

## Velaglucerase alfa in the treatment of Gaucher disease type 1: an update

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by deficiency of the enzyme acid  $\beta$ -glucosidase. Enzyme replacement therapy is the standard of care for the treatment of GD type I. Currently, three preparations, including imiglucerase (Cerezyme<sup>®</sup>, Genzyme Corporation, MA, USA), taliglucerase alfa (Elelyso<sup>®</sup>, Pfizer Inc., NY, USA) and velaglucerase alfa (VPRIV<sup>®</sup>, Shire Human Genetic Therapies Inc., Dublin, Ireland), are commercially available. Here, we will review the recent literature addressing the safety and efficacy of velaglucerase, particularly as compared with the other enzyme replacement therapy products, as well as the treatment of GD type 1 with velaglucerase alfa.

**Keywords:** anemia • enzyme replacement therapy • Gaucher disease • hepatomegaly • lysosomal storage disease • splenomegaly • thrombocytopenia • velaglucerase alfa

### Background

Gaucher disease (GD), an autosomal recessively inherited lysosomal storage disease, is caused by mutations in the gene-encoding acid  $\beta$ -glucosidase, *GBAI*. Insufficient activity of this enzyme results in accumulation of glucosyl ceramide (GL-1) and other glucosphingolipids in visceral tissue. Their accumulation predominantly in cells of monocyte/macrophage origin lead to the majority of visceral manifestations. The worldwide incidence of GD is estimated to be one in 111,111. [1]. Three variants of GD are classically described. Type 1, a variant that does not manifest early onset rapid neuronopathic involvement, is the most commonly diagnosed in the Western world, while the neuronopathic variants (types 2 and 3) appear to be the most prevalent worldwide [1].

The accumulation of 'Gaucher cells,' glucosylceramide-engorged macrophages, in the liver, spleen and bone marrow leads to the primary clinical manifestations of type 1 disease, including hematologic (anemia, thrombocytopenia), visceral (hepatomegaly and splenomegaly) and skeletal (osteoporosis, lytic lesions and bone pain).

GD types 2 and 3 have variably progressive primary CNS manifestations in addition to the visceral signs observed in GD type 1. While individuals of all ages with GD type 1 may develop disease signs and require treatment, onset of GD type 2 is in infancy and neurologic progression occurs rapidly, resulting in death in early childhood. GD type 3 has a more slowly progressive primary neurologic course. While the major clinical features of GD type 1 can be attributed to accumulation of Gaucher cells, the pathogenesis of neurologic abnormalities in the neuronopathic forms of GD are likely more complex, for example, related to inflammation, toxicity of storage material, ultimately leading to neuronal death [1]. Although these classical variants provide a useful clinical nosology, types 2 and 3 variants represent a continuum of phenotypes unified by the similar CNS pathogenesis of neuronal death [2].

Recombinant, exogenously produced acid  $\beta$ -glucosidase has been available since the early 1990s for intravenous administration (enzyme replacement therapy [ERT]) to patients with GD type I. The initial therapeutic (alglucerase) and its successor (imiglu-

K Nicole Weaver<sup>1</sup>, Gregory A Grabowski<sup>1</sup> & Thomas A Burrow<sup>\*1</sup>

<sup>1</sup>Cincinnati Children's Hospital Medical Center, Division of Human Genetics, 3333 Burnet Avenue, MLC 4006, Cincinnati, OH 45229-43039, USA

\*Author for correspondence: thomas.burrow@cchmc.org

cerase) were/are manufactured to contain glycan structures with exposed mannose residues to allow their recognition and internalization by macrophages via the mannose receptor. Although not approved for use in patients with neuronopathic variants of GD, ERT does have positive effects on visceral manifestations of GD type 3 [3]. The blood–brain barrier prevents enzyme entry into the CNS, therefore, it is ineffective at reversing or stabilizing the primary neurologic manifestations [1].

Three ERT products are commercially available and approved by the US FDA and EMA, among other countries, for treatment of GD type 1 in all age groups: imiglucerase (Cerezyme®, Genzyme Corporation, MA, USA), velaglucerase alfa (VPRIV®, Shire Human Genetic Therapies Inc., Dublin, Ireland) and taliglucerase alfa (Elelyso®, Pfizer Inc., NY, USA). Although conceptually similar, differences in production and structures of the products exist. Imiglucerase is produced in Chinese hamster ovary cells engineered to overexpress a recombinant analog of human acid  $\beta$ -glucosidase, velaglucerase alfa is produced in a human fibrosarcoma cell line to overexpress the endogenous GBA1 using gene-activation technology and taliglucerase is produced in carrot root cells expressing recombinant human glucocerebrosidase [4,5]. Related to these differences in production, the glycan chain compositions of the three enzymes are distinct. Imiglucerase contains short chain core mannose residues, which are exposed via *in vitro* exoglycosidase treatment after expression and purification. Velaglucerase contains longer chain high-mannose residues created by incorporation of a mannosidase I inhibitor (kifunensine) during cell culture. Like imiglucerase, taliglucerase contains a shorter chain of mannose residues, but it does not require postproduction modification for mannose exposure as plants naturally have mannose-terminated glycoproteins [4–6]. The amino acid sequences of the three enzymes are also distinct. Velaglucerase has an identical sequence to the natural human protein, but imiglucerase and taliglucerase differ at amino acid residue 495, with histidine replacing the natural arginine [5]. Taliglucerase also contains an additional two amino acids at the N-terminus and seven amino acids at the C-terminus [5].

Studies comparing velaglucerase and imiglucerase have demonstrated that the enzymatic properties are essentially identical, drug elimination is similar and *in vitro* kinetic parameters and pH denaturation are also similar [4–8]. The two drugs performed similarly with regards to half-life and efficacy in the mouse model of GD, and both showed comparable dose and duration-dependent effect on the disappearance of Gaucher cells and glucosylceramide clearance. Phase I/II trials

and early Phase III trials demonstrated that safety and efficacy of velaglucerase are similar to imiglucerase in adults and children, although seroconversion rates with imiglucerase appear greater (seroconversion of 1% for velaglucerase vs ~15% for imiglucerase) [9,10]. Both drugs are effective and have similar profiles of increasing hemoglobin concentration and platelet counts, and reducing liver and spleen volumes in children and adults with type 1 GD. Like imiglucerase, velaglucerase has a proportional dose-sensitive response, with greater improvement in clinical parameters noted at higher dosing [9].

The importance of having multiple products available for ERT of a disease was emphasized by the 2009 global shortage of imiglucerase. This article serves as an update to Burrow and Grabowski's 2011 review article, which addressed velaglucerase alfa treatment of GD type 1 [9]. Key themes of clinically oriented publications published since 2011 include safety and efficacy of switching from imiglucerase to velaglucerase; safety and efficacy of velaglucerase as compared with imiglucerase; evaluation of the effect of velaglucerase on GD-related bone disease and safety and efficacy of velaglucerase in pregnant woman afflicted by GD.

### Safety & efficacy of switching from imiglucerase to velaglucerase

The Early Access Program to velaglucerase in Israel was started in 2009 in response to the impending global shortage of imiglucerase. A retrospective study examined the safety and efficacy of velaglucerase in 71 patients [11]. All 71 were included in the safety report, but only 44 were included in efficacy evaluation because the remaining 27 were either on therapy for less than 6 months or had not had follow-up evaluations at appropriate times. The cohort of 44 included five adult patients who were treatment-naïve, three who had been off imiglucerase for 2–3 years and 36 patients (ten who were <16 years old) who were previously treated with imiglucerase. Among the 36 previously treated patients, the duration without imiglucerase therapy ranged from 0 (14 patients) to 9 months (one patient). The cohort of 27 included three patients who were withdrawn from taliglucerase trials due to allergic reactions. Overall, two drug-related adverse events (AEs) were described: One was an allergic reaction during the first infusion in a patient who previously had an allergic reaction to taliglucerase, and who was positive for IgG antibodies to velaglucerase. The patient continued to use velaglucerase alfa with premedication. The other was a putatively fixed drug eruption on the chin of a switchover patient that resolved spontaneously and never reappeared despite continued use of velaglucerase alfa. Improvements in

the mean hemoglobin concentration, platelet count and spleen and liver volumes were noted in both switchover and ERT-naïve groups. As expected, greater improvements were noted in the ERT-naïve group. A so-called booster effect in platelet count improvement (>30% increase) was claimed for two subgroups of switchover patients: those with longer history of ERT treatment (58–224 months) and children, although no inferential statistical analyses were conducted [11]. In addition, the critical relationship of this ‘booster effect’ to time off of imiglucerase therapy was not provided. Therefore, data are not sufficient to attribute this effect to the switch in therapy in such patients.

A retrospective analysis evaluated the effects of switching from a reduced dosage of imiglucerase to velaglucerase in a cohort of 26 adults with GD type 1 [12]. Prior to the switch, these patients experienced reduced dosage and/or discontinuation of ERT due to the global supply shortage of imiglucerase. Velaglucerase treatment was initiated at a dose equivalent to the preshortage imiglucerase dose in all patients except for one, whose dose was doubled. Clinical outcome measures included hemoglobin concentration, platelet count and liver and spleen volumes. These parameters were assessed 1 year prior to the shortage, at the last visit prior to the onset of the shortage prior to shortage, at time of velaglucerase initiation, and 1 year after velaglucerase initiation. The duration of reduced or discontinued imiglucerase dosing ranged from 1 to 8.5 months. Hemoglobin concentration remained stable during the period of reduced dosing of imiglucerase and after the switch to velaglucerase. Four patients experienced reduction in platelet counts prior to and/or during the imiglucerase shortage. After switching to velaglucerase, platelet count stabilized in one of these patients and increased in the other three. Nine patients had MRI at baseline, 6 and 12 months. In five patients, liver volumes increased by 10% or more after 6 months of treatment with velaglucerase. Liver volume returned to baseline in three of these patients after 12 months treatment. Of note, the potential association between duration of reduced/discontinued imiglucerase dosing and clinical outcome measures was not shown. Only one patient experienced an AE thought to be related to velaglucerase infusion: back pain occurred during the first three infusions but resolved without sequelae during the fourth infusion. The timing of the back pain in relationship to infusion was not discussed [12]. Overall, given the heterogeneity in treatment regimens among this cohort, it is difficult to draw a meaningful conclusion about efficacy based on this study. It is interesting that the authors report inability to evaluate a possible ‘booster effect’ (as described by Elstein *et al.*) as a result of reduced drug dosing in patients. Although there

were no dose reductions in the Elstein study, 22 of 36 switchover patients had experienced discontinued imiglucerase dosing prior to switching [11].

Zimran *et al.* [13] reported on safety and efficacy of velaglucerase alfa in 40 patients, ages 2 years and older, previously treated with imiglucerase for at least 30 months. There was no washout period between medications. Outcomes were measured after 12 months of velaglucerase treatment. The primary outcome was the safety of every other week dosing of velaglucerase in patients previously on imiglucerase. Secondary outcomes included change from baseline to 12 months in hemoglobin concentration, platelet counts and spleen and liver volumes. Mild and moderate AEs were reported in 14/40 and 15/40 patients, respectively. The most frequently reported AEs were headache (12/40), arthralgia (9/40) and nasopharyngitis (8/40). One patient experienced a drug-related serious AE (Grade 2 anaphylactoid reaction) that led to study discontinuation. No antivelaglucerase antibodies were detected in this patient at three time points: prior to, 24 h after and 2 weeks after drug administration. None of the patients developed antibodies to velaglucerase during the study. Two patients who had anti-imiglucerase antibodies showed cross-reacting positivity to velaglucerase. Overall, clinical parameters remained stable over the 12 months of velaglucerase treatment, without clinically or statistically significant differences detected between the beginning and end of the study [13]. This suggests that velaglucerase has similar safety and efficacy as compared with imiglucerase. The clinical significance of antivelaglucerase antibodies (if any) remains to be determined.

A retrospective analysis of nine adults with GD type 1 assessed safety and efficacy of switching from imiglucerase to velaglucerase, without treatment interruption or reduced dosing prior to the switch [14]. Patients who were switched from imiglucerase to velaglucerase between 2010 and 2012 were included, if they had been on imiglucerase for at least 12 months and had not experienced dose reduction or greater than 15 days of treatment interruption. Hemoglobin concentration, platelet count and chitotriosidase (a potential biomarker of macrophages) were assessed at five time points: initiation of treatment, 1 year before switch, time of switch, 6 months after switch and 1 year after switch and after the switch. There was no statistically significant difference detected between these parameters after 1 year of velaglucerase treatment. No AEs were associated with the switch to velaglucerase treatment, supporting the assessment that switching from imiglucerase to velaglucerase was safe [14].

Pastores *et al.* [15] reported on the safety and tolerability of velaglucerase alfa in an open-label treatment

protocol of 205 GD type 1 patients previously treated with imiglucerase and six treatment-naïve patients. The cohort consisted of American patients aged 2 years and older. Information about imiglucerase treatment duration and dosing was not reported since the primary outcome was safety of velaglucerase alfa. Of the six treatment-naïve patients, three experienced treatment-emergent AEs (TEAEs), only one of which was thought to be related to study drug (an infusion-related episode of back pain). Of the 205 previously treated patients, 89 experienced at least one TEAE. The majority of the TEAEs were mild or moderate severity, with the most frequent being headache, nasopharyngitis, nausea and fatigue. Infusion-related AEs were reported in 28/211 patients; no anaphylactoid events were reported. Four treatment-naïve patients and 163 previously treated patients were assessed for presence of velaglucerase alfa reacting antibodies (IgG and IgE, with IgM and IgA assayed as needed). None of the treatment-naïve patients tested positive for such antibodies at any time point during velaglucerase treatment. Thirty-one of the 163 patients previously treated with imiglucerase were positive for antibodies that reacted with imiglucerase at baseline; in ten patients, these anti-imiglucerase antibodies showed cross-reactivity with velaglucerase. One patient with anti-imiglucerase antibodies at baseline developed non-neutralizing antivelaglucerase IgG antibodies over the course of the study. As with previous ERT analyses, the presence of antidrug antibodies did not directly correlate with AEs. Treatment-naïve patients demonstrated increases in hemoglobin and platelet counts, and previously treated patients maintained hemoglobin and platelet counts. Overall, the authors concluded that velaglucerase was generally well tolerated, with a safety profile similar to that observed in controlled trials, and that the data support the safety of initiating velaglucerase treatment or transitioning from imiglucerase to velaglucerase [15].

#### Safety & efficacy: velaglucerase versus imiglucerase

A 9-month randomized, double-blind, multi-institutional noninferiority trial compared the safety and efficacy of velaglucerase to imiglucerase for the treatment of GD type 1 [16]. The primary end point was the difference in mean change from baseline to 9 months between the two treatment groups in hemoglobin concentration. Secondary end points included the difference in changes from baseline between the two treatment groups in mean platelet count, spleen/liver volumes and plasma chitotriosidase and CCL 18 levels. Seventeen treatment-naïve patients, aged 2 years and older, were included in each treatment group. The hemoglobin response in the velaglucerase treatment group was noninferior to that

of the imiglucerase treatment group (+1.624 vs +1.488 g/dl mean change from baseline, respectively). Similar improvements in secondary end points were observed between the two treatment groups. Four of the patients in the imiglucerase treatment group developed antidrug antibodies, while none of the patients in the velaglucerase group developed such antibodies. The anti-imiglucerase antibodies in one patient demonstrated cross-reactivity with velaglucerase. Study drug-related AE reports were reported in 8/17 patients in the velaglucerase group and 6/17 patients in the imiglucerase group, but the study was not powered to detect differences between types of AEs [16].

#### Investigational outcome: skeletal disease

The effect of velaglucerase ERT on bone mineral density (BMD) of the lumbar spine (LS) and femoral neck (FN) was measured as an investigational outcome during the seminal Phase I/II and extension trial conducted at a single site in Jerusalem [17]. Assessment of BMD using dual-energy x-ray absorptiometry (DXA) was performed at baseline, 9 months, 24 months and then yearly in ten patients. Changes from baseline in BMD z-scores at LS and FN were reported up to 69 months. Velaglucerase was initially dosed at 60 units/kg every other week, through the extension trial, but stepwise dosage reduction to 30 units/kg every other week was allowed based on achieving therapeutic goals. Of note, 4 out of 10 patients received bisphosphonates either prior to enrollment or during the trial/extension. Statistically significant improvements in BMD z-scores were noted by month 24 for LS (mean change + 0.39) and by month 33 for FN (mean change + 0.39). Larger improvements were noted in the six patients who were not concurrently receiving bisphosphonates (mean increase in BMD of 0.58 at LS by month 24 and of 0.48 at FN by month 33). In the four patients who were receiving bisphosphonates, the average z-score of BMD at LS and FN increased from baseline, but this was not statistically significant. Across the group, the increase in BMD was continuous and sustained over the 69-month study period [17]. Overall, these data are difficult to interpret in the context of previously published, more robust studies. One double-blind placebo-controlled study of 34 adults with GD type 1 compared effects on BMD of dual therapy with alendronate and ERT with ERT alone. Results demonstrated that alendronate treatment resulted in significant and relatively rapid improvement of BMD compared with placebo (i.e., ERT alone), which had no effect on BMD over the 2-year study period [18]. Another large study compared the effect of imiglucerase to no treatment on BMD in 502 patients with GD type 1 (160 untreated, 342 treated) [19] and

found that imiglucerase treatment was associated with improvement in BMD over a longer time period (8 years to become 'normal'). Larger, controlled studies are needed to determine the effect velaglucerase has on BMD in comparison to bisphosphonates alone or in conjunction with ERT.

Assessment of bone marrow involvement in GD can be performed using quantitative chemical shift imaging (QCSI), or the more widely available MRI-based semiquantitative bone marrow burden (BMB) score [20,21]. A maximum of eight points each can be assigned to the femoral and lumbar sites, with higher score indicating more severe disease. A reduction in femoral or lumbar BMB score of at least two points has previously been shown to be associated with improvement in Gaucher-related skeletal disease and response to ERT [20]. The effect of long-term velaglucerase alfa treatment on BMB score in adults with GD1 was assessed in eight patients who completed the initial and 7-year extension Phase I/II trial [22]. By year 7, all eight patients had a decrease of at least two points from baseline lumbar BMB score, and five of the eight had a decrease of at least four points. Femoral BMB scores were only available for five patients at baseline and during ERT. Four of the five experienced a BMB score reduction of 2; the fifth did not but only had one post-ERT measurement available, which was obtained 9 months after ERT initiation [22].

### Safety/efficacy in pregnancy

Pregnancy outcomes in women receiving velaglucerase from conception to delivery were studied in a retrospective review of 25 pregnancies in 21 women [23]. The live birth rate was 84% (three women had four early first trimester spontaneous abortions). All babies were born at term and were healthy. All had APGAR scores greater than 8 at 5 and 10 min, with the exception of one infant with APGAR score of 5 at 5 min, which was attributed to nuchal cord and the baby recovered shortly thereafter. One woman had two pregnancies included; she was initially in the extension trial and was allowed to continue on compassionate use during pregnancy and then her second pregnancy occurred while on commercial drug. One woman was switched from imiglucerase to velaglucerase and had three pregnancies while on velaglucerase, one of which resulted in an early first trimester spontaneous abortion. The pregnancies and deliveries in the study cohort were generally uncomplicated: One patient had a postpartum hemorrhage secondary to placental bleeding. Two women had previously been denied epidural anesthesia due to thrombocytopenia; they had sufficient platelet levels with velaglucerase ERT to safely receive the epidural block for delivery and were included in this

study. Pre- and postpregnancy hemoglobin and total platelet count were recorded for 22 pregnancies. The mean change in hemoglobin was +9.45% and mean change in total platelet count was +26%. Drug dosage ranged from 20 to 80 units/kg per month and was at the discretion of each patient's prescribing clinician. Overall, the authors concluded that maternal and neonatal outcomes of women with GD treated with velaglucerase during pregnancies were comparable to those reported for imiglucerase [23,24]. It is important to note that the VPRIV package insert currently states that velaglucerase alfa should only be used during pregnancy if clearly needed, due to lack of well-controlled studies of velaglucerase in pregnant women (VPRIV drug label section 8.1).

### Dosage effects

A multinational, Phase III, randomized, double-blind, parallel group, two dose-study evaluated the safety and efficacy of velaglucerase given every other week at 60 or 45 units/kg per dose [25]. The treatment cohort included 25 treatment-naïve patients with GD1 between the age of 4 and 62 years. The primary end point was the change in hemoglobin concentration from baseline to 12 months in the 60 unit/kg dosing group. Secondary end points included change in hemoglobin concentration from baseline to 12 months in the 45 unit/kg dosing group, and change from baseline to 12 months in platelet counts, spleen volume, liver volume, chitotriosidase and CCL18 in both dosing groups. Although the different doses were not directly compared, both dosing regimens were associated with statistically significant increases in mean hemoglobin concentration from baseline. Mean spleen and liver volumes decreased in both dosing groups, although only the decrease in spleen volume was statistically significant. The EMA has predefined three response categories (good, moderate, none) for hemoglobin concentration, platelet count and normalized organ volume at 12 months. Trends in favor of the higher dose were noted for platelet count and liver volume. AEs were reported by 15/25 participants; 14 of these were considered to be infusion related. The most common AEs were headache, nasopharyngitis, traumatic injury, arthralgia, cough, pyrexia, dizziness, influenza, nasal congestion, vomiting, bone pain and prolonged partial thromboplastin time. Three severe or serious AEs occurred and were considered unrelated to ERT. One patient developed neutralizing IgG antibodies to velaglucerase enzyme activity after 12 months of treatments. This patient did not experience any AEs. Of note, two patients included in the analysis were later found to be carriers of GD and not truly affected (both were diagnosed based on a false-positive-dried blood

spot test). A repetition of the analyses excluding these two carriers did not change the conclusions of the study [25].

## Conclusions

Over the past 3 years, research has focused on the safety and efficacy of switching from imiglucerase to velaglucerase, effects on secondary outcome measures and safety in pregnancy. Data suggest that velaglucerase and imiglucerase have comparable safety and efficacy profiles, and importantly, that it is safe to switch directly from imiglucerase to velaglucerase. It is intriguing that one study [11] suggested a 'booster effect' on platelet count in patients who were switched to velaglucerase after long-term treatment with imiglucerase, but did not take into account the time off imiglucerase before initiating velaglucerase. It remains to be determined whether this effect is maintained, or if habituation is a result of treatment duration rather than specific to the drug preparation used; that is, would re-initiation of imiglucerase result in a booster effect after a period of time without treatment? Having multiple treatment options available for ERT of GD type 1

allows physicians and patients the option of personalizing treatment based on experience and drug response. It has been our personal experience that some patients do better clinically on one ERT product versus another (Burrow, Personal Observation). Future studies are likely to focus on resolving these questions through longer-term follow-up. As well, further follow-up will allow additional comparisons of effectiveness between velaglucerase and imiglucerase.

## Financial & competing interests disclosure

GA Grabowski is the Chief Scientific Officer of Synageva BioPharma Corp., and has stock options in that company. He declares no conflicts of interest as Synageva BioPharma Corp. does not have programs that are the subject of this review. TA Burrow has received travel reimbursements and honorariums for advisory activities from Genzyme and Shire. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

## Executive summary

- Data suggest that velaglucerase and imiglucerase have comparable safety and efficacy profiles, and importantly, that it is safe to switch directly from imiglucerase to velaglucerase.
- Having multiple treatment options available for enzyme replacement therapy of Gaucher disease type 1 allows physicians and patients the option of personalizing treatment based on experience and drug response. It has been our personal experience that some patients do better clinically on one enzyme replacement therapy product versus another (Burrow, Personal Observation).
- Future studies are likely to focus on resolving these questions regarding long-term stability in individuals receiving one product versus another.
- Further follow-up will allow additional comparisons of effectiveness between velaglucerase, imiglucerase and taliglucerase alfa.

## References

- 1 Grabowski GA, Petsko GA, Kolodny EH. Gaucher disease. In: *The Online Metabolic and Molecular Bases of Inherited Disease*. Beaudet AL, Vogelstein B, Kinzler KW *et al.* (Eds). The McGraw-Hill Companies Inc., NY, USA (2014).
- 2 Goker-Alpan O, Schiffmann R, Park JK, Stubblefield BK, Tayebi N, Sidransky E. Phenotypic continuum in neuronopathic Gaucher disease: an intermediate phenotype between type 2 and type 3. *J. Pediatr.* 143(2), 273–276 (2003).
- 3 Sechi A, Deroma L, Dardis A *et al.* Long term effects of enzyme replacement therapy in an Italian cohort of type 3 Gaucher patients. *Mol. Genet. Metab.* 113(3), 213–218 (2014).
- 4 Brumshtein B, Salinas P, Peterson B *et al.* Characterization of gene-activated human acid-beta-glucosidase: crystal structure, glycan composition, and internalization into macrophages. *Glycobiology* 20(1), 24–32 (2010).
- 5 Shaaltiel Y, Bartfeld D, Hashmueli S *et al.* Production of glucocerebrosidase with terminal mannose glycans for enzyme replacement therapy of Gaucher's disease using a plant cell system. *Plant Biotechnol. J.* 5(5), 579–590 (2007).
- 6 Tekoah Y, Tzaban S, Kizhner T *et al.* Glycosylation and functionality of recombinant beta-glucocerebrosidase from various production systems. *Biosci. Rep.* 33(5), e00071 (2013).
- 7 Xu YH, Sun Y, Barnes S, Grabowski GA. Comparative therapeutic effects of velaglucerase alfa and imiglucerase in a Gaucher disease mouse model. *PLoS ONE* 5(5), e10750 (2010).
- 8 Zimran A, Loveday K, Fratazzi C, Elstein D. A pharmacokinetic analysis of a novel enzyme replacement therapy with gene-activated human glucocerebrosidase (GA-GCB) in patients with type 1 Gaucher disease. *Blood Cells Mol. Dis.* 39(1), 115–118 (2007).
- 9 Burrow TA, Grabowski GA. Velaglucerase alfa in the treatment of Gaucher disease type 1. *Clin. Investig. (Lond.)* 1(2), 285–293 (2011).

- 10 Starzyk K, Richards S, Yee J, Smith SE, Kingma W. The long-term international safety experience of imiglucerase therapy for Gaucher disease. *Mol. Genet. Metab.* 90(2), 157–163 (2007).
- 11 Elstein D, Altarescu G, Maayan H *et al.* Booster-effect with velaglucerase alfa in patients with Gaucher disease switched from long-term imiglucerase therapy: early access program results from Jerusalem. *Blood Cells Mol. Dis.* 48(1), 45–50 (2012).
- 12 van Dussen L, Cox TM, Hendriks EJ *et al.* Effects of switching from a reduced dose imiglucerase to velaglucerase in type 1 Gaucher disease: clinical and biochemical outcomes. *Haematologica* 97(12), 1850–1854 (2012).
- 13 Zimran A, Pastores GM, Tylki-Szymanska A *et al.* Safety and efficacy of velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase. *Am. J. Hematol.* 88(3), 172–178 (2013).
- 14 Serratrice C, Bengherbia M, Alessandrini M *et al.* Effects of switching from imiglucerase to velaglucerase alfa without dose reduction nor wash out in type 1 Gaucher disease. *Blood Cells Mol. Dis.* 53(1–2), 94–96 (2014).
- 15 Pastores GM, Rosenbloom B, Weinreb N *et al.* A multicenter open-label treatment protocol (HGT-GCB-058) of velaglucerase alfa enzyme replacement therapy in patients with Gaucher disease type 1: safety and tolerability. *Genet. Med.* 16(5), 359–366 (2014).
- 16 Ben Turkia H, Gonzalez DE, Barton NW *et al.* Velaglucerase alfa enzyme replacement therapy compared with imiglucerase in patients with Gaucher disease. *Am. J. Hematol.* 88(3), 179–184 (2013).
- 17 Elstein D, Foldes AJ, Zahrieh D *et al.* Significant and continuous improvement in bone mineral density among type 1 Gaucher disease patients treated with velaglucerase alfa: 69 month experience, including dose reduction. *Blood Cells Mol. Dis.* 47(1), 56–61 (2011).
- 18 Wenstrup RJ, Bailey L, Grabowski GA *et al.* Gaucher disease: alendronate disodium improves bone mineral density in adults receiving enzyme therapy. *Blood* 104(5), 1253–1257 (2004).
- 19 Wenstrup RJ, Kacena KA, Kaplan P *et al.* Effect of enzyme replacement therapy with imiglucerase on BMD in type 1 Gaucher disease. *J. Bone Miner. Res.* 22(1), 119–126 (2007).
- 20 Robertson PL, Maas M, Goldblatt J. Semiquantitative assessment of skeletal response to enzyme replacement therapy for Gaucher's disease using the bone marrow burden score. *Am. J. Roentgenol.* 188(6), 1521–1528 (2007).
- 21 Maas M, van Kuijk C, Stoker J *et al.* Quantification of bone involvement in Gaucher disease: MR imaging bone marrow burden score as an alternative to Dixon quantitative chemical shift MR imaging – initial experience. *Radiology* 229(2), 554–561 (2003).
- 22 Elstein D, Haims AH, Zahrieh D, Cohn GM, Zimran A. Impact of velaglucerase alfa on bone marrow burden score in adult patients with type 1 Gaucher disease: 7 year follow-up. *Blood Cells Mol. Dis.* 53(1–2), 56–60 (2014).
- 23 Elstein D, Hughes D, Goker-Alpan O *et al.* Outcome of pregnancies in women receiving velaglucerase alfa for Gaucher disease. *J. Obstet. Gynaecol. Res.* 40(4), 968–975 (2014).
- 24 Zimran A, Morris E, Mengel E *et al.* The female Gaucher patient: the impact of enzyme replacement therapy around key reproductive events (menstruation, pregnancy and menopause). *Blood Cells Mol. Dis.* 43(3), 264–288 (2009).
- 25 Gonzalez DE, Turkia HB, Lukina EA *et al.* Enzyme replacement therapy with velaglucerase alfa in Gaucher disease: results from a randomized, double-blind, multinational, Phase 3 study. *Am. J. Hematol.* 88(3), 166–171 (2013).