Enzyme Replacement Therapy for the Treatment of Gaucher Disease Type 1: Clinical Effectiveness
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**Cite As:** Enzyme Replacement Therapy for the Treatment of Gaucher Disease Type 1: Clinical Effectiveness. Ottawa: CADTH; 2017 Aug. (CADTH rapid response report: summary of abstracts).

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**Funding:** CADTH receives funding from Canada’s federal, provincial, and territorial governments, with the exception of Quebec.
Research Question
What is the clinical effectiveness of imiglucerase, velaglucerase, and taliglucerase for the treatment of Gaucher disease type 1?

Key Findings
A total of 27 publications were identified regarding the clinical effectiveness of imiglucerase, velaglucerase, and taliglucerase in adults and children with symptomatic Gaucher disease type 1. These publications reported results from systematic reviews, randomized controlled trials and their extension studies or subanalyses, and other non-randomized studies.

Methods
A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to randomized controlled trials, non-randomized studies, health technology assessments, systematic reviews, and meta-analyses. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 2012 and August 2017. Internet links were provided, where available.

Selection Criteria
One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tr>
<td>Population</td>
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<tr>
<td>Interventions</td>
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<tr>
<td>Comparators</td>
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<tr>
<td>Outcomes</td>
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<td>Study Designs</td>
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Results

Rapid Response reports are organized so that health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies. The individual study findings and overall summary are based on a review of abstracts only; the full studies have not been reviewed or appraised for quality.

Two systematic reviews and 25 publications of primary studies (including randomized controlled trials, their extensions or subanalyses, and other non-randomized studies) were identified regarding the clinical effectiveness of imiglucerase, velaglucerase, and taliglucerase in adults and children with symptomatic Gaucher disease type 1. No relevant health technology assessments or meta-analyses were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

A total of 27 publications were identified regarding the clinical effectiveness of imiglucerase, velaglucerase, and taliglucerase in adults and children with symptomatic Gaucher disease type 1. These publications reported results from systematic reviews, \(^1\) randomized controlled trials (RCTs), \(^3\) \(^5\) \(^7\) \(^9\) \(^10\) \(^12\) \(^16\) \(^21\) \(^22\) \(^25\) \(^27\) and non-randomized studies (including extensions or post-hoc analyses of RCTs). \(^6\) \(^7\) \(^9\) \(^10\) \(^12\) \(^16\) \(^21\) \(^22\) \(^25\) \(^27\) Details of the included studies are provided in Table 2.

The literature identified regarding these three drugs is largely composed of observational studies resulting from a global shortage of imiglucerase in 2009. \(^21\) \(^22\) \(^27\) This shortage required many patients with Gaucher disease type 1 to undergo dosage reduction in imiglucerase therapy or to switch to an alternative enzyme replacement therapy (velaglucerase or taliglucerase), creating an opportunity to investigate these drugs using dose comparisons studies, single arm trials, switching studies, and pre-post studies. \(^6\) \(^7\) \(^9\) \(^10\) \(^12\) \(^16\) \(^21\) \(^22\) \(^25\) \(^27\)

Of the 27 identified publications, \(^1\) \(^2\) \(^7\) \(^9\) \(^10\) \(^12\) \(^16\) \(^21\) \(^22\) \(^25\) \(^27\) discuss a comparison between imiglucerase, velaglucerase, and taliglucerase. The RCT by Ben et al. \(^1\) directly compared velaglucerase and imiglucerase. The systematic review by Shemesh et al. \(^7\) discussed effectiveness of imiglucerase, velaglucerase, and taliglucerase at different doses, but it is unclear from the abstract whether these findings were derived from head-to-head trials. Of the remaining publications, six reported comparisons between different doses of taliglucerase, \(^3\) \(^13\) \(^14\) \(^23\) velaglucerase, \(^5\) or imiglucerase. \(^22\) Seven publications reported comparisons of disease measures at baseline and after treatment with or after switching to velaglucerase, \(^7\) \(^8\) \(^27\) taliglucerase, \(^9\) or imiglucerase. \(^11\) \(^24\) \(^26\) Choi et al. \(^15\) described results for patients switching from imiglucerase to Abcertin (marketed as a biosimilar of imiglucerase). Eleven publications on imiglucerase or alglucerase, \(^2\) \(^6\) \(^18\) \(^19\) or velaglucerase \(^10\) \(^12\) \(^16\) \(^17\) \(^20\) \(^21\) \(^25\) reported results from descriptive studies without a comparator group or a clear analysis of a change from baseline, or from studies that did not specify the comparators in the abstract. \(^2\) \(^6\) \(^10\) \(^12\) \(^16\) \(^21\) \(^25\)

A total of five publications \(^9\) \(^13\) \(^14\) \(^20\) \(^22\) reported results for adults with Gaucher disease type 1, while three \(^3\) \(^12\) \(^19\) were conducted in a pediatric population; nine \(^2\) \(^4\) \(^5\) \(^7\) \(^10\) \(^16\) \(^18\) \(^25\) reported results for a mixed population of children and adults, and 10 abstracts \(^1\) \(^6\) \(^8\) \(^11\) \(^15\) \(^21\) \(^23\) \(^24\) \(^26\) \(^27\) did not specify the age of eligible patients. Sample sizes
varied between studies, ranging from five\textsuperscript{7,15} to 1,016\textsuperscript{26} included patients. There were 18 publications\textsuperscript{3-9,11-16,20,22,23,25,27} that reported including fewer than 50 patients.

Overall, the evidence suggested that imiglucerase, velaglucerase, and taliglucerase improve disease parameters (hemoglobin concentration, platelet count, liver and spleen volume, and serum biomarkers), although any conclusions regarding which is more effective are not easy to draw from the current literature due to the limited amount of evidence from head-to-head trials.\textsuperscript{1-27}

Table 2: Summary of Included Studies

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Study Characteristics</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Outcomes</th>
<th>Conclusions</th>
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<tr>
<td><strong>Systematic Reviews</strong></td>
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| Shemesh, 2015\textsuperscript{5} | • 8 included RCTs and qRCTs  
• Patients with Gaucher disease  
• N = 300 | • Enzyme replacement therapies  
• Substrate reduction therapies | • Enzyme replacement therapies  
• Substrate reduction therapies  
• No control group | • Hemoglobin concentration  
• Platelet count  
• Spleen and liver volume  
• Serum biomarkers (chitotriosidase and CCL18) | • Patients receiving either imiglucerase or alglucerase (60 units/kg), imiglucerase or velaglucerase alfa (60 U/kg), taliglucerase alfa at 30 units/kg or 60 units/kg, and velaglucerase alfa at 45 units/g or 60 units/kg had similar increases in hemoglobin  
• There was a benefit in platelet count observed for patients receiving imiglucerase over velaglucerase alfa (at 60 units/kg) |
| Doneda, 2013\textsuperscript{2} | • 28 included articles (case series (n\textsuperscript{\geq}5), clinical trials, systematic reviews, and meta-analyses)  
• Pediatric and adult patients with Gaucher disease type 1  
• N = NR | • Enzyme replacement therapy with alglucerase or imiglucerase | • Not specified the in abstract | • Growth and development  
• Weight  
• Height  
• Malnutrition  
• Overweight  
• Obesity  
• Basal metabolism  
• Hypermetabolism  
• Insulin resistance  
• Diabetes | “ERT tends to normalise the growth of children and adolescents with GD type I, it seems to cause a partial response in relation to some metabolic changes associated with the disease, and it can causes metabolic changes such as weight gain in adult patients. Therefore, additional research is necessary.”\textsuperscript{2} |
| **Randomized Controlled Trials** |
| Zimran, 2015\textsuperscript{3} | • Pediatric patients with Gaucher | • Taliglucerase alfa (30 U/kg) every other  
• Taliglucerase alfa (60 U/kg) every other | • Hemoglobin concentration  
• Platelet count | • Increased median hemoglobin concentrations, |
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<th>First Author, Year</th>
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<tr>
<td>Ben, 2013†</td>
<td>Treatment-naive patients with Gaucher disease type 1, N = 35</td>
<td>Velaglucerase alfa (60 U/kg) every other week for 9 months</td>
<td>Imiglucerase (60 U/kg) every other week for 9 months</td>
<td>Hemoglobin concentration</td>
<td>Velaglucerase alfa demonstrated an increase in hemoglobin concentration that was non-inferior to imiglucerase. There were no significant differences in secondary endpoints.</td>
</tr>
<tr>
<td>Gonzalez, 2013 ‡</td>
<td>Treatment-naive patients with Gaucher disease type 1, N = 25</td>
<td>Velaglucerase alfa 60 (U/kg) every other week for 12 months</td>
<td>Velaglucerase alfa (45 U/kg) every other week for 12 months</td>
<td>Hemoglobin concentration, Platelet count, Spleen volume</td>
<td>“Velaglucerase alfa was generally well tolerated and effective for adults and children with GD1 in this study. All disease-specific parameters measured demonstrated clinically meaningful improvements after 12 months.”</td>
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Non-Randomized Studies, RCT Extension Studies, and Post-Hoc Analyses of RCTs

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<tr>
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<tr>
<td>Goldblatt, 2016 §</td>
<td>Patients with Gaucher disease type 1 who resumed treatment after their ‘drug holiday’, N = 20</td>
<td>Imiglucerase for at least 24 months</td>
<td>No comparator</td>
<td>Bone crisis, Avascular necrosis, Adverse events</td>
<td>“Two years after recommencing ERT after a 6-month drug holiday, no patient had developed an overt irreversible complication of their Gaucher disease, with the majority returning to their previous clinical status.”</td>
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<tr>
<td>Ida, 2016 ‡</td>
<td>Patients with Gaucher disease type 1 or type 3 who were switched from imiglucerase, N = 5</td>
<td>Velaglucerase alfa (51.5 to 60.7 U/kg) every other week for 63 to 78 weeks</td>
<td>Baseline parameters prior to therapy initiation</td>
<td>Hemoglobin concentration, Platelet count, Spleen volume</td>
<td>“The data suggest that velaglucerase alfa was well tolerated and maintained clinical stability in Japanese GD patients over 2 years after switching from imiglucerase.”</td>
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<td>First Author, Year</td>
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| **Laudemann, 2016** | Patients with Gaucher disease type 1  
N = 18  
Retrospective data analysis | Velaglucerase alfa | Baseline parameters prior to therapy initiation | Bone-Marrow-Burden score  
Dusseldorf-Gaucher score  
Vertebra-Disc-Ratio  
Severity Score Index Type 1 | "Velaglucerase alfa therapy is an effective long-term treatment for Gaucher Type 1 patients who are newly diagnosed or switching therapies" |
| **Pastores, 2016** | Adults with Gaucher disease type 1 previously treated with imiglucerase  
N = 18  
Extension study | Taliglucerase alfa for up to 36 months (n = 10 completing treatment) | Baseline parameters prior to therapy initiation or therapy switching | Hemoglobin concentration  
Platelet count  
Spleen and liver volume  
CCL18 concentration  
Anti-drug antibody development | "The 36-month results of switching from imiglucerase to taliglucerase alfa treatment in adults with GD provide further data on the clinical safety and efficacy of taliglucerase alfa beyond the initial 9 months of the original study" |
| **Pastores, 2016** | Patients with Gaucher disease that were either treatment-naive or previously treated with imiglucerase  
N = 289 | Velaglucerase alfa | No comparator | Anti-velaglucerase alfa antibody development  
Hemoglobin concentration  
Platelet count  
Chitotriosidase activity  
CCL18 concentration | "Less than 2% of patients exposed to velaglucerase alfa tested positive for antibodies and there was no apparent correlation between anti-velaglucerase alfa antibodies and adverse events or pharmacodynamic or clinical responses" |
| **Pleat, 2016** | Patients with Gaucher disease type 1 currently treated with velaglucerase alfa  
N = 30  
Post-hoc analysis of eliglustat ENCORE trial | Imiglucerase | Eliglustat | Hemoglobin concentration  
Platelet count  
Spleen and liver volume | "Clinical stability was maintained for 12 months in Gaucher disease type 1 patients in the ENCORE trial who switched from velaglucerase alfa to either eliglustat or imiglucerase" |
| **Smith, 2016** | Pediatric patients with Gaucher disease type 1 that were either  
Velaglucerase alfa (30-60 U/kg) every other week | No comparator | Primary hematological and visceral parameters  
Disease | Exploratory results may suggest benefits of early treatment to enable normal growth in pediatric patients. The safety |
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| Zimran, 2016<sup>13</sup> | Treatment-naive adults with Gaucher disease type 1  
- N = 24  
- Long-term extension study | Taliglucerase alfa (30 U/kg) every other week for 36 months  
Taliglucerase alfa (60 U/kg) every other week for 36 months | hemoglobin concentration  
platelet count  
spleen and liver volume  
chitotriosidase activity | profile and clinical response seen in pediatric patients are consistent with results reported in adults<sup>n12</sup> |
| Zimran, 2016<sup>14</sup> | Adults with Gaucher disease type 1  
- N = 17  
- Long-term RCT results | Taliglucerase alfa (30 U/kg) every other week for 5 years  
Taliglucerase alfa (60 U/kg) every other week for 5 years | hemoglobin concentration  
platelet count  
spleen and liver volume  
chitotriosidase activity  
cCL18 concentration | These 36-month results of taliglucerase alfa in treatment-naive adult patients with GD demonstrate continued improvement in disease parameters with no new safety concerns. These findings extend the taliglucerase alfa clinical safety and efficacy dataset<sup>n13</sup> |
| Choi, 2015<sup>15</sup> | Patients with Gaucher disease type 1 previously treated with imiglucerase  
- N = 5  
- Open-label cross-over trial | Abcertin (imiglucerase for injection; 30-55 U/kg) for 24 weeks | hemoglobin concentration  
platelet count  
spleen and liver volume  
skeletal status  
bone mineral density  
chitotriosidase activity  
cCL18 concentration | No statistically significant changes were observed in all parameters after switching from imiglucerase to Abcertin  
The efficacy and safety of Abcertin was similar to that of imiglucerase |
| Elstein, 2015<sup>16</sup> | Patients with Gaucher disease type 1 previously treated and stable on imiglucerase  
- N = 38  
- 12 month open-label trial and | Velaglucerase alfa  
(comparable dose to previous imiglucerase) | hemoglobin concentration  
platelet count  
spleen and liver volume  
bone mineral density  
chitotriosidase activity  
cCL18 concentration | In conclusion, clinically stable patients can be switched from imiglucerase to velaglucerase alfa ERT and maintain or achieve good therapeutic outcomes<sup>n16</sup> |
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<th>Outcomes</th>
<th>Conclusions</th>
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<tr>
<td>Hughes, 2015</td>
<td>10-50 month extension study</td>
<td>Patients with Gaucher disease type 1, N = 57, Extension study</td>
<td>Velaglucerase alfa (60 U/kg) every other week for 1.2–4.8 years</td>
<td>No comparator</td>
<td>Hematology variables, Organ volumes, Plasma biomarkers, Lumbar spine bone mineral density Z-score, Anti-velaglucerase alfa antibody development, Adverse events</td>
</tr>
<tr>
<td>Stirnemann, 2015</td>
<td>Patients with Gaucher disease type 1, N = 99, Retrospective observational study</td>
<td>Imiglucerase</td>
<td>No comparator</td>
<td>Number of treatment modifications, Imiglucerase discontinuation, Replacement with another ERT, Hemoglobin concentration, Platelet count, Chitotriosidase activity, Angiotensin-converting enzyme concentration, Adverse events</td>
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<td>Camelo Jr, 2014</td>
<td>Latin American children with Gaucher disease type 1 (aged &lt;18 years at start of ERT), N = 443</td>
<td>ERT (imiglucerase or alglucerase)</td>
<td>No comparator</td>
<td>Adverse events, Hemoglobin levels, Platelet count, Liver and spleen volumes, Growth, Bone pain, Bone crises</td>
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“Velaglucerase alfa had a good long-term safety and tolerability profile, and patients continued to respond clinically, which is consistent with the results of the extension study to the phase I/II trial of velaglucerase alfa.”

“The release of recommendations and individuals’ close follow-up allowed satisfactory management of patients during the imiglucerase supply constraint in France. This study suggests that during this period, lowering the dose of imiglucerase had less impact on the outcomes of patients than interrupting treatment. However, general effects (such as fatigue, bone pain) reported in some patients, emphasize the importance of maintaining appropriate individualized dosing.”

“After 8 years of treatment, children showed improvements in mean hemoglobin levels, platelet count, liver and spleen volumes, growth, bone pain and bone crises. Continuous and long-term treatment with imiglucerase improves hematological, visceral and skeletal manifestations of Gaucher disease type 1.”
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<td>Elstein, 2014&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Pregnant women with Gaucher disease</td>
<td>Velaglucerase alfa</td>
<td>No comparator</td>
<td>Live birth rate, Abortion rate, Mean birthweight, APGAR score</td>
<td>“Velaglucerase alfa is safe for conception and pregnancy with good maternal and neonatal outcomes”&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pastores, 2014&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Patients with Gaucher disease type 1 that were either treatment-naive or previously treated with imiglucerase</td>
<td>Velaglucerase alfa (60 U/kg if treatment-naive; 15-60 U/kg if previously treated) every other week</td>
<td>No comparator</td>
<td>Adverse events, Anti-velaglucerase alfa antibody development</td>
<td>“The currently observed safety profile was consistent with those previously reported for imiglucerase and velaglucerase alfa phase III clinical trials. These results support the safety of initiating treatment with velaglucerase alfa or transitioning patients from imiglucerase therapy to velaglucerase alfa therapy”&lt;sup&gt;21&lt;/sup&gt;</td>
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<tr>
<td>Deroma, 2013&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Patients with Gaucher disease type 1 that were forced to reduce imiglucerase dosage (due to global shortage)</td>
<td>Imiglucerase</td>
<td>Imiglucerase at a reduced dosage (average dosage reduction of 35.5%)</td>
<td>Hemoglobin concentration, Platelet count, Leukocyte count, Chitotriosidase activity, Bone pain, Energy, Work or school performance, Concentration, Social life</td>
<td>“Drug reduction did not induce substantial modification in the laboratory values but seems to have influenced the well-being perception of some Gaucher patients. Thus, bone pain, general health and quality of life should be carefully monitored during ERT reductions”&lt;sup&gt;22&lt;/sup&gt;</td>
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<td>van Dussen, 2013&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Patients with Gaucher disease type 1</td>
<td>Taliglucerase alfa (30 U/kg)</td>
<td>Taliglucerase alfa (60 U/kg)</td>
<td>Bone marrow fat fraction</td>
<td>“Treatment with taliglucerase alfa results in significant increases in lumbar spine fat fractions, which indicates clearance of Gaucher cells from the bone marrow”&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>Weinreb, 2013&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Patients with Gaucher disease type 1</td>
<td>Imiglucerase</td>
<td>Baseline parameters from clinical data at first infusion (prior to 10 years of treatment)</td>
<td>Hemoglobin concentration, Platelet count, Organ volume, Bone pain, Bone crises, Adverse events</td>
<td>Significant improvements in hemoglobin levels, platelet count, liver and spleen volumes, and bone crises incidents were reported</td>
</tr>
</tbody>
</table>
| Zimran, 2013<sup>25</sup> | Patients with Gaucher disease type 1 previously | Velaglucerase alfa | No comparator | Adverse events, Anti-velaglucerase alfa antibody | “In conclusion, adult and pediatric patients with GD1, previously treated with imiglucerase, ...
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| treated with imiglucerase | • N = 40  
• 12 month open-label study | | | development  
• Hemoglobin concentration  
• Platelet count  
• Spleen and liver volume | successfully transitioned to velaglucerase alfa, which was generally well tolerated and demonstrated efficacy over 12 months' treatment consistent with that observed in the velaglucerase alfa phase 3 clinical trial program²⁵ |
| Hollak, 2012²⁶ | • Patients with Gaucher disease type 1  
• N = 1,016  
• Retrospective study | • Imiglucerase up to 4–5 years of therapy | • Baseline parameters prior to therapy initiation | • Platelet count  
• Body mass index  
• Anaemia  
• Spleen and liver volume  
• Skeletal assessment | “Statistically significant associations were found between persistent thrombocytopenia and baseline platelet count, splenomegaly, and anaemia. After 4-5 years, statistically significant associations were found with splenomegaly, anaemia, white blood cell count, hepatomegaly and bone pain. Exponential platelet decay in relation to splenomegaly suggests that platelets increase only when spleen volume decreases substantially”²⁷ |
| van Dussen, 2012²⁷ | • Patients with Gaucher disease type 1 previously treated with imiglucerase  
• N = 32 | • Velaglucerase alfa | • Baseline parameters prior to switching therapies | • Hemoglobin concentration  
• Platelet count  
• Chitotriosidase activity  
• Spleen and liver volume  
• Bone marrow fat fraction | “Velaglucerase alfa appears to be a safe and effective alternative for imiglucerase”²⁷ |

AST = aspartate aminotransferase; CCL18 = Chemokine (C-C motif) ligand 18; ERT = enzyme replacement therapy; GD = Gaucher disease; NR = not reported; qRCT = quasi-randomized controlled trials; RCT = randomized controlled trial.
References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-Analyses

   PubMed: PM25812601

   PubMed: PM23570288

Randomized Controlled Trials

   PubMed: PM25453586

   PubMed: PM23400823

   PubMed: PM23386328

Non-Randomized Studies

   PubMed: PM27245534

   PubMed: PM27241455

   PubMed: PM26852653


PubMed: PM25968608


PubMed: PM24612151

PubMed: PM24263462

PubMed: PM23430505

PubMed: PM23199589

PubMed: PM22976765

PubMed: PM23339116

PubMed: PM22640238

PubMed: PM22773601
Appendix — Further Information

Previous CADTH Reports


Non-Randomized Studies

Alternative Intervention – Home infusion for ERT


Uncertain Intervention – ERT drug not specified in abstract


Review Articles


Additional References


See “Clinical Efficacy”