Blood Cells, Molecules and Diseases xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

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

A pooled analysis of adverse events in 393 adults with Gaucher disease type 1 from four clinical trials of oral eliglustat: Evaluation of frequency, timing, and duration

M. Judith Peterschmitt [a,*], Gerald F. Cox [a,1], Jennifer Ibrahim [a], James MacDougall [b], Lisa H. Underhill [a], Palni Patel [a], Sebastiaan J.M. Gaemers [a]

[a] Sanofi Genzyme, 500 Kendall Street, Cambridge, MA 02142, USA
[b] Prometrika, LLC, 100 CambridgePark Drive, Second Floor, Cambridge, MA 02140, USA

ARTICLE INFO

Article history:
Submitted 11 January 2017
Available online xxxx

Keywords:
Gaucher disease type 1
Acid β-glucosidase deficiency
Eliglustat
Substrate reduction therapy
Safety
Adverse events

ABSTRACT

Eliglustat, an oral substrate reduction therapy, is a first-line therapy for adults with Gaucher disease type 1 and a compatible CYP2D6 metabolizer phenotype. Clinicians have requested more information about frequency, timing, and duration of adverse events associated with eliglustat. Adverse event data as of January 31, 2013 for all patients who received at least one dose of eliglustat were pooled from four eliglustat clinical trials (393 patients representing 535 patient-years of exposure). The following 10 adverse events noted in the eliglustat US Prescribing Information (USPI) and EU Summary of Product Characteristics (SmPC) were evaluated with regard to frequency, drug-relatedness, severity, seriousness, duration, and timing of onset: headache, arthralgia, diarrhea, nausea, fatigue, flatulence, abdominal pain, upper abdominal pain, back pain, and extremity pain. Of 393 patients, 334 experienced one or more adverse events. Most patients (92%) continued taking eliglustat; 3% withdrew from a trial due to an adverse event. Among the 10 adverse events evaluated, none was reported as serious and none resulted in discontinuing treatment; most were mild or moderate, reported only once, and not considered eliglustat-related. The majority of adverse events noted in the eliglustat USPI and SmPC were non-serious, occasional, non-severe, and did not lead to drug discontinuation.

1. Introduction

Gaucher disease type 1 (GD1) is an autosomal recessive lysosomal storage disorder caused by deficient activity of the enzyme acid β-glucosidase [1,2]. The resultant lysosomal accumulation of glucosylceramide (GL-1) throughout the body (and particularly in cells of macrophage/monocyte lineage) leads to progressive and debilitating clinical manifestations, including anemia, thrombocytopenia, hepatosplenomegaly, growth retardation, bone pain, osteoporosis, vertebral compression fractures, bone infarction, avascular necrosis, progressive joint destruction, pulmonary disease, and immune dysfunction [1–8]. GD1, the most common form of Gaucher disease, has an estimated incidence of 1:40,000–60,000 patients worldwide [9], with an especially high incidence (1:800) among people of Ashkenazi Jewish ancestry [10].

Two treatment approaches have been used to lower GL-1 accumulation in Gaucher disease. In both approaches, the goal is to restore the balance between synthesis and degradation of GL-1. Intravenous enzyme replacement therapy (ERT) with recombinant acid β-glucosidase augments the patient's residual enzyme activity to break down accumulated GL-1. ERT has been widely used for more than two decades, is generally well tolerated and considered safe. Available ERTs include imiglucerase (Cerezyme®, Sanofi Genzyme, Cambridge, MA, USA; first approved in 1994), velaglucerase alfa (Vpriv®, Shire HGT, Lexington, MA, USA; first approved in 2010), and taliglucerase alfa (Elelyso®, Pfizer, New York, NY, USA; first approved in 2012). Oral substrate reduction therapy (SRT) acts by partially inhibiting glucosylceramide synthase, thereby slowing production of GL-1. Two SRTs are commercially available: miglustat (Zavesca®, Actelion Pharmaceuticals US, Inc., South San Francisco, CA, USA), approved in 2004 for adults with mild or moderate GD1 for whom ERT is unsuitable, and eliglustat (Cerdelga®, Sanofi Genzyme, Cambridge, MA, USA), approved in 2014 (US) and 2015 (EU) as a first-line therapy for adults with GD1 who have a compatible CYP2D6 metabolizer phenotype (>90% of patients).

The eliglustat clinical development program, which has involved 393 patients to date, is the largest ever conducted in Gaucher disease. The safety and efficacy of eliglustat have been evaluated in a Phase 2, open-label, single-arm trial [11–13]; a Phase 3 placebo-controlled trial

* Corresponding author.
E-mail address: Judith.Peterschmitt@sanofi.com (M. Judith Peterschmitt).
[1] Current address: Editas Medicine, Cambridge, MA, USA.

http://dx.doi.org/10.1016/j.bcmd.2017.01.006

in treatment-naïve adults with GD1 [14]; and a Phase 3 imiglucerase-controlled trial in adults with GD1 previously stabilized with at least 3 years of ERT [15]. A third Phase 3 trial evaluated once-daily versus twice-daily dosing of eliglustat in both treatment-naïve and ERT-switch patients who demonstrated clinical stability on a twice-daily dose of eliglustat during a lead-in period up to 18 months.

To better inform patients about what to expect when taking eliglustat, clinicians have requested more information about associated adverse events, particularly with regard to the frequency, timing, and duration. The adverse event information highlighted in the US Prescribing Information (PI) [16] and/or the EU Summary of Product Characteristics (SmPC) [17] is primarily based on 152 patients from the primary analysis periods of the Phase 3 ENGAGE (9 months) and ENCORE (12 months) trials, and 4-year data from the Phase 2 open-label study. As part of their evaluation, however, the regulatory authorities also reviewed a larger safety data set, the Integrated Summary of Safety (ISS), which contains adverse event information on all 393 patients enrolled in ongoing eliglustat clinical trials as of January 31, 2013, including those participating in the Phase 3 dosing study, EDGE. We used this larger data set to evaluate the adverse events highlighted in the two product labels, as these were the events of concern to regulatory bodies.

2. Methods

2.1. Data collection

The ISS dataset included pooled adverse event data for all patients who received at least one dose of eliglustat as of January 31, 2013 in the four eliglustat clinical trials: the Phase 2 single arm study (NCT00358150) [11–13]; the Phase 3 ENGAGE randomized, placebo-controlled trial (NCT00891202) [14]; the Phase 3 ENCORE randomized, imiglucerase-controlled trial (NCT00943111) [15]; and the Phase 3 EDGE randomized, double-blind trial of once-daily versus twice-daily dosing (NCT01074944). The protocols for all four studies were approved by the institutional review board or independent ethics committee. Treatment-emergent adverse events during each trial were obtained through spontaneous reporting or elicited during open-ended questioning. Patients with more than one adverse event with the same preferred term were counted only once for that term. Adverse event severity was classified by the most severe occurrence reported and by the occurrence of any single event considered drug-related by the investigator.

2.2. Analysis of adverse events

Using the ISS dataset, the following adverse events noted in the USPI and/or SmPC were evaluated: headache, arthralgia, diarrhea, nausea, fatigue, flatulence, abdominal pain, upper abdominal pain, back pain, and extremity pain. Also evaluated were additional adverse events highlighted in the drug labels for the other oral SRT, miglustat (weight loss, tremor, and peripheral neuropathy) [18,19], because of concerns that these might be class effects of substrate reduction. All adverse events were evaluated with respect to frequency in the overall ISS population, frequency in individual patients (episodic or chronic), relatedness to eliglustat (as determined by the investigator), severity (mild, moderate, or severe, as classified by the investigator), seriousness (e.g., whether the event led to hospitalization), duration (length of event and proportion of events lasting ≤2 weeks), and timing (time of onset relative to starting eliglustat). Adverse event data were mapped for each individual patient to provide a visual representation of the pattern of event frequency, duration, and severity. Patients were grouped by trial, as each trial had different eligibility criteria.

For missing event start dates, the first day of the month was imputed, and for missing start months, the first day of the year was imputed. Similarly, the last day of the month was imputed when the end day was missing, and the last day of the year was imputed when the end month was missing. Events with missing end dates were considered ongoing. Event duration and event timing are reported as median values with the first and third quartiles of the interquartile range, as the means were skewed due outlier patients with missing end dates.

3. Results

3.1. Patient population and eliglustat exposure

As of January 31, 2013, the ISS dataset included 393 patients who received at least one dose of eliglustat (Table 1), representing 535 patient-years of eliglustat exposure (Table 2). A majority (92%) were continuing eliglustat therapy as of this date. Among the 33 patients (8.4%) who withdrew, 12 (3.1%) withdrew due to adverse events; in 5 of these patients (1.3%) the adverse events were considered related to eliglustat. Dosing in the eliglustat clinical trials involved titration to steady-state plasma concentrations >5 ng/mL. Eliglustat exposure in the ISS dataset represents 141 patient-years at 50 mg twice daily (the initial dose for most patients), 276 patient-years at 100 mg twice daily (the dose that proved therapeutic for most patients), and 112 patient-years at 150 mg twice daily (a dose that 98/393 patients were on at some point).

Table 3 shows the demographics and baseline characteristics of the ISS population. Most patients were diagnosed as young adults and started on treatment approximately 16 years after diagnosis. The mean time on eliglustat was 1.4 years, and 65% of patients had been treated with ERT before receiving eliglustat. Approximately one quarter of patients had undergone total or partial splenectomy. As in the general population [20], most patients (91%) were intermediate or extensive CYP2D6 metabolizers.

3.2. Summary of adverse events

The following adverse events were reported in 10% or more of patients, regardless of relationship to eliglustat: headache (17%), arthralgia (14%), nasopharyngitis (13%), diarrhea (10%), and dizziness (10%). Two adverse events considered related to eliglustat were reported in 5% or more of patients (headache and dizziness, both 5%). No relationship was observed between incidence of adverse events and dose of

Table 1
Patient disposition.

	ALL	Phase 2	Phase 3 ENGAGE	Phase 3 ENCORE	Phase 3 EDGE (LIP)
Treated patients	393	26	40	157	170
Still on eliglustat	360 (92%)	19 (73%)	38 (95%)	145 (92%)	158 (93%)
Withdrawn	33 (8%)	7 (27%)	2 (5%)	12 (8%)	12 (7%)
Adverse event	12 (3%)	3 (12%)	0	7 (4%)	2 (1%)
Wished to withdraw	10 (3%)	1 (4%)	2 (5%)	2 (1%)	5 (3%)
Pregnancy	8 (2%)	3 (12%)	0	1(<1%)	4 (1%)
Noncompliant	1 (<1%)	0	0	0	1 (<1%)
Other	2 (<1%)	0	0	2	0

Cutoff date: 31 January 2013. Analysis represents 393 patients and 535 patient-years of eliglustat exposure.
LIP = Lead-in Period.

Please cite this article as: M. Judith Peterschmitt, et al., Blood Cells Mol. Diseases (2017), http://dx.doi.org/10.1016/j.bcmd.2017.01.006