

Appendix A. Electronic database search strategies

Search 1 -

"Mucopolysaccharidosis I"[Mesh] OR ("mucopolysaccharidosis" AND "type 1") OR "mucopolysaccharidosis I" OR "mucopolysaccharidosis-I" OR "MPS I" OR "Hurler disease" OR "hurler syndrome"

AND

laronidase OR aldurazyme

AND

English language, humans

Results in PubMed = 36

29 additional studies identified using the search in EMBASE = 15 appeared to be unique and possibly relevant

Cochrane search found 4 trials – all are in the database.

Search 2 –

"Mucopolysaccharidosis II"[Mesh] OR (mucopolysaccharidosis AND "type II") OR "mucopolysaccharidosis II" OR "mucopolysaccharidosis-II" OR "MPS II" OR "Hunter disease" OR "hunter syndrome"

AND

"idursulfase" [Supplementary Concept] OR idursulfase OR elaprased

AND

English language, humans

Results in PubMed = 34

67 additional studies identified using the search in EMBASE = 3 appeared to be unique and possibly relevant

Cochrane search found 1 protocol and 2 trials that were unique and added to the database.

Search 3 –

"Mucopolysaccharidosis VI"[Mesh] OR (mucopolysaccharidosis AND "type VI") OR "mucopolysaccharidosis VI" OR "mucopolysaccharidosis-VI" OR "MPS VI" OR "maroteaux-lamy syndrome"

AND

"galsulfase" [Supplementary Concept] OR galsulfase OR naglazyme

AND

English language, humans

Results in PubMed =21

24 additional studies identified using the search in EMBASE = 6 appeared to be unique and possibly relevant

Cochrane search found 1 new technology assessment which was added. Everything else was already there.

Search 4 –

"Fabry Disease"[Mesh] OR "fabry disease" OR "alpha-Galactosidase A Deficiency"

AND

"agalsidase beta" [Supplementary Concept] OR "agalsidase beta" OR fabrazyme

AND

English language, humans

Results in PubMed =132

130 studies identified using the search in EMBASE = 13 appeared to be unique and possibly relevant

Cochrane search found 2 additional trials which were added.

Search 5 -

"Gaucher Disease"[Mesh] OR "gaucher disease" OR "gaucher's disease"

AND

(("alglucerase" [Supplementary Concept]) OR "imiglucerase" [Supplementary Concept]) OR "Velaglucerase alfa, human" [Supplementary Concept] OR alglucerase OR ceredase OR imiglucerase OR cerezyme OR velaglucerase OR "miglustat" [Supplementary Concept] OR miglustat OR zavesca

AND

("type 1" OR "type I") OR various study types (RCT, meta-analysis, comparative study)

AND

English language, humans

Results in PubMed =222

65 clinical studies identified in EMBASE = 4 appeared to be unique and possibly relevant

Cochrane search found 4 additional articles which were added.

Search 6 –

"Glycogen Storage Disease Type II"[Mesh] OR ("glycogen storage disease" AND ("type II" OR "type 2")) OR "pompe disease" OR "pompe's disease"

AND

"GAA protein, human" [Supplementary Concept] OR "alglucosidase alfa" OR myozyme

AND

English language, humans

Results in PubMed =99

41 clinical studies identified in EMBASE = 8 appeared to be unique and possibly relevant

Cochrane search found 2 trials – only 1 unique one – a meeting abstract – was added.

Appendix B. Appendix data abstraction tables

Clinical Trials of Enzyme Replacement Therapy for Lysosomal Storage Diseases

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 st Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
MPS I/ Aldurazyme® (α-L-ironidase) (laronidase)	Clarke, ¹ 2009, international	open label extension to Wraith et al, 2004 ²	none	40	attenuated	16 (6-43)	182	- urinary substrate levels - liver volume - 6-min walk test - pulmonary function - range of motion - mental development - visual acuity - sleep apnea - IgG	- infusion-associated reactions - IgG antibody development
	Giugliani, ³ 2009, international	dose optimization trial	0.58 mg/kg wkly vs 1.2 mg/kg EOW, 1.2 mg/kg wkly, and 1.8 mg/kg EOW	33	severe (n=10) and attenuated (n=23)	8.9 (1.4-20.7)	26	- urinary substrate levels - liver volume - 6-min walk test	- infusion-associated reactions - IgG antibody development - 1 death in pt w/ severe form, considered unlikely related to treatment
	Wraith, ⁴ 2007, international	open label trial for children <5 yrs of age	none	20	severe (n=16) and attenuated (n=4)	2.9 (0.5-5.1)	52	- urinary substrate levels - liver size - cardiac involvement - sleep apnea - growth - mental development	- infusion-associated reactions - IgG antibody development

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 st Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Wraith, ² 2004, international	randomized, double-blind, placebo-controlled trial	placebo	laronidase: 22 placebo: 23	severe (n=1) and attenuated (n=44)	laronidase: 15.6 (7-43) placebo: 15.4 (6-39)	26	- pulmonary function - 6-min walk test - urinary substrate levels - liver size - sleep apnea - range of motion	- infusion-associated reactions - IgG antibody development
MPS II/ Elaprase® (idursulfase)	Okuyama, ⁵ 2010, Japan	open label trial for adults	none	10	attenuated	30.1 (21.1-53.9)	52	- urinary substrate levels - liver size - 6-min walk test - pulmonary function - range of motion - cardiac involvement - sleep apnea	- infusion-associated reactions - IgG antibody development
	Muenzer, ⁶ 2007, US	phase I/II, randomized, double-blind, placebo-controlled trial	3 treatment groups: 0.15, 0.5, and 1.5mg/kg EOW, and placebo	idursulfase : 9 placebo: 3	attenuated	overall: 14 (6-20) 0.15 mg/kg: 11 (9-14) 0.5 mg/kg: 20 (20) 1.5 mg/kg: 8 (6-10) placebo: 17 (13-20)	double-blind trial: 24 open label extension : 26	- urinary substrate levels - liver and spleen volume - 6-min walk test - range of motion - pulmonary function - cardiac involvement - sleep apnea	- infusion-associated reactions - IgG antibody development

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 st Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Muenzer, ⁷ 2006, international	phase II/III, randomized double-blind, placebo-controlled trial	3 treatment groups: 1) 0.5 mg/kg wkly, 2) 0.5 mg/kg EOW, and 3) placebo	1) 32 2) 32 3) 32	each treatment grp had the same distribution of baseline disease scores ranging from 2-6	1) 15.1 (6.3-26.0) 2) 14.4 (5.4-30.9) 3) 13.1 (5.0-29.0)	53	- 6-min walk test - pulmonary function	- infusion-associated reactions - IgG antibody development
MPS VI/ Naglazyme® (galsulfase)	Harmatz, ⁸ 2010, international	extension to phase I/II, II, III trials reporting results up to 48 wks, Harmatz 2004 ⁹	1) 0.2 mg/kg or 1.0 mg/kg 2) 0.2 mg/kg 3) 0.2 mg/kg	1) 7 2) 123 3) 39	symptomatic	phase I/II: 12 (7-16) phase II: 12.1 (6-21) phase III: 13.7 (5-29)	up to 240 weeks	-pulmonary function -height	not reported
	Harmatz, ¹⁰ 2005, international	open label	none	10	rapidly advancing disease	12.7 (6-22)	48	-mobility and physical function -6 and 12 minute walks -3 minute stair climb -oxygenation during sleep -ophthalmology evaluation -liver volume -spleen volume -height	-asthma attack - infusion-associated reactions - IgG antibody development

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 st Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
Fabry/ Replagal® (agalsidase alpha)	Clarke, ¹¹ 2007, international	open label, randomized, dose optimization trial	5 treatment groups: 1) 0.1 mg/kg wkly, 2) 0.2 mg/kg EOW, 3) 0.2 mg/kg wkly, 4) 0.4 mg/kg EOW, 5) 0.4 mg/kg wkly	18	baseline substrate levels were comparable between treatment groups	1) 27.5 (16-36) 2) 37.5 (33-41) 3) 25.0 (20-32) 4) 23.0 (21-25) 5) 28.3 (26-30)	10	- plasma substrate level	- infusion-associated reactions - IgG antibody development
Fabry/ Fabrazyme® (agalsidase beta)	Wraith, ¹² 2008, international	open label trial for children	none	16	no information provided	12.1 (8.5-11.7)	48	- skin and plasma substrate levels - renal function - cardiac function - growth - quality of life - school attendance - low, moderate, high energy level - general health	- infusion-associated reactions - IgG antibody development
	Banikazemi, ¹³ 2007, international	randomized double blind, placebo controlled trial	placebo	agalsidase β: 51 placebo: 31	no information provided	agalsidase β: 46.9 (SD: 9.8) placebo: 44.3 (SD: 9.2)	mean: 74 up to 152	- renal function - cardiac function - cerebrovascular events	- infusion-associated reactions

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 st Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Germain, ¹⁴ 2007, international	open label extension trial	none	58	no information provided	31.1 (17-62)	up to 234	- plasma substrate level - renal function - cardiac function - pain scores	- infusion-associated reactions - IgG antibody development - 5 patients experienced stroke or TIA
	Eto, 2005, ¹⁵ Japan	open label phase 2 bridging study	none	13	no information provided	26.6 (16-34)	20	- renal function - kidney, urine, and plasma substrate levels	- infusion-associated reactions - 1 pt hospitalized with malaise and limb pain
Fabry/ Replagal® (agalsidase alpha) and Fabrazyme® (agalsidase beta)	Vedder, ¹⁶ 2008, Netherlands	dose optimization trial	3 treatment groups: 1) 0.2 mg/kg alpha 2) 0.2 mg/kg beta 3) 1.0 mg/kg beta	1) 18 2) 13 3) 2 1	no information provided	1) 47 (19-62) 2) 49 (25-73) 3) 48 (27-70)	52	- urinary substrate levels - renal function - cardiac function	- IgG antibody development
	Vedder, ¹⁷ 2007, Netherlands	open label randomized, controlled trial	2 treatment groups: 1) 0.2 mg/kg EOW alpha 2) 0.2 mg/kg EOW beta	1) 18 2) 16	stratified within each grp by disease severity	1) 42 (19-60) 2) 48 (24-76)	52-104	- cardiac function - renal function - pain scores - urine and plasma substrate levels	in 1 beta pt: - sensomotor polyneuropathy - oesophagitis

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 st Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
Gaucher/ Ceredase® (alglucerase)	Pastores, 1993, ¹⁸ United States	open label, dose optimization study	30 IU/kg vs 40 IU/kg, vs 50 IU/kg, vs 60 IU/kg EOW	33	symptomatic	32 (2-63)	26-104	-liver volume -spleen volume -anemia -thrombocytopenia -serum acid phosphatase -angiotensin-converting enzyme -skeletal involvement -pulmonary involvement -liver disease -renal disease	- infusion-associated reactions - IgG antibody development
	Altarescu, ¹⁹ 2000, United States	dose optimization trial	1) 60 IU/kg EOW, reduced to 30 IU/kg, then reduced to 15 IU/kg 2) 10 IU/kg EOW	1) 12 2) 32	symptomatic	1) range only (7-58) 2) range only (9-69)	1) 104 2) 52	-splenomegaly -hepatomegaly -thrombocytopenia -anemia -acid phosphatase	not reported
Gaucher/ Cerezyme® (imiglucerase)	Kishnani, ²⁰ 2009, international	open label, randomized, phase IV, dose frequency trial	2 treatment groups: 1) monthly dose biwkly, 2) monthly dose every 4 wks	1) 33 2) 62	at least 2 yrs on imiglucerase	Age at 1 st imiglucerase infusion: 1) 35.9 (10-74) 2) 41.9 (11-75)	104	- anemia - hepato-megaly - spleno-megaly - skeletal pathology - physical score - mental score	- infusion-associated reactions

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 st Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Sims, ²¹ 2008, United States	open label, single cohort prospective	none	33	symptomatic	median 43.0 (12.0-70.0)	208	-splenomegaly -hepatomegaly -thrombocytopenia -anemia -bone pain -bone crisis -bone mineral density -medullary infarction -osteoarticular Infarction -lytic lesions -fractures	-infusion-associated reactions
	de Fost, ²² 2007, Netherlands	randomized, controlled trial	2 treatment groups: 1) original dose (weekly or EOW) 2) dose every 4 weeks	1) 5 2) 6	symptomatic	overall 51 (34-75)	52	-splenomegaly -hepatomegaly -thrombocytopenia -anemia -Chitotriosidase -Hexosaminidase	not reported
Gaucher/ Ceredase® (alglucerase) and Cerezyme® (imiglucerase)	Grabowski, ²³ 1995, United States	randomized, double-blind, parallel trial	2 treatment groups: 1) 60 U/kg EOW Ceredase 2) 60 U/kg EOW Cerezyme	1) 15 2) 15	symptomatic	1)28 (12-52) 2)39 (13-69)	39	-hepatic volume -splenic volume -thrombocytopenia -anemia	- infusion-associated reactions - IgG antibody development
Gaucher/ Velaglucerase ® (velagluceras e alfa)	Elstein, ²⁴ 2011, Israel (same study population as Zimran 2010)	open label, phase I/II study with extension	none	phase I/II: 11 extension (those who have data up to 208 wks): 8	symptomatic	extension: 39 (18-62)	phase I/II: 39 extension : up to 208	- anemia - thrombocytopenia - hepato-megaly - spleno-megaly - skeletal pathology	not reported

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 st Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Zimran, ²⁵ 2010, Israel (same study population as Elstein 2010)	open label, phase I/II study with extension	none	phase I/II: 11 extension: 8	symptomatic	phase I/II: 41 (18-69)	phase I/II: 39 extension : up to 208	- anemia - hepato-megaly - spleno-megaly	- infusion-associated reactions - IgG antibody development - gastro-intestinal disorders - musculo-skeletal/connective tissue disorders
Pompe/ Myozyme [®] (alglucosidase alfa)	van der Ploeg, ²⁶ 2010, international	randomized, double-blind, placebo controlled trial	placebo	Treatment: 60 Placebo: 30	juvenile/adult form	treatment: 45.3 (15.9-70) placebo: 42.6 (11.6)	78	-6-minute walk test -predicted FVC -quantitative muscle testing, leg and arm -maximum inspiratory and expiratory pressure -SF-36 score	- infusion-associated reactions - IgG antibody development - nervous system disorders - skin and subcutaneous tissue disorders - gastro-intestinal disorders - musculoskeletal and connective tissue disorders - eye disorders - ear and labyrinth disorders - vascular disorders

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 st Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Strothotte, ²⁷ 2010, Germany	open label	none	44	juvenile/adult form	48.9 (21-69)	52	-arm function test -Walton Gardner Medwin Scale -timed function tests -6 minute walk test -MRC sum score -PFT measured by FVC -SF-36 -liver enzyme and CK	-moderate allergic reactions -hand edema -acute hearing loss -herpes simplex infection -pollakisuria -prickling in the muscles
	Kishnani, ²⁸ 2009, United States	open label randomized extension to Kishnani, 2006 ²⁹	1) 20 mg/kg EOW 2) 40 mg/kg EOW	16	infantile form	mean age at end of study: 2.8 (1.7-3.5)	60-150	-survival -ventilator use -cardiac parameters -motor development	- infusion-associated reactions - IgG antibody development
	Nicolino, ³⁰ 2009, United States	open label	historical control group	21	infantile and juvenile form	mean age (in months): 15.7 (3.7-43.1)	up to 168	-survival -ventilator use -cardiac function -muscle GAA activity -motor development -functional independence -physical growth -cognitive function	- infusion-associated reactions -6 patients died, none attributed to treatment

Disease/ERT	Author, Year, Country	Study Design	Comparator	No. of Patients	Disease Stage/Type	Mean Age at 1 st Infusion (range) yrs	Length of Follow-up (wks)	Outcomes Measured	Adverse Events
	Levine, ³¹ 2008, international	open label, phase II trial for children, extension study to Kishnani 2006 ²⁹	none	8	infantile form	mean age (in months): 6.1 (2.7-14.6)	52	- cardiac function - pulmonary function	not reported
	McDowell, ³² 2008, international	retrospective study on patients who were in open label trial for children	1) patients with arrhythmias 2) patients without arrhythmias	1) 7 2) 31	infantile form	1) median (in months): 7 (6-13) 2) median (in months): 8 (1-43)	78	-cardiac function (QTc, LVMi, EF)	-arrhythmias
	Kishnani, ²⁹ 2006, international	phase II, open label trial for children, same population as Kishnani 2009 ²⁸	none	8	infantile form	median age (in months) at first treatment: 4.7 (2.7-14.6)	up to 153	-survival -ventilator-free survival -cardiac response -motor response -mental and behavioral development -growth -hearing results -analysis of skeletal muscle	- infusion-associated reactions - IgG antibody development
	Orlikowski, ³³ 2011, France	open label trial in adults	none	5	juvenile/adult form	48 (28-62)	52	-respiratory function -muscle strength -SF-36 -glucose tetrasaccharides	- infusion-associated reactions - IgG antibody development -1 patient died, not attributed to treatment

Appendix C. Summaries of published registry studies

Appendix Table C1. Published Registry Study of ERT for Fabry Disease

Author, Year, Country, Sample Size	ERT	Study Design	Inclusion Criteria	Treatment Groups	Mean Age at 1 st Infusion (range) yrs	Renal function
Warnock, ³⁴ 2011, international N=213 Q1: 53 Q2: 54 Q3: 54 Q4: 52	agalsidase beta	Observational, Fabry Registry	Patients in registry on ERT with baseline measure within 3 months before or after first infusion	Quartiles based on slope of estimated glomerular filtration rates (higher slope = more rapid renal disease progression)	Males: Q1: 35.3 (SD: 11.04) Q2: 40.7 (SD: 11.12) Q3: 37.0 (SD:10.91) Q4: 42.0 (SD: 9.22) Females: Q1: 43.2 (SD: 11.30) Q2: 41.0 (SD: 11.83) Q3: 40.5 (SD:15.12) Q4: 47.4 (SD: 13.09)	•

Appendix Table C2. Published Registry Studies of ERT for Gaucher Disease

Author, Year, Country, Sample Size	ERT	Study Design	Inclusion Criteria	Treatment Groups	Mean Age at 1 st Infusion (range) yrs	Anemia, %	Liver size	Spleen size	Skeletal
Weinreb, ³⁵ 2008, international N=195	imiglucerase	Observational, International Collaborative Gaucher Group (ICGG)	pts in ICGG with 4 yrs followup and data on therapeutic goals	all who met inclusion criteria	27.7 (SD: 21.9)	•	•	•	•
Mistry, ³⁶ 2011, international N=889 1) 156 2) 125 3) 185 4) 423	alglucerase or imiglucerase	Observational, International Collaborative Gaucher Group (ICGG)	pts 5-50 yrs of age in ICGG with bone mineral density data	4 grps by age of ERT initiation: 1) 5-11 yrs 2) 12-19 yrs 3) 20-29 yrs 4) 30-50 yrs	not reported	•	•	•	•
Grabowski, ³⁷ 2009, international N=366 1) 122 2) 122 3) 122		Observational, International Collaborative Gaucher Group (ICGG)	pts in ICGG with intact spleens	3 grps by every other wk dosage: 1) 5-28 U/kg 2) 29-47 U/kg 3) 48-74 U/kg	1) 22.1 (19.9) 2) 22.6 (SD: 19.9) 3) 23.1 (SD: 19.8)	•	•	•	
Weinreb, ³⁸ 2002, international N=1028		Observational, International Collaborative Gaucher Group (ICGG)	pts in ICGG on ERT at least 6 mos and with at least one baseline outcome measure	all who met inclusion criteria	30 (SD: 19)	•	•	•	•

Appendix Table C3. Published Registry Studies of ERT for Hunter's Disease

Author, Year, Country, Sample Size	ERT	Study Design	Inclusion Criteria	Treatment Groups	Mean Age at 1 st Infusion (range) yrs	Substrate level	Liver volume	Spleen size	Mental function	Growth	Range of motion	Pulmonary function	Cardiac symptoms	Discontinuation of home tx
Muenzer, ³⁹ 2011, international, N=124	idursulfase	observational, Hunter Outcome Survey (HOS)	pts in HOS who started ERT prior to 6 yrs of age	all who met inclusion criteria	3.6 (SD: 1.6)	•	•							
Alcalde-Martin, ⁴⁰ 2010, international, N=6		observational, Hunter Outcome Survey	Spanish pts in HOS who started ERT prior to 5 yrs of age	all who met inclusion criteria	3.7 (2.8-4.7)	•	•	•	•	•	•	•	•	
Burton, ⁴¹ 2010, international, N=92		observational, Hunter Outcome Survey	pts in HOS who had received infusions at home or in nonhospital environment	all who met inclusion criteria	at 1 st infusion: median: 8.5 (3.4-17.9) at time of transfer to home tx: median: 9.4 (3.9-21.3)									•

Appendix D. Summaries of unpublished studies

Appendix Table D1. Unpublished Studies From Manufacturer's Scientific Information Packet and Current Registered Clinical Trials

Disease	Product	Manufacturer	Posters	Abstracts	Data on file with Manufacturer	Ongoing studies
Fabry's Disease	Fabrazyme® (agalsidase beta)	Genzyme Corporation	Not reported	Not reported	Not reported	<p>2010: NCT01196871: Drug-Drug Interaction Study Between AT1001 and Agalsidase in Subjects With Fabry Disease</p> <p>NCT01218659: Study to Compare the Efficacy and Safety of Oral AT1001 and Enzyme Replacement Therapy in Patients With Fabry Disease</p> <p>NCT01268241 : The Efficacy and Safety of Switch Between Agalsidase Beta to Agalsidase Alfa for Enzyme Replacement in Patients With Anderson-Fabry Disease (SWITCH)</p> <p>2007: NCT00455104: Canadian Fabry Disease Initiative (CFDI) Enzyme Replacement Therapy (ERT) Study</p> <p><i>(Status has not been verified in more than two years)</i> NCT00487630: Evaluation of Efficacy and Safety of Agalsidase Beta in Heterozygous Females for Fabry Disease (HEART)</p> <p>2005:</p>

						<p>NCT00196742: Fabry Disease Registry</p> <p>NCT00230607: A Study of the Effects of Fabrazyme (Aqalsidase Beta) on Mother's Lactation and on the Growth, Development and Immunologic Response of Their Infants</p>
Gaucher Disease Type I	Ceredase® (alglucerase)	Genzyme Corporation	Not reported	Not reported	Not reported	<p>2006: NCT00302146: Positron Emission Tomography (PET) Imaging in People With Gaucher Mutations</p>
	Cerezyme® (imiglucerase)	Genzyme Corporation	Not reported	Not reported	Not reported	<p>2011: NCT01344096: Thrombocytopenia in Gaucher Disease Patients</p>
	Velaglucerase® (velaglucerase alfa)	Shire Human Genetic Therapies Inc	<p>2008: Zimram A, Altarescu G, Phillips M, Bhirang K, Mensah R, Elstein D. Velaglucerase alfa: a Phase I/II long-term study of enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease [poster]. Presented at: Annual Meeting of the American Society of Human Genetics; November 11-15, 2008: Philadelphia, PA.</p>	<p>2010: Zimran A, Gonzalez D, Crombez E, et al. Enzyme replacement therapy with velaglucerase alfa improves key clinical parameters in a pediatric subgroup with type 1 Gaucher disease [abstract]. Presented at: World Symposium 2010; the Annual Meeting the Lysosomal Disease Network; February 10-12, 2010c; Miami, FL.</p> <p>Zimram A, Gonzalez D, Lukina EA, et al. Enzyme replacement therapy with velaglucerase alfa significantly improves clinical parameters in type 1 Gaucher disease:</p>	<p>2009: A multicenter, randomized, double-blind, parallel-group, two-dose study of gene-activated human glucocerebrosidase (GA-GCB) enzyme replacement therapy in patients with type 1 Gaucher disease. Clinical Study Report: TKT032, Cambridge, MA; Shire Human Genetic Therapies; Jul 2009</p> <p>A multicenter, randomized, double-blind, parallel-group study of gene-activated human</p>	<p>2011: NCT01356537: Home Therapy With VPRIV in Gaucher's Disease</p>

				<p>positive results from a randomized, double-blind, global, phase III study [abstract]. Presented at: World Symposium 2010, the Annual Meeting of the Lysosomal Disease Network; February 10-12, 2010b; Miami, FL.</p>	<p>glucocerebrosidase (GA-GCB) enzyme replacement therapy compared with imiglucerase in patients with type 1 Gaucher disease. Clinical Study Report: HGT-GCB-039, Cambridge, MA; Shire Human Genetic Therapies; Aug 2009.</p> <p>A multicenter open-label study of gene-activated human glucocerebrosidase (GA-GCB) enzyme replacement therapy in patients with type 1 Gaucher disease previously treated with imiglucerase. Clinical Study Report: TKT034, Cambridge, MA; Shire Human Genetic Therapies; Aug 2009.</p> <p>2006:</p> <p>A phase I/II safety study of velaglucerase alfa, a glucocerebrosidase replacement therapy in patients with type 1 Gaucher Disease. Clinical Study Report: TKT025, Final Version 1.0 Cambridge, MA; Shire Human Genetic Therapies; Jun 2006.</p>	
Zavesca®	Actelion	Not reported	Not reported	Not reported	(Status has not been verified)	

	(miglustat)	Pharmaceuticals				<i>in more than two years)</i> 2007: NCT00418847: Pharmacokinetics and Tolerability of Zavesca® (Miglustat) In Patients With Juvenile GM2 Gangliosidosis
Glycogen Storage Disease Type II (Pompe disease)	Myozyme® (alglucosidase alfa)	Genzyme Corporation	Not reported	Not reported	Not reported	2011: NCT01288027: Exploratory Muscle Biopsy Assessment Study in Patients With Late-Onset Pompe Disease Treated With Alglucosidase Alfa NCT01410890 : Pharmacokinetics of Alglucosidase Alfa in Patients Aged 8-18 Years of Age (PAPAYA) 2008: NCT00701701: Immune Tolerance Induction Study 2007: NCT00486889: Growth and Development Study of Myozyme (Alglucosidase Alfa). NCT00566878: Pompe Lactation Sub-Registry NCT00567073: Pompe Pregnancy Sub-Registry
MPS I (Hurler disease)	Aldurazyme® (aronidase)	Genzyme Corporation	Not reported	Not reported	Not reported	2009: NCT00852358: A Study of Intrathecal Enzyme Therapy for Cognitive Decline in MPS I 2008: NCT00638547: Intrathecal

						<p>Enzyme Replacement for Hurler Syndrome</p> <p>NCT00741338: Immune Tolerance Study With Aldurazyme®</p> <p>2007: NCT00418821: A Study of the Effect of Aldurazyme® (Laronidase) Treatment on Lactation in Female Patients With Mucopolysaccharidosis I (MPS I) and Their Breastfed Infants</p> <p>2005: NCT00144768: A Study Investigating the Relationship Between the Development of Laronidase Antibody and Urinary GAG (Glycosaminoglycan) Levels in Aldurazyme® Treated Patients</p> <p>NCT00144794: Mucopolysaccharidosis I (MPS I) Registry</p>
MPS II (Hunter disease)	Elaprase® (idursulfase)	Shire Human Genetic Therapies Inc	Not reported	Not reported	Not reported	<p>2011: NCT01330277: Biomarker for Hunter Disease (BioHunt)</p> <p>NCT01506141: An Extension Study of HGT-HIT-045 Evaluating Long-Term Safety and Clinical Outcomes of Idursulfase (Intrathecal) in Conjunction With Elaprase® in Pediatric Patients With Hunter Syndrome and Cognitive Impairment</p>

						<p>2009: NCT00920647: A Safety and Dose Ranging Study of Idursulfase (Intrathecal) Administration Via an Intrathecal Drug Delivery Device in Pediatric Patients With Hunter Syndrome Who Have Central Nervous System Involvement and Are Receiving Treatment With Elaprase®</p> <p>NCT00937794: A Screening Study to Identify Pediatric Patients With Hunter Syndrome Who Demonstrate Evidence of Central Nervous System (CNS) Involvement and Who Are Currently Receiving Treatment With Elaprase®</p> <p>NCT01449240: Collection and Study of Cerebrospinal Fluid in Patients With Hunter Syndrome</p>
MPS VI (Maroteaux-Lamy syndrome)	Naglazyme® (galsulfase)	BioMarin Pharmaceutical Inc	<p>2011: Kim KH, Burton BK. Treatment with galsulfase results in improved endurance in a MPS VI patient with history of bone marrow transplantation in early childhood. 61st Annual Meeting of the American Society of Human Genetics (ASHG). Montreal, Canada. 11-15 October 2011. Poster.</p> <p>M. L. Raff. Galsulfase enzyme replacement</p>	<p>2010: Braunlin E, Howard R, Christoph K, et al. Long term cardiac effects of Naglazyme(galsulfase) therapy (NRx). 11th International Symposium on Mucopolysaccharide and Related Diseases. Adelaide, Australia: 23-27 June 2010. Abstract.</p> <p>Decker C, Devereaux D, Kim S, et al. Analysis of the clinical impact of immune response to enzyme replacement</p>	<p>2005: NCT00214773: Mucopolysaccharidosis (MPS) VI Clinical Surveillance Program (CSP)</p>	

		<p>therapy improves urine GAG excretion and clinical course in Maroteaux-Lamy syndrome (MPS type VI) after donor-engrafted bone marrow transplant. Genomics Institute, MultiCare Health System, Tacoma, WA. 14 October 2011. Poster.</p> <p>2010: *Acosta A, Giuliani L, Horovitz D, et. al. Experience with enzyme replacement therapy on very young mucopolysaccharide and Related Diseases. Adelaide, Australia: 23-27 June 2010. Poster.</p> <p>Ribeiro EM, Bezerra KRF, Giovannetti D, et al. Enzyme replacement therapy in mucopolysaccharidosis VI: early treatment with galsulfase in three siblings. 11th International Symposium on Mucopolysaccharide and Related Diseases. Adelaide, Australia: 23-27 June 2010. Poster.</p> <p>2008: Lampe C, Miebach E, Arash L, et al. Therapeutic response after two years of Galsulfase enzyme replacement therapy (ERT) in five adult patients with Maroteaux-</p>	<p>therapy with naglazyme. 11th International Symposium on Mucopolysaccharide and Related Diseases. Adelaide, Australia: 23-27 June 2010. Abstract.</p> <p>*Harmatz P, Guffon N, Garcia P, Cheng S, Lagan K, Decker C. A Phase 4 two dose level study of galsulfase in Mucopolysaccharidoses IV infants. J Inherit Metab Dis (2010) 33 (Suppl 1):S1–S197. Abstract.</p> <p>Horovitz DDG, Magalhaes T, Acosta A, et. al. Enzyme replacement therapy in 25 mucopolysaccharidosis type VI Brazilian children under age five. 11th International Symposium on Mucopolysaccharide and Related Diseases. Adelaide, Australia: 23-27 June 2010. Abstract 103.</p> <p>2009: Horovitz DDG, Ribeiro EM, Acosta A, et al. Enzyme replacement therapy in eight mucopolysaccharidosis type VI Brazilian children under age three: preliminary data. 11th International Congress on Inborn Errors of metabolism. San Diego, CA: 29 August - 02</p>		
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