55.0	51.3	44.5
V_z (mL/kg)	29.0	100.0	55.0	65.6	51.4	46.1

Source: Data extracted from studies 08-2344, 10-00813, and 10-05540
Abbreviations: alglu, alglucosidase alfa; AUC, area under the curve; CL, clearance; C_{max}, maximum plasma drug concentration; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; V_z, apparent volume of distribution during terminal phase

In GAAKO mice, significant differences were observed in key pharmacokinetic parameters between avalglucosidase alfa and alglucosidase alfa, following a single 20 mg/kg intravenous administration: These changes were characterized by a decrease in terminal half-life ($t_{½}$) and volume of distribution for avalglucosidase alfa, and a small decrease in exposure, when compared to alglucosidase alfa. In addition, the absorption of avalglucosidase alfa was not impacted when manufactured from alglucosidase alfa containing approximately 5.5 or 7.2 mol/mol sialic acid. Overall, findings from these studies were consistent with those observed

Reference ID: 4836879

in previous studies evaluating alglucosidase alfa and avalglucosidase alfa pharmacokinetics, where systemic exposure was higher following alglucosidase alfa administration.

Single-Dose PK Cross-Species Comparison

In CD-1 mice, following the 1st dose of 4 and 40 mg/kg in repeat-dose study, pharmacokinetic parameters observed were similar to those described above for GAAKO mice following a 20 mg/kg dose, demonstrating that avalglucosidase alfa pharmacokinetics were comparable in the disease model relative to wild-type mice. In addition, saturation kinetics, demonstrated by a prolongation in half-life and increased systemic exposure, with a corresponding decrease in clearance following dose escalation from 4 to 120 mg/kg avalglucosidase alfa, was observed in CD-1 mice (study no. 10-00183).

In monkeys, following the 1st dose in repeat-dose studies, the results established that the elimination half-lives were similar across studies with terminal half-lives of approximately 0.5 and 0.7 hours following administration of 40 and 120 mg/kg avalglucosidase alfa, and approximately 0.5 and 1.4 hours at 50 and 200 mg/kg, respectively. Similar to that in mice, changes in single-dose pharmacokinetic parameters following dose escalation were apparent and were highly suggestive of saturation kinetics (increased half-life and exposure, with decreased clearance) (study nos. 1213-004 and 0658-11097).

The terminal half-life of avalglucosidase alfa appears similar across species. The half-life ranges from approximately 0.5 to 0.74 hours following administration of 4 to 50 mg/kg in both CD-1 mice and cynomolgus monkeys and increases to approximately 1 to 1.5 hours at dose levels between 120 and 200 mg/kg. However, the systemic exposure in cynomolgus monkeys when corrected for dose is slightly lower following 40 and 120 mg/kg avalglucosidase alfa (approximately 20 and 26 µg•h/mL) than that observed in CD-1 mice (approximately 33 and 43 µg•h/mL). This difference in observed exposures may be due to differences in test article administration (IV bolus in mice compared to a 6-hour IV infusion in cynomolgus monkeys

13.1.3.2. Repeat-Dose Pharmacokinetics

Table 45. Repeat-Dose Pharmacokinetics, General Toxicology, Study 10-00183

Study Description	Major Findings
Study title: NeoGAA: 28-Day Pilot Safety Study of NeoGAA Administered Intravenously Every Week to CD-1 Mice Sample collection times: TK timepoints taken at 5, 15, 30 minutes, 1, 2, 4, and 6 hours postdose on 1st and 4th administrations Accumulation: Yes Dose proportionality: No NOAEL: 120 mg/kg, with $AUC_{0\text{-}inf}$ =4513 µg•h/mL based on exclusion of the hypersensitivity reactions, which were observed in all treatment groups (with all positive for ADAs). Safety margin*: 4X * Exposure multiples were based on PK analysis from trial EFC14028, where the maximum clinical dose (20 mg/kg IV every other week in patients with LOPD) resulted in systemic exposure of $AUC_{0\text{-}2w}$ =1230 µg•h/mL	TK parameters were available from only one animal following the 4th administration at 4 mg/kg due to unscheduled deaths. The increase in AUC with dose was disproportionately high. No difference in TK parameters were noted between the 1st and 4th dose. There was no sex difference in exposure. In addition, a dose-dependent increase in $t_{½}$ and a dose-dependent decrease in clearance were observed. These results suggested that the major plasma clearance mechanism, presumably uptake in tissues by CIM6Pr, was saturated at the tested dose levels. There was no gender-related difference.

Da 1 1st IV Dose TK Parameters for the Mouse

Parameter	4 mg/kg (n=5)	40 mg/kg (n=6)	120 mg/kg (n=5)
$t_{1/2}$ (hr)	0.455 ± 0.094	0.767 ± 0.102***	1.23 ± 0.073***,###
CL (mL*kg/hr)	62.2 ± 12.1	30.7 ± 1.06***	23.7 ± 2.83***,###
V_z (mL/kg)	39.6 ± 2.51	33.9 ± 4.66*	41.9 ± 3.38#
C_{max} (µg/mL)	87.6 ± 7.77	942 ± 95.3	2517 ± 203
$AUC_{0\text{-}inf}$ (µg x hr/mL)	66.1 ± 11.5	1306 ± 45.3	5127 ± 611
$AUC_{0\text{-}inf/Dose}$ (µg x hr/mL/Dose)	16.5 ± 2.87	32.7 ± 1.13***	42.7 ± 5.09***,##

Values represent mean ± SD.
* p value <0.05, TK parameter significantly different (4 vs 40 mg/kg)
*** p value <0.001, TK parameter significantly different (4 vs 40 mg/kg and 4 vs 120 mg/kg)
# p value <0.001, TK parameter significantly different (40 vs 120 mg/kg)
p value <0.001, TK parameter significantly different (40 vs 120 mg/kg)
p value <0.001, TK parameter significantly different (40 vs 120 mg/kg)

Da 22 4th IV Dose TK Parameters for the Mouse

Parameter	4 mg/kg (n=1)	40 mg/kg (n=6)	120 mg/kg (n=5)
$t_{1/2}$ (hr)	0.315	0.752 ± 0.242	0.939 ± 0.127$$
CL (mL*kg/hr)	80.0	28.4 ± 8.80	27.0 ± 3.83
V_z (mL/kg)	36.3	29.7 ± 8.46	36.2 ± 4.10$
C_{max} (µg/mL)	68.8	949 ± 161	2866 ± 656
$AUC_{0\text{-}inf}$ (µg x hr/mL)	50.0	1498 ± 368	4513 ± 589
$AUC_{0\text{-}inf/Dose}$ (µg x hr/mL/Dose)	12.5	37.4 ± 9.19	37.6 ± 4.91

Values represent mean ± SD.
$ p value <0.05, TK parameter significantly different (120 mg/kg first vs fourth dose)
$$ p value <0.01, TK parameter significantly different (120 mg/kg first vs fourth dose)

Source: Study 10-00183 study report submitted under module 4.2.3 2.
Abbreviations: ADA, antidrug antibodies; AUC, area under the curve; IV, intravenous; neoGAA, neo alpha-glucosidase; NOAEL, no observed adverse effect level; $t_{1/2}$, terminal half-life; TK, toxicokinetic; V_z, apparent volume of distr bution during terminal phase

Table 46. Repeat-Dose Pharmacokinetics, General Toxicology, Study 1213-004

Study Description	Major Findings
Study title: NeoGAA: A 28-Day Infusion Safety Study in Cynomolgus Monkeys Sample collection times: TK timepoints taken immediately (within 2 mins) following the end of infusion, and 15 and 30 minutes, and 1, 2, 4, 6, 8, and 24 hours after infusion on Days 1 and 22. Accumulation: Yes Dose proportionality: No NOAEL: 120 mg/kg with $AUC_{0\text{-}inf}$ =5900 µg•h/mL Safety margin*: 5X * Exposure multiples were based on PK analysis from trial EFC14028, where the maximum clinical dose (20 mg/kg IV every other week in patients with LOPD) resulted in systemic exposure of $AUC_{0\text{-}2w}$ =1230 µg•h/mL.	Due to the limited serum avalglucosidase alfa concentration data available from the 4 mg/kg dose level, there was no TK data for this dose level. The TK parameters of avalglucosidase alfa were evaluated following the 1st and 4th infusion of 40 and 120 mg/kg. Systemic exposure increased in a greater than dose proportional manner, particularly after the 4th infusion. Values of AUC and C_{max} (from the 4th infusion) were increased relative to those from the 1st infusion. At 40 mg/kg, similar to what was observed in CD-1 mice, there were no significant differences noted between the 1st and 4th infusions. However, at 120 mg/kg, significant differences were noted between 1st and 4th infusions (decreased clearance and increased exposure). The change in TK parameters after repeated dosing may have been related to the presence of antidrug antibodies. Half-life was increased and clearance was decreased with increased dose level. These dose-related changes in TK parameters were only a trend at the 1st infusion but were statistically significant at the 4th infusion. The dose-dependent increase in $t_{½}$ suggested that the major plasma clearance mechanism, presumably uptake in tissues by CIM6Pr (cation-independent mannose 6-phosphate receptor), was saturated at the tested dose levels of avalglucosidase alfa in cynomolgus monkeys. There was no gender-related difference in TK parameters. **Da 1 1st IV Dose TK Parameters for the Monke** **Da 22 4th IV Dose TK Parameters for the Monke**

Da 1 1st IV Dose TK Parameters for the Monke

Parameter	4 mg/kg (n=4)	40 mg/kg (n=4)	120 mg/kg (n=4)
$t_{1/2}$ (hr)	N/A	0.533 ± 0.189	0.729 ± 0.179
Cl (mL/hr)	N/A	53.5 ± 21.5	40.3 ± 10.6
V_z (mL)	N/A	38.4 ± 10.5	44.0 ± 20.2
C_{max} (µg/mL)	N/A	192 ± 63.3	862 ± 302
$AUC_{0\text{-}inf}$ (µg X hr/mL)	N/A	824 ± 260	3155 ± 911
$AUC_{0\text{-}inf/Dose}$ (µg X hr/mL/Dose)	N/A	20.6 ± 6.49	26.3 ± 7.59

Values represent mean ± SD.

Da 22 4th IV Dose TK Parameters for the Monke

Parameter	4 mg/kg (n=4)	40 mg/kg (n=4)	120 mg/kg (n=4)
$t_{1/2}$ (hr)	N/A	0.508 ± 0.184	0.919 ± 0.199*
Cl (mL/hr)	N/A	43.3 ± 8.84	20.5 ± 2.22**, #
V_z (mL)	N/A	33.0 ± 18.5	27.0 ± 6.01
C_{max} (µg/mL)	N/A	258 ± 39.7	1273 ± 214
$AUC_{0\text{-}inf}$ (µg X hr/mL)	N/A	954 ± 202	5900 ± 660 ##
$AUC_{0\text{-}inf/Dose}$ (µg X hr/mL/Dose)	N/A	23.9 ± 5.05	49.2 ± 5.50***, ##

Values represent mean ± SD. Statistics performed below were unpaired t-tests.
* p value <0.05, TK parameter significantly different (40 vs 120 mg/kg fourth infusion)
** p value <0.01, TK parameter significantly different (40 vs 120 mg/kg fourth infusion)
*** p value <0.001, TK parameter significantly different (40 vs 120 mg/kg fourth infusion)
# p value <0.05, TK parameter significantly different (120 mg/kg first vs fourth infusion)
p value <0.01, TK parameter significantly different (120 mg/kg first vs fourth infusion)

Source: Source: Study 1213-004 study report submitted under module 4.2.3.2.
Abbreviations: AUC, area under the curve; Cl, apparent total body clearance of the drug from plasma; C_{max}, maximum plasma drug concentration; IV, intravenous; neoGAA, neo alpha-glucosidase; $t_{1/2}$, terminal half-life; TK, toxicokinetics; V_z, apparent volume of distribution during terminal phase

Table 47. Repeat-Dose Pharmacokinetics, General Toxicology, Study 0658-11097

Study Description	Major Findings
Study title: A 26-week intravenous infusion GLP toxicity study of neoGAA in cynomolgus monkeys Sample collection times: TK timepoints taken at 1st, 7th, and 13th doses (days 1, 85, and 169): predose (within 24 hours), immediately at the end of the infusion, 0.25, 0.5, 1, 2, 4, 6, 8, 24, and 48 hours after the end of infusion. Accumulation: Yes Dose proportionality: No NOAEL: 200 mg/kg, with $AUC_{0\text{-}inf}$ =28162 µg•h/mL, based on reductions in body weight gain (9%) and several organ weights without microscopic findings at 200 mg/kg. Safety margin*: 23X * Exposure multiples were based on PK analysis from trial EFC14028, where the maximum clinical dose (20 mg/kg IV every other week in patients with LOPD) resulted in systemic exposure of $AUC_{0\text{-}2w}$ =1230 µg•h/mL.	TK parameters changed with successive infusions. Following the 1st, 7th, and 13th dose, systemic exposure increased in a greater than dose proportional manner. AUC and C_{max} values from the 7th and 13th infusions were increased relative to those from the first infusion and such time-dependent changes were associated with a statistically significant decrease in clearance. At both the 7th and 13th infusions, these changes were characterized by ~25% increase in half-life, 11% to 52% increase in maximal concentrations and exposure, and 15% to 30% decreases in clearance. These results suggest that the major plasma clearance mechanism, presumably uptake in tissues by CIM6Pr, was saturated at the tested dose levels. There was no gender-related difference in TK parameters. **Day 1 (1st IV Dose) TK Parameters for the Monkey** Parameter / 50 mg/kg (n=12) / 200 mg/kg (n=12) $t_{1/2}$ (hr) / 0.525 ± 0.092 / 1.40 ± 0.209* Cl (mL/hr) / 22.3 ± 6.83 / 10.9 ± 1.59* V_z (mL) / 16.3 ± 3.12 / 21.8 ± 3.38* C_{max} (µg/mL) / 566 ± 157 / 3892 ± 506 $AUC_{0\text{-}inf}$ (µg X hr/mL) / 2423 ± 682 / 18728 ± 2866 $AUC_{0\text{-}inf/Dose}$ (µg X hr/mL/Dose) / 48.5 ± 13.6 / 93.6 ± 14.3* Values represent mean ± SD. *p≤0.05 TK parameter significantly different (50 vs 200 mg/kg) **Day 169 (13th IV Dose) TK Parameters for the Monkey** Parameter / 50 mg/kg (n=10) / 200 mg/kg (n=8) $t_{1/2}$ (hr) / 0.737 ± 0.228 / 1.99 ± 0.240* Cl (mL/hr) / 14.4 ± 4.29 / 7.88 ± 2.44* V_z (mL) / 14.6 ± 3.16 / 22.2 ± 5.84* C_{max} (µg/mL) / 861 ± 189 / 5284 ± 1440 $AUC_{0\text{-}inf}$ (µg X hr/mL) / 3712 ± 977 / 28162 ± 10694 $AUC_{0\text{-}inf/Dose}$ (µg X hr/mL/Dose) / 74.2 ± 19.5 / 141 ± 53.5* Values represent mean ± SD. *p<0.05 TK parameter significantly different (50 vs 200 mg/kg)

Source: Study 06581-11097 study report submitted under module 4.2.3.2.
Abbreviations: AUC, area under the curve; Cl, apparent total body clearance of the drug from plasma; C_{max}, maximum plasma drug concentration; GLP, good laboratory practice; IV, intravenous; LOPD, late-onset Pompe disease; neoGAA, neo alpha-glucosidase; NOAEL, no observed adverse effect level; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; TK, toxicokinetic; V_z, apparent volume of distribution during terminal phase

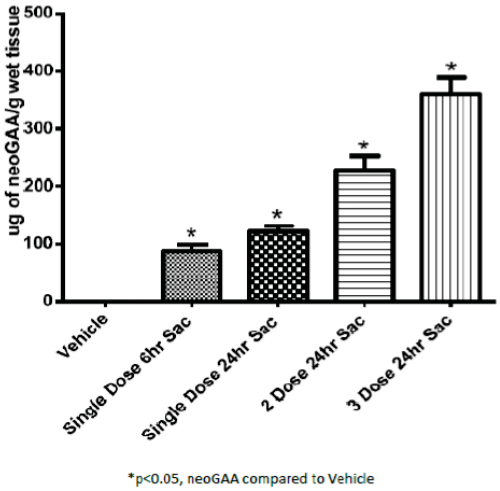
13.1.3.3. Distribution

Table 48. Pharmacokinetics Studies, Distribution, Studies 10-00818 and 09-3559

Study Description	Findings
Study no.: 10-00818 Study title: Biodistribution of rhGAA and neoGAA Following a Single IV Bolus in GAA Knockout Mice. Species/strain: GAAKO mouse Number/sex/group: 6/sex/group Dose: 20 mg/kg Route of administration: Single IV dose	The distribution of avalglucosidase alfa was noted in the liver, heart, and skeletal muscles of GAA knockout mice. The study also demonstrated a similar biodistribution pattern relative to rhGAA. **Percent In ected Dose in Selected Tissues After a Sin le IV Dose**

	Time Point (hours)	Heart	Quadriceps	Liver	Triceps
alglucosidase alfa	1	0.37 ± 0.11	0.04 ± 0.02	51.15 ± 4.38	0.03 ± 0.01
	6	0.22 ± 0.03	0.04 ± 0.01	61.07 ± 3.53	0.02 ± 0.00
	24	0.20 ± 0.02	0.03 ± 0.02	68.36 ± 4.36	0.01 ± 0.01
avalglucosidase alfa	1	0.38 ± 0.11	0.05 ± 0.02	37.91 ± 7.30 *	0.02 ± 0.01
	6	0.30 ± 0.05 *	0.05 ± 0.02	82.35 ± 16.65 *	0.02 ± 0.01
	24	0.32 ± 0.07 *	0.03 ± 0.01	70.57 ± 19.65	0.02 ± 0.01 *

* = p<0.05, avalglucosidase alfa compared to alglucosidase alfa

Study no.: 09-3559 Study title: Biodistribution and Genotoxicity of SAM6-beta Following Single or Multiple IV Bolus Injections in GAA Knockout Mice Species/strain: GAA knockout mouse Number/sex/group: 4/sex/group Dose: 50 mg/kg Route of administration: IV bolus Dosing frequency: Single dose, 2 doses every 4 hours (at time 0 and 4), or 3 doses every 4 hours (at time 0, 4, and 8 hours)	Avalglucosidase alfa distributed, in a dose-dependent manner, to the bone marrow compartment in the GAAKO mouse, supporting the use of the MMN assay to evaluate the potential genetic toxicity of avalglucosidase alfa. **Enzyme Activity of NeoGAA in the Bone Marrow After Single of Multiple Doses** 

Sources: Study 10-00818 study report submitted under module 4.2.2.3 and study 09-3599 study report submitted under module 4.2.2.3.
Abbreviations: GAA, alpha-glucosidase; IV, intravenous; neoGAA, neo alpha-glucosidase; rhGAA, recombinant human acid alpha-glucosidase

13.1.3.4. Metabolism

Nonclinical metabolism studies were not conducted in animals with avalglucosidase alfa. Given that avalglucosidase alfa is a glycoprotein, it is expected to be broken down by the intracellular machinery into small peptides or amino acids for recycling.

13.1.3.5. Elimination and Excretion

No excretion studies have been conducted with avalglucosidase alfa because avalglucosidase alfa is expected to be metabolized by the intracellular machinery into small peptides or amino acids for recycling. Therefore, no drug or metabolites are expected to be excreted.

13.1.3.6. General Toxicology

13.1.3.6.1. Study No. 0658-11097 (A 26-Week Intravenous Infusion GLP Toxicity Study of NeoGAA in Cynomolgus Monkeys)

Key Study Findings

No observed adverse effect level (NOAEL)=200 mg/kg based on the observed effects to reductions in body weight gain (9%) and several organ weights, without microscopic findings, at 200 mg/kg.

Study Information

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 49. Methods, Study 0658-11097

Method	Details
Dose and frequency of dosing:	0 (vehicle), 50, and 200 mg/kg every other week (days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169)
	Design for a 26-Week IV Toxicity Study in Monkeys

Group DEW	Dosage mg/kg	Conc. mg/mL	Terminal Sacrifice		Recovery Sacrifice		Animal No.	
			M	F	M	F	M	F
1	0 (vehicle)	0	4	4	2	2	1-6	19-23
2	50	2.5	4	4	2	2	7-12	25-30
3	200	10	4	4	2	2	13-18	24, 31-37

Animal DEW3F32 was removed alive from study on Day 8 and replaced with animal DEW3F37. DEW3F37 was sacrificed moribund on Day 13 and animal DEW1F24 was moved to the high-dose group.

Route of administration:	IV infusion (6 hours)
Formulation/Vehicle:	10mM L-Histidine, 2% glycine, 2% mannitol, 0.01 Tween-80, pH 6.2
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	4/sex/group (main)
Age:	At least 18 months
Satellite groups/Unique design:	2/sex/group (recovery)
Deviation from study protocol affecting interpretation of results:	None

Source: Study 0658-11097 study report submitted under module 4.2.3.2.
Abbreviation: IV, intravenous

Table 50. Observations and Results, Study 0658-11097

Parameters	Major Findings
Mortality/Clinical signs	2 unscheduled sacrifices (not treatment-related): 1 female at 200 mg/kg/dose was sacrificed on day 13 in a moribund condition prior to dosing, attributed to stress. 1 female at 50 mg/kg/dose was sacrificed on day 168 in a moribund condition with lower body paralysis due to systemic inflammation resulting from contamination of the venous access port.
Body weights/Food consumption	Animals in the 200 mg/kg group showed up to approximately 9% reductions in body weight, body weight gain, and food consumption during the treatment period. Reduced food consumption was more evident in males. The reversibility of these changes was unclear since the recovery groups only had 1 female control and 2 males or females in the 200 mg/kg/dose group
Ophthalmoscopy	No effect
ECG	No effect (heart rate, RR, QT, and QTc intervals)
Safety pharmacology assessment	No effect [CNS parameters (activity level, fasciculations, movement of facial muscles, and visual field), respiratory rate, and core temperatures]
Hematology	No effect
Clinical chemistry	No effect
Urinalysis	Not interpretable due to low number of samples collected.
Gross pathology	No effect
Organ weights	Animals at 200 mg/kg/dose had slight reductions in the absolute weight of several organs, and this effect was dose-dependent in most of these organs. A similar magnitude of reductions in organ weight/body weight ratio and organ weight/brain weight ratio were observed in these organs. **Reductions in Absolute Organ Weights (% Compared to Control Values in Monkeys Treated With 200 mg/kg/dose NeoGAA** **Organ names** / **Group 3 (200 mg/kg/dose)**: **Males** / **Females** adrenal glands: - / -24% epididymes: -23% / - heart: -21% / -15% * kidney: -18% / -10% spleen: - / -17% testes: -16% / - thymus: -27% / -29% thyroid/parathyroid: -18% / -18% *: p< 0.05 At the end of the recovery period, organ weights of epididymis and testes at 200 mg/kg were still lower than the control values (29% and 35%, respectively). In contrast, thymus weight increased by 23% in males in group 3 compared to the control group. No conclusion can be made for female organ weight changes in groups 2 and 3 since there was only one sample available in groups 1 and 2. There were no histopathologic changes in these organs.

Reference ID: 4836879

Parameters	Major Findings
Histopathology Adequate battery: Yes	A variety of vascular or inflammatory findings were observed due to intravenous infusion of avalglucosidase alfa via the implanted femoral catheter and vascular access port (venous access port and/or right/left saphenous veins). These findings included thrombi in the lung, accompanied by inflammation and an occasional fragment of foreign material (catheter), and thrombi, fibrosis, inflammation, and/or hemorrhage in the vein proximal to catheter tip and in the saphenous veins. These findings occurred at comparable incidences in vehicle and test article related monkeys. Thus, there were no test article-related histopathologic changes.
ADA	Positive in all animals treated with avalglucosidase (prior to the 7th infusion and ADA titers increased in the majority of treated animals prior to the 13th infusion when compared to titers at the 7th infusion).

Source: Study 0658-11097 study report submitted under module 4.2.3.2.
Abbreviations: ADA, antidrug antibodies; CNS, central nervous system; neoGAA, neo alpha-glucosidase

13.1.3.6.2. Nonpivotal Studies

Table 51. Nonpivotal General Toxicology Studies

Study No.	Study Details
Study no. FFA00125	14-day exploratory mouse study (50 mg/kg IV bolus injection every other day)
Study no.: 10-00183	28-day pilot mouse study (4, 40, or 120 mg/kg IV bolus injection once a week)
Study no.: 1213-004	28-day monkey study (4, 40, or 120 mg/kg via 6-hour IV infusion once a week)
GLP compliance:	No
Major Findings	
Avalglucosidase alfa was generally well tolerated in both mice and monkeys. Hypersensitivity reactions to this human protein were sometimes noted, most notably in mice, which necessitated pretreatment of mice with diphenhydramine (DPH). In the 14-day mouse study, there were macroscopic observations in the testes, epididymides, and liver. Microscopic evaluations were not performed in this study. However, findings in these organs were not observed in subsequent studies in either mice (28-days repeat-dose study at 120 mg/kg/week; fertility study at 50 mg/kg every other day) or monkeys (28-day repeat-dose study at 120 mg/kg/week; 26-week repeat-dose study at 200 mg/kg every other week). As such, the relationship of the macroscopic finding effects to avalglucosidase alfa in the 14-day exploratory study was considered unlikely.	

Source: Study reports submitted under module 4.2.3.2.
Abbreviations: GLP, good laboratory practice; IV, intravenous

13.1.3.7. Genetic Toxicology

Table 52. Genetic Toxicology Studies

Study No./Study Title	Key Study Findings
Study no.: 09-3559 Study title: Biodistribution and genotoxicity of SAM6-beta following single or multiple IV bolus injection in GAA knockout mice Dose-tested: 0 (vehicle) or 50 mg/kg avalglucosidase alfa (neoGAA) Treatment duration: 1) Single dose: IV injection at Hour 0, necropsy at 24 hours, 2) Single dose: IV injection at Hour 0, necropsy at 24 hours, 4) Two doses: IV injection at Hours 0 and 4, necropsy at 24 hours, 5) Three doses: IV injection at Hours 0, 4, and 8, necropsy at 24 hours. GLP compliance: No Study is valid: Yes	The administration of 1-3 doses of avalglucosidase alfa at 50 mg/kg (up to 150 mg/kg cumulative dose) did not increase the percentage of micronucleated reticulocytes (MN-RET) or micronucleated normochromatic erythrocytes (MN-NCE) compared to the kit positive control compound. The percentage of MN-RET and MN-NCE was comparable to the kit negative control.
Study no.: 10-00184 Study title: 2-week repeat dose genotoxicity study of neoGAA administered intravenously to GAAKO mice Dose-tested: 0 (vehicle) or 50 mg/kg avalglucosidase alfa (neoGAA) Treatment duration: 3 doses over an 8-hour period (0, 4, 8 hours), The mice were euthanized on Days 8 and 15. Note: The Applicant noted that neoGAA may take greater than 24 hours to be metabolized following uptake into tissues and cells, and this metabolism may be necessary for the glycan/linker to be liberated in vivo. Therefore, to evaluate the potential of neoGAA to induce micronuclei formation over time, this study was conducted to evaluate micronuclei formation 7 and 14 days. Following euthanasia, blood was collected for micronucleus analysis using the MicroFlow® assay GLP compliance: No Study is valid: Yes	Avalglucosidase alfa at doses of 50 mg/kg/dose, administered at 0, 4, and 8 hr on day 1, did not increase the number of MN-RET or MN-NCE at 7 or 14 days following the day of treatment, compared to the vehicle group and the negative control provided with the kit.

Source: Study reports submitted under module 4.2.3.3.2.
Abbreviations: GLP, good laboratory practice; IV, intravenous; neoGAA, neo alpha-glucosidase

13.2. Individual Reviews of Studies Submitted to the BLA

13.2.1.1. ADME/TK

Table 53. Juvenile Toxicology Study Review, Study JUV0033

Study Description	Major Findings
Study title: GZ402666 (neoGAA): Intravenous 9-week toxicity study in juvenile mice with a 4-week recovery period Sample collection times: TK timepoints taken on PND 77 approximately 5, 15 and 30 minutes; and 1, 2, 4, 6 and 24 hours postdose. Accumulation: Yes Dose proportionality: No NOAEL: 100 mg/kg with AUC_{0-24}=8100 (M) and 5400 (F) µg•h/mL Safety margin*: 2–4X * Exposure multiples were based on pharmacokinetics analysis from Study No. ACT14132, where the maximum clinical dose (40 mg/kg IV every other week in patients with IOPD) resulted in systemic exposure of AUC_{0-2w} =2200 µg•h/mL.	After repeated administrations of avalglucosidase alfa, C_{max} increased roughly in a dose proportional manner, while the AUC_{0-24} increased in a more than dose-proportional manner over the dose range of 20 to 100 mg/kg. The maximum concentrations were mostly observed at 0.083 h (first sampling time after the intravenous bolus injection) based on the composite serum concentration profiles. Over the 5-fold dose range of 20 to 100 mg/kg, C_{max} increased by 5.88-fold (females) and 5.11-fold (males); AUC_{0-24} increased by 11.5-fold (females) and 14.8-fold (males). In addition, avalglucosidase alfa exposure appeared to be generally lower in females, with female/male AUC_{0-24} ratios ranging from 0.548 to 0.853. **PND77 TK Parameters for the Mouse** Sex | Dose (mg/kg) | PND[a] | t_{max} (h) | C_{max} (µg/mL) | AUC_{0-24} (µg.h/mL) | AUC/Dose[b] | R_{AUC} f/m Male | 20 | 77 | 0.083 | 611 | 550 | 27.5 | NA Male | 50 | 77 | 0.083 | 1750 | 2730 | 54.5 | NA Male | 100 | 77 | 0.25 | 3120 | 8140 | 81.4 | NA Female | 20 | 77 | 0.083 | 422 | 469 | 23.4 | 0.853 Female | 50 | 77 | 0.25 | 1170 | 1490 | 29.9 | 0.548 Female | 100 | 77 | 0.083 | 2480 | 5400 | 54.0 | 0.664 [a] PND: postnatal day. [b] unit is µg/h/kg/mL.mg f: female; m: male; NA: not applicable Most values are rounded to 3 significant figures

Source: Study JUV0033 study report submitted under module 4.2.3.5.4.
Abbreviations: AUC, area under the curve; IOPD, infantile-onset Pompe disease; IV, intravenous; NOAEL, no observed adverse effect level; PND, postnatal day; TK, toxicokinetic

Table 54. Reproductive Toxicology Study Review, Study TER0685

Study Description	Major Finding
Study title: GZ402666 (NeoGAA): Intravenous Embryo-Fetal Toxicity Study in Mice Sample collection times: TK timepoints taken at 5, 15 and 30 minutes, 1, 2, 4, 6, and 24 hours after dosing at GD 6. Accumulation: --	Both GZ402666 C_{max} and AUC_{0-24} increased in a greater than dose-proportional manner. Over the 5-fold dose range of 10 to 50 mg/kg/day, C_{max} increased by 9.90-fold and AUC_{0-24} increased by 12.8-fold. **Mouse EFD TK Parameters, GD 6** Sex: Female; GD: 6; GZ402666 Dose (mg/kg/day): 10; C_{max} (µg/mL): 145; AUC_{0-24} (µg.h/mL): 163 Sex: Female; GD: 6; GZ402666 Dose (mg/kg/day): 20; C_{max} (µg/mL): 454; AUC_{0-24} (µg.h/mL): 582 Sex: Female; GD: 6; GZ402666 Dose (mg/kg/day): 50; C_{max} (µg/mL): 1440; AUC_{0-24} (µg.h/mL): 2080 Values are rounded to 3 significant figures
Dose proportionality: Greater NOAEL (developmental toxicity): 20 mg/kg, with AUC_{0-24}=582 µg•h/mL, based on maternal toxicity related to an immunologic response (including anaphylactoid response), and postimplantation loss and late resorptions at 50 mg/kg/day. Safety margin*: <1X * Exposure multiples were based on pharmacokinetics analysis from trial EFC14028, where the maximum clinical dose (20 mg/kg IV every other week in patients with LOPD) resulted in systemic exposure of AUC_{0-2w} =1230 µg•h/mL.	There was a dose-dependent increase in avalglucosidase alfa concentration in the maternal liver and placenta with no concurrent increase in the fetal liver on GD 18, suggesting that avalglucosidase alfa is not transported from the maternal to the fetal circulation. **Summary of GZ402666 (NeoGAA) Concentrations(µg/g) in CD-1 Mouse Maternal Liver Tissues** GROUP: 1; DOSE: 0; n: 10; MIN: 10.645; MAX: 20.037; MEAN: 16.421; STDEV: 2.795 GROUP: 2; DOSE: 0; n: 10; MIN: 11.882; MAX: 19.022; MEAN: 15.191; STDEV: 2.881 GROUP: 3; DOSE: 10; n: 10; MIN: 134.685; MAX: 301.758; MEAN: 194.995; STDEV: 53.587 GROUP: 4; DOSE: 20; n: 10; MIN: 253.563; MAX: 479.573; MEAN: 350.596; STDEV: 67.324 GROUP: 5; DOSE: 50; n: 10; MIN: 736.684; MAX: 1406.870; MEAN: 887.593; STDEV: 194.537

Source: Study TER0685 study report submitted under module 4.2.3.5.2.
Abbreviations: AUC, area under the curve; EFD, embryo-fetal development; GD, gestation day; IV, intravenous; LOPD, late-onset Pompe disease; neoGAA, neo alpha-glucosidase; NOAEL, no observed adverse effect level; TK, toxicokinetic

Table 55. Reproductive Toxicology Study Review, Study TER0686

Study Description	Major Findings
Study title: GZ402666 (NeoGAA): Intravenous Embryo-Fetal Toxicity Study in Rabbits Sample collection times: TK timepoints taken on GD 6 and 19 at the end of infusion (during the last 1 minute of infusion), 5 and 20 minutes, and 1, 2, 4, 6, and 24 hours after dose administration. Accumulation: No Dose proportionality: Greater NOAEL (developmental toxicity): 100 mg/kg with AUC_{0-24}=7910 µg•h/mL Safety margin*: 6X * Exposure multiples were based on pharmacokinetics analysis from trial EFC14028, where the maximum clinical dose (20 mg/kg IV every other week in patients with LOPD) resulted in systemic exposure of AUC_{0-2w} =1230 µg•h/mL.	Following IV infusion of avalglucosidase alfa, serum avalglucosidase alfa concentrations were measurable in all animals from the end of infusion to 6 hours postinfusion on GD 6. On GD 19, serum avalglucosidase alfa concentrations were generally measurable from end of infusion through 4 hours postinfusion at 30 mg/kg/day, at 6 hours postinfusion at 60 mg/kg/day, and at 24 hours postinfusion at 100 mg/kg/day. Exposure to avalglucosidase alfa, in terms of AUC_{0-24} and C_{max}, increased in a near to greater than dose-proportional manner over the 30 to100 mg/kg/day dose range. Specifically, an approximate 3-fold increase in dose resulted in approximate 4- and 6-fold increases in AUC_{0-24} on GD 6 and GD 19, respectively, and in a 3-fold increase in C_{max} on both evaluation days. **Rabbit EFD TK Parameters, GD 6 and GD 19**

Dosage Level (mg/kg/day)	AUClast (µg*h/mL)	AUC0–24 (µg*h/mL)	Cmax (µg/mL)	Tmax[a] (h post-infusion)
Gestation Day 6				
30	2040	2160	991	0.083
60	3920	4330	1830	0.083
100	7240	8110	3220	0.083
Gestation Day 19				
30	1230	1260	772	0.083
60	3180	3310	1530	0.083
100	7920	7910	2530	0.083

[a] Tmax values presented as median.

Source: Study TER0686 study report submitted under module 4.2.3.5.2.
Abbreviations: AUC, area under the curve; EFD, embryo-fetal development; GD, gestation day; IV intravenous; LOPD, late-onset Pompe disease; neoGAA, neo alpha-glucosidase; TK, toxicokinetic

13.2.1.2. Carcinogenicity

No studies were conducted to evaluate the carcinogenic potential of avalglucosidase alfa. The Applicant provided a carcinogenicity risk assessment for avalglucosidase alfa (as described below) and concluded that there would be minimal risk of exposure to hydrazine and hydrazine-containing compounds following administration of avalglucosidase alfa.

- An evaluation of avalglucosidase alfa nonclinical toxicity from (1) repeat-dose toxicity studies in mice and monkeys, and (2) an exploratory in vivo genotoxicity study in mice. Considerations were given to the potential for hypersensitivity reactions, including anaphylactoid, in mice administered a humanized product such as avalglucosidase alfa, regarding the feasibility of conducting long-term carcinogenicity studies.
- A review of the marketed Pompe drugs Myozyme and Lumizyme and any relationship to tumor development or cancer as per (1) clinical trials, (2) epidemiology data, (3) global pharmacovigilance database, (4) external databases, and (5) published literature.

- A review of [redacted] (b) (4) impurity [redacted] (b) (4) genotoxicity search, (2) the published literature, (3) a repeat-dose toxicity study of avalglucosidase alfa spiked with elevated [redacted] (b) (4) concentrations in monkeys, and (4) in vitro genotoxicity studies on [redacted] (b) (4).
- The potential release of the linker moiety of Genz-669342 and other hydrazine containing compounds in an administered dose of avalglucosidase alfa was evaluated in terms of the carcinogenic potential of avalglucosidase alfa (under clinical pharmacology studies). The calculated maximal theoretical amount of linker in a 20 mg/kg dose of avalglucosidase alfa (21.6 µg/kg/dose) was within the acceptable limit of lifetime adjusted acceptable intake of Genz-669342 linker (25.8 µg/kg per dose). In addition, in vitro metabolism studies showed that avalglucosidase alfa and Genz-669342 did not form Genz-669342 linker and other hydrazine containing compounds after incubation in human hepatocytes.

13.2.1.3. Reproductive Toxicology

13.2.1.3.1. Study No. FER0511 (Intravenous Male and Female Fertility Study in Mice)

Key Study Findings

There were deaths in all groups treated with avalglucosidase alfa, attributable to immunologic response (including an anaphylactoid response). No other adverse effects were observed. NOAEL =50 mg/kg/dose.

Study Information

Conducting laboratory and location: [redacted] (b) (4)

GLP compliance: Yes

Table 56. Methods, Reproductive and Developmental Toxicology (Fertility and Early Embryonic Development), Study FER0511

Methods	Details
Dose and frequency of dosing:	0 (vehicle), 0 (vehicle/DPH), 10, 20, or 50 mg/kg/dose every other day
Route of administration:	Intravenous bolus injection
Formulation/Vehicle:	10mM histidine pH 6.2 [redacted] (b) (4) 0.01% Tween 80, 2% mannitol, 2% glycine
Species/Strain:	Crl:CD1 (ICR) mouse
Number/Sex/Group:	22/sex/group
Satellite groups:	--
Study design:	This study determined the effects of GZ402666 (avalglucosidase alfa, neoGAA) on mating performance, fertility and early embryonic development of male and female mice when administered intravenously every other day prior to cohabitation (males: 10 weeks, females: 2 weeks), through mating and conception, to gestation day (GD) 7. Cesarean-section of the mice was performed at midgestation on GD 14. The following parameters and endpoints were evaluated for mice in this study: viability, clinical observations, body weights, body weight gains, food consumption, estrous cycle evaluation, cohabitation/mating, ovarian and uterine examinations, male reproductive assessments (sperm motility and

concentration), organ weights, gross necropsy findings and histopathologic examinations.

Group Information, Study FER0511

Group No.	Test Material	Dose Level (mg/kg/dose)	Concentration (mg/mL)	Dose Volume (mL/kg)	Route of Administration	No. of Animals	
						Males	Females
1	Control Article[a]	0	0	10	IV injection[b]	22	22
2	Control Article[a]/DPH[c]	0/5	0/5	10/1	IV injection[b]/ IP injection[d]	22	22
3	GZ402666[c]	10	1/5	10/1	IV injection[b]/ IP injection[d]	22	22
4	GZ402666[c]	20	2/5	10/1	IV injection[b]/ IP injection[d]	22	22
5	GZ402666[c]	50	5/5	10/1	IV injection[b]/ IP injection[d]	22	22

[a] Control article (10 mM Histidine pH 6.2 (b) (4) 0.01% Tween 80, 2% Mannitol, 2% Glycine)
[b] Intravenous administration by bolus.
[c] Diphenhydramine Hydrochloride was administered following Dose #6 for males and Dose #2 for females (see Appendix 1 - Protocol, Amended Protocol, and Deviations).
[d] Intraperitoneal injection for DPH administration only.

Deviation from study protocol affecting interpretation of results:	No

Source: Study FER0511 study report submitted under module 4.2.3.5.1.

Table 57. Observations and Results, Study FER0511

Parameters	Major Findings
Mortality	For males, there were 4, 7, and 3 animals that were found dead following dosing in the 10, 20, and 50 mg/kg/dose groups, respectively. These deaths occurred between 3 minutes and 1 hour and 40 minutes post dose administration in conjunction with adverse clinical observations and were considered related to avalglucosidase alfa (GZA402666) administration and to an immunologic response (including an anaphylactoid response).

Mortality in Male Mice, Study FER0511

Mortality - Males

Animal No.	Dose (mg/kg/dose)	Study Day (DS)	Time of Death Postdose	Clinical Observations Prior to Death
5152	10	11	36 minutes	-
5159	10	105	8 minutes	Decreased motor activity (DS 11); Labored breathing (DS 105)
5160	10	13	1 hour 12 minutes	Decreased motor activity, low carriage (DS 11, DS 13), tremors (DS 11), ataxia, labored breathing (DS 13)
5166	10	9	1 hour 33 minutes	-
5168	20	9	1 hour 39 minutes	-
5170	20	9	1 hour 39 minutes	-
5180	20	9	1 hour 36 minutes	-
5182	20	13	1 hour 7 minutes	Decreased motor activity (DS 9)
5183	20	9	1 hour 39 minutes	-
5184	20	27	3 minutes	Hunched posture (DS 13)
5185	20	9	1 hour 40 minutes	-
5190	50	9	1 hour 38 minutes	-
5198	50	9	1 hour 36 minutes	Decreased motor activity (DS 9)
5210	50	9	1 hour 33 minutes	-

- = Not Applicable

For females, there were 2, 3, and 1 animals that were found dead following dosing in the 10, 20, and 50 mg/kg/dose groups, respectively. These deaths occurred within 1 hour and 2 minutes post dose administration of avalglucosidase alfa and were considered related to avalglucosidase alfa administration and to an immunologic response (including an anaphylactoid response) based on the observed adverse clinical observations or time of death following avalglucosidase alfa administration. One female at 20 mg/kg/dose was euthanized on day of study 9 (DS 9) due to adverse clinical observations following dose administration.

Parameters	Major Findings
	Mortality in Female Mice, Study FER0511

Mortality - Females

Animal No.	Dose (mg/kg/dose)	Study Day (DS) or Gestation Day (GD)	Time of Death Postdose	Clinical Observations Prior to Death
5361	10	DS 9	55 minutes	Decreased motor activity (DS 9)
5362	10	DS 9	17 minutes	-
5370	20	DS 9	44 minutes	Decreased motor activity (DS 9)
5375	20	DS 9	17 minutes	-
5382[a]	20	DS 9	3 hours 34 minutes	Decreased motor activity, ataxia, labored breathing, lost righting reflex (DS 9)
5384	20	DS 11	Within 15 minutes following dose administration	Decreased motor activity, lost righting reflex (DS 11)
5410	50	GD 7	1 hour 2 minutes	Decreased motor activity, ataxia (DS 11)

- = Not Applicable
[a] Euthanized on DS 9 following dose administration due to adverse clinical observations.

Clinical signs	For males, clinical signs were generally limited to the mice that were found dead, and included decreased motor activity, low carriage, tremors, ataxia, and labored breathing. Other clinical observations considered related to avalglucosidase alfa administration included hyperreactivity to touch at 50 mg/kg/dose and hunched posture in all avalglucosidase alfa groups. For females, clinical signs were generally limited to the mice that were found dead or euthanized due to adverse signs, and included decreased motor activity, ataxia, and loss of righting reflex. Other clinical observations in the treated females considered related to avalglucosidase alfa administration included hyperreactivity to touch.
Body weights	No effect
Gross pathology	No effect
Organ weight	For males, no test article-related effects were noted on terminal body weights or the absolute and relative weights of the male reproductive organs (i.e., prostate, seminal vesicles, and testes). For females, no test article-related effects were noted on terminal body weights or the absolute and relative weights of the ovaries at any dose level.
Histopathology	No test article-related microscopic findings were noted in the testes or epididymides
Fertility	No effect on days in cohabitation, mating index, or fertility
Pregnancy and c-section data	No effect on pregnancy, resorption, corpora lutea, implantations, live fetuses
Sperm evaluation	No effect on sperm motility and sperm density

Source: Study FER0511 study report submitted under module 4.2.3.5.1.

13.2.1.3.2. Study No. FER0685 (GZ402666 (NeoGAA): Intravenous Embryo-Fetal Toxicity Study in Mice)

Key Study Findings

Two mice at 50 mg/kg/day were found dead on gestation day 14, attributed to an immunologic response (including an anaphylactoid response). Two deaths at 10 mg/kg/day were related to the blood collection procedure. Increased postimplantation loss and mean number of late resorptions were observed at 50 mg/kg/day. Such embryofetal effects were likely due to maternal toxicity

relating to the immunologic response. NOAEL (maternal)=50 mg/kg/day. NOAEL (developmental)=20 mg/kg/day.

Study Information

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 58. Study Methods, Reproductive and Developmental Toxicology (Embryonic and Fetal Development), Study FER0685

Methods	
Dose and frequency of dosing:	0 (vehicle), 0 (vehicle/DPH), 10, 20, and 50 mg/kg/day from GDs 6–15
Route of administration:	IV bolus injection
Formulation/Vehicle:	10mM Histidine pH 6.2 (b) (4) 0.01% Tween 80, 2% mannitol, 2% glycine
Species/Strain:	Crl:CD (ICR) mouse
Number/Sex/Group:	22/group
Satellite groups:	TK phase
Study design:	Female mice were administered the control article (groups 1 and 2), or the test article formulations (groups 3 through 5) via intravenous (bolus) injection to the lateral tail vein once daily on GDs 6 through 15. The following parameters and end points were evaluated: viability, clinical signs, maternal body weights, maternal body weight changes, gross observations, ovarian and uterine contents, maternal and fetal tissue analysis, fetal viability, fetal sex, fetal body weights, and fetal external, visceral, and skeletal morphology. Blood samples were collected from toxicokinetic animals at 5, 15 and 30 minutes, and 1, 2, 4, 6, and 24 hrs after the GD 6 dose to determine concentration of GZ402666 (neoGAA).

Group Information, Study FER0685

Group No.	Test Material	Dose Level (mg/kg/day)	Concentration (mg/mL)	Dose Volume (mL/kg)	Route of Administration	No. of Animals Assigned	
						Main Study	TK Phase[d]
1	Control Article[a]	0	0	10	IV injection[b]	22	9
2	Control Article/DPH[c]	0/5	0/5	10/1	IV injection[b]	22	-
3	GZ402666	10	1	10	IV injection[b]	22	20
4	GZ402666	20	2	10	IV injection[b]	22	20
5	GZ402666	50	5	10	IV injection[b]	22	20

DPH = Diphenhydramine Hydrochloride
[a] Control article (10 mM Histidine pH 6.2 (b) (4) 0.01% Tween 80, 2% Mannitol, 2% Glycine)
[b] Intravenous administration by bolus.
[c] Group 2 was included in the study as a control for intraperitoneal DPH administration, should it have been required to counteract signs of anaphylaxis that may have occurred following dose administration in Groups 3 through 5. However, no signs of anaphylaxis were observed and it was not necessary to administer DPH.
[d] Toxicokinetic (TK) animals were used for TK evaluation only.

Deviation from study protocol affecting interpretation of results:	No

Source: Study FER0685 study report submitted under module 4.2.3.5.2.
Abbreviations: DPH, diphenhydramine; GD, gestation day; IV, intravenous; neoGAA, neo alpha-glucosidase; TK, toxicokinetic

Table 59. Observations and Results, Study FER0685

Parameters	Major Findings
F0 dams	
Mortality	No test article-related mortality
Clinical signs	The only test article-related clinical sign was decreased activity in a limited number of mice in the 10, 20, and 50 mg/kg/day groups (1, 3, and 2 mice on 1, 3, and 5 occasions, respectively). Since this occurred in a limited number of mice and did not appear in a dose-dependent manner, this effect was not considered adverse. Injection site observations of swollen tail (soft or hard) and purple skin on the tail, occurred in all groups, including the controls.
Body weights	No effect
Histopathology	No effect
C-section data (GD 18)	Cesarean-sectioning observations (ovarian and uterine examinations and litter observations) were based on 22, 21, 20, 21, and 20 pregnant females in the 0 (control group 1), 0 (control group 2), 10, 20, and 50 mg/kg/day groups, respectively. Fetal evaluations were based on 282, 287 264, 270, and 249 live, GD 18 cesarean-delivered fetuses in 22, 21, 20, 21, and 20 litters in the 0, 0, 10, 20, and 50 mg/kg/day dose groups, respectively. In the 50 mg/kg/day group, there were 2 mice, with 62.5% and 78.6% postimplantation loss, respectively. While the percent postimplantation loss for the 50 mg/kg group (15.68%) is within the Testing Facility Historical Control Data range for definitive studies (3.9% to 23.2%), there were more mice in this group with greater than 10% postimplantation loss compared to any other test article group, or control group. In addition, the mean number of late resorptions in this group (1.4) was increased and outside of the Testing Facility Historical Control Data range for definitive studies (mean 0.2; range 0.0 to 0.5). Based on the number of mice in this group with increased percent of postimplantation loss, and the higher mean number of late resorptions, this was considered treatment-related. There were no effects on the mean numbers of corpora lutea, number of implants, percent preimplantation loss, number of live and dead fetuses, percent male fetuses per litter, and fetal body weights up to 50 mg/kg/day. Total and female fetal body weights were significantly reduced ($p \leq 0.05$ or $p \leq 0.01$) as compared to Group 1 in the 20 mg/kg/day dose group, but these changes were not considered to be test article-related because they were not dose dependent.
F1 offspring	
Fetal examination	Each of these fetuses was examined for gross external abnormalities. Of these respective fetuses, 134, 136, 128, 131, and 119 fetuses were examined for visceral abnormalities, and 148, 151, 136, 139, and 130 fetuses were examined for skeletal abnormalities and fetal ossification site averages. <u>External</u>: No test article-related findings. Malformations were observed in a limited number of fetuses across all groups and included open eyes, cleft palate, and malrotated hindlimb. There was one fetus with multiple malformations, including gastroschisis, in the 20 mg/kg/day group.

Parameters	Major Findings
	Visceral (Wilson): No test-article-related findings. Malformations were observed in a limited number of fetuses across all groups and included one fetus with absent lens in the 10 mg/kg/day group, one fetus with misshapen liver (corresponding to the finding of gastroschisis) and cleft palate in the 20 mg/kg/day group, and hermaphroditism in one fetus in the 50 mg/kg/day group. Skeletal: No test article-related findings. There were no malformations observed in any of the groups. Variations were observed across all groups and did not occur in a dose dependent manner. Fetal ossification: No test article-related findings. No statistically significant or biologically important differences among the dose groups in the average numbers of ossification sites per fetus for the hyoid, cervical, thoracic, lumbar, sacral, and caudal vertebrae, ribs, manubrium, sternal centra, xiphoid, carpals, metacarpals, or tarsals, and forelimb or hindlimb phalanges. A decrease in mean tarsal counts was observed in the 10 and 20 mg/kg/day groups but did not occur in a dose dependent-manner, and the 50 mg/kg/day group was comparable to the control value.

Source: Study report submitted under module 4.2.3.5.2.
Abbreviation: GD, gestation day

13.2.1.3.3. Study No. FER0686 (GZ402666 (NeoGAA): Intravenous Embryo-Fetal Toxicity Study in Rabbits)

Key Study Findings

Reduced body weight and food consumption were noted in 60 and/or 100 mg/kg/day treatment groups. There were no effects on intrauterine growth or survival. No malformations or abnormal developmental variations were observed. NOAEL (maternal)=30 mg/kg/day. NOAEL (fetal)=100 mg/kg/day.

Study Information

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 60. Study Methods, Reproductive and Developmental Toxicology (Embryonic and Fetal Development), Study FER0686

Methods	
Dose and frequency of dosing:	0, 30, 60, and 100 mg/kg/day from GDs 6–19
Route of administration:	Intravenous infusion
Formulation/Vehicle:	10mM histidine (pH 6.2 (b) (4)), 0.01% (v/v) Tween® 80, 2% (w/v) mannitol, 2% (w/v) glycine
Species/Strain:	New Zealand white rabbit
Number/Sex/Group:	24/group
Satellite groups:	TK (3/group)

Methods	
Study design:	GZ402666 (neoGAA) in the control article (also known as neoGAA control article) was administered by an intravenous infusion (over approximately 10 minutes) to 3 groups of 24 rabbits once daily from Gestation Days (GDs) 6–19. All animals were observed twice daily for mortality and moribundity. Clinical observations, body weights, and food consumption were recorded at appropriate intervals. On GD 29, a laparohysterectomy was performed on each surviving female. The uteri, placentae, and ovaries were examined, and the numbers of fetuses, early and late resorptions, total implantations, and corpora lutea were recorded. Gravid uterine weights were recorded, and net body weights and net body weight changes were calculated. The fetuses were weighed, sexed, and examined for external, visceral, and skeletal malformations and developmental variations.

Group Information, Study FER0686

Group No.	Treatment	Dosage level (mg/kg/day)	Test article concentration (mg/mL)	Number of females	
				Main study	Toxicokinetic phase
1	Control Article	0	0	24	3
2	GZ402666 (neoGAA)	30	3	24	3
3	GZ402666 (neoGAA)	60	6	24	3
4	GZ402666 (neoGAA)	100	10	24	3

Deviation from study protocol affecting interpretation of results:	No

Source: Study FER0686 final study report in module 4.2.3.5.2.
Abbreviations: GD, gestation day; GLP, good laboratory practice; neoGAA, neo alpha-glucosidase; TK, toxicokinetics

Table 61. Observations and Results, Study FER0686

Parameters	Major Findings
F0 dams	
Mortality	No treatment-related mortality
Clinical signs	No treatment-related clinical signs
Body weights	Slightly lower mean body weight gains (26.3% and 23.1%) were noted in the 60 and 100 mg/kg/day groups, respectively, during GD 13–20 compared to the control group, including a significant ($p<0.05$) mean body weight loss of 6 g in the 100 mg/kg/day group during GD 19–20; the other differences were not statistically significant. These changes in the 60 and 100 mg/kg/day groups were considered test article-related and adverse. However, mean net body weights, net body weight changes, and gravid uterine weights in the 60 and 100 mg/kg/day groups were generally comparable to the control group. Mean body weights and body weight gains throughout the study, net body weight, net body weight change, and gravid uterine weight in the 30 mg/kg/day group were unaffected by test article administration.
Feed consumption	Lower mean food consumption was noted in the 60 and 100 mg/kg/day groups during GD 13–20 and when the entire treatment period (GD 6–20) was evaluated; the differences were generally significant ($p<0.05$ or $p<0.01$). The effect on food consumption in these groups corresponded to lower mean body weight gains and was therefore considered test article-related and adverse. However, the decreases did not occur in a dose-related manner or result in statistically significantly lower mean absolute body weights.

Reference ID: 4836879

Parameters	Major Findings
Necropsy GD 29 Gross pathology	No effect.
Cesarean section data	No effect
F1 offspring	
Fetal examination	No test article-related external, visceral and skeletal findings

Source: Study FER0686 final study report in module 4.2.3.5.2.
Abbreviation: GD, gestation day

13.2.1.3.4. Study No. DPN0378 (GZ402666 (NeoGAA): Intravenous (IV) Pre- and Postnatal Developmental Toxicity Study in Mice

Key Study Findings

No adverse effects were noted. NOAEL (maternal)=50 mg/kg. NOAEL (offspring)=50 mg/kg.

Study Information

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 62. Study Methods, Reproductive and Developmental Toxicology (Prenatal and Postnatal Development), Study DPN0378

Methods	
Dose and frequency of dosing:	0 (saline), 0 (vehicle), 10, 20, and 50 mg/kg once every other day from GD6–LD19
Route of administration:	Intravenous bolus injection
Formulation/Vehicle:	10mM histidine (pH 6.2 (b) (4), 0.01% (v/v) Tween® 80, 2% (w/v) mannitol, 2% (w/v) glycine
Species/Strain:	Crl: CD1 mouse
Number/Sex/Group:	25/group
Satellite groups:	--
Study design:	F0 generation female mice were administered the control article (groups 1 and 2), or the test article formulations (groups 3 through 5) via intravenous (bolus) injection to the lateral tail vein once every other day on gestation day (GD) 6 through GD 22 (mice that did not deliver a litter) or day 19 or 20 postpartum (mice that delivered a litter). Any dam in the process of parturition was not given the test article or control article until the day following scheduled dose administration. Mice that delivered on GD 17 or 19, or mice that were not dosed on GD 18 because they were in the process of parturition received the next dose on LD 1 and continued to be dosed on lactation day (LD) 3, 5, 7, 9, 11, 13, 15, 17 and 19. Mice that were dosed and delivered on GD 18 received the next dose on LD 2 and continued to be dosed on LD 4, 6, 8, 10, 12, 14, 16, 18, and 20. Dams were dosed up to, but not past LD 20.

Methods

Doses were adjusted based on the most recently recorded body weight and administered at approximately the same time each day.

The following parameters were evaluated for the F0 generation: viability, clinical observations, body weight, body weight gains, natural delivery observations, maternal observations, ovarian and uterine examinations, and gross necropsy observations.

Group Information, Study DPN0378

Group No.	Test Material	Dose Level (mg/kg/dose)	Concentration (mg/mL)	Dose Volume (mL/kg)	Route of Administration	No. of Females
1	Control Article[a]/Saline[e]	0/0	0	10/1	IV injection[b]/ IP injection[e]	25
2	Control Article[a]/ DPH[c]	0/5	0/5	10/1	IV injection[b]/ IP injection[d]	25
3	GZ402666/ DPH[c]	10/5	1/5	10/1	IV injection[b]/ IP injection[d]	25
4	GZ402666/ DPH[c]	20/5	2/5	10/1	IV injection[b]/ IP injection[d]	25
5	GZ402666/ DPH[c]	50/5	5/5	10/1	IV injection[b]/ IP injection[d]	25

[a] Control article (10 mM Histidine pH 6.2 (b) (4) 0.01% Tween 80, 2% Mannitol, 2% Glycine)
[b] Intravenous administration by bolus.
[c] Diphenhydramine Hydrochloride, as outlined in Section 4.7.1.1, F0 Generation.
[d] Intraperitoneal injection for DPH administration as outlined in Section 4.7.1.1, F0 Generation.
[e] Intraperitoneal injection for Saline administration, as outlined in Section 4.7.1.1, F0 Generation.

Deviation from study protocol affecting interpretation of results: No

Source: Study DPN0378 final study report in module 4.2.3.5.3
Abbreviations: GD, gestation day; GLP, good laboratory practice; LD, lactation day

Table 63. Observations and Results, Study DPN0378

Parameters	Major Findings
F0 dams	
Mortality	No test article-related mortalities in the F0 generation female mice.
Clinical signs	No test article-related clinical signs
Body weights	No effect
Gross pathology	No test article-related macroscopic findings
Cesarean section data	No effect
F1 offspring	
Preweaning (pups)	
Offspring	No clinical observation in the F1 generation pups were attributed to dosages of avalglucosidase alfa as high as 50 mg/kg/dose.
Postweaning (>day 21 postpartum) F1 generation	
Mortality	No test article-related mortalities
Clinical signs	No test article-related clinical signs
Body weight	No effect
Sexual maturation	No effect. The average day on which preputial separation (29.0 to 30.0 days) or vaginal patency (30.7 to 31.8 days) occurred was comparable among the five dose groups.

Reference ID: 4836879

Parameters	Major Findings
Passive avoidance	No effect on learning, short-term retention, long-term retention, or response inhibition
Motor activity	No effect on either ambulation or fine movement in the males and females when evaluated on postnatal day (PND) 60
Acoustic startle	No effect on either maximum response amplitude (MAX; reactivity to auditory stimuli) or latency to MAX (habituation of responses) when evaluated on PND 65
Mating and fertility	No effect
Necropsy observations	No effect
Terminal body weights and testes and epididymides weights	No effect
Cesarean section observation/litter parameters (GD13)	No effect

Source: Study DPN0378 final study report submitted under module 4.2.3.5.3.

13.2.1.3.5. Study No. JUV0033 (GZ402666 (NeoGAA): Intravenous 9-Week Toxicity Study in Juvenile Mice With a 4-Week Recovery Period)

Key Study Findings

There were 25 unscheduled deaths. Even though the cause of death was undetermined, they were most likely related to an immunologic response (including an anaphylactoid response). Increased total leukocytes, lymphocytes, monocytes, segmented neutrophils, basophils and eosinophils were observed in treated males, consistent with the mortality related to the immunologic (anaphylactoid) response. No other adverse findings were noted. NOAEL =100 mg/kg every other week.

Study Information

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 64. Study Methods, Juvenile Toxicity, Study JUV0033

Methods	
Dose and frequency of dosing:	0 (saline), 0 (vehicle), 20, 50, and 100 mg/kg once every other week (a total of 5 or 6 doses)
Route of administration:	Intravenous bolus
Formulation/Vehicle:	10mM Histidine pH 6.2 (b) (4) 0.01% Tween 80, 2% Mannitol, 2% Glycine
Species/Strain:	Crl:CD1 mouse
Number/Sex/Group:	20/sex/group
Satellite groups:	TK and recovery groups

Methods

Study design: This study determined the potential toxicity of GZ402666 when given by intravenous injection to juvenile mice once every other week for approximately 9 weeks (a total of 5 or 6 doses) from postnatal day (PND) 21 through PND 77 (or PND 91 for males in the fertility cohort only) with a nondosing recovery period to PND 111 or 112. This study included four cohorts: Fertility, Toxicokinetics (TK), Main and Recovery.

Endpoints included general toxicity, growth, reproductive and neurobehavioral development and function, delayed toxicity, toxicokinetics and immunogenicity.

Group Information, Study JUV0033

Group No.	Test Materials	Dose Level (mg/kg)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Route of Administration	No. of Fertility Animals		No. of Toxicokinetic Animals		No. of Main Animals		No. of Recovery Animals	
						M	F	M	F	M	F	M	F
1	Control Article[a]/ Saline[b]	0/0	10[a]/1[b]	0/0	IV injection[c]/ IP injection	20	20	3	3	10	10	5	5
2	Saline[d]/ DPH[e]	0/5	10[d]/1[e]	0/5	IV injection[c]/ IP injection	20	20	-	-	10	10	5	5
3	Test Article[f]/ DPH[e]	20 [25][f,g]/5[e]	8[f,g]/1[e]	2.5/5	IV injection[c]/ IP injection	20	20	9	9	10	10	5	5
4	Test Article[f]/ DPH[e]	50[f]/5[e]	10[f]/1[e]	5/5	IV injection[c]/ IP injection	20	20	9	9	10	10	5	5
5	Test Article[f]/ DPH[e]	100[f]/5[e]	10[f]/1[e]	10/5	IV injection[c]/ IP injection	20	20	9	9	10	10	5	5

M= Males; F= Females; DPH = Diphenhydramine Hydrochloride; - = Not Applicable

[a] Control Article (10 mM Histidine pH 6.2[(b) (4)]/0.01% Tween 80/2% Mannitol/2% Glycine), administered from first dose.

[b] Saline (1 mL/kg) administered via intraperitoneal injection to Group 1 mice, 10 to 20 minutes prior to the 2nd administration and each dose thereafter.

[c] Intravenous administration by slow bolus

[d] Saline (10 mL/kg) administered intravenously (bolus) in Group 2 starting from the first day of dosing.

[e] DPH (5 mg/mL) administered at 1 mL/kg via intraperitoneal injection (to Groups 2 through 5) 10 to 20 minutes prior to the 2nd dose administration of either saline (Group 2) or test article (Groups 3 to 5), and prior to each dose thereafter. DPH was administered to Groups 3 to 5 to prevent hypersensitivity to the test article, see Section 4.8.3 (Administration of Treatment Article [DPH]).

[f] GZ402666 (neoGAA)

[g] Males assigned to Group 3 (Main Cohort) had a dose volume entered as 10 mL/kg, rather than 8 mL/kg and therefore received a dose level of 25 mg/kg, rather than 20 mg/kg.

Deviation from study protocol affecting interpretation of results: No

Nonpivotal DRF rabbit studies: Nonpregnant New Zealand White (NZW) rabbits were administered avalglucosidase alfa IV once daily at 0, 20, 40, or 80 mg/kg/day for 7 days. No adverse effects occurred at any dose. In an exploratory embryo-fetal toxicity study, avalglucosidase alfa (40 mg/kg/dose IV) was administered to pregnant NZW rabbits once daily on GD 6–19; GD 6–12; GD 13–19; and on GD 6, 10, 13, 16, and 19. Control rabbits received vehicle once daily from GD 6–19. C-sections were performed on GD 29. No adverse effects were observed in either the dams or the fetuses.

Source: Study JUV0033 final study report in module 4.2.3.5.4
Abbreviations: GD, gestation day; GLP, good laboratory practice; IV, intravenous

Table 65. Observations and Results, Study JUV0033

Parameters	Major Findings
Mortality	For males, there was a total of 15 unscheduled necropsies during the study. Two mice were euthanized prematurely on PND 54 (in control fertility cohort, adverse clinical signs with kidney abnormalities) and PND 74 (in 20 mg/kg TK cohort, due to injuries). Thirteen mice were found dead. The cause of death in all these male mice was undetermined, but it was likely related to an immunologic response (including an anaphylactoid response) as would be expected based on the timing of death (28 minutes to approximately 3 hours postdosing) and the low incidence of deaths across all dose groups, with a slightly higher incidence in the low dose groups.

Summary of Mortality – Male Mice Assigned to Main, Fertility, Recovery, and TK Cohorts

Cohort	Dose Group				
	0/0 mg/kg (Control Article/Saline)	0/5 mg/kg (Saline/DPH)	20 [25]/5 mg/kg (GZ402666/DPH)	50/5 mg/kg (GZ402666/DPH)	100/5 mg/kg (GZ402666/DPH)
Main Cohort	-	-	2 (FD)	1 (FD)	-
Fertility Cohort	1 (UE)	-	4 (FD)	1 (FD)	-
Recovery Cohort	-	-	-	-	-
TK Cohort	-	-	3 (FD)/1 (UE)	1 (FD)	1 (FD)
Total	1	0	10	3	1

FD=found dead; UE=unscheduled euthanasia; - = no deaths

Source: Study JUV0033 final study report in module 4.2.3.5.4

For females, there was a total of 10 unscheduled necropsies during this study. Two mice were euthanized prematurely on PND100 (in control fertility cohort) and on PND 55 (in 50 mg/kg fertility cohort, due to swelling in the urogenital area). Eight mice were found dead. Similar to that for males, the cause of death in all these female mice was undetermined, but it was likely related to an immunologic response (including an anaphylactoid response) as would be expected based on the timing of death (28 minutes to approximately 1 hour 20 minutes postdosing) and the low incidence of deaths across all dose groups, with a slightly higher incidence in the low dose groups.

Summary of Mortality – Female Mice Assigned to Main, Fertility, Recovery, and TK Cohort

Cohort	Dose Group				
	0/0 mg/kg (Control Article/Saline)	0/5 mg/kg (Saline/DPH)	20/5 mg/kg (GZ402666/DPH)	50/5 mg/kg (GZ402666/DPH)	100/5 mg/kg (GZ402666/DPH)
Main Cohort	-	-	4 (FD)	-	-
Fertility Cohort	1 (DE)	-	1 (FD)	1 (UE)	-
Recovery Cohort	-	-	-	-	-
TK Cohort	-	-	2 (FD)	1 (FD)	-
Total	1	0	7	2	0

FD=found dead; DE=delivered and euthanized; UE=unscheduled euthanasia; - = no deaths

Source: Study JUV0033 final study report in module 4.2.3.5.4

Clinical signs	No effect
Body weights	No effect
Feed consumption	No effect

Parameters	Major Findings
Hematology	For males, there were some dose-related changes and occasional statistical significance ($p<0.05$) in hematology parameters on PND 80 to 82 (main cohort) and PND 111 to 112 (recovery cohort) that were considered related to GZ402666. These changes included a mild to severe increase in total leukocyte counts, lymphocytes, monocytes, segmented neutrophils, basophils (20, 50, and 100 mg/kg) and eosinophils (50 and 100 mg/kg). These changes in hematology parameters were consistent with the increase in mortality in the test article-treated groups that were presumed to be related to an immunologic response. **Summary of Hematology Changes in Male Mice Administered GZ402666** Parameter / Units / Time Point / 20 mg/kg / 50 mg/kg / 100 mg/kg Leukocytes / 10^3 cmm / PND 80 to 82 / 60.9% / 92.0% / **132.0%** Leukocytes / 10^3 cmm / PND 111 to 112 / 42.5% / 109.3% / **122.1%** Lymphocytes / 10^3 cmm / PND 80 to 82 / 47.1% / 95.5% / **133.0%** Lymphocytes / 10^3 cmm / PND 111 to 112 / 50.8% / 62.8% / 90.9% Monocytes / 10^3 cmm / PND 80 to 82 / 150.0% / 154.2% / 113.3% Monocytes / 10^3 cmm / PND 111 to 112 / 35.9% / 180.4% / 176.1% Segmented Neutrophils / 10^3 cmm / PND 80 to 82 / 131.0% / 77.2% / 114.8% Segmented Neutrophils / 10^3 cmm / PND 111 to 112 / 14.9% / 298.8% / **254.9%** Basophils / 10^3 cmm / PND 80 to 82 / 38.9% / 52.8% / 144.4% Basophils / 10^3 cmm / PND 111 to 112 / 75.0% / **280.0%** / **360.0%** Eosinophils / 10^3 cmm / PND 80 to 82 / - / 58.9% / 216.7% Eosinophils / 10^3 cmm / PND 111 to 112 / - / 31.3% / 36.5% [a] Changes are expressed as % difference from Group 2 mean control value. '–': indicates results were not considered to be meaningfully different from mean control value. Based upon statistical analysis of group means, values highlighted in **bold** were significantly different from the DPH/saline control group (Group 2). For females, there were no treatment-related effects on any hematology parameter evaluated at any dose level in the main and recovery cohorts.
Clinical chemistry	No effect
Gross pathology	No effect
Organ weights	No effect
Bone evaluation	No effect
Histopathology	No effect
CNS/Neurobehavioral assessment	No effect (open field evaluation on PND 65, passive avoidance on PND 56, auditory startle on PND 72, and motor activity on PND 61).
Sexual maturation	No effect (25.4 to 26.0 days for male balano-preputial separation and 24.9 to 25.9 days for female vaginal patency)
Reproductive capacity	No effect (estrous cyclicity, mating and fertility).
Cesarean-section observations	No effect
Sperm parameters	No effect
Antidrug antibodies	Positive ADA titers observed in all mice treated with avalglucosidase alfa on PND 48, 76, and 110/111 (expect one mouse in group 5 that was negative on PND 48 and 111). In general, while there was a large variation in titer between mice in the same treatment group, individual titers were consistent between time points, with titers generally increasing with repeated dose administration. Since ADA samples were taken from recovery animals, not from TK animals, no conclusion can be made regarding the ADA impact on drug exposure.

Source: Study JUV0033 final study report in module 4.2.3.5.4
Abbreviations: ADA, antidrug antibodies; PND, postnatal day; TK, toxicokinetics

Reference ID: 4836879

13.2.1.4. Impurities/Degradants

13.2.1.4.1. Drug Substance and Drug Product Impurities

Per ICH *Q3B(R2) Impurities in New Drug Products* (July 2006), a maximum avalglucosidase alfa dose of 2.4 g/day was considered (40 mg/kg dose, 60 kg body weight) as the anticipated label claims for the patients with late- [redacted] (b) (4) onset Pompe disease.

Drug Substance

There were process-related and product-related impurities raised from raw materials, manufacturing process, avalglucosidase alfa variants, and avalglucosidase alfa degradation.

- Prosses-related impurities: Most are related to the synthesis of [redacted] (b) (4). Only impurities specified at levels [redacted] (b) (4) above the applicable ICH safety limits were considered impurities, which required control in the drug substance. Prosses-related impurities requiring routinely testing were [redacted] (b) (4)
- Product-related impurities: Product-related impurities included processed forms of [redacted] (b) (4) These levels of product related impurities were determined using release and characterization tests.

Drug Product

- Drug substance-related impurities includ [redacted] (b) (4) Based upon the results from GLP toxicology studies, an acceptance criterion of ≤ [redacted] (b) (4) µg/mL for [redacted] (b) (4) was established.

Table 66. Summary of Drug Substance-Related Impurities of Avalglucosidase Alfa Drug Product Usin the Pro osed Commercial Process

DS Related Impurity	Test	Acceptance Criteria for PPQ Batches	Process Performance Qualification Lots (C2B)			Historical Process C1/C2A Range
			8W2667	8W2680	8W2830	
[redacted] (b) (4)						

Source: Characterization of Impurities from module 3.2.P.5.5.
Abbreviations: DS, drug substance; PPQ, process performance qualification

- Formulation process-related impurities: There were no formulation process-related impurities for avalglucosidase alfa drug product. Only Generally Recognized as Safe excipients are used in the formulation for which the quality meets the respective pharmacopoeia requirements.

- Container closure-related impurities (extractables and leachables): There were no container closure-related impurities which need to be controlled in avalglucosidase alfa drug product.
  - Extractable study: An assessment of extractable components was performed by exposing the drug substance (DS) container [redacted] (b) (4) Samples were taken on different time points ranging from ½ day until 70 days. The extractable results were used as an analytical guide to determine if these impurities, if present, would be picked up during a leachable study.
  - Leachable study: To determine whether the [redacted] (b) (4) will leach undesirable substances into the DS under normal cooled storage conditions, a leachable study was performed [redacted] (b) (4) The leachable evaluation of the [redacted] (b) (4) containers identified three potential leachables above the analytical evaluation threshold of [redacted] (b) (4) µg/dose limit.

Table 67. Toxicological and Risk Assessments of Avalglucosidase Alfa Leachables

Leachables	Max Leachable Quantity	Toxicological Assessment	Risk Assessment
[redacted] (b) (4)			Based on maximum leachable quantity of these components obtained during the leachable study in combination with the toxicological assessment of the identified components, it is concluded that the potential presence of these leachables does not present a risk for the patient.

Source: Container Closure System from module 3.2.S.6
Abbreviations: PDE, permitted daily exposure; SCT, safety concern threshold

- Elemental impurities: There were no elemental impurities which need to be controlled as per ICH guidance for industry *Q3D(R1) Elemental Impurities* (March 2020) in avalglucosidase alfa drug product.

13.2.1.4.2. Impurity Studies

Table 68. General Toxicology (Impurity), Study No. TXC1530

Study Description	Major Findings
Study title: 13-Week Intermittent Intravenous Infusion Toxicity and Toxicokinetic Study (b) (4) in Cynomolgus Monkeys with a 4-Week Recovery Sample collection times: TK timepoints taken days 1 and 85 of the dosing phase within 5 minutes of the end of infusion and approximately 0.25, 0.5, 1, 2, 4, 6, 8, 24, and 48 hours postdose. Accumulation: Yes Dose proportionality: No NOAEL: (b) (4) Safety margin*: 9.7X *Exposure multiples were based on the amended limit of (b) (4) µg/mL (based on (b) (4) mg/m^2 (b) (4) as the worst-case exposure with administration of 20 mg/kg avalglucosidase alfa [2 mL/kg] in adult patients.	Following single and repeated intravenous administration of 50 mg/kg (b) (4) once every 14 days for 13 weeks, (b) (4) concentrations were quantifiable in all animals up to 54 hours from the start of infusion. However, the (b) (4) concentrations were close to the range of endogenous levels (as determined by the vehicle animals) by 12-14 hours postdose in the majority of animals. Maximum concentrations were generally observed at a median time of 6 hours from the start of infusion (i.e., at the end of infusion). Increasing concentrations of (b) (4)) in the avalglucosidase alfa had no effect on toxicity up to the high dose of 50 mg/kg avalglucosidase alfa / (b) (4) once every other week. (b) (4) Spiking (b) (4) with different levels of (b) (4) had no apparent effect (b) (4) From a nonclinical viewpoint, the proposed increase in the (b) (4) specification to = (b) (4) µg/mL in drug product is acceptable. **Da s 1 and 85 TK Parameters for the Monke** Sex Male Female (b) (4)

Source: Study TXC1530 study report in module 4.2.3.7.6.
Abbreviations: (b) (4) NOAEL, no observed adverse effect level; TK, toxicokinetic

Table 69. Other Special Toxicology Studies, Genotoxicity (Impurity)

Study Description	Findings
Study no. HIS2129 To evaluate the genotoxic potential of (b) (4) AMES Test system: Five *Salmonella typhimurium* strains: TA1535, TA1537, TA98, TA100 and TA102 with and without metabolic activation ((b) (4) -induced rat liver S9). The number of revertant colonies grown on minimal selective agar medium was determined 48 hours after treatment. GLP compliance: Yes	(b) (4) did not precipitate on the plates up to the highest investigated dose level of 5000 µg/plate (i.e., the highest dose level recommended for this test), with and without metabolic activation in the plate incorporation and preincubation method. In the presence or absence of the metabolic activation, (b) (4) did not cause biological relevant increases in the number of revertant colonies in any of the bacterial strains.
Study no. MAF0153 To evaluate the genotoxic potential of (b) (4): chromosomal aberrations Test system: Cultured human peripheral lymphocytes: cells from two different healthy donors were exposed for 3 or 20 hours to the test article without S9-mix and 3 hours with S9-mix. GLP compliance: Yes	No relevant cytotoxicity was observed in the 3-hour experiments. After 20 hours continuous treatment, minimal cytotoxicity was observed starting at 350 µg/mL. The highest evaluated concentration for all treatment conditions was 500 µg/mL, the maximum recommended concentration for the present test. Under the experimental conditions reported, neither a statistically significant nor a biologically relevant increase in the number of structural or numerical aberrations was found in cultures treated with the test article when compared to the solvent control.
Study no. HIS2317 To evaluate the mutagenic potential of (b) (4) AMES Test system: Five *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102 GLP compliance: Yes	(b) (4) did not precipitate on the plates up to the highest investigated dose level of 5000 µg/plate with and without metabolic activation. under the experimental conditions of the study, (b) (4) was found negative in the bacterial reverse mutation test conducted on *Salmonella typhimurium* strains TA100, TA1535, TA1537, TA98, and TA102 in the presence and absence of metabolic activation, at dose levels up to 5000 µg/plate.

Study Description	Findings
Study no. MAR0099 To assesses the mutagenic hazard of the actual and potential impurities of [redacted] (b) (4) In silico systems: DEREK Nexus and Leadscope	Impurities identified per ICH M7[1] • Cohort of concern: no impurity was identified. • Class 1 (known mutagenic carcinogens): 3 impurities were identified. [redacted] (b) (4) • Class 2 (known mutagens): No impurity was identified. • Class 3 (alerting structure, unrelated to the drug substance structure, no mutagenicity data): 5 impurities were identified. [redacted] (b) (4) • Class 4 (nonmutagenic mutagens): 9 impurities were identified [redacted] (b) (4) • Class 5 (nonmutagenic): 9 impurities were identified [redacted] (b) (4)

Source: Study reports submitted under module 4.2.3.7.
[1] ICH guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (June 2020)

13.2.1.4.3. Risk Assessment on Potential Genotoxic Impurities (Per ICH M7)

The presence of mutagenic impurities in avalglucosidase alfa according to ICH draft guidance for industry *M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk - Questions and Answers* (June 2020) was evaluated based upon the intended clinical dose, duration of clinical administration, and therapeutic indication. The quality and toxicological information relevant for the evaluation of the actual and potential mutagenic impurities, as well as the acceptable daily intake and the control strategy, were defined. The safety and quality data available indicated that there was no apparent risk for humans.

Table 70. Potential Genotoxic Impurities Per ICH M7[1]: Class I

Impurity	Specification Limits	Impurity Level	Risk Assessment
(b) (4)	(b) (4) with an acceptance criterion of (b) (4)	The levels of (b) (4) have been (b) (4) µg/g, which was well below compound specific (b) (4)	(b) (4) is not expected to be a degradant of avalglucosidase alfa drug substance as confirmed during forced degradation studies. Therefore, (b) (4) levels in (b) (4) is not considered to be a CQA for avalglucosidase alfa and no additional control in the avalglucosidase alfa drug substance is needed.
	Based on ICH M7[1], the acceptable daily intake (b) (4) for (b) (4) µg/day. An (b) (4) for (b) (4) in avalglucosidase alfa was generated using twice monthly dosing regimen (5 years cumulative dosing, (b) (4)) and a max daily dose of 2.4 avalglucosidase alfa. Using the highest amount of glycan that would be used for DS manufacturing ((b) (4) this corresponds to an (b) (4)		
(b) (4)	(b) (4) is specified in (b) (4), with an acceptance criterion of (b) (4).	The levels of (b) (4) ave been (b) (4) µg/g, well below the compound specific (b) (4)	(b) (4) Therefore, (b) (4) levels are not considered to be a CQA for avalglucosidase alfa and no additional control in the avalglucosidase alfa drug substance is required.
	Based on the published carcinogenicity toxic dose (TD) 50 value, the (b) (4) for (b) (4) µg/day. An (b) (4) for (b) (4) µg/g in avalglucosidase alfa was generated using the twice monthly dosing regimen (5 years cumulative dosing, (b) (4)) and a maximum daily dose for avalglucosidase alfa (2.4 g). Using the highest amount of glycan that would be used for DS manufacturing (b) (4) g glycan/g avalglucosidase alfa), this corresponded to an (b) (4) for (b) (4) µg/g glycan.		
(b) (4)	µg/mL (ppm)	The level of residual (b) (4) is consistently below limit of quantification (LOQ).	Routine testing for residual (b) (4) for commercial release of avalglucosidase alfa DS is not proposed.
	Per ICH M7[1], the (b) (4) for (b) (4) mg /day. (b) (4) is not a carcinogen via oral intake; therefore, recommended intakes are based upon noncancer endpoints. Health Canada, International Program on Chemical Safety (World Health Organization) and U.S. Environmental Protection Agency (applying the Integrated Risk Information System [IRIS]) recommend an oral limit of (b) (4) mg/kg/day, or (b) (4) mg/person/day for a 50 kg person. Considering an additional safety factor of (b) (4) to consider the difference in bioavailability of (b) (4) between oral and intravenous routes, an acceptable intake of (b) (4) mg/person/day by intravenous route (the intended route of administration in human) could be defined. Using the twice monthly dosing regimen (5 years cumulative dosing, (b) (4) and maximum daily dose for avalglucosidase alfa (2.4 g), this corresponded to an (b) (4) for (b) (4) in avalglucosidase alfa of (b) (4) µg/mL, assuming an average protein concentration (b) (4)).		

Reference ID: 4836879

Impurity	Specification Limits	Impurity Level	Risk Assessment
	Per ICH Q3A[2], based on an avalglucosidase alfa dose of 2400 mg, the reporting threshold for an impurity present in a drug dosed at (b) (4) g/day is equal to (b) (4)%, which equals to (b) (4) mg impurities/g avalglucosidase alfa. One gram of avalglucosidase alfa equals to (b) (4) mL (assuming a target protein concentration of (b) (4) mg impurities/g avalglucosidase alfa = (b) (4) µg/mL. The acceptance criterion for residual (b) (4) was therefore set as ≤ (b) (4) µg/mL based on the ICH Q3A reporting threshold as it is stricter than the calculated (b) (4) for ICH M7[1].		

Source: Study report submitted under module 3.2.s.3.2.
[1] ICH draft guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk – Questions and Answers* (June 2020)
[2] ICH guidance for industry *Q3A(R) Impurities in New Drug Substances* (June 2008)
Abbreviations: CQA, critical quality attr bute; DS, drug substance

Table 71. Potential Genotoxic Impurities Per ICH M7[1]: Class III

Impurity	Specification Limits	Impurity Level	Risk Assessment
(b) (4)	(b) (4) µg/mL	The level of (b) (4) is consistently below limit of quantification (LOQ).	Routine testing for residual (b) (4) for commercial release of avalglucosidase alfa DS is not proposed.
	There are no published recommended daily intake (RDI) levels for (b) (4) in food. There are no published data on human plasma concentrations of (b) (4) However, (b) (4) With the published plasma concentration of (b) (4) in humans is (b) (4) the molecular weight (MW) of (b) (4) (b) (4) (b) (4) and the published plasma volume in humans is (b) (4) mL/kg, there would be (b) (4)		
(b) (4)	Using a 23-fold safety margin over the endogenous glycolate concentrations because the (b) (4) ratio is unknown, an acceptable daily intake (b) (4) (b) (4) (b) (4) (after adjusted in relation to the stability profile)	The level of (b) (4) is consistently below limit of quantification (LOQ).	Routine testing for (b) (4) for commercial release of avalglucosidase alfa DS and DP were done.
	Per ICH M7 (R1)[2], since the mutagenic alerting structure for (b) (4) the permissible daily exposure (PDE) of (b) (4) was used as a starting point. Avalglucosidase alfa is administered twice monthly, so a total duration of treatment is >1 to 10 years (26 dosing days per year, lifetime treatment taken at 70 years, 26×70=1820 dosing days, ~5 years in cumulative exposure). As done in ICH M7[1] for threshold of toxicological concern (TTC), an adjustment on the (b) (4) would be similar to (b) (4) µg for >10 years and (b) (4) µg for 1–10 years, for (b) (4) adjustments for dosing duration.		
	Since (b) (4) is a very large compound compared to (b) (4), an adjustment based on molecular weight differences (b) (4) was applied to the AI of (b) (4) This resulted in a (b) (4)		

Reference ID: 4836879

Impurity	Specification Limits	Impurity Level	Risk Assessment
	ICH Q3B[3] applies since (b) (4) is a degradant of avalglucosidase alfa and residual glycan measured in the DP. The qualification threshold of (b) (4)% corresponds with an acceptance criterion of ≤ (b) (4) µg/g avalglucosidase alfa. Since the qualification threshold of ICH Q3B[3] delivers a lower (b) (4) in comparison with the calculated ICH M7[1] Class 3 compound specific (b) (4) described above, the stricter criterion of (b) (4) µg/g is proposed as the specification for (b) (4) in avalglucosidase alfa DP. Any level above this proposed acceptance criterion would require qualification of this impurity in GLP toxicity studies. An acceptance criterion of ≤(b) (4) µg/g for the DS was established based on the stability trend and hold time of the DS prior to generation of the DP.		
(b) (4)	µg/g	The level of (b) (4) is consistently below limit of quantification (LOQ).	(b) (4) ere class 5 compounds and were treated as nonmutagenic impurities. NHS was sufficiently controlled in (b) (4) can synthesis and was not considered to be a CQA for avalglucosidase alfa.
	Per ICH M7 addendum (R1)[4], a TTC approach was followed, considering a dosage regimen of 40 mg/kg every 2 weeks, i.e., 26 dosing days per year. Considering a lifetime treatment (taken at 70 years in ICH M7[1]), it means: 26 doses/year × 70 years =1820 dosing days in a lifetime, i.e., 5 years in cumulative exposure. Based on ICH M7[1], this corresponded to 1–10 years treatment duration, corresponding to a default threshold of toxicological concern (TTC) (b) (4) µg per day. Therefore, the (b) (4) µg/day. Using a maximum daily dose for avalglucosidase alfa (2.4 g), this corresponded to a (b) (4)		
(b) (4)	µg/g	The level of (b) (4) is consistently below limit of quantification (LOQ).	Routine testing for residual (b) (4) for commercial release of (b) (4) is not proposed
	Per ICH M7[1], (b) (4) µg/g. See above for calculation.		

Source: Study report submitted under module 3.2.s.3.2.
[1] ICH draft guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk – Questions and Answers* (June 2020)
[2] ICH guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (March 2018)
[3] ICH guidance for industry *Q3B(R2) Impurities in New Drug Products* (July 2006)
[4] ICH draft guidance for industry *M7(R1) Addendum to ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk; Application of the Principles of the ICH M7 Guidance to Calculation of Compound-Specific Acceptable Intakes*
Abbreviations: AL, acceptable limit; DP, drug product; DS, drug substance; GLP, good laboratory practice

Reference ID: 4836879

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Study PDD0035: Metabolism/Degradation of GZ402666 [redacted] (b) (4).

The objective of this study was to assess avalglucosidase alfa uptake in human cryopreserved hepatocytes and metabolism/degradation of GZ402666 (avalglucosidase alfa) [redacted] (b) (4) in human plasma and cryopreserved hepatocytes. Samples were collected after in vitro incubation of GZ402666 [redacted] (b) (4) with hepatocytes or plasma and were analyzed to quantify potential metabolites or degradation products including [redacted] (b) (4) containing degradation products, [redacted] (b) (4) were assayed with exploratory LC-MS/MS methods (0.025µM, ≤0.050µM, ≤0.250µM and 0.050µM, respectively).

- The in vitro cryopreserved human hepatocytes model was evaluated by measurement GAA activity after incubation of GZ402666 at 0.04µM, 0.1µM, and 0.4µM. GAA activities were increased in a concentration-dependent manner. GAA activities were reduced with no evidence of a concentration-dependent effect in the presence of NH_4Cl by inducing a pH increase of lysosomes and blocking the autophagy flux.
- After incubation of 4µM GZ402666 [redacted] (b) (4) in cryopreserved human hepatocytes from two donors at 37°C for 48 hours, [redacted] (b) (4) containing degradation products remained below the LLOQ at all incubation times but one [redacted] (b) (4).
- After incubation of 4µM GZ402666 [redacted] (b) (4) in culture medium for 48 hours at 37°C/5% CO_2 without hepatocytes, [redacted] (b) (4) concentrations remained below their LLOQ at any time-point.
- After incubation of 0.4µM or 4µM GZ402666 in human plasma at 37°C for 24 hours, [redacted] (b) (4) concentrations remained below their LLOQ at any time-point.

Study MIV0740: Metabolism/Degradation of Genz-669342 Linker

The objective of this study was to assess [redacted] (b) (4) metabolism/degradation product profile in human plasma and hepatocyte culture medium. [redacted] (b) (4) containing degradation products, [redacted] (b) (4), were assayed with exploratory LC-MS/MS methods (≤0.050µM, 0.250µM and 0.050µM, respectively).

- After incubation of [redacted] (b) (4) in hepatocyte culture medium for 24 hours at 4µM or 40µM, [redacted] (b) (4) concentrations decreased by 45% and 63%, respectively, resulting in low [redacted] (b) (4) concentrations [redacted] (b) (4) concentrations).
- After incubations of [redacted] (b) (4) with two batches of human hepatocytes at 4µM or 40µM, the [redacted] (b) (4) was degraded by [redacted] (b) (4) %. [redacted] (b) (4) concentrations

increased marginally (representing (b) (4)% or less of the initial incubated (b) (4) concentrations). (b) (4) concentrations remained very low.

- After incubation of (b) (4) in sodium heparin human plasma at 4µM or 40µM for 24 hours, the (b) (4) was degraded by approximately (b) (4) (b) (4) and (b) (4) accounted for (b) (4) % of (b) (4) degradation, respectively.
- (b) (4) was present at T_{0h} in all experimental conditions. The Applicant concluded that presence of (b) (4) at T_{0h} may have been generated by the degradation of the (b) (4) (b) (4) during the time between dilution of the (b) (4) working solution in water or culture medium and start of the incubation.
- No (b) (4) was quantified in all tested matrices (culture medium, human hepatocytes, and human plasma at LOQ = (b) (4) µM).

14.2. In Vivo Studies

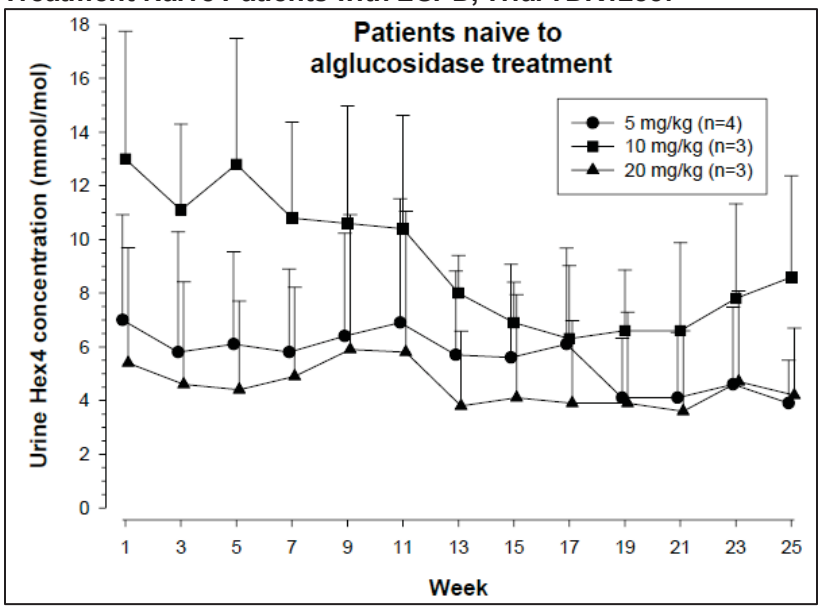
Phase 1/2 Trial TDR12857: PK and PD of Avalglucosidase Alfa in LOPD Patients

Study TDR12857 is an open-label, ascending dose study of the safety, tolerability, PK, PD, and exploratory efficacy of avalglucosidase alfa in naïve and alglucosidase alfa treated patients with LOPD. Avalglucosidase alfa was administered as an IV infusion at 5, 10, or 20 mg/kg qow for 24 weeks. Among the 24 treated patients, 21 completed the study (i.e., 9/10 naïve patients and 12/14 previously alglucosidase alfa-treated patients). PK samples were collected at Weeks 1, 13, and 25, at pre-dose, during infusion and up to 48 hours after the end of the infusion.

Avalglucosidase alfa exposures increased in dose proportionality from 5 to 20 mg/kg with no accumulation after qow dosing. No differences in PK profiles were observed between treatment-naïve patients and patients previously treated with alglucosidase alfa.

In both treatment-naïve patients and patients previously treated with alglucosidase alfa, urinary Hex4 levels decreased at all avalglucosidase alfa dose levels. At Week 25, mean decreases by 13.2% to 36% were observed in naïve patients with no clear relationship to dose level (Figure 22). A similar response was observed in patients previously treated with alglucosidase alfa with mean decreases of 7.5% to 20.5% and no evidence of dose response.

Figure 22. Urinary Hex4 Over Time After Avalglucosidase Alfa 5, 10 and 20 mg/kg qow in Treatment-Naïve Patients with LOPD, Trial TDR12857



Source: Figure 9, Summary of Clinical Pharmacology Studies. Mean (SD).

14.3. Immunogenicity Summary

Immunogenicity of the avalglucosidase alfa and/or the active comparator alglucosidase alfa was evaluated in all four clinical trials which included 124 patients with LOPD (123 adult and 1 pediatric patients) and 22 pediatric patients with IOPD. Of these, 134 patients were included in the ADA evaluable population which was used for immunogenicity analyses.

CRIM Status and Immune Tolerance Induction (ITI) Therapies in Clinical Trials

The Applicant did not perform CRIM status assessment for patients with LOPD in trials EFC14028, TDR12857/LTS13769, because patients with LOPD were expected to have residual enzyme activity and were considered to be CRIM-positive.

In trial ACT14132, pediatric patients with IOPD were tested for CRIM status and all patients except for two were CRIM-positive. Both CRIM-negative patients received an ITI regimen treatment consisting of rituximab/methotrexate prior to study enrollment. The first CRIM-negative patient enrolled in cohort 2 received avalglucosidase alfa 40 mg/kg qow and entered the extension study. This patient was negative for ADA at study entry, had titer of 200 at week 9 and highest ADA titer of 3,200 at week 49, which dropped to a titer of 800 at week 61. The patient did not develop NAb. The second CRIM-negative patient enrolled in cohort 3 received alglucosidase alfa 40 mg/kg qow. This patient was negative for ADA to alglucosidase alfa at study entry and did not develop ADA to either alglucosidase alfa or avalglucosidase alfa at last available timepoint at week 25. In addition, one CRIM-positive patient in trial ACT14132 received two courses of the ITI regimen treatment consisting of rituximab, methotrexate and polyclonal immunoglobulins prior to study enrollment. This patient was positive for ADA to avalglucosidase alfa at study entry with a titer of 100 and was negative for ADA at all subsequent timepoints including the last available timepoint at week 97. The patient did not develop NAb.

Reference ID: 4836879

Immunogenicity Incidences

Blood samples for immunogenicity assessment were collected in all clinical trials. The immunogenicity assessment followed a tiered approach (i.e., ADA screening, confirmatory assay, ADA titer and NAb characterization in ADA-positive samples). NAb to avalglucosidase alfa was assessed by determination of inhibition of enzyme catalytic activity or inhibition of cellular uptake. Furthermore, ADA cross-reactivity to alglucosidase alfa and avalglucosidase alfa were assessed at week 25 and week 49. The incidence of ADA response in patients with LOPD and IOPD are presented in Table 72.

- The majority of treatment-naïve patients with LOPD (58 of 61) developed treatment emergent ADA. A total of three patients showed ADA negative status. The median time to seroconversion was 8.3 weeks. Among the 58 patients with treatment emergent ADA, 56 patients had treatment-induced ADA and 2 patients had treatment-boosted ADA. Among the 56 patients with treatment-induced ADA, 49 patients had persistence ADA response. Among the 49 patients with persistence ADA response, 8 had low (100-800 peak titer), 28 patients had intermediate (1,600-6,400 peak titer), and 13 patients had high (≥12,800 peak titer) ADA responses. The median peak titer was 3,200.
- Among adult patients with LOPD previously treated with alglucosidase alfa, the majority (43 of 58) had pre-existing ADA at baseline and 32 patients developed treatment emergent ADA.
- Among pediatric patients with IOPD who had previous treatment with alglucosidase alfa, 2 of 16 patients had pre-existing ADA at baseline. One of the six patients treated with 20 mg/kg qow avalglucosidase alfa developed treatment emergent ADA. Of the 10 patients treated with 40 mg/kg qow avalglucosidase alfa, 5 patients developed treatment emergent ADA.
- Among treatment-naïve patients with LOPD, 17 patients developed NAb that inhibited avalglucosidase alfa catalytic activity, 24 patients developed NAb that inhibited cellular uptake.
- Among adult patients with LOPD who had previous treatment with alglucosidase alfa, 10 adult patients developed NAb that inhibited avalglucosidase alfa catalytic activity, 12 patients developed NAb that inhibited cellular uptake.
- One pediatric patient with IOPD treated with 40 mg/kg qow avalglucosidase alfa developed NAb that inhibited avalglucosidase alfa cellular uptake.
- The ADA cross-reactivity evaluations showed that the majority of patients generate antibodies that are cross-reactive to alglucosidase alfa.

Table 72. Incidence of Antidrug Antibody Responses in Patients With LOPD and IOPD

	Avalglucosidase Alfa				Alglucosidase Alfa	
	Treatment-Naïve Patients (N=61)	Treatment-Experienced Patients (N=74)			In Primary Analysis Period (N=54)	
Types of Antibodies	Adult/ Pediatric 20 mg/kg qow	Adult 20 mg/kg qow	Pediatric 20 mg/kg qow	Pediatric 40 mg/kg qow	Adult 20 mg/kg qow	Pediatric 20 mg/kg qow to 40 mg/kg qw
N	61[1]	58	6	10	48	6
Antidrug Antibodies						
ADA at baseline	2 (3)	43 (74)	1 (17)	1 (10)	2 (4)	3 (50)
Treatment-emergent ADA[2]	58 (95)	32 (55)	1 (17)	5 (50)	46 (96)	3 (50)
Treatment-induced ADA[3]	56 (95)	9 (60)	1 (17)	4 (40)	44 (96)	1 (33)
Treatment-boosted ADA[4]	2 (100)	18 (45)	0	1 (10)	2 (100)	2 (67)
Neutralizing Antibodies						
Both NAb types	13 (21)	3 (5)	0	0	ND	ND
Inhibition enzyme activity	17 (28)	10 (18)	0	0	4 (8)	2 (33)
Inhibition of enzyme uptake	24 (39)	12 (21)	0	1 (10)	19 (40)	0

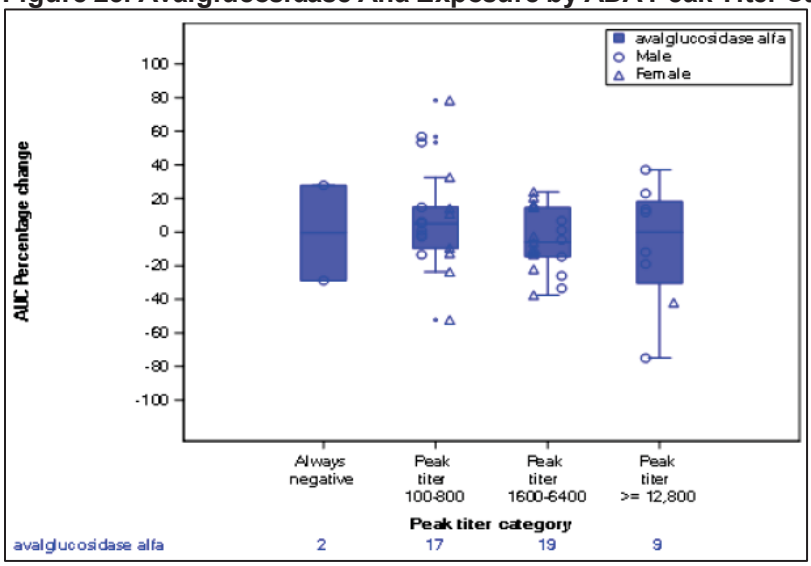
Source: Applicant's Summary of Immunogenicity
All values are expressed as n (%) unless specified otherwise.
[1] Includes n=1 pediatric patient
[2] Treatment emergent = treatment induced + treatment boosted
[3] Treatment-induced ADA incidence =100 times (treatment induced ADA positive patients) /(number of evaluable patients with ADA negative at baseline)
[4] Treatment-boosted ADA incidence =100 times (treatment boosted ADA positive patients) /(number of evaluable patients with ADA positive at baseline)
Abbreviations: ADA, antidrug antibodies; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; ND, not determined; qow, every other week; qw, once per week

Impact of Immunogenicity on PK

Descriptive statistics of avalglucosidase alfa exposure by ADA peak titer category and NAb positivity in treatment-naive patients with LOPD was utilized to evaluate the effect of ADA on avalglucosidase alfa PK. Changes in median AUC were not observed between week 1 and week 49 irrespective of peak titer category. There was no apparent trend in change of AUC based on ADA peak titer category (Figure 23) or NAb positivity (Figure 24). Of note, a popPK modeling approach was used to evaluate whether ADA affected avalglucosidase alfa PK in patients with LOPD. The popPK analysis, including 75 patients with LOPD, did not identify ADA as a significant covariate influencing avalglucosidase alfa PK.

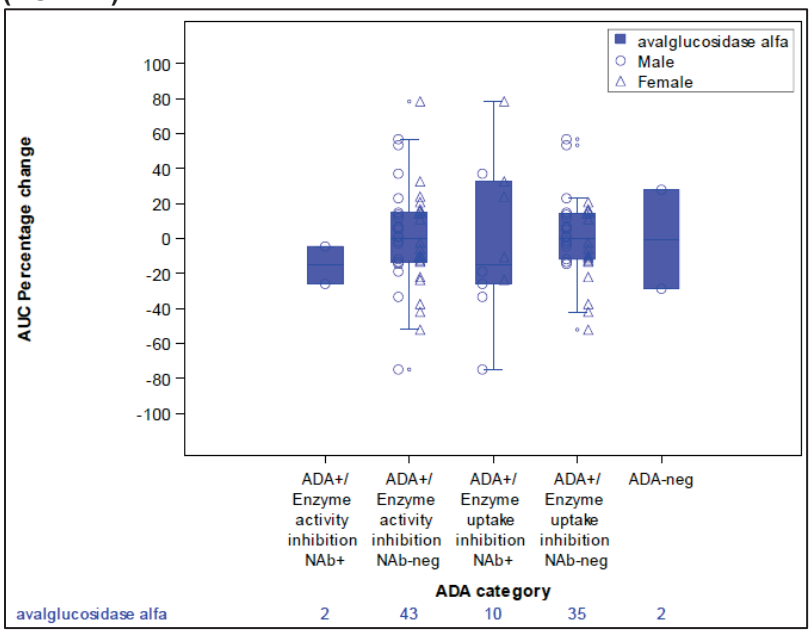
Reference ID: 4836879

Figure 23. Avalglucosidase Alfa Exposure by ADA Peak Titer Category, Trial EFC14028 (COMET)



Source: Figure 22, Summary of Clinical Pharmacology Studies.

Figure 24. Avalglucosidase Alfa Exposure by Neutralizing Antibody Status, Trial EFC14028 (COMET)



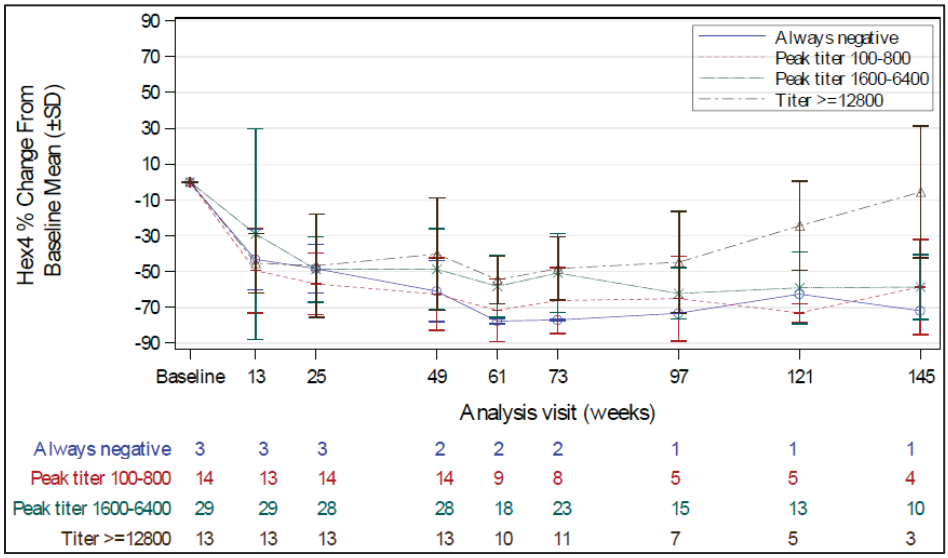
Source: Figure 23, Summary of Clinical Pharmacology Studies.

Reference ID: 4836879

Impact of Immunogenicity on Pharmacodynamics

The percentage change of urinary Hex4 from baseline by ADA peak titer category was investigated in treatment-naive patients from trials EFC14028 and TDR12857/LTS13769. Urinary Hex4 in all ADA titer groups dropped by week 13 and by week 25 the intermediate and high titer group appeared to stabilize through week 73. Between weeks 73 and 145 an increase in Hex4 was observed in the high titer group as compared to ADA-negative or the other ADA titer groups (Figure 25).

Figure 25. The Percent Change of Hex4 From Baseline by Antidrug Antibody Peak Titer Categories for Treatment-Naïve Patients

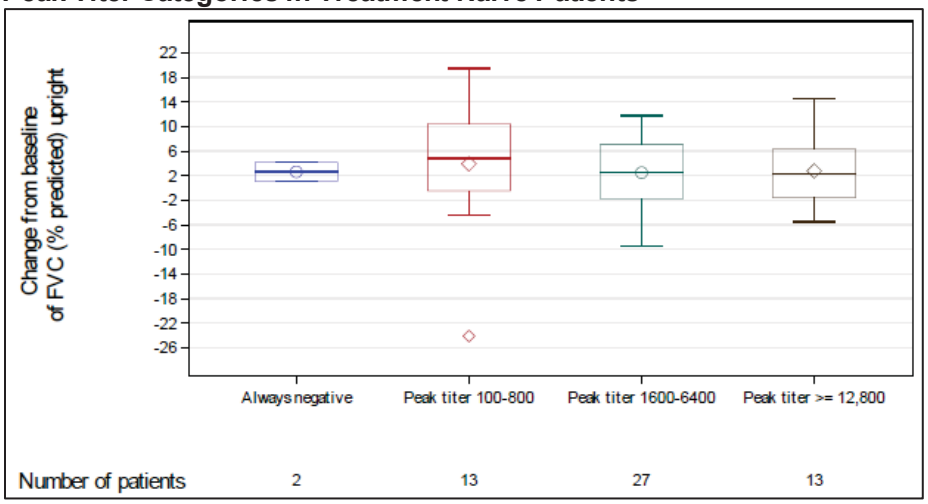


Source: Figure 9, Integrated Summary of Immunogenicity.
Abbreviations: ADA, antidrug antibodies; SD, standard deviation

Impact of Immunogenicity on Efficacy

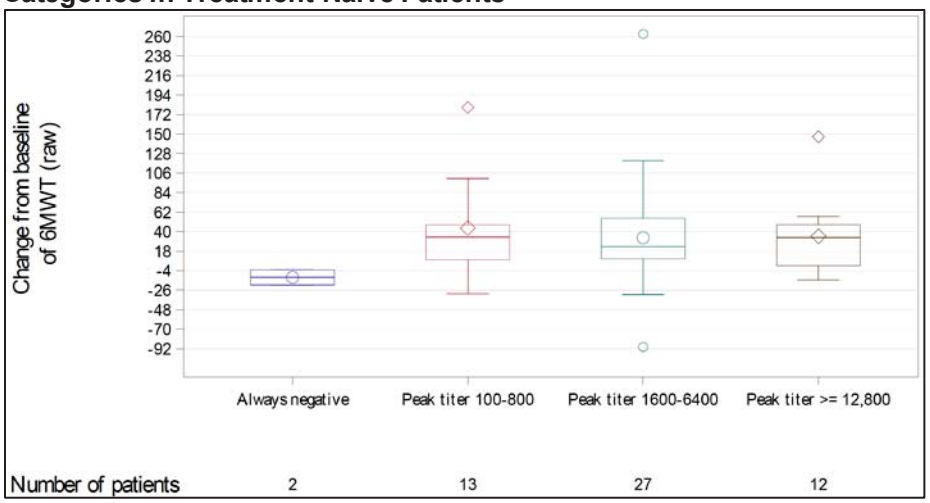
There was no apparent association between ADA status (positive versus negative, or by peak titer categories) and the clinical efficacy results measured by FVC (% predicted) and 6MWT in trial EFC14028. The median change from baseline to week 49 for FVC (% predicted) for 55 treatment-naïve patients with treatment emergent ADA was 3.72 compared to 2.62 for the 2 ADA negative patients. The mean [SD] for the three ADA peak titer categories were 3.31 [14.13], 2.53 [6.0] and 2.77 [5.43], respectively, from low to high titers (Figure 26). The median change from baseline to week 49 for 6MWT (distance walked) is 29.1 for 54 treatment-naïve patients with treatment emergent ADA compared to -11.5 for the 2 ADA negative patients. The mean [SD] for the three ADA peak titer categories were 53.86 [66.11], 33.55 [62.13] and 34.73 [43.26], respectively, from low to high titers (Figure 27).

Figure 26. Change From Baseline of FVC (% Predicted) Upright by Antidrug Antibody Status and Peak Titer Categories in Treatment-Naïve Patients



Source: Figure 10, Integrated Summary of Immunogenicity

Figure 27. Change From Baseline of 6MWT (Distance Walked) by Antidrug Antibody Peak Titer Categories in Treatment-Naïve Patients



Source: Figure 11, Integrated Summary of Immunogenicity

Impact of Immunogenicity on Safety

The incidence of TEAE and serious TEAE was similar in treatment-naive patients who developed treatment emergent ADA versus patients who were ADA negative (Table 73). Hypersensitivity TEAE occurred in 2/3 patients who were ADA-negative compared to 15/58 patients who developed treatment-emergent ADA. There were 4 treatment-naive adult patients who met the broad SMQ for anaphylactic reaction; and 3 of the four patients had treatment emergent ADA.

There was an increase in the incidence of IAR with increasing ADA peak titer with the highest reported in patients with ADA peak titer ≥12,800 (8/13, 62%), compared to the incidences of IAR in patients with ADA titer 1,600-6,400 (7/29, 24%), ADA titer 100-800 (1/14, 7%), and ADA-negative patients (1/3, 33%) (Table 74). There was also a trend for increased incidence of

hypersensitivity events with increasing ADA titers: 100-800 peak titer (2/14, 14%), 1,600-6,400 peak titer (8/29, 28%) and ≥12,800 peak titer (4/13, 31%) (Table 74).

Table 73. Summary of Treatment-Emergent Adverse Events by Antidrug Antibody Status in Treatment-Naïve Patients

Patient Category	Positive at Baseline (n=2)	Positive Postbaseline (n=56)	Treatment-Emergent ADA (n=58)	ADA Negative (n=3)	Overall (N=61)
Patients with any TEAE	2 (100%)	53 (95%)	55 (95%)	3 (100%)	58 (95%)
Patients with any serious TEAE	1 (50%)	16 (29%)	17 (29%)	1 (33%)	18 (30%)
Patients with any protocol defined IAR	2 (100%)	16 (29%)	18 (31%)	1 (33%)	19 (31%)
Patients with any hypersensitivity (narrow SMQ)	1 (50%)	14 (25%)	15 (26%)	2 (67%)	17 (28%)
Patients with any anaphylactic reaction (broad SMQ)	0	3 (5%)	3 (5%)	1 (33%)	4 (7%)

Source: Table 1.1. CSR-GLOBAL-1-EN
Positive at baseline = pre-existing ADA
Positive post baseline = negative at baseline and seroconverted following avalglucosidase alfa treatment
ADA evaluable population in avalglucosidase alfa safety set is defined as all randomized or enrolled patients who received at least 1 infusion (partial or completed) of avalglucosidase alfa and had at least one ADA sample taken postbaseline after avalglucosidase alfa infusion that is appropriate for ADA testing with a reportable result.
Abbreviations: ADA, antidrug antibodies; IAR, infusion associated reaction; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse events that developed, worsened or became serious on or after the 1st infusion of avalglucosidase alfa study drug, and up to 28 days after last infusion

Table 74. Summary of Treatment-Emergent Adverse Events by Antidrug Antibody Peak Titer Category for Treatment-Naïve Patients (N=61)

Patient Category	ADA Negative (n=3)	ADA Titer 100-800 (n=14)	ADA Titer 1600-6400 (n=29)	ADA Titer ≥12800 (n=13)
Patients with any TEAE	3 (100%)	13 (93%)	27 (93%)	13 (100%)
Patients with any serious TEAE	1 (33%)	3 (21%)	10 (35%)	3 (23%)
Patients with any protocol defined IAR	1 (33%)	1 (7%)	7 (24%)	8 (62%)
Patients with any hypersensitivity (narrow SMQ)	2 (67%)	2 (14%)	8 (28%)	4 (31%)
Patients with any anaphylactic reaction (broad SMQ)	1 (33%)	0	2 (7%)	1 (8%)

Source: Table 1.4. CSR-GLOBAL-1-EN
Peak titer: highest ADA titer from first infusion of avalglucosidase alfa for naïve patients that were seroconverted.
Abbreviations: ADA, antidrug antibodies; IAR, infusion associated reaction; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse events that developed, worsen or became serious on or after the 1st infusion of avalglucosidase alfa study drug, and up to 28 days after last infusion

Reference ID: 4836879

14.4. Bioanalytical Methods

PK assay: bioanalytical methods for the measurement of avalglucosidase alfa concentrations in human plasma

Avalglucosidase alfa concentrations in human plasma were determined with a sensitive enzymatic activity assay with fluorometric detection using a 4-methylumbelliferyl (4-MU)-α-D-glucoside substrate to detect avalglucosidase alfa activity. Two methods were validated, study DOH1429 with a LLOQ of 0.0125 µg/mL in neat plasma and study DOH1626 with a LLOQ of 0.0120 µg/mL in neat plasma. The two methods were cross-validated.

Summary of life cycle information of assay methods used during development, assay validation parameters, and performance of assays used in clinical trials are provided in Table 75, Table 76, Table 77, Table 78, and Table 79 below.

Table 75. Bioanalytical Method Life Cycle Information

Variable	Method Validation #1	Method Validation #2	Method Validation #3	TDR12857	LTS13769 (Before June 2019)	LTS13769 (After June 2019)	ACT14132	EFC14028
Analyte	Avalglucosidase alfa	Avalglucosidase alfa	Avalglucosidase alfa	Avalglucosidase alfa	Avalglucosidase alfa	Avalglucosidase alfa	Avalglucosidase alfa	Avalglucosidase alfa
Validation typ	Qualification	Full validation	Full validation	In-study	In-study	In-study	In-study	In-study
CTD ref #	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4	5.3.1.4
Method ID	ITR-629-0413	DOH1429	DOH1626	ITR-629-0413	ITR-629-0413/ DOH1429	DOH1626/ 2016426	DOH1626/ 2016426	DOH1626/ 2016426
BA site	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences)	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences)	(b) (4)	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences)	Sanofi US, Biomarkers and Clinical Bioanalyses, 1 The Mountain Rd, Framingham, MA 01701 USA (Previously Genzyme Clinical Laboratory Sciences)	(b) (4)		
Matrix	Sodium heparin plasma							
Platform	Enzyme activity assay							

Reference ID: 4836879

Variable	Method Validation #1	Method Validation #2	Method Validation #3	TDR12857	LTS13769 (Before June 2019)	LTS13769 (After June 2019)	ACT14132	EFC14028
Format	A validated enzymatic assay with fluorometric detection using a 4-MU substrate to detect avalglucosidase alfa activity in human plasma for the determination of avalglucosidase alfa concentrations							
Stock reference & lot (expiry)	Drug Lot# C1028097 Standard Lot# 19037-101 (15Apr2015)	Drug Lot# C1043865 Standard Lot# 16-GA-034 (04Mar2019) Drug Lot# 8W2680 Standard Lot#19NG026 (03 Apr 2021)	Drug Lot# C1079384 (Oct2020) Lot# C6616C01 (Jun2019)	Drug Lot# C1028097 Standard Lot# 19037-101 (15Apr2015)	Drug Lot# C1028097 Standard Lot# 19037-101 (15Apr2015) Drug Lot# C1043401 Standard Lot# 15-CRE-050 (07Jul2017) Drug Lot# C1043865 Standard Lot# 16-GA-034 (04Mar2019)	Drug Lot# 8W1579/ C1079384 (Oct2020)	Drug Lot# 8W1579/ C1079384 (Oct2020)	Drug Lot# 8W1579/ C1079384 (Oct2020)
Calibration range from the LLOQ to ULOQ	2.47 ng/mL to 600 ng/mL	2.47 ng/mL to 600 ng/mL	2.4 ng/mL to 600 ng/mL	2.47 ng/mL to 600 ng/mL	2.47 ng/mL to 600 ng/mL	2.4 ng/mL to 600 ng/mL	2.4 ng/mL to 600 ng/mL	2.4 ng/mL to 600 ng/mL
Matrix/study population	Normal plasma	Normal plasma	Normal plasma	Pompe disease patients	Pompe disease patients	Pompe disease patients	Pompe disease patients	Pompe disease patients
Relevant reference and applicable report amendment	ITR-629-0413	DOH1429	DOH1626	ITR-777-0415	LTS13769	No 20183572	No 20183574	No 20183578
Amendment history	Not applicable							

Source: Table 3, Appendix A, Summary of Biopharmaceutic studies and associated analytical methods.
Abbreviations: BA, bioavailability

Table 76. Summary Method Performance, Study ITR-629-0413

Parameter	Summary
Bioanalytical method validation report name and amendments	ITR-629-0413 (Study ITR-629-0413) Qualification Report: Recombinant Human NeoGAA Enzymatic Activity PK Assay In Human Plasma
Method description	A validated enzymatic assay with fluorometric detection using a 4MU-α-D-glucoside substrate to detect avalglucosidase alfa activity in human plasma for the determination of avalglucosidase alfa concentrations.
Materials used for calibration curve & concentration	NeoGAA enzyme standard stock solution at 100 µg/mL
Validated assay range	Curve range: 2.5 ng/mL to 600 ng/mL 0.0125 to 3.00 µg/mL in neat plasma
Material used for QCs & concentration	Pooled normal human plasma (heparin) spiked with NeoGAA at various concentrations spanning the range of the standard curve. Concentrations are in neat plasma. Qualification sample 1: 3000 ng/mL Qualification sample 2: 750 ng/mL Qualification sample 3: 12.5 ng/mL Positive control 1: 2250 ng/mL Positive control 3: 37.5 ng/mL Pooled normal human plasma (heparin) spiked with 4MU Positive control 2: equivalent to ~50ng/mL of NeoGAA
Minimum required dilutions (MRDs)	5
Source & lot of reagents (LBA)	5 mg/mL NeoGAA stock Lot # 19063-049 (14Jan2015) NeoGAA enzyme standard Lot#19037-101 (15Apr2015) 4MU-α-D-Glucoside substrate Sigma Lot #19244-55 24Sep20164-MU-α-D-Glucoside substrate Sigma Lot #19244-55 (24Sep2016) Positive Control-1 Lot#19063-93 10Apr2015 Positive Control-1 Lot#19063-93 (10Apr2015) Positive Control-2 Lot#19063-124 (02May2015) Positive Control-3 Lot#19063-95 (10 Apr2015) Normal Plasma pool Lot # 19063-127 (30Mar2018) Qualification Samples (QS) Lot#19244-56a (24Sep2016), QS2 Lot#19244-56b (24Sep2016), QS3 Lot#19244-56c (24Sep2016)
Regression model & weighting	4-parameter curve fit, no weighting

Validation Parameters	Method Validation Summary	
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	6 (plus 1 anchor point)
	Cumulative accuracy (%bias)	Cumulative accuracy ranged from –7.1 to 12.2%
	Cumulative precision (%CV) from LLOQ to ULOQ	Precision (%CV) ranged from 0 to 4.0%

Validation Parameters	Method Validation Summary	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 3 QS and PC1 and 3	Overall accuracy ranged from 0.3 to 14.2% bias
	Interbatch %CV QCs: 3 QS and 3 PC	Overall precision ranged from 3.6 to 7.6% CV
	Total error QCs: 3 QS and PC1 and PC3	Total error ranged from 4.1 to 20.7%
Selectivity & matrix effect	9 of 10 plasma samples spiked with neoGAA at 25 ng/mL, 250 ng/mL, and 2500 ng/mL demonstrated acceptable recovery ranging from 87.2 to 105.4%	
Interference & specificity	Not evaluated	
Hemolysis effect	Not evaluated	
Lipemic effect	Not evaluated	
Dilution linearity & hook effect	Pooled normal human plasma spiked with 60 µg/mL was diluted to the MRD and then serial diluted 1/3 for eight additional dilutions. For dilutions falling within the reportable range of the curve, %RE ranged from –6.6 to 6.8%.	
	No hook effect is evident in this assay up to a concentration of 12 000ng/mL NeoGAA.	
Bench-top/process stability	Up to 60 minutes on wet ice Samples diluted to 1/5 in assay buffer are stable: up to 72 hrs at 2-8°C Up to 60 min at ambient temperature	
Freeze-thaw stability	Stable up to 5 freeze/thaw cycles	
Long-term storage	3 years and 5 months at ≤ -60°C	
Parallelism	N/A	
Carry over	N/A	

Source: Table 3a, Appendix A, Summary of Biopharmaceutic studies and associated analytical methods.

Table 77. Summary Method Performance, Study DOH1429

Parameter	Summary
Bioanalytical method validation report name and amendments	DOH1429 (Study DOH1429) Validation Of A Fluorometric Enzyme Activity Assay for the Quantitation of NeoGAA in Human Plasma
Method description	A validated enzymatic assay with fluorometric detection using a 4-MU-α-D-glucoside substrate to detect avalglucosidase alfa activity in human plasma for the determination of avalglucosidase alfa concentrations.
Materials used for calibration curve & concentration	NeoGAA enzyme standard stock solution at 100 µg/mL
Validated assay range	Curve range: 2.5 ng/mL to 600 ng/mL 0.0125 to 3.00 µg/mL in neat plasma
Material used for QCs & concentration	Pooled normal human plasma (heparin) spiked with NeoGAA at various concentrations spanning the range of the standard curve. Concentrations are in neat plasma. LLOQ: 12.5 ng/mL LQC: 37.5 ng/mL MQC: 1500 ng/mL HQC: 2250 ng/mL ULOQ: 3000 ng/mL
Minimum required dilutions (MRDs)	5
Source & lot of reagents (expiration date)	NeoGAA enzyme standard Lot#16GA034 (22Sep2016) Note: This date was later extended to 04Mar2019. 4MU-α-D-Glucoside substrate Sigma Lot #16-CRE-018 (23Aug2021) Pooled Normal Human Plasma Lot # BRH1216625 (12Sep2020) Validation Samples (VS) Lot #s 16GA019a-e, (04Mar2019)
Regression model & weighting	4-parameter curve fit, 1/y2 weighting

Validation Parameters	Method Validation Summary	
Calibration curve performance during validation	Number of standard calibrators from LLOQ to ULOQ	6 (plus 1 anchor point)
	Cumulative accuracy (%bias) from LLOQ to ULOQ	Cumulative accuracy ranged from –5.9 to 8.1%
	Cumulative precision (%CV) from LLOQ to ULOQ	Precision (%CV) ranged from 1.0 to 4.0%
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 VS	Overall accuracy ranged from -0.8 to –19.9% bias
	Interbatch %CV QCs: 5 VS	Overall precision ranged from 3.4 to 7.9% CV
	Total error QCs: 5 VS	Total error ranged from 5.4 to 27.8%
Selectivity & matrix effect	100% of the selectivity samples demonstrated acceptable recovery at ULOQ, whereas 90% of the samples demonstrated acceptable recovery at LLOQ; 100% of the unspiked samples had values that were below quantification limit (BQL).	

Parameter	Summary
Validation Parameters	**Method Validation Summary**
Interference & specificity	Specificity was performed by spiking pooled human plasma with a high level of neoGAA (400 ng/mL post 1/5 dilution) as well as two irrelevant enzymes, at a similar level, rh-iduronidase and rh-α-galactosidase. Back-calculated concentration of the neoGAA-spiked sample was within 20% of nominal and that of the irrelevant enzymes was BQL.
Hemolysis effect	Not evaluated
Lipemic effect	Not evaluated
Dilution linearity & hook effect	Samples with concentrations up to 300 µg/mL diluted acceptably and linearly within the range of the Standard curve. The precision of the final concentrations across all dilutions within the range of the standard curve was 5.5% and their back-calculated concentrations were within ±20%. The Mean relative fluorescence units (RFUs) for all the dilutions above the range of the curve were greater than the RFU for the top calibrator. There was no evidence of prozone.
Bench-top/process stability	Samples stored directly at -20°C were not stable after 24 hours. Samples that were snap-frozen on dry ice, immediately after preparation, were stable for 72 hours, but failed stability at 1 and 3 weeks as well as one month. Samples that were thawed and incubated on ice were stable up to 2 hours.
Freeze-thaw stability	Stable up to 4 freeze/thaw cycles
Long-term storage	3 years and 5 months at ≤-60°C
Parallelism	N/A
Carry over	N/A

Source: Table 3a, Appendix A, Summary of Biopharmaceutic studies and associated analytical methods.
Abbreviations: BQL, below quantification limit; CV, coefficient of variation; HQC, higher quality control; LLOQ, lower limit of quantification; LQC, lower quality control; MQC, mid quality control; neoGAA, neo alpha-glucosidase; QC, quality control; ULOQ, upper limit of quantification; VS, validation sample

Reference ID: 4836879

Table 78. Summary Method Performance, Study DOH1626

Parameter	Summary
Bioanalytical method validation report name and amendments	Testing Facility Study No. 20169426 Study DOH1626 (Study DOH1626) Validation of a 4-MU Enzyme Assay for the Determination of GZ402666 (neoGAA) in Human Plasma (Heparin)
Method description	A validated enzymatic assay with fluorometric detection using a 4MU-α-D-glucoside substrate to detect avalglucosidase alfa activity in human plasma for the determination of avalglucosidase alfa concentrations.
Materials used for calibration curve & concentration	NeoGAA enzyme standard stock solution at 100 µg/mL
Validated assay range	Curve range: 2.45 ng/mL to 600 ng/mL 0.0120 to 3.00 µg/mL in neat plasma
Material used for QCs & concentration	Pooled normal human plasma (heparin) spiked with NeoGAA at various concentrations spanning the range of the standard curve. Concentrations are in neat plasma. LLOQ: 12 ng/mL Low (QC1): 36 ng/mL Medium (QC2): 300 ng/mL High (QC3): 2000 ng/mL ULOQ: 3000 ng/mL
Minimum required dilutions (MRDs)	5
Source & lot of reagents (expiration date)	Pooled Normal Human Plasma Lot # BRH1565321 (pooled lot) and BRH1577795-BRH1577814 (individual lots) (30 Sep 2023 (pooled lot), 31 Oct 2023 (individuals lots)
Regression model & weighting	4-parameter curve fit, $1/y^2$ weighting

Validation Parameters	Method Validation Summary	
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	10 (plus 1 anchor point)
	Cumulative accuracy (%bias) from LLOQ to ULOQ	Cumulative accuracy ranged from -8 to 11%
	Cumulative precision (%CV) from LLOQ to ULOQ	Precision (%CV) ranged from 2 to 5%
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 VS	Overall accuracy ranged from 3 to 17% bias
	Interbatch %CV QCs: 5 VS	Overall precision ranged from 4 to 7% CV
	Total error QCs: 5 VS	Total error was ≤30%
Selectivity & matrix effect	Ten out of 10 individual lots (100%) of human plasma spiked at LLOQ and QC3 levels met the acceptance criteria (within ±25% RE at the LLOQ and ±20% RE at QC3 levels). Ten of 10 individual lots (100%) of human plasma had fluorescence values below the lower limit of quantification when tested in the assay.	

Parameter	Summary
Interference & specificity	Specificity was performed by spiking pooled human plasma with a high level of neoGAA (400 ng/mL post 1/5 dilution) as well as two irrelevant enzymes, at a similar level, rh-iduronidase and rh-α-galactosidase. Back-calculated concentration of the neoGAA-spiked sample was within 20% of nominal and that of the irrelevant enzymes was BQL.
Hemolysis effect	The nonspecific interference testing met all acceptance criteria with a %RE of -16% for the hemolyzed sample.
Lipemic effect	The nonspecific interference testing met all acceptance criteria with a %RE of -16% for the lipemic sample.
Dilution linearity & hook effect	Dilution linearity of the assay met acceptance criteria with a combined CV% of 17% for dilution linearity samples falling within range of the curve, and 2/3 of the dilutions having %RE within ±20%, therefore demonstrating dilution linearity. neoGAA samples were analyzed at a concentration of 500 µg/mL (166.67 times the ULOQ) in human plasma and a prozone effect was not observed as the samples had relative fluorescence unit (RFU) values above the ULOQ.
Bench-top/process stability	Samples that were thawed and incubated on ice were stable up to 4 hours.
Freeze-thaw stability	Stable up to 3 freeze/thaw cycles
Long-term storage	3 years and 5 months at ≤ -60°C
Parallelism	N/A
Carry over	N/A

Source: Table 3a, Appendix A, Summary of Biopharmaceutic studies and associated analytical methods.
Abbreviations: BQL, below quantification limit; CV, coefficient of variation; LLOQ, lower limit of quantification; neoGAA, neo alpha-glucosidase; QC, quality control; RE, random error; ULOQ, upper limit of quantification; VS, validation sample

Table 79. Summary Method Performance, Trials TDR12857, LTS13769, ACT14132, and EFC14028

Variable	Trial #TDR12857	Trial #LTS13769 (Through June 2019)	Trial #ACT14132	Trial #EFC14028	Trial #LTS13769 (After June 2019)
Reference no.	ITR-777-0415	LTS13769	20183574	20183578	20183572
Assay passing rate	89.6% passing rate (5 failed out of 48 total)	90% passing rate (3 failed out of 30 total)	93% passing rate (1 failed out of 14 total)	88% passing rate (6 failed out of 51 total)	% passing rate (failed out of total) 73% passing rate (3 failed out of total 11)
Standard curve performance	Cumulative bias range: -0.1 to 10.5%	Cumulative bias range: -7.8 to 3.9%	Cumulative bias range: -5% to 10%	Cumulative bias range: -7% to 6%	Cumulative bias range: -10 to 11%
	Cumulative precision: 0 to 2.1%	Cumulative precision: -0.25 to 12.2%	Cumulative precision: 3 to 10%	Cumulative precision: 2% to 6%	Cumulative precision: 1% to 5%CV
QC performance	Cumulative bias range: 3. 27 to 7. 86%	Cumulative bias range: -2.6 to -11.6%	Cumulative bias range: -5% to 2%	Cumulative bias range: -5% to 6%	Cumulative bias range: -8 to 1%
	Cumulative precision: ≤9.1% CV	Cumulative precision: 5.9% to 9.6% CV	Cumulative precision: 10 to 11% CV	Cumulative precision: 7% to 13%CV	Cumulative precision: 12% to 15%CV
	TE: ≤14.7%	TE: ≤17.9%	TE: ≤15%	TE: ≤19%	TE: ≤20%
Method reproducibility	Incurred sample reanalysis was not performed in this study.	Incurred sample reanalysis was not performed in this study.	ISR was conducted on 30 plasma samples (at the time of this interim report). Twenty-eight of the 30 samples (93.3%) passed acceptance criteria with % difference ≤30% between the original and repeat analyses.	Incurred sample reanalysis was conducted on 96 neoGAA plasma samples. Ninety-five of the 96 neoGAA samples (99.0%) passed acceptance criteria with % difference ≤30% between the original and repeat analyses.	Incurred sample reanalysis was conducted Incurred sample reanalysis was not conducted for this study.
Study sample analysis/ stability	Long term stability is currently established up to 3 years and 5 months at <-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability.	Long term stability is currently established up to 3 years and 5 months at <-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability.	Long term stability is currently established up to 3 years and 5 months at <-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability.	Long term stability is currently established up to 3 years and 5 months at <-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability.	Long term stability is currently established up to 3 years and 5 months at <-60°C. All standards, QCs and samples tested in this assay were analyzed within established stability.

Reference ID: 4836879

Variable	Trial #TDR12857	Trial #LTS13769 (Through June 2019)	Trial #ACT14132	Trial #EFC14028	Trial #LTS13769 (After June 2019)
Standard calibration curve performance during accuracy and precision runs	6 standard curve points from LLOQ to ULOQ (plus 1 anchor points)	6 standard curve points from LLOQ to ULOQ (plus 1 anchor points)	10 standard curve points from LLOQ to ULOQ (plus 1 anchor points)	10 standard curve points from LLOQ to ULOQ (plus 1 anchor points)	10 standard curve points from LLOQ to ULOQ (plus 1 anchor points)

Source: Table 3a, Appendix A, Summary of Biopharmaceutic studies and associated analytical methods.

PD assay: bioanalytical method for the measurement of Glc4 concentration in human urine.
The Applicant developed an LC-MS/MS method to quantify hexose tetrasaccharide (Hex4) in human urine. The urinary Hex4 assay measures its major component, glucose tetrasaccharide (Glc4). The urine Glc4 concentration was normalized by urine creatinine and reported as mmol Glc4/mol creatinine. Urine creatinine was measured using the kinetic Jaffe colorimetric method on the Randox RX Daytona bench-top automated clinical chemistry analyzer.

The range of the Glc assay was 0.5 to 400 µg/mL in neat urine. Intra-assay and inter-assay accuracy ranged between -0.38 to 11.9%, and -0.63 to 3.11%, respectively. Intra-assay and inter-assay precision ranged from 0.35 to 12%, and 1.14 to 8.98%, respectively. No carry-over effect was observed. Glc4 was shown to be stable in human urine after 5 freeze and thaw cycles and for 5 days at 2-8°C. The long-term stability testing of urine samples showed samples are stable for up to 2 years at -20°C; and are stable for up to 18 months at LQC level and up to 2 years at HQC level at -80°C.

14.5. Pharmacometrics Review

A population pharmacokinetics (popPK) model was developed by the Applicant to characterize the PK of avalglucosidase alpha in patients with LOPD and IOPD. Subjects intrinsic and extrinsic factors which influence the PK and PK variability of avalglucosidase alpha were identified. Individual avalglucosidase alpha exposure metrics were derived from popPK model or noncompartment analysis (NCA) for subsequent exposure-response (E-R) analyses for efficacy and safety. In this review, the FDA Pharmacometrics Reviewer verified the Applicant's popPK model and E-R analyses, and conducted independent analyses to evaluate the Applicant's dose selection.

14.5.1. Population PK Analyses

Two phase 1/2 trials (TDR12857 and its follow-up trial LTS13769), one phase 3 trial (EFC14028 (COMET)) and a phase 2 trial (ACT14132) were included in the popPK analyses (Table 80). Total of 2583 PK samples collected from 91 patients (75 patients with LOPD and 16 pediatric patients with IOPD) across the four trials were included in the final popPK analysis. Out of the 2583 PK samples, 2257 sample concentrations were above the lower limit of quantification (LLOQ) and 326 sample concentrations were below LLOQ. Specifically, in patients with IOPD (ACT14132), among the 218 samples included in the dataset, 200 had concentrations above the LLOQ and 18 below the LLOQ. The demographic characteristics at baseline of the patients included in the popPK analysis are summarized in Tables 81 and 82.

Table 80. Summary of Clinical Trials Included in the Population PK Analysis

Phase	Clinical trial	Dose Levels	Regimen/ Duration	Patients	PK Sampling	N[a]	Status at the Time of Filing
1	TDR12857	5, 10 and 20 mg/kg (parallel groups)	QOW/ 6 months	LOPD	Dense sampling[b]	24	Completed
2	LTS13769	5[c], 10[c] and 20 mg/kg	QOW/ Follow-up up to 6 year	LOPD	Dense sampling[d]	19[g]	Ongoing Cut off Date : November 4th 2019
3	EFC14028	20 mg/kg	QOW/ 49 weeks[g]	LOPD	Dense sampling[e]	51	Ongoing Cut off Date : November 4th 2019 PK snapshot on January 14th 2020
4	ACT14132	20 and 40 mg/kg	QOW/ 25 weeks[h]	IOPD	Dense sampling[f]	16	Primary Analysis Period completed

Source: Applicant's response to IR sent on Nov 13, 2020
[a] For patients included in EFC14028 and ACT14132, only patients under avalglucosidase alfa treatment are considered
[b] Planned PK: predose, EOI (end of infusion) then 1, 2, 4, 8, 12, 16, 24, 32 and 48 h postdose on week 1, week 13 and week 25
[c] Patients switched to 20 mg/kg after 2 to 3 years in the course
[d] Planned PK: predose, EOI, 1, 4, 8, 12, and 24 h postdose on week 26, week 52 and then once a year (planned)
[e] Planned PK: predose, EOI, 2, 4, 6 and 8 h post dose on week 1 and week 49 + EOI / 2 h postdose timepoints on weeks 13, 25 and 37.
[f] Planned PK: predose, EOI, 2, 4, 6 and 8 h postdose on week 1 and week 25 + predose and 2 h postdose timepoints on week 13. For patients treated with 40 mg/kg, additional samples at 12 and 16 hours postdose are planned
[g] One patient had no PK data in LTS13679
[h] Primary analysis period including PK evaluation completed. Extension treatment period is ongoing
Abbreviations: IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; PK, pharmacokinetics; QOW, every other week

Table 81. Demographic Characteristics (Baseline Values) of the Patients Included in the PopPK Anal sis

Demographic characteristic or covariate	Modality	Counts by study (n, %)			
		TDR12857 (n=24)	EFC14028 (n=51)	ACT14132 (n=16)	All (n=91)
Sex	Males	12 (50%)	27 (52.9%)	10 (62.5%)	49 (53.8%)
	Females	12 (50%)	24 (47.1%)	6 (37.5%)	42 (46.2%)
Race	Caucasian	21 (87.5%)	47 (92.2%)	8 (50%)	76 (83.5%)
	Black	1 (4.2%)	1 (2.0%)	0 (0%)	2 (2.2%)
	Asian	0 (0%)	3 (5.9%)	8 (50%)	11 (12.1%)
	Other	2 (8.3%)	0 (0%)	0 (0%)	2 (2.2%)
Age	<6 years	0 (0%)	0 (0%)	4 (25%)	4 (4.4%)
	≥6 and <12 years	0 (0%)	0 (0%)	12 (75%)	12 (13.2%)
	≥12 and <18 years	0 (0%)	1 (2.0%)	0 (0%)	1 (1.1%)
	18-64 years	20 (83.3%)	45 (88.2%)	0 (0%)	65 (71.4%)
	65 years	4 (16.7%)	5 (9.8%)	0 (0%)	9 (9.9%)
Pretreatment with alglucosidase alfa	Naive	10 (41.7%)	51 (100%)	0 (0%)	61 (67.0%)
	Pre-treated	14 (58.3%)	0 (0%)	16 (100%)	30 (33.0%)
Initial Dose[a]	5 mg/kg	8 (33.3%)	0 (0%)	0 (0%)	8 (8.8%)
	10 mg/kg	7 (29.2%)	0 (0%)	0 (0%)	7 (7.7%)
	20 mg/kg	9 (37.5%)	51 (100%)	6 (37.5%)	66 (72.5%)
	40 mg/kg	0 (0%)	0 (0%)	10 (62.5%)	10 (11.0%)
ADA[b]	Negative	19 (79.2%)	49 (96.1%)	14 (87.5%)	82 (90.1%)
	Positive	5 (20.8%)	2 (3.9%)	2 (12.5%)	9 (9.9%)
ADAMAX[c]	Negative	4 (16.7%)	2 (3.9%)	9 (56.3%)	15 (16.5 %)
	Positive	20 (83.3%)	49 (96.1%)	7 (43.8%)	76 (83.5 %)

Source: Applicant's response to IR sent on Nov 13, 2020
[a] For TDR12857 initial dose is provided. Patients continuing in LTS13769 were progressively shifted to 20 mg/kg dose
[b] Baseline value of ADA, this covariate being the longitudinal binary covariate indicating the presence (1) or absence (0) of anti-avalglucosidase alfa antibodies
[c] ADAMAX is an ID unique binary covariate indicating the absence at any time (0) or the presence at least once (1) along studies follow-up of anti-avalglucosidase alfa antibodies
Abbreviations: ADA, antidrug antibodies; popPK, population pharmacokinetics

Table 82. Descriptive Statistics on Continuous Demographic or Covariate at Baseline for Patients Included in the PopPK Analysis

Covariate or demographic characteristic	TDR12857 (N=24)	EFC14028 (N=51)	ACT14132 (n=16)	All (N=91)
Age (AGE, years)	46.0 (16.6) [41.5; 19.8-78.4]	46.1 (14.5) [47.7; 16.5-78.3]	6.9 (3.21) [7.5; 1-11]	39.2 (20.3) [40.3; 1-78.4]
Body Weight (WT, kg)	72.0 (14.5) [73.5; 48.0-111]	77.8 (22.1) [75.9; 38-129]	29.2 (15.4) [25.4; 9.9-63.5]	67.7 (26.3) [68.1; 9.9-129]
Albumin (ALB, g/L)	40.4 (3.27) [40.5;35-47]	46.0 (2.09) [46.0; 40-50]	45.0 (3.81) [46.0; 36-52]	44.3 (3.67) [45.0; 35-52]
Alkaline Phosphatase (ALP, IU/L)	61.7 (18.2) [58.5; 28.0-114]	72.4 (17.3)[a] [72.0; 48.0-125]	212 (78.5) [200; 118-394]	94.2 (65.7)[b] [28-394]
Alanine Amino Transferase (ALT, IU/L)	51.1 (34.3) [43.5; 19.0-182]	81.5 (56.4)[a] [69.0; 24-319]	140 (55.7] [131; 47-231]	83.8 (58.6)[b] [65.5; 19-319]
Aspartate Amino Transferase (AST, IU/L)	55.5 (41.7) [44.5; 23.0-212]	80.0 (55.5)[a] [59.0; 27.3-285]	222 (125) [184; 64-507]	98.8 (90.6)[b] [61.5; 23-507]
Total Bilirubin (BILI, µmol/L)	10.1 (5.50) [8.60; 3.40-22.2]	8.50 (4.37)[a] [7.42; 3-23]	5.13 (2.28) [4.79; 2.57-10.6]	8.35 (4.69)[b] [6.82; 2.57-23]
Creatine Kinase (CK, IU/L)	500 (310) [429; 83-1330]	746 (580)[a] [583; 158-3128]	1243 (643) [12457; 318-2607]	769 (583)[b] [577; 83-3128]
Normalized Creatinine Clearance (CL_{CRN}, mL/min)	134 (42.8) [139; 50.2-205]	157 (43.5)[a] [156; 67.6-246]	338 (119) [324; 141-529]	183 (95.9)[b] [161; 50.2-529]

Source: Applicant's response to IR sent on Nov 13, 2020
Descriptive statistics are: mean (standard deviation) [Median; minimum-maximum]
[a] n=50
[b] n=90
Abbreviations: popPK, population pharmacokinetics

The PK of avalglucosidase alpha is described by a 3-compartment model with parallel linear/nonlinear clearances from the central compartment. The two concatenated peripheral compartments were added to characterize the secondary kinetic phase. The second peripheric compartment was linked to the central one through a low clearance responsible for drug returning to the systemic circulation. The final model estimates and bootstrap median and the 2.5th and 97.5th percentiles are summarized in Table 83.

Table 83. Summary of the Final PopPK Model Parameters and Bootstra Results

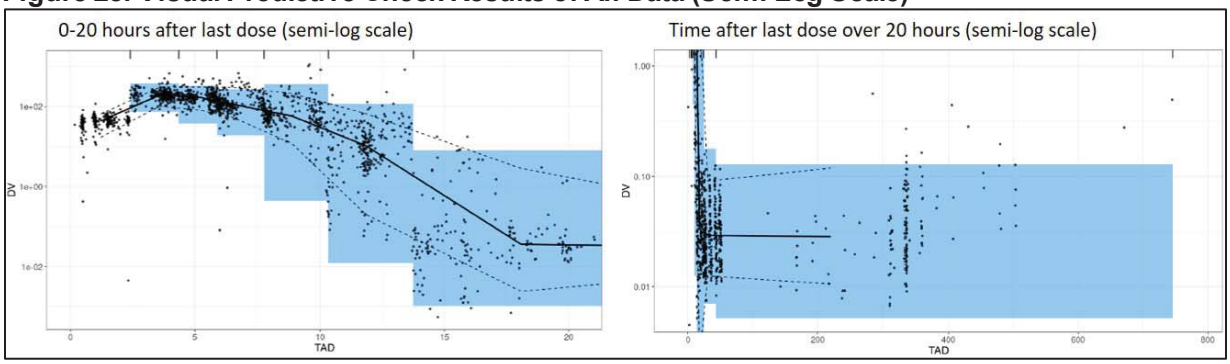
	Final updated model	Bootstrap (n=846)	
Parameter	**Estimate**	**Estimate**	**[95%CI]**
Typical value of CL (θ1, L/h)	0.808	0.796	[0.674 ; 0.874]
Typical value of V1 (θ2, L)	3.37	3.36	[3 ; 3.57]
Typical value of VM (θ3, mg/h)	12	12.2	[9.28 ; 15.1]
Typical value of KM (θ4, µg/mL)	0.541	0.55	[0.395 ; 0.728]
Typical value of Q2 (θ5, L/h)	0.254 (Fixed)	0.254 (Fixed)	NA
Typical value of V2 (θ6, L)	296 (Fixed)	296 (Fixed)	NA
Typical value of Q3 (θ7, L/h)	1.87 (Fixed)	1.87 (Fixed)	NA
Typical value of V3 (θ8, L)	1.31 (Fixed)	1.31 (Fixed)	NA
Typical value of QPC (θ9, L/h)	0.0157	0.0134	[0.00826 ; 0.0227]
Effect of WT on CL (θ10) [a]	0.896	0.889	[0.618 ; 1.1]
Effect of WT on V1 (θ11) [b]	0.661	0.652	[0.484 ; 0.78]
Effect of WT on Vm (θ12) [c]	0.463	0.472	[0.166 ; 0.652]
	Inter-individual variability		
ω^2 CL	0.0907	0.0896	[0.0573 ; 0.136]
ω^2 V1	0.0184	0.0189	[0.00476 ; 0.0388]
ω^2 VM	0.118	0.117	[0.0201 ; 0.236]
ω^2 KM	0.243	0.214	[0.0702 ; 0.417]
ω^2 QPC	1.23	1.72	[0.492 ; 3.48]
	Residual variability		
Proportional	0.12	0.116	[0.0967 ; 0.136]

Source: Applicant's response to IR sent on Nov 13, 2020
QPC is the clearance from second peripheric to central compartments and was nonreversible.
θ and ω are the PopPK parameters (θ) and the variance of their associated interindividual variability (ω^2)
[a] The expression of the linear clearance (CL) including covariates effects is: CL = TVCL x (WT/70.5)**θ10. WT is the weight and 70.5 the median of weight values corresponding to 70.5 kg
[b] The expression of the linear clearance (CL) including covariates effects is: V1 = TVV1 x (WT/70.5)**θ11. WT is the weight and 70.5 the median of weight values corresponding to 70.5 kg
[c] The expression of the nonlinear clearance Vm parameter including covariate effect is: Vm = TVVm x (WT/70.5)**θ12. WT is the weight and 70.5 the median of weight values corresponding to 70.5 kg
Abbreviations: CI: confidence interval; NA, not applicable; popPK, population pharmacokinetics; %RSE, percentage of relative standard error (100% * SE / Estimate)

Reference ID: 4836879

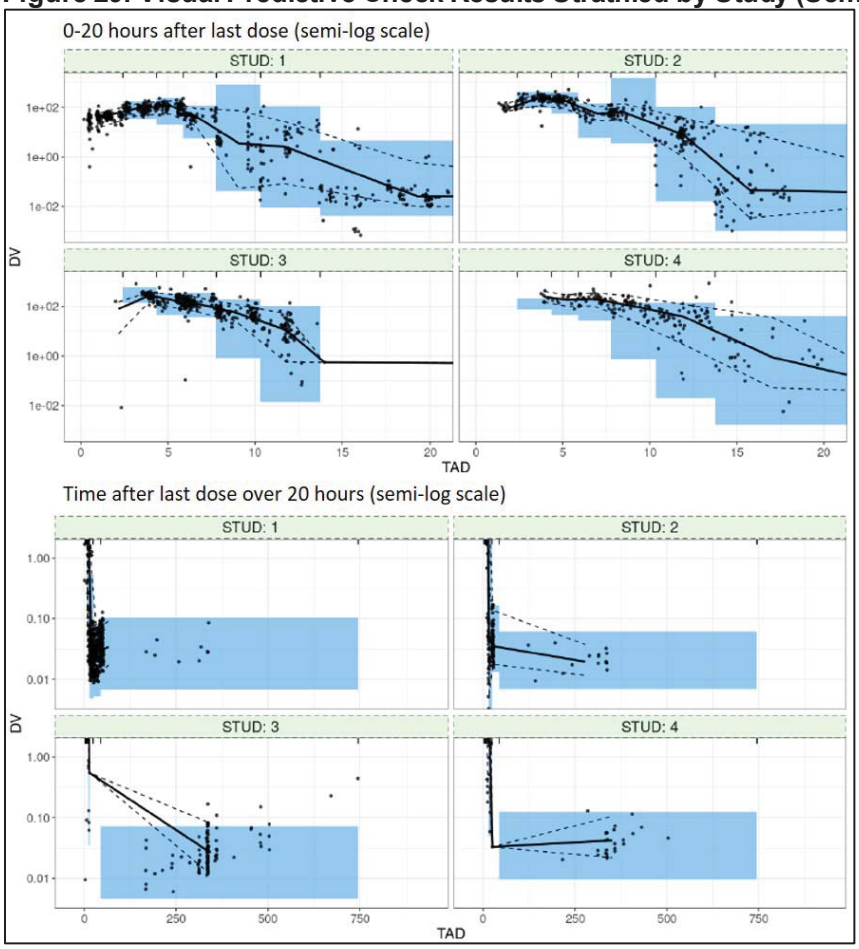
The visual predictive check (VPC) results of all data and stratified by study are shown in Figures 28 and 29, respectively.

Figure 28. Visual Predictive Check Results of All Data (Semi-Log Scale)



Source: Applicant's response to IR sent on Nov 13, 2020
Dark black dots: Observations; continuous and dashed line: Median and 90% confidence interval of observations.
Blue areas: Prediction interval. Generated from 1000 simulations

Figure 29. Visual Predictive Check Results Stratified by Study (Semi-Log Scale)



Source: Applicant's Response to IR Sent on Nov 13, 2020
Dark Black Dots: Observations; Continuous and Dashed Line: Median and 90% Confidence Interval of Observations. Blue Areas: Prediction Interval. Generated From 1000 Simulations

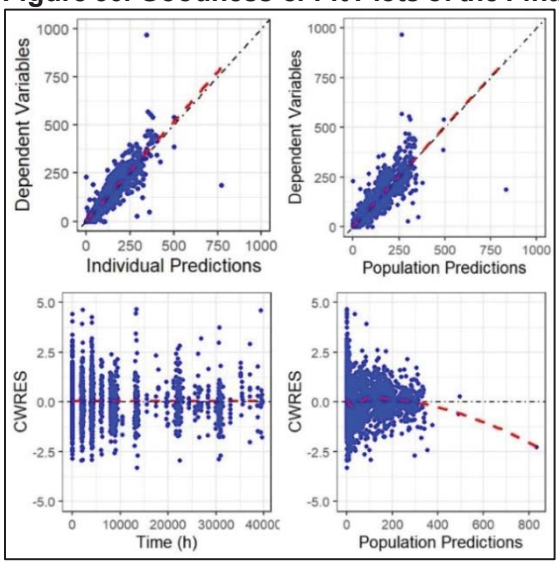
Reference ID: 4836879

Reviewer's comment:

The Applicant's original popPK analysis did not include patients with IOPD. Upon FDA's request, additional data from 16 patients with IOPD were included in the updated (final) popPK model development. Compared to the original popPK model, which did not identify any significant covariate, the updated popPK model identified body weight as a significant covariate on CL, V1 and Vm in subjects with wider body weight range, supporting the proposed body weight-based dosing regimen. The final model results did not show remarkable changes to those estimated by the original model.

Based on the Applicant's VPC plots, the final popPK model appears acceptable to describe the PK of avalglucosidase alfa in the patients with Pompe disease. FDA also evaluated the goodness-of-fit (GOF) plots in all subjects (Figure 30), and stratified by naïve/non-naïve (Figure 31), study (Figure 32), ADA status (Figure 33), and disease type (Figure 34). The results confirmed that the Applicant's final popPK model was able to describe the PK of avalglucosidase alfa reasonably well in each subpopulations.

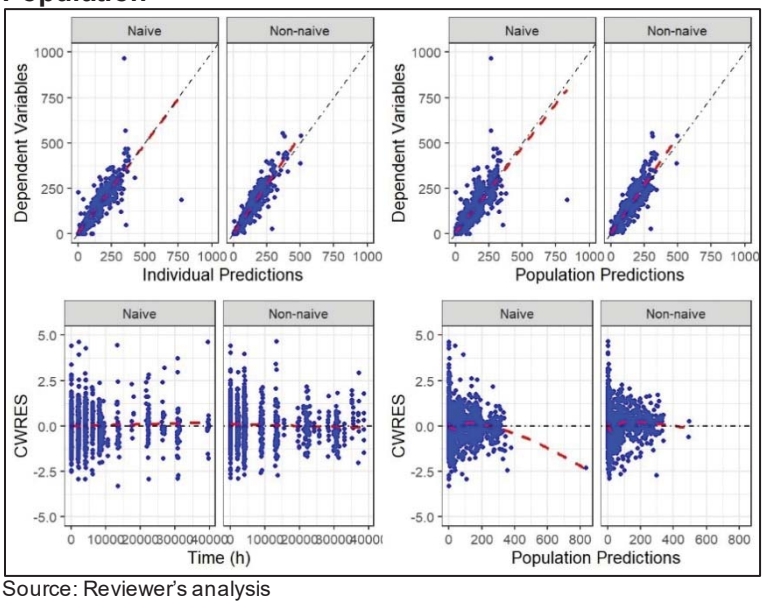
Figure 30. Goodness-of-Fit Plots of the Final PopPK Model (All Subjects)



Source: Reviewer's analysis
Abbreviations: CWRES, conditional weighted residuals; popPK, population pharmacokinetics

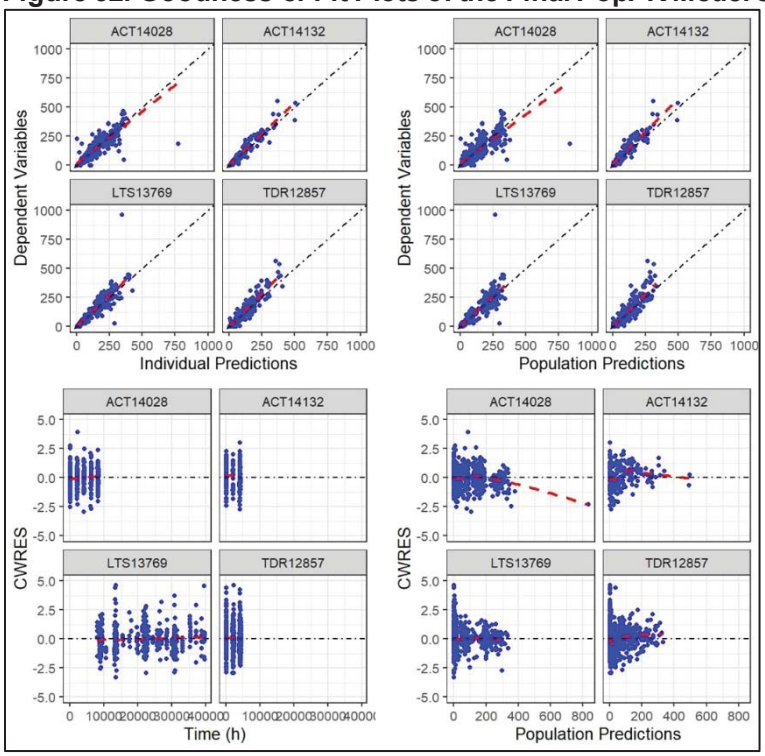
Reference ID: 4836879

Figure 31. Goodness-of-Fit Plots of the Final PopPK Model Stratified by Naive/Non-Naïve Patient Population



Source: Reviewer's analysis
Abbreviations: CWRES, conditional weighted residuals; popPK, population pharmacokinetics

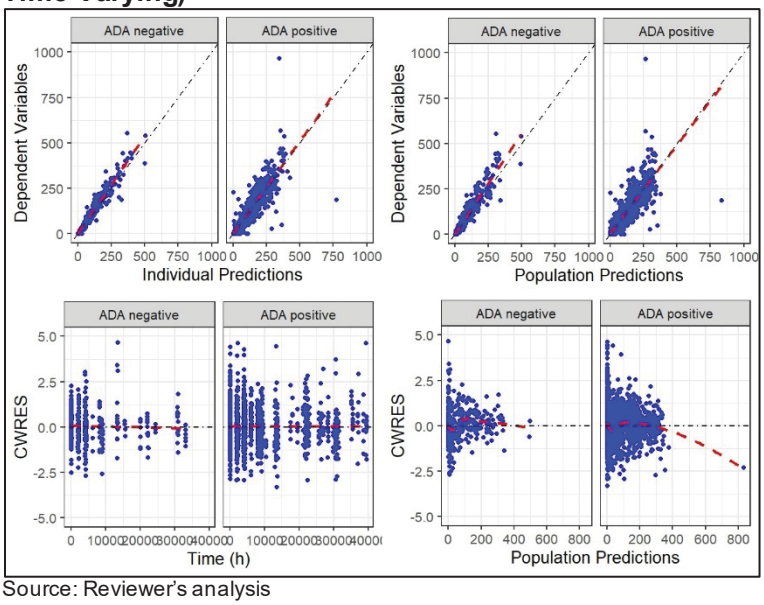
Figure 32. Goodness-of-Fit Plots of the Final PopPK Model Stratified by Study



Source: Reviewer's analysis
Abbreviations: CWRES, conditional weighted residuals; popPK, population pharmacokinetics

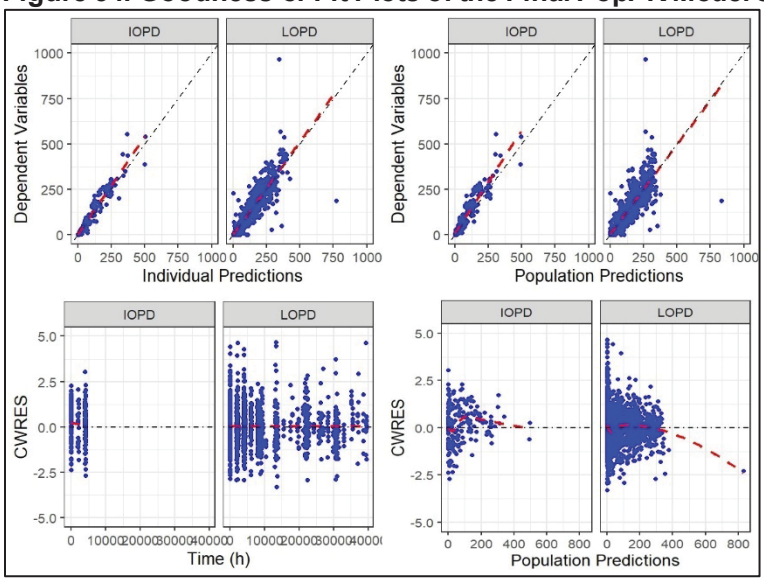
Reference ID: 4836879

Figure 33. Goodness-of-Fit Plots of the Final PopPK Model Stratified by ADA Status (Constant, Not Time-Varying)



Source: Reviewer's analysis
Abbreviations: ADA, antidrug antibodies; CWRES, conditional weighted residuals; popPK, population pharmacokinetics

Figure 34. Goodness-of-Fit Plots of the Final PopPK Model Stratified by Disease Type



Source: Reviewer's analysis
Abbreviations: CWRES, conditional weighted residuals; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease, popPK, population pharmacokinetics

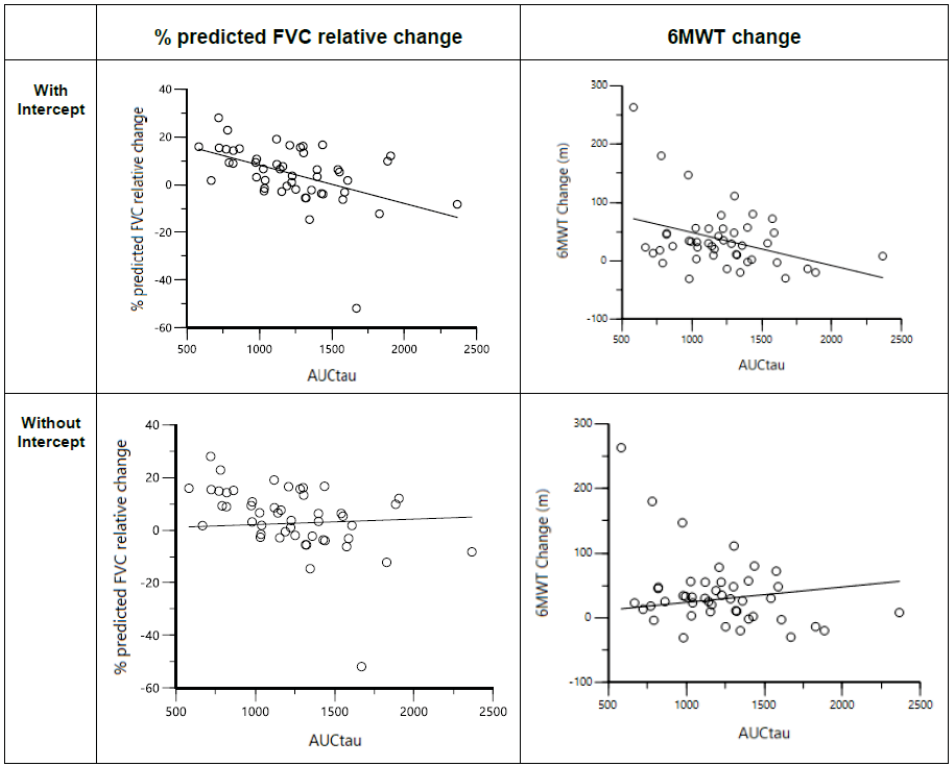
Reference ID: 4836879

14.5.2. Exposure-Response Analyses

14.5.2.1. Exposure-Response Analyses for Efficacy

The efficacy data from the phase 3 trial EFC14028 avalglucosidase alfa (20 mg/kg) treated patients (n=51) were included in the analysis. The primary and secondary efficacy endpoints evaluated were percent predicted forced vital capacity (%FVC) change from baseline and 6-minute walk test (6MWT) change from baseline, respectively. The efficacy parameters were determined at weeks 1 (baseline), 13, 25, 37 and 49. The individual exposure metrics (AUCτ, C_{max}) were derived from the final popPK model. For each efficacy endpoint and exposure metric combination, linear regressions were conducted either with or without intercept estimates (forcing at 0). The analysis results are shown in Figure 35 and Table 84.

Figure 35. Percent Predicted FVC and 6MWT Change Versus Baseline as Function of AUCτ, Week 9



Source: Applicant Study Report POH0817
Abbreviations: 6MWT, 6-minute walk test; AUC, area under the concentration-time curve; FVC, forced vital capacity

Reference ID: 4836879

Table 84. Inferential Statistics of Efficac Parameters Versus Ex osure Linear Re ressions

Efficacy Parameter	Regressor	Method	Regression Parameter	Estimate	r^2	p-value
FVC	AUC	Without Intercept	Slope	0.00208	0.0420	0.153
		With Intercept	Intercept	24.2	0.221	**0.0000850**
			Slope	-0.0161		**0.000646**
6MWT	AUC	Without Intercept	Slope	0.0238	0.216	**0.00101**
		With Intercept	Intercept	105	0.136	**0.000344**
			Slope	-0.0567		**0.0117**

Bold numbers correspond to p-value < 0.05 thus indicating statistically significant slope or intercept., r2: coefficient of determination

Source: Applicant Study Report POH0817
Abbreviations: 6MWT, 6-minute walk test; AUC, area under the concentration-time curve; FVC, forced vital capacity

Reviewer's comment:

The Applicant's E-R analyses for efficacy were based on the exposure metrics derived from the original popPK model. Because the parameter estimates by original model are very similar to the updated ones, the update of the popPK model is not expected to significantly impact the derived exposure metrics for each individual patient from the phase 3 trial EFC14028. Thus, the E-R analyses for efficacy based on the exposure metrics derived from the original popPK model is still considered acceptable. However, it is not appropriate to fix the intercept at 0. Further, given that this is univariate analysis, potential imbalance in patient's baseline factors across the exposure quantiles could have contributed to the negative trend of the E-R relationship.

Upon request, the Applicant summarized and compared the baseline demographic and disease characteristics by different exposure quartiles (Table 85). Consistent with the popPK findings on body weight effect, heavier and older patients were mostly distributed in higher AUC quartiles 3 and 4. In addition, patients in the lowest AUC quartile 1 appear to have higher FVC and 6MWT at baseline compared to quartile 4, which may have contributed to the negative E-R relationship for efficacy.

Table 85. Overview of the Baseline Demographic and Disease Characteristics by Avalglucosidase Alfa AUCT Quartile, Trial EFC14028 COMET

Subgroup	Category	Patients counts (N(%)) AUC quartiles			
		Quartile 1 (n=13)	Quartile 2 (n=13)	Quartile 3 (n=13)	Quartile 4 (n=12)
Body weight at baseline	<75.9 kg[a]	13 (100)	6 (46.2)	4 (30.8)	2 (16.7)
	>=75.9 kg[a]	0 (0)	7 (53.8)	9 (69.2)	10 (83.3)
Age at baseline	<45 years	10 (76.9)	8 (61.5)	3 (23.1)	3 (25.0)
	>=45years	3 (23.1)	5 (38.5)	10 (76.9)	9 (75.0)
6MWT at baseline	<403.5 m[a]	5 (38.5)	7 (53.8)	4 (30.8)	6 (50.0)
	>=403.5 m[a]	8 (61.5)	6 (46.2)	9 (69.2)	6 (50.0)
FVC at baseline	<55%	3 (23.1)	4 (30.8)	4 (30.8)	5 (41.7)
	>=55%	10 (76.9)	9 (69.2)	9 (69.2)	7 (58.3)
Disease duration at inclusion	No data	1 (7.69)	0 (0)	0 (0)	0 (0)
	<10.7 years[a]	6 (46.2)	4 (30.8)	7 (53.8)	7 (58.3)
	>=10.7 years[a]	6 (46.2)	9 (69.2)	6 (46.2)	5 (41.7)
Gender	Female	9 (69.2)	6 (46.2)	4 (30.8)	5 (41.7)
	Male	4 (30.8)	7 (53.8)	9 (69.2)	7 (58.3)
Region	Non US	12 (92.3)	10 (76.9)	10 (76.9)	7 (58.3)
	US	1 (7.69)	3 (23.1)	3 (23.1)	5 (41.7)
Use of walking device	No	12 (92.3)	10 (76.9)	11 (84.6)	11 (91.7)
	Yes	1 (7.69)	3 (23.1)	2 (15.4)	1 (8.33)

a Median value at baseline
Source: Applicant's response to an IR on June 29 2021

14.5.2.2. Exposure-Response Analyses for Safety

Upon the FDA's request, the Applicant conducted multivariate E-R analyses for safety using the pooled data from trials TDR12857, LTS13769, EFC14028, and ACT14132. The evaluated safety endpoints included any TEAEs, treatment-emergent SAEs, severe TEAEs, protocol-defined infusion associated reaction (IAR), algorithm-defined IARs, nasopharyngitis, headache, diarrhea, back pain, fall, and nausea. Comprehensive blood sampling schedules were implemented in all clinical trials to allow for noncompartmental analysis (NCA). Thus, the multivariate E-R analyses for safety were conducted based on the AUC_{last} determined by NCA. Both AUC_{last} and $\log(AUC_{last})$ were evaluated. Analyses were performed in all patients and each subgroup of patients with IOPD, patients with LOPD, treatment-naïve and non-naïve patients. For safety endpoints included in the Applicant's exposure-response analyses, no significant trend of higher incidence of events for higher exposure is observed. Table 86 shows the multivariate logistic regression results for the probability of experiencing a TEAE.

Table 86. Logistic Regression Representing the Probability of Experiencing a TEAE as Function of AUC or log(AUC) Adjusted by Baseline Covariates (Age at Baseline, Disease Type/Treatment-Naïve/Treatment Experienced)

Parameters	Odds Ratio (95% CI)	P-Value
Exposure (AUC)	1.00 (1.000,1.003)	0.1548
Age at baseline	1.03 (0.974,1.098)	0.2661
Disease type (LOPD vs. IOPD)	0.36 (0.018,7.389)	0.5075
Lack of fit of the model		0.3065
Exposure log(AUC)	1.71 (0.447,6.537)	0.4337
Age at baseline	1.04 (0.977,1.102)	0.2332
Disease type (LOPD vs. IOPD)	0.25 (0.013,4.961)	0.3638
Lack of fit of the model		0.4968
Exposure (AUC)	1.00 (1.000,1.003)	0.1299
Age at baseline	1.04 (0.986,1.099)	0.1439
Treatment-naïve vs. treatment-experienced	0.15 (0.012,1.777)	0.1318
Lack of fit of the model		0.7900
Exposure log(AUC)	2.04 (0.494,8.458)	0.3239
Age at baseline	1.04 (0.986,1.102)	0.1405
Treatment-naïve vs. treatment-experienced	0.13 (0.010,1.617)	0.1120
Lack of fit of the model		0.3694

Source: adapted from the Applicant's response appendix to the IR sent on Nov 13, 2020.
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease; TEAE, treatment-emergent adverse event

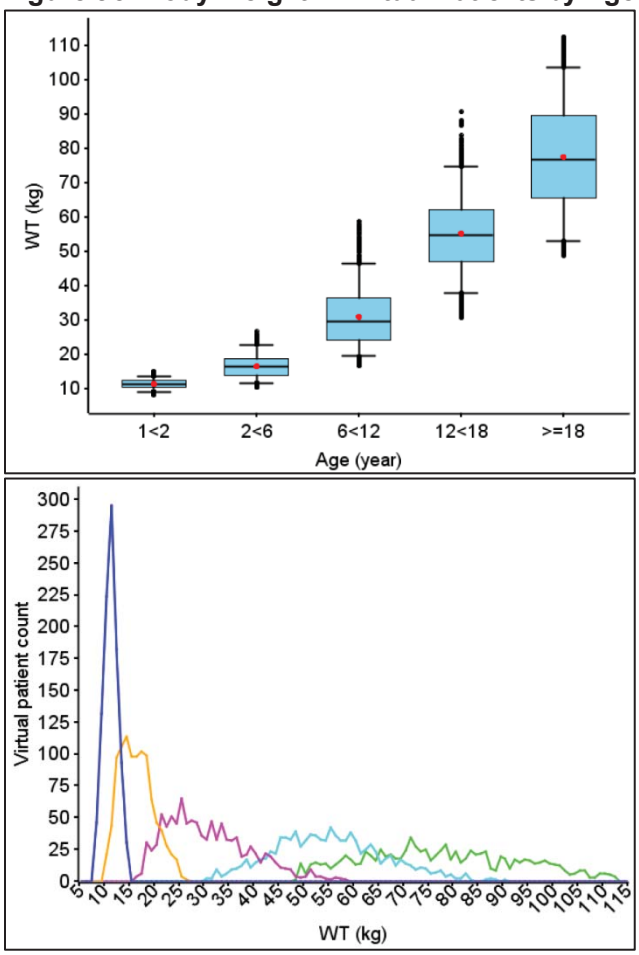
Reviewer's comment:

The Applicant's E-R analysis for safety is acceptable. No major positive exposure-safety relationship was identified in patients with LOPD and IOPD at the studied dose and exposure range. The safety profiles from the pediatric patients with IOPD are considered adequate to support safety in the extrapolation based on exposure matching strategy for pediatric patients with LOPD (discussed in the following section).

14.5.3. Pediatric Dose Selection

Although the enrollment for the LOPD phase 3 trial (EFC14028) was open to patients 3 years and above, only one pediatric patient with the age of 16 years was included in the analyses. To determine whether the dosing regimen of 20 mg/kg qow is appropriate across different age or body weight groups, the Applicant conducted simulation to evaluate the exposure following 20 mg/kg for patients with LOPD who were 1 year of age and older upon FDA's request. The virtual population for pediatric age groups (<18 years) was generated based on CDC weight-for-age growth chart. The virtual population for adults (≥18 years) was consistent with body weight from the available adult patients from trials TDR12857 and EFC14028 (n=74). The body weight distribution in virtual patients by age group is shown in Figure 36.

Figure 36. Body Weight in Virtual Patients by Age Group

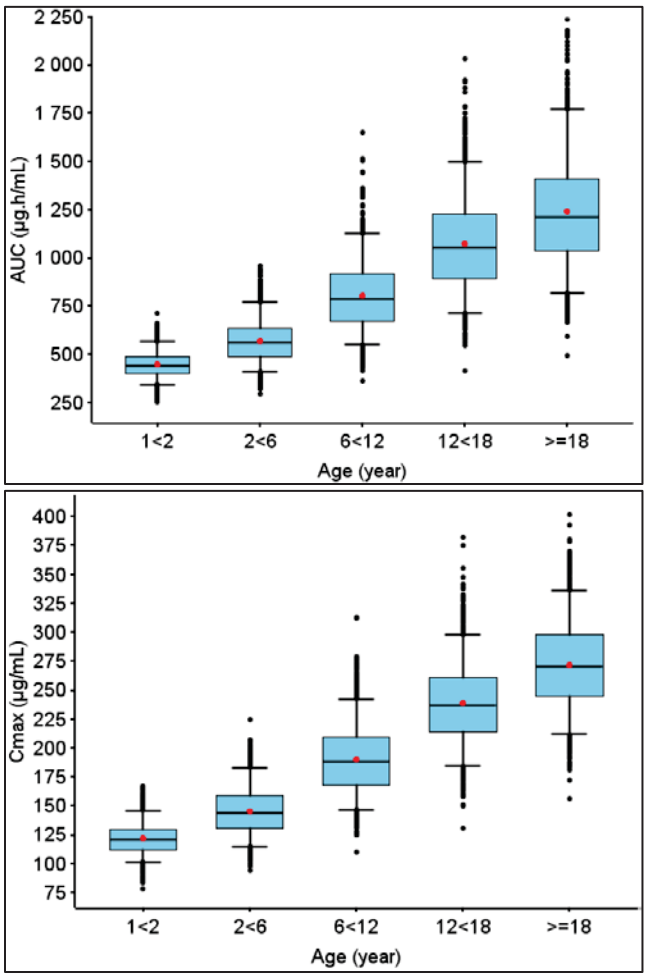


Source: Applicant's response to an IR "PK response-12mar2021.pdf"
Note: Box plot: 5th, 25th, median, 75th, and 95th percentiles, Red symbols: mean; Black symbols: individual values (minimum to 5th percentile and 95th percentile to maximum); Blue: 1 to <2 years; Orange: 2 to <6 years; Pink: 6 to <12 years; Cyan: 12 to <18 years; Green: ≥18 years
Abbreviation: WT, weight

Based on the Applicant's simulation, when received the dose of 20 mg/kg qow, smaller patients tend to have lower exposure. Compared to the median exposures in adult patients, patients within 1 to <2 years of age are expected to have approximately 60% lower exposures; patients within 2 to <6 years of age are expected to have approximately 50% lower exposure; patients within 6 to 12 years of age are expected to have approximately 30% lower exposure; and patients within 12 to 18 years of age are expected to have approximately 12% lower exposure (Figure 37). These results indicated that smaller pediatric patients would need higher dose to achieve a comparable exposure to adult patients.

Reference ID: 4836879

Figure 37. Simulated Avalglucosidase Alfa $AUC_{0\text{-}2W}$ and C_{max} by Age Category (1 to <2 Years, 2 to <6 Years, 6 to <12 Years, 12 to <18 Years, and ≥18 Years Old) at 20 mg/kg Every Other Week in Patients With LOPD



Source: Applicant's response to an IR "PK response-12mar2021.pdf"
Note: Box plot: 5th, 25th, median, 75th, and 95th percentiles, Red symbols: mean; Black symbols: individual values (minimum to 5th percentile and 95th percentile to maximum)

Pediatric patients with LOPD are expected to have similar response to the ERT treatment compared to the adult patients with LOPD (refer to Section 6.3.2). Thus, PK extrapolation approach based on modeling and simulation was utilized to select the appropriate dosing regimen for pediatric patients with LOPD. FDA conducted independent simulation to compare the exposures at 40 mg/kg and 20 mg/kg across different body weight groups. As shown in Figure 13, for subjects with body weight <30 kg, 40 mg/kg qow is expected to provide a similar or slightly higher exposure (AUC_{2W}) compared to that in adult patients receiving 20 mg/kg qow (target exposure, blue dash line), while within the observed range from the patients with IOPD received 40 mg/kg in trial ACT14132. Similarly, for subjects weighing 30 kg and above, the exposure at 20 mg/kg qow is predicted to be within the observed range in adult patients with LOPD from trial EFC14028. In addition, no apparent E-R relationship was identified for safety endpoints in patients with IOPD and LOPD following the dosing regimen of 20 or 40 mg/kg qow. During the review, 40 kg was evaluated as an alterntaive body weight cut-off considering the following:

Reference ID: 4836879

- 40 kg is closer to the lower end of the observed body weight range of patients receiving 20 mg/kg (38 kg-129 kg) in the LOPD trial EFC14028. There is very limited efficacy data available at exposure level of 20 mg/kg in patients weighing 30-40 kg.
- For subjects weighing 30 to < 40 kg, a considerable proportion (>30%) of patients who receive 20 mg/kg would have AUC2W lower than the 5th percentile of simulated AUC2W in adults receiving 20 mg/kg.
- The predicted AUC2W for patients who receive 40 mg/kg in this body weight range would be higher and still within the range observed in patients with IOPD receiving 40 mg/kg.

However, there is limited safety data at the higher dose/exposure level in patients with IOPD to support 40 mg/kg in patients weighing 30-40 kg. Thus, FDA recommended 40 mg/kg for pediatric patients weighing <30 kg, and 20 mg/kg for patients weighing ≥30 kg.

Applicant's Position Based on Alglucosidase Alfa (Lumizyme®)

(b) (4) To support the newly proposed dosing regimen for patients with LOPD with the age of 1 year old and above, the Applicant provided following justifications:

(b) (4)

Reviewer's comment:

Based on the label for alglucosidase alfa (Lumizyme®), the youngest alglucosidase alfa-treated patient in the LOPD trial was 16 years of age. Thus, there is lack of efficacy data in younger patients with lower body weight, and the Applicant did not provide any data for alglucosidase alfa from younger patients during the review cycle for avalglucosidase alfa (b) (4) *. In addition, "early-onset" is likely associated younger age and lower body weight. The Applicant's statement in the second bullet indicated that 40 mg/kg may provide additional benefit for patients with*

Reference ID: 4836879

younger age and lower body weight compared to 20 mg/kg qow. However, it is difficult to define the "severity" of the disease course in the label. (b) (4) *based on the experience with alglucosidase alfa, 40 mg/kg would be a better option for younger patients with lower body weight.*

Applicant's Position Based on Avalglucosidase Alfa

- Data with avalglucosidase alfa do not support a lower efficacy in Pompe patients with lower body weight. No evidence of a PK/PD or PK/efficacy relationship was observed at 20 mg/kg qow in patient with LOPD in trial EFC14028.
- The lower plasma exposures in patients with lower body weight are correlated with a higher clearance, the likely result of faster cellular uptake in patients with lower body weight. Avalglucosidase alfa is cleared from the plasma by cellular uptake and then internalized into the lysosomes.

Reviewer's comment:

- *The observed PK/PD or PK-efficacy relationship for efficacy in trial EFC14028 was based on single dose level of 20 mg/kg, with the lowest body weight included in the analysis being 38 kg associated with a 16 years old subject. No E-R information is available at dose/exposure lower than the observed range, or in patients with younger age and lower body weight to rule out potential lower efficacy in this group.*
- *There is no data/evidence provided to support the hypothesis of faster cellular uptake in patients with lower body weight. Even if it is true, higher cellular uptake may only contribute partially to the lower plasma exposure of avalglucosidase alfa. The effect of body weight on lower plasma exposure could not be excluded.* (b) (4)

The safety of 40 mg/kg qow in patients with body weight <30 kg is supported by the safety data from patients with IOPD (weighing 9.9 to 63.5 kg) following 40 mg/kg qow regimen, in which the observed avalglucosidase alfa concentration could cover the model predicted exposure following 40 mg/kg qow in patients with LOPD whose body weight is <30 kg. More importantly, sufficient early intervention is critical for the improved prognosis in patients with LOPD with relatively earlier onset. Therefore, 40 mg/kg qow for younger patients with body weight less than 30 kg is likely to provide a more favorable benefit-risk profile compared to 20 mg/kg qow.

In conclusion, FDA recommends the following dosing regimen for patients ages 1 year and above with LOPD:

- For patients with body weight <30 kg, 40 mg/kg qow
- For patients with body weight 30 kg and above, 20 mg/kg qow

15. Trial Design: Additional Information and Assessment

See Section 6.2 for details.

16. Efficacy: Additional Information and Assessment

Applicant's Tipping Point Analysis for Primary Efficacy Endpoint in EFC14028 (COMET)

The Applicant performed a tipping point analysis to investigate the severity of departures from the missing-at-random (MAR) assumption needed to overturn the noninferiority (NI) conclusion from the primary analysis in trial EFC14028. The tipping point analysis proceeded as follows:

- Step 1: Missing values for the primary endpoint (change from baseline to week 49 in FVC (% predicted)) were explicitly imputed based on the MAR assumption using multiple imputation methods. Specifically, missing data were imputed 1000 times to generate 1000 complete datasets with the SAS PROC MI procedure. A two-step approach was used as follows:
  - Intermittent (nonmonotone) missing data were imputed first using a Markov chain Monte Carlo (MCMC) method within each treatment arm
  - The remaining monotone missing data were imputed using the sequential regression method, where a separate regression model was estimated for imputation of FVC (% predicted) at each time point. Each regression model included treatment, baseline FVC (% predicted), age, gender, FVC (% predicted) values at all previous visits.
- Step 2: The imputed values in step 1 were shifted in favor of alglucosidase alfa. In particular, the imputed values in the avalglucosidase alfa arm were decreased by δ_1 (>0) while the imputed values in the alglucosidase alfa arm were increased by δ_2 (>0). Note that a higher value of the primary endpoint was indicative of a better improvement in FVC (% predicted).

Table 87 presents the results of the tipping point analysis.

Table 87. Tipping Point Analysis of FVC (% Predicted), Trial EFC14028 COMET

	LS Mean Difference Between Avalglucosidase alfa vs Alglucosidase Alfa at Week 49 (P value for non-inferiority) Shift in Alglucosidase Alfa								
Shift in Avalglucosidase alfa	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
-16	1.60 (0.0537)	1.48 (0.0662)	1.36 (0.0813)	1.25 (0.0993)	1.13 (0.1203)	1.01 (0.1446)	0.89 (0.1725)	0.78 (0.2040)	0.66 (0.2391)
-15	1.64 (0.0488)	1.52 (0.0605)	1.40 (0.0747)	1.29 (0.0917)	1.17 (0.1116)	1.05 (0.1349)	0.93 (0.1616)	0.82 (0.1920)	0.70 (0.2261)
-14	1.68 (0.0443)	1.56 (0.0552)	1.44 (0.0686)	1.33 (0.0845)	1.21 (0.1035)	1.09 (0.1257)	0.97 (0.1514)	0.85 (0.1806)	0.74 (0.2136)
-13	1.72 (0.0402)	1.60 (0.0504)	1.48 (0.0629)	1.36 (0.0779)	1.25 (0.0959)	1.13 (0.1170)	1.01 (0.1416)	0.89 (0.1698)	0.78 (0.2016)
-12	1.76 (0.0364)	1.64 (0.0459)	1.52 (0.0576)	1.40 (0.0718)	1.29 (0.0888)	1.17 (0.1089)	1.05 (0.1324)	0.93 (0.1595)	0.82 (0.1902)
-11	1.79 (0.0330)	1.68 (0.0418)	1.56 (0.0528)	1.44 (0.0661)	1.33 (0.0821)	1.21 (0.1013)	1.09 (0.1237)	0.97 (0.1497)	0.85 (0.1794)
-10	1.83 (0.0299)	1.72 (0.0381)	1.60 (0.0483)	1.48 (0.0608)	1.36 (0.0760)	1.25 (0.0941)	1.13 (0.1155)	1.01 (0.1404)	0.89 (0.1690)
-9	1.87 (0.0271)	1.76 (0.0347)	1.64 (0.0442)	1.52 (0.0560)	1.40 (0.0703)	1.29 (0.0875)	1.17 (0.1079)	1.05 (0.1317)	0.93 (0.1592)
-8	1.91 (0.0246)	1.80 (0.0316)	1.68 (0.0405)	1.56 (0.0515)	1.44 (0.0650)	1.33 (0.0813)	1.21 (0.1007)	1.09 (0.1235)	0.97 (0.1499)
-7	1.95 (0.0223)	1.83 (0.0288)	1.72 (0.0371)	1.60 (0.0474)	1.48 (0.0601)	1.36 (0.0755)	1.25 (0.0940)	1.13 (0.1158)	1.01 (0.1412)
-6	1.99 (0.0202)	1.87 (0.0263)	1.76 (0.0340)	1.64 (0.0436)	1.52 (0.0556)	1.40 (0.0702)	1.29 (0.0877)	1.17 (0.1086)	1.05 (0.1329)
-5	2.03 (0.0184)	1.91 (0.0240)	1.79 (0.0312)	1.68 (0.0402)	1.56 (0.0514)	1.44 (0.0652)	1.32 (0.0819)	1.21 (0.1018)	1.09 (0.1251)
-4	2.07 (0.0167)	1.95 (0.0219)	1.83 (0.0286)	1.72 (0.0371)	1.60 (0.0476)	1.48 (0.0607)	1.36 (0.0765)	1.25 (0.0955)	1.13 (0.1178)
-3	2.11 (0.0152)	1.99 (0.0201)	1.87 (0.0263)	1.76 (0.0342)	1.64 (0.0441)	1.52 (0.0564)	1.40 (0.0715)	1.28 (0.0895)	1.17 (0.1109)
-2	2.15 (0.0139)	2.03 (0.0184)	1.91 (0.0242)	1.79 (0.0316)	1.68 (0.0409)	1.56 (0.0526)	1.44 (0.0668)	1.32 (0.0841)	1.21 (0.1045)

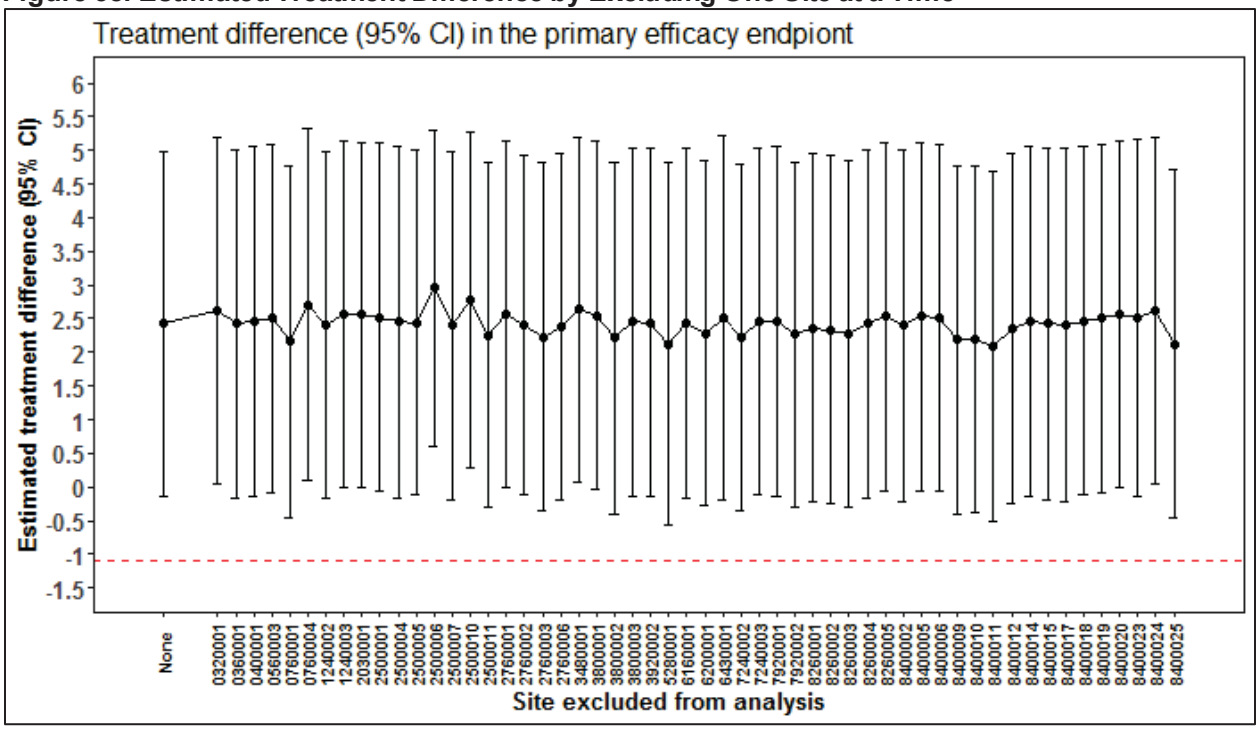
FVC (% Predicted) values imputed under the assumption of MAR in Avalglucosidase alfa group are subtracted by the shifting value at all visits.
FVC (% Predicted) values imputed under the assumption of MAR in Alglucosidase alfa group are added by the shifting value at all visits.
P value is estimated from MMRM model that includes baseline FVC (% predicted, as continuous), sex, age (in years, at baseline), treatment group, visit, interaction term between treatment group and visit as fixed effects.

Source: Table 15 of Clinical Study Report for Trial EFC14028.
Abbreviations: FVC, forced vital capacity; LS, least squares

Review Team's Additional Sensitivity Analysis for Primary Efficacy Endpoint in EFC14028 (COMET)

The review team conducted additional sensitivity analyses to assess the impact of a single site on the primary analysis results. The treatment difference was estimated by excluding one site at a time using the MMRM. Figure 38 indicates the results. The red dotted line is the NI marge of -1.1%. As the lower bounds of the 95% confidence intervals (CIs) are larger than -1.1%, the NI conclusion remains the same.

Figure 38. Estimated Treatment Difference by Excluding One Site at a Time



Source: This figure was produced by review team based on the adre.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets
Abbreviation: CI, confidence interval

Subgroup Analysis of Primary Endpoint by Baseline FVC (% Predicted) in EFC14028

Table 88 presents the numerical summaries of change from baseline to week 49 by the predefined subgroups by baseline FVC (% predicted).

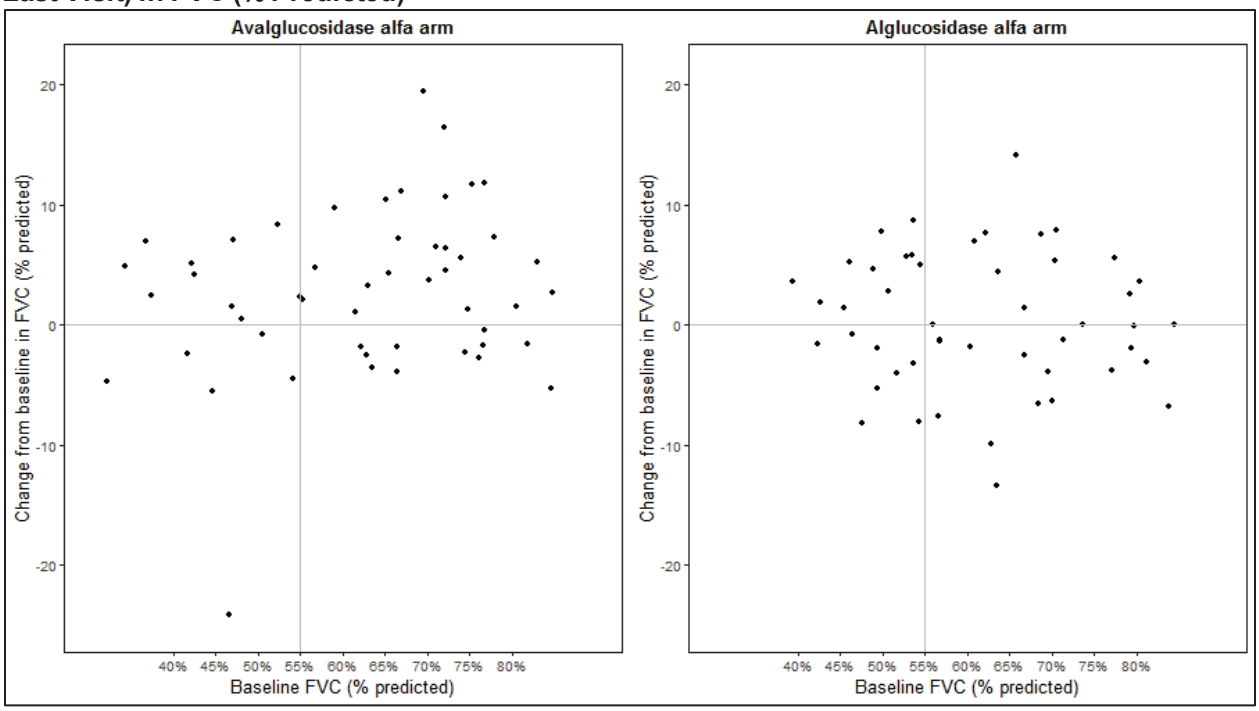
Table 88. Change in FVC (% Predicted) From Baseline to Week 49 by Subgroups of Baseline FVC (% Predicted), mITT Population, Trial EFC14028 (COMET)

Time Point	Baseline FVC <55%		Baseline FVC ≥55%	
Statistics	Avalgluco	Alglu	Avalgluco	Alglu
Baseline	N=16	N=19	N=35	N=30
Mean (SD)	44.5 (6.9)	49.1 (4.5)	70.8 (7.8)	69.5 (8.6)
Median	45.5	49.4	72.1	69.2
Min, Max	32.1, 54.9	39.3, 54.5	55.3, 84.8	56.0, 84.5
Week 49	N=16	N=18	N=33	N=25
Mean (SD)	44.6 (10.0)	49.6 (6.8)	75.6 (9.2)	69.5 (10.6)
Median	47.0	47.6	76.3	70.1
Min, Max	22.4, 60.7	39.4, 62.3	57.3, 89.0	49.0, 84.0

Time Point	Baseline FVC <55%		Baseline FVC ≥55%	
Statistics	Avalgluco	Alglu	Avalgluco	Alglu
Change from Baseline to Week 49	N=16	N=18	N=33	N=25
Mean (SD)	0.1 (7.8)	0.8 (5.2)	4.5 (5.9)	-0.6 (6.3)
Median	1.9	1.6	4.3	-1.3
Min, Max	-24.1, 8.3	-8.2, 8.7	-5.3, 19.4	-13.3, 14.1

Source: This table was produced by review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
Abbreviations: alglu, alglucosidase alfa; avalgluco, avalglucosidase alfa

Figure 39. Scatter Plot of Baseline FVC (% Predicted) by Change From Baseline to Week 49 (or Last Visit) in FVC (% Predicted)

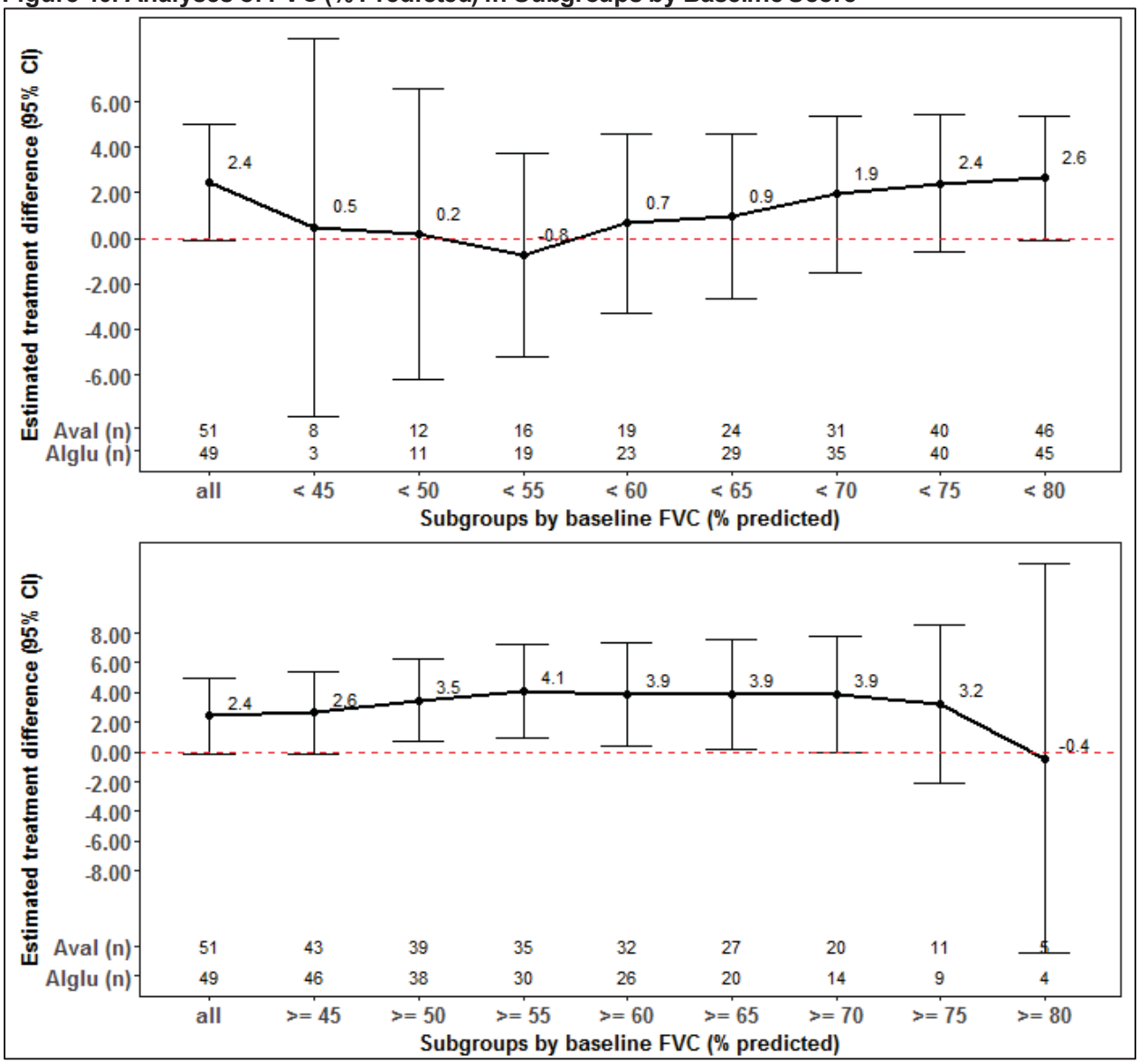


Source: This figure was produced by review team based on the adre.xpt dataset located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
Abbreviation: FVC, forced vital capacity

The review team conducted additional subgroup analyses defined by baseline FVC (% predicted). Various values (from 45% to 80%) for the threshold of baseline FVC (% predicted) to define subgroups were used. Figure 40 depicts the estimated difference (95% CI) between the two arms in the mean change in FVC (% predicted) from baseline to week 49. Estimated treatment differences numerically favor the avalglucosidase alfa arm in all subgroups except the following two subgroups: the subgroup of patients with baseline FVC (% predicted) of <55% and the subgroup of patients with baseline FVC (% predicted) of ≥80%. No notable pattern was observed.

Reference ID: 4836879

Figure 40. Analyses of FVC (% Predicted) in Subgroups by Baseline Score

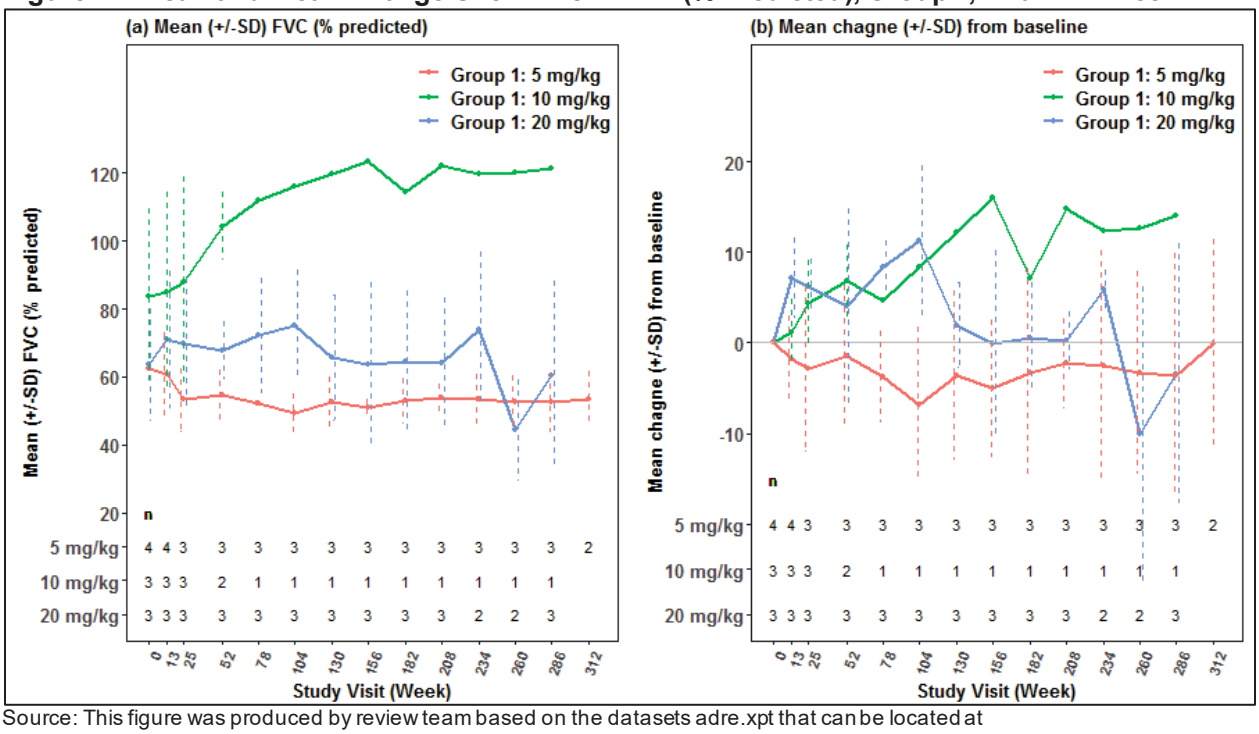


Source: Review team's analysis based on the adrew97.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets. The rows 'Aval (n)' and 'Alglu (n)' present the number of patients in the avalglucosidase alfa arm and in the alglucosidase alfa arm, respectively. For each subgroup, the estimated treatment difference (95% CI) in the mean change from baseline to week 49 was obtained from MMRM including treatment, visit, treatment-by-visit interaction, age (continuous), and gender.
Abbreviations: Alglu, alglucosidase alfa; aval, avalglucosidase alfa; CI, confidence interval; FVC, forced vital capacity

Mean Change From Baseline in FVC (% Predicted) Over Time in TDR12857 and LTS13769

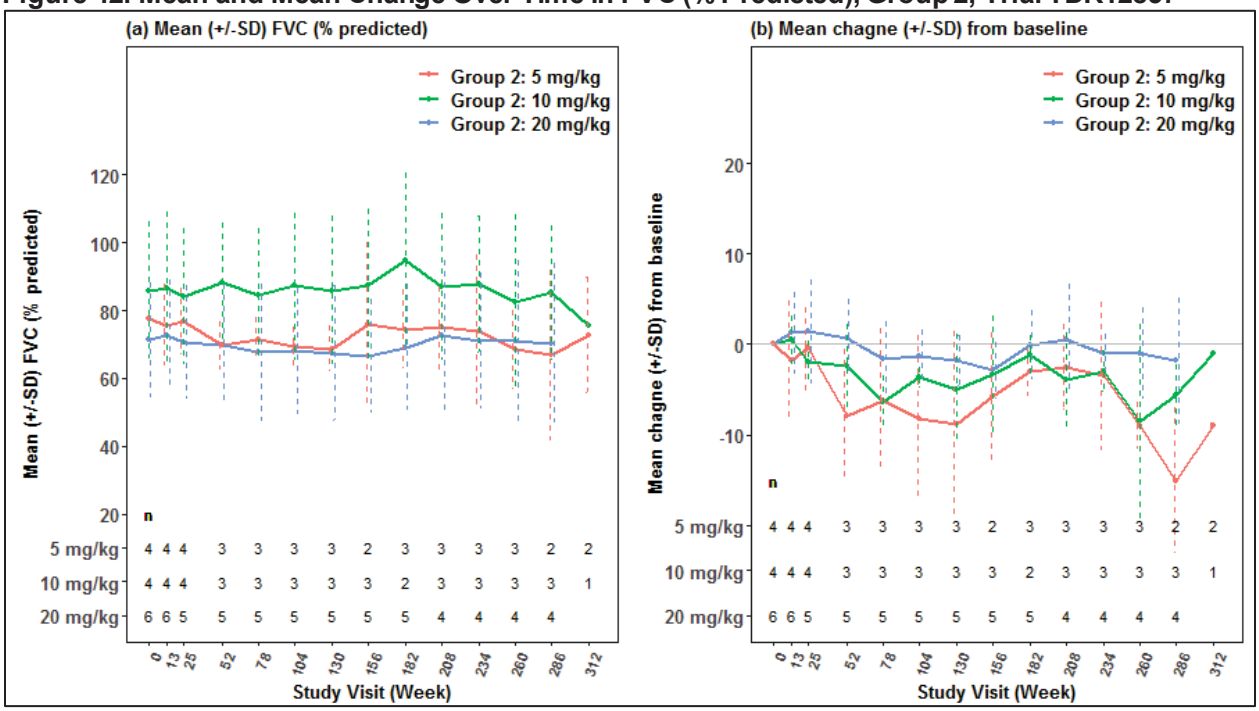
Figures 41 and 42 present the mean and mean change from baseline in FVC (% predicted) over time by initial dose for group 1 (treatment-naïve patients) and group 2 (ERT-experienced patients), respectively.

Figure 41. Mean and Mean Change Over Time in FVC (% Predicted), Group 1, Trial TDR12857



Source: This figure was produced by review team based on the datasets adre.xpt that can be located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\lts13769\analysis\adam\datasets.
Abbreviations: FVC, forced vital capacity; SD, standard deviation

Figure 42. Mean and Mean Change Over Time in FVC (% Predicted), Group 2, Trial TDR12857

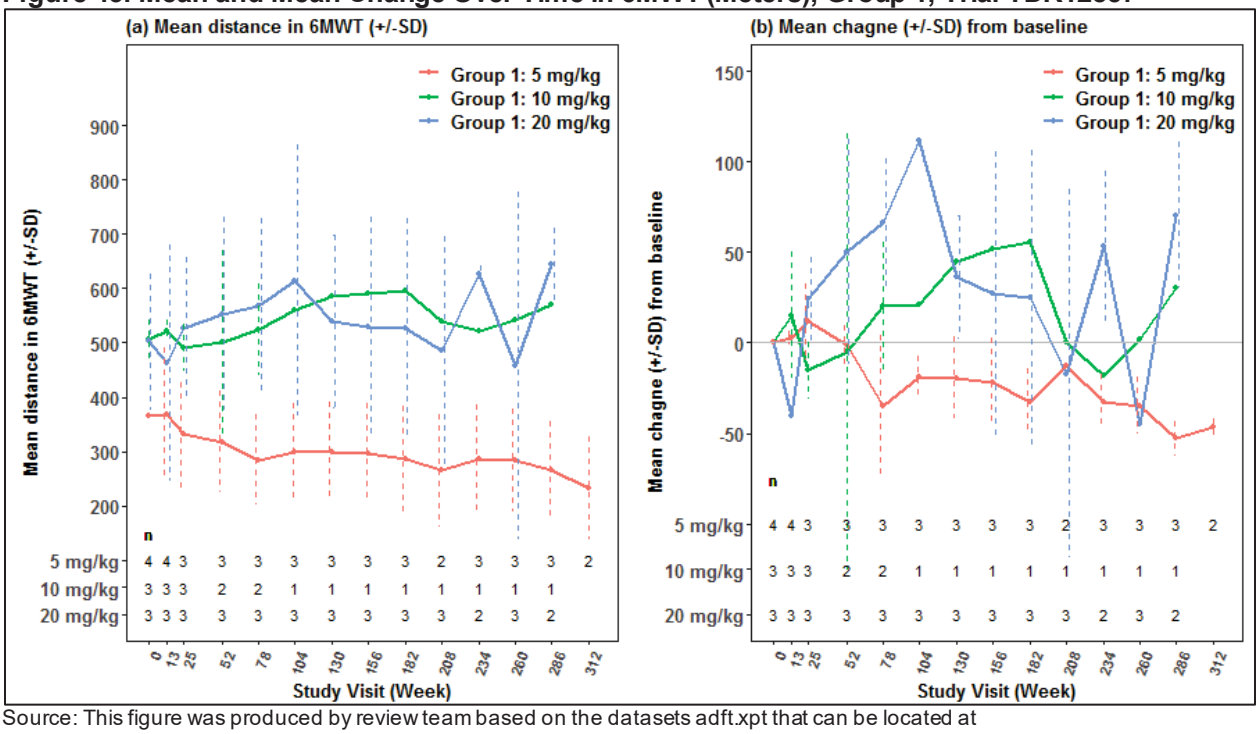


Source: This figure was produced by review team based on the datasets adre.xpt that can be located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\lts13769\analysis\adam\datasets.
Abbreviations: FVC, forced vital capacity; SD, standard deviation

Mean Change From Baseline in 6MWT (Meters) Over Time in TDR12857 and LTS13769

Figures 43 and 44 indicate the mean and mean change from baseline in distance walked in 6MWT (meters) over time by initial dose for group 1 (treatment-naïve patients) and group 2 (ERT-experienced patients), respectively.

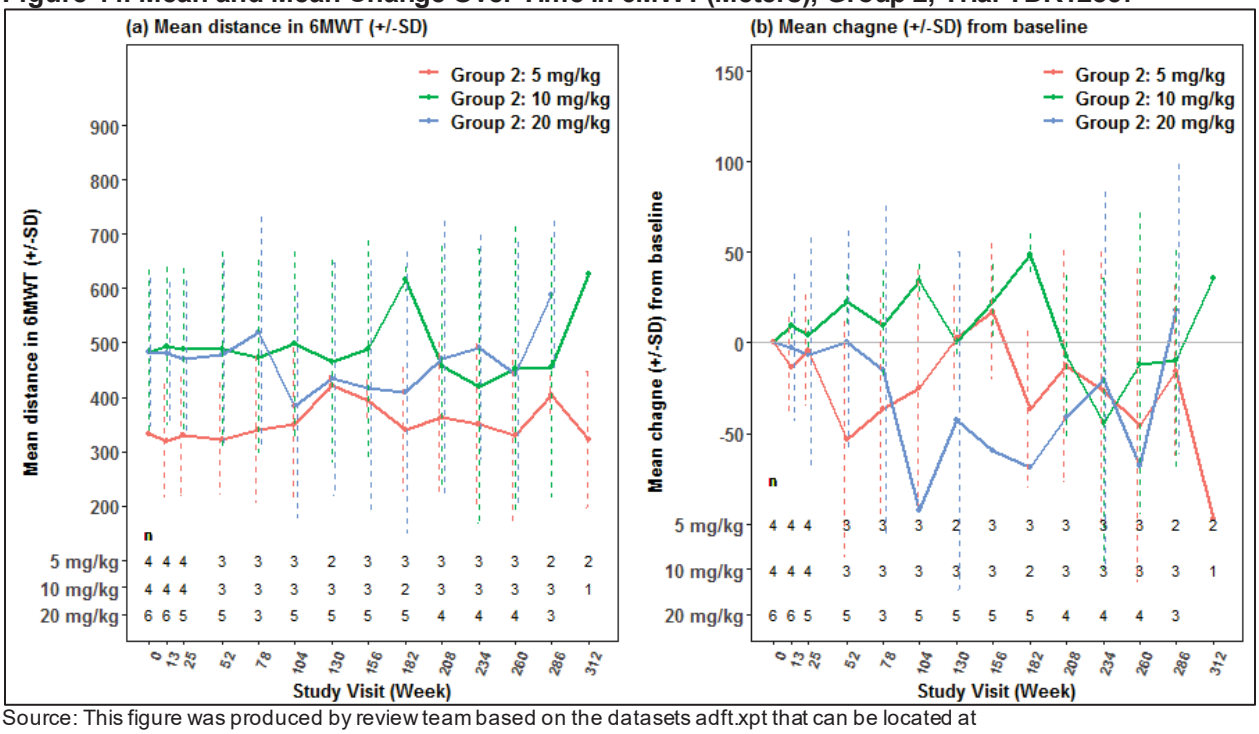
Figure 43. Mean and Mean Change Over Time in 6MWT (Meters), Group 1, Trial TDR12857



Source: This figure was produced by review team based on the datasets adft.xpt that can be located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\lts13769\analysis\adam\datasets.
Abbreviations: 6MWT, 6-minute walk test; SD, standard deviation

Reference ID: 4836879

Figure 44. Mean and Mean Change Over Time in 6MWT (Meters), Group 2, Trial TDR12857



Source: This figure was produced by review team based on the datasets adft.xpt that can be located at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\lts13769\analysis\adam\datasets
Abbreviations: 6MWT, 6-minute walk test; SD, standard deviation

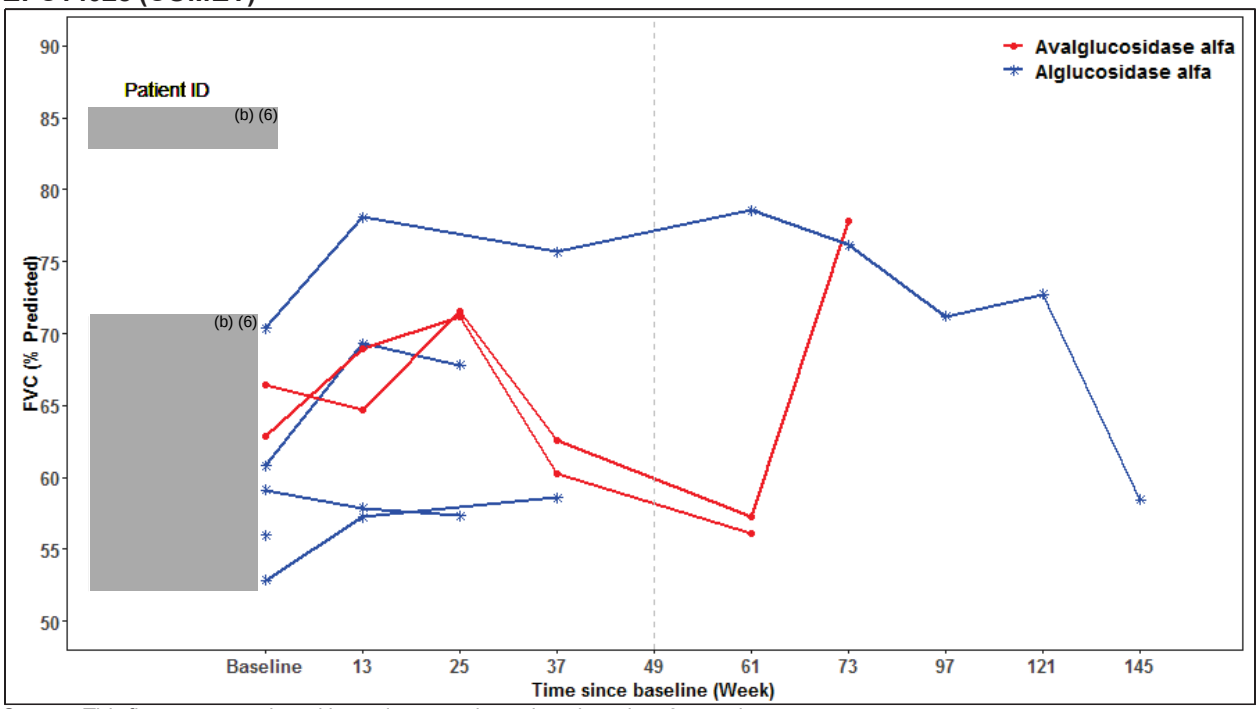
FVC (% Predicted) Over Time for Patients Not Having Measurements at Week 49 in EFC14028 (COMET)

A total of eight (8%) patients had missing FVC (% predicted) value at week 49 (two patients in the avalglucosidase alfa arm and six patients in the alglucosidase alfa arm). Figure 45 presents the time profile of the FVC (% predicted) for the eight patients. The following are the key observations:

- Patients [redacted] (b) (6) and [redacted] (b) (6) did not discontinue the trial prior to week 49. Their FVC (% predicted) values after week 49 are available. The two patients in the avalglucosidase alfa arm showed numerical improvement at week 25 compared to baseline and then numerical decline from week 25 to week 37. FVC (% predicted) value of patient [redacted] (b) (6) appears to be recovered at week 73. It is difficult to statically judge whether the MAR assumption is appropriate for the three patients.
- Five patients in the alglucosidase alfa arm discontinued the trial prior to week 49. Two of them did not have any postbaseline values; two of them showed numerical improvement at their last visits compared to baseline; one of them showed slight decline over them. In general, discontinuation of these five patients does not appear to be related to lack of efficacy.

Reference ID: 4836879

Figure 45. FVC (% Predicted) Over Time for Patients Having Missing Value at Week 49, Trial EFC14028 (COMET)

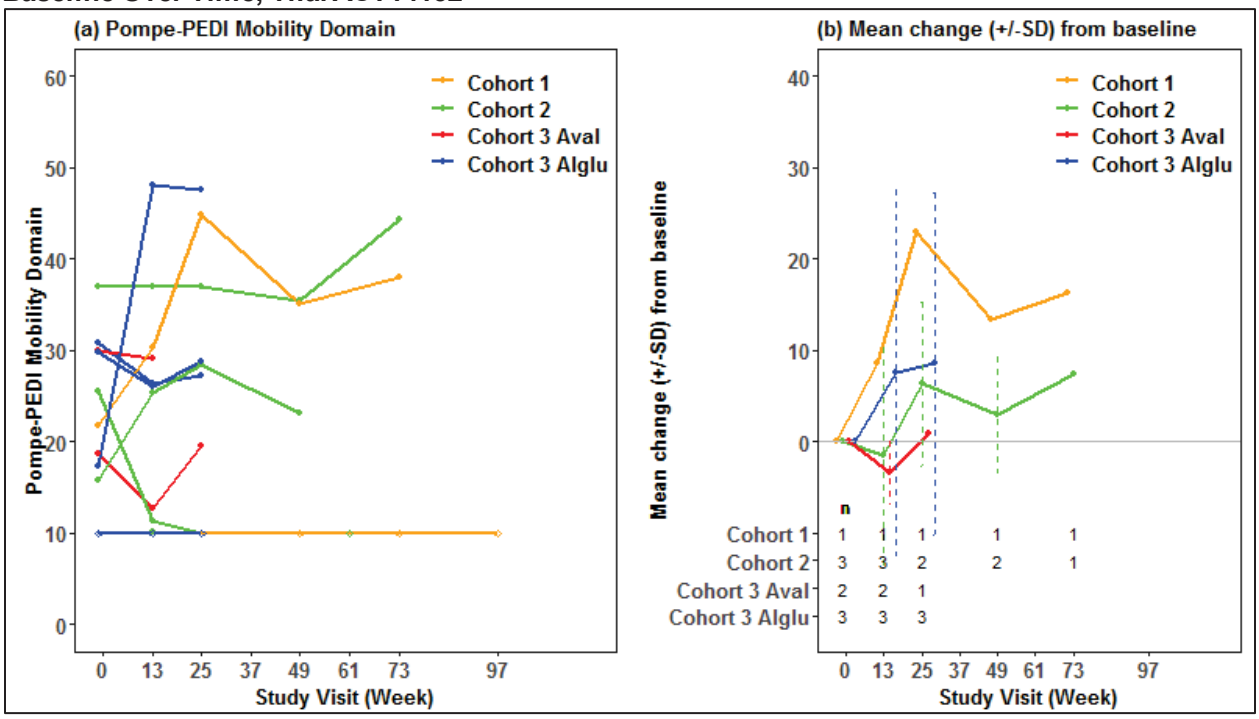


Source: This figure was produced by review team based on the adrew97.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets.
Abbreviation: FVC, forced vital capacity

Pompe-PEDI Mobility Domain Normative Standard Score and Mean Change From Baseline Over Time, Trial ACT14132

Figure 46 depicts the time profile of the Pompe-PEDI Mobility Domain normative standard score and mean change from baseline.

Figure 46. Pompe-PEDI Mobility Domain Normative Standard Score and Mean Change From Baseline Over Time, Trial ACT14132



Source: Figure 7 of Clinical Study Report. This table was produced by review team based on the adcc.xpt dataset at \\CDSESUB1\evsprod\BLA761194\0002\m5\datasets\efc14028\analysis\adam\datasets
Abbreviations: alglu, alglucosidase alfa; aval, avalglucosidase alfa; SD, standard deviation

Reference ID: 4836879

17. Clinical Safety: Additional Information and Assessment

The review team conducted additional safety analyses using narrow FMQ terms to assess for potential safety imbalances in the ISS population (Table 89) and the PAP for trial EFC14028 (Table 90).

Table 89. Adverse Events by System Organ Class and FDA Medical Query (Narrow), Integrated Safety Population

	Patient Description				
System Organ Class FMQ (Narrow)	**Naive N=61**	**Experienced N=77**	**Adult N=118**	**Pediatric N=20**	**All N=138**
Blood and lymphatic system disorders					
Anemia	2 (3.3)	4 (5.2)	5 (4.2)	1 (5.0)	6 (4.3)
Leukopenia	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Cardiac disorders					
Systemic hypertension	6 (9.8)	5 (6.5)	11 (9.3)	0	11 (8.0)
Arrhythmia	5 (8.2)	5 (6.5)	10 (8.5)	0	10 (7.2)
Tachycardia	3 (4.9)	3 (3.9)	5 (4.2)	1 (5.0)	6 (4.3)
Myocardial ischemia	2 (3.3)	3 (3.9)	5 (4.2)	0	5 (3.6)
Palpitations	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Acute coronary syndrome	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Myocardial infarction	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Ear and labyrinth disorders					
Vertigo	3 (4.9)	1 (1.3)	4 (3.4)	0	4 (2.9)
Endocrine disorders					
Hypoglycemia	2 (3.3)	0	2 (1.7)	0	2 (1.4)
Gastrointestinal disorders					
Diarrhea	17 (27.9)	18 (23.4)	31 (26.3)	4 (20.0)	35 (25.4)
Nausea	17 (27.9)	11 (14.3)	26 (22.0)	2 (10.0)	28 (20.3)
Abdominal pain	11 (18.0)	14 (18.2)	21 (17.8)	4 (20.0)	25 (18.1)
Vomiting	9 (14.8)	12 (15.6)	16 (13.6)	5 (25.0)	21 (15.2)
Dyspepsia	9 (14.8)	6 (7.8)	15 (12.7)	0	15 (10.9)
Constipation	3 (4.9)	3 (3.9)	5 (4.2)	1 (5.0)	6 (4.3)
General disorders and administration site conditions					
Fatigue	17 (27.9)	13 (16.9)	27 (22.9)	3 (15.0)	30 (21.7)
Pyrexia	10 (16.4)	11 (14.3)	15 (12.7)	6 (30.0)	21 (15.2)
Local administration reactions	8 (13.1)	10 (13.0)	16 (13.6)	2 (10.0)	18 (13.0)
Peripheral edema	8 (13.1)	4 (5.2)	11 (9.3)	1 (5.0)	12 (8.7)
Decreased appetite	1 (1.6)	0	1 (0.8)	0	1 (0.7)

Reference ID: 4836879

System Organ Class FMQ (Narrow)	Naive N=61	Experienced N=77	Adult N=118	Pediatric N=20	All N=138
		Patient Description			
Hepatobiliary disorders					
Hepatic injury	3 (4.9)	5 (6.5)	8 (6.8)	0	8 (5.8)
Cholecystitis	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Immune system disorders					
Angioedema	1 (1.6)	3 (3.9)	3 (2.5)	1 (5.0)	4 (2.9)
Infections and infestations					
Nasopharyngitis	25 (41.0)	27 (35.1)	50 (42.4)	2 (10.0)	52 (37.7)
Pneumonia	2 (3.3)	8 (10.4)	5 (4.2)	5 (25.0)	10 (7.2)
Musculoskeletal and connective tissue disorders					
Back pain	21 (34.4)	13 (16.9)	32 (27.1)	2 (10.0)	34 (24.6)
Myalgia	12 (19.7)	9 (11.7)	20 (16.9)	1 (5.0)	21 (15.2)
Arthritis	2 (3.3)	3 (3.9)	5 (4.2)	0	5 (3.6)
Arthralgia	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Malignancy	3 (4.9)	3 (3.9)	6 (5.1)	0	6 (4.3)
Nervous system disorders					
Headache	20 (32.8)	21 (27.3)	37 (31.4)	4 (20.0)	41 (29.7)
Dizziness	18 (29.5)	8 (10.4)	25 (21.2)	1 (5.0)	26 (18.8)
Paresthesia	9 (14.8)	4 (5.2)	13 (11.0)	0	13 (9.4)
Syncope	4 (6.6)	2 (2.6)	6 (5.1)	0	6 (4.3)
Somnolence	2 (3.3)	2 (2.6)	4 (3.4)	0	4 (2.9)
Tremor	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Seizure	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Psychiatric disorders					
Anxiety	4 (6.6)	3 (3.9)	7 (5.9)	0	7 (5.1)
Insomnia	4 (6.6)	1 (1.3)	5 (4.2)	0	5 (3.6)
Sexual dysfunction	3 (4.9)	0	3 (2.5)	0	3 (2.2)
Depression	2 (3.3)	0	2 (1.7)	0	2 (1.4)
Psychosis	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Mania	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Parasomnia	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Renal and urinary disorders					
Acute kidney injury	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Urinary retention	0	3 (3.9)	3 (2.5)	0	3 (2.2)

Reference ID: 4836879

System Organ Class FMQ (Narrow)	Patient Description Naive N=61	Experienced N=77	Adult N=118	Pediatric N=20	All N=138
Reproductive system and breast disorders					
Abnormal uterine bleeding	2 (3.3)	1 (1.3)	3 (2.5)	0	3 (2.2)
Erectile dysfunction	2 (3.3)	0	2 (1.7)	0	2 (1.4)
Gynecomastia	1 (1.6)	0	1 (0.8)	0	1 (0.7)
Excessive menstrual bleeding	0	1 (1.3)	1 (0.8)	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders					
Dyspnea	6 (9.8)	6 (7.8)	11 (9.3)	1 (5.0)	12 (8.7)
Cough	5 (8.2)	8 (10.4)	9 (7.6)	4 (20.0)	13 (9.4)
Bronchospasm	1 (1.6)	2 (2.6)	2 (1.7)	1 (5.0)	3 (2.2)
Skin and subcutaneous tissue disorders					
Rash	13 (21.3)	22 (28.6)	27 (22.9)	8 (40.0)	35 (25.4)
Pruritus	9 (14.8)	11 (14.3)	20 (16.9)	0	20 (14.5)
Erythema	8 (13.1)	6 (7.8)	12 (10.2)	2 (10.0)	14 (10.1)
Urticaria	5 (8.2)	6 (7.8)	10 (8.5)	1 (5.0)	11 (8.0)
Alopecia	0	1 (1.3)	0	1 (5.0)	1 (0.7)
Vascular disorders					
Hemorrhage	19 (31.1)	17 (22.1)	32 (27.1)	4 (20.0)	36 (26.1)
Hypotension	5 (8.2)	3 (3.9)	8 (6.8)	0	8 (5.8)

Source: adae.xpt; Software: Python
All values are expressed as n (%).Treatment-emergent adverse events defined as AEs that developed or worsened or became serious during the treatment epoch
For specific preferred terms under each FMQ, see the table "Adverse Events by FDA Medical Query (Narrow) and Preferred Term…." Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Reference ID: 4836879

Table 90. Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial EFC14028 (COMET)

System Organ Class FMQ (Narrow)	Avalglucosidase alfa N=51 n (%)	Alglu N=49 n (%)	Risk Difference (95% CI)[1]
Blood and lymphatic system disorders			
Anemia	0	1 (2.0)	-2.0 (-6.0, 2.0)
Cardiac disorders			
Arrhythmia	3 (5.9)	1 (2.0)	3.9 (-3.7, 11.5)
Tachycardia	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Acute coronary syndrome	0	1 (2.0)	-2.0 (-6.0, 2.0)
Myocardial infarction	0	1 (2.0)	-2.0 (-6.0, 2.0)
Myocardial ischemia	0	2 (4.1)	-4.1 (-9.6, 1.4)
Systemic hypertension	1 (2.0)	4 (8.2)	-6.2 (-14.8, 2.4)
Ear and labyrinth disorders			
Vertigo	0	2 (4.1)	-4.1 (-9.6, 1.4)
Gastrointestinal disorders			
Vomiting	4 (7.8)	3 (6.1)	1.7 (-8.3, 11.7)
Dyspepsia	4 (7.8)	5 (10.2)	-2.4 (-13.6, 8.8)
Nausea	6 (11.8)	7 (14.3)	-2.5 (-15.7, 10.7)
Constipation	0	2 (4.1)	-4.1 (-9.6, 1.4)
Diarrhea	6 (11.8)	8 (16.3)	-4.5 (-18.1, 9.1)
Abdominal pain	3 (5.9)	7 (14.3)	-8.4 (-20.1, 3.3)
General disorders and administration site conditions			
Fatigue	11 (21.6)	7 (14.3)	7.3 (-7.6, 22.2)
Decreased appetite	1 (2.0)	0	2.0 (-1.8, 5.8)
Peripheral edema	4 (7.8)	5 (10.2)	-2.4 (-13.6, 8.8)
Pyrexia	2 (3.9)	4 (8.2)	-4.3 (-13.6, 5.0)
Local administration reactions	4 (7.8)	7 (14.3)	-6.5 (-18.8, 5.8)
Hepatobiliary disorders			
Hepatic injury	2 (3.9)	3 (6.1)	-2.2 (-10.8, 6.4)
Immune system disorders			
Angioedema	1 (2.0)	0	2.0 (-1.8, 5.8)
Infections and infestations			
Pneumonia	1 (2.0)	2 (4.1)	-2.1 (-8.8, 4.6)
Nasopharyngitis	15 (29.4)	16 (32.7)	-3.3 (-21.4, 14.8)

Reference ID: 4836879

System Organ Class FMQ (Narrow)	Avalglucosidase alfa N=51 n (%)	Alglu N=49 n (%)	Risk Difference (95% CI)[1]
Musculoskeletal and connective tissue disorders			
Back pain	12 (23.5)	5 (10.2)	13.3 (-1.1, 27.7)
Arthralgia	1 (2.0)	0	2.0 (-1.8, 5.8)
Arthritis	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Myalgia	5 (9.8)	7 (14.3)	-4.5 (-17.3, 8.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignancy	2 (3.9)	0	3.9 (-1.4, 9.2)
Nervous system disorders			
Paresthesia	5 (9.8)	3 (6.1)	3.7 (-6.9, 14.3)
Syncope	1 (2.0)	0	2.0 (-1.8, 5.8)
Tremor	1 (2.0)	0	2.0 (-1.8, 5.8)
Dizziness	7 (13.7)	6 (12.2)	1.5 (-11.7, 14.7)
Confusional state	0	1 (2.0)	-2.0 (-6.0, 2.0)
Somnolence	0	1 (2.0)	-2.0 (-6.0, 2.0)
Headache	12 (23.5)	17 (34.7)	-11.2 (-28.9, 6.5)
Psychiatric disorders			
Anxiety	2 (3.9)	1 (2.0)	1.9 (-4.7, 8.5)
Insomnia	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Depression	2 (3.9)	2 (4.1)	-0.2 (-7.9, 7.5)
Sexual dysfunction	0	1 (2.0)	-2.0 (-6.0, 2.0)
Reproductive system and breast disorders			
Abnormal uterine bleeding	1 (2.0)	1 (2.0)	0.0 (-5.5, 5.5)
Excessive menstrual bleeding	0	1 (2.0)	-2.0 (-6.0, 2.0)
Respiratory, thoracic and mediastinal disorders			
Dyspnea	3 (5.9)	4 (8.2)	-2.3 (-12.3, 7.7)
Cough	2 (3.9)	5 (10.2)	-6.3 (-16.3, 3.7)
Skin and subcutaneous tissue disorders			
Urticaria	3 (5.9)	1 (2.0)	3.9 (-3.7, 11.5)
Pruritus	6 (11.8)	4 (8.2)	3.6 (-8.1, 15.3)
Rash	5 (9.8)	6 (12.2)	-2.4 (-14.7, 9.9)
Erythema	3 (5.9)	6 (12.2)	-6.3 (-17.5, 4.9)

Reference ID: 4836879

System Organ Class FMQ (Narrow)	Avalglucosidase alfa N=51 n (%)	Alglu N=49 n (%)	Risk Difference (95% CI)[1]
Vascular disorders			
Hypotension	0	1 (2.0)	-2.0 (-6.0, 2.0)
Hemorrhage	7 (13.7)	10 (20.4)	-6.7 (-21.4, 8.0)

Source: adae2.xpt; Software: Python
Treatment-emergent adverse events defined as AEs that developed or worsened or became serious during the treatment epoch
For specific preferred terms under each FMQ, see the table "Adverse Events by FDA Medical Query (Narrow) and Preferred Term…"
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator. Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

18. Mechanism of Action / Drug Resistance: Additional Information and Assessment

Not applicable.

19. Other Drug Development Considerations: Additional Information and Assessment

Active Comparator: U.S.-Lumizyme and EU-Myozyme Information

The review team sent an information request to clarify whether the drug product batches used as the active comparator, alglucosidase alfa, in the clinical trials was the U.S.-licensed Lumizyme. The Applicant responded that the clinical trial drug product batches included both U.S.-licensed Lumizyme and EU-approved Myozyme, and that the U.S.-licensed Lumizyme is the same product as the EU-approved Myozyme. The manufacturing scale for the drug product has changed over time [redacted] (b) (4)). Alglucosidase alfa produced at the [redacted] (b) (4) scale was approved in the EU in February 2009 for Myozyme and approved in the United States in May 2010 as Lumizyme under BLA 125291.

The Applicant provided the release results for U.S.-licensed (Lumizyme) and EU-approved (Myozyme) alglucosidase alfa drug substance, formulated drug substance, and drug product batches that were used in the clinical trials EFC14028 and ACT14132. For clinical and commercial manufacturing of alglucosidase alfa, only the [redacted] (b) (4) scale is currently used. All drug product batches for the clinical trials were manufactured after approval of the [redacted] (b) (4) scale (Table 91). The alglucosidase alfa drug product manufacturing process, formulation, and container closure systems are the same for the U.S.-licensed Lumizyme and EU-approved Myozyme.

Table 91. Dru Product Batches and Batch Histor

Study	Drug Product			Drug Substance	
	Batch number	Manufacturing Date (dd.mm.yyyy)	Myozyme or Lumizyme	Batch number	Manufacturing Date (dd.mm.yyyy)
ACT14132	7W0713	18.04.2017	Myozyme	7GG0559	13.03.2017
	8W0842	04.05.2018	Myozyme	8GG0279	19.02.2018
EFC14028	C5414	27.10.2015	Lumizyme	21501644	03.08.2015
	C6318	21.02.2016	Myozyme	5GG0418	01.12.2015
	C6370	26.08.2016	Myozyme	6GG0827	04.05.2016
	7W0002A	20.01.2017	Myozyme	6GG2443	12.11.2016
	7W0713	18.04.2017	Myozyme	7GG0559	13.03.2017
	7W0942	10.06.2017	Myozyme	7GG1049	11.04.2017
	8W0625	25.03.2018	Myozyme	7GG3514 7GG3718	21.11.2017 01.12.2017
	8W0842	04.05.2018	Myozyme	8GG0279	19.02.2018
	8W2527	18.10.2018	Myozyme	8GG2902	07.08.2018

Source: Response to FDA Clinical Information Request dated January 28, 2021

Reference ID: 4836879

Two representative executed batch records for alglucosidase alfa drug substance were also provided, one for a Myozyme batch that was used in the comparator arm of the avalglucosidase alfa clinical trial and one for a recently manufactured Lumizyme batch.

Based on this information, we conclude that the release results from the one Lumizyme batch and nine Myozyme batches that were used in the clinical trials as well as the executed batch records for Lumizyme and Myozyme support the claim that Lumizyme and Myozyme are the same product. Therefore, these two products are adequate to be used as the active comparator for the clinical trials, and use of both in the clinical trials would not have any adverse impact upon safety or efficacy.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

See Section 7.7.6 and the clinical inspection summary dated March 19, 2021 (Marks et al. 2021) for details of the inspection.

20.1. Biopharmaceutical Inspection

Issue

Delay in timing of biopharmaceutical inspections due to travel restrictions to the COVID19 pandemic.

Background

The primary analytical site generated the 11 ADA assay validation reports used to support the phase 3 pivotal trial, EFC14028. The assays were conducted at the Sanofi/Genzyme Biomarker and Clinical Bioanalysis (BCB) Boston facility in Framingham, MA. This facility was last inspected by OSIS in 2004, which was prior to the facility being acquired by Sanofi United States and Genzyme.

Assessment

Due to travel restrictions, the review team considered the possibility of a remote record review (RRR), but later determined that an RRR would not be able to be completed within the PDUFA timeline due to current workloads and the public health emergency. The review team determined that the various immunogenicity assays used in the pivotal clinical trials were suitable for the intended purpose. In addition, the available clinical immunogenicity data confirm acceptable in-study assay performance, and the BCB facility is an experienced bioanalytical facility involved in clinical pharmacology and immunogenicity studies for multiple Genzyme ERT BLAs, including BLA 125141 for Lumizyme and BLA125291 for Myozyme. Therefore, the lack of an OSIS bioanalytical inspection during the current review cycle is not considered a potential approvability issue.

Reference ID: 4836879

Conclusion

The review team concluded that waiver of the biopharmaceutical inspection is acceptable. In addition, no postmarketing studies are necessary.

21. Labeling Summary of Considerations and Key Additional Information

See the approved Prescribing Information for the final agreed upon language. A summary of the significant changes made to the Full Prescribing Information from the Applicant's proposed label (submitted on September 18, 2020) is shown below in Table 92. Highlights and Table of Contents were revised for consistency with the rest of the Prescribing Information.

Table 92. Major Prescribing Information Changes

PI Section	Labeling Recommendation
HIGHLIGHTS	• Boxed warning required to communicate class effects of hypersensitivity reactions (including anaphylaxis), IARs, and risk of acute cardiorespiratory failure.
1 INDICATIONS AND USAGE	• Indication was limited to treatment of patients 1 year of age and older with LOPD (refer to Section 6.3.3 for additional details).
5 WARNINGS AND PRECAUTIONS	• Limited description of mild to moderate symptoms to those that warrant risk mitigation. • Removed [redacted] (b) (4)
6 ADVERSE REACTIONS	• Removed [redacted] (b) (4) . • Removed [redacted] (b) (4)
8 USE IN SPECIFIC POPULATIONS	• In Section 8.1, updated the risk summary to reflect that there is not enough information about the risks of avalglucosidase alfa in pregnant women. Updated the embryo-fetal toxicity data. Updated reporting of exposure during pregnancy to "Pregnant women exposed to NEXVIAZYME, or their healthcare providers, should report NEXVIAZYME exposure by calling 1-800-745-4447, extension 15500." • In Section 8.2, added the sentence "Available published literature suggests the presence of alglucosidase alfa (another hydrolytic lysosomal glycogen-specific enzyme) in human mi k." • In Section 8.4, indicated that the safety and effectiveness of avalglucosidase alfa have only been established in pediatric patients 1 year of age and older and not in pediatric patients younger than 1 year of age. • In Section 8.5, indicated that clinical trials of avalglucosidase alfa did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.
[redacted] (b) (4)	
12 CLINICAL PHARMACOLOGY	• Added an introductory sentence in Section 12.2 to explain the overall PD effect and recommended reporting PD data using Glc4 concentrations because this is what the bioanalytical assay measures.

PI Section	Labeling Recommendation
14 CLINICAL STUDIES	• Added separate subsections for each of the study populations. • Removed [redacted] (b) (4) • Removed [redacted] (b) (4)

Source: Review team
Abbreviations: ADA, antidrug antibodies; IAR, infusion-associated reaction; LOPD, late-onset Pompe disease; PD, pharmacodynamic

22. Postmarketing Requirements and Commitments

The following PMR and PMC were agreed upon with the Applicant and will be issued at the time of approval.

PMR

- PMR 4026-1
  - Conduct a worldwide, descriptive safety study that collects data in women and their offspring who are exposed to Nexviazyme (avalglucosidase alfa-ngpt) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Outcomes of exposed infants, including growth and development, will be assessed through at least the first year of life. The study will collect information for 10 years.
  - PMR Schedule Milestones:
    - Draft Protocol Submission: 02/2022
    - Final Protocol Submission: 10/2022
    - Study Completion: 10/2032
    - Final Report Submission: 04/2033

PMC

- PMC 4026-2
  - Provide bioburden test method qualification reports for drug substance in-process samples using two additional batches.
  - PMC Schedule Milestones:
    - Final Report Submission: 08/2021

- PMC 4026-3
  - Provide M6P content specification for drug substance and drug product.
  - PMC Schedule Milestones:
    - Final Report Submission: 06/2022

Reference ID: 4836879

23. Financial Disclosure

Table 93. Covered Clinical Studies: EFC14028, ACT14132

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 583		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 22		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 22 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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Guidance for industry *Investigational Enzyme Replacement Therapy Products: Nonclinical Assessment* (October 2019)

Guidance for industry *Q3B(R2) Impurities in New Drug Products* (July 2006)

International Conference on Harmonisation draft guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk - Questions and Answers* (June 2020)

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25. Review Team

Table 94. Reviewers of Integrated Assessment

Role	Names
Regulatory Project Manager	CAPTAIN Jenny Doan, MSN, BSN
Chief Program Management Staff	Michael White, PhD
Nonclinical Reviewer	Miyun Tsai-Turton, Ph.D., M.S., Pharmacologist
Nonclinical Team Leader	Mukesh Summan, PhD, Division Director
Office of Clinical Pharmacology Reviewers	Katarzyna (Kate) Drozda, PharmD, MS, Clin Pharm/Genomics Reviewer Ruojing Li, PhD, Pharmacometrics Reviewer
Office of Clinical Pharmacology Team Leaders	Jie (Jack) Wang, PhD, Clinical Pharmacology Team Leader Lian Ma, PhD, Pharmacometrics Team Leader
Clinical Reviewer	Ann Punnoose, MD
Clinical Team Leader	Linda Jeng, MD, PhD
Statistical Reviewer	Wonyul Lee, PhD
Statistical Team Leader	Yan Wang, PhD
Cross-Disciplinary Team Leader	Linda Jeng, MD, PhD
Division Director (ORO)	Pamela Lucarelli
Division Director (pharm/tox)	Mukesh Summan, PhD
Division Director (OCP)	Michael Pacanowski, PharmD, MPH
Division Director (OB)	Dionne Price, PhD
Division Director (clinical)	Kathleen M. Donohue, MD, MSc
Office Director (or designated signatory authority)	Janet Maynard, MD, MHS

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics; ORO, Office of Regulatory Operations

Table 95. Additional Reviewers of Application

Office or Discipline	Names
Labeling	Eric Brodsky, Associate Director for Labeling
Division of Pediatrics and Maternal Health	Maternal Health: Kristie Baisden, DO, FACOG, Medical Reviewer Maternal Health: Tamara Johnson, MD, Team Leader Pediatrics: Ethan Hausman, MD, Medical Reviewer Pediatrics: Shetarra Walker, MD, Team Leader Lynn Yao, MD, Division Director John Alexander, MD, Deputy Director Denise Johnson-Lyles, PhD, Regulatory Project Manager George Greeley, Chief Program Management Staff
New Drug Transition Team	Jinzhong Liu, Clinical Data Scientist Hyo Sook Song, Medical Editor Monika Deshpande, Medical Editor
Office of Biotechnology	Susan Kirshner, PhD, Application Team Leader Fabiola Gomez, PhD, CMC Reviewer Joao Pedras-Vasconcelos, Immunogenicity Reviewer Vicky Borders-Hemphill, PharmD, Labeling Reviewer Melinda Bauerlien, MS, Regulatory Business Project Manger
Office of Pharmaceutical Quality (OPQ)	Sharon Kelly, PhD, ONDP DS Assessor Donna Christner, PhD, ONDP DS Team Leader
Office of Pharmaceutical Manufacturing Assessment (OPMA)/OPQ	Reyes Candau-Chacon, PhD, Microbiology Reviewer Michael shanks, PhD, Facility Reviewer Virginia Carroll, PhD, Micro and Facility Team Leader
Office of Prescription Drug Promotion (OPDP)	Adewale Adeleye, PharmD, MBA, Regulatory Reviewer
Office of Scientific Investigations (OSI)	Zana Handy Marks, MD, Medical Officer Karen Bleich, MD, Medical Team Leader
Office of Surveillance & Epidemiology (OSE)/DEPI	Catherine Lerro, Reviewer Catherine Callahan, PhD, MA, Team Leader
OSE/DMEPA	Sherly Abraham, PharmD, Reviewer Idalia Rychlik, PharmD, Team Leader
OSE/DPV	Mohamed Mohamoud, PharmD, Reviewer Ivone Kim, MD, Medical Reviewer Carmen Cheng, MD, Team Leader
OSE/DRISK	Theresa Ng, PharmD, Reviewer Laura Zendel, PharmD, Team Leader
OSE/RPM	Su-Lin Sun, RPh, PharmD, GWCPM, Safety Regulatory Project Manager Aleksander Winiarski, PharmD, RPh, Team Leader

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

Table 96. Signatures of Reviewers

See attached signatures page.

Reference ID: 4836879

Table 66 Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Signatory Authority	**Signature:** Kathleen Donohue, M.D. Digita ly signed by Kathleen Donohue M D DN cn=Kathleen Donohue M D o=FDA ou=DG EP OND CDER email=Ka hleen Donohue@fda hhs gov c=US Date 2021 07 27 11 42 49 04 00'		
Clinical	Kathleen M. Donohue, MD, MSc Director	OND/Division of Rare Diseases and Medical Genetics (DRDMG)	All ☐ Authored ☐ Contributed ☒ Approved

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Linda Jeng, MD, PhD	OND/DRDMG	All ☐ Authored ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Linda Jeng -S Digitally signed by Linda Jeng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Linda Jeng -S, 0.9.2342.19200300.100.1.1=2002457782 Date: 2021.07.27 17:45:55 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Ann Punnoose, MD	OND/DRDMG	1,2,3,4,6,7,8,10,11,12,15,16,17, 20, 21,22,23,24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Ann R. Punnoose -S Digitally signed by Ann R. Punnoose -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002971919, cn=Ann R. Punnoose -S Date: 2021.08.02 07:52:00 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Pamela Lucarelli	OND/Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine (DRO-RPURM)	12, 25 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Pamela K. Lucarelli -S Digitally signed by Pamela K. Lucarelli -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000426455, cn=Pamela K. Lucarelli -S Date: 2021.07.27 13:40:54 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table XX. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
CPMS	Michael G. White, PhD	OND/DRO-RPURM	12, 25 ☐ Authored ☒ Contributed ☒ Approved
Project Manager	**Signature:** Michael White -S	Digitally signed by Michael White -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Michael White -S, 0.9.2342.19200300.100.1.1=2001600058 Date: 2021.08.04 10:19:12 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Jenny Doan, MSN, BSN	OND/DRO-RPURM	12, 25 ☒ Authored ☐ Contributed ☐ Approved
Project Manager	**Signature:** Jenny Doan -S	Digitally signed by Jenny Doan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jenny Doan -S, 0.9.2342.19200300.100.1.1=0010124444 Date: 2021.07.27 10:55:50 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Mukesh Summan, PhD	OND/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine/Specialty Medicine (DPT-ORPURM/SM)	5.1, 7.1, 7.7, 8.4, 13.1, 13.2 ☐ Authored ☒ Contributed ☒ Approved
Division Director	**Signature:** Mukesh Summan -S	Digitally signed by Mukesh Summan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mukesh Summan -S, 0.9 2342.19200300.100.1.1=2000337340 Date: 2021.08.05 09:16:43 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Miyun Tsai-Turton, Ph.D., M.S., Ph.D.	OB/Division of Pharm/Tox for Rare Diseases, Pediatric, Urologic and Reproductive Medicine (DPT-ORPURM)	5.1, 7.1, 7.7, 8.4, 13.1, 13.2 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Miyun Tsai Turton -S	Digitally signed by M yun Tsai Turton S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=2000581291 cn=Miyun Tsai Turton S Date: 2021 08 02 12 07:38 04 00	

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Michael Pacanowski, PharmD, MPH	OTS/OCP/ Division of Translational and Precision Medicine (DTPM)	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Michael Pacanowski -S	Digitally signed by Michael Pacanowski -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000350707, cn=Michael Pacanowski -S Date: 2021.07.28 10:53:38 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Jie (Jack) Wang, PhD	OTS/OCP/DTPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☒ Authored ☒ Contributed ☐ Approved
Team Leader	**Signature:** Jie Wang -S	Digital y signed by Jie Wang S DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=Jie Wang S 0 9 2342 19200300 100 1 1=2000739081 Date: 2021 07 30 08:24:18 04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Katarzyna (Kate) Drozda, PharmD, MS	OTS/OCP/DTPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Katarzyna Drozda -S	Digitally signed by Katarzyna Drozda -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001644139, cn=Katarzyna Drozda -S Date: 2021.07.30 09:04:28 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Lian Ma, PhD	OTS/OCP/Division of Pharmacometrics (DPM)	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Lian Ma -S	Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2021.07.29 22:30:40 -04'00'	

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology/Pharmacometrics	Ruojing Li, PhD	OTS/OCP/DPM	5, 6.1, 6.3, 7.7, 8.1, 8.2, 14, 22, 24 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Ruojing Li -S (Affiliate)	Digitally signed by Ruojing Li -S (Affiliate) DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002080834, cn=Ruojing Li -S (Affiliate) Date: 2021.07.27 11:10:42 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Dionne Price, PhD, Director	OB/Division of Biometrics IV (DBIV)	6.2, 6.3, and 16 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Dionne L. Price -S	Digitally signed by Dionne L. Price -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300164533, cn=Dionne L. Price -S Date: 2021.07.28 15:24:02 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Yan Wang, PhD	OB/DBIV	6.2, 6.3, and 16 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Yan Wang -S	Digitally signed by Yan Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yan Wang -S, 0.9.2342.19200300.100.1.1=1300380164 Date: 2021.07.27 13:21:07 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Biometrics	Wonyul Lee, PhD	OB/DBIV	6.2, 6.3, and 16 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Wonyul Lee -S	Digitally signed by Wonyul Lee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Wonyul Lee -S, 0 9 2342.19200300.100.1.1=2002140374 Date: 2021.07 27 13:12:09 -04'00'	

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Cross-Disciplinary	Susan Kirshner, PhD	OPQ/Office of Biotechnology	9 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Susan L. Kirshner -S	Digitally signed by Susan L. Kirshner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300194629, cn=Susan L. Kirshner -S Date: 2021.08.03 13:09:52 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Fabiola Gomez, PhD	OPQ/ Office of Biotechnology	9 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Fabiola C. Gomez -S	Digitally signed by Fabiola C Gomez S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=2001603304 cn=Fabiola C Gomez S Date: 2021 08 03 08:11:26 04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Tamara Johnson, MD Team Leader	OND/Division of Pediatric and Maternal Health	8.4 ☐ Authored ☒ Contributed ☒ Approved
Consult	**Signature:** Tamara N. Johnson -S	Digitally signed by Tamara N. Johnson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300394304, cn=Tamara N. Johnson -S Date: 2021.07.28 12:47:33 -04'00'	

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Kristie Baisden, DO, FACOG Primary Reviewer	OND/Division of Pediatric and Maternal Health	8.4 ☒ Authored ☐ Contributed ☐ Approved
Consult	**Signature:** Kristie W. Baisden -S	Digitally signed by Kristie W. Baisden -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002275699, cn=Kristie W. Baisden -S Date: 2021.07.27 14 30:03 -04'00'	

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNY N DOAN
08/05/2021 09:38:55 AM

JANET W MAYNARD
08/05/2021 09:42:00 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	109,569
Supporting document/s:	54
Sponsor's letter date:	June 23, 2015
CDER stamp date:	June 23, 2015
Product:	neoGAA (recombinant human α-glucosidase conjugated with synthetic bis-mannose-6-phosphate-Man6 glycan)
Indication:	Pompe disease
Sponsor:	Genzyme Corporation Cambridge, MA
Review Division:	Division of Gastroenterology and Inborn Errors Products
Reviewer:	Fang Cai, PhD
Supervisor/Team Leader:	David B. Joseph, PhD
Division Director:	Donna Griebel, MD
Project Manager:	Lisa Pitt

Drug: neoGAA; a recombinant human acid α-glucosidase (rhGAA) expressed in Chinese Hamster Ovary (CHO) cells, conjugated to multiple copies of a synthetic bis-mannose-6-phosphate-containing hexasaccharide (Genz-669342).

Molecular formula/molecular weight:

alglucosidase alfa moiety: $C_{4488}H_{6826}N_{1196}O_{1297}S_{33}$ (approximate molecular formula)

Genz-669342 moieties (6-8 glycan units conjugated): $C_{42}H_{75}N_3O_{40}P_2$

NeoGAA has an approximate total molecular weight of 120,000 Da.

Pharmacological class: enzyme replacement therapy

Indication: Pompe disease

Route of administration: intravenous

Background:

The Sponsor submitted this IND for the development of neoGAA (recombinant human α-glucosidase conjugated with synthetic bis-mannose-6-phosphate-Man6 glycan) for treatment of Pompe disease. NeoGAA is produced by conjugating a synthetic glycan (Genz-669342) to oxidized sialic acid residues on rhGAA through a synthetic linker with an aminoxy moiety. The synthetic linker portion of Genz-669342 is structurally similar to hydroxylamine, which has the potential to be genotoxic. However, Genz-669342 was negative in the Ames test and chromosomal aberration assay. In the initial IND submitted on 03/28/2013, the Sponsor proposed a specification limit of (b) (4) μg/mL for unconjugated Genz-669342 in the drug product. At this limit, the maximum potential dose of unconjugated Genz-669342 from neoGAA would have been (b) (4) mg/infusion (assuming a 60-kg body weight, and a maximum dose of 20 mg/kg neoGAA in the proposed phase 1 clinical study), which greatly exceeded the recommended ICH qualification threshold (b) (4) mg/infusion for a 60-kg patient). Although the neoGAA batch used in the toxicology studies contained unconjugated Genz-669342, the pivotal 26-week IV toxicity study in monkeys did not provide an assurance of safety for the proposed specification limit of (b) (4) μg/mL. Therefore, on April 25, 2013, the Sponsor agreed with the Agency's recommended specification limit of (b) (4) μg/mL unconjugated Genz-669342 (free glycan) in the proposed Phase 1 clinical trial. Subsequently, the Sponsor conducted a 3-month IV toxicity study in monkeys with neoGAA spiked with free glycan (unconjugated Genz-669342), to support the safety of a higher limit in future clinical studies.

In the current amendment, the Sponsor submitted the 3-month IV toxicity study in monkeys using neoGAA spiked with free glycan. The study is reviewed below.

13-Week Intermittent Intravenous Infusion Toxicity and Toxicokinetic Study of neoGAA with Elevated Levels of Glycan in Cynomolgus Monkeys with a 4-Week Recovery

Study title:

Study no.: 8299651
Study report location: Module 4 (nonclinical study reports)
Conducting laboratory and location: [redacted] (b) (4)
Date of study initiation: May 29, 2014
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: See Sponsor's tables below.

Test Article	Storage	Batch No.	Stability	Purity
GZ402666 (neoGAA)	In a freezer, set to maintain -60 to -80°C and protected from light.	neoGAA-1001-14	Confirmed through at least 28Feb15	96%[a]
		neoGAA-1002-14	Confirmed through at least 14Mar15	97%[a]

a Method SDS-PAGE (Non Reduced) Coomassie

Test Article Spiking Agent	Storage	Lot No.	Retest Date	Purity
Glycan	In a freezer, set to maintain -10 to -30°C and protected from light.	GENZ669342-19294-71 (purified X0589)	Sep 2014	94.8%[a]
		GENZ669342-19294-121 (purified X0589)	Apr 2015	94.6%[a]

a Method LC-UV area %

Key Study Findings

Cynomolgus monkeys were treated with 50 mg/kg neoGAA spiked with 3, 6, or 12.55 mg/kg glycan (unconjugated) every other week intravenously. Emesis and vomitus were observed in all treatment group animals without apparent dose-dependent effects following infusion. The test-article at all doses produced slight to moderate reductions (not significant) in absolute and relative weights of male reproductive organs (epididymis, prostate and testis). No histopathological changes were associated with reduced male reproductive organ weights. The NOAEL for glycan was considered to be 12.55 mg/kg.

Methods

Doses:	neoGAA (GZ402666): 50 mg/kg glycan [redacted] (b) (4) unconjugated Genz-669342): 3, 6, or 12.55 mg/kg
Frequency of dosing:	Bi-weekly (once every two weeks)
Route of administration:	intravenous infusion (for approximately 6 hours/day) via a catheter implanted in a jugular vein
Dose volume:	20 mL/kg/dose, 3.33 mL/kg/hr
Formulation/Vehicle:	10 mM histidine, pH 6.2, 0.01% Tween® 80, 2% mannitol, and 2% glycine
Species/Strain:	cynomolgus monkeys
Number/Sex/Group:	4
Age:	2 to 3 years old
Weight:	2.2 to 2.9 kg for males and 2.2 to 2.9 kg for females
Satellite groups:	1/sex/group
Unique study design:	Spiking of glycan at different concentrations in neo-GAA
Deviation from study protocol:	The impact of deviation on interpretation of results is discussed in the Dosing Solution Analysis section.

The study design is shown in the Sponsor's table below.

	No. of Animals[a]		Dose Level		Dose Concentration[b]	
Group	Male	Female	neoGAA (mg/kg)	Glycan (mg/kg)	neoGAA (mg/mL)	Glycan (mg/mL)
1 (Control)[c]	5	5	0	0	0	0
2 (Low)	5	5	50	3	2.5	0.15
3 (Mid)	5	5	50	6	2.5	0.3
4 (High)	5	5	50	12.55	2.5	0.6275

a Animals designated for the terminal sacrifice (four animals/sex/group) were sacrificed on Day 92 of the dosing phase following infusion once every 14 days (Days 1, 15, 29, 43, 57, 71, and 85 of the dosing phase), for approximately 6 hours/day for 13 weeks (a total of seven doses). Animals designated for the recovery sacrifice (one animal/sex/group) were sacrificed on Day 29 of the recovery phase following infusion once every 14 days (Days 1, 15, 29, 43, 57, 71, and 85 of the dosing phase), for approximately 6 hours/day for 13 weeks (a total of seven doses) followed by 4 weeks of recovery.

b Concentrations were based on the test article and spiking agent as provided by the sponsor.

c Group 1 received vehicle control article/diluent only (10 mM histidine, pH 6.2, 0.01% [v/v] Tween® 80, 2% [w/v] mannitol, and 2% [w/v] glycine provided preformulated by the sponsor).

Observations and Results

Mortality

Mortality was observed daily. There were no deaths.

Clinical Signs

Cageside observations were conducted for each animal once daily, and detailed observations were conducted weekly.

One male in the 50 mg/kg neoGAA + 6 mg/kg glycan group had vomitus and/or emesis on days 29 and 43 (doses 3 and 4) and erythema and swelling in the face on day 29 (dose 3), which occurred at approximately 1 hour after infusion and started diminishing approximately 15 minutes later.

As shown in the Sponsor's table below, vomitus was observed within 30 minutes after infusion in two males and three females in the 50 mg/kg neoGAA + 3 mg/kg glycan group, four males and one female in the 50 mg/kg neoGAA + 6 mg/kg glycan group, and two females in the 50 mg/kg neoGAA + 12.55 mg/kg glycan on dosing days 29, 43, 57, 71, and/or 85.

The Sponsor concluded that these observations were due to an infusion-related hypersensitivity reaction, and were not considered adverse because they were transient, not dose-limiting, resolved without veterinary intervention, and did not affect body weight. However, the same or similar reactions were not observed in monkeys treated with 50 mg/kg neoGAA bi-weekly in the 26-week intravenous infusion toxicity study (# 0658-11097) that was submitted in the initial IND. It is noted that these two studies were conducted at different test facilities. Thus, it is likely that the vomitus was due the presence of glycan in the test article, although this effect did not appear to be dose-dependent.

Text Table 4.2: Incidence of Select Clinical Observations during the Infusion Dosing

Total Number of Animals With Clinical Observation[a]								
Sex	Male				Female			
Dose (mg neoGAA/kg)	0	50	50	50	0	50	50	50
Dose (mg glycan/kg)	0	3	6	12.55	0	3	6	12.55
Emesis								
Day 43	-	-	1	-	-	-	-	1
Day 71	-	1	-	-	-	2	-	-
Vomitus								
Day 29	-	1	1	-	-	1	-	1
Day 43	-	1	2	-	-	2	-	2
Day 57	-	-	2	-	-	2	-	-
Day 71	-	1	2	-	-	2	1	-
Day 85	-	-	1	-	-	1	-	-

- = Observation not seen

a Multiple incidences for one animal on the same day were noted as a single incident

Body Weights

Body weights were recorded during the pre-dose phase, on day -1, and weekly thereafter during the dosing phase. There were no treatment-related changes in body weight or body weight gain.

Feed Consumption

Qualitative food consumption was recorded once daily. No test article-related effect on qualitative food consumption was observed.

Ophthalmoscopy

Ophthalmic examinations were conducted once during the pre-dose phase and once on day 88 of the dosing phase. There were no treatment-related changes.

ECG and Vital Signs

Body temperature, respiration, and heart rates were collected on animals anesthetized with ketamine once during the pre-dose phase and once on days 2, 30, and 86 of the dosing phase (approximately 24 hours after the end of infusion). Body temperature measurements were also collected on day 25 of the recovery phase. Respiration and heart rates were not monitored during the recovery phase because of the absence of abnormalities at the end of the dosing phase.

Blood pressure measurements were recorded in animals anesthetized with ketamine once during the pre-dose phase and on days 2, 30, and 86 of the dosing phase (approximately 24 hours after the end of infusion). Blood pressure was not monitored during the recovery phase because of the absence of abnormalities at the end of the dosing phase.

There were no adverse effects on heart rate or blood pressure (systolic, diastolic and mean arterial pressures).

Reduced respiratory rate (18% in mid-dose males, 22% in high-dose males, and 14% in high-dose females) was observed on day 30 only. Thus, reduced respiratory rate was not considered to be treatment-related.

Males in all treatment groups had a slight increase in body temperature, ranging from of 0.2 to 1.1^{0}C, during the treatment period, compared to control males. There was no correlation between increased body temperature and post-dose vomitus or emesis. No consistent dose-dependent or duration-dependent effects were observed. On day 25 of the recovery phase, a slight increase in body temperature was observed in males given 50 mg/kg neoGAA spiked with 3 or 6 mg/kg glycan (1-0.5^{0}C) and in females given 50 mg/kg neoGAA spiked with 6 mg/kg glycan (0.7^{0}C). Animals in the high-dose group had no increased body temperature. Since there was only one animal/sex in the

recovery group, it is difficult to establish conclusions from the recovery group data. Thus, the change in body temperature was not considered to be treatment-related.

Hematology

Blood samples for hematology and coagulation were collected from fasted animals via the femoral vein on days 26, 41, and 71 of the pre-dose phase, at approximately 24 hours after the end of infusion on days 30, 58, and 86 of the dosing phase, and on the days of scheduled necropsies (day 92 of the dosing phase and day 29 of the recovery phase).

There was a trend towards a slight but non-significant decrease (↓up to 6%) in red cell mass (RBC, hemoglobin, and Hct). No other changes were observed during the treatment period. The recovery group data is inconclusive due to the use of only one animal/sex in each group.

Clinical Chemistry

Blood samples for clinical chemistry were collected from fasted animals via the femoral vein on days 26, 41, and 71 of the pre-dose phase, at approximately 24 hours after the end of infusion on days 30, 58, and 86 of the dosing phase, and on the days of scheduled necropsies (day 92 of the dosing phase and day 29 of the recovery phase). There were no treatment-related effects.

Urinalysis

Urine samples were collected during the overnight period on days 41 and 44 of the pre-dose phase, on day 92 of the dosing phase, and on day 29 of the recovery phase. There were no treatment-related changes.

Gross Pathology

All animals were subjected to necropsy at termination. There were no treatment-related changes.

Organ Weights

At scheduled termination, the following organs (when present) were weighed (paired organs were weighed together): adrenal, brain, epididymis, heart, kidney, lung, liver, gall bladder, ovary, pituitary gland, prostate, seminal vesicle, spleen, testis, thymus, thyroid with parathyroid, and uterus.

There was a dose-dependent decrease in absolute and relative weights of epididymis (at all doses), prostate, and testis (mid- and high-dose levels) as shown in the table below. The recovery group data is inconclusive due to the use of only one animal/sex in each group.

Decreased absolute and relative weights of epididymis, prostate and testis

	Absolute	Relative to body weight	Relative to brain weight
Groups	**Epididymis (g)**		
1 (Control)	2.446 ± 3.0457	0.0836 ± 0.1	3.6446 ± 4.6317
2	1.033 ± 0.87 (↓58%)	0.034 ±0.026 (↓59%)	1.378 ± 1.168 (↓62%0
3	0.785 ± 0.186 (↓68%)	0.028 ± 0.0049 (↓67%)	1.164 ± 0.267 (↓68%)
4	0.643 ± 0.1096 (↓74%)	0.024 ± 0.0037 (↓71%)	0.869±0.1499 (↓76%)
	Prostate (g)		
1 (Control)	0.576 ± 0.2465	0.02 ± 0.0088	0.8389 ± 0.365
2	0.808 ± 0.826	0.0264 ± 0.025	1.0753 ± 1.105
3	0.469 ± 0.175 (↓19%)	0.0166 + 0.0052 (↓17%)	0.6927 ± 0.25 (↓17%)
4	0.366 ± 0.1266 (↓37%)	0.0138 ± 0.005 (↓31%)	0.48 ± 0.1157 (↓43%)
	Testis (g)		
1 (Control)	1.725 ± 0.37	0.0611 ± 0.0093	2.513 ± 0.633
3	1.129 ± 0.48 (↓35%)	0.04 ± 0.016 (↓35%)	1.668 ± 0.71 (↓34%)
4	0.956 ± 0.263 (↓45%)	0.0354 ± 0.007 (↓42%)	1.2959 ± 0.38* (↓48%)

*P ≤ 0.05

In the 26-week IV toxicity study in monkeys submitted in the initial IND, neoGAA at 50 mg/kg every other week had no effects on absolute and relative weights of epididymis, testis, and prostate, whereas 200 mg/kg decreased absolute weights of epididymis (↓23%) and testes (↓16%). Thus, it is likely the decreased absolute and relative weights in male reproductive organs are related to the free glycan. However, no histopathological changes were observed in these organs.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

At the scheduled termination, the following tissues (when present) were collected from each animal and were preserved in 10% neutral-buffered formalin unless otherwise indicated: adrenal glands, aorta (thoracic), brain, catheterization site (jugular vein), cecum, cervix, colon, duodenum, femur with bone marrow (articular surface of the distal

end including the femorotibial joint capsule), epididymis [a], esophagus, eyes[a], gallbladder, gut-associated lymph tissues, heart, ileum, infusion site (anterior vena cava at catheter tip), infusion site A (anterior vena cava or right atrium of heart, 1 to 2 cm anterior to the catheter tip), jejunum, kidneys, lacrimal gland, larynx[d], liver, lungs, lymph nodes (cervical and mesenteric), mammary gland (region), muscle (diaphragm, quadriceps), nasal turbinates[d], optic nerves, ovaries, oviducts, pancreas, parathyroid, pituitary, prostate, rectum, salivary gland (mandibular, parotid, sublingual), sciatic nerve, seminal vesicles, skin, spinal cord (cervical and thoracic), spleen, sternum with marrow, stomach, testes[a], thymus (region), thyroids, tongue, trachea, urinary bladder, uterus, vagina, infusion sites (at catheter tip, and 1 to 2 cm anterior to catheter tip), exteriorization site, and any gross lesions.

a: the testes and eyes including the optic nerve were fixed using a modified Davidson's fixative.

d: Retained in fixative.

Histological Findings

Testes were described as immature (4/4, 3/4, 4/4, and 3/4 in groups 1, 2, 3 and 4, respectively), or peri-pubertal (1/4 and 1/4 in the groups 2 and 4). The different stages of maturity in testis among the males is unlikely to be related to the decrease in absolute and relative weights of testis in the treatment groups.

Focal right atrial endocardial thickening was observed in each of the four females in all treatment groups, with a severity of slight to moderate (high-dose female only).
In addition, as shown in the Sponsor's table below, intima or endocardium thickening at the infusion site A (anterior vena cava or right atrium of heart, 1 to 2 cm anterior to the catheter tip) was observed at comparable incidence and severity in all animals with or without treatment. Thus, it is likely that the focal right atrial endocardial thickening (hyperplasia) in females was procedure-related.

Table
Summary of Severity for Selected Microscopic Observations
Terminal Sacrifice (Dosing Phase)

Test Article	(dosage)	1	2	3	4
GZ402666(neoGAA)	mg/kg	0	50	50	50
Glycan	mg/kg	0	3	6	12.55

Tissue/ Observation	Group/Sex: / Number of Animals:	1/M	2/M	3/M	4/M	1/F	2/F	3/F	4/F
		4	4	4	4	4	4	4	4
Infusion Site, A	Number Examined:	4	4	4	4	4	4	4	4
	Unremarkable:	1	1	0	0	1	0	1	1
Inflammation									
	finding not present -	4	4	3	4	3	4	4	4
	minimal 1	0	0	1	0	0	0	0	0
	slight 2	0	0	0	0	1	0	0	0
	Total Incidence:	0	0	1	0	1	0	0	0
	Average Severity:	0.0	0.0	1.0	0.0	2.0	0.0	0.0	0.0
Intima/endocardium, thickened									
	finding not present -	2	1	0	1	1	2	3	2
	minimal 1	0	0	2	1	0	1	1	1
	slight 2	1	0	2	1	0	1	0	1
	moderate 3	1	3	0	1	3	0	0	0
	Total Incidence:	2	3	4	3	3	2	1	2
	Average Severity:	2.5	3.0	1.5	2.0	3.0	1.5	1.0	1.5
Thrombus									
	finding not present -	4	4	3	3	4	4	3	4
	minimal 1	0	0	0	0	0	0	1	0
	slight 2	0	0	0	1	0	0	0	0
	moderate 3	0	0	1	0	0	0	0	0
	Total Incidence:	0	0	1	1	0	0	1	0
	Average Severity:	0.0	0.0	3.0	2.0	0.0	0.0	1.0	0.0

Special Evaluation

Anti-Drug Antibody Sample Collection

Blood samples were collected and stored for potential analysis of anti-drug antibody prior to treatment and on day 84.

Toxicokinetics

Blood samples were collected on days 1 and 85 of the dosing phase at the following time-points: within 5 minutes of the end of infusion and at approximately 0.25, 0.5, 1, 2, 4, 6, 8, 24, and 48 hours after the end of infusion. The concentrations of neoGAA in serum were determined using a validated 4-methylumbelliferyl fluorescence assay. The lower limit of quantitation (LLOQ) was 0.1 µg/mL.

Following single and repeated administration of 50 mg/kg neoGAA spiked with glycan, neoGAA concentrations were quantifiable in all animals up to 54 hours from the start of infusion. Maximum concentrations were generally observed at the end of infusion. There was no accumulation following repeated dosing. Glycan had no effects on systemic exposure to neoGAA. There were no apparent sex-related differences, although females showed a slightly lower exposure (female to male $AUC_{0\text{-}54hr}$ ratios of

0.640 to 0.938 on day 1 and 0.625 to 0.881 on day 85). The PK parameters are summarized in the Sponsor's table below.

Mean Serum Toxicokinetic Parameters of neoGAA

Sex	neoGAA Dose (mg/kg)	Glycan Dose (mg/kg)	C_{max} (µg/mL)		AUC_{0-54} (µg.h/mL)	
			Day 1	Day 85	Day 1	Day 85
Male		3	606	740	2580	3560
	50	6	1030	683	4470	3180
		12.55	876	784	3770	3920
Female		3	557	652	2420	2860
	50	6	676	667	2860	2800
		12.55	798	565	3530	2450

Values are rounded to 3 significant figures

Dosing Solution Analysis

neoGAA:

Protein concentrations for vehicle and neoGAA dosing formulations prepared for administration on days 1, 15, 43, and 85 of the dosing phase were analyzed. Concentrations for neoGAA formulations for all dose groups were all within the acceptable range of ± 20% of the expected concentration. Percent recovery values ranged from 86.4% (only formulation for group 1 on day 1) to 117.7% with %CV values ≤ 3.9%. The formulations were stable when compared to concentrations from pre-dose and post-dose samples.

Spiked Glycan:

Glycan concentrations in the formulation for administration on day 1 were 53.2-74.7% of expected concentrations due to lower concentration of the glycan stock solution (1.864 mg/mL rather 2.5 mg/mL). Therefore, the formulations for subsequent dosing on days 15, 43, and 85 were prepared using another glycan stock solution containing 2.37 mg/mL. As shown in the Sponsor's table below, glycan concentrations in the formulation for group 2 for administration on days 43 and 85 were 73.7-79.5% of expected concentration. However, the glycan concentrations in formulations for groups 3 and 4 for all dosing days ranged from 81.6-112.5% of the expected concentrations. The glycan concentrations in formulations for the group 4 animals were 93-112.5% of the expected concentration on dosing days 15, 43, and 85. Therefore, animals in group 4 (high-dose) were exposed to the intended concentration (dose) of glycan, in contrast to animals in groups 2 and 3. Thus, the lower than expected exposure to glycan in groups 2 and 3 is unlikely to impact the overall conclusions of the study.

Summary of Glycan Concentration Results in Formulations

Dosage Group	Timepoint		Test Article	Expected Glycan Concentration (µg/mL)	Mean Measured Glycan Concentration (µg/mL)	% Recovery
1	Day 1	Pre	Vehicle Control Article	0	BQL	NA
		Post			BQL	NA
	Day 15	Pre			BQL	NA
		Post			BQL	NA
	Day 43	Post			BQL	NA
	Day 85	Post			BQL	NA
2	Day 1	Pre	neoGAA spiked with glycan	150	79.8	53.2
		Post			90.2	60.1
	Day 15	Pre			156.5	104.3
		Post			156.2	104.1
	Day 43	Post			119.3	79.5
	Day 85	Post			110.5	73.7
3	Day 1	Pre	neoGAA spiked with glycan	300	181.3	60.4
		Post			184.6	61.5
	Day 15	Pre			275.6	91.9
		Post			272.5	90.8
	Day 43	Post			264.4	88.1
	Day 85	Post			244.7	81.6
4	Day 1	Pre	neoGAA spiked with glycan	627.5	458.6	73.1
		Post			469.0	74.7
	Day 15	Pre			583.7	93.0
		Post			607.0	96.7
	Day 43	Post			662.0	105.5
	Day 85	Post			706.1	112.5

Summary and Safety Evaluation:

In the submitted 13-week toxicity study, cynomolgus monkeys were treated with 50 mg/kg neoGAA spiked with 3, 6, or 12.55 mg/kg free glycan (unconjugated Genz-669342) every other week intravenously. Emesis and vomitus were observed in all treatment group animals following infusion, although this effect was not dose-dependent. All doses of the test article produced slight to moderate reductions in absolute and relative weights of epididymis, prostate, and testis. However, no microscopic changes were observed in these tissues. Therefore, the weight reductions in male reproductive organs are not considered adverse. No target organs of toxicity were identified. The NOAEL for free glycan was considered to be 12.55 mg/kg.

The weight reductions in male reproductive organs appear to be caused by the free glycan, based on the dose-dependency observed in the present study using spiked neoGAA, and the previous 26-week toxicity study in monkeys with multiple dose levels of neoGAA that contained a lower level of free glycan.

The Sponsor submitted the current amendment to support a proposed increase in the specification limit for residual glycan (unconjugated Genz-669342) in the drug product, based on the current 13-week toxicity study in monkeys. The Sponsor has increased the residual glycan specification from (b) (4) µg/mL in the drug product.

The establishment of a NOAEL in monkeys at 12.55 mg/kg free glycan (150.6 mg/m^2) in the 13-week toxicity study results in a safety margin of 9.7 for the amended limit of (b) (4) µg/mL (based on (b) (4) mg/m^2 residual glycan as the worst-case exposure with administration of 20 mg/kg neoGAA [(b) (4) mL/kg] in adult patients). The dose of 20 mg/kg neoGAA is the highest dose tested in clinical studies. Therefore, the submitted toxicity study in monkeys qualifies residual glycan at the amended limit of (b) (4) µg/mL in the drug product.

RECOMMENDATIONS:

From a nonclinical viewpoint, the proposed increase in the residual glycan specification to ≤ (b) (4) µg/mL in drug product is acceptable.

Fang Cai, Ph.D.
Pharmacologist, DGIEP

Date

David B. Joseph, Ph.D.
Pharmacology Team Leader, DGIEP

Date

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FANG CAI
02/18/2020 10:44:22 AM
From a nonclinical viewpoint, the proposed increase in the residual glycan specification to = (b) (4) µg/mL in drug product is acceptable.

DAVID B JOSEPH
02/18/2020 01:55:37 PM
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	109569
Supporting document/s:	135
Sponsor's letter date:	April 3, 2018
CDER stamp date:	April 3, 2018
Product:	NeoGAA (Avalglucosidase)
Indication:	Pompe disease
Sponsor:	Sanofi Genzyme Cambridge, MA
Review Division:	Gastroenterology and Inborn Errors Products
Reviewer:	Fang Cai, PhD
Supervisor/Team Leader:	David B. Joseph, PhD
Acting Division Director:	Roman Dragos, MD
Project Manager:	Jenny Doan

1. Background

Pompe disease (also known as acid maltase deficiency or glycogen storage disease (GSD) type II) is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid α-glucosidase (GAA). Due to lack of GAA, accumulation of glycogen in body tissues, especially cardiac muscle and respiratory and limb skeletal muscle, results in changes in architecture and function of the affected myocytes and leads to multi-systemic pathology and ultimately death. The approved recombinant human acid α-glucosidase (rhGAA, alglucosidase alfa with the trade names Myozyme® and Lumizyme®) improved cardiac muscle function, but not skeletal muscle. rhGAA is transferred to lysosomes via the cation-independent mannose-6-phosphate receptor (CIM6Pr), which thus plays an essential role in cellular binding and uptake. Furthermore, studies showed that the CIM6Pr is present in relatively low levels in human skeletal muscle compared to that of cardiac tissue, and that bis-phosphorylated glycans (bis-M6P) have a significantly higher affinity for the CIM6Pr as compared to the mono-phosphorylated forms. Therefore, it is plausible that increased levels of bis-M6P on rhGAA may enhance the uptake of rhGAA into skeletal muscle.

NeoGAA (Avalglucosidase) is a modified form of the approved drug alglucosidase alfa (Myozyme® and Lumizyme®), an enzyme replacement therapy (ERT). The active ingredient in the neoGAA drug product is a chemically-modified form of recombinant human α-glucosidase (rhGAA) expressed in Chinese Hamster Ovary (CHO) cells. NeoGAA is produced by conjugating a synthetic glycan to oxidized sialic acid residues on alglucosidase alfa through a synthetic linker with an aminoxy moiety. NeoGAA binding to M6Pr on the cell surface is mediated by the conjugated synthetic bismannose-6-phosphate-Man6 glycan. After neoGAA is internalized and transported into lysosomes, neoGAA degrades glycogen into glucose by catalyzing the hydrolysis of α-1,4- and α-1,6- glycosidic linkages of lysosomal glycogen.

In GAA knock out mice, neoGAA at doses of 4, 12, and 20 mg/kg/week produced glycogen reduction in the heart, quadriceps, and diaphragm similar to that observed with rhGAA administered at 20, 60 and 100 mg/kg, respectively. The results suggest that neoGAA was approximately 5-fold more potent than rhGAA under the study conditions.

2. Assessment of Carcinogenicity Potential

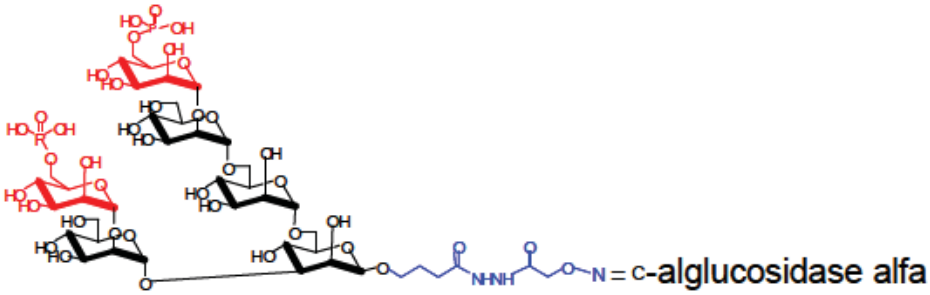
The Sponsor submitted an assessment of carcinogenicity potential for neoGAA, but did not conduct any carcinogenicity studies. The Sponsor proposed that carcinogenicity studies are not necessary based on their assessment.

NeoGAA is a chemically-modified lysosomal enzyme that degrades glycogen into glucose by catalyzing the hydrolysis of α-1,4- and α-1,6-glycosidic linkages of lysosomal glycogen. The mechanism of action does not raise a concern regarding the potential for neoplasm induction or tumor promotion.

Reference ID: 4840607

However, neoGAA is produced by conjugating a synthetic glycan (Genz-669342) to oxidized sialic acid residues on rhGAA. Genz-669342 contains six mannose units and a synthetic linker with an aminoxy moiety. The structure of neoGAA is shown below, with the linker displayed as blue.

Figure 1 - Avalglucosidase alpha structural formula



Genz-669342 was negative in the Ames test and chromosomal aberration test in cultured human peripheral blood lymphocytes. In addition, neoGAA at up to150 mg/kg was negative in two micronucleus assays in GAA knock out mice. Thus, neither neoGAA nor its synthetic glycan moiety exhibits genotoxic potential.

Monkeys that were administered neoGAA (50 mg/kg) spiked with Genz-669342 at doses up to 12.55 mg/kg IV every other week for 13 weeks did not show any proliferative lesions. Furthermore, there were no proliferative lesions in the 26-week monkey study, in which the animals were treated with neoGAA at doses up to 200 mg/kg IV every other week.

The carcinogenic potential of neoGAA appears to be low, based on the mechanism of action and the toxicity profile of the synthetic glycan moiety (Genz-669342). However, the available data does not provide an adequate basis for evaluating the carcinogenicity potential of the linker moiety of Genz-669342, and the Sponsor has not provided information about the metabolic fate of the linker moiety. Given the possibility that the linker moiety may be released in an unconjugated form after administration of neoGAA (i.e. cleaved from both GAA and the oligosaccharide moiety of Genz-669342), additional information is needed to support the Sponsor's conclusion that carcinogenicity studies are unnecessary. Therefore, it is premature to agree to a waiver of carcinogenicity studies.

To facilitate further evaluation of the carcinogenicity potential of neoGAA, the Sponsor should provide an estimate of the worst case exposure (on a mg/kg or µg/kg basis) to the unconjugated linker moiety of Genz-669342. This estimate should include the maximum amount of linker that could be released from unconjugated (b) (4) present in the drug product at the acceptance criterion (i.e. (b) (4) µg/mL Genz-

Reference ID: 4840607

669342 for the clinical dose of 20 mg/kg neoGAA), in addition to the maximum amount of linker that could be released from neoGAA. The Sponsor should provide all details of the supporting calculations for this estimate.

To address our concern about the potential release of the linker moiety after administration of neoGAA, we will also consider ADME data that directly describes the metabolic fate and excretion of the linker moiety, if any such data is available.

RECOMMENDATIONS:

1. We do not agree with the Sponsor's conclusion that carcinogenicity studies are unnecessary. Since the metabolic fate of the synthetic linker moiety of Genz-669342 is unknown, there is a deficiency in the current dataset that precludes an adequate assessment of the carcinogenicity potential of neoGAA. The available data does not provide an adequate basis for evaluating the carcinogenicity potential of the unconjugated synthetic linker moiety, which may be released after administration of neoGAA.

2. To facilitate further evaluation of the carcinogenicity potential of neoGAA, the Sponsor should provide an estimate of the worst case exposure (on a mg/kg or µg/kg basis) to the unconjugated linker moiety of Genz-669342. This estimate should include the maximum amount of linker that could be released from unconjugated (b) (4) present in the drug product at the acceptance criterion (i.e. (b) (4) µg/mL (b) (4) for the clinical dose of 20 mg/kg neoGAA), in addition to the maximum amount of linker that could be released from neoGAA (based on assumption of 100% release of the linker). The Sponsor should provide all details of the supporting calculations for this estimate.

3. To address our concern about the potential release of the linker moiety after administration of neoGAA, the Sponsor can also submit ADME data that directly describes the metabolic fate and excretion of the linker moiety, if any such data is available. However, an estimate of the worst case exposure to the unconjugated linker moiety should still be provided, as requested above.

Reference ID: 4840607

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FANG CAI
08/27/2018
Please convey recommendations included in the review to the Sponsor.

DAVID B JOSEPH
08/27/2018
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	109,569
Supporting document/s:	18
Sponsor's letter date:	December 4, 2013
CDER stamp date:	December 4, 2013
Product:	neoGAA (recombinant human α-glucosidase conjugated with synthetic bis-mannose-6-phosphate-Man6 glycan)
Indication:	Treatment of Pompe disease
Sponsor:	Genzyme Corporation Cambridge, MA
Review Division:	Division of Gastroenterology and Inborn Errors Products
Reviewer:	Fang Cai, Ph.D.
Supervisor/Team Leader:	David B. Joseph, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Elizabeth Ford, R.N.

Drug: neoGAA; a recombinant human acid α-glucosidase (rhGAA) expressed in Chinese Hamster Ovary (CHO) cells, conjugated to multiple copies of a synthetic bis-mannose-6-phosphate-containing hexasaccharide (Genz-669342).

Molecular formula/molecular weight: The approximate molecular formula is alglucosidase alfa ($C_{4488}H_{6826}N_{1196}O_{1297}S_{33}$, protein formula) + 6-8 glycan units ($C_{42}H_{75}N_3O_{40}P_2$). NeoGAA has an approximate total molecular weight of 120,000 Da.

Pharmacological class: enzyme replacement therapy

Indication: treatment of Pompe disease

Route of administration: intravenous

Background:

The Sponsor submitted this IND for the development of neoGAA for treatment of Pompe disease. The initial submission contained a protocol for a Phase 1, multicenter, multinational, open-label, ascending dose, intravenous infusion study to evaluate the efficacy and safety of neoGAA in patients with Pompe disease. Patients in each group will receive 13 bi-weekly intravenous infusions of neoGAA for a total of 24 weeks (week 1 to week 25). The dose levels will be 5, 10, and 20 mg/kg.

NeoGAA is produced by conjugating a synthetic glycan (Genz-669342) to oxidized sialic acid residues on rhGAA through a synthetic linker with an aminoxy moiety. The synthetic linker portion of Genz-669342 is structurally similar to hydroxylamine, which has the potential to be genotoxic. However, Genz-669342 was negative in the Ames test and chromosomal aberration assay. In the initial IND submitted on 3/28/2013, the Sponsor proposed a specification limit of (b) (4) µg/ml for unconjugated Genz-669342 in the drug product. At this limit, the maximum potential daily dose of unconjugated Genz-669342 from neoGAA would have been (b) (4) mg (assuming a 60-kg body weight, and a dose of 20 mg/kg neoGAA), which greatly exceeded the recommended ICH limit (i.e. (b) (4) mg/day for a 60-kg patient). Although the neoGAA batch used in the toxicology studies contained unconjugated Genz-669342, the pivotal 26-week IV toxicity study in monkeys did not provide an assurance of safety for the proposed specification limit of (b) (4) µg/ml.

A teleconference was held with the Sponsor on April 25, 2013 to discuss the safety concern related to the proposed limit for unconjugated Genz-669342 (free glycan). The Sponsor agreed to the Agency's recommended limit of (b) (4) µg/ml, and submitted a written response on April 26, 2013 (SD # 5) that reflects this agreement. The following recommendation was communicated in a letter to the Sponsor dated July 26, 2013:

"In the absence of additional nonclinical data, the limit for free glycan (i.e., unconjugated Genz-669342) in the drug product should not exceed the current limit of (b) (4) µg/ml. If you plan to increase the limit for free glycan, submit a

proposal for a chronic toxicity study to support the safety of a higher limit, in addition to the proposed new limit for free glycan."

The details of the safety assessment of unconjugated Genz-669342 and rationale for the recommended limit in the drug product are described in the Pharmacology/ Toxicology preliminary safety review dated July 3, 2013. On August 23, 2013, the Sponsor submitted a protocol outline for a 3-month toxicity study in monkeys to support a higher limit for free glycan levels in the drug product. During the review process, an information request was sent to the Sponsor to clarify the dose volume in the proposed study and the intended new specification limit for free glycan. The Sponsor submitted a revised study protocol on December 4, 2013, and also indicated their intent to increase the limit for free glycan in the drug product to (b) (4) µg/ml. The proposed study is reviewed below.

Study Outline for a 3-Month Repeated Dose Toxicity Study of neoGAA with Elevated Residual Glycan Levels in Cynomolgous Monkeys

Sponsor's proposed study design:

The proposed study will be GLP compliant. Cynomolgous monkeys at least 18 months of age will be treated intravenously with neoGAA containing different levels of residual glycan (i.e. unconjugated Genz-669342). neoGAA will be administered as a 6-hr infusion once every two weeks for 13 weeks (total of 7 doses). The study design is shown in the Sponsor's table below. The dose volume will be approximately 20 ml/kg, with all groups receiving 50 mg/kg neoGAA. The vehicle will be a solution containing 10 mM histidine pH 6 (b) (4) 0.01% Tween 80, 2% mannitol, and 2% glycine. The recovery groups will be sacrificed at 4 weeks after the final dose. Clinical signs, mortality, food consumption, body weight, respiratory rate, heart rate, core temperature, and blood pressure will be monitored. Evaluations of hematology, clinical chemistry, urinalysis, and ophthalmology will be performed. Blood samples for toxicokinetics evaluation will be collected at the following time-points after the 1st and 7th doses: pre-dose (within 24 hours), immediately at the end of infusion, 0.25, 0.5, 1, 2 ,4 , 6, 8, 24, and 48 hours after the end of infusion. Blood samples for measurement of anti-neoGAA antibodies will be collected prior to the first and seventh doses, but will only be analyzed if necessary. All animals will be subjected to necropsy and histopathological examination. (b) (4) .

Study Design

Group DEW	Dosage mg/kg	Residual Glycan Level µg/mL (Approximate Levels)	Terminal Sacrifice		Recovery Sacrifice	
			M	F	M	F
1	50	(b) (4)	2	2	1	1
2	50	600	2	2	1	1
3	50	1200	2	2	1	1
4	50	2510	2	2	1	1

Comments:

1. The Agency requested a chronic toxicity study (i.e. 6 months in rodents or 9 months in nonrodents for small molecules) to support the qualification of free glycan (unconjugated Genz-669342) at levels greater than 50 µg/ml in the drug product. However, the Sponsor has proposed a 3-month toxicity study in cynomolgus monkeys. Since the duration of the proposed study is in accordance with recommendations in ICH guidances Q3A and Q3B, the proposed study duration is acceptable.

2. The proposed dose level of neoGAA (50 mg/kg) in all treatment groups is acceptable, given that this dose was the NOAEL in the 26-week toxicity study in monkeys (see Pharmacology/Toxicology preliminary safety review dated July 3, 2013).

3. The establishment of a NOAEL or a tolerated dose in monkeys at the 600 µg/ml free glycan level (i.e. 144 mg/m^2) in the proposed study will result in a safety margin of (b) (4) for the proposed limit of (b) (4) µg/ml (i.e. (b) (4) mg/m^2 in humans), based on the intended dose volumes of 20 ml/kg in monkeys and (b) (4) ml/kg in humans. Therefore, the proposed study can qualify free glycan at the proposed limit of (b) (4) µg/ml in the drug product. However, toxicity that may occur in monkeys at the higher levels of free glycan ((b) (4) µg/ml) should also be considered in the safety assessment of the proposed limit.

4. The study should include 4 monkeys/sex in the groups designated for sacrifice at the end of the treatment period.

5. The proposed control group (b) (4) is unacceptable. A vehicle control group should be included in this study.

RECOMMENDATIONS:

1. The proposed study should include 4 monkeys/sex in the groups designated for sacrifice at the end of the treatment period.

2. The proposed control group [redacted] (b) (4) is unacceptable. A vehicle control group should be included in this study.

Fang Cai, Ph.D.
Pharmacologist, DGIEP

Date

David B. Joseph, Ph.D.
Pharmacology Team Leader, DGIEP

Date

cc:
IND
DGIEP
DGIEP/PM
DGIEP/Dr. Cai
DGIEP/Dr. Joseph
R/D Init.: D. Joseph 1/7/14

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

/s/

FANG CAI
01/08/2014

DAVID B JOSEPH
01/08/2014
I concur.

Pharmacologist's Preliminary Safety Review of IND 109,569

Date/type of submission: March 28, 2013/Initial

Sponsor and/or agent: Genzyme Corporation
Cambridge, MA

Reviewer name: Fang Cai, Ph.D.

Date of Preliminary Safety Review: July 3, 2013

Division name: Division of Gastroenterology and Inborn Errors Products

Drug: neoGAA; a recombinant human acid α-glucosidase (rhGAA) expressed in Chinese Hamster Ovary (CHO) cells, conjugated to multiple copies of a synthetic bismannose-6-phosphate-containing hexasaccharide (Genz-669342).

Clinical Formulation:

The neoGAA drug product is a sterile lyophilized product. The composition of neoGAA drug product is provided in the Sponsor's table below.

Table 1: NeoGAA Drug Product Composition

Name of Ingredient	Amount Per Vial	Amount per 1mL	Function	Grade
neoGAA	(b) (4) mg	(b) (4) mg	Active ingredient	In-house
Inactive Ingredients				
L-(+)-Histidine	(b) (4)			USP/EP
L-Histidine hydrochloride				EP
Polysorbate 80				NF/EP/JP
Mannitol				USP/EP/JP
Glycine				USP
(b) (4)				
Approximate weight of (b) (4) (b) (4)				N/A

For clinical trial administration, each vial of neoGAA drug product will be reconstituted with 10 mL of Water For Injection (WFI) to give a total volume of (b) (4) mL. The reconstituted solution contains neoGAA at a concentration of 10 mg/mL, 2% mannitol, 2% glycine, and 0.01% polysorbate 80 in 10 mM histidine buffer, pH 6.2.

Trade name: None

Code name: GZ402666

Molecular formula/molecular weight: The approximate molecular formula is alglucosidase alfa ($C_{4488}H_{6826}N_{1196}O_{1297}S_{33}$, protein formula) + 6-8 glycan units ($C_{42}H_{75}N_3O_{40}P_2$). NeoGAA has an approximate total molecular weight of 120,000 Da.

Pharmacological class: enzyme replacement therapy

Indication: treatment of Pompe disease

Route of administration: intravenous (IV)

Related INDs: none

Introduction and Proposed Clinical Study:

NeoGAA is a modified form of the approved drug alglucosidase alfa (Myozyme® and Lumizyme®), an enzyme replacement therapy (ERT). The active ingredient in the neoGAA drug product (lyophilized powder for solution) is recombinant human α-glucosidase (rhGAA) expressed in Chinese Hamster Ovary (CHO) cells, conjugated with synthetic bismannose-6-phosphate-Man6 glycan. GAA is a lysosomal enzyme that degrades glycogen into glucose by catalyzing the hydrolysis of α-1,4- and α-1,6- glycosidic linkages of lysosomal glycogen. Pompe disease (also known as acid maltase deficiency or glycogen storage disease (GSD) type II) is a rare, autosomal recessive genetic disease caused by the deficiency of lysosomal acid α-glucosidase (GAA). The resulting accumulation of glycogen in body tissues, especially cardiac muscle and respiratory and limb skeletal muscle, disrupts the architecture and function of the affected myocytes leading to multi-systemic pathology and ultimately death. The approved recombinant human acid α-glucosidase (rhGAA, alglucosidase alfa with the trade names Myozyme® and Lumizyme®) efficiently improved cardiac muscle function, but not skeletal muscle. rhGAA is transferred to lysosomes via the cation-independent mannose-6-phosphate receptor (CIM6Pr), which thus plays an essential role in cellular binding and uptake. Furthermore, studies showed that the CIM6Pr is present in relatively low levels in human skeletal muscle compared to that of cardiac tissue, and that bis-phosphorylated glycans (bis-M6P) have a significantly higher affinity for the CIM6Pr as compared to the mono-phosphorylated forms. Therefore, it is plausible that increased levels of bis-M6P on rhGAA may enhance the uptake of rhGAA into skeletal muscle. Thus, the Sponsor is developing recombinant human α-glucosidase (rhGAA) conjugated with synthetic bismannose-6-phosphate-Man6 glycan as a second generation therapy for Pompe disease.

In the present IND, the Sponsor proposes a Phase 1, multicenter, multinational, open-label, ascending dose, intravenous infusion study to evaluate the efficacy

and safety of neoGAA in patients with Pompe disease. A total of 21 patients at least 18 years of age will be enrolled in this study. Naïve patients with late-onset Pompe disease will be assigned to group 1 (n = 9) and late-onset Pompe disease patients previously treated with alglucosidase alfa will be assigned to group 2 (n = 12). Patients in each group will receive 13 bi-weekly intravenous infusions of neoGAA for a total of 24 weeks (week 1 to week 25). Group 1 and group 2 will be initiated simultaneously; each group will have 3 dose levels. Subjects are not allowed to participate in more than 1 dose group in the study. The dose levels will be 5, 10, or 20 mg/kg. Three patients will be included in each dose cohort in group 1. In group 2, each of the 5 and 10 mg/kg dose cohorts will include 3 patients, and 6 patients will be in the 20 mg/kg cohort. Dosing in the next cohort will begin after safety assessment is completed following 3 infusions in the previous cohort. Patients will receive each dose level bi-weekly for a total of 13 doses, and the dose volume will be determined by bodyweight and dose level. The study design is summarized in the table below.

Table 2: Study Design

Group 1		Group 2	
Number of patients	Dose cohorts (mg/kg)	Number of patients	Dose Cohorts (mg/kg)
3	5	3	5
3	10	3	10
3	20	6	20

Vital signs, ECGs, safety laboratory analysis (liver function test, renal function test, clinical chemistry, urinalysis, and hematology) and adverse events will be monitored pre-dose, during the treatment period, and at week 25. Physical examinations will be performed. Immunogenicity (anti-neoGAA IgG and neutralizing antibodies in IgG positive patients, and anti-alglucosidase alfa IgG antibodies) will be evaluated. Blood samples will be collected at weeks 1, 13, and 25 to analyze neoGAA levels. Pharmacodynamic markers (e.g. skeletal muscle biopsy and urine Hex4) will be monitored pre-dose, during the treatment period, and at weeks 25 and 27. Function tests including the 6 minute walk test, GSGC (Gait, Stair, Gower's Maneuver, and Chair), Gross Motor Function Measure-88, Quick Motor Function Test, and pulmonary function testing, with additional patient assessment through the PedsQL (Pediatric Quality of Life Inventory Multidimensional Fatigue Scale) will be conducted pre-dose and at weeks 13 and 25.

To support the proposed clinical study, the Sponsor submitted the following nonclinical studies: pharmacology studies, pharmacokinetics (plasma kinetics and distribution), repeated-dose intravenous toxicity studies in mice and monkeys, and genotoxicity studies on a glycan (b) (4) The safety

pharmacology of neoGAA was assessed in a 26-week toxicity study in cynomolgus monkeys. No reproductive and developmental toxicity studies were submitted.

Pharmacology Studies

Glycogen Clearance Following Administration of 4 Weekly Doses of neoGAA and rhGAA in GAA Knockout Mice (Genzyme Study 07-1948)

NeoGAA (lot #: 07-BD-0418) was administrated to GAA knockout mice (3/sex/group, 3 - 6 months old) via intravenous injection at doses of 4, 12, and 20 mg/kg/week for 4 weeks. For comparison, GAA mice (3/sex/group, 3 - 6 months old) were treated with rhGAA at doses of 20, 60, and 100 mg/kg/week via IV injection for 4 weeks. Starting with the second dose, mice were pretreated with diphenhydramine (5 mg/kg IP) at 10-20 minutes prior to dosing with the test article, to prevent hypersensitivity reactions. All animals were sacrificed 7 days following the last dose. Glycogen depletion in heart, quadriceps, and triceps was assessed using a biochemical glycogen assay. Serum was analyzed for anti-drug antibodies.

There was a dose-dependent reduction of glycogen in heart, quadriceps, and triceps in neoGAA- and rhGAA-treated animals. After 4 weekly treatments, administration of 12 and 20 mg/kg neoGAA resulted in equivalent glycogen depletion in heart compared to groups administered 60 and 100 mg/kg rhGAA, respectively. NeoGAA at 4 mg/kg significantly increased glycogen depletion in the heart tissue compared to 20 mg/kg rhGAA. Similar glycogen depletion was observed in the skeletal muscle of treated animals following administration of 4, 12 and 20 mg/kg neoGAA compared to 20, 60 and 100 mg/kg rhGAA, respectively. The results suggest that neoGAA was approximately 5-fold more potent than rhGAA under the study conditions.

Anti-drug antibodies were identified in all treated animals with no differences between dose levels and across treatments. There appeared to be a dose responsive increase in antibody titers in animals treated with neoGAA.

Glycogen Clearance Following Administration of 4 Weekly Doses of rhGAA and neoGAA in GAA Knockout Mice (Genzyme Study 10-00587)

NeoGAA (lot #: NE006, also used in the 26-week toxicology study in cynomolgus monkeys) was administered to GAA knockout mice (6/sex/group, 3 - 6 months old) via intravenous injection at doses of 4, 12, and 20 mg/kg/week for 4 weeks. For comparison, GAA knockout mice (3/sex/group, 3 - 6 months old) were treated with rhGAA at doses of 20, 60, and 100 mg/kg/week via IV injection for 4 weeks. Starting with the second dose, mice were pretreated with diphenhydramine (5 mg/kg IP) at 10-20 minutes prior to dosing to prevent hypersensitivity reactions. All animals were sacrificed 7 days following the last dose. Glycogen depletion in heart, quadriceps, triceps, psoas, and diaphragm

was evaluated using a biochemical glycogen assay. Serum was analyzed for anti-drug antibodies.

NeoGAA at doses of 4, 12, and 20 mg/kg/week produced a similar glycogen reduction in the heart, quadriceps and diaphragm tissue compared to rhGAA administered at 20, 60 and 100 mg/kg, respectively. Glycogen levels were similar in the triceps muscle following administration of 4 and 12 mg/kg neoGAA compared to 20 and 60 mg/kg rhGAA, respectively. However, glycogen levels in triceps muscle were significantly lower following administration of 100 mg/kg rhGAA compared to 20 mg/kg neoGAA. Glycogen levels in the psoas of mice dosed with 12 mg/kg neoGAA were similar to mice that received 60 mg/kg rhGAA. However, 20 mg/kg neoGAA did not produce a similar reduction of glycogen in psoas as that in mice treated with rhGAA at 100 mg/kg. NeoGAA at 4 mg/kg and rhGAA at 20 mg/kg had no effects on glycogen levels in psoas. Overall, the results indicated that neoGAA and rhGAA reduced glycogen to similar levels in most tissues, and that neoGAA was approximately 5-fold more potent than rhGAA. Antibody titers were similar between all groups of animals irrespective of test article or dose level administered.

Pharmacodynamics of neoGAA Produced from rhGAA Containing Different Levels of Sialic Acid following 4 Weekly Intravenous Doses in the GAA Knockout Mouse (Genzyme Study 11-02367)

The objective of this study was to evaluate glycogen clearance from tissues in the GAA knockout mouse following administration of neoGAA produced from rhGAA containing either 5.5 mol/mol sialic acid (neoGAA-5SA) or 7.2 mol/mol sialic acid (neoGAA-7SA). These two lots of neoGAA contained approximately 5 or 7 synthetic glycan moieties (Genz-669342) per neoGAA molecule, respectively.

GAA knockout mice (3/sex/group, 3 - 6 months old) were administered either neoGAA-5SA or neoGAA-7SA via intravenous injection at doses of 0, 4, and 12 mg/kg/week for 4 weeks. Starting with the second dose, mice were pre-treated with diphenhydramine at 5 mg/kg IP 10-20 minutes prior to dosing with the test article to prevent hypersensitivity reactions. All animals were sacrificed 7 days following the last dose. Glycogen depletion in heart, quadriceps, and triceps was evaluated using a biochemical glycogen assay.

NeoGAA-5SA and neoGAA-7SA at doses of 4 and 12 mg/kg/week produced similar glycogen depletion in the heart. NeoGAA-5SA and neoGAA-7SA at doses of 4 and 12 mg/kg had little or no effects on glycogen level in quadriceps. In triceps, glycogen was depleted with administration of 12 mg/kg neoGAA-7SA, whereas no depletion was observed with neoGAA-5SA. Under the study conditions, the results suggested that there was no consistent difference in tissue glycogen reduction following administration of neoGAA when produced from rhGAA containing 5.5 or 7.2 mol/mol sialic acid.

Safety Pharmacology

The effects of neoGAA in the CNS, pulmonary system, and cardiovascular system were evaluated in the 26-week intravenous toxicity study in cynomolgus monkeys (see Toxicology section below). Hemodynamic data (systolic, diastolic, and mean arterial pressure) was not monitored in this study. The Sponsor will monitor hemodynamics closely in the clinical trial.

Toxicology

1. Repeated-dose Toxicity

Intravenous Administration 50 mg/kg neoGAA or rhGAA Every Other Day for 14 Days (b) (4) Study FFA00125)

This was not a GLP study. CD-1 mice (10/sex/group, 8-10 weeks old) were treated with vehicle, neoGAA, or rhGAA at doses of 0 or 50 mg/kg via IV bolus injection to the tail vein on days 1, 3, 5, 7, 9, 11, and 13. Starting on day 9 (dose number 5), animals were administered 5 mg/kg diphenhydramine (DPH) intraperitoneally (IP) at 10-20 minutes prior to test article administration to prevent hypersensitivity reactions; the DPH pretreatment was continued for all doses thereafter. Daily clinical observations and weekly body weight and food consumption were recorded. On day 14, all animals were euthanized and subjected to a complete gross necropsy and tissue collection. The following organs were weighed: (adrenal glands, brain, heart, kidney, lung, liver, spleen, pancreas, pituitary gland, epididymis, prostate, salivary glands, seminal vesicles, testes, thymus, thyroid gland, quadriceps, and triceps). Selected tissues were examined microscopically (brain, heart, kidney, lung, liver, spleen, pancreas, quadriceps, triceps, and urinary bladder). The study design is described in the following table (taken from the study report).

Table 3: Study Design for a 14-day Toxicity Study in Mice

Test Article (Lot Number)	Route	Dose Levels (mg/kg)	Dose Regimen	Number of Animals per Group (Gender)	Age
rhGAA Vehicle[1] (07LS130)	IV	0	IV bolus on Days 1, 3, 5, 7, 9, 11, and 13	20 (10M/10F)	8-10 Weeks
rhGAA (A7053)		50			
neoGAA (08-BD-0019)		50			

[1] rhGAA vehicle composition: (b) (4) 2% Mannitol, (b) (4) Polysorbate 80

There were no neoGAA or rhGAA treatment-related deaths. Administration of neoGAA or rhGAA had no effects on clinical signs, body weight, food consumption, hematology or clinical chemistry parameters. Spleen weights were increased in male animals treated with rhGAA (↑28%, $p \leq 0.05$) and neoGAA (↑41%, $p \leq 0.05$) and in female animals treated with neoGAA (↑32%, $p \leq 0.05$) when compared to controls. However, there were no associated histopathologic changes. Macroscopic findings including small testis, black and red foci over testis, and discoloration of testis were observed in 1 of 10 male animals from the rhGAA-treated group and 3 of 10 male animals from the neoGAA-treated groups. These tissues were not subjected to microscopic evaluation, and a relationship with administration of neoGAA could not be established. Male animals administered 50 mg/kg neoGAA had minimal multifocal hepatocellular necrosis throughout the parenchyma in 3 of 10 males, and minimal (2/10 males) to mild (1/10 males) inflammatory infiltrates in the hepatic parenchyma.

In conclusion, IV administration of rhGAA at 50 mg/kg every other day was tolerated in mice. rhGAA and neoGAA at 50 mg/kg were associated with macroscopic findings in the male reproductive tract (small testis, black and red foci over testis, discoloration of testis). In the liver, minimal to mild multifocal necrosis and inflammatory infiltrates were present after IV administration of neoGAA at 50 mg/kg every other day.

28-Day Pilot Study of neoGAA Administered Intravenously Every Week to CD-1 Mice (Genzyme Study 10-00183)

This was not a GLP study. CD-1 mice (6/sex/group, 8-10 weeks old) were treated with vehicle or neoGAA at doses of 4, 40 or 120 mg/kg via IV bolus injection to the tail vein on days 1, 8, 15, and 22. Mice in the toxicokinetic (TK) groups (3/sex/group) received the same treatment regimen, and blood samples were collected at 5, 15, and 30 minutes, and 1, 2, 4, and 6 hours following the first and 4th dose. The study design is summarized in the Sponsor's table below.

Table 4: Study design for a 28-day IV pilot toxicity study in CD-1 mice

Test Article (Lot Number)	Route	Dose Levels (mg/kg)	Dose Regimen	Number of Animals per Group (Gender)	Age
Vehicle[1] (10LS004)	IV	0	IV bolus on Days 1, 8, 15, and 22	Main study 6 (3M/3F) TK 12 (6M/6F)	8-10 weeks of age
neoGAA (17265-118)		4			
neoGAA (17265-118)		40			
neoGAA (17265-118)		120			

[1] Vehicle composition: 10 mM L-Histidine, 2% Glycine, 2% Mannitol, 0.01% Polysorbate 80, pH (b) (4)

Beginning with the third dose, animals in the 4 mg/kg/week group were treated with 10 mg/kg DPH (IP) at 10-20 minutes prior to dosing with the test article due to signs of hypersensitivity (e.g. lethargy and scruffy coat). Animals in the 40 and 120 mg/kg/week groups also were prophylactically treated with 10 mg/kg DPH IP, 10-20 minutes prior to administration of neoGAA. Thereafter, all mice were treated with DPH at a dose of 20 mg/kg IP, 10-20 minutes prior to administration of neoGAA. In some instances a second dose of DPH IP at 10-20 mg/kg was administered to animals that continued to show signs of hypersensitivity following neoGAA administration, despite pretreatment with DPH.

Clinical signs were observed prior to and following administration of each dose. Body weight was recorded weekly. On day 29, all animals were euthanized and subjected to a complete gross necropsy and tissue collection. Blood was collected for analysis of clinical pathology parameters and antibody levels. Organs (brain, heart, kidney, lung, liver, spleen, testes, and ovaries) were weighed. Tissues from all main study animals in groups 1 and 4 were evaluated through microscopic examination.

There were a total of 3 unscheduled deaths due to hypersensitivity reactions to neoGAA. Within 1 hr following administration of neoGAA on day 22, two males in the 4 mg/kg group died and one female in the 4 mg/kg group was euthanized. Hypersensitivity reactions (hunched position and lethargy) were observed in all neoGAA treatment groups beginning with the third dose. There were no treatment-related effects on body weight or body weight gain.

Compared to the vehicle control (group 1), animals in groups 3 and 4 had a significant decrease in triglycerides (213, 115, and 126 mg/dl for groups 1, 3 and 4, respectively, $p < 0.01$). There was a dose-dependent increase in WBC (7.81 x 10^3/µl, 7.36 x 10^3/µl, 9.29 x 10^3/µl, and 11* x 10^3/µl for groups 1, 2, 3 and 4, respectively, * $p < 0.01$ compared to group 1 value). NeoGAA at 40 and 120 mg/kg produced an increase in absolute lymphocytes (15% and 45%, respectively), and neoGAA at all doses produced in an increase in relative lymphocyte count (up to 23%). The Sponsor stated that the reduction in triglycerides in neoGAA-treated animals was likely due to some variability in food consumption prior to blood collection. The increase in lymphocytes was attributed to the hypersensitivity response to neoGAA.

NeoGAA at all doses had no effects on organ weights, organ to body weight ratios, and organ to brain weight ratios. There were no treatment-related macroscopic or microscopic changes.

All mice treated with neoGAA were positive for anti-neoGAA antibodies (IgG).

Toxicokinetic parameters were available from only one animal following the fourth administration at 4 mg/kg due to unscheduled deaths. The increase in AUC with dose was disproportionately high. In addition, a dose-dependent increase in $t_{1/2}$ and a dose-dependent decrease in clearance were observed. These results suggest that the major plasma clearance mechanism, presumably uptake in tissues by CIM6Pr, was saturated at the tested dose levels. There was no gender-related difference. TK data is summarized in the Sponsor's table below.

Table 5: Toxicokinetic parameters for neoGAA following the first and fourth intravenous dose to CD-1 mice in a 28-day toxicity study

	First Dose			Fourth Dose		
	4 mg/kg (n=5)	40 mg/kg (n=6)	120 mg/kg (n=5)	4 mg/kg (n=1)	40 mg/kg (n=6)	120 mg/kg (n=5)
$t_{1/2}$ (hr)	0.455 ± 0.094	0.767 ± 0.102*	1.23 ± 0.073*,#	0.315	0.752 ± 0.242	0.939 ± 0.127$
CL (mL/hr/kg)	62.2 ± 12.1	30.7 ± 1.06*	23.7 ± 2.83*,#	80.0	28.4 ± 8.80	27.0 ± 3.83
V_z (mL/kg)	39.6 ± 2.51	33.9 ± 4.66^	41.9 ± 3.38#	36.3	29.7 ± 8.46	36.2 ± 4.10$
C_{max} (µg/mL)	87.6 ± 7.77	942 ± 95.3	2517 ± 203	68.8	949 ± 161	2866 ± 656
AUC (µg x hr/mL)	66.1 ± 11.5	1306 ± 45.3	5127 ± 611	50.0	1498 ± 368	4513 ± 589
AUC/Dose (hr*kg*µg/mL/mg)	16.5 ± 2.87	32.7 ± 1.13*	42.7 ± 5.09*,#	12.5	37.4 ± 9.19	37.6 ± 4.91

^ $p<0.05$, 4 mg/kg compared to 40 mg/kg
* $p <0.05$, 4mg/kg compared to 40 mg/kg and 120 mg/kg
# $p <0.05$, 40 mg/kg compared to 120 mg/kg
$ $p <0.05$, first dose compared to fourth dose

In summary, CD-1 mice were treated with neoGAA at doses of 0, 4, 40, or 120 mg/kg/week IV for 28-days. There were no treatment-related changes in body weight, body weight gain, hematology, or clinical chemistry. No macroscopic or microscopic changes were observed. Hypersensitivity reactions were observed in all treatment groups, and all mice treated with neoGAA were positive for anti-drug antibodies. Plasma kinetics were indicative of saturation of plasma clearance. The no-observed-adverse-effect-level (NOAEL) was 120 mg/kg/week (IV) in CD-1 mice, based on exclusion of the hypersensitivity reactions from the toxicity assessment.

A 28-Day Infusion Study in Cynomolgus Monkeys (MPI Study 1213-004)

Cynomolgus monkeys (2/sex/group) were administered vehicle or neoGAA at dose levels of 4, 40, and 120 mg/kg/dose via 6 hour IV infusion through a surgically implanted femoral catheter and vascular access port (VAP), once weekly for 28 days. The study design is summarized in the Sponsor's table below. Blood samples for TK analysis were collected immediately at the end of infusion following the first and last infusion.

Table 6: Study design for a 28-day IV toxicity study in cynomolgus monkeys

Test Article (Lot Number)	Route	Dose Levels (mg/kg)	Dose Regimen	Number of Animals per Group (Gender)	Age
Vehicle[1] (10LS004)	IV	0	IV Infusion on Days 1, 8, 15, and 22	4 (2M/2F)	2-4 years of age
neoGAA (17265-118)		4			
neoGAA (17265-118)		40			
neoGAA (17265-118)		120			

[1] Vehicle composition: 10 mM L-Histidine, 2% Glycine, 2% Mannitol, 0.01% Polysorbate 80, pH (b) (4)

Clinical signs, morbidity, and mortality were observed twice daily. Body weight was recorded prior to study and weekly thereafter. Blood samples for clinical pathology (hematology and clinical chemistry parameters) evaluations were collected from all animals pre-dose and prior to the terminal necropsy. Serum antibodies from all animals were determined on days -1 and 21. At termination, 7 days following the fourth dose, urine samples were collected and all animals were subjected to necropsy examinations. Organ weights (adrenal, brain, epididymis, heart, kidney, lung, liver, pituitary, salivary gland, spleen,

thyroid/parathyroid, thymus, testes, and ovaries) were recorded, and all tissues were subjected to microscopic examination.

There were no treatment-related changes in clinical signs, body weight, body weight gain, hematology, clinical chemistry, urinalysis, and coagulation parameters. Thyroid/parathyroid gland weights were higher in females at 120 mg/kg/dose compared to controls (↑82%, ↑80%, and ↑80% for absolute weight, organ/body weight ratio, and organ/brain weight ratio, respectively). However, these increased weights were not considered treatment-related due to absence of similar finding in males and the lack of microscopic correlates. Minimal to moderate vascular degeneration/regeneration and minimal mononuclear cell infiltrate at the infusion site were observed in control animals and all animals treated with neoGAA. There were no treatment-related macroscopic or microscopic changes.

Due to the limited serum neoGAA concentration data available from the 4 mg/kg dose level, there was no TK data for this dose level. NeoGAA toxicokinetic parameters were evaluated following the first and fourth infusion of 40 and 120 mg/kg. Systemic exposure increased in a greater than dose proportional manner, particularly after the fourth infusion. AUC and C_{max} values from the 4th infusion were increased relative to those from the first infusion. These time-dependent changes were associated with a statistically significant decrease in clearance in the 120 mg/kg group. The change in TK parameters after repeated dosing may have been related to the presence of anti-drug antibodies. Half-life was increased and clearance was decreased with increased dose level. These dose-related changes in TK parameters were only a trend at the first infusion, but were statistically significant at the fourth infusion. The dose-dependent increase in $t_{1/2}$ suggests that the major plasma clearance mechanism, presumably uptake in tissues by CIM6Pr, was saturated at the tested dose levels of neoGAA in cynomolgus monkeys. Overall, there was no gender-related difference in TK parameters. The TK data is summarized in the Sponsor's table below.

Table 7: Toxicokinetic parameters for neoGAA following the first and fourth intravenous infusion to cynomolgus monkeys in a 28-day toxicity study

	First Dose			Fourth Dose		
	4 mg/kg	**40 mg/kg**	**120 mg/kg**	**4 mg/kg**	**40 mg/kg**	**120 mg/kg**
$t_{1/2}$ (hr)	N/A	0.533 ± 0.189	0.729 ± 0.179	N/A	0.508 ± 0.184	0.919 ± 0.199*
Cl (mL/hr/kg)	N/A	53.5 ± 21.5	40.3 ± 10.6	N/A	43.3 ± 8.84	20.5 ± 2.22*, #
V_z (mL/kg)	N/A	38.4 ± 10.5	44.0 ± 20.2	N/A	33.0 ± 18.5	27.0 ± 6.01
C_{max} (µg/mL)	N/A	192 ± 63.3	862 ± 302	N/A	258 ± 39.7	1273 ± 214
AUC (µg X hr/mL)	N/A	824 ± 260	3155 ± 911	N/A	954 ± 202	5900 ± 660 #
AUC/Dose (hr*kg*µg/ml/mg)	N/A	20.6 ± 6.49	26.3 ± 7.59	N/A	23.9 ± 5.05	49.2 ± 5.50*, #

* $p < 0.05$, 40 mg/kg compared to 120 mg/kg
\# $p < 0.05$, first dose compared to fourth dose

In summary, cynomolgus monkeys were treated with neoGAA at doses of 4, 40, and 120 mg/kg/week via an intravenous infusion for 28-days. There were no treatment-related changes in body weight, body weight gain, hematology, or clinical chemistry. No treatment-related macroscopic or microscopic changes were observed. All monkeys treated with neoGAA were positive for anti-neoGAA antibodies. The TK data suggested that saturation of plasma clearance had occurred. The NOAEL was 120 mg/kg/week (IV) in monkeys.

A 26-Week Intravenous Infusion Toxicity Study of neoGAA in Cynomolgus Monkeys ([redacted] (b) (4) Study 0658-11097)

This was a GLP study. Cynomolgus monkeys (5-6/sex/group, at least 18 months of age) were administered vehicle or neoGAA at dose levels of 0 (vehicle), 50, and 200 mg/kg/dose via 6-hr IV infusion through a surgically implanted femoral catheter and vascular access port (VAP), every other week for 26 weeks followed by a 4-week recovery period. The vehicle was 10 mM L-histine, 2% glycine, 2% mannitol, and 0.01% polysorbate 80, pH 6.2. The study design is summarized in the Sponsor's table below. Due to an apparently compromised venous access port, one of the 200 mg/kg females was replaced on Day 8. This replacement monkey died prior to dosing on Day 13; therefore, a control female was moved to the 200 mg/kg dose group on day 13 resulting in 5 females in the vehicle control group.

Table 8: Study design for a 26-week IV toxicity study in monkeys

Group DEW	Dosage mg/kg	Conc. mg/mL	Terminal Sacrifice		Recovery Sacrifice		Animal No.	
			M	F	M	F	M	F
1	0 (vehicle)	0	4	4	2	2	1-6	19-23
2	50	2.5	4	4	2	2	7-12	25-30
3	200	10	4	4	2	2	13-18	24, 31-37

Animal DEW3F32 was removed alive from study on Day 8 and replaced with animal DEW3F37. DEW3F37 was sacrificed moribund on Day 13 and animal DEW1F24 was moved to the high-dose group.

Mortality and clinical signs were observed twice daily. Body weight and food consumption were recorded weekly or daily, respectively. Electrocardiogram, neurobehavioral examination, ophthalmic examination, respiratory rate, heart rate, and core body temperature were performed or recorded pre-study, and during the treatment and recovery periods. Blood samples were collected prior to study, during the dosing period, and at the end of the treatment and recovery periods for evaluation of hematology, clinical chemistry, anti-neoGAA antibody titers, and TK parameters. Urine was collected from all animals at the scheduled euthanasia. All animals were subjected to necropsy and gross examination. Selected organs were weighed and a complete set of tissues from all dose groups were microscopically examined.

There were two unscheduled sacrifices. On day 13, one female monkey in group 3 (200 mg/kg/dose, DEW3F37) was sacrificed in a moribund condition prior to dosing. The Sponsor attributed the death to severe stress based on profound lymphoid depletion of the thymus, spleen, lymph nodes, and focal necrosis in the liver. On day 168, one female monkey in group 2 (50 mg/kg/dose, DEW2F29) was sacrificed in a moribund condition with lower body paralysis due to systemic inflammation resulting from contamination of the venous access port. This female had paralysis of the hind limbs and tail. Microscopic examination revealed suppurative inflammation of the meninges surrounding the lumbar spinal cord and hemorrhage into the submeningeal and interstitial areas of the spinal cord and cauda equina. Axonal swelling was noted throughout the nerve tracts comprising the cauda equina. There was marked inflammation and necrosis around the access port. Acute hemorrhage throughout the lobes of the lung and distension of the urinary bladder were observed.

There were no test article-related changes in CNS evaluation (activity level, fasciculations, movement of facial muscles, and visual field), respiratory rate, core temperatures, ophthalmic examination and ECG (heart rate, RR, QT, and QT_c intervals). Animals in the 200 mg/kg group showed up to approximately 9%

reductions in body weight, body weight gain, and food consumption during the treatment period. Reduced food consumption was more evident in males. Whether the changes in body weight, body weight gain, and food consumption were reversible is unclear since the recovery groups included only one female control and two males or females in the 200 mg/kg/dose group. NeoGAA had no effects on clinical signs, hematology, coagulation, and clinical chemistry. Due to the low number of samples (n = 0 - 2) collected at necropsy by cystocentesis, the urinalysis data are not interpretable.

Monkeys in group 3 (200 mg/kg/dose) had slight reductions in the absolute weight of several organs (see table below), and this effect was dose-dependent in most of these organs. A similar magnitude of reductions in organ weight/body weight ratio and organ weight/brain weight ratio were observed in these organs. At the end of the recovery period, organ weights of epididymes and testes at 200 mg/kg were still lower than the control values (29% and 35%, respectively). In contrast, thymus weight increased by 23% in males in group 3 compared to the control group. No conclusion can be made for female organ weight changes in groups 2 and 3 since there was only one sample available in groups 1 and 2. There were no histopathologic changes in these organs.

Table 9: Reductions in Absolute Organ Weights (% compared to control values) in Monkeys Treated with 200 mg/kg/dose neoGAA

Organ names	Group 3 (200 mg/kg/dose)	
	Males	Females
adrenal glands	-	-24%
epididymes	-23%	-
heart	-21%	-15% *
kidney	-18%	-10%
spleen	-	-17%
testes	-16%	-
thymus	-27%	-29%
thyroid/parathyroid	-18%	-18%

*: $p < 0.05$

A variety of vascular or inflammatory findings were observed due to intravenous infusion of neoGAA via the implanted femoral catheter and vascular access port (venous access port and/or right/left saphenous veins). These findings included thrombi in the lung, accompanied by inflammation and an occasional fragment of foreign material (catheter), and thrombi, fibrosis, inflammation, and/or hemorrhage in the vein proximal to catheter tip and in the saphenous veins. These findings occurred at comparable incidences in vehicle and test article-treated monkeys. Thus, there were no neoGAA treatment-related histopathologic changes.

Anti-neoGAA antibody titers were detected in all neoGAA-treated animals prior to the 7th infusion. Anti-neoGAA antibody titers were increased in the majority of neoGAA-treated animals prior to the 13th infusion when compared to titers at the 7th infusion.

Following the first, seventh, and thirteenth dose, systemic exposure increased in a greater than dose proportional manner. AUC and C_{max} values from the 7th and 13th infusions were increased relative to those from the first infusion. These time-dependent changes were associated with a statistically significant decrease in clearance. Half-life was increased and clearance was decreased with increased dose level. These results suggest that the major plasma clearance mechanism, presumably uptake in tissues by CIM6Pr, was saturated at the tested dose levels. Furthermore, the change in TK parameters after repeated dosing may have been related to the presence of anti-drug antibodies. Overall, there was no gender-related difference in TK parameters. The TK data is summarized in the Sponsor's table below.

Table 10: Toxicokinetic parameters for neoGAA following the first, seventh and thirteenth intravenous infusion to cynomolgus monkeys at doses of 50 and 200 mg/kg

	50 mg/kg			200 mg/kg		
	First Infusion (n=12)	**Seventh Infusion (n=11)**	**Thirteenth Infusion (n=10)**	**First Infusion (n=12)**	**Seventh Infusion (n=11)**	**Thirteenth Infusion (n=8)**
t1/2 (hr)	0.525 ± 0.092	0.577 ± 0.114	0.737 ± 0.228#	1.40 ± 0.209*	1.72 ± 0.100*#	1.99 ± 0.240*#$
Cl (mL/hr/kg)	22.3 ± 6.83	15.7 ± 3.82#	14.4 ± 4.29#	10.9 ± 1.59*	9.33 ± 1.75*	7.88 ± 2.44*#
Vz (mL/kg)	16.3 ± 3.12	12.7 ± 2.33#	14.6 ± 3.16	21.8 ± 3.38*	23.0 ± 4.01*	22.2 ± 5.84*
Cmax (µg/mL)	566 ± 157	818 ± 177#	861 ± 189#	3892 ± 506	4347 ± 894	5284 ± 1440#
AUC (µg X hr/mL)	2423 ± 682	3341 ± 748#	3712 ± 977#	18728 ± 2866	22463 ± 6268	28162 ± 10694#
AUC/Dose (hr*kg*µg/mL/mg)	48.5 ± 13.6	66.8 ± 15.0#	74.2 ± 19.5#	93.6 ± 14.3*	112 ± 31.3*	141 ± 53.5*#

*p<0.05 50 mg/kg compared to 200 mg/kg
# p <0.05, first infusion compared to seventh and thirteenth infusion at the same dose
$ p <0.05, seventh infusion compared to thirteenth infusion at the same dose

In summary, cynomolgus monkeys were treated with neoGAA at doses of 50 or 200 mg/kg every two weeks via an intravenous infusion for 26-weeks. There were no treatment-related changes in clinical signs, ophthalmic examination, ECG, neurobehavioral parameters, respiratory rate, core temperature, hematology, coagulation, or clinical chemistry. Animals in the 200 mg/kg group showed slight decreases in body weight gain and food consumption during the treatment period. A dose-dependent decrease in some organ weights was observed. However, there were no neoGAA-related macroscopic or microscopic findings. The TK data suggested that saturation of plasma clearance had occurred. All animals treated with neoGAA were positive for anti-neoGAA antibodies. Target organs of toxicity were not identified. The NOAEL was 50 mg/kg, based on impaired weight gain in the 200 mg/kg group. However, 200 mg/kg is considered to be a tolerated dose, given that the observed effects were limited to small reductions in weight gain and organ weights.

Genotoxicity Studies

NeoGAA is produced by conjugating a synthetic glycan (Genz-669342) to oxidized sialic acid residues on rhGAA through a synthetic linker with an aminoxy moiety. The synthetic linker portion of Genz-669342 is structurally similar to hydroxylamine, which has the potential to be genotoxic. Thus, the Sponsor conducted *in vitro* and *in vivo* genotoxicity studies to evaluate the genotoxic potential of Genz-669342 and neoGAA.

Genz-669342 was negative in the Ames test and chromosomal aberration test in cultured human peripheral blood lymphocytes.

The genotoxic potential of neoGAA was evaluated in two mouse micronucleus assays in GAA knockout mice. Since neoGAA is a biotechnology-derived pharmaceutical, the methods used in these studies were not compliant with the recommendations in ICH guidance S2(R1), nor were the studies GLP-compliant.

(1). Genotoxicity of neoGAA following Single or Multiple IV Bolus Injections in GAA Knockout Mice (Genzyme Study 09-3559)

The study design is described in the table below (taken from the study report). Animals in the last 2 groups were euthanized 24 hours following the first dose. Immediately following euthanasia, whole blood was collected and placed in fixative for micronuclei assessment. Micronuclei formation was determined using the MicroFlow® detection kit (b) (4) per the manufacturer's instructions.

Table 11: Study Design for Micronucleus Assay with neoGAA following Single or Multiple IV Bolus Injections in GAA Knockout Mice

Test Article (Lot Number)	Route	Dose Levels (mg/kg)	Dose Regimen	Number of Animals per Group (Gender)	Age
Vehicle[1] (09LS018)	IV	0	IV injection at Hour 0, Necropsy at 24 hours	8 (4 M / 4 F)	3-6 months of age
neoGAA (08-BD-0605)		50	IV injection at Hour 0, Necropsy at 6 hours		
			IV injection at Hour 0, Necropsy at 24 hours		
			IV injection at Hours 0 and 4, Necropsy at 24 hours		
			IV injection at Hours 0, 4, and 8, Necropsy at 24 hours		

[1] Vehicle composition: 25mM Sodium Phosphate (pH 6.2), 2% Mannitol, 0.005% Polysorbate 80

Under the test conditions, the administration of 1-3 doses of neoGAA at 50 mg/kg (up to 150 mg/kg cumulative dose) did not increase the percentage of micronucleated reticulocytes (MN-RET) or micronucleated normochromatic erythrocytes (MN-NCE) compared to the kit positive control compound. The percentage of MN-RET and MN-NCE was comparable to the kit negative control.

(2). Repeat Dose Genotoxicity Study of neoGAA Administered Intravenously to GAA KO Mice (Genzyme Study 10-00184)

GAA knockout mice were administered vehicle or neoGAA intravenously at doses of 0 and 50 mg/kg on day 1, for a total of 3 doses over an 8 hour period (0, 4, and 8 hours) via lateral tail vein. The mice were euthanized on days 8 and 15. The study design is summarized in the Sponsor's table below. The Sponsor provided the following rationale for the study design:

"NeoGAA may take greater than 24 hours to be metabolized following uptake into tissues and cells, and this metabolism may be necessary for the glycan/linker to be liberated *in vivo*. Therefore, to evaluate the potential of neoGAA to induce micronuclei formation over time, Genzyme Study 10-00184 was conducted to evaluate micronuclei formation 7 and 14 days following administration of neoGAA."

Following euthanasia, blood was collected for micronucleus analysis using the MicroFlow® assay.

Table 12: Study Design for Repeat Dose Micronucleus Assay with neoGAA Administered Intravenously to GAA KO Mice

Test Article (Lot Number)	Route	Dose Levels (mg/kg)	Dose Regimen	Number of Animals per Group (Gender)	Age
Vehicle[1] (10LS004)	IV	0	IV Injection at 0, 4, and 8 hours on Day 1, Necropsy on Day 8	10 (5M/5F)	8-10 weeks of age
neoGAA (17265-118)		50			
Vehicle[1] (10LS004)		0	IV Injection at 0, 4, and 8 hours on Day 1, Necropsy on Day 15		
neoGAA (17265-118)		50			

[1] Vehicle composition: 10 mM L-Histidine, 2% w/v Glycine, 2% w/v Mannitol, 0.01% Polysorbate 80, pH (b) (4)

Under the conditions of this study, neoGAA at doses of 50 mg/kg/dose, administered at 0, 4, and 8 hr on day 1, did not increase the number of MN-RET or MN-NCE at 7 or 14 days following the day of treatment, compared to the vehicle group and the negative control provided with the kit.

SUMMARY AND EVALUATION:

In order to support the proposed Phase 1 clinical study design, nonclinical toxicity studies for a duration of 6 months in a rodent and nonrodent species are needed for safety evaluation. The Sponsor conducted short-term (up to 1 month duration) general toxicology studies in mice and monkeys, and the toxicological findings from these studies are similar. Therefore, a 6-month toxicity study in one species is considered sufficient for safety assessment.

In the 26-week intravenous toxicity study in cynomolgus monkeys (18 months of age) with a 4-week recovery period, neoGAA was administered at doses of 50 and 200 mg/kg, every other week. NeoGAA had no effects on clinical signs, ophthalmic examination, ECG, neurobehavioral parameters, respiratory rate, core temperature, hematology, clinical chemistry, or histopathology. Animals in the 200 mg/kg group showed slight body weight reduction, decreased body weight gain, and decreased food consumption during the treatment period. A

dose-dependent decrease in some organ weights was observed. No target organ of toxicity was identified. Anti-neoGAA antibodies were detected in all animals treated with neoGAA. The NOAEL was 50 mg/kg, based on impaired weight gain in the 200 mg/kg group. However, 200 mg/kg (2400 mg/m^2) is considered to be a tolerated dose, given that the observed effects were limited to small reductions in weight gain and organ weights. Based on a body surface area comparison, the tolerated dose provides a 13-fold safety margin for the starting dose of 5 mg/kg (185 mg/m^2 given every other week) in the proposed clinical study, and a 3.2-fold safety margin for the proposed maximum dose of 20 mg/kg (740 mg/m^2). Therefore, the chronic toxicity study in monkeys provides a reasonable assurance of safety for the proposed clinical study.

NeoGAA is produced by conjugating a synthetic glycan (Genz-669342) to oxidized sialic acid residues on rhGAA through a synthetic linker with an aminoxy moiety. The synthetic linker portion of Genz-669342 is structurally similar to hydroxylamine, which has the potential to be genotoxic. However, Genz-669342 was negative in the Ames test and chromosomal aberration assay.

The Sponsor measured levels of unconjugated Genz-669342 in two clinical batches, and in four nonclinical batches that were used in the 26-week toxicity study in monkeys. The levels of unconjugated Genz-669342 in the current two clinical batches are lower or slightly higher than the qualification limit stated in ICH Q3B(R2) (0.2%, equivalent to 2.4 mg unconjugated Genz-669342 at the maximum neoGAA dose of 20 mg/kg, assuming a 60-kg bodyweight). In addition, the 26-week IV toxicity study in monkeys provided a 5.2-fold safety margin, based on body surface area, for the current levels of unconjugated Genz-669342 in clinical batches (up to (b) (4) µg/ml; see table below). This safety margin provides a reasonable assurance of safety for unconjugated Genz-669342 in the current clinical batches.

However, the Sponsor proposed a specification limit of (b) (4) µg/ml for unconjugated Genz-669342 in the drug product. Based on this limit, the maximum potential daily dose of unconjugated Genz-669342 from neoGAA will be (b) (4) mg (assuming a 60-kg body weight, and a dose of 20 mg/kg neoGAA), which will greatly exceed the recommended ICH limit (2.4 mg/day). Furthermore, the maximum potential daily exposure to unconjugated Genz-669342 in patients will be (b) (4)-fold higher, based on body surface area comparison, than the tolerated dose in the 26-week IV toxicity study in monkeys (see table below). Therefore, the 26-week monkey study cannot provide an assurance of safety for the proposed specification limit of (b) (4) µg/ml for unconjugated Genz-669342. Thus, the proposed limit is unacceptable without additional toxicity studies to allow for safety assessment.

Table 13: Comparison of maximum daily exposure to free glycan in monkeys at 200 mg/kg neoGAA (tolerated dose) to the potential free glycan exposure in humans at 20 mg/kg neoGAA

	Nonclinical batches	Current clinical batches		Future clinical batches
	NE006 NE007 NE008 NE009	12CT010	12CT011	
Concentrations of residual free glycan (Genz-669342)	(b) (4) µg/ml *	(b) (4) µg/ml	(b) (4) µg/ml	(b) (4) µg/ml (proposed limit)
Maximum daily exposure to Genz-669342 in monkeys based on body weight	20 ml/kg x (b) (4) µg/ml = µg/kg	N/A	N/A	N/A
Maximum daily exposure to Genz-669342 in humans based on body weight	N/A	2 ml/kg x (b) (4) µg/ml = µg/kg	2 ml/kg x (b) (4) µg/ml = (b) (4) µg/kg	2 ml/kg x (b) (4) µg/ml = (b) (4) µg/kg
Maximum daily exposure to Genz-669342 in monkeys and humans based on body surface area	(b) (4) µg/m^2 (monkeys)	(b) (4) µg/m^2 (humans)	(b) (4) µg/m^2 (humans)	(b) (4) µg/m^2 (humans)
Safety margins based on body surface area (µg/m^2)	N/A	(b) (4)		
Human total daily intake (assumed body weight of 60 kg)	N/A	(b) (4) µg/kg x 60 kg = (b) (4) µg/day mg/day	(b) (4) µg/ml x 60 kg = (b) (4) µg/day = (b) (4) mg/day	(b) (4) µg/kg x 60 kg = (b) (4) µg/day mg/day

***: The level of residual glycan was an average of the three batches.**

A teleconference was held with the Sponsor on April 25, 2013 to discuss the safety concern related to the proposed limit for unconjugated Genz-669342 (free glycan). The Sponsor clarified that all batches (nonclinical and clinical) were manufactured using the same process. The concentration of free glycan in each batch is shown in the table below.

Table 2: Residual Glycan Levels in Nonclinical and Current Clinical Trial Batches

	Lot numbers of Nonclinical batches				Lot numbers of Current clinical trial batches	
	NE006	NE007	NE008	NE009	12CT010	12CT011
Residual glycan level (µg/ml)	(b) (4)					

In light of the observed levels of free glycan in the neoGAA batches, the Agency recommended a limit of (b) (4) µg/ml for this impurity. This limit was selected to provide assurance that free glycan levels in future clinical batches are likely to be compliant with the specification, while still providing a reasonable assurance of safety for patients. The maximum potential dose of free glycan will be (b) (4) µg/m^2 in patients, at the limit of (b) (4) µg/ml. The 26-week IV toxicity study in monkeys provides a (b) (4)-fold safety margin based on a µg/m^2 comparison. This small margin is considered to be acceptable for assurance of safety, given that the tolerated dose was the highest dose tested (i.e. no major signs of toxicity were observed at any dose level). The Sponsor agreed to the Agency's recommended limit, and submitted a written response on April 26, 2013 (SD # 5) that reflects this agreement.

During the teleconference, the Agency also informed the Sponsor that an additional chronic toxicity study would be needed to support an increase in the limit for free glycan. In the amendment submitted on April 26, 2013, the Sponsor stated that they will likely contact the Agency to discuss the requirements and design for a chronic toxicity study to support qualification of free glycan above (b) (4) µg/ml.

RECOMMENDATIONS:

1. From a nonclinical viewpoint, the proposed clinical study is safe to proceed.

2. In the absence of additional nonclinical data, the limit for free glycan (unconjugated Genz-669342) in the drug product should not be increased above the current limit o (b) (4) µg/ml. If the Sponsor prefers to increase the limit for free glycan, the Agency recommends that the Sponsor submit a proposal for a chronic toxicity study, in addition to the proposed new limit for free glycan. .

REVIEWER SIGNATURE _____

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cc:
IND
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R/D INIT.: D. JOSEPH 5/31/13

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

/s/

FANG CAI
07/03/2013

DAVID B JOSEPH
07/03/2013
I concur.