Molecular Genetics and Metabolism Reports 9 (2016) 25–28

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Stability is maintained in adults with Gaucher disease type 1 switched from velaglucerase alfa to eliglustat or imiglucerase: A sub-analysis of the eliglustat ENCORE trial

Rebecca Pleat [a], Timothy M. Cox [b], T. Andrew Burrow [c], Pilar Giraldo [d], Ozlem Goker-Alpan [e], Barry E. Rosenbloom [f], Laura R. Croal [a], Lisa H. Underhill [a], Sebastiaan J.M. Gaemers [a], M. Judith Peterschmitt [a,*]

[a] Sanofi Genzyme, Cambridge, MA, USA
[b] Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
[c] Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[d] Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), IISAragón, Zaragoza, Spain
[e] Lysosomal Disorders Research and Treatment Unit, Center for Clinical Trials, O&O Alpan, LLC, Fairfax, VA, USA
[f] Cedars-Sinai/Tower Hematology Oncology, Beverly Hills, CA, USA

ARTICLE INFO

Article history:
Received 4 August 2016
Received in revised form 24 August 2016
Accepted 24 August 2016
Available online 30 September 2016

Keywords:
Composite endpoint
Eliglustat
Gaucher disease type 1
Imiglucerase
Non-inferiority trial
Velaglucerase alfa

ABSTRACT

Gaucher disease type 1 is an autosomal recessive disorder caused by deficient activity of the lysosomal enzyme acid β-glucosidase resulting in accumulation of glucosylceramide and clinical manifestations of anemia, thrombocytopenia, hepatosplenomegaly, and skeletal disease. The historic standard of care is intravenous recombinant enzyme therapy with imiglucerase. Eliglustat, an oral substrate reduction therapy, is a first-line treatment for adults with Gaucher disease type 1 who have a compatible CYP2D6-metabolizer phenotype (≈95% of patients). The 12-month ENCORE trial (NCT00943111) found eliglustat non-inferior to imiglucerase in maintaining stability in adult Gaucher patients previously stabilized after ≥3 years of enzyme therapy (imiglucerase or velaglucerase alfa). This post-hoc analysis examined safety and efficacy in the 30 ENCORE patients who were receiving velaglucerase alfa at study entry and were randomized to eliglustat (n = 22) or imiglucerase (n = 8). Efficacy and safety in velaglucerase alfa-transitioned patients were consistent with the full ENCORE trial population; 90% of patients switched to eliglustat and 88% of patients switched to imiglucerase met the composite endpoint (stable hemoglobin concentration, platelet count, spleen volume, 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.

1. Introduction

Gaucher disease type 1 is an autosomal recessive disorder caused by reduced activity of the lysosomal enzyme acid β-glucosidase leading to pathologic accumulation of glucosylceramide, primarily in macrophages. Clinical manifestations include hepatosplenomegaly, anemia, thrombocytopenia, and skeletal disease [1]. Two treatment approaches exist: intravenous enzyme therapy using human recombinant acid β-glucosidase and oral substrate reduction therapy. Enzyme therapy augments the ability of macrophages to break down substrate. Currently, three enzyme therapies are available for the treatment of Gaucher disease type 1: imiglucerase (Cerezyme®, Sanofi Genzyme, first available in 1994, produced in a Chinese hamster ovary cell line), velaglucerase alfa (VPRIV®, Shire Pharmaceuticals, first available in 2010, produced in a human fibrosarcoma cell line), and taliglucerase alfa (Elelyso®, Pfizer/Protalix, first available in 2012, produced in a genetically modified carrot cell line). In addition to their different production platforms, these human recombinant acid β-glucosidase products have minor structural differences and, thus, are not considered biosimilar agents by the United States Food and Drug Administration [2].

Substrate reduction therapy selectively inhibits glucosylceramide synthase, thereby slowing the production of glucosylceramide [3]. Currently, two such therapies are available: miglustat (Zavesca®, Actelion Therapeutics), a second-line therapy for adults with Gaucher disease type 1 who are not candidates for enzyme therapy, and eliglustat (Cerdelga®, Sanofi Genzyme), which was approved in the United States in 2014 and the European Union in 2015 as a first-line treatment for adults with Gaucher disease type 1 who are poor, intermediate, or extensive CYP2D6 metabolizers (≈95% of patients [4]). Clinical trials of eliglustat in adults with Gaucher disease showed hematologic,

* Corresponding author at: Sanofi Genzyme, 500 Kendall Street, Cambridge, MA 02142, USA.
E-mail address: Judith.Peterschmitt@genzyme.com (M.J. Peterschmitt).

http://dx.doi.org/10.1016/j.ymgmr.2016.08.009

visceral, and skeletal improvements in treatment-naïve patients [5–9] and, in patients previously treated with intravenous enzyme therapy, the drug maintained disease stability [10].

With up to five therapeutic options for Gaucher disease, it is important for clinicians to understand the potential implications of switching from one treatment to another. Several switch studies have assessed the outcome of switching from imiglucerase (the historic standard of care) to velaglucerase alfa [11], taliglucerase alfa [12], or miglustat [13]. The eliglustat ENCORE study (NCT00943111, sponsored by Sanofi Genzyme) assessed the outcome of patients switching from enzyme therapy (imiglucerase or velaglucerase alfa) to eliglustat. The primary analysis of this imiglucerase-controlled study found eliglustat non-inferior to imiglucerase in maintaining clinical stability for 12 months [10]. Since a subset of patients in ENCORE were being treated with velaglucerase alfa at baseline, this trial also offers the opportunity to perform a post-hoc analysis of two other switch populations that have not been evaluated to date: patients switching from velaglucerase alfa to eliglustat and patients switching from velaglucerase alfa to imiglucerase.

2. Patients and methods

The randomized, multinational, open-label Phase 3 ENCORE trial evaluated 159 adults with confirmed acid β-glucosidase deficiency who had achieved the following pre-specified therapeutic goals after ≥3 years of enzyme therapy: hemoglobin concentration ≥11g/dL (women), ≥12 g/dL (men); platelet count ≥100 × 10^9/L, spleen volume <10 multiples of normal (MN); liver volume <1.5 MN; and no bone crisis or symptomatic bone disease within the last year [10]. Patients were stratified on the basis of their previous enzyme therapy dose (<35 units/kg/2 weeks or ≥35 units/kg/2 weeks) and randomized 2:1 to receive either oral eliglustat (n = 106) or imiglucerase infusions (n = 53) for 12 months.

The composite primary efficacy endpoint was the percentage of patients meeting all four pre-specified stability parameters. In relation to baseline measurements, hemoglobin concentration could not decrease by >1.5 g/dL, platelet count could not decrease by >25%, and spleen and liver volumes could not increase by >25% and >20%, respectively [10]. As this was a non-inferiority study, efficacy analyses were carried out on the 99 eliglustat and 47 imiglucerase patients in the per-protocol population. Secondary endpoints were the percentage of patients who met the stability criterion for each individual component of the primary endpoint (hemoglobin concentration, platelet count, spleen volume, and liver volume) [10].

This post-hoc analysis examined efficacy and safety in the subset of ENCORE patients whose enzyme therapy at baseline was velaglucerase alfa. As in the primary analysis, efficacy analyses were done on the per-protocol population and safety data were evaluated in all treated patients; however, results are descriptive only as the trial was not designed to compare velaglucerase alfa with eliglustat or imiglucerase.

3. Results

Of the 159 patients who participated in ENCORE, 30 were receiving velaglucerase alfa at baseline and were randomized to eliglustat (n = 22) or imiglucerase (n = 8). Baseline characteristics of these subgroups were similar to the two treatment arms of ENCORE except for a higher proportion of females to males in the subgroup of patients who transitioned from velaglucerase alfa to imiglucerase (Table 1) [10]. Since all patients had to have received enzyme therapy for ≥3 years before study entry and velaglucerase alfa became available <3 years before the trial began, all patients who transitioned from velaglucerase alfa had previously received imiglucerase (mean duration of prior imiglucerase treatment for the entire trial population was 10 years) [10]. All but two of the 30 patients were included in the per-protocol population; both exclusions were in the eliglustat group — one patient withdrew (see below) and the other was excluded because of <80% dosing compliance (Fig. 1).

Table 1
Baseline characteristics of patients whose enzyme therapy at baseline was velaglucerase alfa.

Treatment arm	Eliglustat (*N* = 22)	Imiglucerase (*N* = 8)
Sex, n (%)		
Male	13 (59)	1 (12)
Female	9 (41)	7 (88)
Race, n (%)		
White/non-Jewish	10 (46)	4 (50)
White/Ashkenazi Jewish	6 (27)	4 (50)
Hispanic	4 (18)	0
Black/African American	1 (4.5)	0
White/American Indian	1 (4.5)	0
Randomization stratification (based on enzyme therapy dose), n (%)		
≥35 units/kg/2 weeks	16 (73)	4 (50)
<35 units/kg/2 weeks	6 (27)	4 (50)
Metabolizer status, n (%)		
Extensive	13 (59)	6 (75)
Intermediate	6 (29)	2 (25)
Ultra-rapid	2 (10)	0
Poor	1 (5)	0
Splenectomy performed, n (%)		
Partial	0	0
Total	5 (23)	3 (38)
Disease and treatment history		
Mean age at first Gaucher symptom in years (min, max)[a]	11.1 (1.0, 35.1) (n = 19)	8.4 (3, 26)
Mean age at Gaucher type 1 diagnosis in years (min, max)	17.2 (2, 51.3)	14.7 (3.5, 46.6)
Mean age at start of enzyme therapy in years (min, max)	39.9 (18.1, 57.7)	41.5 (22.4, 58.2)
Mean years on imiglucerase before switch to velaglucerase alfa (min, max)[b]	8.2 (1.05, 14.9) (n = 20)	11.2 (4.7, 14.3)
Mean years on velaglucerase alfa before randomization (min, max)	1.4 (0.5, 3.1)	1.9 (1.0, 3.3)
Mean dose of prior velaglucerase alfa (U/kg/2 weeks) (min, max)	48.5 (15, 65)	39.8 (27, 60)

[a] 3 patients did not have data for age at first Gaucher disease symptom.
[b] All patients in the ENCORE trial had received treatment with imiglucerase at some point in their treatment history; this subset of 30 patients was receiving velaglucerase alfa in the time period before study entry. The imiglucerase start date was missing for 2 patients.

Hemoglobin concentration, platelet count, spleen volume, and liver volume remained stable among patients transitioned from velaglucerase alfa in both the eliglustat and imiglucerase trial arms over 12 months (Fig. 2). Overall, 18/20 (90%) velaglucerase alfa to eliglustat patients and 7/8 (88%) velaglucerase alfa to imiglucerase patients met the primary composite endpoint. These numbers were similar in the intent-to-treat population; 19/22 (86%) velaglucerase alfa to eliglustat patients and 7/8 (88%) velaglucerase alfa to imiglucerase patients met the primary composite endpoint.

The three patients in the per-protocol population who did not meet the composite endpoint each missed by a single criterion: hemoglobin concentration (eliglustat patient), platelet count (eliglustat patient), and liver volume (imiglucerase patient). In all three cases, there was no clinical deterioration despite the change from baseline, and patients maintained absolute values for these endpoints that remained within therapeutic goals for enzyme therapy as defined by Pastores et al. [14]. With respect to individual stability goals (secondary endpoints), in the eliglustat arm 19/20 (95%) patients met the stability criterion for hemoglobin and platelet counts, and 20/20 (100%) for spleen and liver volumes. In the imiglucerase arm, 8/8 (100%) patients met stability criteria for hemoglobin, platelets, and spleen volume and 7/8 (83%) for liver volume.

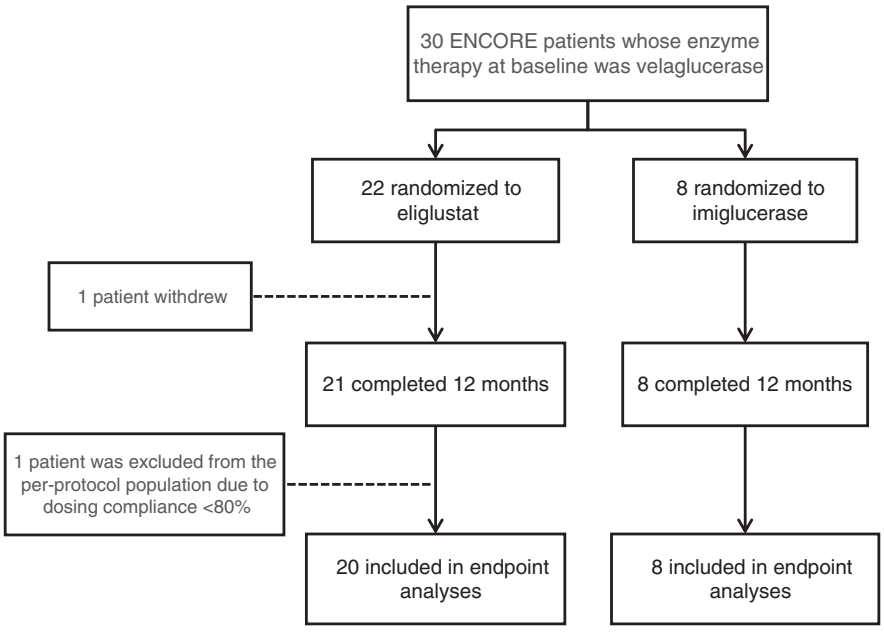

Fig. 1. Patient disposition.

These efficacy results are consistent with those observed in the primary analysis of the ENCORE trial, in which 84/99 (85%) eliglustat-treated patients and 44/47 (94%) imiglucerase-treated patients met the primary composite endpoint, with the lower bound of the 95% CI of the between-group difference (−17.6%) falling within the pre-specified 25% threshold for non-inferiority [10].

As expected in a population with stable disease on enzyme therapy, mean baseline bone mineral density scores for both lumbar spine and femur were in the reference (normal) range. Mean bone marrow burden scores were in the moderate infiltration range. As was reported in the full trial population, patients transitioned from velaglucerase alfa had stable bone measures after 12 months [10].

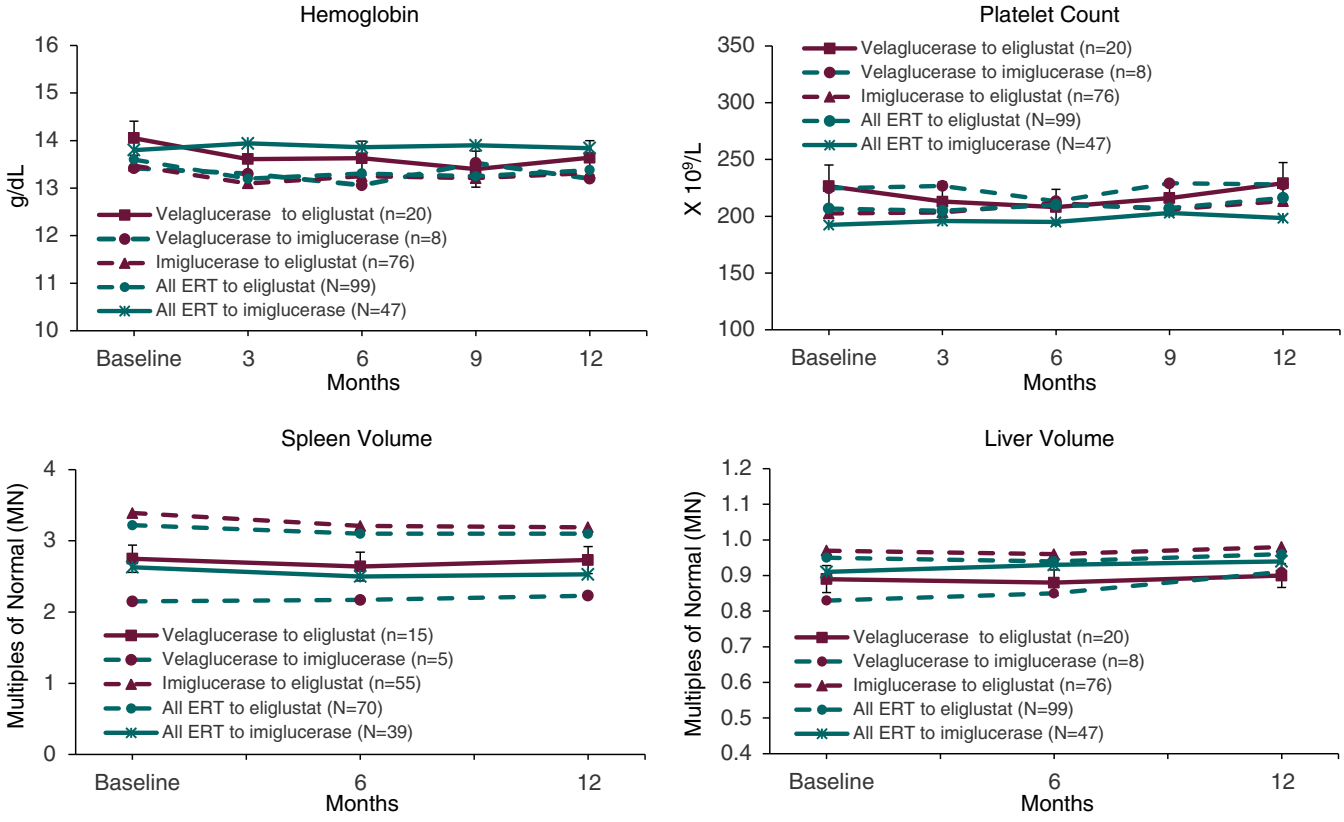

Fig. 2. Mean values over time in secondary endpoints during 12 months of treatment. The mean values for hemoglobin concentration, platelet count, spleen volume, and liver volume over time are depicted for the five patient populations shown. Error bars depict the standard error of the mean for the velaglucerase alfa to eliglustat cohort. Splenectomized patients were excluded from the spleen volume analysis.

The frequency and severity of adverse events in the patients transitioned from velaglucerase alfa were consistent with those reported in the full trial population [10]. Most adverse events were mild or moderate in severity, and there were no treatment-related serious adverse events (Table 2). In the 22 patients randomized to eliglustat, treatment-related events occurring in ≥2 patients were diarrhea, fatigue, headache, pain in extremity, palpitations, and throat irritation; each occurred in two (9%) patients. Four serious adverse events occurred: appendicitis, syncope, ischemic colitis, and uterine leiomyoma. All were considered unrelated to treatment and none resulted in study withdrawal. The one withdrawal was due to an adverse event (palpitations) that was moderate in severity and considered possibly related to eliglustat; the event resolved without treatment. Among the eight patients who were transitioned from velaglucerase alfa and randomized to imiglucerase, two events (anxiety and back pain) in two patients were considered related to treatment, and there were no serious adverse events. After the 12-month primary analysis period, 29/30 (97%) patients who transitioned from velaglucerase alfa entered the open-label extension study.

4. Discussion and conclusions

The data from this post-hoc analysis of a clinical trial subpopulation suggest that eliglustat and imiglucerase were well-tolerated and maintained clinical stability in adults (n = 30) with Gaucher disease type 1 who were previously treated with velaglucerase alfa. Study limitations include limited number of patients receiving either maintenance therapy with eliglustat (n = 20, 1 withdrawn, 1 excluded because of dosing <80% as per protocol) and imiglucerase (n = 8). Safety and efficacy in these patients were consistent with what was observed for the entire ENCORE trial population.

4.1. Authorship statement

Contributions: MJP designed the study and RP and LU drafted the manuscript. TMC, TAB, BR, PG, OGA recruited patients and participated in study research. All authors participated in data interpretation and critical review of the manuscript, approved the final submitted version, and are jointly responsible for the content and editorial decisions related to the manuscript. The decision to submit the manuscript for publication was made jointly by all authors.

Conflict of interest

Conflict of interest disclosures: The study was funded and conducted by Sanofi Genzyme. RP, LRC, LHU, SJMG, and MJP are employees of Sanofi Genzyme. TMC, PG, OGA, and BR are principal investigators in the eliglustat ENCORE trial and have received honoraria and travel reimbursement from Sanofi Genzyme. TAB is a principal investigator in the eliglustat ENCORE trial and has received honoraria and travel reimbursement from Sanofi Genzyme and BioMarin.

Table 2
Adverse event summary.

	Velaglucerase alfa to eliglustat (N = 22)		Velaglucerase alfa to imiglucerase (N = 8)	
	Patients	Events	Patients	Events
Any adverse event	22	232	8	50
Mild	22	157	8	33
Moderate	13	53	6	13
Severe	8	22	3	4
Treatment-related	14	49	2	2
Leading to withdrawal	1	1	0	0
Any serious adverse event	4	4	0	0
Mild	0	0	0	0
Moderate	2	2	0	0
Severe	2	2	0	0
Treatment-related	0	0	0	0
Leading to withdrawal	0	0	0	0
Deaths	0	0	0	0

Acknowledgments

We thank Gerald F. Cox, MD, PhD, and Jennifer Angell of Sanofi Genzyme for their review of the manuscript, and Regina Tayag, MA, of Prometrika (Cambridge, MA, funded by Sanofi Genzyme) for statistical consultation and data review.

References

[1] G.A. Grabowski, E.H. Kolodny, N.J. Weinreb, B.E. Rosenbloom, A. Prakash-Cheng, P. Kaplan, J. Charrow, G.M. Pastores, P.K. Mistry, Gaucher disease: phenotypic and genetic variation, in: D. Valle, A.L. Beaudet, B. Vogelstein, K.W. Kinzler, S.E. Antonarakis, A. Ballabio, K. Gibson, G. Mitchell (Eds.), OMMBID: The Online Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill, New York, NY, 2011.
[2] J.A. Barranger, R.O. Brady, G.A. Grabowski, H. Mankin, P.K. Mistry, N.J. Weinreb, Position statement: National Gaucher Foundation Medical Advisory Board, January 7, 2014, Am. J. Hematol. 89 (5) (2014) 457–458.
[3] J.A. Shayman, Eliglustat tartrate: glucosylceramide synthase inhibitor treatment of type 1 Gaucher disease, Drugs Future 35 (8) (2010) 613–620.
[4] J.K. Hicks, J.J. Swen, C.F. Thorn, K. Sangkuhl, E.D. Kharasch, V.L. Ellingrod, T.C. Skaar, D.J. Muller, A. Gaedigk, J.C. Stingl, Clinical pharmacogenetics implementation. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants, Clin. Pharmacol. Ther. 93 (5) (2013) 402–408.
[5] R.S. Kamath, E. Lukina, N. Watman, M. Dragosky, G.M. Pastores, E.A. Arreguin, H. Rosenbaum, A. Zimran, R. Aguzzi, A.C. Puga, A.M. Norfleet, M.J. Peterschmitt, D.I. Rosenthal, Skeletal improvement in patients with Gaucher disease type 1: a phase 2 trial of oral eliglustat, Skelet. Radiol. 43 (10) (2014) 1353–1360.
[6] E. Lukina, N. Watman, E.A. Arreguin, M. Banikazemi, M. Dragosky, M. Iastrebner, H. Rosenbaum, M. Phillips, G.M. Pastores, D.I. Rosenthal, M. Kaper, T. Singh, A.C. Puga, P.L. Bonate, M.J. Peterschmitt, A phase 2 study of eliglustat tartrate (Genz-112638), an oral substrate reduction therapy for Gaucher disease type 1, Blood 116 (6) (2010) 893–899.
[7] E. Lukina, N. Watman, E.A. Arreguin, M. Dragosky, M. Iastrebner, H. Rosenbaum, M. Phillips, G.M. Pastores, R.S. Kamath, D.I. Rosenthal, M. Kaper, T. Singh, A.C. Puga, M.J. Peterschmitt, Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study, Blood 116 (20) (2010) 4095–4098.
[8] E. Lukina, N. Watman, M. Dragosky, G.M. Pastores, E.A. Arreguin, H. Rosenbaum, A. Zimran, J. Angell, L. Ross, A.C. Puga, J.M. Peterschmitt, Eliglustat, an investigational oral therapy for Gaucher disease type 1: phase 2 trial results after 4 years of treatment, Blood Cells Mol. Dis. 53 (4) (2014) 274–276.
[9] P.K. Mistry, E. Lukina, H. Ben Turkia, D. Amato, H. Baris, M. Dasouki, M. Ghosn, A. Mehta, S. Packman, G. Pastores, M. Petakov, S. Assouline, M. Balwani, S. Danda, E. Hadjiev, A. Ortega, S. Shankar, M.H. Solano, L. Ross, J. Angell, M.J. Peterschmitt, Effect of oral eliglustat on splenomegaly in patients with Gaucher disease type 1: the ENGAGE randomized clinical trial, JAMA 313 (7) (2015) 695–706.
[10] T.M. Cox, G. Drelichman, R. Cravo, M. Balwani, T.A. Burrow, A.M. Martins, E. Lukina, B. Rosenbloom, L. Ross, J. Angell, A.C. Puga, Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial, Lancet 385 (9985) (2015) 2355–2362.
[11] A. Zimran, G.M. Pastores, A. Tylki-Szymanska, D.A. Hughes, D. Elstein, R. Mardach, C. Eng, L. Smith, M. Heisel-Kurth, J. Charrow, P. Harmatz, P. Fernhoff, W. Rhead, N. Longo, P. Giraldo, J.A. Ruiz, D. Zahrieh, E. Crombez, G.A. Grabowski, Safety and efficacy of velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase, Am. J. Hematol. 88 (3) (2013) 172–178.
[12] G.M. Pastores, M. Petakov, P. Giraldo, H. Rosenbaum, J. Szer, P.B. Deegan, D.J. Amato, E. Mengel, E.S. Tan, R. Chertkoff, E. Brill-Almon, A. Zimran, A Phase 3, multicenter, open-label, switchover trial to assess the safety and efficacy of taliglucerase alfa, a plant cell-expressed recombinant human glucocerebrosidase, in adult and pediatric patients with Gaucher disease previously treated with imiglucerase, Blood Cells Mol. Dis. 53 (4) (2014) 253–260.
[13] T.M. Cox, D. Amato, C.E. Hollak, C. Luzy, M. Silkey, R. Giorgino, R.D. Steiner, Evaluation of miglustat as maintenance therapy after enzyme therapy in adults with stable type 1 Gaucher disease: a prospective, open-label non-inferiority study, Orphanet J. Rare Dis. 7 (1) (2012) 102.
[14] G.M. Pastores, N.J. Weinreb, H. Aerts, G. Andria, T.M. Cox, M. Giralt, G.A. Grabowski, P.K. Mistry, A. Tylki-Szymanska, Therapeutic goals in the treatment of Gaucher disease, Semin. Hematol. 41 (4 Suppl. 5) (2004) 4–14.